endocrines

Review

Overview of Nutraceuticals and Cardiometabolic Diseases following Socio-Economic Analysis

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Abstract: The importance of functional food and nutraceutical products to deal with cardiometabolic diseases (CMDs) and metabolic syndrome (MetS) has gained attention in the past few years. The aim of this narrative review is to highlight the potential and effectiveness of nutraceutical in the improvement of CMDs and MetS biomarkers, alongside their burden of disease and economic health expenditure. A science database search was conducted between May and June 2021. A total of 35 studies were included in this paper. We included male and female subjects, children, and adults, in good health or with cardiovascular or metabolic disease. CMDs and MetS have gradually become worldwide health problems, becoming two of the major causes of morbidity and mortality in western countries. The results indicate a positive link between daily consumption of nutraceutical products and an improvement in cardiometabolic and anthropometric biomarkers. In this paper we included a wide range of nutraceutical products. Most of them showed promising data, indicating that nutraceuticals could provide a new therapeutic treatment to reduce prevalence and pharmaceutical expenditures attributed to CMDs and MetS. Unfortunately, there is a huge vacuum of data on nutraceutical usage, savings, and burden reduction. Therefore, further clinical and pharmaco-economic research in the field is highly required.

Keywords: cardiometabolic diseases; metabolic syndrome; cardiovascular diseases; diabetes; non-alcoholic fatty liver disease; burden of disease; nutraceuticals

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1. Introduction

Cardiometabolic diseases (CMDs) include cardiovascular diseases (CVDs), type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), chronic kidney disease (CKD) [1] and overweight issues. CMD prevalence has increased all over the world at a dizzying pace, especially in Africa, Latin America, and China, involving both men and women of any age, racial or ethnic background [2,3].

As far as CVD is concerned, in 2017 there were 108.7 million people living with it, and the number of new cases was 19.9 million in the 54 member states of the European society of cardiology (ESC) [4]. In 2019, worldwide CVD cases amounted to 523 million [5]. Therefore, CVD should be considered as a global pandemic. Regarding T2DM, in 2014 the global prevalence of the disease was estimated at 422 million people, up from the 108 million estimated in 1980. Diabetes caused 1.5 million deaths in 2012 [6]. In 2020, in the United States of America (USA), 30 million people were estimated to be diabetic [7]. In China and India, 116 million and 80 million people were affected by T2DM, respectively [7]. In 2020, the worldwide prevalence of diabetes was estimated at 463 million cases, up from the 108 million in 1980 [6,7]. Furthermore, if we considered people with pre-diabetes, the total amount would exceed a billion individuals [7]. According to the International Diabetes Federation (IDF), there will be 642 million diabetic people by 2040 [8]. Metabolic syndrome

(MetS) is a cluster of risk factors and conditions of multifactorial etiology strictly linked to CVD, T2DM and NAFLD, as it is directly involved in their development [9].

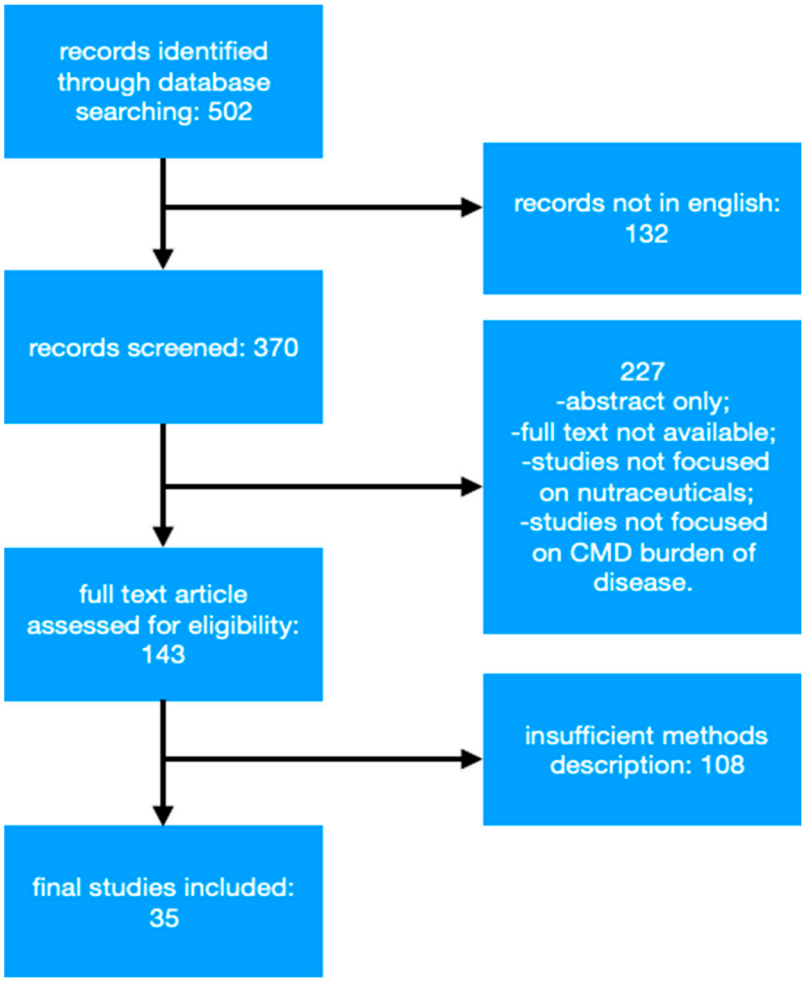
Apart from the relevant implications on a health level, all the economic resources involved, and public health interventions carried out to contain this cluster of pathologies should also be mentioned. For instance, patients with MetS require greater medical care, resulting in a 20% increase in health expenditure for each risk factor [10]. In fact, as far as the economic impact is concerned, it is crucial to point out that both CMDs and MetS constitute a huge burden for society all over the world; their impact, both direct and indirect, is challenging and has increased for years, involving hundreds of millions of people and billions in money spent to deal with them, both by society and by national health services. Evidence suggests that a healthy lifestyle, including daily physical activity and adequate drug therapy, is fundamental in prevention and treatment. Some important drugs for the treatment of cardiometabolic diseases, normally used in the classic pharmacological approach, are orlistat, metformin, thiazolidinediones, statins, ezetimibe, fibrates, sequestering bile acids, and antihypertensive. Alongside the current usage of the aforementioned drugs, a non-pharmacological approach has gained attention, both under its efficacy and economic convenience. The non-pharmacological approach consists of the administration of functional foods (foods containing substances capable of positively influencing our health) or nutraceuticals. Other approaches consist of extracts or products based on substances of animal, vegetable, or microbial origins, determined to be beneficial for human health, including the prevention and treatment of some diseases. Some types of nutraceutical products, analyzed in this review, resulted in improving outcomes related to cardiovascular and metabolic risks, such as total cholesterol level (CT), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels, systolic blood pressure (SBP), diastolic blood pressure (DBP), Homeostasis Model Assessment-Insulin Resistance (HOMA-IR), pro-inflammatory interleukin 6 (IL-6) levels, Body Mass Index (BMI), and waist circumference (WC). As a consequence, an improvement in the outcomes related to these pathologies and conditions may result in a reduction in the huge expenditures that each country bears. The resulting savings for patients, national health services and the society may turn out to be deeply useful, especially in a period marked by increasing public expenditures and debts due to the COVID-19 pandemic.

Therefore, in this narrative review we focused our attention on several nutraceuticals that could play a role in improving outcomes and analyzed the burden of disease linked to CMDs, considering CVD, T2DM, NAFLD, and MetS, in order to build up a picture of the possible savings that a non-pharmacological approach in these fields may have. Nevertheless, we found a deep vacuum in the international literature concerning the nutra-economics field, meaning there is a serious lack of studies evaluating the possible economic impact that nutraceuticals may have in dealing with CMDs and MetS, for which we stress the high need to carry out research.

2. Materials and Methods

According to the guidelines published in the CRD guide and PRISMA statement, the narrative review was carried out on PubMed, Scopus, and Google scholar, between May and June 2021, through the following keywords: nutraceuticals, cardiometabolic health, cardiometabolic diseases, cardiometabolic risks, burden of disease cardiometabolic diseases, burden of disease cardiovascular disease, burden of disease of T2DM, burden of NAFLD, and burden of disease metabolic syndrome. Moreover, the review was conducted using the Boolean operator "AND", filtering only the results deriving from systematic reviews, meta-analyses, RCTs, cross-sectional and case–control studies, prospective studies and open label studies. Studies not focused on nutraceuticals or CMDs and MetS were excluded. Abstract-only studies were excluded. We included only full texts published in English. For each study, the following data were extracted: author, country and date of publication, study perspective, study design, population size, baseline characteristics (outcome before starting treatment), and outcome where the nutraceutical product or active ingredient was

taken. Following the aforementioned criteria, 35 studies were included, over a total number of 502 studies analyzed, as can be seen in Scheme 1.



Scheme 1. Flow diagram on the studies' selection process.

This narrative review includes RCTs, systematic reviews, and meta-analyses of RCTs. We included only RCTs presenting a pool of data, suggesting a link between nutraceuticals intake and cardiometabolic and anthropometric measurements, with particular attention on what concerns the reduction and the general improvement in these outcomes. RCTs not specifically focused on the reduction in these biomarkers were excluded as well as trials not involving the nutraceutical products listed in this paper. RCTs with particularly unclear data, not focusing on the outcomes listed below, were excluded: HbA1c levels, HOMA-IR levels, triglycerides' levels (TG), CT levels, LDL levels, HDL levels, SBP levels, DBP levels, fasting blood glucose levels (FBG), blood glucose (BG) levels, Carotid Intima-Media Thickness levels (CIMT), body weight (BW), BMI, WC, and body fat mass (BFM). Moreover, studies not conducted on human beings, presenting only in vitro data, were excluded. Studies entirely focused on a specific population, or ethnicity, where the results could be affected by physiological differences (for example, lack of a particular enzyme in a population) were excluded.

Even though there is not a globally shared definition of nutraceuticals, we followed the one by De Felice [11]. We included products for which scientific literature was abundant and where there was no lack of information or data. Studies that did not conform to the inclusion criteria listed above were also excluded. We took into account the most common and recent classification on traditional nutraceuticals, presented by Helal et al. [12], for which they are divided into: chemical constituents including micronutrients and plant bioactives (nutrients

including vitamins; herbals; phytochemicals including polyphenols, anthocyanins, and bergamot polyphenols subgroups; polyunsaturated fatty acids), probiotics and prebiotics, and nutraceutical enzymes.

Given the abundance of sources, it was not possible to include all nutraceutical products involved in cardiometabolic therapy, so we tried to include nutraceuticals and other products widely used in the global market. In fact, vitamins (D and K), omega-3, polyphenols, probiotic, and prebiotic can be easily found in the current market. Furthermore, evidence suggesting their capability in reducing MetS, CVD, T2DM and NAFLD biomarkers is well established, with a vast scientific literature focusing on their benefits.

Products involved in MetS, T2DM, NAFLD and CVD, but lacking a strong literature background, were excluded.

3. Results

3.1. Burden of Disease

CMDs come with high costs for people and for the national health services all over the world. Taking into consideration a recent American study on the subject, the total annual cost of CMDs in the USA was estimated to be USD 50.4 billion, of which USD 42.6 billion (84.3% of the total amount) accounted for acute care [13].

3.1.1. Burden of CVD

According to the American Heart Association [5], CVD is the leading cause of death globally, and by 2030 it will be responsible for 23.6 million deaths or more. Worldwide, cases of cardiovascular issues increased from 271 million in 1990 to 523 million in 2019 [14]; consequently, the number of deaths caused by CVD rose from 12.1 million (1990) to 18.6 million (2019). As far as the United States of America (USA) is concerned, in a 2019 report by the American Heart Association (AHA) [5], the prevalence of CVD resulted in 121.5 million. Regarding mortality, it can be said that among cardiovascular diseases, coronary heart disease (CHD) is the leading cause of death in the USA (43.2%), followed by heart attack (16.9%), high blood pressure (9.8%), heart failure (9.3%), arterial problems, and other minor causes of CVD (17.7%). CVD age-adjusted death rate decreased from a value of 269.6 per 100,000 population in 2006 to 219.4 per 100,000 in 2016 (with a total decrease of 18.6%). According to the data collected in 2016 [5], it can be said that CVD claims more victims than cancer and chronic lung disease combined. In fact, the number of people who died from CVD in 2016 was 840,678 (428,434 men, 412,244 women), while the deaths caused by the cancer were 598,031 (Figure 1). A total of 161,438 Americans under the age of 65 died of CVD, and 306,638 died of CVD before the age of 75. It should be noted that the average life expectancy in the US was 78.6 years in 2016. Still remaining on American soil, according to the Medical Expenditure Panel Survey (MEPS) and the National Heart, Lung, and Blood institute (NHLBI), the total estimate of direct costs for the treatment of CVD in the period 2014–2015 was USD 351.2 billion (Table 1) [5]. In particular, the economic outlay for direct costs (that include the cost of professional visits, hospital services, prescription drugs and home health care but not nursing home care) was USD 213.8 billion, up from USD 103.5 billion estimated in 1996–1997. The loss in future productivity was around USD 137.4 billion [5]. CVD and stroke accounted for 14% of US health expenditures in the period 2014–2015.

