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Biomarkers of the metabolic syndrome: influence of selected foodstuffs, containing bioactive components

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- ALA: α -linoleic acid
- ALAT: alanine aminotransferase
- BMI: body mass index
- CRP: C-reactive protein
- CVD: cardiovascular disease
- DHA: docosahexaenoic acid
- EGCG: epigallocatechin-3-gallate
- EPA: eicosapentaenoic acid
- GABA: gamma aminobutyric acid
- HDL: high-density lipoprotein
- HDL-c: HDL-cholesterol
- HOMA-IR: homeostasis assessment-insulin resistance index
- hs-CRP: high sensitivity-CRP
- IL: interleukin
- iNOS: inducible nitric oxide synthetase
- LDL: low-density lipoprotein
- LDL-c: LDL-cholesterol
- MCP-1: monocyte chemoattractant protein-1
- MDA: malondialdehyde
- MetS: metabolic syndrome
- MUFA: monounsaturated fatty acids
- NO: nitric oxide
- oxLDL: oxidized LDL
- PUFA: polyunsaturated fatty acids
- RBP-4: retinol-binding protein 4
- sICAM: soluble intercellular adhesion molecule

-TAG: triacylglyceride

-TC: total cholesterol

-TG: triglyceride

-TNF- α : tumor necrosis factor- α

-VLDL: very-low density lipoprotein

-VLDL-c: VLDL-cholesterol

Abstract

The influence of various non-nutritive bioactive foodstuffs and food components on the biomarkers of the metabolic syndrome in humans is critically reviewed.

Tea, coffee, cocoa, soy, olive oil, fruit and nuts are most of the time found to be effective in improving lipid profiles, CRP and adiponectin.

Spices (garlic, curcumin and cinnamon), carotenoids and the phytosterol/-stanols are frequently related to lower risk of metabolic syndrome and improved biomarkers.

Since food is a complex matrix and the heterogeneity of studied population and served diets are not always well-defined, this could explain some contradictory results found in literature.

Other factors jeopardizing definite conclusions are mentioned.

Introduction

Metabolic syndrome (MetS), also called “insulin resistance syndrome” (De Fronzo and Ferrannini 1991), “deadly quartet” (Kaplan 1989), or “syndrome X” (Reaven 1988), is characterized by abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol level, increased blood pressure, and elevated serum glucose concentration (Grundy et al. 2005).

Although the exact mechanism underlying metabolic syndrome has not yet been completely elucidated, many cross-sectional or longitudinal studies have shown that MetS is strongly associated with insulin resistance (Lann and LeRoith 2007), oxidative stress (Onat et al. 2006), inflammation (Festa et al. 2000), endothelial dysfunction (Isomaa et al. 2001) and risk of cardiovascular diseases (Lakka et al. 2002; Hajer et al. 2007).

The basis of this endemic is either a diet too often characterized by excessive consumption of saturated and trans-esterified fatty acids, simple sugars and salt, either a sedentary lifestyle or a combination of both.

Most research groups use a mixture of biomarkers as risk factors for the occurrence of metabolic syndrome (Mansoub et al. 2006). Metabolic overload (high caloric intake) evokes oxidative stress, which can lead to low-grade inflammation and result in a cardiovascular risk. Therefore, due to this sequence of actions, dividing the biomarkers of MetS into four groups (dyslipidemias, markers of oxidative stress and inflammation, and cardio-metabolic markers) seems quite logic. We have discussed the biochemical action and clinical significance of these markers in an extensive review article (Robberecht and Hermans 2016).

Effect of various types of diets on biomarkers of MetS are reviewed (Robberecht et al. 2016a), while in two other articles we discussed the influences of minerals, oligo and trace elements (Robberecht et al. 2016b) and of caloric intake, various food groups and vitamins (Robberecht et al. 2017) on the biomarkers of MetS.

While some review papers focus on the dietary management of the MetS beyond macronutrients (Minich and Bland 2008; Graf et al. 2010; Davi et al. 2010; Cicero et al. 2014; Cicero and Colletti 2015), here we intend to discuss some foodstuffs, spices, containing various biologically active components and their effect on biomarkers of MetS.

Literature is screened by using keywords “metabolic syndrome”, “biomarkers” in combination with the selected foodstuffs and bioactive components. References from 2000 onwards are used or some important previous references cited therein.

We have tried to limit this report to papers reporting reviews, meta-analyses, or original clinical trials studying influence of the foodstuffs with bioactive components on biomarkers in humans with MetS. However, the selection is not always that straightforward, since description of sampled population is sometimes poor defined.

Biological active food components

1. Introduction

Certain dietary components and various plants can help in the prevention or amelioration of MetS by assisting homeostatic mechanisms.

Functional foods are foods (or food constituents) providing health benefits beyond the expected nutritional function, and including prevention and treatment of a disease (Davi et al. 2010; Suhaila 2014). Nutraceuticals are those foods or compounds thereof, marketed in a pharmaceutical dosage form such as tablets or capsules. Unfortunately, terminology is confusing, and sometimes both terms are being interchanged (Espin et al. 2007; Rubio-Ruiz et al. 2013; Kaur et al. 2015; Brown et al. 2015; Cicero and Colletti 2015).

Also herbal-, food- or dietary supplements can contain those compounds, and sometimes they are referred to as phytochemicals or plant-derived therapeutics

One way of dividing them up into major classes can be as follows:

- dietary fibers (from fruit, beans, barley, oats)
- antioxidant vitamins and provitamins (vitamin C, vitamin E and carotenoids)
- polyphenols, also having antioxidant capacities (non-flavonoids, flavonoids and tannins, phyto-estrogens)
- ω -3 fatty acids
- spices (garlic, curcumin, cinnamon) (Cicero et Colletti 2015).

Key issues, such as bioavailability, metabolism, dose/response and toxicity of these food bioactive components are reviewed elsewhere (Espin et al. 2007; Ozen et al. 2012).

We are aware of the fact that bioactive components present are of various types of which some have different mechanisms of action and can display their activity in an additive, synergistic or antagonistic way. Sometimes there is a thin line between a nutraceutical and a drug. Therefore we have omitted the discussion on effect of fermented red yeast rice on biomarkers of the MetS (Patel 2016; Cicero et al. 2016), since this product can be classified as a food supplement or even as a drug.

2. Various foodstuffs

2.1. Tea

Although all types of *Camellia siniensis* derived beverages contain polyphenols, important differences exist between green, white and black tea.

Several different biologically active polyphenolic compounds might offer variable protection against a variety of human diseases.

The tea catechin epigallocatechin-3-gallate (EGCG) is generally considered to be the most active component (Lorenz 2013, Keske et al. 2015; Legeay et al. 2015). In cell cultures and animal models of obesity, tea components reduce adipocyte differentiation and proliferation, lipogenesis, fat mass, body weight, fat absorption, plasma levels of triglycerides, free fatty acids, cholesterol, glucose, insulin and leptin, as well as increase beta-oxidation and thermogenesis (Wolfram et al. 2006; Oh et al. 2009). Green tea extracts reduce adipogenesis by decreasing expression of transcription factor C/EBP α and PPAR γ during adipocyte differentiation (Yang et al. 2014).

