The effects of antioxidant dietary supplements on oxidative stress and its implications in Metabolic Syndrome: a review

Efeitos da suplementação de antioxidantes sobre o estresse oxidativo e suas implicações na Síndrome Metabólica: uma revisão

Giuseppe Potrick Stefani[1], Bruna Marmett[2], Cláudia Ramos Rhoden[3]

[1]Nutricionista, graduado pela Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), doutorando em Ciências da Reabilitação pela Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), docente da Escola de Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS).
[2]Nutricionista, graduada pela Universidade Federal de Ciências da Saúde de Porto Alegre, Doutoranda em Ciências da Saúde (UFCSPA). Nutrição Clínica e Esportiva pelo IPGS.
[3]Farmacêutica, doutora em Ciências Biológicas (Fisiologia) pela Universidade Federal do Rio Grande do Sul (2000), docente da Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA).

Email para contato: gpotrick@gmail.com - Giuseppe Potrick Stefani

Keywords

Metabolic Syndrome X
Dietary supplements
Antioxidant
Oxidative stress

The aim was to perform a review in order to elucidate the actions and efficacy of different antioxidant supplements used on Metabolic Syndrome. The articles were searched during October of 2015 to December of 2018, using the databases PubMed and Web of Knowledge. The keywords used were: "Metabolic Syndrome" AND "dietary supplements" OR "antioxidant". The included articles were published from 2010 and in English. It was applied for articles selection inclusion and exclusion criteria. The articles that fulfilled criteria were analyzed through a full-text reading. Search results in 368 articles (PubMed: 198; Web of Knowledge: 170). After eliminating duplicated data and applying criteria, 16 articles were included to the review. The antioxidant supplements used on the studies included eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), nigella sativa (NS) and garlic, superoxide dismutase (SOD), cholecalciferol, Coenzyme Q10 (CoQ10), quercetin dehydrate, glycine, α-lipoic acid (ALA), glutathione precursor (F1), taurine, phenolic acids, red yeast rice-olive extract, curcumin, goji berry and arginine. Findings demonstrate a decrease in oxidative stress by increasing antioxidant enzyme activity, G6DH, Nrf2 with a consequently positive effect on insulin sensitivity, glucose tolerance, improvement in lipid profile, decrease on inflammatory and endothelium dysfunction markers with antioxidant supplements. Therefore, we could conclude that supplementation with antioxidant potential is able to ameliorate parameters of Metabolic Syndrome.

Palavras-chave

Síndrome X metabólica
Suplementos dietéticos
Antioxidantes
Estresse oxidativo

O propósito desta revisão foi elucidar as ações e a eficácia de diferentes suplementos antioxidantes utilizados na Síndrome Metabólica. Os artigos foram pesquisados no período durante Outubro de 2015 a dezembro de 2018, utilizando as bases de dados PubMed e Web of Knowledge. As palavras-chave usadas foram: "Metabolic Syndrome" AND "dietary supplements" OR "antioxidant". Foram incluídos os artigos publicados a partir de 2010 e no idioma inglês. Os critérios de inclusão e exclusão foram aplicados para a seleção dos artigos, e aqueles que preencheram os critérios foram analisados por meio da leitura completa do texto. A busca resultou em 368 artigos (PubMed: 198; Web of Knowledge: 170) e, após a eliminação dos artigos duplicados e a aplicação dos critérios, 16 artigos foram selecionados para revisão. Os suplementos antioxidantes utilizados incluíram ácido eicosapentaenóico (EPA) e ácido docosahexanóico (DHA), Nigella sativa (NS) e alho, superóxido dismutase (SOD), colecalciferol, Coenzima Q10 (CoQ10), quercetina, glicina, ácido α-lipóico (ALA), precursor da glutationa (F1), taurina, ácidos fenólicos, red yeast rice-olive extract, curcumina, goji berry e arginina. Os resultados demonstraram que a utilização dos suplementos antioxidantes levou à uma redução no estresse oxidativo devido ao aumento da atividade das enzimas antioxidantes, G6DH e Nrf2, com um consequente efeito positivo na sensibilidade à insulina, tolerância à glicose, melhora no perfil lipídico, redução de marcadores de inflamação e de disfunção endotelial. Portanto, a partir dos resultados atuais é possível concluir que suplementos com potencial antioxidante podem melhorar parâmetros envolvidos na síndrome metabólica.

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INTRODUCTION

Metabolic Syndrome (MetS) has a direct relationship with an increased risk of the chronic non-communicable diseases (NCD) mainly type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) development. In Brazil the prevalence of MetS ranges between 18% to 30% depending on the region, being more frequent in the elderly[1-8]. The diagnosis consists in the inclusion of three or more variables, related to glucose metabolism, obesity and increase in visceral fat, dyslipidemia and hypertension. If the incidence of MetS is not reversed, can represent the main risk factor for NCD[9-11].