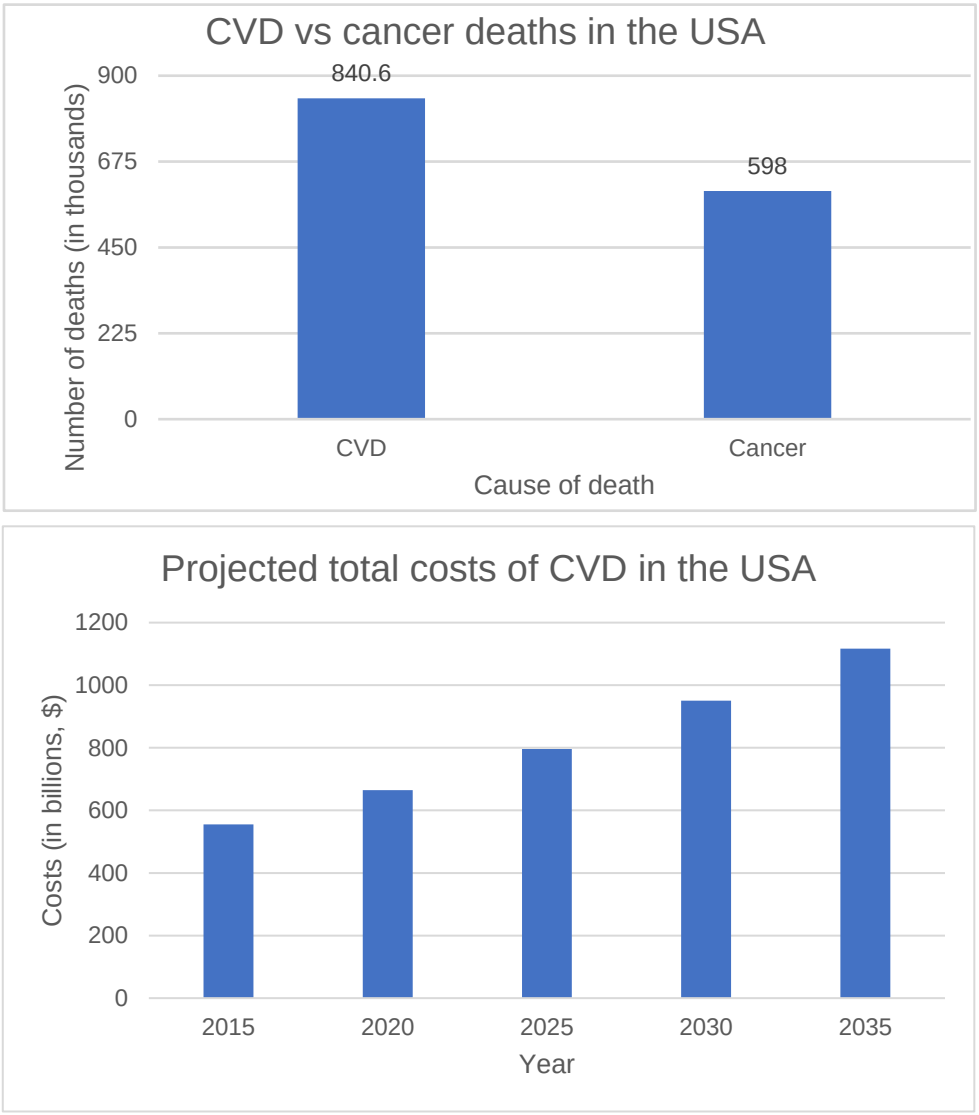


Figure 1. CVD vs cancer deaths (year 2016) and projected total costs of CVD (years 2015–2035) in the USA (illustration content elaborated and modified form the original work by Benjamin et al., 2020 [5]).

Table 1. Estimated direct and indirect costs (in billions, $) of CVD in the USA 2014–2015 (table content elaborated and modified from the original work by Benjamin et al., 2020 [5]).

	Heart Disease	Stroke	Hypertensive Disease	Other Circulatory Conditions	Total CVD
DIRECT COSTS	109.4	28.0	51.3	25.1	213.8
INDIRECT COSTS	109.3	17.5	4.6	6.1	137.4
GRAND TOTAL	218.7	45.5	55.9	31.2	351.2

The direct costs of treatment are extremely higher than those estimated for cancer by the Agency for Healthcare Research and Quality-AHRQ (USD 84.0 billion, of which 55% is for medical or outpatient visits, 32% for hospitalizations, 9% drug prescriptions) [5]. According to the projections by AHA, by 2035, 45.1% of American citizens will develop some forms of CVD. Between 2015 and 2035, direct costs for CVD treatment are estimated to increase to USD 749 billion (55% hospital costs, 15.3% medications, 15% medical examination costs, 7.2% nursing home care, 5.5% home health care, 1.5% other costs) [5]. Indirect costs will increase by 55%, reaching an amount of around USD 368 billion. As

a consequence, overall costs (direct and indirect costs) are projected to increase to USD 1116.6 billion (Figure 1). People over the age of 45 years will become the most involved in the rise of CVD prevalence and incidence, with a steady increase up to the age of 80, meaning they will be the most deeply affected by high expenses [5].

Focusing on European territory, according to the ESC [4], in 2017, 19.9 million new CVD cases were discovered among the 54 countries of ESC. The mean age standardized incidence of CVD was 1133 per 100,000 inhabitants, with Austria, Czech Republic, Finland, Iceland, Luxembourg, and Slovenia exceeding 1400 cases. Instead, regarding middle-income countries, the average value was 1039 (with peaks greater than 1300 in Romania and Bulgaria) [4]. The incidence of new CVD cases proved to be higher in women (10.3 million) than in men (9.6 million). Between 1990 and 2017, the median age standardized incidence of CVD per 100,000 people changed from 1186 to 1133. The prevalence of CVD in 2017 was equal to 108.7 million cases, with more women than men affected (55.7 million and 52.9 million, respectively) [4]. The median age standardized prevalence per 100,000 inhabitants found an average value of 6595, with Norway and Bulgaria acting as extremes (5254 and 8766, respectively); instead, for middle-income countries, this value was higher than in high-income countries (7022 and 6245, respectively) [4]. According to data derived from the World Health Organization (WHO) database, CVD remains the leading cause of death in the 54 ESC countries, with 2.2 million deaths reported among women and 1.9 million among men [4]. In the ESC countries, CVD mortality is far greater than the one for cancer (887,668 for women, 1.1 million for men); in detail, CVD deaths overcome cancer deaths in ESC middle-income countries, while in ESC high-income countries (such as the UK, Norway, Denmark, France, Belgium, The Netherlands, Spain, Portugal, and Switzerland), cancer has become the most common cause of death [4]. Another interesting fact to analyze is the Potential Years of Life Lost (PYLL) due to premature death, calculated by multiplying the number of deaths by life expectancy standard at the age at which death occurred. CVD found PYLL parameters, respectively, in the order of 28 million for women (37% of all years lost) and 38 million (34% of all years lost) for men; to make a comparison, cancer had PYLL values of 18.7 million (25%) for women and 25.5 million (22%) for men. In middle-income countries, CVD PYLL was found to be greater than in high-income countries (43% vs. 28% in women and 39% vs. 28% in men). In high-income countries, on the other hand, cancer had higher PYLL values than CVD (34% vs. 19% in women and 35% vs. 18% in men) [4].

According to the European Heart Network (EHN) [15], each year, CVD causes 3.9 million deaths in Europe and over 1.8 million deaths in the European Union (EU). Moreover, it constitutes 45% of all deaths in Europe and 37% of all deaths in the EU. In 2015, there were around 11.3 million new CVD cases in Europe and 6.1 million in the EU. In 2015, more than 85 million people in Europe were living with CVD and almost 49 million people in the EU [16]. In 2015, the treatment of CVD in the EU costed € 210 billion, showing a huge increase from the 2009 estimate of € 106 billion. 53% of the total expenditures (€ 111 billion) were for direct healthcare costs (Figure 2) [16]. In Bulgaria, Croatia, Romania, Latvia, Lithuania, and Cyprus, direct costs per capita were inferior to € 100,000, while in Finland they were equal to € 365,000. The pharmaceutical expenditure constituted 28% of the total costs of CVD in Greece, and 7% for Sweden, Finland, and Estonia. Indirect costs amounted to € 54 billion (26%) for productivity loss and € 45 billion (21%) for informal care, with the latter ranging from 7% of total expenditure in Finland to 30% or more in Portugal and Croatia [16].

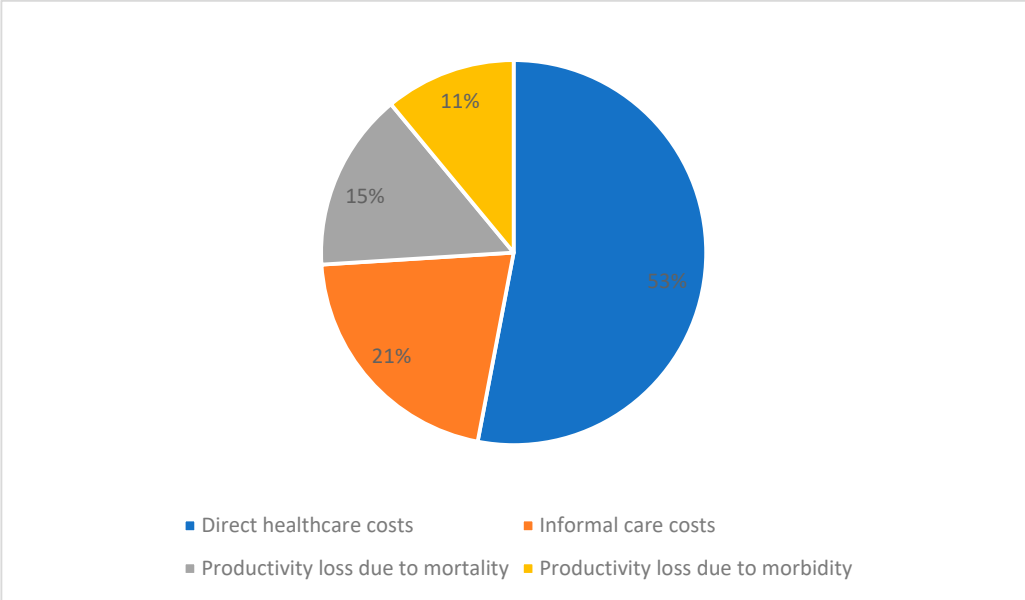


Figure 2. CVD cost shares in the EU (illustration content elaborated and modified from the original work by Timmis et al., 2020 [4]).

3.1.2. Burden of MetS

According to the National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2014 [5], in the USA, MetS prevalence was estimated at around 34.3% (35.3% for men and 33.3% for women) in the period 2007–2014. In the meta-analysis by Gami et al. [17], the chance of developing CVD increases with the number of MetS cases reported (risk ratio 1.78). A higher risk ratio (RR), equal to 2.35, was found in a meta-analysis of 87 studies involving a total of 951,083 individuals [18]. According to Franco et al. [19], the highest risk of developing CVD is reported with the presence of concomitant obesity, high blood pressure, and hyperglycemia. In the meta-analysis by Ju et al. [20], comprising 20 studies and 57,202 participants aged over 60 years, the presence of MetS increases CVD mortality (RR 1.29 for men and 1.20 for women) and all-cause mortality (RR 1.20 in men, RR 1.22 for women). In the meta-analysis of 16 studies by Li et al. [21], 116,496 participants without CVD were analyzed. Those with MetS show a greater trend in the risk of incident stroke (RR 1.70) compared to individuals not affected by MetS [22–24]. Regarding Europe, in a BioSHaRE report [25] concerning seven countries, age-adjusted prevalence of MetS resulted in 24–65% for obese women and 43–78% for obese men. In Germany, Spain, and Italy, an attempt was made to evaluate the economic burden of MetS in patients over 20 years of age suffering from MetS and hypertension at once [26]. The results reported a prevalence of subjects with Mets and hypertension equal to: 36% in Germany: subjects affected by MetS and hypertension were about 60% of all subjects suffering from hypertension, but they contributed to about 80% of the cost of illness of hypertension; 11% in Spain: patients with MetS and hypertension were 22% of all patients suffering from hypertension, but they contributed to 50% of the cost of illness of hypertension; 10% in Italy: people with MetS and hypertension were 21% of all patients suffering from hypertension, but they contributed to half of the cost of illness of hypertension. The study [26] also tried to evaluate the prevalence and incidence of CVD and type II diabetes in hypertensive subjects in conjunction with the presence or absence of MetS (Table 2). In subjects suffering from hypertension alone, the incidence of CVD events and mortality was about half compared to that found in people with hypertension and MetS. The prevalence of type II diabetes was approximately six-times higher in subjects with hypertension and MetS, compared to those not affected by MetS [26].

Table 2. Annual number and event rate per 1000 hypertensive patients of incident CVD cases, incident mortality and prevalent cases of diabetes type II (table content elaborated and modified from the original article by Scholze et al., 2010 [26]).

		Germany	Spain	Italy
		Event Rate per 1000	**Event Rate per 1000**	**Event Rate per 1000**
Annual incidence of CVD events	MetS	27	25	24
	Without MetS	14	13	13
Annual mortality	MetS	3	2.74	2.64
	Without MetS	1.49	1.45	1.40
Annual prevalence of type II diabetes	MetS	248	281	308
	Without MetS	45	51	52

As for expenditures for treating patients with both hypertension and MetS (Table 3), they resulted in: € 24,427 in Germany, corresponding to 82% of the annual expenditures for hypertension treatment; € 1909 in Spain, corresponding to 42% of the annual expenditure for hypertension treatment; and € 4877 in Italy, corresponding to 45% of the annual expenditure for hypertension treatment [26].

Table 3. Annual cost (in millions, €) of hypertension and costs due to MetS (table content elaborated and modified from the original article by Scholze et al., 2010 [26]).

