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Paradoxical Effects of Plant-Originated Antioxidants on Hyperlipidemia: A Review

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ABSTRACT

Antioxidants protect the body's organs, but under certain conditions, they may increase oxidative stress and potentially induce organ damage. High-density lipoprotein (HDL) helps prevent cardiovascular disease by reducing oxidative stress and Low-density lipoprotein (LDL) oxidation. Although lipid oxidation contributes to atherosclerosis and antioxidants are generally beneficial, their exact impact remains unclear. A close relationship exists between medicinal plants and antioxidants, as many medicinal plants contain antioxidant compounds that can contribute to the health of the body. Medicinal plants are a class of plants that naturally contain various types of antioxidants. A number of antioxidant compounds have been identified in medicinal plants, including polyphenols, flavonoids, tannins, vitamins C and E. This review updates the recent findings and action mechanisms of antioxidants, focusing on the positive and negative roles of antioxidants in atherosclerosis with the aim of clarifying the knowledge gap. This article reviews the publications from 1991 to 2025 sourced from Google Scholar, PubMed, Web of Science, and Scopus, using terms such as Antioxidants, oxidative stress, free radicals, hyperlipidemia, lipid profile, and inflammation. The study updates the effects of Beta-carotene, Lutein, Quercetin, Silymarin, Betaine, Carotenoids, Lycopene, Flavonoids, Vitamins A, D, E, Selenium, Coenzyme Q10, and Epicatechin on blood lipids. Reactive oxygen species (ROS) contribute to heart diseases and hyperlipidemia. Antioxidants neutralize ROS and reduce oxidative stress, but the circumstances under which they may act as prooxidants should be considered in atherosclerosis therapy.
Keywords: Antioxidants, Oxidation, Free Radicals, Hyperlipidemia, Inflammation

INTRODUCTION

Several forms of reactive oxygen stress (ROS) are created within the body and contribute to the development of various diseases while also performing ROS-related physiological tasks. They are balanced by an antioxidant defense network that controls their activity to moderate ROS levels, allowing them to perform their physiological functions while reducing oxidative damage, which can contribute to disease progression [1]. The potential positive effects of antioxidants on the metabolic system include maintenance of balance by reducing oxidative stress in the body and beneficial effects on blood lipids. Antioxidants have been proven to be beneficial compounds that can prevent damage to cells caused by free radicals and have beneficial effects on blood lipids by reducing inflammation. It is evident that chronic inflammation is a contributing factor to increased blood lipid levels and the development of heart disease [2]. Furthermore, sufficient antioxidants may synergistically inhibit oxidative lipid damage and delay disease progression. Among the well-known peroxyl scavengers that block the chain reaction of lipid peroxidation, Vitamin C plays a pivotal role in lipid regulation by preventing LDL oxidation in the cell membrane [3]. It has been demonstrated that this substance enhances HDL levels while simultaneously protecting against LDL [4]. Although vitamin E is a potent antioxidant in its own right, its efficacy is augmented when taken in conjunction with other antioxidants, particularly beta-carotene and vitamin C. After neutralizing free radicals, vitamin E is regenerated from its oxidized form [5, 6]. Vitamin C helps to preserve vitamin E in its reduced state, thereby increasing the antioxidant power of α-tocopherol. These observations suggest that boosting total antioxidant capacity (TAC) levels and improving lipid profile, particularly by lowering the LDL/HDL ratio, may help prevent or reduce the course of cardiovascular disease (CVD) and related disorders. Thus, the unfavorable correlation between TAC and LDL levels is verified [5].

TAC is regarded as a reliable factor in controlling ROS-induced damage [7], preventing or treating various diseases, including cardiac disorders [8, 9]. Antioxidants are thought to protect against cardiovascular disorders by raising HDL levels. They have the capacity to minimize LDL oxidation, and by managing LDL levels, they may diminish the intensity of oxidative stress in the direction of atherosclerotic problems, CVD, blood pressure, or lipids [5, 9, 10].