In conditions related to the development of MetS, such as, obesity, type 2 diabetes mellitus (DM) and hypertension there is a high production of oxidative compounds, which is associated with oxidative stress[12]. There are several pathways that are directly or indirectly related to the formation of reactive oxygen species (ROS), such as the leaking in electron transport chain, xanthine oxidase pathway, in cases of DM the sorbitol pathway, among others mechanisms. One of the main mechanisms that augments this vicious cycle in MetS is the excessive production of anion superoxide ($O_2\bullet-$) through mitochondrial electron chain transport and via nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase). Additionally, this enzyme can be activated after chronic exposure of glucose, causing hyperglycemia that overloads the stimulation of insulin receptors, hence occurs the production of hydrogen peroxide (H_2O_2), that could be utilized as substrate to Fenton reaction, leading to hydroxyl radical ($HO\bullet$)[13, 14]. Thus, these free radicals could disturb metabolic pathways and establishing oxidative stress, resulting in oxidation of proteins, lipids and nucleic acids. Besides, oxidative stress induce higher expression of proinflammatory interleukin occasioning inflammation[15, 16].

Obesity, as the leading factor to MetS, along with dyslipidemia, DM and hypertension, increase $O_2\bullet-$, H_2O_2, NADPH oxidase, lipid peroxidation, as well as tumor necrosis factor alpha (TNF-α), C reactive protein (CRP), plasmatic cholesterol, oxidized low density lipoprotein cholesterol (LDL), moreover reducing antioxidant enzymes, like superoxide dismutase (SOD), catalase (CAT) and ratio of reduced glutathione to oxidized glutathione (GSH/GSSG)[17]. Besides, studies investigating antioxidant status on patients diagnosed with MetS shows a low content of antioxidant like, vitamin E, vitamin C and carotenoid that was inversely related with MetS[18, 19].

Antioxidant compounds are used as a strategy to manage risks involved on MetS, these supplements act increasing antioxidant defense and attenuating oxidative stress, through scavenging properties of free radicals. This scavenging effect consequently affects reducing inflammation, which is induced by ROS, as well as oxidation of protein and lipid peroxidation. Also, the dietary antioxidants could modulate glucose and fat metabolism, reduce plasma glucose, blood pressure and oxidation of LDL cholesterol and improve high density lipoprotein cholesterol (HDL), preventing co-morbidities of this syndrome, being beneficial to the conditions[9, 10, 20].

Considering the strict relation of MetS with oxidative stress and the beneficial effects performed by antioxidant supplements, the aim of this study is to perform a review in order to investigate actions and efficacy of antioxidant supplements used in MetS.

METHODS

In this review we performed a review of the literature regarding the antioxidant supplementation used in MetS and actions attributed to its use. The articles were searched during October of 2015 to December of 2018, utilizing databases Public Medline (PubMed) and Web of Knowledge.

The inclusion criteria to select the articles were: 1) studies published from 2010 to 2015; 2) written in English; 3) randomized clinical trials; 4) experimental studies performed with humans, rats, mice and hamsters; 5) experimental studies using high fat diet or fructose administration as method to induce MetS; 6) present as outcome antioxidant analysis. The exclusion criteria were: 1) articles without abstract; 2) in vitro studies; 3) administration of supplement by addition on water or food/beverage with antioxidant content; 4) articles without MetS variables; 5) not containing supplement protocol.

Those articles that fulfilled the criteria were selected to full-text analyzes. The analysis consisted in reading studies and collect data of each research, specifically: authors/date, sample, methodological aspects and main results. Thus, was possible to identify relevant aspects in the reading of the studies. In order to search the published articles, we used MeSH terms for keywords: "Metabolic Syndrome", "dietary supplements" and "antioxidant".

RESULTS

The search resulted in 16 articles, after applied the inclusion and exclusion criteria (Figure 1). Additionally, the selected studies are organized in order to elucidate the

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characteristics of each protocol, as well its main outcomes (Chart 1).

Figure 1: Process of article selection.

Effects of antioxidant supplementation on MetS

The supplements used on the studies selected to our review comprise eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which is the most common n-3 polyunsaturated fatty acid (PUFA) in fish oil, nigella stevia (NS) and garlic, SOD, cholecalciferol, Coenzyme Q10 (CoQ10), quercetin dehydrate, glycine, α-lipoic acid (ALA), glutathione precursor (F1), taurine, phenolic acids, red yeast rice-olive extract, curcumin, phospholipidated curcumin, goji berry and arginine. All of these compounds are considered dietary supplements with potential antioxidant effect.