		Drug Annual Costs	**Physician Costs**	**CVD Costs**	**T2DM Costs**	**Total Costs**
Germany	MetS	628	1952	5265	16,582	24,472
Germany	Without MetS	407	1264	1703	1967	5341
Spain	MetS	116	126	699	968	1909
Spain	Without MetS	397	432	1256	597	2682
Italy	MetS	258	330	817	3472	4877
Italy	Without MetS	958	1222	1599	2178	5957

The high costs come from the treatment of complications, such as type II diabetes and CVD, which resulted, respectively in about 67% and 22% of the total costs in Germany, 50% and 37% in Spain, and 71% and 17% in Italy. Furthermore, in hypertensive and MetS patients, the average annual costs were three-times higher compared to subjects without MetS [26].

Furthermore, in hypertensive and MetS patients, the average annual costs were three times higher compared to subjects without MetS.

As previously stated, MetS represents a cluster of cardiometabolic diseases. A US study [27] set out to analyze the economic impact of these cardiometabolic risks (CMRFCs) by assessing individuals with BMI $\geq$ 25 [((weight in pounds)/(height in inches)2) $\times$ 703] and two risk factors (including hypertension, hyperlipidemia, and diabetes). The national direct medical expenditure attributable to CMRFCs in the USA resulted in USD 79.8 billion, while the average individual medical expenditure was USD 9115, compared to that of individuals without CMRFCs, that was USD 3064. Moreover, USD 5477 per individual was spent for additional medical drugs, including USD 1832 for prescription drugs (the national spending for prescription drugs was USD 26.7 billion). The out-of-pocket expense for medical bills for each individual with CMRFCs was USD 1668. In a study by Nichols GA et al. [28], the components of MetS (impaired FBG, BMI, hypertension, HDL, and TG levels) were analyzed with a 5-year follow-up involving 57,420 adults over 30 years old, without manifestations of diabetes and with all MetS parameters measured. It resulted that

each individual component of the MetS is associated with an increase in medical costs. The annual increase in medical costs per patient with each MetS component is shown in Table 4.

Table 4. Annual medical cost increase per patient with each metabolic syndrome component (table content elaborated and modified form the original work by Nichols et al., 2011 [28]).

	Total Annual Cost Increase per Patient (in USD, $)
Impaired FBG	161
Impaired BMI	408
Impaired blood pressure (BP)	657
Impaired HDL	481
Impaired TG	423

3.1.3. Burden of T2DM

Regarding T2DM, it affects around 90% of all the people suffering from diabetes [29]. Einarson et al. [8], in a systematic review of 24 studies, pointed out that according to the IDF, in 2015, the global number of people affected by diabetes amounted to 415 million, with a total expenditure of USD 673 billion. Moreover, probabilistic projections for the year 2040 showed that the affected people would increase to 642 million, with a total expenditure of USD 802 billion. Cardiovascular problems are to affect about 32.2% of people suffering from diabetes. According to Hu et al. [30], CVD is responsible for 47.2% of deaths in people with diabetes, while in people not suffering from diabetes the mortality caused by CVD drops to 20.1%. According to a World Health organization report (WHO), "Global prevalence of type II diabetes" [31] and data from the International Diabetes Federation (IDF) [29], the incidence of this disease is estimated to be 9% among adults; in 2013, at a global level, people affected by T2DM were estimated to be 400 million, and by the year 2035, this number was supposed to reach 600 million. The 2013 global prevalence was 8.3%, with China and India reaching prevalence rates between 10% and 9%, corresponding to 100 million and 65 million cases, respectively. High prevalence rates were found in Mexico (12.6%), Egypt (16.8%), USA (9.2%), and Germany (8.2%) [29]. In the USA, the healthcare expenditure to deal with this disease and its complications was USD 360 billion in the year 2010 and was estimated to largely exceed this number by 2030. Furthermore, still according to the WHO, losses in national income due to T2DM and CVD will reach 557 billion in International Dollars (ID or Int$) in China, Int$303 billion in Russia, and Int$236 billion in India [31].

3.1.4. Burden of NAFLD

NAFLD is considered the manifestation of MetS in the liver and therefore it is thought to be the most common form of liver disease all over the world due to metabolic disorder [32]. Several genetic, epigenetic, environmental and lifestyle factors enhance NAFLD risk, but currently, the mechanisms inducing NAFLD are not completely clarified [32]. NAFLD patients are most affected by obesity, insulin resistance and/or type 2 diabetes, dyslipidemia, hypertriglyceridemia, and hypertension, which are all risk factors for cardiovascular dis-eases (CVDs) [33]. Therefore, the prevalence of NAFLD in patients with components of MetS is quite high. NAFLD has been reported in over 76% of type 2 diabetics. Furthermore, over 90% of obese patients have NAFLD [33]. Given the common risk factors between NAFLD and CVDs, cardiac-related death is one of the leading causes of death for NAFLD patients. NAFLD prevalence in the USA is 10–30% [33]. In a nutshell, NAFLD is characterized by accumulation of fat as TG in the liver (>5%), due to excessive intake of fatty acids derived from the diet, or augmented lipogenesis. Accumulation of fat in the liver is associated with insulin resistance (measured thanks to HOMA-IR biomarkers) [32].

3.2. Nutraceuticals

In this narrative review, we considered the following nutraceuticals: micronutrients such as vitamins D and K, omega-3 PUFA, plant bioactives such as polyphenols, including

anthocyanins and bergamot, probiotics and prebiotics. The actual benefits in reducing biomarkers indicating CMDs are listed below, divided by type of substance underlying the composition of the nutraceutical product.

3.2.1. Vitamin D

Vitamin D occurs naturally as vitamin D3 or cholecalciferol and vitamin D2 or calcitriol. The active form of vitamin D3 is calcitriol. Sources of vitamin D are mainly foods of animal origin. Vitamin D deficiency can be a risk factor for the development of cardiometabolic diseases such as hypertension and type II diabetes [34]. In fact, vitamin D is essential for insulin excretion [35]. In particular, the study by Salehpour et al. [36] tried to evaluate the effects that a vitamin D3 supplement could have on glucose homeostasis in overweight or obese premenopausal women. Vitamin D deficiency represents a risk factor if associated, as in the case of this study, also with a concomitant condition of obesity: in fact, an indirect relationship has been shown between the level of 25(OH)D (inactive form of vitamin D circulating) and obesity [37–39]. Conducted over 3 months (90 days from November 2009 to February 2010) and comprising 85 female participants with an age between 18 and 50 years, without manifestations of diabetes mellitus, this RCT saw the random formation of two groups, to which were, respectively assigned 25 micrograms/day of vitamin D3 or cholecalciferol and 25 micrograms of placebo consisting of lactose. The main anthropometric and biochemical outcomes to be evaluated included: Body Weight (BW), Waist Circumference (WC), Fasting Blood Glucose (FBG), 2 h post load glycemic serum insulin (INS), Hemoglobin A1c (HbA1c), HOMA-IR (Homeostasis Model Assessment-Insulin Resistance). At the end of the 90 days, the results proved to be of little significance: FBG did indeed see a decrease in patients receiving vitamin D, but the same results were also obtained by administering placebo (-0.28 ± 0.4 vs. -0.65 ± 0.4 mmol/L), thus invalidating the efficacy of the administration of vitamin D3; the same goes for FBG concentration. Regarding HbA1c, no significant differences were found in the two groups. Consequently, Vitamin D3 has not been shown to have any effect on glucose homeostasis. Another study, an RCT conducted by Forouhi et al. [40], investigated whether an intake of vitamin D2 and vitamin D3 can lead to a reduction in glycemic levels and an improvement in cardiometabolic risk factors in people prone to develop type II diabetes mellitus. Approximately 340 participants, between 30 and 75 years of age, were considered at high risk of developing type 2 diabetes, who were given one of the following products: 3300 IU/day of ergocalciferol vitamin D2, 3300 IU/day of chole-calciferol vitamin D3 or placebo. The main outcomes evaluated were changes in the blood concentration of HbA1c, and the levels of SBP and DBP, TC, HDL cholesterol, and apolipoproteins apoA1 and ApoB. In detail, 112 participants were given Vitamin D2, 114 received vitamin D3, and the remaining 114 received placebos. Obviously, in patients who were given vitamin D, levels of blood 25(OH)D (metabolite of vitamin D in the blood) increased from 5.2 to 53.9 nmol/L for vitamin D2 and from 45.8 to 83.8 nmol/L for vitamin D3. In the remaining variables, there was no significant difference between the vitamin D and placebo groups, except for a small reduction in blood levels of ApoB, ApoA1, and HDL by vitamin D2, as well as a small reduction in ApoB, perpetrated by vitamin D3. In another study, a systematic review by Manousopoulou et al. [41], including 17 RCTs, vitamin D was provided as a supplement with a mean value between 1000 IU/day and 120,000 IU fortnightly in 10 out of 17 studies in overweight patients (BMI between 25 and 30) or obese (BMI higher than 30 kg/sq m) without diabetes. As far as anthropometric measures are concerned, only one study demonstrated a significant reduction in mean body fat mass (active -2.7 ± 2 kg, placebo: -0.4 ± 2 kg) after supplementation with vitamin D (Salehpour et al. [36]), while the other studies showed no significant changes. On blood pressure, a study (Wamberg et al. [42]) reported a marginal decrease in SBP and DBP in the group that was given vitamin D (SBP: active 135 ± 18 mmHg at baseline versus 129 ± 13 mmHg after 12 months and placebo at baseline 132 ± 15 mmHg vs. 131 ± 16 after 12 months; DBP: baseline 85 ± 10 mmHg, 12 months after 84 ± 11 mmHg). A significant decrease in SBP and DBP was found in only one study (Al-Daghri et al. [43]) (SBP: baseline

118.3 ± 15.4 and after 12 months 112.6 ± 12.6 mmHg; DBP: 76 ± 11 mmHg at baseline, after 12 months 75.9 ± 10.8 mmHg) while a second RCT (Jorde et al. [44]). Five studies (Salehpour et al. [36], Maki et al. [45], Zhou et al. [46], Nagpal et al. [47], Sneve et al. [48]) reported an increase in SBP following vitamin D supplementation, but no effects on DBP were found. Out of eight studies that measured the lipid fraction, positive effects with an increase in HDL were verified only in two (Salehpour et al. [36], Al-Daghri et al. [43]): active 0.07 ± 0.02 mmol/L, placebo −0.03 ± 0.2 mmol/L; baseline 0.66 ± 0.25 mmol/L, 12 months after 1.05 ± 0.33 mmol/L. Zittermann et al. [49], found a reduction in the level of trigriglycerides (active −0.19 ± 0.54 mmol/L; placebo 0.03 ± 0.05). Salehpour et al. [36], and Zittermann et al. [49], also found an increase in LDL (0.13 ± 0.5 active, placebo −0.3 ± 0.5; active 0.19 ± 1.03, placebo −0.09 ± 0.64, respectively). Salehpout et al. [36], Nagpal et al. [47], and Sneve et al. [48] did not report any change in HDL-C after supplementing with vitamin D. Regarding the glucose tolerance/insulin sensitivity indicator measured by seven studies, only one found an increase in glucose insulin sensitivity (active: 21.17 ± 67.86 mL/min/Kg, placebo −11.43 ± 60.97 mL/min/Kg). Salehpour et al. [36], Nagpal et al. [47], Kamycheva et al. [50], and Sneve et al. [48]. reported no effects on HOMA-IR. The systematic review by Pittas et al. [51], analyzing the effects of vitamin D on people generally considered to be in good health (only 20% of the participants had chronic problems at the start of the research) and relating it to various outcomes, is divided into three groups of RCTs:

I. RCTs regarding the relationship between vitamin D and type II diabetes: five out of 18 trials (Nilas et al. [52], Pittas et al. [51], von Hurts et al. [53], Hsia et al. [54], de Boer et al. [55]) found that vitamin D had no effect on FBG (−0.002 mmol/L vitamin D vs. placebo). In a subgroup analysis of participants with impaired FBG at baseline, a combined administration of vitamin D and calcium carbonate (700 iu/day and 500 mg/day) resulted in attenuated FBG (Pittas et al. [51]).

II. RCTs that analyzed outcomes concerning hypertension: two studies reported how supplementation with vitamin D brought about a positive lowering of SBP of −7 mmHg and −14 mmHg, respectively (Pfeifer et al. [56], and Sugden et al. [57]). In a study (Margolis et al. [58]) with 7 years of follow up, supplementation of vitamin D and calcium carbonate (400 iu/day and 1000 mg/day) had no effect on the improvement of parameters related to hypertension. In all other studies, there was no significant improvement in SBP and DBP, either with vitamin D supplement alone or in combination with calcium.

III. RCTs analyzing the relationship between vitamin D and cardiovascular disease: five studies (Hsia et al. [54], Trivedi et al. [59], Brazier et al. [60], LaCroix et al. [61], Price et al. [62]) analyzed the effect of vit-amin D with or without calcium on various cardiovascular outcomes including myocardial infarction, stroke, and other cardiac and cerebrovascular outcomes. In patients' follow-up period (from 1 year to 5–7 years), no study showed any statistically significant effect. Another systematic review, the one conducted by Dolinsky et al. [63], aimed to investigate the effects of vitamin D on young children in health or affected by type II diabetes. The 35 studies analyzed in the study evaluated the relationship between vitamin D and some cardiometabolic biomarkers. We therefore found relationships between:

- vitamin D and arterial stiffness: A study (Dong et al. [64]) that involved the randomized administration of 400 IU/day (control group) or 2000 IU/day (experimental group) of vitamin D for 16 weeks to black adolescents and the subsequent measurement of the femoral carotid value pulse found an increase in the latter in the first group (from 5.38 to 5.71 m/s), thus indicating a worsening of the arterial stiffness, while in the second group the value decreased (5.41 to 5.33 m/s).
- Vitamin D and endothelial dysfunction: This relationship was evaluated only in one study, which however did not find any correlation worthy of note.