Human studies report reduced body weight and fat (Vieira Senger et al. 2012; Zhong et al. 2015), as well as increased fat oxidation and thermogenesis, as confirmed in animal findings (Hursel et al. 2013). Green tea consumption (3 cups/day, 1 g/sachet) or extract supplementation (2 capsules/day) for 60 days significantly decreased body weight and BMI (Vieira Senger et al. 2012). Moreover it lowered lipid peroxidation (decreased malondialdehyde and hydroxynonenals) versus age- and gender-matched controls (Basu et al. 2010). Green tea (4 cups/day) and polyphenolic extracts (2 capsules/day) significantly increased plasma antioxidant capacity and whole blood glutathione versus controls after 8 weeks (Basu et al. 2013). This supports the hypothesis that green tea may provide antioxidant protection in MetS (Gao et al. 2015), but the optimal dose has not yet been established (Hosoda et al. 2003; Tsuneki et al. 2004).

An exact report on the composition of the tea or tested extract is often lacking, and therefore the tested dose (e.g. 2 capsules/day with the extract) offers no information on the amount of specific components responsible for the observed activity. Moreover, also indications like “1 g tea/sachet” yield little information, since time of contact and water temperature strongly influence the amount of dissolved compounds.

Pooled analysis of six studies exploring the association between tea consumption and MetS resulted in the conclusion of decreased odds of MetS for individuals consuming more tea (type of tea not specified; Marventano et al. 2016).

The cardiovascular health promoting effects are primarily attributed to the antioxidant properties of EGCG (Imai and Nakachi 1995; Pearson et al. 1998, Princen et al. 1998; Serafini et al. 2000; Nakachi et al. 2000; Sasazuki et al. 2000; Sano et al. 2004; Sung H et al. 2005; Basu et al. 2010; Basu et al. 2013), although research in recent years has also uncovered their prooxidant properties (Lorenz 2013).

LDL-oxidation is found to be decreased in most cases (Pearson et al. 1998, Serafini et al. 2000; Sung et al. 2005, Basu et al. 2010a) and soluble vascular cell adhesion molecule-1 was decreased (Sung et al. 2005). CRP-concentration (Vernarelli and Lambert 2013) and a lipid profile modulation have been observed (Pearson et al. 1998; Sasazuki et al. 2000; Vernarelli and Lambert 2013; Grosso et al. 2014; Onakpoya et al. 2014), while other studies report no differences (Princen et al. 1998; Sug et al. 2005; Wolfram et al. 2006; Mielgo-Ayuso et al. 2014, Zhong et al. 2015). Sometimes this beneficial effect is observed only in women (Grosso et al. 2015).

Rye-bread enriched with green tea extract (intake of 210 mg of EGCG) did not influence the lipid parameters (Bajerska et al. 2015).

On the other hand, one publication could be traced which mentioned that frequent tea drinking is a risk factor for the MetS (Yu et al. 2014), without a clear cause/effect relationship.

2.2. Coffee

Coffee is one of the most widely consumed beverages and rich in polyphenols, acting as antioxidants (Devasagayam et al. 1996; Shen 2012), but multiple mechanisms should underlie the beneficial effects of coffee consumption. Many different mechanisms have been proposed to contribute to the biological activity of polyphenols in affecting the MetS (Annuzzi et al. 2014; Amiot et al. 2016), including the regulation of cellular signals (Virgili and Marino 2008) and the modulation of the activity of numerous enzymes and redox-sensitive transcription factors.

Results of animal studies focusing on the effect of coffee consumption on the risk of MetS showed that supplementation attenuated the expected onset of an adverse profile in animals fed high-fat diets (Fukushima et al. 2009; Panchai et al. 2012a; Panchai et al. 2012b; Abrahao et al. 2013).

Human clinical and epidemiological studies and conclusions from review articles generally show an inverse association between coffee consumption and the risk of MetS (Hino et al. 2007; Matsuura et al. 2012; Takami et al. 2013; Mure et al. 2013; Uemura et al. 2013; Yesil and Yilmaz 2013; Nordestgaard et al. 2015; Shang et al. 2016), however the question of causality remains unsolved (Shang et al. 2016).

All components of MetS (blood pressure, glucose level, triglyceride concentration) except HDL-cholesterol were significant ($p < 0.01$) and inversely related to coffee consumption (Hino et al. 2007; Matsuura et al. 2012; Takami et al. 2013; Mure et al. 2013; Uemura et al. 2013; Yesil and Yilmaz 2013; Nordestgaard et al. 2015; Shang et al. 2016; Sarria et al. 2016).

The two longitudinal studies not showing statistically significant results were both from the same cohort (the Amsterdam Growth and Health Longitudinal Study) consisting of young persons with a low prevalence of MetS (Driessen et al. 2009; Balk et al. 2009). Therefore the lack of the association between coffee consumption and the MetS in that case might have been due to the specific characteristics of the investigated cohort, consisting of relatively healthy people.

Also in a Mediterranean population no direct association between caffeine intake and the biomarkers of MetS have been observed, however coffee and tea consumption was significantly related to reduced odds of MetS (Onakpoya et al. 2014).

Moderate coffee consumption showed a significant inverse association with MetS-related biomarkers possibly involving adiponectin, which is inversely associated with visceral fat accumulation (Mure et al. 2013).

Coffee consumption was also inversely associated with arterial stiffness (Uemura et al. 2013). This association may be partly mediated by reducing circulating triglycerides (Shang et al. 2016).

On the other hand, consumption of coffee, particularly instant coffee mix, may have harmful effects on MetS, perhaps deriving from a probable concomitant excessive intake of sugar and powder creamer (Kim et al. 2014).

The manuscript of Platt et al. (2016) claimed that caffeine impact on metabolic syndrome components is modulated by a CYP1A2 variant.

2.3. Cocoa

Cocoa (*Theobroma cacao*) is a dietary ingredient with worldwide popularity. It is often associated with the high-caloric confection and chocolate, but it is also consumed via diverse foods and beverages.

Mechanisms by which cocoa flavanols improve MetS and related disorders were recently published by Strat et al. (2016). A number of observational and clinical studies indicated that cocoa or cocoa-containing products may improve CVD-related risk factors such as LDL-oxidation, inflammation (Ding et al. 2006; Fernandez-Murga et al. 2011; Gu and Lambert 2013; Amiot et al. 2016), endothelial function (Davison et al. 2008; Davison and Howe 2015) and the blood lipid profile (Jia et al. 2010; Shrimpe et al. 2011; Tokede et al. 2011). Dose-response relationship (Uemura et al. 2013), as well as the underlying mechanisms of action still need to be clarified more (Gu and Lambert 2013).

Several clinical studies showed that cocoa increases HDL-cholesterol concentrations (Mursu et al. 2004; Baba et al. 2007; Mellor et al. 2010; Khan et al. 2012), although other studies did not confirm such a beneficial effect (Wan et al. 2001; Engler et al. 2004; Balzer et al. 2008; Muniyappa et al. 2008; Tokede et al. 2012). The reason for this still remains to be explained. However, amount of consumption (Buitrago-Lopez et al. 2011), type of chocolate and percentage of containing cocoa should be considered (Tokede et al. 2012). Polyphenol-rich dark chocolate offers metabolic benefits on biomarkers of cardiovascular risk (Almoosawi et al. 2012).

It is not clear whether flavonoids (Galleano et al; 2012) or possibly another bioactive component of cocoa (f.i., theobromine; Nuefinglerl et al. 2013) are responsible for the reported increase in serum or plasma HDL-cholesterol.

A randomized controlled trial proved that theobromine independently increased serum HDL-cholesterol concentrations (Nuefinglerl et al. 2013). However, to deliver 850 mg theobromine (the daily dose which was provided in that study) about 100 g dark or 200 g milk chocolate are needed (Smit 2011).