It has been demonstrated that certain antioxidant supplements, including β-carotene, have the potential to elevate the risk of developing lung cancer in smokers and heart disease [11]. Moreover, the efficacy of antioxidant supplements in preventing or reducing the risk of several diseases, including bladder cancer, colon cancer, and non-melanoma skin cancer, has not been substantiated by scientific evidence [12]. In this regard, in some conditions, such as elevated concentrations, antioxidants may act as prooxidants, thereby amplifying oxidative stress rather than reducing it. This has the potential to result in an elevated risk of carcinogenesis and immunosuppression [13].

Antioxidants play an important role in preventing chronic diseases, such as cancer, heart disease, diabetes, and high blood pressure [14, 15]. Many medicinal and edible plants are rich sources of natural antioxidants. Consuming these plants can promote overall health. In

addition to medicinal herbs, plant foods such as berries, nuts, olive oil, tomatoes, potatoes, and mushrooms are rich in antioxidants, and consuming them is recommended [16].

This review updates the recent findings and action mechanisms of antioxidants, focusing on the positive and negative roles of antioxidants in atherosclerosis with the aim of clarifying the knowledge gap.

MATERIALS AND METHODS

Related articles between 1991 and 2025 were used from Google Scholar, PubMed, Web of Science, and Scopus scientific databases using the terms antioxidants, oxidative stress, free radicals, hyperlipidemia, lipid profile, and inflammation. We included randomized controlled trials, cohort studies, case-control studies, and meta-analyses that examined the effects of natural antioxidants on lipid levels. Studies that focused on synthetic antioxidants or those not related to lipid metabolism were excluded. Potential biases, including publication bias, funding bias, and selection bias, should be considered when interpreting studies on antioxidants and blood lipids.

RESULTS

A comprehensive list of antioxidants and their mechanisms of action related to hyperlipidemia is presented in Table 1. The effects of Beta-carotene, Lutein, Quercetin, Silymarin, Betaine, Vitamin A, Carotenoids, Lycopene, Flavonoids, Vitamins E, A, D, and Selenium antioxidants in blood fat have been focused on and discussed below.

Table 1 A comprehensive list of antioxidants and their mechanisms of action related to hyperlipidemia is presented

Row	Name	Mechanism	Study done	References
1	Beta Carotene	Lowers cholesterol, TG, LDL, and VLDL. Increases HDL	Marcelino G, *et al*: 2020	١٦
		Reduces insulin resistance and dyslipidemia	Rodriguez-Concepcion M *et al*: 2018	١٧
		Decreases the expression of CYP2E1 and apoptosis	Lin WT *et al*: 2009	18
			Yang S-C *et al*: 2004	١٩
2	Lutein	Reduces the level of lipid peroxidation and fibrosis, TNF-α, IL-1, IL-6,	Martin KR, *et al*: 2000	28
		Decreases gene expression of E-selectin, ICAM-1, and VCAM-1	Armoza A, *et al*: 2013	29
		*Decreases LDL cholesterol	Chung RW, *et a*l: 2017	30
			Hajizadeh-Sharafabad F, *et al*: 2019	31
3	Quercetin	Anti-inflammatory	Hajizadeh-Sharafabad F, *et al*: 2019	31
		Antioxidant	Ahmad N , *et al*: 2023	32
		Reducing the level of IL-6 ،IL-8 و ،TNF-α	Molina MF, *et al:*2003	33
		Increasing the levels of SOD, CAT, and GSH		
4	Silymarin	Decreased the levels of lipid peroxidation and TNF, increased GSH	Song Z, *et al*: 2006	34
		By inducing CYP2E1, it inhibited the production of ROS; it inhibited the oxidation of LDL cholesterol	Habib-ur-Rehman M, *et al:* 2008	35
			Brandon-Warner E, *et al*: 2010	39
5	Betaine	Increases vitamin A and GSH levels, decreases MDA levels	Kanbak G, *et al:* 2001	41
		Decreased liver level of lipids, homocysteine, endoplasmic reticulum stress, and apoptosis	Ji C, *et al:* 2003	42
6	Vitamin A	As a ligand for PPARβ/δ, regulation of lipid and sugar homeostasis	Barish, GD., *et al:* 2006	52
		It suppresses fat and insulin resistance	Lee, C. H, *et al:* 2006	53
			Gervois, P, *et al*: 2000	54
			Rabelo, R, *et al*: 1996	55
7	Carotenoids	*Decrease B (NF-κB) and 2 (Nrf2)	Kaulmann A, *et al*: 2014	58
		*Anti-inflammatory action	Bonet ML., *et al*: 2015	
		*Increased ROS		
		*Fat reduction activity		
8	Lycopene	Anti-ROS	Han G.-M, *et al:* 2016	[83, 84, 88]
		Anti-inflammatory	Luvizotto *et al*: 2013	73
		Increased HDL and reduced TC, LDL-c, TG	Guerendiain M, *et al:* 2017	77
		Decrease in Apo-A1 and Apo-B levels. Increase of GSH-Px, SOD, and CAT	Fenni S *et al:* 2017	84
			El-Khadragy MF *et al*: 2020	
9	Flavonoids	Anti-ROS	Goliomytis *et al:* 2014	88
		Anti-inflammatory	Pradeep *et al:* 2008	93
		Increased GSH, GSHPx, GR, GST, and reduced MDA	Rajadurai *et al*: 2009	92
		Increased HDL and reduced TC, LDL-c, TG, and MDA	Zhang, N *et al*:2010	95
		*Reduced the level of, IL-6, IL-8,,TNF-α	Wang, S *et al:*2010	94
10	Vitamins A, D, E	Anti-ROS	Ziegler M, *et al*: 2020	101
		Anti-inflammatory		
		Reduction of TC , TG, LDL		
11	Selenium	Anti-ROS[156]	Oztürk, *et al:* 2015	116
		Increased NO, GPx, and decreased MDA	Cosentino-Gomes D, *et al:* 2012	119
		Improved endothelial function		