- Vitamin D and BP: Out of a total of 16 studies evaluating this parameter, 3 (Dong et al. [65], Ashraf et al. [66], Pirgon et al. [67]) found no significant changes in SBP or DBP. 10 (Ganji et al. [68], Ashraf et al. [66], Williams et al. [69], Kumar et al. [70], Reis et al. [71], Dong et al. [65], Pacifico et al. [72], Al-Daghri et al. [73], Nsiah-Kumi et al. [74], Zhou et al. [75]) found an inverse correlation between SBP and 25(OH)D, while four (Kumar et al. [70], Al-Daghri et al. [73], Nsiah-Kumi et al. [74], Sharma et al. [76]) found an inverse correlation between DBP and 25(OH)D.
- Vitamin D and lipid levels: Of 22 studies evaluating this correlation, one (Ashraf et al. [66]) found a positive correlation between vitamin D and a decrease in LDL cholesterol, while a second study (Boucher-Berry et al. [77]) found a negative relationship. Between vitamin D and HDL, out of six studies, five (Ganji et al. [68], Williams et al. [69], Kumar et al. [70], Smotkin-Tangorra et al. [78], Johnson et al. [79]) demonstrated an increase in HDL concomitant with the administration of vitamin D. Of eight studies evaluating the correlation with the level of triglycerides, six found an inverse correlation between levels of vitamin D and TG. Finally, of 18 studies evaluating the relationship between vitamin D and total cholesterol, only two studies (Kumar et al. [70], Delvin et al. [80]) actually found a positive correlation.
- Vitamin D, glucose, and insulin metabolism: This association was evaluated in 30 studies. Nunle Bland et al. [81], study found a correlation between HOMA and 25(OH)D, while Olson et al. [82], an inverse correlation. Another study (Pirgon et al. [67]) proposed to hire 87 obese children with or without non-alcoholic Fatty Liver Disease (NAFLD) for the evaluation. An association was found between HOMA and 25(OH)D in the group of obese children with concomitant manifestation of NAFLD, but not in the group not affected by NAFLD. Two studies (Reis et al. [71], Johnson et al. [79]) showed that as the concentration of endogenous vitamin D increased, FBG decreased (of which one of 0.09% for 2.5 noml/L). Out of 17 studies, eight found an inverse relationship between 25(OH)D and FBG and one a positive relationship. Of eight studies evaluating the relationship between 25(OH)D and HbA1c, only one (Williams et al. [69]) resulted in a positive finding. Finally, among the 12 studies evaluating the correspondence between HOMA and 25(OH)D, just over half (7) noted an inverse relationship. The 16 studies analyzed by Kunutsor et al. [83] provided for a variable administration of vitamin D2 ergocalciferol or D3 cholecalciferol with a range of doses between 800 and 8571 IU/day, with an average of 600 IU/day, involving a minimum of 34 subjects up to a maximum of 438, including both healthy individuals and obese, with type II diabetes or hypertension. The main evaluated outcome was BP, calculated in the levels of SBP and DBP. The duration of the studies ranged from 5 weeks to 12 months. No significant results were found for the desired outcomes of SBP or DBP, but a subgroup of analyses, including only patients with a history of previous cardiometabolic disorders, showed a significant and positive lowering of DBP (−0.34 mmHg). Alkharfy et al. [84] conducted a study with a total duration of 12 months involving 499 Saudi women and men, with or without T2DM, divided into eight groups: 151 subjects without type 2 diabetes mellitus T2DM, called "control group"; 49 diabetic subjects treated with oral hypoglycemic agent rosiglitazone; 15 subjects with diabetes subjected to a particular diet; 55 diabetic subjects who were only given insulin; 12 diabetic subjects who were given insulin in combination with other oral drugs; 121 diabetic patients who received metformin; 37 diabetics undergoing a combined administration of oral hypoglycemic agents; and 59 diabetic subjects taking sulfonylureas. All these subjects were also given 2000 IU/day vitamin D, except for non-T2DM, who, however, were encouraged to expose themselves to sunlight, known to

be a beneficial factor for increasing endogenous vitamin D levels via termoisomerization of provitamin D3. The results of this study were as follows: the levels of 25(OH)D naturally increased, except for the dietary group and the group with a combination of oral agents; BMI levels did not show noteworthy changes; SBP levels decreased only in males who were given insulin in combination with oral agents and in the group of women and men who were combined with oral agents; DBP was increased in the rosiglitazone-taking group and in males treated with insulin plus oral agents and in the group undergoing treatment with a combination of oral agents; as far as lipid levels are concerned, the average cholesterol levels improved both in males and females receiving insulin plus oral agents and in females with single insulin administration. A lowering of TG levels was noted in the rosiglitazone-taking group, as well as in the groups receiving insulin plus oral agents and in males receiving a combination of oral agents only. Finally, the non-T2DM control group saw its HDL levels increase.

3.2.2. Vitamin K

Vitamin K occurs naturally in two forms, namely vitamin K1 or phylloquinone, present mainly in green vegetables, and vitamin K2 or menaquinone, present in meat and eggs [85–87]. There is also a third vitamin called vitamin K3 or menadione. In the systematic review conducted by Rees et al. [88], analyzing five studies consisting of one trial and four cohort studies (Erkkila et al. [89], Erkkila et al. [90], Gast et al. [91], Geleijnse et al. [92], Shea et al. [93]), vitamins K1 and K2 were administered and biomarkers, indicating coronary heart disease (CHD), stroke or diabetes, were evaluated as outcomes. No significant association was found between vitamin K1 and CHD-related outcomes; no significant associations were found between vitamin K1 and stroke risk outcomes. In the 200 participants with a diabetes rate of 6%, no significant results were seen from vitamin K1. Excellent results were found regarding the link between vitamin K2 and CHD: two studies found a correlation between increased vitamin K2 and decreased CHD; 32.7 or 29.1 micrograms per day of vitamin K2 demonstrated a 41% or 9% decrease in the risk of developing CHD.

3.2.3. Omega-3 Polyunsaturated Acids

Omega-3 are polyunsaturated fatty acids (PUFA), meaning they contain more than one double bond in their backbone: they are naturally present both in plants (mainly algae but also walnut, flaxseed, clary sage, edible seeds, seed) and in products of animal origin (fish, squid, krill), i.e., living beings that feed on algae. In July 2017, O'Mahoney et al. [94] proposed to carry out a meta-analysis of 45 RCTs, comprising a total of 2764 patients between 33 and 70 years of age with type II diabetes (T2DM). Each patient was offered a daily dose of n. 3 PUFA between 0.40 and 18 g/day. The duration of the treatment varied between 2 and 104 weeks. The results of the administration of Omega-3 in relation to outcomes on the lipid profile, blood pressure, and glycemic index are as follows: a decrease in LDL was found, as well as a small reduction in the level of TG. HDL, total cholesterol, ApoA1, and ApoB did not show significant changes in their levels. It must be said, however, that by excluding 3 RCTs, the HDL level has improved favorably. CRP (C-reactive protein) did not change significantly, and no effect on SBP and DBP was found. Moreover, regarding glycemic control indices, a small but significant reduction was found in HbA1c. FBG and HOMA-IR remained unchanged. In the double blind, randomized, placebo-controlled study, by Rao et al. [95], on the one hand it was noted that in animal oils (mainly fish oils) PUFAs are usually combined in indivisible mixtures of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In phytoplankton algae, on the other hand, we can find EPA without DHA [96,97]. It is precisely from this type of algae that the nutraceutical product under investigation, Almega PL, comes; it is a polar rich oil (contains more than 15% of polar lipids) derived from the *Nannochloropsis* microalgae, which contain only EPA in a

percentage greater than 25, derives. A total of 104 volunteers over the age of 25 completed the study, which provided half patients with 1 g/day Almega PL, containing 250 mg of EPA, 150 mg of polar lipids, 40 mg of arachidonic acid, and 90 mg of palmitoleic acid. The other half of the volunteers was given a placebo for 12 weeks. The main findings are listed below:

- omega-3 (OI3) levels: At the sixth week, the level of omega-3 index rose in the group of patients taking Almega PL by 5.51 $\pm$ 1.05%, while after 12 weeks the values were found to be 5.75 $\pm$ 0.90%; moreover, the levels of EPA and DPA also saw an increase.
- Cardiometabolic markers: Total cholesterol (TC) levels decreased by 3% and VLDL by 25%. No difference was found in the levels of HDL, LDL and triglycerides.
- Anthropometric measures: The administration of Almega PL for 12 weeks led to a significant reduction in BW and hip circumference.
- Inflammation markers: No difference between the intervention group and patients taking placebo was found.

3.2.4. Polyphenols

Polyphenols are a group of bioactive compounds found in plants as secondary metabolites; in nature there are about 8000 different types of polyphenols. Fruits, vegetables, whole grains, tea, chocolate, and wine are a rich source of polyphenols [98]. The purpose of the systematic review conducted by Hausenblas et al. [99] was to evaluate the effect of a resveratrol supplement on biomarkers in patients with type II diabetes and already undergoing pharmaceutical treatment. The main outcomes identified were: HbA1c, FBG, insulin and creatinine levels, HOMA-IR, LDL and HDL lipoprotein levels, TG, and SBP and DBP values. This systematic review includes six studies that administered a dose of resveratrol, ranging from 10 to 5000 mg/day for a minimum of 4 weeks up to a maximum of 12 months. A total of 196 patients were involved (104 taking resveratrol, 92 receiving a placebo), all with type II diabetes. One study noted a significant improvement in HbA1c (hemoglobin A1c) and creatinine levels, while two studies (Bhatt et al. [100], Kumar et al. [101], Movahed et al. [102]) found an improvement in SBP levels. In particular, it should be emphasized that a lowering of HbA1c levels is associated with a decrease in complications from diabetes and ultimately in the risk of death (UKPDS, Stratton et al. [103]). For all the remaining studies, however, no significant improvements were found following the intake of resveratrol, except for one study that noted an improvement (raising) in HDL levels. Menezes et al. [104] conducted a meta-analysis of 18 RCTs that involved the formation of an intervention group of patients, who were actually administered either pure flavonols (9 of 10 with quercetin) or a mix of flavonols with a range of doses ranging from 16 mg to 1200 mg, and a group to which a placebo was given. The total number of patients was 987 (679 assigned to the flavonols group, 672 assigned to the placebo group) with an average age between 40 and 50 years. Many of these studies included patients with dyslipidemia, impaired glucose tolerance (IGT), hypertension, rheumatoid arthritis or MetS, with a high percentage of obese or overweight patients. Blood lipid levels saw a significant reduction in the levels of triacylglycerols (TAG) (DM, or difference in means, equal to -0.10 mmol/L), TC (DM -0.11 mmol/L) and LDL (DM -0.14 mmol/L) and an increase in HDL levels (DM 0.05 mmol/L). By removing the results at risk of bias, these data remained significant for all of these outcomes. Regarding blood pressure, 15 studies observed a benefit of flavonoid supplementation, with SBP and DBP levels being lowered (DM -3.05 mmHg and DM -2.62 mmHg, respectively). These results were maintained even after carrying out a sensitive analysis. Finally, a noticeable reduction in FBG was found (DM -0.18 mmol/L); the sensitivity analysis maintained the same results. Instead, in the study conducted by Boccellino et al. [105], that analyzed nine studies, including randomized double-blind placebo-controlled trials and randomized clinical trials having as their main topic the effects of three types of polyphenols (curcumin, quercin, and resveratrol) on some cardiometabolic biomarkers, the main findings were as follows: as far as curcumin is concerned, the daily dose of curcumin recommended by WHO and