Oxidative stress measures performed on articles showed an increase on antioxidant defense with the supplementation protocols, as demonstrated by the study of Ibitoye & Ajiboye, which observed an increase in SOD, CAT, GPx and GSH-Red with supplementation of phenolic acids[50]. As well as, an increase on SOD and CAT activity with different ratios of EPA:DHA mixtures, GSH, CAT activity and total antioxidant capacity with goji berry[23, 51, 53-55]. Besides, an increase in pro-oxidant–antioxidant balance after curcumin supplementation, an improvement on CAT activity in NS and garlic supplementation and restore levels of SOD and CAT in adipose tissue with SOD supplementation demonstrated by Al-Rasheed and Carillon, respectively[21, 22, 52].

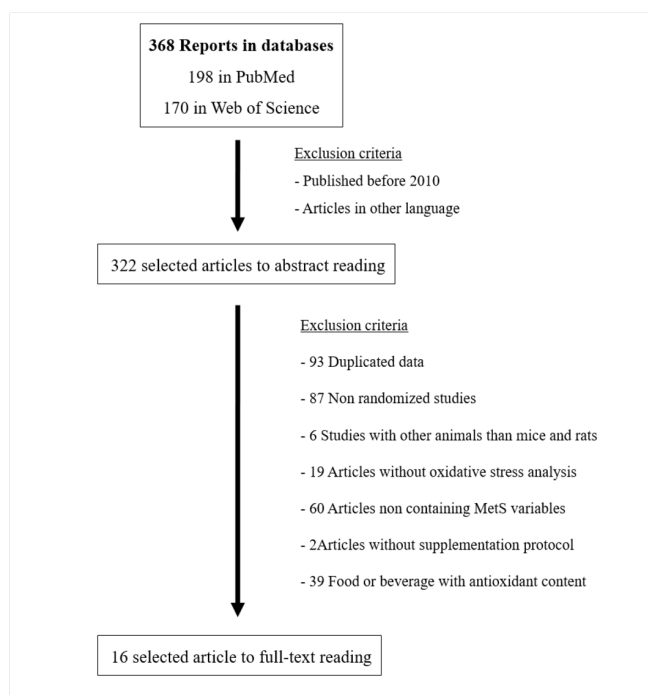Chart 1: Main results of articles selected to review.

Study	Sample	Aim	Intervention	Duration	Main results
Ibitoye & Ajiboye, 2018	Male Wistar rats (n=35)	Evaluated the effect of caffeic, ferulic, gallic and protocatechuic acids on insulin resistance, hyperglycaemia, dyslipidaemia, inflammation and oxidative stress in high-fructose diet-induced metabolic syndrome in rats.	High-fructose diet for six weeks to indice MetS. Supplemtnation of caffeic, ferulic, gallic and protocatechuic acids (40 mg/kg body weight) for four weeks starting from sixth week of diet treatments.	10 weeks	↓Body weight, BMI and abdominal circumference ↓Blood glucose, HOMA-IR and insulin ↑Adiponectin and HDL-c ↓Total cholesterol, LDL-C, VLDL-c and TG ↓Cardiac index, atherogenic index and Coronary artery index ↓TNF-α, IL-6 and IL-8 ↑ SOD, CAT, GPx, GSH-Red, G6PD
Hermens *et al.,* 2017	Patients with MetS (>18y) (n=50)	Investigate the anti-oxidative effect of a supplement combining red yeast rice and olive extract.	Supplementation of red yeast rice-olive extract (RYR-olive extract; 10.82 mg of monacolins and 9.32 mg of hydroxytyrosol per Cholesfytolplus capsule) or placebo. One capsule/day.	8 weeks	↓ Lp-PLA2 ↓Plasma OxLDL No difference in MDA and 8-OHdG
Ghazimoradi *et al.,* 2017	Patients with MetS (18-65y) (n=120)	Investigate the effect of curcumin supplementation on the serum pro-oxidant–antioxidant balance (PAB).	Patients received 1 g/day of simple curcumin or phospholipidated curcumin (containing 200 mg of pure curcumin), or placebo.	6 weeks	↑Pro-oxidant–antioxidant balance No difference in phospholipidated curcumin
Zanchet *et al.,* 2017	Patients with MetS (32-7y) (n=50)	Examine anthropometric and biochemical parameters in patients with metabolic syndrome after the consumption of goji berry.	Addition of 14 g of the natural form of goji berry in the diet.	45 days	↓Waist circumference ↓Total cholesterol, LDL-c and VLDL-c ↑ HDL-c ↓ Lipid peroxidation ↑ GSH, total antioxidant, CAT No difference in inflammatory biomarkers

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Chart 1 (continued)

