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Review article

Dietary non-nutrients in the prevention of non-communicable diseases: Potentially related mechanisms

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ABSTRACT

Among the 10 leading causes of death in developed countries are chronic non-communicable diseases (NCDs). The effect of these multifactorial diseases on public health has stimulated considerable research aimed at investigating their primary risk factors (genetic factors, stress, food intake, and amount of physical exercise). Thus, healthful foods (e.g., fruits, vegetables, oils, grains, and seeds) are sources of bioactive compounds that promote good health and disease prevention. Among their components are non-caloric substances identified as non-nutrients (polyphenols, phytosterols, saponins, and phytates), which have been found to have a role in modulating metabolic pathways, maintaining health, and preventing NCDs. The aim of this study is to demonstrate and review the performance of some non-nutrients, such as their antioxidant and anti-inflammatory action, modulation of the antiatherogenic lipid profile (higher high-density lipoprotein cholesterol, lower oxidized low-density lipoprotein, and triacylglycerols), reduction of glucose and fat intestinal absorption, increase in insulin sensitivity, and stimulation of nitic oxide synthesis.

Introduction

Non-communicable diseases (NCDs) such as cardiovascular disease (CVD), diabetes mellitus (DM), and obesity account for 40 million deaths a year, equivalent to 70% of all deaths worldwide [1,2]. By the year 2020, it is estimated that NCDs will represent 80% of the global burden of diseases [3]. Furthermore, NCDs are the main causes of poor health and disability and account for the majority of health care spending. As a result, NCDs also represent a barrier to social and economic growth, accumulating an economic loss of >$7 million over the next 15 y [1,3].

A balanced diet plays a significant role in the prevention and treatment of NCDs because it participates in the genesis, development, and treatment of these diseases. There is growing interest in bioactive foods and food components that provide better health as a way to find therapeutic alternatives to and prevention of NCDs [4].

With that in mind, there is growing interest in bioactive compounds such as non-nutrients, which might provide better health. In this context, we define non-nutrients as substances that do not fit into the category of nutrients, yet play an important role in regulating bodily functions and disease prevention [5]. These compounds may have an antioxidant action because of the oxide-reducing potential of certain molecules, the ability to compete for active sites and receptors in the various cellular structures, or the ability to modulate the expression of gene-encoding proteins involved in intracellular defense mechanisms against degenerative cellular structure processes [6]. The performance of some dietary compounds in specific metabolic pathways (oxidative stress, inflammation, and adipogenesis) has been demonstrated and is believed to

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have the potential to become the future of primary prevention in general and the treatment and prevention of NCDs in particular [7].

Overall, this review aimed to address the more closely studied non-nutrients and their action mechanisms against NCDs.

Methods

Articles pertaining to non-nutrients and their action on the metabolic pathways of obesity, DM, hypertension, dyslipidemia, and CVD were selected. The descriptors "obesity," "diabetes," "hypertension," "dyslipidemia," and "cardiovascular diseases" were used in combination with the terms "mechanisms," "non-nutrients," "flavonoids," "polyphenols," "phytates," "phytosterols," and "saponins." PubMed and Science Direct databases were used. The search was performed from October 2016 to June 2017. Studies concerning the effects of non-nutrients on chronic NCDs are presented in Table 1.

Polyphenols

Polyphenols are secondary plant metabolites widely distributed in nature, found more abundantly in fruits and vegetables [8]. They represent a wide variety of compounds, separated into classes according to their chemical structure: phenolic acids (hydroxybenzoic and hydroxycinnamic acids), flavonoids (flavonols, flavanols, flavones, isoflavones, flavanones, and anthocyanins), stilbenes, lignans, and curcuminoids [9].

Polyphenols have a relevant antioxidant capacity by capturing alkoxyl radicals (RO·), alkylperoxyl (ROO·), superoxide ($O2\cdot-$), hydroxyl (HO·), nitric oxide (NO·), and peroxynitrite oxidant ($ONOO-/ONOOH$). Polyphenols can reduce the power of the aromatic hydroxyl group, which reduces reactive free radicals and produces the phenoxyl radical. Also, these phenolic compounds lower the production of superoxide anions and hydrogen peroxide (H_2O_2), preserving the total glutathione content and the activity of glutathione reductase and glutathione peroxidase. Furthermore, studies have shown that polyphenols (e.g., hesperidin, naringenin, and resveratrol) increase the expression of NF-E2-related factor 2 (NRF2), a key regulator of antioxidant enzyme expression [10,11]. All these mechanisms benefit a favorable redox state and reduce oxidative stress [12]. It is believed that a high dietary intake of polyphenols is associated with a lower risk for CVD, inflammatory and metabolic diseases, and some cancers because polyphenols interact with cell signaling pathways, modulating the transcription factors and gene expression [13].