FAO is 1 mg per kg of body weight. Out of 5 studies involving this polyphenol, 1 study (Mohammadi et al. [106]) saw 30 obese subjects treated with 1 g/day of curcumin for 30 days developing a lowering of the level of TG. A second RCT (Ganjali and Sahebkar [107]) noted that a 30-day treatment with curcumin 1 g/day resulted in a reduction in blood levels of pro-inflammatory cytokines, Interleukin 1 beta (IL-1 beta), and Interleukin 4 (IL-4), in 30 obese people. A weight and adipose tissue administration activity perpetrated from 30 days of administration of curcumin in 44 overweight subjects was found in a third study (Di Pierro et al. [108]). Finally, a study involving 60 obese and overweight women who were given 500 mg/day of curcumin (95%) also found beneficial effects on BMI, WC, HC, HDL, and on triglycerides/HDL ratio (Saraf-Bank et al. [109]). Regarding quercetin, which is found mainly in onions, garlic, ginger, apples, and wine, one study (Pfeuffer et al. [110]) noted that quercetin consumption (150 mg/day for 8 weeks) in obese or overweight subjects led to waist circumference and triacylglycerol levels. Concerning resveratrol, one study (Timmers et al. [111]), involving the administration of 150 mg/day of resveratrol, found an increase in energy expenditure, a reduction in biomarkers indicating damage from inflammation and a lipolytic of adipose tissue and a decrease in glycerol and plasma fatty acids in obese men. In one study (Koning et al. [112]), resveratrol 150 mg/day per 30 days in obese men was found to have a different effect of subcutaneous adiposity. Arzola-Paniagua et al. [113], found no reduction in BMI, WC, TG levels, and leptin (hormone playing a key role in the endogenous energy metabolism), but they found an increase in total cholesterol levels and in LDL lipoprotein levels, which turned out to be counterproductive and brought no benefits. Finally, one last study (Poulsen et al. [114]) found no evidence regarding the anti-obesity potential of resveratrol in obese men, since no effects on BP, lipid oxidation or reduction in inflammation and cardiometabolic biomarkers were noted. Martinez-Maqueda et al. [115] analyzed the effect of grape pomace with a high content of polyphenols (29.63%) on 49 subjects between 20 and 65 years with at least two characteristic symptoms of MetS. The partition into two groups was envisaged: the active group received 8 g of dried grape pomace per day; the other (control group) did not get the treatment. The duration period was 6 weeks. Regarding glucose homeostasis, on the one hand, FBG and postprandial glucose did not show changes; on the other hand, basal insulin decreased after supplementation with 8 g/day of pomace, as well as a decrease in HOMA-IR. As far as cardiometabolic risk factor is concerned, no significant effect was found, except for a slight decrease in TC and LDL. Regarding anthropometric measurements, no difference in parameters, such as BMI, WC, BFM, and BW, was found. Amiot et al. [116] conducted a systematic review concerning the effects of polyphenols on subjects affected by MetS, in relation to parameters such as obesity, BP, dyslipidemia, FBG insulin resistance, and derived complications such as oxidative stress, inflammation and vascular dysfunction. Firstly, as far as obesity is concerned, one study (Basu et al. [117]), analyzing 35 subjects with MetS, involved the formation of 3 groups (control, supplement with green tea, and supplement with tea extract). A decrease in BW (-2.5 ± 0.7 kg in green tea and -1.9 ± 0.6 kg in green tea extract) and BMI (-0.9 ± 0.3 kg in green tea and -0.7 ± 0.2 kg in green tea extract) was found. Another study (Nagao et al. [118]), still with the objective of evaluating the effects of polyphenols contained in green tea, pointed out a decrease in the levels of BW, BMI, WC, and BFM. A third study (Suliburska et al. [119]), in which a supplementation of green tea extracts was administered for 12 weeks, found a decrease in BMI and WC levels in male subjects. Soy-derived isoflavones were used as a supplement for 12 weeks in subjects with MetS in a study (Allison et al. [120]) that saw a dramatic improvement in BW (-7.1 kg vs. -2.5 kg in experimental and control group) and BFM (-4.3 kg vs. -1.4 kg in experimental and control group) levels. One last study (Mendez-del Villar et al. [121]), in which resveratrol 500 mg was administered for a period of 3 months, led to a decrease in anthropometric measures (BW, BMI, and WC). Then, regarding SBP and DBP, no significant results were found, except for one study that involved the administration of chokeberry, which led to the reduction in DBP and SBP after 2 months; a second study, that involved the subjects taking a daily administration of 150 mg of quercin for 6 weeks, noticed an improve-

ment in SBP and DBP levels, especially in subjects between 25 and 50 years (respectively the levels were found to be greater than 120 and 80 mmHg); a third study saw DBP levels rise after administration of resveratrol 150 mg/day for 4 weeks. Concerning dyslipidemia, four studies (Basu et al. [122], Chu et al. [123], Suliburska et al. [119], Belcaro et al. [124]) demonstrated how a green tea supplements can have positive effects on HDL cholesterol levels, whilst six studies found this beneficial effect on TG, of which a lowering was noted. One study (Di Renzo et al. [125]), evaluating regular consumption of dark chocolate in women with normal weight obese syndrome, found a beneficial effect on HDL lipoproteins. In 27 middle-aged people affected by MetS with high BMI levels, 50 g of freeze-dried strawberry for 8 weeks led to a 10% and 11% lowering in TC and LDL, respectively, but with no effect in HDL or TG according to the research conducted by another study (Basu et al. [122]). One study (Bronce et al. [126]) evaluated 25 MetS affected subjects who were given 300 mg aronia extract; the results were a lowering of TC, LDL, and TG after 2 weeks, while HDL remained unchanged. A study (Allison et al. [120]) administering isoflavone-rich soy supplements in 100 patients aged 35 to 65 with MetS observed a reduction in LDL; one last study demonstrated a reduction in LDL lipoprotein levels after a flavanone supplementation, consisting of 300 mL of citrus juice or hesperides 500 mg per day for 3 weeks. Concerning blood glucose and insulin resistance, one study (Davison et al. [127]), in which 902 mg/day of cocoa with a high flavanol content was administered to 49 obese individuals for 6 weeks, found a reduction in insulin resistance, demonstrated by a 0.31% decrease in HOMA2-IR. Two separate studies showed that strawberry and cranberry did not bring any change to FBG, that instead declined after a sea buckthorn diet carried out by 80 patients and lasting 8 weeks in another study. A 500 mg/day hesperidin supplement saw improved blood glucose and insulin resistance levels after 3 weeks in 28 patients in another study (Rizza et al. [128]). Finally, a 12-week cinnamon extract in 22 MetS patients led to a decrease in FBG (Ziegenfuss et al. [129]). As far as oxidative stress is concerned, according to four studies (Basu et al. [122], Chu et al. [123], Suliburska et al. [119], Belcaro et al. [124]), green tea has been shown to have antioxidant properties in patients with MetS, while, according to two studies (Broncel et al. [126], Basu et al. [122]), a treatment based on strawberry, aronia, and cranberry reduced lipid oxidation and increased the levels of antioxidant processes thanks to an increase in the superoxide dismutase enzyme (with antioxidant properties) of 47%. In one last study (Egert et al. [130]), making use of a quercetin supplement, a reduction in oxidized LDL levels was noticed. Regarding inflammatory biomarkers, obesity and the risk of coronary heart disease are related to an increase in pro-inflammatory cytokines; one of these inflammation markers, the sensitive C reactive protein (CRP), stimulates the proliferation of other inflammatory cells and reduces the expression of NO synthase. Therefore, the reduction in CRP, found in the study by Rizza et al. [128], after the administration of citrus-based juice and hesperidin in the form of a supplementation (500 mg/day for 3 weeks), is associated with an improvement in the inflammation processes that contributes to the development of MetS. Two different studies (Lehtonen et al. [131], Egert et al. [130]) found a decrease in TNF-alpha (tumor necrosis factor, cytokine that stimulates the reactions of the acute phase of inflammation) after administration of bilberries and sea buckthorn and quercetin 150 mg/day (respectively 8 weeks in 80 patients and 6 weeks in 96 patients). Concerning vascular disfunction, a cocoa drink supplement containing high doses of flavanols improves flow mediated dilatation (dilatation of the artery when blood flow increases in the latter) by 2.4% after 2 h, and by 1.6% after 12 weeks in patients with MetS (Davison et al. [127]), as well as grape polyphenols increased flow mediated dilatation in 25 patients with MetS (Barona et al. [132]). The study by Rizza et al. [128], found that, after oral administration of hesperidin 500 mg once a day for 3 weeks, there was an increase in flow mediated dilatation in MetS subject (10.26 + 1.19 vs. 7.78 + 0.76%); a study by Fujitaka et al. [133], found that the supplementation of 100 mg/day of resveratrol in 6 months improved flow mediated dilatation in 34 patients with MetS. Finally, one last study (Broncel et al. [126]) noted how 300 mg/day of chokeberry, administered for 2 months in 25 MetS patients, reduced plasma endothelin-1

(a protein that normally constricts blood vessels causing an increase in blood pressure). Two studies evaluated the link between resveratrol intake, a polyphenolic compound, and NAFLD (Tarantino et al., 2021 [32]). In a double blind, placebo controlled RCT, the administration of 300 mg of resveratrol twice daily for 3 months significantly decreased LDL, TC and HOMA-IR, while in another double-blind crossover study, an intake of 250 mL of bayberry twice daily for 4 weeks led to a decrease in inflammatory response involved in NAFLD; an increase in HDL levels was also noticed.

3.2.5. Bergamot Flavonoids

The study by Giglio et al. [134], investigating the effects of bergamot on dyslipidemia, assumes that particular types of flavonoids, contained in bergamot, HMGF, have properties very similar to those of statins, drugs used to inhibit the synthesis of endogenous cholesterol. In particular, three clinical studies conducted on volunteers are analyzed: in the first 2013 study (Gliozzi et al. [135]), 77 participants with mixed dyslipidemia were divided into 5 groups: 15 placebo recipients, 16 recipients rosuvastatin 10 mg daily for 30 days, 16 recipients rosuvastatin 20 mg daily for 30 days, 15 bergamot recipients 1000 mg per day for 30 days, and 15 recipients rosuvastatin 10 mg per day plus bergamot 1000 micrograms per day for 30 days. Both an administration of rosuvastatin in both doses and an administration of bergamot alone led to a reduction in TC (195 $\pm$ 3174 $\pm$ 4191 $\pm$ 5 mg/dL vs. 275 $\pm$ 4 mg/dL placebo), LDL (115 $\pm$ 4, 87 $\pm$ 3 and 113 $\pm$ 4 mg/dL vs. 190 $\pm$ 2 mg/dL placebo), and the LDL/HDL ratio. The addition of bergamot to rosuvastatin therapy enhanced its effects (152 $\pm$ 5 mg/dL and 200 $\pm$ 4 mg/dL, respectively vs. 235 $\pm$ 5 mg/dL). The second study (Gliozzi et al. [136]) analyzed 107 patients with MetS and NAFLD (non-alcoholic fatty liver disease). Divided into 2 groups, half received placebo, the other half 650 mg of bergamot twice a day. In the latter group, a significant improvement was noted, coinciding with the lowering of circulating glucose levels, LDL and TG, and an increase in HDL levels. In addition, a reduction in NAFLD biomarkers was also noted. Finally, the third study (Mollace et al. [137]), conducted in 2011, saw the subdivision of the subjects who took part into 4 groups: 104 subjects with hypercholesterolemia treated with bergamot 500 mg per day, 42 subjects with hyperlipidemia treated with bergamot 1000 mg per day, 59 patients with hyperlipidemia plus plasma glucose levels above 110 mg/dL (MetS group) treated with placebo, 32 patients who had to discontinue previous simvastatin treatment due to muscle cramps and elevated blood creatinine levels treated with 1500 mg/day of bergamot. Treatment with bergamot in patients with hypercholesterolemia, and those with hyperlipidemia led to a lowering of TC levels (21.8% in 500 mg and 29.4% in 1000 mg versus 0.1% placebo), LDL (24.1% and 30.6% in 500 and 1000 versus 1.1% placebo) and an increase in HDL (22.3% and 40.1% in 500 and 1000 versus 1.2% placebo). TG was also lowered in patients with hypercholesterolemia (28.2% in 500 mg/day and 37.9% in 1000 mg/day vs. placebo 0.1%). In the 59 patients of the MetS group there was a reduction in blood glucose levels of 18.9 and 22.4 500 mg and 1000 mg percentile versus placebo 0.5%. In patients with statin therapy that was discontinued, TC and LDL levels were reduced by the 25th and 27.6th percentiles at 1500 mg/day.

In this study by Toth et al. [138], an attempt was made to evaluate the effectiveness of "Bergavit" product, with an average content of about 28–30% of flavonoids such as neoeriocitrin, neohesperidin, and naringin. A total of 80 patients, with an average age of 55 years and moderate hypercholesterolemia, received treatment based on Bergavit 150 mg/day containing 16% neoeriocitrin, 47% dineohesperidin, and 37% naringin. The outcomes evaluated were TC, TG, HDL and LDL levels. After a 6-month treatment with Bergavit, an improvement in the anthropometric parameters BMI, BW, WC was found. A decrease in levels of TC (from 6.6 $\pm$ 0.4 to 5.8 $\pm$ 1.1 mmol/L), TG (from 1.8 $\pm$ 0.6 to 1.5 $\pm$ 0.9 mmol/L) and LDL (from 4.6 $\pm$ 0.2 to 3.7 $\pm$ 1.0 mmol/L) was recorded, while HDL levels increased (from 1.3 $\pm$ 0.2 to 1.4 $\pm$ 0.4 mmol/L). In the study conducted by Raimondo et al. [139], the properties of the nutraceutical product CitraVes, obtained from Citrus limon juice and containing nanovesicles of the latter, were analyzed. A chemical

analysis of CitraVes revealed a composition characterized by the presence of flavanones hesperidin and eriocitrin. In total, 1000 mg/day of this product was administered to 20 healthy adult patients for a total duration of 3 months. The results obtained are the following: regarding the anthropometric markers, no significant difference was noted, except for WC in women after 4 and 12 weeks (respectively 85.4 and 85 cm compared with the baseline which obtained a value of 87.6 cm). No difference was noted in men (after 4 weeks: 102.0 cm, after 12 weeks: 100.0 cm and at baseline: 100.3 cm). As far as biochemical markers are concerned, blood glucose levels increased over 12 weeks (from a baseline of 81 mg/dL to a value of 86 mg/dL after this time), while HbA1c decreased over time (from 35 to 33 mmol/mol after 12 weeks). TG increased in men after 4 and 12 weeks (by 125.2 mg/dL and 125.5 mg/dL, respectively when compared with a baseline of 100.9 mg/DL), while no noteworthy differences were noted in women. LDL lipoprotein levels settled at 101 mg/DL after 4 weeks and 81 mg/dL after 12 weeks, indicating a reduction in the latter case compared to baseline (value of 97 mg/dL).