Study	Sample	Aim	Intervention	Duration	Main results
Medeiros *et al.*, 2017	Male Wistar rats (n=35)	Investigate the isolated and combined effects of aerobic training and arginine supplementation on metabolic variables and vascular reactivity in rats at high risk for developing the metabolic syndrome.	Supplementation of 880 mg/kg/day of L-arginine and aerobic training with moderate-intensity (50–75% maximal running speed) with a 0–7% inclination on a treadmill, 4 d/week.	8 weeks	↓ Adipose tissue ↓ Insulin ↑ Endothelium-dependent vasodilation ↑ Hyperreactivity to phenylephrine
Mohammadi *et al.*, 2017	Patients with MetS (18-65y) (n=120)	Investigate the effect of curcumin supplementation on serum vitamin E levels.	Patients received 1 g/day of unformulated curcumin or lecithinized curcumin (containing 200 mg of pure curcumin), or placebo.	6 weeks	No change of serum vitamin E pre and post: ↓Vit E/total cholesterol↓Vit E/LDL-c ↓Vit E/HDL-c ↓Vit E/TG
Molinar-Toribio *et al.*, 2015	Female SHROB rats, as an animal model for the MetS (n=28)	Evaluate the effect EPA/DHA supplementation on the markers of CVD and OS.	Supplementation of EPA/DHA mixtures at different proportions, namely 0,8ml/kg of 1:1, 2:1 and 1:2.	13 weeks	↓LDL-c ↓total cholesterol in 2:1 and 1:2 EPA/DHA ↓TAG concentrations 1:1 and 2:1 ↓ CRP in 1:1 and 2:1 ↑VCAM-1 in 1:2 group No influence on plasma levels of PAI-1 ↑SOD activity in the erythrocytes, kidneys, abdominal fat, heart and brain (1:1), kidneys and heart (2:1) and in the heart (1:2) ↑ CAT activity erythrocytes and kidneys (2:1) ↓ CAT in brain of the (1:1) ↓GSH:GSSG the kidneys of the 1:1 and 2:1
Al-Rasheed *et al.*, 2014	Male Wistar rats (n=50)	Investigate if co-administration of *nigella sativa* and garlic in prevention or amelioration of MetS.	Supplementation of *nigella sativa* (200mg/day) and garlic (250mg/kg/day).	8 weeks	↓ Body weight ↓ Blood glucose ↓ TAG ↓TC and LDL-c ↑ HDL-c ↑CAT activity, G-6-PDH, LDH
Carillon *et al.*, 2014	Male golden Syrian hamsters 3 weeks old (n=17)	Evaluation of SOD supplementation on metabolic parameters in cafeteria diet to induce obesity in hamsters.	Supplementation of SOD (10 U/day).	4 weeks	↓Body weight No change in food intake ↓Insulin resistance (HOMA-IR) and insulinemia ↓adipose tissue weight ↓adipocytes size No effect on adipocytes hyperplasia ↓hydroxylproline content in adipose tissue ↓percentage of fibrous tissue ↑lipolytic activity through restoring HSL expression ↑expression of antioxidant enzymes
Erbas *et al.*, 2014	Adult male Sprague-Dawley rats (n=18)	Assessment of cholecalciferol supplementation for on systemic inflammation and memory.	Supplementation of cholecalciferol (0.3 µg/kg/day).	2 weeks	Positive effects on memory in hepatosteatosis rats No difference in liver tissue histopathology ↓ brain TNF-α in control and hepatosteatosis rats ↓plasma MDA in control and hepatosteatosis rats
Orlando *et al.*, 2014	Male rats with MetS (n=40)	Determine the effect of HFD and CoQ10 supplementation on the redox state of hemoglobin in erythrocytes.	CoQ10 supplementation 40 mL/100g.	4 weeks diet/30 days supplementation	↑content of CoQ10/cholesterol in plasma Efficiently counteract the HFD associated oxidation in the circulatory system. ↓hemoglobin oxidation ↓CoQ10 oxidation in lipoproteins

Chart 1 (continued)