Moreover, some studies have demonstrated the role of polyphenols in the prevention of atherosclerosis and the incidence of CVD [14,15]. The estimated dietary intake of these compounds is 1 to 1.2 g/d, and the consumption of flavonoids corresponds to 40%, with the study of this group being regarded as important [9]. Several experimental and clinical studies using normal or hyperlipidic diets with added flavonoids, such as morine, myricetin, naringenin, rutin, camphor, tannic acid, and ellagic acid, have demonstrated the beneficial effect of non-nutrients on dyslipidemias, whether by reducing total low-density lipoprotein cholesterol (LDL-C) and triacylglycerols (TGs) or increasing high-density lipoprotein cholesterol (HDL-C) [16,17]. In a cross-sectional study, a higher flavonoid intake was associated with both increased HDL-C concentrations and reduced serum glycosaminoglycan (GAG) concentration [18].

In fact, improving the lipid profile is related to the antioxidant power of flavonoids, which act to prevent LDL-C oxidation, the main cause of endothelial injury and induction of proinflammatory molecule expression in endothelial cells, avoiding damage to the endothelium and to atherosclerosis [7,19]. Isoflavones and flavonoids are notably present in legumes of the *Vicia* and *Phaseolus genera*, acting on the β-estrogen receptor in the liver, leading to an increase in the number of hepatic LDL-C receptors and favoring cholesterol catabolism and β-oxidation of fatty acids [20]. The antioxidant effect of isoflavone protects against copper-dependent LDL-C oxidation and favors a serum lipid profile associated with protection against atherosclerosis [21]. Previous studies have reported that resveratrol protects lipids from peroxidative degradation and disrupts the uptake of oxidized (ox) LDL-C in the vessel wall in a concentration-dependent manner [22,23]. Quercetin has been associated with the prevention of oxidation and atherosclerosis by reducing LDL-C and postprandial concentrations of glycosaminoglycan and increasing HDL-C in adults [24,25]. It is one of the flavonoids abundantly found in food and has been associated with antioxidant characteristics, reacting with superoxide anions, singlet oxygen, and peroxyl radicals and capable of forming complexes with transition metals, such as iron, preventing the formation of oxygen radicals and preserving ascorbic acid [25,26].

Regarding the effect of polyphenol on glucose control, in vivo and in vitro studies have shown that dietary polyphenols inhibit α-amylase and α-glucosidase, suppressing glucose uptake of glucose in the gut by the sodium-dependent sodium glucose transporter, stimulating insulin secretion and reducing insulin production. Polyphenols also increase insulin-dependent glucose uptake by activating 5′adenosine kinase of monophosphate-activated proteins (AMPK), modifying the microbiota, and having anti-inflammatory effects [27]. Studies of fructose-fed rats have demonstrated that resveratrol is more effective than metformin in improving insulin sensitivity and attenuating metabolic syndrome [11]. Thus, polyphenols are involved in regulating glucose homeostasis and insulin sensitivity.

The hypotensive effect of polyphenol has been investigated. Some polyphenols inhibit the angiotensin-converting enzyme, including procyanidins, catechins, and epicycles found in cocoa, red wine, and other products of plant origin, as well as organic sulfate compounds capable of producing hydrogen sulfate (H_2S). Procyanidins have been described as compounds capable of binding proteins and peptides by altering their activities. Moreover, polyphenols may also contribute to the increase of vasodilation by intensifying the production of nitric oxide (NO) [28].