3.2.6. Probiotics

In the randomized clinical trial conducted by Szulinska et al. [140], lasted 12 weeks, an attempt was made to evaluate the relationship between a probiotic product, lipid levels, and the cardiometabolic profile of subjects affected by obesity. The multispecies probiotic product in question is called Ecologic Barrier and it is marked by the presence of different bacterial strains: bifidobacteria, lactobacilli and lactococci. A total of 71 obese postmenopausal women were divided into 3 groups (24 in the placebo groups, 24 receiving low dose probiotic LD 2.5 per 10 at 9 colony forming units CFU per day, 23 high dose probiotic HD 1 per 10 at 10 CFU per day). On the one hand, the administration of a high dose of probiotic product resulted in a lowering of LPS by 20.14%, WC by 1.7%, FM by 3.44%, TC by 7.32%, TG by 7.05%, LDL of 3.99%, BG of 7.92%, insulin levels of 22.41%, and HOMA-IR levels of 27.27%. On the other hand, a low dose of probiotic resulted in changes in WC by 3.8%, FM by 3.3%, TC by 4.85%, LDL by 6.36.%, insulin levels by 15.2%, HOMA-IR levels by 15.25%. Kasinska et al. [141] conducted a meta-analysis on a total of 8 RCTs trying to investigate the efficacy of administering probiotics in 438 male subjects with type II diabetes mellitus. Different types of probiotic products were used, all however containing bacterial strains attributable to lactobacillus or bifidobacterium, and with a bacterial load between 1×10^7 CFU and 2×10^{10} CFU. The main results of the study were as follows:

- FBG: of the six studies that evaluated it, five found a decrease in FBG, while one (Asemi et al. [142]) did not, but in general there were no significant results.
- Hemoglobin A1c levels: three studies (Asemi et al. [143], Ejtahed et al. [144], Judiono et al. [145]) noted a decrease in HbA1c levels in obese patients taking probiotics (SMD-standardized mean difference: −0.81).
- Insulin levels: three studies (Asemi et al. [142], Asemi et al. [143], Mazloom et al. [146]) showed a decrease in insulin levels after the administration of probiotics, but without having uniform results from the point of view of scientific relevance.
- Insulin resistance: three studies (Asemi et al. [142], Asemi et al. [143], Mazloom et al. [146]) found a decrease in HOMA-IR levels (SMD: −2.10) after taking probiotics.
- Total CT cholesterol level: only two of five studies have shown a lowering of CT levels (Asemi et al. [142], Moroti et al. [147]).
- TG regarding this data, three studies (out of five) showed a lowering of triglyceride levels (Asemi et al. [143], Mazloom et al. [146], Moroti et al. [147]).
- LDL: of four studies evaluating this parameter, only 1 (Asemi et al. [142]) found a lowering of LDL levels.
- HDL: only two (out of five) studies showed an increase in HDL levels after probiotic administration (Asemi et al. [143], Mahboobi et al. [148]).

- Levels of C reactive protein (CRP): only two out of four studies showed a significant decrease in this value after taking probiotics; however, the overall effect was found to be insignificant (SMD: −1.73).

3.2.7. Prebiotics

The systematic review conducted by Kellow et al. [149] analyzed 26 RCTs for a total of 831 participants, including healthy subjects or subjects suffering from disorders such as overweight, type II diabetes, obesity, hypercholesterolemia, or gastroesophageal reflux. Subjects in the review were also undergoing various types of treatments with prebiotic products (fructooligosaccharides, oligofructose, inulin and galactooligosaccharides), whose quantity varied within a range from 2 g/day to 21 g/day (only one study provided for the administration of an out-of-average amount, equal to 200 g/day) for a total variable from 1 to 28 weeks. The main outcomes that were assessed are listed below:

- BW: Of five trials evaluating this parameter, two (Genta et al. [150], Parnell et al. [151]) demonstrated a significant reduction, while the other three (Dehghan et al. [152], De Luis et al. [153], Seidel et al. [154]) showed no effect after administration of prebiotic products. In general, however, it can be stated that, in this study, no significant general values of BW reduction (SMD: −0.48) were found; glucose homeostasis: of four studies measuring the effect of prebiotics on postprandial glucose levels, only two found a significant reduction in blood glucose levels in obese and overweight patients (Cani et al. [155], Dewulf et al. [156]). After the meta-analysis, the SMD turned out to be −0.76, which indicates a significant effect of supplementation with prebiotics. Two of three studies found a reduction in postprandial insulin levels in overweight and hypercholesterolemic individuals. The SMD index for this value turned out to be −0.77. A reduction in HbA1c was found in healthy patients after 5 weeks of supplementation (Russo et al. [157]), and in women with type II diabetes after 8 weeks (Dehghan et al. [152]), while no reduction in HbA1c in obese women was found in a third study after prebiotic supplementation for 3 months (Dewulf et al. [156]).
- Cardiovascular and hepatic outcomes: No significant evidence of a reduction in LDL cholesterol or lipid levels.
- Outcomes evaluating the degree of inflammation: Out of four studies evaluating C reactive protein (biomarker inflammation), three (Dehghan et al. [152], De Luis et al. [153], Vulevic et al. [158]) noted a significant reduction in this parameter in obese and overweight adults, and women with type II diabetes. The results were considered non-significant when a -0.85 SMD was found.

3.2.8. Nutraceuticals Main Findings

The main findings of the work regarding the included nutraceuticals are reported in Table 5.

Table 5. Nutraceuticals main findings.

	Number of Studies	Study Design	Year of Publication	Country	Authors	Main Findings	References
Vitamin D	7	Double blind, placebo-controlled RCT; systematic review and meta-analysis of RCTs; prospective review	2010–2015	Iran, UK, USA, Saudi Arabia, Greece	Salehpour A et al., Forouhi NG et al., Manousopoulou A et al., Pittas GA et al., Dolinsky DH et al., Kunutsor SK et al., Alkharfy KM et al.	Non-significant results or ↓DBP ↓↑SBP ↓FBG ↓TC ↓TG ↓↑LDL ↑HDL ↓HOMA-IR	[36,40,41,51,63,83,84]
Vitamin K	1	Systematic review	2010	UK	Rees K et al.	Non-significant results	[88]
Omega-3	2	Meta-analysis of RCTs; double blind, randomized, placebo-controlled study	2018 2020	UK, USA, Australia	O'Mahoney LL et al., Rao A et al.	↓BW ↓TC ↓TG ↓LDL ↑HDL ↓VLDL ↓HbA1c	[94,95]
Polyphenols	5	Systematic review, meta-analysis of RCTs, double blind placebo-controlled RCT, double-blind crossover study	2015–2020	USA, Italy, Spain, France	Hausenblas HA et al., Menezes R et al., Boccellino M et al., Martinez-Maqueda D et al., Amiot MJ et al.	↓HbA1c ↓creatinine ↓HOMA-IR ↓TAG ↓TG ↓FG ↓TC ↓LDL ↑↓HDL ↓SBP ↓DBP ↓BMI ↓WC ↓BW ↓BFM	[99,104,105,115,116]

Table 5. *Cont.*

	Number of Studies	Study Design	Year of Publication	Country	Authors	Main Findings	References
Polyphenols (bergamot flavonoids)	3	RCT, prospective study, open label study	2015 2016 2021	Italy, USA	Giglio RV et al., Toth PP et al., Raimondo S et al.	↓HbA1c ↑glucose ↓TC ↓LDL ↑HDL ↓↑TG ↓BG ↓WC	[134,138,139]
Probiotics	2	RCT, meta-analysis	2015 2018	Poland	Szulinska M et al., Kasinska MA et al.	↓LPS ↓WC ↓BFM ↓TC ↓TG ↓LDL ↓FBG ↓INS ↓HOMA-IR ↓HbA1c	[140,141]
Prebiotics	1	Systematic-review	2013	Australia	Kellow NJ et al.	↓INS ↓BG	[149]

4. Discussion

In order to fully understand the opportunities of nutraceuticals, there is high need to highlight the real burden of disease of CMDs and the cluster of risk factors and conditions represented by MetS on both the epidemiological and economic points of view. Regarding CVD, among the several aforementioned results, it is sufficient to point out that it is the leading cause of death all over the world, estimated to cause 23.6 million deaths by 2030 [5]. Moreover, the impact of cardiovascular problems has increased for decades, rising from 271 million people affected and 12.1 million deaths in 1990 to 523 million people affected and 18.6 million deaths in 2019 [14]. One of the most hit countries in the World is the USA, where the prevalence of CVD is estimated in 121.5 million cases, as stated in a report by the American Heart Association [5]. Considering the impact of CVD on American soil, it is definitely useful to highlight that CVD causes more deaths than cancer, with an amount of 840,678 and 598,031 deaths, respectively. Such a huge epidemiological impact has an effect on expenditures, resulting in USD 351.2 billion in the period 2014–2015 [5]. As far as Europe is concerned, data show that 85 million people in Europe and 49 million people in the EU live with CVD, which causes 3.9 million deaths in Europe and over 1.8 million deaths in the EU per year. If we consider this in terms of proportions, 45% of all deaths in Europe and 37% of all deaths in the EU are caused by CVD. The economic impact of CVD on European soil is consequently high, resulting in € 210 billion in 2015, showing a huge increase from the amount estimated in 2009, equal to € 106 billion [16]. This fact highlights the continuous increase in prevalence and costs related to CVD, that, in around five years, doubled its economic impact on the EU society. It is interesting to see the huge economic impact of CVD in some European countries, such as in Germany, France, and the UK, where total expenditures are estimated, respectively in € 34.7 billion, € 5.1 billion, and € 15.8 billion [4]. Finally, nowadays CVD constitute a real challenging issue for people all over the world, showing a constant increase in prevalence, deaths, and costs, which have risen to hundreds of billions, representing a serious burden for patients, families, and healthcare systems. As far as MetS is concerned, it is considered as a leading global public health challenge [159]. MetS can be analyzed as a cluster of cardiometabolic risk factors, and it can lead to the outbreak of CVD, T2DM, and NAFLD. The prevalence of MetS is higher than expected in the population. As a matter of fact, taking into account Japan, China, Brazil and Mexico, the prevalence in the population is estimated, respectively, at 19.3% [160], 21.3% [161], 29.6% [162] and 54.8% [163]. In the EU, the prevalence of subjects suffering from both hypertension and MetS is estimated at 8–13%. In particular, this amount is equal to 36% in Germany, 11% in Spain, and 10% in Italy. Deeply interesting data comes from the fact that MetS is found in several patients suffering from hypertension, accounting for 60%, 22% and 21% of all patients with hypertension in Germany, Spain, and Italy, respectively. Still focusing on these three countries, the economic impact per person with both hypertension and MetS is equal to € 24,427 in Germany, € 1909 in Spain, and € 4877 in Italy [26]. As stated above, as MetS has a cluster of cardiometabolic risk factors, leading to the outset of CVD, T2DM and NAFLD, its economic impact is strictly linked to these health issues, that turn out to deeply affect the costs of treatment of this syndrome. In particular, diabetes is estimated to cause 1.5 million deaths worldwide [31]: more than 80% of T2DM-related deaths take place in low and middle-income countries. Seuring et al. [29] found out that direct costs linked to diabetes ranged from USD 242 for Mexico in 2010 to USD 11,917 for the USA in 2007, while indirect costs ranged from USD 45 for Pakistan in 2006 to USD 16,914 for the Bahamas in 2000. Furthermore, NAFLD has been reported in over 76% of type 2 diabetics (Younossi et al., 2016 [33]).

In a nutshell, it is possible to affirm that CMDs constitute challenging public health issues worldwide, worsened by the role MetS plays, determining a huge impact on society, on both the epidemiological level, with hundreds of millions of people affected and millions of deaths, and the economic level, causing high costs. Nutraceuticals could establish a new therapeutic pathway to deal with these pathologies, prevent them and contain or decrease their economic burden, which, as seen above, has increased at high speed in recent years.

In our study, we have evaluated most of the nutrients, bioactive compounds, vitamins, and lipids that are part of the composition of nutraceutical products available on the market. Their properties have been evaluated and analyzed on the basis of their potential and effectiveness in reducing biomarkers indicating both cardiac and metabolic dysfunctions. We have shown that some of these nutraceuticals proved to be more effective than others. The actual benefits in reducing biomarkers indicating MetS and CVD are listed below, divided by type of substance underlying the composition of the nutraceutical product. The first nutraceutical analyzed is vitamin D, which occurs naturally as vitamin D3, also known as cholecalciferol, and vitamin D2, also known as ergocalciferol. The active form of vitamin D3 is calcitriol, which is produced by the kidneys when levels of parathyroid hormone (PHT) and prolactin rise, or when intracellular calcium levels drop below 2.5 mM. Its function is expressed in an increased reabsorption of calcium and phosphate at the gastrointestinal and renal levels, and in a decrease in the levels of calcitonin (hormone that lowers calcium levels in the blood). Calcitriol is important for our metabolism as it intervenes in the processes of muscle contraction, nervous excitation, maintenance of bone mineralization, and calcium homeostasis. Vitamin D is also important for the heart in order to prevent cardiovascular diseases, such as hypertension, heart failure, and ischemic heart disease. Vitamin D could also reduce the phenomenon of insulin resistance and increase insulin excretion in cases of type II diabetes mellitus, acting on calcium homeostasis [164]. There is therefore an indirect association between the indicator of vitamin D in the blood, 25 hydroxyvitamin D (25(OH)D), type II diabetes mellitus, and cardiovascular disease and hypertension: the lower the levels of this indicator in the blood are, the higher the risk of development of these diseases is [165]. A high blood pressure level is a symptom of cardiovascular problems [83,166]. Vitamin D deficiency can cause the activation of an inflammatory cascade that leads to endothelial dysfunction and an increase in arterial stiffness; both factors contribute to an increase in blood pressure and, consequently, expose a greater risk of incurring in cardiovascular diseases [167,168]. To confirm this, it has been shown that the risk of developing CVD is higher in patients with a level of 25(OH)D below 25 nmol/L than in patients with a level of 25(OH)D above 100 nmol/L [169] and that the association between vitamin D deficiency and an increased risk of fatal CVD is 62% [170]. Therefore, vitamin D assumption in order to reduce this parameter must be considered. Vitamin D deficiencies can also manifest themselves with symptoms such as rickets in infants or osteoporosis in adults. Sources of vitamin D are mainly foods of animal origin. Although, as it can be seen below, some of these results are, from a certain point of view, inconclusive, interest in vitamin D and its protective role against cardiometabolic risks has not diminished. Some mechanisms of action that have been hypothesized to underlie the activity of vitamin D include, in addition to the aforementioned effect on calcium metabolism, also effects on vascular cells, such as the stimulating action of the proliferation of apolipoprotein ApoA1 involved in the growth process of HDL cholesterol, responsible for reverse cholesterol transport [171,172], suppression of the renin angiotensin aldosterone system and action on inflammation and oxidative stress processes, thus decreasing the level of pro-inflammatory mediators, such as prostaglandins and interleukins [173–175]. In the first double-blind randomized placebo-controlled clinical trial, vitamin D3 supplementation did not lead to any improvement in maintaining adequate blood glucose concentrations. The randomized placebo-controlled clinical trial conducted by Forouhi et al. [40] obtained as the only significant result, following a supplementation of vitamin D2 and D3 in patients at risk of developing type II diabetes, an increase in levels of 25(OH)D, respectively by 38.3 nmol/L for vitamin D3 supplementation and 31.2 nmol/L following administration of vitamin D2. Furthermore, after administration with vitamin D2, small reductions in the levels of good HDL cholesterol and ApoA1, the main component of HDL apolipoprotein were noted, as well as a positive but small reduction in the levels of TC and ApoB (component of LDL or bad cholesterol). Similar conflicting results were also found in 2 studies analyzed in the systematic review by Manousopoulou et al. [41], who found an increase in LDL levels following vitamin D supplementation, along with no significant or