Combinations of whey protein isolate and cocoa polyphenols improved adiponectin level as was proven in a recent study (Campell et al. 2016).

2.4. Soy

Soy products, which are a rich source of antioxidants and isoflavones also contain specific proteins and peptides, which attracted significant attention for their possible health effects (Matthan et al. 2007).

The cholesterol-lowering effect of soy is one of the well-documented physiological effects.

a. Isoflavonoids

Earlier studies have attributed the health benefits of soy primarily to its isoflavonoids (Wong et al. 1998). This fraction, consisting primarily of genistein, daidzein and glycitein, has been shown to have a hypocholesterolemic effect in animals and humans (Potter 1998).

Although meta-analysis revealed that the isoflavonoid content of soy might be responsible for this, there is no direct dose-response relationship between soy isoflavone content and its lipid-lowering effect (Zhuo et al. 2004).

Data on the effects of separate isoflavones on metabolic health are limited (Amani et al. 2005). Some studies have indicated that genistein, as a main isoflavone in soy products, might affect cardiovascular health through its inhibitory effect on tyrosine kinase (Anderson et al. 2005).

b. Proteins and peptides

In addition to the isoflavonoids, many other compounds in soy products, such as saponins, beta-conglycinin (7S globulin) protein fractions, dietary fiber, and unsaturated fats might be beneficial. Some in vitro studies have shown that a 7S globulin protein present in soy possibly up-regulates LDL receptors thereby reducing serum LDL concentrations (Wong et al. 1998).

Regular consumption of soy proteins can result in significant reductions in total cholesterol (9.3 %), LDL-cholesterol (12.9 %), and triglycerides (10.5 %), with a small but insignificant increase (2.4 %) in high-density lipoprotein cholesterol. Linear regression analysis indicated that the threshold level of soy intake at which the effects on blood lipids became significant was 25 g.

Although the findings on lipid profiles are somewhat conflicting, the combined results of a meta-analysis have suggested significant reductions of 9 % in total serum cholesterol concentration, 13 %

in LDL-c, and 12 % in triglycerides with an average consumption of 47 g/day of soy protein (Potter 1998).

It has been hypothesized that also the unique amino acid profile of soybean might have an influence on the effects (Taku et al. 2007; de Souza Ferreira et al. 2011). Experimental data have shown hypercholesterolemic effects of lysine and methionine, but a hypocholesterolemic effect of arginine. Therefore, the higher arginine to lysine and methionine ratio in soy might explain, in part, its hypocholesterolemic effect (Cederroth and Nef 2009).

c. Soy, as a whole product

Soy bean is a whole-soy product that contains all beneficial ingredients of soy. Various soy products are obtained through different processing methods. Due to processing-induced ingredient loss, each product has different composition of soybean ingredients. For instance, alcohol extraction and acid precipitation used to produce soy protein results in isoflavone loss (Zhang et al. 2009). Other procedures can alter soy bean fiber, fat, sugars, phytic acid, and saponin content (Zhang et al. 2009).

The potential mechanisms by which soy protein and/or isoflavonoids induce a decrease of blood cholesterol concentrations include thyroid status, bile acid balance and the estrogenic effects of genistein and daidzein. Studies have further indicated that isoflavones exhibit antioxidant properties (Khan et al. 2013).

Findings on the effect of soy consumption on serum apolipoprotein levels in both normal and hyperlipidemic individuals are inconsistent (McVeigh et al. 2006; Blachier et al. 2010).

Earlier studies on soy and inflammation have shown conflicting results too (Blum et al. 2003; Beavers et al. 2009; Bakhtiary et al. 2012). It seems that the effects of soy consumption on inflammation are product-dependent. While the beneficial effects of soy bean and soy milk consumption on inflammation have been shown, textured soy protein or isoflavone supplements alone are reported to be neutral (Reinwald et al. 2010). Co-existence of unsaturated fats along with lecithin, isoflavones, essential fatty acids, phytosterols, polyphenols, inositol, and dietary fiber as well as other bioactive compounds make soy bean a more effective food than other soy products in improving metabolic abnormalities (Reinwald et al. 2010; Bakhtiary et al. 2012).

Consumption of soy and soy-products also seems to affect cardio-metabolic health to a variable extent, which sometimes was gender-dependent (Azadbakht et al. 2007a; Pan et al. 2010).

The reduction in cardiovascular risk in postmenopausal women was greater among producers of equol, an estrogen metabolite (Azadbakht et al. 2007a).

The reduced risk can occur via various components and mechanisms (lowering total and LDL-cholesterol and glucose; Simao et al. 2014), to which blood pressure lowering effect can be added. Increased adiponectin and NO values could be responsible for this effect (Simao et al. 2010; Simoa et al. 2012).

Studies are required to determine the optimal amounts of soy bean and soy protein for inclusion in the diets of patients with MetS (Azadbakht and Esmaildazeh 2012).

Experimental studies as well as randomized clinical trials have demonstrated a role for soy products in the management of MetS (Dyrskog et al. 2005; Azadbakht et al. 2007a; Azadbakht et al. 2007b; Azadbakht et al. 2007c; Bahls et al. 2011; Bakhtiary et al. 2012;). Bakhtiary et al. (2012) found that both textured soy protein or soy bean consumption for 12 weeks resulted in reduced levels of serum total- and LDL-cholesterol, apolipoprotein B100, and VLDL concentration in addition to increased

levels of serum apolipoprotein A1. However, the authors have failed to find significant effects on serum hs-CRP, fibrinogen, triglyceride, and HDL levels, as well as on blood pressure.

Azadbakht et al. (2007c) reported a similarity in the lipid profile, however they also observed beneficial effects of soy bean consumption on inflammatory biomarkers (2007b) and proved an enhanced antioxidant status (Azadbakht et al. 2007a).

In postmenopausal women with MetS on a soy diet, significant reductions in blood pressure, TG, CRP and sICAM were noted among equol (an estrogen metabolite) producers (Acharjee et al. 2015).

Supplementation of soy products in combination with other phytochemicals resulted in better lipid profiles (Lerman et al. 2008; Lerman et al. 2010; Jones et al. 2012; Lee et al. 2012, Guevara-Cruz et al 2012; Simao et al. 2014) or increased adiponectin (Guevara-Cruz et al. 2012).

2.5. Olive oil

Olive oil consumption has proven beneficial effects on lipid profile (Andersen-Vasquez et al. 2015), fatty acid composition (Mayneris-Perachs et al. 2014), insulin sensitivity, lipid and DNA oxidation (Mtjavilla et al. 2013, Ventarini et al. 2015), inflammation, endothelial function, thrombotic factors and blood pressure (Lopez-Meranda et al. 2008). Therefore olive oil is considered as a key food for preventing metabolic syndrome, related micro-inflammation (Viscogliosi et al. 2013) and a reduced cardiovascular risk (Ros et al. 2014; Covas et al. 2015).

Several studies have suggested that olive oil in hyperlipidemic patients could reduce the susceptibility of LDL to oxidation, not only because of its high monounsaturated fatty acid content (Ruidavets et al. 2007), but probably also because of the antioxidative activity of its phenolic compounds (Masella et al. 2001). Virgin olive oil containing phenolics (Rigacci et al. 2016) shows a more pronounced antioxidant effect on this LDL oxidation than refined olive oil (Fito et al. 2000; Sialvera et al. 2012; Oliveras-Lopez et al. 2014) and reduces the postprandial inflammatory response (Camargo et al. 2014).