12	Coenzyme Q10	It is an intracellular antioxidant that prevents senescence and dysfunction caused by oxidative stress CoQ10 deficiency, which usually occurs with aging, has been shown to increase the risk of type 2 diabetes mellitus (T2DM) CoQ10 supplementation significantly decreased lipoprotein (a) [Lp(a)] levels among patients with obesity, T2DM, and CVD, mainly in those with Lp(a) ≥ 30 mg/dL.	Singh U, *et al:* 2007 Shen Q, *et al*: 2007 Suksomboon N, *et al*: 2015	122 124 127
13	Epicatechin	A notable finding was the significant reduction in serum levels of IL-6 and 8-isoprostane in WKY-HFHC rats. Reducing TAG, MDA, and LDL levels.	Morrison M, *et al*: 2014 Gutiérrez-Salmeán G, *et al*: 2014 Xiong M, et al: 2014	130 131 132

TG (Triglycerides), LDL (Low-Density Lipoprotein), VLDL (Very Low-Density Lipoprotein), HDL (High-Density Lipoprotein), PPARβ/δ (Peroxisome Proliferator-Activated Receptor Beta/Delta), ROS (Reactive Oxygen Species), GSH (Glutathione), SOD (Superoxide Dismutase), CAT (Catalase), GSH-Px (Glutathione Peroxidase), GR (Glutathione Reductase), GST (Glutathione S-Transferase), MDA (Malondialdehyde), Apo-A1 (Apolipoprotein A1), Apo-B (Apolipoprotein B), NF-κB (Nuclear Factor Kappa B), Nrf2 (Nuclear Factor Erythroid 2-Related Factor 2), ICAM-1 (Intercellular Adhesion Molecule 1), VCAM-1 (Vascular Cell Adhesion Molecule 1), IL-6 (Interleukin-6), IL-8 (Interleukin-8), TNF-α (Tumor Necrosis Factor Alpha), CYP2E1 (Cytochrome P450 2E1), NO (Nitric Oxide), GPx (Glutathione Peroxidase), CoQ10 (Coenzyme Q10), T2DM (Diabetes mellitus type 2), TAG(Triglyceride), MDA(Malondialdehyde).

