Antioxidants and Cardiovascular Diseases: A Summary of the Evidence

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Abstract
The implication of oxidative stress in the etiology of Cardiovascular disease (CVD) suggests that antioxidant therapy represents a promising avenue for treatment. Although experimental studies in cell cultures and animals have indicated that antioxidants such as β-carotene, ascorbic acid, or α-tocopherol may reduce oxidative stress, human intervention studies do not support a beneficial effect. Strategies for the intervention and prevention of CVD require an understanding of the basic molecular mechanisms by prophylactic agents (synthetic antioxidants, dietary antioxidant factors from food plants and medicinal plants) that may potentially prevent or reverse the promotion or progression of the disease. New knowledge of mechanisms involved in oxidant stress in tissues, reactive oxygen species production, and the fate of antioxidants after their administration may lead to progress in improved outcomes and refined therapies for CVD. In this article, we will review the evidence with and the evidence against using antioxidants either from diet or in a supplemental form in clinical trials.

Keywords — Antioxidant vitamins, Cardiovascular disease, Free radicals, Oxidative stress.

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I. BACKGROUND
Cardiovascular disease (CVD) is becoming increasingly prevalent globally, and particularly amongst younger people. Despite the significant decline in CVD mortality in the western world over the past several decades, CVD remains the major cause of death [1]. The etiology and pathophysiology of CVD are complex, but the major risk factors include an unhealthy lifestyle and behaviors coupled with a multi-factorial complex interaction between environmental and genetic factors [2].

Due to their antioxidant properties, carotenoids, vitamin E, and vitamin C may protect against free radicals and lipid peroxidation and accordingly inhibit the development of atherosclerosis. Abundant data from epidemiologic studies suggest that greater intake of antioxidant vitamins such as vitamin E, vitamin C, and beta carotene are associated with reduced risk of atherosclerotic diseases [3]. The postulated mechanism for such an effect derives from basic research demonstrating the ability of antioxidants to inhibit the oxidation of LDL-cholesterol, which is thought to play an important role in the development of atherosclerosis [4]. Animal studies are largely consistent with the concept that dietary supplementation with antioxidant reduce the progression of atherosclerosis. These combined observations have led to the concept that supplementation with antioxidant vitamins could be used therapeutically to reduce risk of CVD. Antioxidant vitamins remain a promising area of research in the prevention of CVD, although there have been several intervention studies that have failed to show benefit in this condition [5,6]. In this article, we will review the evidence with and the evidence against using antioxidants either from diet or in a supplemental form in clinical trials.

Role of Reactive Species and Free Radicals
Excessively high levels of free radicals cause damage to cellular proteins, membrane lipids, and nucleic acids, and eventually cell death. Growing evidence suggests that highly reactive oxygen species (ROS) and reactive nitrogen species (RNS) of endogenous or environmental origin play a significant role in the genesis and progression of various forms of CVD [7].

Several mechanisms have been suggested to contribute to the formation of these ROS. Oxidative stress results from an imbalance between generation of ROS/RNS and the activity of the antioxidant defenses [8]. Oxidative stress and inflammation are key mechanistic pathways involved in endothelial dysfunction leading to atherosclerosis. Inflammatory processes also play a crucial role in the development of CVD, but the cause of inflammation is uncertain [9]. Inflammation may be caused by oxidative stress, and may therefore be a potential target for a next wave of cardiovascular therapeutics [10].

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Antioxidants Hypothesis

It is suggested that the total antioxidant content of dietary plants may be a useful tool for testing the antioxidant network hypothesis. The ‘antioxidant hypothesis’ evolved from Gey report [11], with the proposal that high intakes of dietary antioxidants prevent oxidation of plasma and thereby provide protection against diseases induced by oxidative stress.

Given the evidence that single antioxidant supplements showed no beneficial effects on preventing CVD [6], as well as the fact that diets high in antioxidants such as fruits, vegetables, and tea has been widely reported to have beneficial health effects [5], dietary total antioxidants capacity (TAC) that considers all the antioxidants present in diet and the synergistic effects between them are drawing increasing attention. While this is still a topic of intense debate, the possibility that other dietary components affect the in vivo antioxidant properties of specific foods needs to be further investigated and might have an effect on the outcome of epidemiological studies. Most information acquired in humans to date relates to lipid peroxidation. Therefore, reliable quantitative indices of in vivo oxidant stress must be available.