Hydroxytyrosol, an ingredient of olive oil, reduces triglyceride accumulation and promotes lipolysis in adipocytes (Stefanon et al. 2016).

Vissers et al (2004) however claimed, after reviewing bioavailability and antioxidant effect of olive oil phenols, that there was no evidence that consumption of polyphenols in the amounts provided by dietary olive oil will protect LDL against oxidative modification to any important extent.

Virgin olive seems to repress *in vivo* expression of several pro-inflammatory genes (Camargo et al. 2010).

A Mediterranean dietary pattern, characterized by a high consumption of nuts and olive oil, has been associated with a reduced risk of MetS (Martinez-Gonzalez et al. 2013).

The relationship between Mediterranean diet, olive oil and MetS and potential mechanisms by which this food can help in disease prevention and treatment are discussed (Soriguer et al. 2007; Perez-Martinez et al. 2011).

An olive oil diet rich in MUFA, but with low α -linolenic acid (ALA) content, resulted after a 6-month period in reduced levels of total and LDL-cholesterol (Baxheinrich et al. 2012).

Olive oil consumption has only marginal beneficial effects on serum resistin levels in healthy men (Machowetz et al. 2008).

2.6. Fruit

This group contains a lot of different fruits, berries, juices, and phytochemicals. We intend to divide them in berries, citrus fruits and miscellaneous others, although any division has some limitations

(common use of term “berry”, instead of botanical use). The intention is not to go to different botanical plant parts, but rather categorize herbal foods according to their common consumption.

2.6.1. Berries

Interventional studies on the therapeutic roles of strawberries, blueberries and cranberries in MetS have demonstrated the following effects: strawberries lowered total and LDL-cholesterol, but not triglycerides and decreased biomarkers of atherosclerosis (malondialdehyde and adhesion molecules); blueberries lowered systolic and diastolic blood pressure and lipid oxidation and improved insulin resistance; and low-caloric cranberry juice selectively decreased biomarkers of inflammation (adhesion molecules) in MetS (Basu and Lyons 2012).

These observations could be due to an up-regulation of endothelial nitric acid synthase activity, reduction of renal oxidative damage, and inhibition of carbohydrate digestive enzymes or angiotensin-converting enzyme by the berries (Basu and Lyons 2012).

Strawberries are an especially good source of phytochemicals, particularly anthocyanins and ellagic acid, which have potent antioxidant and anti-inflammatory functions (Hannum et al. 2004).

Short-term supplementation of freeze-dried strawberries appeared to exert hypocholesterolemic effects and decreased lipid peroxidation in women with MetS (Basu et al. 2009).

Plasma oxidized LDL, serum malondialdehyde and hydroxynonenal concentration decreased in a group with MetS eating blueberries. The authors claimed that selected features of the syndrome and related cardiovascular risk factors can be improved at dietary achievable dosis (Basu et al. 2010b).

Vascular cell-adhesion molecule-1 levels decreased after strawberry supplementation (50 g/day) (Basu et al. 2010c).

Cranberry juice significantly increased plasma antioxidant capacity and decreased oxidized low-density lipoprotein and malondialdehyde. However, the consumption does not cause a significant improvement in blood pressure, glucose, lipid profiles, C-reactive protein, and IL-6 (Basu et al. 2011). Folic acid and adiponectin were increased and homocysteine and oxidative stress were reduced (Simao et al. 2013).

On the other hand, low-calorie cranberry juice lowers markers of cardiometabolic risk, including blood pressure and circulating CRP, triglyceride, and glucose concentration in healthy adults (Novotny et al. 2015).

In addition to the widely recognized antioxidant power of berry extracts, both commercial berry varieties and wild species have been linked to hypoglycemic activity, inhibition of adipogenesis, amelioration of CVD risk factors, anti-inflammatory capacity and ability to induce satiety and counteract overweight (Lila et al. 2011). Proanthocyanidins or anthocyanins may be the active agents.

Lowering the levels of alanine aminotransferase (ALAT) may be regarded as nutritionally significant by enhancing the liver function (Lehtonen et al. 2010), but berries and berry fractions have various other but slightly positive effects on vascular cell adhesion molecule and intercellular adhesion molecules (Lehtonen et al. 2011).

Consumption of fruit pulp from berries of *Euterpe oleracea* Mart. resulted in a reduction of total cholesterol, but no effect on blood pressure was observed. hs-CRP was observed (Udani et al. 2011).

Bilberries (*Vaccinium myrtillus*) reduce low-grade inflammation in individuals with features of MetS: lower hs-CRP, IL-6, IL-12 and lipopolysaccharides (Kolehmainen et al. 2012). Diets high in fatty fish, bilberries and whole grain products lower plasma E-selectin and hs-CRP (de Mello et al. 2011). A recent review indicates that regular long-term consumption of different berries could potentially delay the progression of MetS and comorbidities (Kowalski et al. 2016).

2.6.2. Citrus fruits

Citrus flavonoids constitute an important source of flavonoids and were found to display strong anti-inflammatory and antioxidant activities. Several lines of investigations suggest that naringin supplementation is beneficial for the treatment of obesity, diabetes, hypertension, and MetS. A number of molecular mechanisms underlying these activities have been elucidated (Alam et al. 2014). Their effect on obesity and MetS still remains to be fully established. Naringenin is claimed to prevent dyslipidemia, apoB overproduction and hyperinsulinemia in LKL-receptor null mice with diet-induced insulin resistance (Mulvihill et al. 2009).

Daily intake of 300 ml of a citrus-based juice during 6 months improved the biomarkers of oxidative stress in MetS (Bernabé et al. 2013). Also lipid profile and inflammation markers were improved after consumption of a citrus-based juice (Mulero et al. 2012).

Hesperidin, a citrus flavonoid glycoside, and its metabolite hesperetin have vascular actions with health benefits. Hesperidin treatment increased flow-mediated dilation and reduced concentration of circulating inflammatory biomarkers (hs-CRP, serum amyloid A protein and soluble E-selectin) (Rizza et al. 2011).

Daily consumption (twice a day) of grape fruit for 6 weeks reduces urine F2-isoprostanes in overweight adults but has no effect on plasma hs-CRP or soluble vascular cellular adhesion molecule-1 (Dow et al. 2013).

Pure orange juice consumption is associated with lower total and LDL-cholesterol and LDL-cholesterol serum levels (O'Neil et al. 2012a).

2.6.3. Other fruits

Higher intakes of fruit and vegetables are associated with a lower risk of MetS. This may be the result of lower CRP concentrations (Esmailzadeh et al. 2006). However, encapsulated fruit and vegetable fruit powder concentrates did not alter insulin or glucose measures in a sample of adults with MetS (Alli et al. 2011).

A meta-analysis of randomized controlled trials suggested that there is an inverse association between fruit and vegetable consumption and diastolic blood pressure in MetS-patients (Shin et al. 2015).

Consumption of 46 g of lyophilized grape powder resulted in an increased level of plasma adiponectin, and IL-10 and in increased expression of inducible nitric oxide synthase (iNOS) only in patients without dyslipidemia. This suggested that grape consumption shows an anti-oxidative and anti-inflammatory action in absence of the inflammatory status associated with dyslipidemias (Barona et al. 2012). It increases anti-inflammatory markers and upregulates nitric oxide synthase even in the absence of dyslipidemias in men with MetS (Barona et al. 2012).

Resveratrol is a stilbene with main dietary sources grapes, rhubarb and red wine. Supplementation with this compound in various amounts and duration does not result in significant changes of

oxidative and inflammatory markers, neither did it change the lipid profiles (Fujita et al. 2011; Dash et al. 2013; Mendez-del Villar et al. 2014; Van der Made et al. 2015).