Study	Sample	Aim	Intervention	Duration	Main results
Pfeuffer *et al.*, 2013	Subjects with MetS (48-68 y) (n=49)	Investigate the impact of quercetin intervention on endothelial function in patients carriers of the APOE4 allele.	Quercetin dihydrate supplementation (150 mg/day).	8 weeks	↓Waist circumference ↓BMI and body weight in APOE3 ↑BMI slightly in APOE4 ↑HDL-C concentrations ↓Triacylglycerols ↓Total GSH concentration in erythrocytes ↑ TNF-α concentration
Diaz-Flores *et al.*, 2013	Subjects with MetS (35-65 y) (n=60)	Evaluate the effects of daily administration of glycine supplement on antioxidant enzymes and lipid peroxidation.	Glycine supplementation (15 g/day).	12 weeks	↑HDL-c and TC in male ↑HDL-c in female ↓LDL-c ↓A1c levels ↑G6PD ↓ LPX ↑SNO-Hb ↓ SOD2 mRNA levels
Ozdogan *et al.*, 2012	Adult male Sprague-Dawley rats (n=34)	Effect of α-lipoic acid and CoQ$_{10}$ supplementation on plasma levels of lipids, asymmetric dimethyl arginine, oxidative stress and vascular changes.	α-lipoic acid (100 mg/kg/day) and CoQ$_{10}$ (10 mg/kg/day) supplementation.	5 weeks	↓ Body weight ↓ Total cholesterol LDL-c, TG ↑ HDL-c ↓Glucose, HOMA-IR levels ↓ADMA, MDA andNO ↑Total and reduced glutathione ↓Perivascular lymphocytic infiltration
Sinha-Hikim *et al.*, 2011	Male mice Apo E -/- (n=24)	Investigate a preventive role of a glutathione precursor on hepatic steatosis.	Cystine supplementation (3 mg/kg).	16 weeks	↓ Weight gain ↓ Hepatomegaly ↓ TG levels Prevent hepatic steatosis and accumulation of lipids on hepatocytes ↓ apoptosis index on liver ↑ GSH/GSSG ratio ↓8-OHdG levels ↓4-HNE expression ↑ Nrf2 Supress FAS levels Restore phospho-AMPK ↓Phospho-JNK and phospho-p38 MAPK
Mesallamy *et al.*, 2010	Male Wistar rats (n=32)	Effects of taurine supplementation for 35 days in HFD-induced IR.	Taurine supplementation (300 mg/day).	35 days	↓ Weight gain ↓ OGTT and HOMA ↑ Glucose tolerance ↓TG levels ↓Total cholesterol, LDL-c and atherogenic index ↑TAC PON ↓NOx No change in HHcy

4-HNE: 4-hydroxynonenal protein; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; A1c: glycated hemoglobin; ALA: α-lipoic acid; AMPK: 5': adenosine monophosphate-activated protein kinase; APOE: apolipoprotein E; BMI: body mass index; CAT: catalase; CoQ$_{10}$: Coenzyme Q$_{10}$; CRP: C-reactive protein; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; FAS: fatty acid synthase; FFA: free fatty acids; G6PD: glucose-6-phosphate dehydrogenase; GPx: glutathione peroxidase; GSH/GSSG: ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG); GSH-Red: reduced glutathione; HDL-c: high density lipoprotein cholesterol; HFD: high fat diet; HHcy: hyperhomocysteinemia; HOMA-IR: homeostatic model assessments a measure of insulin resistance; ADMA: asymmetric dimethyl arginine; HSL: hormone sensitive lipase; ICAM-1: intercellular adhesionmolecule-1; JNK: c-Jun-NH2-terminal kinase; LDL-c: low density lipoprotein cholesterol; LPX: lipid peroxidation; Lp-PLA2: lipoprotein-associated phospholipase A2; MetS: metabolic syndrome; MDA: malondialdehyde; NO: nitric oxide; NOx: nitric oxide metabolites concentration; Nrf2: nuclear factor-erythroid-2-related factor 2; OGTT: oral glucose tolerance test; OxLDL: oxidised low-density lipoprotein; p-38 MAPK: p38 mitogen-activated protein kinase; PAI-1: plasminogen activator inhibitor-1; PON: paraoxonase activity; SDMA: symmetric dimethyl arginine; SHROB: Spontaneously hypertensive obese; SNO-Hb: S-nitrosohemoglobin; SOD: superoxide dismutase; TAC: total

A reduction on plasmatic malondialdeyde (MDA) was observed with cholecalciferol, α-lipoic acid, CoQ1, glycine and goji berry supplementation. In addition glycine, phenolic acids and NS and garlic supplementation improve glucose-6-phosphate dehydrogenase (G6PD)[21, 24-26, 50, 53]. Also, the glutathione precursor, F1, decreased 4-hydroxynonenal protein (4-HNE), which represents one of the products of lipid peroxidation. Additionally, it was demonstrated a reduction in 8-hydroxy-2'-deoxyguanosine levels (8-OHdG), which indicate oxidative DNA damage. Beyond that, the redox sensitive transcriptor factor (Nrf2) was significantly augmented with a novel cysteine based glutathione precursor[27].

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The supplementation of α-lipoic acid, CoQ10, F1 and 1:1, 2:1 mixtures of EPA:DHA were able to improve GSH/GSSG ratio[23, 24, 27]. Taurine supplementation improved total antioxidant capacity (TAC), paraoxomase activity (PON) and reduced the concentration of nitric oxide metabolites (NOx)[28]. In the study of Orlando and colleagues (2014), CoQ10 supplementation ameliorated the oxidation of hemoglobin and plasmatic ubiquinone and increased the synthesis of methemoglobin (Met-Hb), all variables induced by HFD[29].

Conversely, quercetin does not appears to be a worthy antioxidant supplement, based on Pfeuffer, 2013, in view of the slightly reduction in GSH concentration and higher TNF-α in both genotypes APOE in post prandial analysis[30]. Also, curcumin and lecithinized curcumin supplementation demonstrated no effects on vitamin E serum levels[55].