Resveratrol also appears to promote vasodilation through mechanisms that involve the stimulation of calcium and potassium channels and the production of NO, boosting the expression of the enzyme nitric oxide synthase (NOS) and reducing the clearance of this compound. Two animal studies demonstrated that chronic administration of resveratrol was able to lower blood pressure, increase NO concentration in the blood, and reduce peripheral vascular resistance in hypertensive rats. Thus, this may be one of the mechanisms through which the hypotensive effect of grapes and wine was confirmed [23,24]. It has been found that both the phenolics of grape seed and the bark of grapevines trigger angiotensin-converting enzyme inhibitory activity [11].

Finally, anticarcinogenic effects of polyphenols in human cells, especially in the oral cavity, lungs, liver, duodenum, colon, stomach, mammary glands, and skin tissues have been demonstrated [29]. In fact, polyphenols improve cell survival as antioxidants, induce apoptosis, and prevent the development of neoplasms as pro-oxidants [19]. Antiaging and neuroprotective effects of polyphenols have been considered, mainly because of their antioxidant capacity [29].

Current scientific research has indicated the biological, anti-inflammatory, and antioxidant effects of polyphenols, with positive results in terms of reducing the risk for developing NCDs and their beneficial effects on health. However, several factors that influence the amounts of polyphenols in foods, such as processing, storage, maturation, and environmental factors [30] should be taken into account. The antioxidant efficacy of polyphenols in vivo also needs

Table 1
Main studies that assess the effect of non-nutrient intake on outcomes related to NCD

Bioactive compound	Model	Outcome related to NCD	Food source	Duration	Mechanism	Reference
Polyphenol	PBMC and polymorphonuclear cells	Inflammation and oxidative stress	Sorghum (0.5 g of the leaf sheath powder)	NA	Positive regulation of CD69 activation marker in CD3-CD56 + NK, CD56 + NKT cells, CD3 + T lymphocytes and monocytes. ↑ CCL5, Mip-1 α/CCL3 and MIP-1 β/CCL4 ↓ Free radicals.	Benson et al., 2013 [67]
Polyphenol (mangiferin, quercetin)	Wistar rats	CVD and IR	Ubá mango juice (35 mL/d)	7 d	↓ HDL-C, PPAR-γ, and LPL. Improved glucose tolerance, ↓ TC, fasting glycemia ↑ expression of PPAR-γ and LPL related to lipid hydrolysis; ↓ expression of the FAS enzyme that catalyzes the synthesis of long-chain AGS.	Natal et al., 2016 [68]
Polyphenol (catechin, epicatechin, procyanidin, quercetin)	Wistar rats	Obesity and antioxidant effect	Cacao extract roasted and raw	4 wk	↓ TG, adipose tissue ↑ serum ACL and GSH: GSSG ratio in the liver, regardless of extract quality (raw or roasted).	Żyżelewicz et al., 2016 [69]
Polyphenol (oleocanthal, oleuropein, byproducts hydroxytyrosol, tyrosol)	Sprague-Dawley rats	Inflammation and oxidative stress	Olive oil rich in polyphenols (0.29 mg / kg)	6 wk	↓ TG, ↑ de Glut2 e AKT; ↓ TNF-α, COX-2	Lama et al., 2017 [70]
Polyphenol (hesperidin, narirutin, didimina)	Overweight adults (18–65 y)	Metabolic syndrome and antioxidant effect	Orange juice (0.6 g/L: normal polyphenol concentration and 1.5 g/L: high polyphenol concentration)	12 wk: G1 to 500 mL (1.5 g/L); G2- 500 mL (0.6 g/L); 7 wk: washout Reverse distribution	↓ glucose and insulin concentrations, TG and apoB ↓ in the activity of GR enzymes and catalase; ↑ in the SOD activity.	Rangel-Huerta et al., 2015 [71]
Phytosterol	Hypercholesterolemic individuals (20–69 y)	CVD	1.6 g/d of vegetable oils	21 d	↓ LDL-C	Clifton et al., 2008 [72]
Phytosterol	Men and women with normal and hypercholesterolemic individuals (19–60 y)	CVD	Low- and moderate-fat soy milk enriched with phytosterols (2 g and 3.5 g phytosterols)	28 d	↓ LDL-C, TC, LDL: HDL and TG.	Rideout et al., 2009 [73]
Phytosterol	Moderately hypercholesterolemic individuals (20–50 y)	CVD	Yogurt enriched with plant stanol esters (4 g of plant stanol esters)	4 wk (28 d)	↓ TC, LDL-c ↓ absorption of cholesterol from the diet and biliary	Vásquez-Trespalacios, Romero-Palacio, 2014 [74]
Phytosterol	Adults (20-59y) with mild to moderate hyperlipidemia	CVD	Soy milk powder (2 g phytosterol)	6 mo (180 d)	↓ TC, LDL-C, non-HDL-C	Dong et al., 2016 [75]
Phytosterol	Women with gestational diabetes mellitus	CVD and IR	Phytosterol-enriched margarine spread (2 g phytosterol)	16 wk (112 d)	↓ TG, LDL-C, TC, fasting glycemia, insulin, HOMA-IR, HOMA-β and QUICKI. ↑ HDL-C	Li, Xing, 2016 [76]
Saponin	Hyperlipidemic BRL cells	Cholesterol metabolism	Alfalfa extract (0.5, 1, and 1.5 mL/L)	24 h	↑ expression of the regulatory Ldlr genes. ↑ expression of the LXRα and FXR genes by regulating the expression of Cyp7 a1 in the cholesterol catabolic pathway.	Liang et al., 2015 [77]
Saponin	Predipocytes 3 T3-L1	Obesity	Soy (968 and 1025 mg saponin)	24 h	↓ expression of PPAR-γ and CEBPα, transcription factors related to adipogenesis. ↓ expression of PPAR-γ and	Yang et al., 2015 [50]