Consumption of fruit and vegetables in the US were lower among people with MetS (Ford et al. 2003). These foodstuffs contribute to an increased dietary intake of antioxidants, resulting in an oxLDL decrease. Moreover, a decrease in BMI, waist circumference, fat mass and triglyceride levels was associated with the decreased oxLDL levels (De la Iglesia et al. 2013).

The presence of antioxidant vitamins (Robberecht et al. 2017) in fruit may be a contributing factor to a risk reduction of MetS as was observed in a long-term supplementation study. Baseline serum antioxidant concentrations of β -carotene and vitamin C were negatively associated with the risk of MetS (Czernichow et al. 2009).

A mangosteen juice blend reduced CRP-levels, but other markers of inflammation (inflammatory cytokines) or a marker of lipid peroxidation (F_2 -isoprostane) did not show any significant differences when compared with placebo (Udani et al. 2009).

2.7. Nuts

The commonly used term "nut" encompasses a wide range of seeds that based on botanical definitions, may not actually be nuts. While hazelnuts meet the botanical definition of nut, almonds, pistachios and walnuts, which are all seeds of stone fruits or drupes, do not. Despite this inconsistency, this variable group of seeds has been clustered together under the collective term "tree nuts".

Tree nuts are healthy foods because of their fatty acid profile (low in saturated fats and high in mono- and polyunsaturated fats (MUFA and PUFA, respectively) and low available carbohydrate content, as well as being good sources of vegetable protein, fibre, phytosterols, polysterols, vitamins and minerals (Phillips et al. 2006; Segura et al. 2006).

Nuts may therefore be a useful component of a dietary strategy aimed at improving the risk factors of the MetS, diabetes and CVD (O'Neil et al. 2015; Brown et al. 2015).

The ability of nuts to improve the blood lipid profile (Blanco Mejia et al. 2014) and reduce the CVD risk is now well established (Kendall et al. 2010; Lee et al. 2014).

Pooled analyses of clinical trials showed that nut intake is inversely related to triglyceride concentrations only in subjects with hypertriglyceridemia. An inverse association was found between the frequency of nut consumption and the incidence of MetS (Salas-Salvado et al. 2014).

Out-of-hand nut consumption (1/4 oz or more per day) is associated with higher HDL-cholesterol and lower CRP-levels (O'Neil et al. 2012b). This biomarkers of low-grade inflammation (CRP), together with leucocyte and platelet count) is reduced in nut consumers (Bonaccio et al. 2015).

Compared with a low-fat diet, a Mediterranean diet enriched in nuts (Salas-Salvado et al. 2008), or olive oil and nuts (Babio et al. 2014) could be beneficial for MetS management (Urpi-Sarda et al. 2012). Nuts and virgin olive oil are regarded as key foods of the Mediterranean diet affecting inflammatory biomarkers (IL-6, TNF-receptor, intercellular adhesion molecule 1), related to atherosclerosis (Urpi-Sarda et al. 2012). Probably this could be explained by the moderation of inflammation and oxidation, resulting in an improved endothelial function (Salas-Salvado et al. 2008). Protection against LDL oxidation by nut intake has been documented in some, but not all, clinical studies (Mukuddem-Petersen et al. 2007; Lopez-Uriarte et al. 2010). Regarding inflammation, cross-sectional studies have shown that nut consumption is associated with lower concentrations of

circulating inflammatory molecules and higher levels of adiponectin, a potent anti-inflammatory adipokine (Ros 2009).

Short-term walnut consumption increased circulating total adiponectin and apolipoprotein A concentrations, but does not affect other markers of inflammation in obese humans with MetS (Aronis et al. 2012). A diet enriched with this type of nuts reduced fasting non-HDL-cholesterol and apolipoprotein B in healthy subjects (Wu et al. 2014).

Beneficial effects of walnut consumption on vascular activity and endothelial function may be ascribed to several constituents of the nut: L-arginine, α -linolenic acid and polyphenolic antioxidants (Katz et al. 2012). The effect on haemostatic factors was not observed for high walnut and cashew diets (Pieters et al. 2005).

The inclusion of 2 portions of pistachios in a moderate-fat diet favourably affects the cardiometabolic profile (lower LDL level and TAG/HDL-ratio) (Holligan et al. 2014).

Contradictory results found in literature [a weak (Jaceldo-Siegl et al. 2014), no correlation (Mukuddem-Petersen et al. 2007) or only an improved insulin sensitivity (Casas-Agustench et al. 2011)] could be due to the variability of the diet and additional components (olive oil, nuts).

Table 1 summarizes most important effect of the various foodstuffs on biomarkers of MetS.

3. Spices

3.1. Garlic

Garlic (*Allium sativum*) belongs to the group of plants with medicinal and health supporting activity. Garlic health benefits result from the content of over 200 biologically active substances (Swiderski et al. 2007).

Individuals with MetS frequently have significantly higher levels of IL-6, TNF- α and lower levels of adiponectin, than those without MetS (Swiderski et al. 2007; Maury et al. 2010; Koster et al. 2010; Chakraborty et al. 2010). Of the clinical trials conducted to evaluate the effect of garlic on inflammatory cytokines, three have shown that garlic has an effect on these biomarkers (Williams et al. 2005; Van Doorn et al. 2006; Sharifi et al. 2010). One study (Gomez-Arbelaez et al. 2013) claimed that 12 weeks administration of aged garlic extracts increased plasma adiponectin in patients with MetS. This suggests that garlic might be useful to increase this biomarker and prevent cardiovascular complications in individuals with MetS.

Supplementation of aged black garlic (6 g/day for 12 weeks) reduced atherogenic markers (increased HDL-cholesterol and decreased apo-lipoprotein B) in patients with mild hypercholesterolemia (Jung et al. 2014).

Garlic, fermented with *Monascus pilosus*, decreased triglyceride and cholesterol in serum of normal to mildly hyperlipidemic individuals (Higashikawa et al. 2012).

Human reports are quite scarce (Hosseini and Hosseinzadeh 2015), however, studies in rats demonstrate that raw garlic homogenate (Padiya et al. 2011; Al-Rasheed et al. 2014) or S-methyl-L-cysteine, a hydrophilic cysteine-containing compound found in garlic (Thomas et al. 2015), is

effective in improving insulin sensitivity while attenuating MetS and oxidative stress in fructose-fed rats.

The abundant data in literature on the beneficial influence of garlic on lipid parameters in animal studies are not confirmed in clinical trials, maybe due to 1) the doses of garlic used in the human trials are far below those used in animal studies; 2) the different garlic products (fresh or cooked, aged or fresh, fermented, black garlic or garlic extracts) (Gorinstein et al. 2005), which are composed of different organosulfur compounds, of which the concentration changes after the treatment; 3) the omitted importance of bioavailability; 4) the different response to garlic by specific groups, and 5) soil composition, in which the garlic is cultivated (Zheng et al. 2015).

3.2. Curcumin

Curcumin (diferuloylmethane) is a yellow-orange pigment of *Curcuma longa* rhizomes (turmeric). This molecule has been shown to be safe (Di Pierro et al. 2015) and interact with multiple molecular targets that are involved in the pathogenesis of MetS (Sahebkar 2013) and other diseases (Pulido-Moran et al. 2016).

Curcumin has antihyperglycemic and insulin sensitizer effects (Ghorbani et al. 2014).