Beta-carotene

Plant families that contain beta-carotene include the Apiaceae and Rutaceae families, as well as dark green plants [17]. Beta-carotene (β-carotene), the most metabolically active carotenoid, has been intensively examined for its possible health benefits. Dietary inclusion of β-carotene from Indigofera leaves in a high-fat diet significantly lowered hepatic fatty acid synthesis due to the inhibition of acetyl-CoA carboxylase. This effect on the liver results in lower triglyceride levels in the blood and may lead to significant fat reduction in the liver. In addition, β-carotene helps to lower cholesterol but does not affect the HDL level [18].

Several epidemiological studies have found an inverse relationship between circulating β-carotene levels and the risk of hypertension, type 2 diabetes, cardiovascular disease, and obesity [19, 20] Furthermore, β-carotene consumption contributes to the prevention of metabolic risk factors, particularly the reduction of LDL and VLDL cholesterol, the increase of HDL cholesterol, and the improvement of insulin resistance [21].

In general, β-carotene protects against the development of oxidative stress-related disorders by inhibiting insulin resistance, dyslipidemia, degenerative diseases, and certain types of cancer [22].

The main source of β-carotene, which is a precursor to vitamin A, is found in a wide range of foods, including spinach, amaranth, carrots, mangoes, corn, lentils, and other dark green leafy vegetables. In vitro experiments using hepatocytes from ethanol-fed rats have demonstrated that β-carotene has benefits that go beyond its basic nutritional role. These benefits include increased CAT activity, cell viability, and glutathione levels, all of which are important for maintaining cellular health. The study of the effects of ethanol on rat liver cells has determined that the use of β-carotene is essential for reducing hepatic damage because, in addition to enhancing antioxidant defenses and attenuating oxidative stress, it inhibits apoptosis and the expression of CYP2E1 [23-25].

β-carotene's protective benefits are directly related to the action of nuclear factor erythroid 2-related factor 2 (NRF2), a basic leucine zipper protein (bZIP) that regulates the synthesis of antioxidant proteins, avoiding oxidative damage caused by injury or inflammation. β-carotene, by activating NRF2, may further reduce caspase activity, avoiding apoptosis, and function as a lipotropic agent, increasing fat mobility from the liver and lowering lipid synthesis [26, 27].

Studies have demonstrated that β-carotene plays a dual role in lipid oxidation, acting either as an antioxidant or a pro-oxidant depending on the surrounding conditions. Under mild to moderate oxidative stress, β-carotene serves as an effective antioxidant by neutralizing ROS and preventing lipid peroxidation. Its protective effect is particularly notable in quenching singlet oxygen and capturing lipid radicals, thereby helping to preserve the integrity of lipid membranes [28].

Conversely, in environments with high oxygen levels, such as the lungs of smokers, β-carotene may shift to a pro-oxidant role. In these conditions, it can actually promote lipid peroxidation and increase oxidative stress, potentially contributing to harmful outcomes like a heightened risk of cancer. This pro-oxidant effect becomes more pronounced at elevated concentrations, where β-carotene may facilitate oxidation reactions through auto-catalytic mechanisms[29].