Overview of Antioxidants

When ROS/RNS are generated in vivo, their actions are opposed by coordinated antioxidant lines of defense systems (Figure 1).

These include enzymatic and non-enzymatic antioxidants that repair oxidative cellular damage (Table 1).
Moreover, dietary vitamins may act either directly or require micronutrients as integral components of protective enzymes (for example, selenium in glutathione peroxidase, and copper and zinc in superoxide dismutase). Other dietary antioxidants include α-lipoic acid, Ubiquinone (coenzyme Q10), several bioflavonoids, and the cofactors (trace elements). Antioxidants also interact in recycling processes to generate reduced forms of the vitamins (Figure 2).

Nevertheless, accumulation of antioxidant radicals has been proposed to be one of the reasons for the adverse effects seen in some of the randomized intervention trials using single antioxidant supplements. Hence the best protection may be obtained by a combination of antioxidants, as suggested by experimental data of diets rich in antioxidants such as vitamin C, vitamin E, or β-carotene exhibiting beneficial effects on CVD prevention [14]. However, secondary prevention trials with a combination of vitamins E, vitamin C, and β-carotene demonstrated no cardiovascular benefits [5,15,16].

Epidemiologic studies that have explored the antioxidant vitamin hypothesis include descriptive and prospective cohort study designs, as well as several small randomized clinical trials. Findings from these studies are not totally consistent as shown in Table (2).

However, it is important to emphasize that a minimum of oxidant stress is necessary to maintain the integrity of biological systems, with a physiologic concentration of superoxide once the normal cellular environment is reduced [38]. This explains why high antioxidant supplementation have failed to improve health and is not recommended.

**Protective Role of Dietary Antioxidants Against CVD**

Lifestyle factors, including nutrition, play an important role in the etiology and prevention of CVD. Optimal nutrition could be considered as non-pharmacological prevention and therapy of CVD [39]. Consequently, it is recommended that the general population should consume a balanced diet (e.g., the Dietary Approaches to Stop Hypertension (DASH), Mediterranean, and Portfolio diets) with emphasis on antioxidant-rich fruits and vegetables and whole grains [40]. Although scientific literature on diet and health is large, until recently, researchers have focused mainly on the effects of individual nutrients or foods. Much less often has the focus been on dietary patterns, in part because of their complexity, although there have been important exceptions such as the Seven Countries Study [41] among others. However, regardless of the diversity in scientific approach, evidence converges around the notion that diets associated with reduced risk of CVD and some cancers are heavy in vegetables and fruit (therefore rich in phytonutrients and antioxidants) but reduced in meat, refined grains, saturated fat, sugar, salt, and full-fat dairy products [42].

| Table 1 Antioxidant defense systems classes |
|-----------------------------------------|
| **Enzymatic** (the first line of defense) | **Non-enzymatic** (the second line of defense) |
| **Primary** | **Endogenous** (inside body) | **Exogenous** (diet) |
| - Superoxide dismutase | - Glutathione | - Vitamins (fat-soluble + water-soluble vitamins) |
| - Catalase | - Bilirubin | - Carotenoids (β-carotene + lycopene) |
| - Glutathione peroxidase | - Albumin | - Polyphenols (Flavonoids + phenolic acids) |
| | - Caeruloplasmin | - Cofactors (Coenzymes Q10) |
| | - Uric acid | - Trace elements (copper + zinc + selenium) |

Many endogenously produced compounds, such as glutathione, uric acid, albumin, bilirubin, N-acetyl cysteine, and caeruloplasmin also exhibit antioxidant functions and often act synergistically with antioxidants of dietary origin and against different types of free radicals.