The anti-diabetic activity was partly due to the induction of heme-oxygenase-1 activity (Son et al. 2013).

Other experiments demonstrated the lipid-lowering effect of curcumin in cell culture and animal models (Yao et al. 2014) or of curcumin or a curcuminoids-piperine combination in humans (Panahi et al. 2014; Yang et al. 2014). Curcumin improved serum levels of adiponectin and leptin in patients with MetS (Panahi et al. 2016).

A systemic review and meta-analysis of randomized controlled trials investigating the effects of curcumin on blood lipid levels proved that there was apparently no effect when considering heterogeneous populations (Sahebkar et al. 2014). Therefore, proposed cardiovascular protective effects of curcumin could be attributed to mechanisms other than lipid lowering and HDL-C enhancing activities. Some examples may be improvement of lipid peroxidation (Soni et al. 1992) and LDL-oxidation (Xu et al. 2007), platelet aggregation (Mayanglambam et al. 2010), thrombosis (Srivastava et al. 1985; Shah et al. 1999), vascular smooth muscle cell proliferation (Chen et al. 1998), endothelial dysfunction (Ramaswanmi et al. 2004; Rungseesantivanon et al. 2010) and inflammation (Jurenka 2009). Curcumin is considered as an orally applied blocker of TNF and other pro-inflammatory biomarkers (Aggarwal et al. 2013)

Studies to prove that curcumin can be used as an alternative approach against MetS have involved a small number of subjects and been of short duration (Perez-Torres et al. 2013). Future studies are needed to prove the preventive effect.

The possible limited bioavailability of this compound and the combination with other components also ought to be taken into account (Cherniak 2011). Very recently a manuscript reviews the essential medicinal chemistry of curcumin and provides evidence that curcumin is an unstable, reactive, nonbioavailable compound (Nelson et al. 2017).

3.3. Cinnamon

Common cinnamon (*Cinnamomum verum*, *C. zeylanicum*) has a long history of use as a spice, flavoring agent, preservative, and pharmacological agent. It is traditionally used to treat elevated blood sugar levels (Broadhurst et al. 2000).

Different publications deal with this spice on reducing risk factors associated with diabetes (Khan et al. 2003), MetS and cardiovascular disease in animal models (Couturier et al. 2010) and man (Ziegenfuss et al. 2006; Qin et al. 2010; Power et al. 2011; Shen et al. 2012; Cicero et al. 2014). Especially lipid profiles are improved (Khan et al. 2003).

Table 2 summarizes most important effect of spices on biomarkers of MetS.

4. Specific biologically active components in foodstuffs

We have selected some specific groups of biologically active compounds with promising effects on the biomarkers of MetS. Representatives of a certain group show similar activities, thus, although the compounds are present in various foodstuffs, we chose to discuss these groups separately.

4.1. ω -3 fatty acids

Reviews on the role of ω -3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases are published (Carpentier et al. 2006; Gillingham et al. 2011; Hosseinpour-Niazi et al. 2015).

Beneficial effects of type of fatty acids on lipid profiles (Ebrahimi et al. 2009; Pirillo et al. 2013; Tardiva et al. 2015; Bays et al. 2015), markers of inflammation (Ebrahimi et al. 2009; Khorson et al. 2014; Tardiva et al. 2015, Tortosa-Caparros et al. 2016; Masquío et al. 2016) or autoimmunity (Ebrahimi et al. 2009) have been published and very recently reviewed (Robberecht et al. 2017).

4.2. Phytosterols and stanols

The term “phytosterols’ refers to sterols and stanols, lipophilic triterpenes of plant origin (Rondanelli et al. 2013).

Plant sterols and stanols are structurally related to cholesterol, but are characterized by an extra ethyl (sitosterol) or methyl group (campesterol) in the side chain (Grundy 1983; Normen et al. 2000). Sitosterol, campesterol and stigmasterol are the most common plant sterols in nature (Heinemann et al. 1993). Stanols, like sitostanol and campestanol are saturated plant sterols, which are found in nature in much smaller amounts than plant sterols.

Recent meta-analyses have summarized the results of more than 100 randomized clinical trials and have established that LDL-cholesterol is reduced by 9-12 % with consumption of phytosterol-fortified foods at doses of 2-3 g/day (Cofan and Ros 2015).

Molecular actions of phytosterols and stanols in synthesis and absorption of cholesterol (Assmann et al. 2007; Calpe-Berdiel et al. 2009) or lipoprotein metabolism (Plat and Mensink 2009; Gylling and Simonen 2015) are published.

It seems obvious that the most atherogenic lipoprotein particles are diminished by phytosterol and stanol treatment (Gylling and Simonen 2015).

After 2 months supplementation with phytosterols and -stanols, a significant reduction in total cholesterol, LDL-cholesterol, small and dense LDL levels, as well as, apoB and triglyceride concentrations were observed. No differences were found in levels of HDL-c, apoA1, glucose, CRP, fibrinogen levels and blood pressure (Sialvera et al. 2012).

One publication claimed that a low intestinal cholesterol absorption is associated with a reduced efficacy of phytosterols as hypolipemic agents in patients with MetS (Hernandez-Mijares et al. 2011),

which could explain the observations of Ooi and coworkers, who did not observe an influence of plant sterol supplementation on lipid or lipoprotein metabolism (Ooi et al. 2007).

Phytosterols and/or stanols are claimed to improve endothelial dysfunction in subjects at risk for cardiovascular diseases (Baumgartner et al. 2011).

Regular intake of phytosterols-enriched food did not significantly change CRP, but further studies with higher doses may provide more definite conclusions on a potential anti-inflammatory effect of this phytosterol intake (Rocha et al. 2007).

Supplementation does not affect plasma antioxidant capacity in patients with MetS (Sialvera et al. 2013).

Nutritional supplementation with essential amino acids and phytosterols (Coker et al. 2015), as well as with soy protein, phytosterols, hops *rho* iso-alpha acids and *Acacia nilotica* (gum Arabic tree) proanthocyanidins may reduce risk for MetS and cardiovascular disease in overweight individuals with hyperlipidemia (Lerman et al. 2010) or hypercholesterolemia (Lerman et al. 2008).

Low glycemic index diet with 30 g soy protein and 4 g of phytosterols/day showed statistically significant decreases of total cholesterol (15 %) and triglycerides (45 %) (Lukaczer et al. 2006).

Consumption of a plant stanolester-containing spread by moderately hypercholesterolemic patients reduced TC, LDL-c, and also the inflammation marker hs-CRP (Athiros et al. 2011).

Intake of fermented milk products containing lactotripeptides and plant sterol esters showed a lipid-lowering effect of borderline significance (Hautaniemi et al. 2015).

4.3. Carotenoids

Carotenoids (lutein, zeaxanthin, cryptoxanthin, lycopene, α - and β -carotene, and vitamin A and retinol) are components primarily from plants and their chemistry, metabolism, absorption, nutritional value and allied health claims are comprehensively reviewed (Perveen et al. 2015). Some have shown to be potent antioxidant nutrients, which play a role in MetS (Gregorio et al. 2016).

Researchers working in this field should carefully check the components studied in the experiments (retinol, β -carotene, vitamin A, zeaxanthin, lutein or lycopenes), before taking up references into their conclusions.

Total carotenoid intakes were inversely related to adiposity (Zulet et al. 2008), subclinical inflammation (Zimmerman and Aeberli 2008) and risk of MetS (Sluijs et al. 2009).