The improvement on antioxidant defense, consequently improving antioxidant state, was related with a reduction of insulin resistance, blood glucose, glycated hemoglobin and enhancement on glucose tolerance with NS and garlic, SOD, α-lipoic acid, CoQ10, glycine, taurine supplementation, phenolic acids and arginine[21, 22, 24, 25, 28, 50, 54]. In addition, it was observed higher lipolytic activity and lower percentage of fibrous tissue, reducing adipocyte size and tissue weight with SOD supplementation in the study of Carillon and colleagues, furthermore, F1 supplementation effectively suppressed FAS levels[22, 27].

When assessed inflammation biomarkers, phenolic acids supplementation reduced TNF-α and IL-8, while cholecalciferol supplementation reduced TNF-α and EPA:DHA mixtures decreased CRP, despite increased vascular cell adhesion molecule (VCAM)[23, 26, 50]. Besides α-lipoic acid and CoQ10 reduced nitric oxide (NO), asymmetric dimethyl arginine (ADMA) and perivascular lymphocytic infiltration and glycine supplementation improved S-nitrosohemoglobin (SNO-Hb), indicating positive antioxidant activity of these compounds[24, 25].

Related to lipid profile, it was observed a reduction in TC, LDL-c, TG and an increase in HDL-c levels on EPA:DHA, α-lipoic acid, CoQ10, glycine supplementation, F1, taurine, phenolic acids and goji berry. As well as, a reduction in plasma oxidised-LDL (OxLDL) and lipoprotein-associated phospholipase A2 (Lp-PLA2) after supplementation of red yeast rice and olive extract [23-25, 27, 28, 50, 51, 53]. In addition, F1 and taurine supplementation reduced atherogenic index and apoptosis index, respectively, while phenolic acids supplementation was able to reduced atherogenic, cardiac and coronary artery indices[27, 30, 50]. In Pfeuffer and colleagues study, despite no beneficial effect on oxidative stress

variables showed an increase in HDL-c and a reduction in TG[27, 30].

Regarding endothelial function, Medeiros and colleagues demonstrated an increase in endothelium-dependent vasodilation and hyperreactivity to phenylephrine in rats supplemented with arginine[54].

DISCUSSION

Antioxidant supplementation on oxidative stress

The main finding of the present review is the efficacy of dietary supplements on MetS, specifically its effects on oxidative stress biomarkers. The articles selected in this review demonstrate that occurs oxidative stress in MetS. This condition is generated owing to an elevated formation of ROS induced predominantly by the chronic state of hyperglycemia, as consequence of non-enzymatic protein glycation, formation of advanced glycation end products (AGEs) and glucose autoxidation. The majority of the selected studies was composed by experimental investigations with rats, so our discussion should be interpreted with wariness to not directly extrapolate to clinical repercussions. Likewise, the production of $O_2\bullet-$ through activation of NADPH oxidase is a parallel process, which occurs after stimulation of insulin receptors[13, 31]. This context could be prevented and reversed when associated with antioxidant supplements, mainly through an increase on antioxidant defense, for instance, intrinsic antioxidant enzymes, such as CAT, SOD, GPx activities in addition with an improvement of the ratio of GSH/GSSG and G6PD, as well as, increased pro-oxidant–antioxidant balance and total antioxidant capacity, knowing that these parameters are notably reduced in hyperglycemia and in hypercholesterolaemia[13, 15, 32, 33, 52, 53].

The increase on antioxidant enzymes activity observed with supplements, such as EPA:DHA, garlic and NS, phenolic acids and goji berry which are known to perform hypoglycemic and hypocholesterolemic effect, may happen due to the activation of signaling pathways, expression of genes and enhancement of endogenous antioxidants[21-24, 50, 53]. The transcriptional factor Nrf2, which was activated with F1 administration, appears to be the mechanism in common of antioxidant supplements responsible for enhancing antioxidant capacity, in addition with antioxidant response element (ARE) pathway, therefore promotes the transcription of a large number of cytoprotective genes. The increase of ROS production lead to activation of Nrf2 and increase of ARE that cause amplification of antioxidant defense [27, 34].

In addition, the improvement of the ratio of GSH/GSSG, observed with ALA, CoQ10, glutathione and phenolic acids and goji berry supplementation, occurs owing to increasing G6PD, in view of the necessity of this enzyme to formation of NADPH, which is required to maintain GSH in its reduced form. Contributing to this, phenolic acids supplementation demonstrated an increase in G6FD together with the increase in GPx and GSH-Red. Considering that, the G6PD activity is associated with lower peroxidation of lipids and higher gene expression of mitochondrial SOD2 observed after glycine administration, it might be suggested that this antioxidant generate a redox status. These actions are sustained through glycine ability to increase GSH synthesis in tissues, by being one of the key amino acids of GSH molecule[35, 36, 50, 53]. In El Mesallamy study, a consequently reestablishment of TAC, as well as PON activity, it was observed with the increase in GSH levels, due to taurine supplementation may spare a precursor amino acid of GSH, cysteine [28].