even no effect or adverse effects in the decrease in SBP or DBP. The only significant results were obtained from 4 studies (decrease in FM, TG and increase in HDL and oral glucose insulin sensitivity) which administered a not too high amount of vitamin D, ranging from 1000 IU/day to 120,000 IU/day fortnightly for a duration of a minimum of 8 weeks to a maximum of 1 year. Therefore, it can be deduced that it is not necessary to administer high doses of vitamin D, but the right ones as demonstrated by the minimum administration of 5000 IU/day for 5 months which proved to be the most effective. Furthermore, from the systematic review by Pittas et al. [51], we realize how the positive cardiometabolic effects of a vitamin D supplementation are found only in those individuals suffering from vitamin D deficiency; a fact that corroborates this thesis can be found in the study by Kunutsor et al. [83], in which the only significant results of a decrease in DBP (1.3 mmHg), after supplementation with vitamin D, were obtained in a group of individuals already suffering from cardiometabolic syndrome and with low levels of 25(OH)D. High levels of endogenous vitamin D (i.e., above 75 nmol/L) do not necessarily indicate a reduction in the risk of developing complications, but, on the other hand, a decrease in the endogenous values of this vitamin (defined as a concentration of 25(OH)D below 25 mmol/L) are associated with an increase in cardiometabolic risks. A systematic review of 35 trials analyzing the relationship between vitamin D and cardiometabolic outcomes in children [63] found contradictory results on the arterial stiffness parameter. Of these 35 studies, 10 gave results indicating a decrease in SBP, four a decrease in DBP, five an increase in HDL lipoproteins, seven an increase in HOMA-IR, and two a decrease in FBG, but they are still believed to be of little significance. Finally, in the study by Alkharfy et al. [84], beneficial effects were found in taking antidiabetic drugs concomitantly with vitamin D. Rosiglitazone acted as an agonist towards 25(OH)D levels, which led to improved triglyceride levels, and increased insulin intake. The association of insulin, oral drugs, and vitamin D led to an improvement in triglyceride levels, total and HDL cholesterol and in SBP. This indicates that vit. D supplementation could be used alongside antidiabetic therapy or in the prevention of hypertension. Another crucial vitamin in MetS is Vitamin K, which naturally occurs in 3 forms: vitamin K1 or phylloquinone (present in all green leafy vegetables), vitamin K2 or menaquinone (in foods of animal origin, as it is produced by the intestinal bacterial flora), and vitamin K3 or menadione (a synthetic product). The role of vitamin K is to act in the coagulation cascade: it allows the glutamic acid of thrombin to change into gamma carboxyglutamic acid (Gla), a component of pro-thrombin or factor II of the coagulation cascade, which allows the latter enzyme (prothrombin) a better interaction with the calcium molecules present in the damaged site of the connective tissue where the clot will have to be formed. Basically, vitamin K acts as a co-substrate for the enzyme that catalyzes the carboxylation of glutamic acid, that is gamma glutamyl carboxylase. The resulting Gla is a potent inhibitor of vascular calcification. Therefore, a vitamin K deficiency could lead to a Gla deficiency and, thus, to an increase in intra–vessel calcium deposition, artery calcification, and, ultimately, cardiovascular problems [176,177]. Some studies [178–180] have also shown how vitamin K can be associated with a lowering of insulin resistance: 500 micrograms of vitamin K per day for 3 years had a protective effect against the progress of insulin resistance in older men. Rees et al. [88], analyzing the relationship between vitamin K1 and vitamin K2 with cardiometabolic outcomes, obtained positive results only after supplementation with vitamin K2 (reduction in CHD events). This fact could be due to the different nature of vitamin K2 (animal) compared to vitamin K1 (vegetable) or to the major effect of vitamin K2 in preventing calcification of blood vessels. Omega 3 is a polyunsaturated fatty acid (PUFA) presenting with more unsaturation, namely double bonds within the carbon chain; omega-3 is naturally present both in plants (mainly algae but also walnut, flaxseed, clary sage, edible seeds, and seed) and in products of animal origin (fish, squid, and krill) and in living beings that feed on algae. Omega 3, also called linolenic acids, together with omega 6 or linoleic acids, are essential fatty acids: our body does not foresee an endogenous synthesis and it must therefore necessarily be introduced with the diet. Omega-3 and Omega-6 together contribute to the formation of vitamin F, useful in the fight

against cardiovascular diseases, atherosclerosis, and thrombosis. The eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can derive from linolenic acid, while the arachidonic acid (AA) derives from linoleic acid. The American Heart Association (AHA) and European Food Safety Agency (EFSA) have recognized omega 3-based products as effective nutraceuticals in preventing CVD: in fact, a daily intake of 2 g of EPA and DHA is recommended to maintain an adequate (i.e., low) blood level of triglycerides [181]. In addition, EPA and DHA reduce the hepatic synthesis of LDL and VLDL lipoproteins, thus decreasing the cholesterol rate, increase beta oxidation, reduce the endogenous synthesis of fatty acids, and increase the synthesis of phospholipids [182]. CVD is a health issue that is deeply felt in the USA; in fact, a study was conducted there, and it noted that 14.7% of deaths from cardiometabolic diseases are related to a poor consumption of omega-3, EPA, and DHA [183]. In fact, an omega-3 index (O3I) less than 4% is associated with a high risk of developing CVD, a value of 4–8% a moderate risk, and a value greater than 8% is associated with a low risk [182]. It has therefore been hypothesized that EPA and DHA may be effective to treat diseases such as NAFLD, diabetes type II and CVDs affections, whose genesis may lead to the onset of MetS [184–186]. The studies by Savada et al. [187] and Jacobo et al. [188] have proposed some mechanisms of action that see omega-3 able to improve, in addition to the excessive production of triglycerides, also hyperglycemia, insulin secretion and glucose metabolism, as well as improve the levels of WC, and HOMA-IR. Moreover, the meta-analysis by O'Mahoney et al. [94] found a reduction in LDL, HDL (sensitive analysis) and TG levels, following an omega-3 supplementation in diabetic patients. There was also a small reduction in HbA1c. A reduction in BW, TC and VLDL levels occurred in the randomized placebo-controlled study conducted by Rao et al. [95], where VLDLs decreased by 25%. However, no effects were noted either on HDL or LDL, or on inflammation biomarkers. Treatment with the omega 3-based product, Almega PL, was analyzed, resulting in OI3 levels increasing from 4.97 $\pm$ 0.89 to 5.74 $\pm$ 0.93% in 12 weeks. Therefore, omega 3 could be used to treat symptoms related to Mets and CVD, narrowing their economic burden, and establishing a real therapeutic alternative in order to deal with outcome related to these diseases. Another nutraceutical group analyzed in this study consists of polyphenols, bioactive compounds found in plants as secondary metabolites; in nature, there are about 8000 different types of polyphenols. Fruits, vegetables, whole grains, tea, chocolate, and wine are rich source of polyphenols [98]. There are two categories of polyphenols distinguishable on the basis of the chemical structure: flavonoids (flavanols/flavan-3-ols, including catechins; flavonols; flavones; flavanones; isoflavones; anthocyanins and cyanidins) and non-flavonoids (phenolic acids, i.e., hydroxycinnamic and hydroxybenzoic; stilbenes; lignans; others, including curcumin). A diet rich in polyphenols derived from fruits and vegetables has been associated with a reduction in CVD risks thanks to the anti-inflammatory and antiatherogenic properties of these compounds, such as the inhibition of platelet aggregation and the expression of adenosine molecules of the endothelium, as well as through an action of protection from the oxidation of LDL lipoproteins [189]. In fact, oxidative stress has also been associated with the development of obesity problems: excessive levels of reactive oxygen species (ROS) can lead to a block of the cellular respiration process, ultimately resulting in an increase in the energy storage function of adipocytes, with a concomitant decrease in their energy consumption function. Polyphenols are essential in limiting the risk of developing ROS and RNS, i.e., radical reactive species of oxygen and nitrogen; the former are mainly produced in the cytosol, mitochondria, RE, and lysosomes, while the latter derive from the metabolism of amino acids [190–192]. ROS and RNS are involved in the processes of cellular aging and inflammation [193–195]. Sources of derivation of these radical species can be NADPH and its oxidation, which produces O_2 and H_2O_2; if not suppressed, this oxidative cascade can lead to damage related to aging and inflammation [191,196]. Polyphenols, therefore, act on cell signaling mechanisms correlated with oxidative stress and inflammation, leading to an improvement in TG and TC levels, vascular functions, SBP and DBP, and glucose metabolism [195,197]. For example, in one of the most common and consumed fruits in

the world, the apple, are present: flavonols (quercitin, kaempferol, and rutin), dihydrochalcones (phloretin and phloridzin), flavan-3-ols (epicatechin and procyanidins), and phenolic acids (caffeic acid and cumaric) [198,199]. These compounds present with:

- Antidiabetic properties: Phloridzin has been shown to have properties capable of improving dyslipidemia and decreasing the level of glucose in the blood [200], as well as a reduction in beta cells that usually lead to insulin resistance, and an improvement in hyperglycemia [201]. In addition, phloridzin, in a study by Chai et al. [202], was shown to lower BW and decrease FBG and TG; it also improved the levels of the enzyme glucokinase in the liver [203]. In general, the phenols derived from apples inhibit the sodium/glucose co-transporter in the intestine and kidney and consequently decrease the renal reabsorption of glucose.
- Cardioprotective effects: Phenols present in apples have been found to have a lowering effect on TC levels, which naturally leads to a lowering of the risk of developing CVD. They also decrease LDL levels by limiting oxidation processes [204,205]. Chai et al. [202] found lower total and LDL cholesterol levels in postmenopausal women who consumed apples daily. In particular, the flavonoid phloretin limits the expression of TNF alpha in a dose-dependent manner (1–100 micromol/L) [206]. The systematic review by Hausenblas et al. [99] saw the polyphenol resveratrol as the subject. The action mechanism of resveratrol, a polyphenol found in red wine, tea, berries, blueberries, pomegranates and nuts is as follows: it activates the SIRT1 receptor (sirtuin family of transcription factors), whose main function is to regulate the energy metabolism and homeostasis of mitochondria, and the AMP-dependent protein kinase (AMPK), that present with a lipid-lowering effect, essential in the regulation of diabetes [207–210] and for a contrasting effect on obesity, promoting lipolysis, and inhibiting lipogenesis [211]. These biochemical signals are also activated by exercise and a decrease in caloric intake, which, in their turn, are associated with a decrease in the risk of developing type II diabetes, NAFLD and cardiometabolic risks and are also the target of antidiabetic drugs, such as metformin [212]. Therefore, resveratrol could lead to improvement in antidiabetic therapy, and may be able, in the future, to replace metformin use or improve adherence to this therapy, representing a new therapeutic choice able to reduce the costs of direct drugs spent on antidiabetic treatment. Resveratrol has also shown to improve blood flow and vascular endothelial function [213,214]. Concretely, in this study, the most significant results to be found were: an increase in HDL levels, and reduction in SBP and in the levels of glycated hemoglobin HbA1c (high in diabetic subjects, symptom of an imbalance in glycemic levels) and creatinine, the high rates of which are indicative of nephropathy. In two studies analyzed by Bocellino et al. [105], resveratrol was instead shown to be effective in reducing TG levels, BFM, and WC indices. Resveratrol can also be useful in reducing TC, LDL, and HOMA-IR levels in NAFLD patients. Flavonols are a subtype of flavonoids that can be found in onions, spinach, asparagus, and some berries. A very important type of flavonols is quercetin [215,216], found mainly in vegetables such as onions, garlic and ginger, apples, and wine. Its mechanism of action has been hypothesized to be the following: it acts by decreasing BP through an improvement in endothelial function, an action on the renin angiotensin aldosterone system, and a down regulation of sodium channels in the kidneys [217,218]. Quercetin was also the object of evaluation of two studies analyzed by Boccellino et al. [105], in which the administration of 150 mg/day–162 mg/day for 8–6 weeks was found to be effective in lowering TG and WC levels in overweight or obese subjects; moreover, in a study carried out by Amiot et al. [116], quercetin was found to be effective in decreasing the levels of SBP, DBP, and TNF-alpha. A meta-analysis conducted by Menezes et al. [104] analyzed the effects of flavonols relative to cardiometabolic biomarkers: TG, TC, SBP, DBP, FBG, and LDL levels decreased, while HDL levels increased; the most interesting real finding was found in a higher incidence of results, that turned out to be more significant when they included an Asian population and patients with