Inverse association of serum concentration of carotenoids with MetS was evident (Sugiura et al. 2008; Czernichow et al. 2009; Villaca Chaves et al. 2010; Suzuki et al. 2011; Li et al. 2013; Liu et al. 2014; Kabat et al. 2015; Sugiura et al. 2015; Wei et al. 2016), in smokers (Sugiura et al. 2008), as well as in non-smokers (Suzuki et al. 2011).

A Mediterranean-style low glycemic-load diet increases plasma carotenoids and decreases LDL-oxidation in women with MetS (Barona et al. 2012). Higher circulating plasma levels of carotenoids resulted in higher levels of anti-inflammatory cytokine IL-10 and lower MDA (Azzini et al. 2011). Total carotenoids were inversely related to HOMA-IR (Beydoun et al. 2012) and CRP (Beydoun et al. 2012; Zeba et al. 2013) in MetS patients.

There was a positive association of plasma β -carotene concentration with adiponectin in obese subjects (Ben Amara et al. 2015) and leptin and RBP-4 in overweight children (Zimmerman and Aeberli 2008).

Plasma vitamin A levels (Godala et al. 2014; Teske et al. 2014), as well as skin carotenoid concentration (Zhang et al. 2012; Holt et al. 2014) were significantly lower in MetS patients than in healthy individuals.

Egg intake, with the carotenoids lutein and zeaxanthin (Andersen 2015) improves carotenoid status and results in increased plasma HDL-cholesterol in adults with MetS (Blesso et al. 2013).

Administration of natural astaxanthin lowers triglycerides and increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia (Yoshida et al. 2010).

A recent systematic review and meta-analysis claimed that higher lutein concentration was associated with a lower risk of MetS (Leermakers et al. 2016).

Most of the time these studies are observational (Leermakers et al. 2016), therefore a large population-based prospective cohort study do not support the hypothesis that lutein intake early in life has a beneficial role for later cardio-metabolic health (Leermakers et al. 2015).

Longitudinal studies may further help to determine whether the inverse association for the various carotenoids is causally related to the MetS, or a result of the pathology (Coyne et al. 2009).

Two publications could be traced, where no association was found between the dietary carotenoid (Wei et al. 2015) or serum vitamin A (Suriyaprom et al. 2014) and MetS.

The most probable explanation for this could be the fact that most of the time more than one carotenoid form is taken in and also combinations of biologically active components (Baroni et al. 2012; Park et al. 2015; Silveira et al. 2015) can jeopardize the conclusions.

This is the best illustrated by the red-fleshed sweet orange juice, where the antioxidant activity of citrus flavonoids and carotenoids are added to the lycopene content of this type of juice, resulting in a decreased LDL-cholesterol and CRP-level (Silveira et al. 2015).

Table 3 summarizes most important results of the biologically active components on biomarkers of MetS.

Conclusion

Tea, coffee, cocoa, soy, olive oil, fruit (berries and juices) and nuts are most of the time found to be effective in improving lipid profiles (TC, TG, HDL-c), the inflammatory marker CRP and the cytokine adiponectin.

The potential role of green tea catechines in the prevention of MetS can result from 1) a reduction of body fat, 2) improved glucose tolerance, 3) maintaining a healthy cardiovascular system by the antioxidant activity and 4) blood pressure control (Thielecke and Boschmann 2009).

Because of the cholesterol- and triglyceride-lowering effects (Plat et al. 2009), and this in a dose-dependent manner (Sirtori et al. 2009) plant sterols/stanols are incorporated nowadays into a wide variety of food products, referred to as functional foods (de Jong et al. 2003).

Key points to maximum effectiveness and safety are the following: a) plant sterols should be taken with meals; b) the optimal dosage is 2-2.5 g/day in a single dose (more than 3 g/day has not been found to have any additional effect and increases the risk of side effects); and, 3) the food matrix used to dissolve the sterols should contain a certain amount of fat (like e.g. milk-based matrix)

(Rondanelli et al. 2013). The treatment may be considered 1) in individuals with high cholesterol levels at intermediate or low global cardiovascular risk who do not qualify for pharmacotherapy, 2) as an adjunct to pharmacologic therapy in high and very high risk patients who fail to achieve LDL-c targets on statins or are statin-intolerant, 3) and in adults and children (>6 years) with familial hypercholesterolaemia (Gylling et al. 2014).

The contradictory results sometimes found in literature could be due to the variability of the diet with additionally or synergistically/antagonistically acting other components. The effects on MetS may be due to the entire dietary pattern, rather than to the individual food components.

Also for the same foodstuff (tea), which contains polyphenols, important differences exist between green, white and black tea.

Most of the time limited information on bioavailability is available.

Furthermore the studied population, the duration and size of the served portions are influencing factors. Fruits and nuts have different bioactive components with varying content (antioxidants, MUFAs, carotenoids, vitamins and trace elements). Sometimes a component, not taken into consideration, may be responsible for the observed effect. The high selenium content of Brazil nuts may be acting by enhancing the selenium status (Thomson et al. 2008), resulting in an improvement of lipid profiles, oxidative and microvascular markers (Maranhao et al. 2011).

And finally, more definite conclusions are limited due to the set-up of some trials. Cross-sectional studies restrict the interpretation of the observed associations in terms of cause and effect.

Longitudinal studies are required for further investigation. Also a single assessment of blood samples or food intake may introduce some errors.

Significant between-study heterogeneity (Blanco Mejia et al. 2014) plays an additional role. Not only a low amount of patients, but also a variation in description of the studied population. This can vary from MetS, hypercholesterolemic (Blum et al. 2003; Wang-Polagruto et al. 2006; Matthan et al. 2007; Lerman et al. 2008; Cicero et al. 2016), obese (Davison et al. 2008; Udani et al. 2009; Villaca Chaves et al. 2010; Lehtonen et al. 2011; Teske et al. 2014; Bajerska et al. 2015), overweight (van Doorn et al. 2006; Zimmermann et al. 2008; Lehtonen et al. 2011; Udani et al. 2011; Coker et al. 2015; Van der Made et al. 2015), people with dyslipidemia (Masella et al. 2001; Yoshida et al. 2010; Tardiva et al. 2015) risk of MetS (Davi et al. 2010) to diabetics (Mellor et al. 2010).

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Table 1: Effect of various foodstuffs on biomarkers of MetS

Foodstuff	Specification	Risk of MetS	Biomarkers	Ref.
tea	six studies - - - - - -	decreased increased - - - - no difference	- - oxLDL↓ cell adhesion molecule↓ CRP↓ improved lipid profile -	Imai et al. 1995 Devasagayan et al. 1996 Nakachi et al. 2000; Vernarelli et al. 2013; Basu et al.2013 Vernarelli et al. 2013 Grosso et al. 2014 Princen et al. 1998, Serafini et al. 2000; Sasazuki et al. 2000; Sano et al. 2004, Grosso et al. 2014; Mielgo-Ayuso et al. 2014; Onakpoya et al. 2014; Grosso et al. 2015 Serafini et al. 2000Oh et al. 2009;; Vernarelli and Lambert 2013; Bajerski et al. 2015
coffee	- - - -	decreased - no relation reduced odd - -	- TG↓, HDL-c↑ - adiponectin↑ TG↓	Imai et al. 1995; Matsuuraa et al. 2012; Takami et al. 2013; Mure et al. 2013; Uemura et al. 2013; Yesil et al. 2013; Nordestgaard et al. 2015; Shang et al. 2016; Sarria et al. 2016 Driessen et al. 2009; Matsuuraa et al. 2012 Balk et al. 2009; Kim et al. 2014 Grosso et al. 2015 Uemura et al. 2013 Sarria et al. 2016
cocoa	- - - polyphenol-rich chocolate flavonoids theobromine	- - no effect - -	oxLDL↓ HDL-c↑ improved cardiomarkers HDL-c↑ HDL-c↑	Davison et al. 2008; Fernandez-Murga et al. 2011; Gu and Lambert 2013; Amiot et al. 2016 Wan et al. 2001; Mursu et al. 2004; Wang-Polagruto et al. 2006; Mellor et al. 2010; Khan et al. 2012 Engler et al. 2004; Balzer et al. 2008. Muniyappa et al. 2008; Buitrago-Lopez et al. 2011; Tokede et al. 2012 Galleano et al. 2012 Nuefingerl et al. 2013 Smit 2011
soy	isoflavonoids protein/peptides protein/peptides	- - -	TC↓ HDL-c↑ TC↓, LDL-c↓	Zhuo et al. 2004 Potter 1998 Zhuo et al. 2004, Reinwald et al. 2010