(*continued on next page*)

Table 1 (*Continued*)

Bioactive compound	Model	Outcome related to NCD	Food source	Duration	Mechanism	Reference
					CEBPα, transcription factors related to adipogenesis.	
Saponin	Predipocytes 3 T3-L1	Obesity	Quinoa (25 and 12.5 μg/mL)	24 h	↓ accumulation of lipids during differentiation. Suppression of the expression PPAR-γ, CEBPα and SREBP1c, transcription factors related to adipogenesis. ↓ expression of LPL aP2 and Glut4 that are involved in fatty acidmetabolism.	Yao et al., 2015 [78]
Saponin	Sprague Dawley rats	CVD	Alfalfa extract (240 mg•kg•d^{-1})	4 wk	↓ TC, LDL, and TG ↑ HDL in liver and serum ↑ expression of *Hmgcr* and *Acat2* genes ↑ expression of *Cyp7* a1 and *Ldlr* regulatory genes	Shi et al., 2014 [79]
Saponin	Mice C57 BL	Obesity	Soy (200 nmol/kg)	8 d	↓ deposits of perirenal and retroperitoneal fat	Singh et al., 2016 [80]

aP2, adipocyte protein 2; apoB, B apolipoprotein; BRL, Buffalo rat liver cells; CCL, motif chemokine ligand; CEBPα, CCAAT binding enhancing alpha protein; CVD, cardiovascular disease; FXR, Farnesoid X receptor; Glut4, glucose transporter type 4; GR, glutathione reductase; GSH, glutathione; GSSG, glutathione disulfide; HDL-C, high-density lipoprotein cholesterol; *Hmgcr*, 3-hydroxy-3-methylglutaryl-CoA reductase; HOMA, homeostatis model of assessment; IR, insulin resistance; LCA, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; *Ldlr*, low-density lipoprotein receptor; LPL, lipoprotein lipase; LXRα, liver X receptor alpha; Mip-1 α, macrophage inflammatory protein 1 alpha; NCD, non-communicable disease; NK, natural killer; PBMC, peripheral blood mononuclear cells; PPAR-γ, peroxisome proliferator-activated receptor gamma; Preadipocytes 3 T3-L1, cells from embryos of prematurely extracted Swiss mice; QUICKI, quantitative insulin sensitivity check index; SREBP1c, sterol regulatory element-binding transcription factor 1; SOD, superoxide dismutase; TC, total cholesterol; TG, triacylglycerols

to be better evaluated, as little is known about their bioavailability [19,30,31].

Phytosterols

Phytosterols are plant-derived sterols that are structurally similar and functionally analogous to cholesterol in vertebrate animals [32]. Sitosterol and campesterol are the most commonly found phytosterols in food, followed by stigmasterol. Vegetable oils, legumes, nuts, and seeds have relatively high concentrations of phytosterol, whereas cereal grains, fruits, and vegetables contain only modest amounts [33].