a diagnosis of disease rather than healthy ones. Curcumin is the most abundant polyphenol present in Curcuma longa [105]. It has been shown to have properties that in five studies analyzed led to a lowering of the levels of TG, pro-inflammatory interleukin 4 (IL-4) and interleukin 1-beta (IL-1-beta) in individuals suffering from obesity; it also led to a decrease in WC levels and an increase in HDL lipoproteins. Additionally, in NAFLD patients, supplementation with curcumin was associated with reduction in BMI, WC, TG, LDL, FBG, HOMA-IR Grape polyphenols have shown to be effective in reducing the levels of HOMA-IR, TC, and LDL, but, above all, of insulin in subjects at high risk of developing cardiometabolic disease [115]. One of the possible mechanisms proposed could be the interaction of grape pomace polyphenols with the insulin receptor, thus decreasing the levels of phosphorylated serine, preventing the inactivation of glycogen synthase kinase, and increasing the levels of the receptor for the proliferation of peroxisomes (gamma PPAR). Finally, a high number of polyphenols of different derivations were analyzed in relation to some changes that they implemented in cardiometabolic biomarkers related to obesity, SBP, DBP, dyslipidemia, glycemic levels, insulin resistance, oxidative stress, inflammation, and cardiovascular dysfunctions. Regarding obesity, the use of green tea, rich in catechins, in particular in epigallocatechin 3-O gallate and 5-O-galloylquinic acid, is noteworthy [219]. Catechin-polyphenols act by inhibiting the degradation of cAMP via a phosphodiesterase, as well as inhibiting catechol-O-methyltransferase, which would normally degrade noradrenaline. Furthermore, these green tea polyphenols could stimulate the catabolic process of energy consumption by the cells, which would lead to a decrease in body weight intake and expression of fatty acid synthesis. They have been shown to be effective in decreasing TG and HDL levels, and BW, BMI, and WC. Improvement in these anthropometric biomarkers could be useful in the prevention of obesity manifestation and metabolic disfunction, eventually protecting the subjects at high risk of developing MetS complications and leading, consequently, to a reduction in economic burden of metabolic syndrome. Regarding blood glucose and insulin resistance, this study by Amiot et al. [116] proposed a mechanism of action of polyphenols, which is expressed through: inhibition of glucose uptake via SGLT1 (intestinal sodium glucose transporter), protection of pancreatic beta cells from glucotoxicity, suppression of glucose release from liver, and also through the improvement of glucose uptake via the GLUT4 transporter [220]. Their relationship with oxidative stress and vascular dysfunctions is also being evaluated: polyphenols have an antioxidant effect since they reduce, as previously mentioned, the formation of reactive oxygen species produced in the mitochondria, by NADPH oxidase and NO synthase [221] and increase the production of vasodilator substances such as NO and endothelium-derived hyperpolarizing factor by stimulating AMP kinase and preventing ROS degradation of NO by reducing NADPH oxidase gene expression [221]. Bergamot, or citrus bergamia has a high content of flavonoids (neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin, and poncirin) [194,222]. In particular, three flavonoids extracted from bergamot peel, with the acronym HMGF 3-hydroxy-3-methylglutaryl falavanones (brutieridin, melitidin and neoeriocitrin), have been shown to own activities that mimic the effects of a statin, simvastatin. In fact, both simvastatin and HMGF lower the total level of circulating cholesterol, LDL cholesterol, and raise HDL [223]. HMGFs act by inhibiting HMG-CoA reductase, which leads to a reduction in the formation of cholesterol esters. There is therefore an alternative therapy for the treatment of dyslipidemia and CVD's complications in those patients who experience adverse effects after taking statins, such as myalgia, myopathy, rhabdomyolysis or liver damage, i.e., products of nutraceutical derivation containing bergamot extracts (object of three clinical studies covered by the paper by Giglio et al. [134]). This is a very important aspect, because the use of bergamot flavonoids in subjects not undergoing statin-lowering cholesterol therapy could lead to an improvement in terms of therapy adherence and, consequently, to a reduction in CVD treatment's

annual costs. These HMGF flavonoids can lower blood glucose and lipid levels [137] through an increase in their consumption by an activation of mitochondrial oxidation, a decrease in VLDL, and an increase in the transcription of the LDL receptor via PKC and gamma PPAR, thus reducing the risk of CVD development [224]. A product based on flavonoids extracted from bergamot (Bergavit) has been shown to be effective in reducing TC and TG levels, but also in anthropometric outcomes through some proposed action mechanisms [138]:

- Activation of AMPK alpha (adenosine monophosphate-activated protein kinase), which leads to fatty acid oxidation by acylcarnitine transferase and reduces VLDL by inhibition of hepatocytic nuclear factor 4 (HNF4) [225–230];
- Activation of protein kinase C (PKC), which, through some gene transcription pathways, leads to the sequestration of circulating LDL.
- Activation of the receptor activating the proliferation of peroxisomes (PPAR) which also sequesters LDL. Another flavanone-based product (subgroup of flavonoids) of bergamot hesperidin and eriocitrin, called CitraVes was analyzed by Raimondo et al. [139] to understand the effects on TC levels and WC. The aglycones of hesperidin, naringenin and hesperetin have been shown to be effective in inhibiting the enzyme acylCoA cholesterol acyltransferase (ACAT) and the microsomal transfer protein, known to be responsible for the synthesis of cholesterol and its esterification in the liver. Consequently, they bring about a reduction in the levels of VLDL and LDL lipoproteins [231]. In addition, hesperidin also has antioxidant and anti-inflammatory activities, while erythrocin can lead to the reduction in LDL and protection from metabolic disorders and an increase in adipose tissue [232,233]. Probiotics are defined as live and vital microorganisms that confer health benefits to the host when consumed, able to reach the intestine, multiply there, and exert a physiological balance action on the bacterial microflora. They must be safe for use in humans and provide at least 109 live cells per day. The intestinal bacterial flora performs functions aimed at maintaining the wellbeing of the host organism:
- stimulates the development of the immune system;
- forms a barrier that protects us from attack by pathogens or viruses (through mechanisms of antagonism for the competition of nutrients and for the attachment sites to the intestinal epithelium);
- intervenes in the digestion processes;
- participates in the synthesis of vitamins;
- promotes the absorption of calcium, magnesium, and iron. The complex of microbes, bacteria, viruses, and archaea, called "Intestinal microbiota", is very important for our health; if altered, as for example in the case of endotoxemia, it can cause the spread of Gram-bacteria through the intestinal mucosa and throughout circulation causing inflammation [234], leading to conditions like obesity, diabetes, non-alcoholic fatty liver disease, and arteriosclerosis [234–236]. The intestinal microbiota can also be altered by drugs such as antibiotics but also by other factors such as advancing age, incorrect diet, and genetic predisposition of the host [237,238]. Therefore, to restore the correct intestinal flora, probiotic products can be used, as they have been shown to be effective in improving the barrier function of the intestinal epithelium, thus preventing the microbiota from passing into the circulation [239,240]. Probiotic supplementation had a beneficial effect on the lipid profile in obese post-menopausal women, who were given two different doses of Ecologic barrier, a multi-species probiotic product. The administration of the higher dose (1×1010 CFU per day) resulted in a greater reduction in glucose, insulin, and HOMA-IR levels when compared with administration of the lower dose. The benefits were therefore dose dependent. In general, however, both doses had significant effects in reducing TC and LDL lipoprotein levels. It was also noted that individuals with type II diabetes have fewer bacteria producing butyric acid, a short-chain fatty acid [241–243] which serves as a substrate in gluconeogenesis, lipogenesis, and modulation of expression of some

genes [244]. Butyric acid binds to a G protein coupled receptor and brings some beneficial effects, such as the regulation of glucagon-like peptide 1, as also happens for probiotics, associated with an improvement in insulin excretion and therefore a lowering glucose level [245]. It has also a trophic action on the mucous membranes of the intestine, stabilizing their turnover and thus exerting a protective effect against the onset of colon cancer. Probiotics, like this acid, have the task of preventing the influx of pro-inflammatory cytokines from the intestine to the bloodstream [245,246]. Therefore, a correct balance of the intestinal microbiota obtained by administering probiotics is of fundamental importance for a regular maintenance of glucose, lipid, and protein metabolism. In this meta-analysis [141], probiotics were found to be effective in having a lowering effect on HbA1c, HOMA-IR and lowering glucose levels in patients with type 2 diabetes mellitus. According to Einarson et al. [8], for the year 2040 the number of people with diabetes would increase to 642 million; to face this enormous number, indicating a future announced global disease, it will be very important to witness the ability of probiotics in the prevention of diabetes type II. Additionally, probiotics could be used alongside classic diabetic therapy (thanks to their ability of mimic butyric acid action) such as metformin, sulfonylureas, glitazones, in order to assist their action. When Gram-bacteria, normally found in our intestinal microbiota, end up in the bloodstream, they cause, as stated above, metabolic endotoxemia [247]. In fact, they stimulate the production of pro-inflammatory cytokines by macrophages and reactive oxygen species, which can cause systemic inflammation, insulin resistance, and weight gain [248,249]. It is possible to stimulate the growth of microorganisms that bring benefits to the patient, preventing the passage of bacteria such as the aforementioned Gram- from our intestinal bacterial flora to the systemic circulation, through the intake of prebiotics, defined as non-digestible but fermentable carbohydrates deriving from plants that act as a fermentation substrate in the colon for those intestinal microbes that confer benefits to the patient's health [250]. They therefore help to develop the intestinal bacterial flora already present in our body. In the case of concomitant or previous intake of probiotics, prebiotics assist in their growth, development, and action. Some carbohydrates with a prebiotic effect are insulin-type fructans (inulin, oligofructose and fructo-oligosaccharides) and galactans (galactooligosaccharides), which stimulate the production of bifidobacteria and lactic acid-producing lactobacilli [251]. The intestinal microbiota plays a fundamental role in the development of the host's immune system, modulation of inflammatory processes, in the regulation of glucose and lipid metabolism, in the production of vitamins and in the regulation of intestinal permeability [247,252,253]. For these reasons, therefore, a prebiotic supplement that is capable of favoring the intestinal bacterial flora could represent a therapeutic strategy for the prevention and treatment of metabolic diseases. The fermentation of prebiotic bacteria in the colon also leads to the production of short-chain fatty acids (SCFAs): acetate, propionate, and butyrate (already addressed previously). SCFAs have an important role in maintaining intestinal health and in modulating metabolic and immune processes. In fact, they have two G proteins in the intestine, stimulating the secretion of energy peptides, that is the YY and GLP-1 peptides, hormones that reduce the level of appetite, increase insulin sensitivity, and eliminate gastric emptying. SCFA propionate appears positive in the liver to inhibit cholesterol synthesis by altering a key enzyme [254]. However, in the systematic review conducted by Kellow et al. [149], contradictory and insignificant results were found on the reduction in TC, LDL, and HDL.

5. Conclusions

Once, German philosopher L. Feuerbach said: "a man is what he eats". At the end of this narrative review, we believe that such a simple sentence comes with some truthfulness. The food we eat can be either the best form of medicine or the worst kind of poison; health is wealth, and we should invest in it. In fact, daily intake of nutraceutical-derived products

such as vitamin D, vitamin K, polyphenols, omega-3 fatty acids, probiotics and prebiotics can lead to an improvement in cardiometabolic biomarkers, decreasing LDL, blood glucose, blood pressure levels, and reducing inflammation and oxidative stress pathogenesis. In particular, nowadays, CMDs are very prevalent all over the world, determining a heavy burden on patients and healthcare systems. With a relevant pharmacological therapy that can lead to side effects (such as the statin one, causing sometimes steatosis and kidney damages) and a low adherence to treatment, a new therapeutic strategy, based on nutraceutical products, would therefore be helpful. Furthermore, as far as pharmacoeconomics and nutra-economics are concerned, the use of nutraceuticals could really allow patients to save money, thanks to the reduction in side effects and relative costs, common in a standard therapy. Since nutraceuticals are available not only in pharmacies, but also in other types of small businesses, such as herbalist's shops and supermarkets, more social awareness is required. The safety and care concerning these products must be properly understood and communicated to consumers. In order to make the most of nutraceuticals, closer relationship and dialogue between the patient, the general practitioner and pharmacist is crucial, thus leading to an improvement in disease management, in clinical outcomes and a reduction in the related costs. However, as stated above, there is a lack of economic studies analyzing the link between nutraceuticals' use and savings in terms of direct and indirect medical costs. Moreover, there are few studies focused on the burden of CMDs and MetS directly related to nutraceutical therapies. For some nutraceuticals there are still conflicting data about their efficacy. In fact, we found a deep vacuum in the international literature concerning the nutra-economics field, meaning there is a serious lack of studies evaluating the possible economic impact that nutraceuticals may have in dealing with CMDs and MetS. For these reasons, further research is highly needed, especially with a focus on the use of these types of compounds in frail patients, children, elderly people, and those undergoing drug treatments. Only with research we will be able to shed light on this unique field that could provide so much in terms of health and savings to patients all over the world.

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