**Fig. 2:** Cross-talk between lipophilic and hydrophilic antioxidants. Adapted from Kalyanaraman,2013 [13]. Vitamin E which is lipophilic (located in the biological membrane) will react with the lipid peroxyl radical produced during lipid peroxidation process. Vitamin C is water-soluble and will react rapidly with a variety of reactive oxygen species including superoxide and hydroxyl radical forming the ascorbate radical, which reacts with another ascorbate radical forming dehydroascorbate and ascorbate. Although ascorbate is present in the cytosol, it can recycle the membrane-associated vitamin E radical back to vitamin E, thereby increasing the total antioxidant potential. The Pentose Phosphate Pathway keeps the ascorbate and vitamin E in the reduced form through the intracellular reductant, glutathione.
| Study | Daily Dose | Outcome | Reference |
|-------|------------|---------|-----------|
| Health Professionals’ Follow Up Study | > 100 IU vitamin E for > 2 years | reduced coronary risk with vitamin E and beneficial effect of β-carotene among smokers only lower rate cardiovascular mortality | [17] |
| Physicians’ Health Study (PHS) | 50mg β-carotene and/or aspirin on alternate days for 12 years | No effect on incidence of MI, CVD, and cardiovascular mortality | [15] |
| Nurses’ Health Study | > 100 IU vitamin E for > 2 years | reduced coronary risk with vitamin E no benefit from β-carotene and vitamin C on major coronary events | [18] [19] |
| Alpha Tocopherol Beta Carotene Cancer Prevention Study (ATBC) | 50mg α-tocopherol for 4.7 years | No effect on incidence of MI and cardiovascular mortality and an increase in hemorrhagic stroke and reduction in cerebral infarction among vitamin E group Increased risk of MI and cardiovascular mortality and an increase in hemorrhagic stroke among β-carotene group | [20] [21] [22] |
| Women’s Health Study (WHS) | 50mg β-carotene on alternate days for 2.1 years | No significant effect on incidence of MI, stroke, and cardiovascular mortality | [23] [24] |
| Heart Outcomes Prevention Evaluation Study (HOPE) | 400IU natural α-tocopherol and/or ACE inhibitor for 4.5 years | No effect of vitamin E on incidence of MI, cardiovascular mortality, and stroke | [25] |
| Primary Prevention Project (PPP) | Low-dose aspirin and/or 300mg synthetic α-tocopherol for 3.6 years | No effect of vitamin E on incidence of MI, cardiovascular mortality, and stroke | [26] |
| Beta Carotene and Retinol Efficacy Trial (CARET) | 30mg β-carotene, 25,000IU retinol for 4 years | 26% ↑ in CVD and 17% ↑ in total mortality | [27] |
| Supplementation en Vitamines et Mine`raux AntioXydants (SU.VI.MAX) | 6mg β-carotene, 30mg α-tocopherol, 120mg vitamin C, 100mg selenium and 20mg zinc | Unpublished data show no effect on CVD | [28] |
| First National Health and Nutrition Examination Survey (NHNES) | >50 mg vitamin C | lower overall total mortality rate, and in particular lower mortality from CVD | [29] |
| Women’s Antioxidant Cardiovascular Study (WACS) | 50mg β-carotene (alternate days), 600IU α-tocopherol (alternate days), and 500mg vitamin C on alternate days for 9.4 years | Effect on CVD awaited no cardiovascular benefits of a combination of vitamin E, vitamin C, and β-carotene Decreased non-fatal acute MI and no benefit on CVD mortality | [30] [31] [32] |
| Cambridge Heart Antioxidant Study (CHAOS) | 400 or 800 IU α-tocopherol for 1.4 years | | |
| Alpha Tocopherol Beta Carotene Cancer Prevention Study (ATBC) | 50mg vitamin E for 5.3 years | 38% reduction in MI | [33] |
| Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardio (GISSI) Prevenzione Trial | 300mg synthetic α-tocopherol and/or 1g n-3PUFA for 3.5 years | No effect of vitamin E on MI, cardiovascular mortality, and stroke | [34] |
| Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study | 182d-α-tocopherol and 500mg vitamin C for 3 years | Progression of MI for men but not women | [35] |
| Intravascular Ultrasonography Study (IUS) | 500mg vitamin C and 400IU vitamin E for 1 year | Greater IMT increase in placebo group | [36] |
| Heart Protection Study (HPS) | 600mg vitamin E, 250mg vitamin C, and 20mg β-carotene for 5 years | No effect of combined antioxidant therapy on cardiovascular mortality, fatal or non-fatal MI, and stroke | [37] |
| HOPE-TOO | long-term vitamin E supplementation | did not prevent major cardiovascular events and could increase the risk for heart failure | [16] |