Regarding NCDs, clinical studies have reported the efficacy of a high-phytosterol diet in reducing hypercholesterolemia, an important action against CVD [34,35]. The exact mechanisms have still not been well defined. Several hypotheses have been proposed, one of which is that these compounds have a chemical structure similar to cholesterol, leading to physical competition between them for incorporation in the micelles, thus compromising the absorption of cholesterol into the enterocyte [36,37]. Thus, unabsorbed cholesterol would be excreted in the feces, reducing absorption and circulating pool. Considering this mechanism of action, daily doses of phytosterol would be needed to ensure their interaction with dietary cholesterol, facilitating the excretion of intestinal cholesterol and bile acids [38].

Another proposed mechanism is that phytosterol can be absorbed by cells [39], regulating genes, and proteins related to cholesterol metabolism, such as peroxisome receptor-activated proliferators (PPARs) and liver X-receptor [40]. Furthermore, it induces the expression of cholesterol-7-α-hydroxylase (CYP7 A1), which regulates bile acid synthesis, thus indicating increased cholesterol excretion through bile acids as an additional cholesterol-lowering mechanism [32]. Phytosterol also appears to modulate sterol regulatory element-binding proteins (SREBP) [41,42], which are a family of transcription factors that regulate lipid homeostasis by controlling the expression of 30 genes involved in the biosynthesis of cholesterol, TGs, phospholipids, and fatty acids [43].

Another biological property has been ascribed to these plant compounds, such as that of an antidiabetic agent. One of the first studies to identify the hypoglycemic properties of phytosterols demonstrated that, in hyperglycemic rats, the glucose level was reduced and the insulin level was increased after oral administration of β-sitosterol [44]. Changes in intestinal cholesterol absorption may then correlate with insulin sensitivity [45]. The increased glucose uptake by β-sitosterol also appears to be mediated by AMPK. As a result of the activation of AMPK in hepatocytes, a reduction in glucose production, suppression of fatty acid synthesis, and the activation of catabolic pathways, such as fatty acid oxidation or glycolysis, can be observed [46,47].

However, the protective effect of phytosterol consumption on the development or regression of diabetes was not found in an experimental mouse model of diet-induced obesity, insulin resistance, and diabetes [48]. There are two possible explanations for this controversial data: One is the nature of the plant sterol and the other is the animal model used [48]. More studies are needed to determine the mechanism of the effects of phytosterols in different animal models of type 2 DM.

Saponins

Saponins are bioactive glycosides derived from the secondary metabolism of plants. They consist of a portion of sugar that normally contains glucose, galactose, glucuronic acid, xylose, rhamnose, or methylpentose, glycosidically attached to a hydrophobic

aglycone. They present diverse molecular structures with different biological and pharmacologic activities [49,50].

In the cellular model, saponins have acted on the transcription factors (PPARγ and CEBPα) and inhibited the differentiation of adipocytes by downregulating the genes related to adipogenesis. The authors proposed that these compounds could act beneficially in the treatment of obesity [51]. Their antiobesity effect was observed in animal models with a reduction of gastric emptying, along with decreased appetite, food intake, and levels of neuropeptide Y mRNA, an important regulator of weight gain [52]. There is also evidence of the action of saponins, on the reduction of pancreatic lipase activity and inhibition of intestinal fat absorption, especially Platycodin D [53].

Regarding the role of saponins on the prevention of lipid peroxidation, an effect possibly attributed to the stimulation of the secretion of thyroid hormones associated with lipid metabolism has been demonstrated [54]. They may act on cell membrane lipids and exert positive effects on hypercholesterolemia [55]. The proposed mechanisms for plasma lipid reduction include the regulation of LDL receptors, inhibition of intestinal absorption of cholesterol, and increase of biliary excretion. Saponins form insoluble complexes with cholesterol and bile acids in the intestines, rendering them unavailable for absorption. Increased bile acid excretion causes a compensatory reaction that stimulates the synthesis of these components by the liver, a process that requires the removal of cholesterol from the bloodstream and leads to a reduction in its serum levels. In addition, saponins interfere in the hepatic circulation of bile acids by forming mixed high–molecular-weight micelles, which are unable to be resorbed by the terminal ileum [55,56].