As G6PD is the main source of NADPH, which is used by eNOS to synthesize NO, it improves NO bioavailability that are impaired on oxidative stress, since the generation of $O_2\bullet-$ produces peroxynitrite ($NOO\bullet$) by reacting with NO. Therefore, a higher expression of G6PD can lower ROS formation and increase antioxidant capacity, reversing oxidative stress[24]. Besides, a reduction on NOx concentration, that indicates lower NO bioavailability and possible peroxynitrite formation, it was observed with taurine supplementation, which may occur by inhibiting iNOS expression and scavenging $O_2\bullet-$ [28, 37].

Additionally, can be demonstrated an improvement on oxidation of hemoglobin (Met-Hb) and plasmatic ubiquinone, after CoQ10 supplementation. A decrease in Met-Hb formation represents positive results by reducing the incorporation of glucose by non-enzymatic processes in vulnerable sites of Hb protein. The Met-Hb is used as a marker of oxidative stress since when oxidized can release $O_2\bullet-$, increasing its products, H_2O_2 or hydroxyl radicals[38]. A decrease on plasmatic CoQ10 concentration was observed jointly with oxidized CoQ10 and Met-Hb, induced by the available high fat diet. CoQ10 supplementation was able to reverse all these variables demonstrating a systemic enhancement of antioxidant defenses. Moreover the antioxidant supplements decrease on 4-HNE that is a product of lipoperoxidation and 8-OHdG levels, which indicates DNA damage, both products increased on oxidative stress, thus complementing the beneficial effects performed by supplementation protocols[27, 29].

Pfeuffer and colleagues designed a clinical study in patients with MetS undergoing a 8-week protocol of quercetin supplementation. This is one of the few studies selected in the present systematic review that the humans composed the sample. In contrast with the beneficial findings, the supplementation of quercetin when analyzing APOE4 allele, demonstrated a high cardiovascular risk, and APOE3, appears to be a weak antioxidant supplement, due to the reduction in GSH concentration and higher TNF-α formation[30]. Also, Mohammadi and colleagues investigate the effects of curcumin supplementation on serum vitamin E levels in patients with MetS and found no significant difference, indicating that antioxidant effects of curcumin might be mainly directed by the modulatory effects on enzymatic antioxidant rather than non-enzymatic, like vitamin E[55]. In another study, it was not presented antioxidant effect with quercetin and concluded that both allele of APOE has same antioxidant capacity[39]. These findings are important to separate from experimental data with animals due to the fact that humans represent the ideal scenario of clinical changes of different potential antioxidant supplements. Not all experimental data observed in rats or mice are completely extrapolatable to humans.

Antioxidant supplementation on glucose metabolism

In MetS, combined with hyperglycemia occurs an increase of FFA and TG flux on blood, this supports impairment of insulin sensitivity, glucose intolerance, increase on blood glucose and glycated hemoglobin. Conversely, an enhancement on these factors was achieved by NS and garlic, SOD, α-lipoic acid, CoQ10, glycine, taurine, phenolic acids, goji berry and arginine supplementation[21, 22, 24, 25, 28, 50, 53, 54]. Studies demonstrated that the improvement in antioxidant defense, consequently reducing oxidative stress, was related with a reduction of insulin resistance[40, 41]. Thereby follows a higher lipolytic activity, repairing HSL expression and decreasing the percentage of fibrous tissue, reducing adipocyte size and tissue, which might occur due to the improvement on insulin signaling performed by supplements. By this logic, insulin inhibits adipocyte lipolysis and enhances adipocyte differentiation, consequently increase insulin sensitivity, which leads to the reduction of fibrosis[22, 40, 42]. In this way, antioxidant supplementation could improve glucose metabolism through the increase of antioxidant activity in MetS condition leading to improve in insulin sensitivity.

Antioxidant supplementation on inflammation

The improvement in oxidative stress probably lead to reduced inflammation, idea supported by reducing inflammatory biomarkers, such as PCR, TNF-α, IL-6 and IL-8

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after supplementation with antioxidants[23, 26, 43, 50]. Possibly owing to ROS up-regulating inflammatory genes, inducing nuclear factor (NF)-κB and increasing the expression of TNF-α, IL-1, IL-6, which intensifies the inflammatory response (31). Beyond a decrease on central inflammation, the process might be related with positive effects on the limbic system when associated with cholecalciferol supplementation. This is supported that pro-inflammatory cytokines affects the permeability of blood brain barrier, so a decrease of the concentration of TNF-α in brain could lead to the improvement of cognition and memories latency period[26, 44]. Moreover, EPA:DHA mixtures diminishes PCR levels, indicating enhancement on systemic inflammation in mixtures with proportions of 1:1 and 2:1, however it was demonstrated an increase in VCAM, which is a marker of auxiliary inflammation, with 1:2 mixture. Hence, it seems that EPA performed a superior anti-inflammatory effect than DHA[23, 26, 44, 45]. In MetS scenario, a chronic inflammatory process is established, so the reduction of inflammation observed in the previous studies discussed might probably play a beneficial role in this disease.