ACE – angiotensin-converting enzyme; CHD – coronary heart disease; MI – myocardial infarction; PUFA – polyunsaturated fatty acids.
Conversely, epidemiological studies have shown that certain foods with antioxidant properties are associated with a reduction in inflammatory markers and LDL oxidation, and consequently, improved endothelial function [43,44]. Intake of fruits, vegetables, and whole grains has long been associated with a lower risk for several chronic diseases mediated by oxidative stress [45,46]. Plant-derived foods contain hundreds of active antioxidant compounds, including ascorbic acid, tocopherols, carotenoids, and polyphenols were thought to be protective of the cardiovascular system through suppressing oxidative stress, as suggested by preclinical studies. Many in vitro and animal studies have shown that a large range of dietary antioxidants, taken as extracts or as part of the food, can attenuate the atherogenic process. Among these, polyphenols are the most studied and have shown very interesting results [47].

Epidemiological Evidence of Antioxidants Effects in CVD

Protective effects of exogenously administered antioxidants have been extensively studied in animal models, thus providing some insight into the relationship between free radicals and CVD [48,49]. In vitro and clinical studies may provide additional useful ways to probe the interconnections of oxidant stress and CVD, and there is a need to continue to explore the mechanisms by which increased oxidative stress accelerates the development of CVD.

While being supported by observational studies, randomized controlled trials have not supported a role for vitamins in the primary or secondary prevention of CVD, and have in some cases even indicated increased mortality in those with pre-existing late-stage atherosclerosis. Indeed the underlying mechanisms for the null or adverse effects are still not well known, however, some design points are worth discussing and improvement in future studies. For example, inclusion of patients taking vitamins supplements in clinical trials of antioxidants would dilute the population susceptible to benefit and undermine the calculation of sample sizes needed to detect such effects. In terms of supplement dose, the non-linear relationships between antioxidant intake and disease risks indicate that a cut-off value exists for optimal health for some antioxidants.

Studies have also indicated that β carotene mediates pro-oxidant effects. The trials that used a combination of vitamins that include β carotene have been disappointing. Studies also suggest that vitamins would be beneficial to individuals who are antioxidant-deficient [50]. A recent trial reported that consumption of a multivitamin had no effect on CVD risk in men [51]. Indeed, supplementation with antioxidants has often resulted in no effect or even adverse disease outcomes [52].

Several reviews and meta-analyses failed to show the benefit of antioxidant vitamin supplementation for diverse populations, which makes interpretation of the results difficult for clinicians and has further restricted its application in clinical prevention [5,53]. In a meta-analysis of 56 trials with a low risk of bias, the antioxidant supplements modestly increased mortality (RR = 1.04, 95% CI 1.01–1.07). In intervention trials including vitamins A, C, E, β-carotene, and selenium, no beneficial effect was detected on all-cause mortality in secondary prevention. Vitamin A, β-carotene, and vitamin E supplementation increased total mortality (RR = 1.06, CI 95% 1.04–1.10) [6]. Similarly, a recent systematic review of 15 cohort studies showed an inverse association between higher intake of vitamin C (diet and supplement) and risk of coronary artery disease (RR 0.84; 95% CI 0.73–0.95), but the results were not confirmed with the use of supplemental vitamin C only in the same study [54].

One possible explanation may be that the beneficial health effect is due to other antioxidants in fruits and vegetables, such as, carotenoids occur in 1000 natural variants, over 8000 plant phenols have been isolated [55]. Nevertheless, it seems likely that a mixture of different antioxidants is needed to keep the plant cell healthy and protected against oxidative stress [56]. Thus, maybe a combination of a variety of different antioxidants is needed to keep the animal cells protected from oxidative stress. Antioxidants with different chemical properties may recharge each other in an integrated manner, and may be needed for proper protection of all compartments in a cell or an organism [57].

Although the reason of this paradox is unclear, inherent confounding in epidemiological studies and different physical conditions in study populations may partly explain it. Moreover, inconsistency of the results from these studies may, in part, be due to a lack of power to detect associations, misclassification of antioxidant intake, unsatisfactory control for potential confounding factors, or an inability to investigate subpopulations.