Saponins also have beneficial effects on lipid metabolism disorders [57], with a reduction in total cholesterol (TC), LDL-C, and serum TGs, along with normalizing insulin, leptin, and adiponectin levels in mice submitted to a high-fat diet by means of gene modulation [58]. In fact, the reducing effect of cholesterol absorption associated with saponins [59] could help human patients by minimizing the risk for CVDs, such as atherosclerosis [57]. Evidence points to saponins as being promising natural cardioprotective agents whose actions, as described in the literature, include inhibition of platelet aggregation, anticoagulant, antithrombotic, antiatherosclerotic, anti-inflammatory, lipid-lowering, and protective against apoptosis [60].

Furthermore, the role of saponins in controlling hyperglycemia and ameliorating hyperinsulinemia has been proven, involving gene modulation of enzymes and transporters related to carbohydrate metabolism [61]. Other mechanisms proposed by experimental models include the inhibition of the activity and gene expression of glucose-6-phosphatase and hepatic glycogen phosphorylase, increased pyruvate kinase activity and inhibition of digestion and absorption of carbohydrates by reducing intestinal disaccharidases, inhibition of α-amylase and α-glycosidase activity, increased glycogen accumulation, and GLUT4 translocation in the membranes. All of them result in lower glucose and insulin concentrations and improved insulin resistance.

Phytic acid (phytate)

Phytic acid (phytate) is a natural component of foods of plant origin, mainly grains and seeds. It is the main form of phosphorus storage in seeds and is found in corn, wheat, barley, rice, and beans. Because it is negatively charged, it is able to bind strongly to metal cations of calcium, iron, potassium, magnesium, manganese, and zinc, forming insoluble complexes unavailable for intestinal absorption [62].

Although the literature emphasizes its performance as an antinutritional factor owing to mineral chelation and attenuated bioavailability of nutrients, recent studies have demonstrated potential benefits of phytate, including lowering the risk for NCDs [63,64].

The role of phytate in CVD is related to its effect on hypercholesterolemia. The proposed mechanism suggests a hypolipidemic effect that seems to be related to inhibiting hepatic enzymes involved in lipogenesis [65]. More specifically in coronary disease, phytate may contribute to reducing serum zinc concentrations and the ratio of zinc to copper. Phytate is known to preferentially bind to zinc and that these minerals compete for common transporters in the gut. Considering that disturbances in zinc and copper metabolism predispose to coronary disease, its effect on the balance of these minerals is presumed to be beneficial [64]. Moreover, diabetic rats supplemented with phytate [63] showed a decline in TGs and weight gain and an increase in HDL. The authors suggest that such effects could be beneficial in controlling diabetes, although the effects of supplementation in humans are still unclear.

Regarding the effect of phytate on glucose control, a reduction of glycemia and glycated hemoglobin in diabetic mice supplemented with phytate was demonstrated, highlighting the antihyperglycemic effect of this component [66]. The negative correlation between phytate intake and glycemic response could be modulated by insulin secretion. The mechanisms of action have not yet been fully established; phytate appears to regulate insulin secretion through its effect on calcium channels, specifically inhibiting the activity of serine threonine protein phosphatase, which, in turn, opens the calcium channels and triggers insulin release [65].

Finally, the use of phytate as an antioxidant has been related to its ability to chelate with iron and remove it from circulation. In this process, iron-hydroxyl radical formation and the suppression of iron-catalyzed lipid peroxidation would be blocked [67]. That way, it would be possible to reduce iron-mediated oxidative reactions, especially the formation of free radicals, thus avoiding cellular injury and DNA damage [65].

Final considerations

The mechanisms of non-nutrients against NCDs reviewed in the present work, such as antioxidant and anti-inflammatory action, a modulated antiatherogenic lipid profile (higher HDL-C, lower ox-LDL, and TGs), moderation in glucose and fat intestinal absorption, greater insulin sensitivity, and NO synthesis stimulation make it possible to explain the strong relationship between food and disease. The findings also reinforce food as a complex matrix capable of supplying the nutrients essential to life as well as dietary compounds with a beneficial synergic effect on health and NCD prevention. However, these non-nutrients do not yet have specific daily intake recommendations by international agencies. Thus, dietary non-nutrients represent a specific and potential strategy for the management of NCD.

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