Antioxidant supplementation on endothelial function

Once established the insulin resistance in MetS, a decrease of NO formation induced by insulin follows with an impairment of vasodilatation related to insulin, featuring an endothelial dysfunction[9, 13]. Improvement on endothelium function and decreasing high blood pressure can be attributed to antioxidant supplements by protecting against oxidative stress. Also, arginine supplementation was able to increase endothelium-dependent vasodilation and hyperreactivity to phenylephrinein, indicating that this supplement could reverse vascular dysfunction caused by metabolic syndrome[54]. Glycine supplementation was able to decrease systolic blood pressure through the increasing availability of NO via SNO-Hb, endothelium reservoir of NO being a blood pressure regulator and protect NO to react with anion superoxide and form peroxinitrite. The α-lipoic acid and CoQ10 supplementation decreased the impaired NO synthesis by preventing the upregulation of inducible nitric oxide synthase (iNOS). It is possible in view of a related reduction of ADMA, that is an inhibitor of endogenous NOS, besides it can possibly reverse an endothelial dysfunction by the decrease in perivascular lymphocytic infiltration[24, 25, 46, 54]. The antioxidant supplementation in experimental studies could ameliorate endothelial dysfunction, in view, that hypertension is one of the criteria for MetS diagnosis and oxidative stress has a major role in both of these conditions.

Antioxidant supplementation on lipid profile

In MetS, combined with hyperglycemia occurs augment on adipose lipolysis that lead to increase of lipid deposits on tissues, such as higher levels of LDL and lower levels of HDL. Lipid profile analysis demonstrated high levels of total cholesterol, LDL-c, triglycerides, fatty acids and lower on HDL-c levels. It is created the hypothesis that this condition is associated with the activation of sterol regulatory element binding protein-1C (SREBP-1c), which in turn contributes to lipid synthesis. When associated with antioxidant supplementation, such as F1, EPA:DHA, garlic, NS, queracetin, glycine, ALA, CoQ10, taurine, phenolic acids, red yeast rice-olive extract and goji berry levels of cholesterol, LDL-c, triglycerides and fatty acid are notably normalized, as well as, it was possible to observe an decrease in LDL oxidation and lower levels of Lp-PLA2, an enzyme that catalyses OxLDL hydrolysis, producing pro-inflammatory mediators[21, 23-25, 50, 51, 53]. The proposed mechanism can be explained by preserving the activity of AMPK which suppresses FAS levels through inhibition of SREB1-c[21, 23-25, 27, 28, 30, 47]. It was also observed that supplements appears to down-regulate the genes of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), which are activated in insulin resistance, hyperinsulinemia, by reducing expression of SREBP-1c. Thus, the supplementation is responsible for inhibition of cholesterol synthesis and reduces LDL due to upregulation of LDL-receptor gene. In addition, taurine supplementation was able to reduce atherogenic index, associated to the decrease on total cholesterol observed with the supplementation[28, 48, 49]. A beneficial role in lipid profile was observed in the studies reviewed, indicating a promissory effect of supplements with antioxidant potential in MetS.

Antioxidant supplementation on cellular damage

The antioxidant effect of these supplements lead to a reduction in oxidative stress, which is responsible to stress sensitive signaling system and promoters of apoptosis that could result in cellular damage. Besides the inflammatory process, the activation of NF-κB by the ROS formation lead to apoptosis and necrosis. It was also observed a suppression of the expression of c-Jun-NH2-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38MAP), as well as a decrease on apoptosis index associated with F1 supplementation[27, 28, 43].

Limitations

The present review has a limitation that explain discussion. Due to our search strategy the majority of studies included in this review are experimental ones, so the results

should be carefully extrapolated to human application. However, the studies reviewed were relevant to the field and pointed a promising effect of antioxidant supplementation on the metabolic syndrome Also, the experimental studies are crucial for further clinical trials, once the recommendation for clinical use of antioxidant supplements must be based in well-designed randomized clinical trials.

CONCLUSION

In conclusion, this review demonstrated that supplementation with antioxidant potential is able to ameliorate parameters of MetS. Antioxidant supplementation act improving the oxidative state by increasing antioxidant defense, which reduces oxidation of biomolecules. Furthermore, the supplementation could reduce inflammation, insulin impairment, and improve lipid profile and endothelium dysfunction. Thus, the supplementation with antioxidant potential could be the focus of further studies aiming to improve the complex and multifactorial scenario of MetS.

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