This may, in part, be explained by a recently proposed hypothesis that atherogenesis is a progressive, but step-wise process that requires an ordered sequence of events to take place. Furthermore, progress along the disease pathway is driven by risk factor bundles that may differ with the stage of disease, vary between individuals and may not require the inclusion of any of the traditional risk factors [58]. In this context, the hypothesis would predict that single risk factors have a poor power of discrimination, and that treatment of individual risk factors would not lead to benefit in the majority of patients. It would also predict that whilst a multi-factorial intervention approach may improve outcomes further, a substantial proportion of the population would still develop disease. If specific risk factors do not exert a uniformly important influence along the entire disease pathway, for those factors that have a predominant effect early in atherogenesis, treatment in the latter stages of disease will have little impact on outcomes.

Apparently, current intervention studies do not allow the recommendation of antioxidant supplementation for the sole purpose of preventing and/or treating CVD. Several reasons can be given for these disparities. First, free radicals are necessary for the transduction of certain signals, including that of insulin, making their excessive neutralization deleterious. Second, the antioxidant capacity of dietary antioxidants may be modified by environmental conditions such as pH, the presence of metal ions, or their concentration. In fact, antioxidants can
become pro-oxidants beyond certain concentrations [59]. Third, digestion metabolism leading to the production of specific potent metabolites and conjugated derivatives and the complexity of food matrix synergism may explain some of the differences found between in vivo and in vitro studies. Fourth, the efficiency of most natural products and/or diet supplements possessing antioxidant-like actions is not restricted to their antioxidative capacity, which can further add to the variability in response, depending on the model studied.

**Therapeutic Use of Antioxidants in CVD**

Particular attention has been given to the applicability of antioxidant therapy in the prevention and management of CVD [46]. It is critical that any therapies for CVD include the direct and/or indirect reduction of oxidative stress. Although numerous experimental studies have indicated that antioxidants and scavenging ROS could prevent pathological events leading to atherosclerosis, translating this concept into the treatment of human disease has been problematic. This could be due to a number of reasons; treatment commencement could be too late while profound changes of ROS are usually observed in advanced stages of CVD. Therapeutic interventions on the level of global redox status inside cells might not be sufficient to correct these disturbances. Therefore, future antioxidant therapies need to be more specific in targeting the site of action, be devoid of deleterious effects on other signaling pathways, and be targeted to a specific ROS or cellular compartment [60]. Novel strategies should instead target a specific cellular antioxidant enzyme by either inhibiting or mimicking the activity following an in-depth study for selective function of each antioxidant enzyme.

Antioxidant nutrients may complement cardiovascular therapies described below to reduce oxidative stress. In general, exogenous antioxidants can compensate for the lower plasma antioxidant levels often observed in atherosclerotic patients, whether their CVD is primarily genetic in origin or due to obesity and a sedentary lifestyle. It has long been suspected that the consumption of fruits and vegetables rich in vitamin and other antioxidants can increase overall antioxidant status [61]. Hence, most randomized controlled trials evaluated the effects of combination of vitamins on the risk of major cardiovascular outcomes. However, their effects on cardiovascular outcomes remain inconclusive. Thus, future trials of antioxidant therapy in CVD should be targeted toward patients with high levels of oxidant stress or patients with depletion of natural antioxidant defense systems, and the dose of antioxidant should be chosen based on a rationale surrogate readout that is a reliable, reproducible and easily obtainable in vivo measure of oxidant stress.

**Safety and Effectiveness of Antioxidant Vitamins Supplementation**

High dose of antioxidant intake may result in toxicity to human bodies [62]. Most of the antioxidants such as vitamin E, carotenoids, and uric acid can play a role as oxidants in vivo at their high concentrations. Different physical conditions and family CVD history of the participants might also contribute to the diverse results seen in different studies. As shown in the Physicians’ Health Study II, vitamin E supplement had significant interaction with parental history of myocardial infarction <60 years, with a lower CVD risk seen in persons with a family history [16]. Nevertheless, vitamin C can act as a pro-oxidant interacting with free iron [63]. Alternatively, vitamin C could have promoted protein glycation [64] and stimulated lipid peroxidation [65], with a possibly deleterious effect on the cardiovascular system as higher doses were administered. The use of more than 300 mg/day of vitamin C by supplementation was associated with increased cardiovascular risk [66]. Furthermore, The ATBC trial found increased mortality in the subjects taking 20 mg/day β-carotene, with trends to increased lung cancer and ischemic heart disease [67]. Similarly, the β-Carotene and Retinol Efficacy Trial (CARET) had to be stopped early because of increased incidence of lung cancer in the β-carotene and retinol group [20].