	protein/peptides protein/peptides arginine ↑	- - -	TC ↓ apoA1 ↑, apoB100 ↓ TC ↓	Zhuo et al. 2004 Reinwald et al. 2010 Cederroth et al. 2009; Zhang et al. 2009; de Souza Ferreira et al. 2011
	beans beans diet +phytochemicals	- - - -	improved lipid profile inflammation markers ↓ TG ↓, CRP ↓, sICAM ↓ improved lipid profile	Bahls et al. 2011 Bahls et al. 2011 Lerman et al. 2008 Lerman et al. 2010; Jones et al. 2012; Lee et al. 2012; Azadbakht and Esmailzadeh 2012; Guevara et al. 2012; Simao et al. 2014; Anderson-Vasquez et al. 2015
	+phytochemicals	-	adiponectin ↑	Simao et al. 2014
olive oil	- - diet	- lower -	improved lipid profile - TC ↓, LDL-c ↓	Mayneris-Perxachs et al. 2014 Ros et al. 2014 Machowetz et al. 2008
fruit	strawberries strawberries strawberries cranberry juice cranberry juice bilberries citrus fruit citrus fruit grape fruit orange juice mangosteen	- - - - - - - - - - -	TC ↓ LDL-c ↓ atherosclerosis ↓ adiponectin ↑, homocysteine ↓ CRP ↓, TG ↓ hs-CRP ↓, IL-6 ↓, IL-12 ↓ oxidative stress ↓ hs-CRP ↓, amyloidA ↓, selectin ↓ no effect on hs-CRP TC ↓, LDL-c ↓ CRP ↓	Hannum et al. 2004; Basu et al. 2010a Hannum et al. 2004 Hannum et al. 2004; Basu et al. 2010b Novotny et al. 2015 Lila et al. 2011 Kohlemainen et al. 2012 Bernabé et al. 2013 Riza et al. 2011 Dow et al. 2013 O'Neil et al. 2012a Udani et al. 2009
nuts	high walnut, cashew nut - - - walnut walnut Brazil nut Brazil nut	- - - - - - -	no effect improved lipid profiles HDL-c ↑, CRP ↓ adiponectin ↑ adiponectin ↑, apoA ↑ apoB ↑, non-HDL-c ↓ improved lipid profiles oxidative markers ↓	Mukuddem-Petersen et al. 2007 Lee et al. 2014 O'Neil et al. 2012b Ros 2009 Aronis et al. 2012 Wu et al. 2014 Maranhao et al. 2011 Maranhao et al. 2011

apoA1: apolipoprotein A1; apoB: apolipoproteinB; apoB100: apolipoprotein B100; CRP: C-reactive protein; HDL-c: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity CRP; IL-6: interleukin-6; interleukin-10; LDL-c: low-density lipoprotein cholesterol; non-HDL-c: non-HDL-cholesterol; sICAM: soluble intercellular adhesion molecule; TC: total cholesterol; TG: triglycerides

Table 2: Effect of spices on biomarkers of MetS			
Type of spice	Risk of MetS	Biomarkers	Ref.
garlic	no effect	inflammatory cytokines	Sharifi et al. 2010
aged garlic	-	adiponectin↑	Gomez-Arbelaez et al. 2013
aged black garlic	-	HDL-c↑, apoB↓	Jung et al. 2014
fermented garlic	-	TG↓, TC↓	Higashikawa et al. 2012
curcumin	-	improved lipid profiles	Yang et al. 2014
-	-	adiponectin↑, improved leptin	Panahi et al. 2016
-	-	no effect on lipid profile	Sahebkar et al. 2014
cinnamon	lower	-	Ziegenfuss et al. 2006; Qin et al. 2010
			Power et al. 2011
			Shen et al. 2012
			Cicero et al. 2014
	-	improved lipid profiles	Khan et al. 2003
apoB: apolipoprotein B; HDL-c: high-density lipoprotein-cholesterol; TC: total cholesterol; TG: triglycerides			

Table 3: Effect of biological active components in foodstuffs on biomarkers of MetS			
Component	Risk of MetS	Biomarkers	Ref.
ω-3 fatty acids	-	improved lipid profiles	Ebrahimi et al. 2009 Pirillo et al. 2013 Tardiva et al. 2015 Bays et al. 2015 Robberecht et al. 2017
-	-	markers of inflammation↓	Ebrahimi et al.2009 Tardiva et al. 2015 Tortosa-Caparros et al. 2016 Masquio et al. 2016 Robberecht et al. 2017
-	-	markers of autoimmunity↓	Ebrahimi et al. 2009 Robberecht et al. 2017
phytosterols/-stanols	-	TC↓, TG↓	de Jong et al. 2003 Sirtori et al. 2009
-	-	LDL-c↓(9-12 %)	Cofan and Ros 2015
-	-	TC↓, TG↓, LDL-c↓, apoB↓	Sialvera et al. 2012
-	-	no effect on HDL-c, apoA1, CRP, fibrinogen	Sialvera et al. 2012
carotenoids (-)	lower	-	Sugiura et al. 2008; Czernichow et al. 2009; Villaca Chaves et al. 2010; Suzuki et al. 2011; Li et al. 2013; Liu et al. 2014; Kabat et al. 2015; Sugiura et al. 2015; Wei et al. 2016
carotenoids (-)	-	IL-10↑, MDA↓	Azzini et al. 2011
carotenoids (-)	-	HOMA-IR↓	Beydoun et al. 2012
carotenoids (-)	-	CRP↓	Beydoun et al. 2012; Zeba et al. 2013
carotenoids (-)	-	adiponectin↑	Ben Amara et al. 2015
carotenoids (-)	-	leptin↑, RBP-4↑	Zimmerman and Aeberli 2008
carotenoids (egg intake)	-	HDL-c↑	Blesso et al. 2013
carotenoids (astaxantin)	-	TG↓, HDL-c↑, adiponectin↑	Yoshida et al. 2010
carotenoids (lutein)	lower	-	Leermakers et al. 2015
carotenoids (-)	-	no association	Suriyaprom et al. 2014 Wei et al. 2015

apoA1: apolipoprotein A1; apoB: apolipoprotein B; CRP: C-reactive protein; HDL-c: high-density lipoprotein cholesterol; HOMA-IR: homeostasis-associated –insulin resistance index; IL-10: interleukin 10; LDL-c: low-density lipoprotein cholesterol; MDA: malondialdehyde; RPB-4: retinol-binding protein 4; TC: total cholesterol; TG: triglycerides