The effectiveness of a dietary antioxidant will depend on a number of factors, such as which ROS or RNS is being scavenged, how and where they are being generated and the accessibility of the antioxidant to possible sites of damage [68]. Some data suggest that certain plant compounds, but not α-tocopherol and ascorbic acid, may have a dual role in supporting the antioxidant defense. First, the antioxidant can donate an electron to a ROS or RNS in a classical redox reaction. Then, the antioxidant radical which is formed in the reaction may additionally activate gene expression of antioxidant and phase 2 enzymes [69]. Therefore, it may be important to re-evaluate the selection of foods rich in antioxidant compounds rather than the selection of supplements of these substances. Furthermore, trials that investigate the effect of a balanced combination of antioxidants at levels achievable by diet are clearly needed.

**Pharmacological Compounds with Antioxidant Activity**

Because lifestyle habits are major risk factors for the development of CVD, the most effective method for its prevention and treatment, beside cardiovascular therapeutics, is lifestyle habits modification, such as smoking cessation, consumption of a healthy diet, weight reduction, and physical exercise. Additionally, the pharmaceutical industry has developed a number of lipid-lowering agents that act as antioxidants. A number of studies have been conducted to explore the roles of various antioxidants in CVD (Table 3).

**Potential Novel ROS Targeted Therapeutics**

Taken together, the results of recently conducted research studying the molecular, subcellular organelles, and cellular mechanisms involved in mediating the ROS actions offer promising venues as they propose novel potential therapeutic agents for the ROS-linked diseases. The complexity and multifaceted nature of the process of redox regulation make it essential to better understand the key players in the process and then to design a targeted means of controlling these players.
An obvious example is the JNK signaling pathway, which is activated by various cell stressors including ROS [86]. Obesity may induce metabolic disturbance resulting in insulin resistance and, ultimately, type 2 diabetes mellitus. Results published by Ozcan and colleagues [87] have suggested that JNK signaling pathway inhibitors could specifically ameliorate endoplasmic reticulum-stress response associated activation of this pathway, thereby offering new opportunities for preventing and treating type 2 diabetes mellitus.

Increased expression of SIRT3, a member of the sirtuin family of proteins that promote longevity in many organisms, is an endogenous negative regulator of cardiac hypertrophy in the mouse heart, which protects hearts by suppressing cellular levels of ROS [88]. In primary cultures of cardiomyocytes, Sirt3 blocked cardiac hypertrophy by activating the forkhead box O3a–dependent (Foxo3a-dependent), antioxidant-encoding genes manganese superoxide dismutase and catalase, thereby decreasing cellular levels of ROS. Reduced ROS levels suppressed RAS activation and downstream signaling through the MAPK/ERK and PI3K/Akt pathways. This resulted in repressed activity of transcription factors, specifically GATA4 and NFKB, and translation factors, which are involved in the development of cardiac hypertrophy.

The importance of a regular use of olive oil in the benefits of traditional Mediterranean diet on CVD has been repeatedly emphasized [89]. Nutraceutical properties of virgin olive oil have been recently attributed to its phenolic components: oleuropein and hydroxytyrosol. With their catecholic structure, they are able to scavenge the peroxyl radicals and break peroxidative chain reactions, as described by in vitro and in vivo experimental data obtained with isolated compounds [90]. However, this approach is usually neither predictable nor straightforward; therefore in vitro, as well as experimental animal models studies have to be conducted first, and based on their results, carefully designed human intervention studies could be proposed. Even with such design, the hypothesis of targeting a specific signaling pathway with the objective of

| Drug | Action | Antioxidant effect | Ref. |
|------|--------|----------------------|------|
| hydroxymethylglutaryl-CoA reductase inhibitors | lipid-modifying agents | • results in a markedly lower risk of cardiovascular events related to atherosclerosis | [70] |
|  |  | • antiatherosclerotic effect may be independent of their LDL-lowering effect | [71] |
| Diphenyleneiodonium (DPI) | inhibitor of NADH/NADPH oxidase enzyme | suppress p38 MAP kinase-mediated VSMC hypertrophy in vitro | [72] |
| N-acetyl-L-cysteine (NAC) | radical scavenger and intracellular glutathione precursor | inhibited endothelin-induced ROS generation, c-Jun N-terminal kinases (JNK) activation and VSMC proliferation | [73] |
| Angiotensin II type 1 receptor (AT1R) blockers and angiotensin converting enzyme (ACE) inhibitors | Treatment of hypertension and/or congestive heart failure | • inhibit the expression of pro-atherogenic factors by decreasing ROS production in vascular endothelial cells and in animal models | [74] |
|  |  | • Statins and AT1R blockers exert synergistic effects on the inhibition of atherosclerotic lesions in the apo E-knockout mice placed on a high cholesterol diet | [75] |
| Peroxisome proliferator-activated receptor gamma (PPAR-γ) ligands | treatment of type II diabetes | • potent antioxidants | [77] |
|  |  | • thiazolidinedione reduces the size and number of atherosclerotic lesions in the vessel wall by modulating foam cell formation and inflammatory responses of macrophages | [78] |
| Trolox C | water-soluble vitamin E analogue | with vitamin C abolished the stimulatory effect of angiotensin II on JNK and p38 activity in VSMC | [79] |
| superoxide dismutase mimetics | Treatment of hypertension | improve vascular structure and function in experimental and human hypertension | [80] |
| Epoetin δ | prescribed to patients who are at increased risk of developing anemia | antioxidant capacity in primary human renal tubular cells | [81] |
| Sildenafil | protective against | • induce | [82] |

| Drug | Action | Antioxidant effect | Ref. |
|------|--------|----------------------|------|
| Metformin | Treatment of diabetes mellitus | Inhibits hyperglycemia-induced PKC-β2 translocation in endothelial cells because of a direct antioxidant effect | [84] |
| D-4F | an apolipoprotein A-I mimic peptide that restores HDL-C function in mice | reduces atherosclerosis development, and prevent diabetes-induced oxidized lipid accumulation in a mouse model of diabetes | [85] |
ameliorating the redox stress-associated diseases remains subject to either approval or refutation. A good example was testing the benefit of doxycycline, a transcription factor activator protein-1 inhibitor (AP-1), in a clinical trial involving patients with peripheral arterial disease based on experimental studies results. Unfortunately, the drug did not affect any of the markers of inflammation and vascular dysfunction. This has led the authors to conclude that AP-1 proved not to be a therapeutic target for progressive human vascular diseases [91].

II. CONCLUSION

The implication of oxidative stress in the etiology of CVD suggests that antioxidant therapy represents a promising avenue for treatment. Although experimental studies in cell cultures and animals have indicated that antioxidants such as β-carotene, ascorbic acid, or α-tocopherol may reduce oxidative stress, human intervention studies do not support a beneficial effect. Hence, most studies have used supplements in the form of one or two vitamins associated or not with trace elements, however, plants naturally contain a multitude of antioxidants with various levels of bioavailability. Among the countless compounds present in a particular plant food, it is often difficult to identify the one that plays the critical part; also, the overall total antioxidants of the diet might be more important than the presence of any particular food. Nevertheless, some authors have debated about the applicability of the extrapolation of dietary TAC data to its antioxidant contribution in vivo [92]. Moreover, the ideal antioxidant supplement for cardiovascular prevention will certainly be one that will be able to reproduce as closely as possible the innate combination of antioxidants found in plant foods even if we cannot exclude the fact that the beneficial effects of the latter might be synergistic with other compounds. Strategies for the intervention and prevention of CVD require an understanding of the basic molecular mechanism(s) by prophylactic agents (synthetic antioxidants, dietary antioxidant factors from food plants and medicinal plants) that may potentially prevent or reverse the promotion or progression of the disease. It remains unequivocal that emerging scientific literature needs to balance by addressing toxicological concerns [93]. New knowledge of mechanisms involved in oxidant stress in tissues, ROS production, and the fate of antioxidants after their administration may lead to progress in improved outcomes and refined therapies for CVD.

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