Lutein

Lutein, a naturally occurring xanthophyll and carotenoid, is high in green leafy vegetables such as *Brassica oleracea* (Fig. 1), kale, and spinach, as well as fruits like avocado and kiwi. It has been well established that lutein has very strong anti-ROS activities. Thus, the hepatic protective effects of lutein have gained much attention. In terms of animal studies, it was established that lutein exerts substantially hepato-protective action against a wide spectrum of xenobiotics, including paracetamol, carbon tetrachloride, and alcohol. These studies revealed that lutein supplementation could significantly reduce liver damage markers such as aminotransferases, alkaline phosphatase, and bilirubin. Besides, lutein decreases lipid peroxidation and conjugated hydroperoxides that act as oxidative stress indicators and liver damage. In ethanol-exposed rats, lutein has been shown to reverse the hepatic histological changes, mainly by decreasing hydroxyproline levels, which is an indicator of fibrosis. This liver protection has been improved by an increase in important antioxidant enzymes, including superoxide dismutase (SOD), glutathione (GSH), and Glutathione *S*-transferase (GST). Lutein has been shown to lower inflammatory cytokines in serum, including IL-6, IL-1β, TNF-α, and MCP-1, indicating its anti-inflammatory properties. Furthermore, the beneficial modulation of NRF2 expression in the liver shows that lutein strengthens the body's natural defenses against oxidative stress. Beyond its liver-protective properties, besides protecting the liver, lutein improves lipid metabolism. Lutein supplementation has improved lipid profiles [30, 31], probably due to an increase in HDL, which has protective effects against cardiovascular disease [32]. Lutein has been shown to decrease adhesion molecule expressions, including VCAM-1. E-selectin and ICAM-1 in IL-1β-stimulated human aortic endothelial cells (HAECs) [33]. It reduces leukocyte adherence to the endothelium by lowering ICAM-1 and VCAM-1 expression, which is a key stage in the development of atherosclerosis [34]. Furthermore, Chang et al. found that lutein supplementation reduced peripheral blood mononuclear cells (PBMCs) in patients with stable angina in a dose-dependent manner, indicating that it has the potential to reduce inflammatory processes associated with cardiovascular conditions [35]. Another mechanistic review previously explored the effects of lutein on cardiovascular risk factors, placing a special emphasis on dyslipidemia. The authors concluded that the positive effects of lutein on the lipid profile are modulated almost entirely by its influence on some key receptors involved in lipid metabolism. Lutein appears to improve the function of LDL-cholesterol receptors and SR-B1. These receptors play an important role in the removal of LDL cholesterol from the bloodstream and the transfer of cholesterol from peripheral tissues to the liver. Lutein promotes these activities, which help to lower plasma cholesterol and enhance overall lipid profiles [36].

Fig. 1 *Brassica oleracea*

Quercetin

Quercetin is a flavonoid available in various foods and herbs such as tea (*Camellia sinensis*), citrus fruits, black wheat, cabbage, peppers (*Capsicum annuum*), ephedra (*Ephedra gerardiana*), strawberries, *Achillea chamomile*, *Hypericum perforatum*, and onions (Fig. 2) [37]. Quercetin expresses an extended profile of antioxidant and anti-free radical activity, which counteracts the process of oxidative stress, protecting cells from being damaged. Besides, it has anti-inflammatory properties that add to the general health advantages and therapeutic potential. Quercetin exerts remarkable hepatoprotective and anticancer activity. In vitro studies have shown a potential capacity for quercetin to reduce lipid peroxidation and GSH levels, thereby reducing ethanol-induced liver cell damage. It also suppresses the release of AST and LDH from liver cells, while increasing heme oxygenase-1 by activating the MAPK/NRF2 signaling in the liver [38].

In animal studies, the protective benefits of quercetin have been revealed against hepatotoxicity. Quercetin therapy significantly lowered serum levels of TG, ADH, AST, ALT, GGT, and pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6). Similarly, in ethanol-intoxicated rats, it has been reported that quercetin treatment not only significantly reversed the ethanol-induced elevation of blood aminotransferases but also reversed liver tissue lipid peroxides and hydroperoxides. Additionally, quercetin enhanced the activity of key antioxidant enzymes, including glutathione peroxidase (GPx), glutathione reductase, and SOD, further emphasizing its hepatoprotective and antioxidative capabilities [39].

Fig. 2 *Camellia sinensis*

Silymarin

Silymarin is a flavonoid compound extracted from the seeds of the milk thistle plant, *Silybum marianum* plant [40]. Silymarin, prepared from *Silybum marianum* (Fig. 3), is used for liver disease [40]. This compound contains a multitude of flavonolignans, such as silibinin A and B, isosilibinin A and B, silydianin, and silychristin. Silymarin has demonstrated considerable liver protection in both acute and chronic ethanol poisoning models. It decreases liver lipid peroxidation and TNF production, restores the level of GSH, and treats liver microvesicular steatosis. Furthermore, silymarin lowers oxidative stress in the liver caused by ethanol, principally by inhibiting ethanol-induced lipid buildup, downregulating mRNA expression for procollagen alpha 1 (I), and decreasing collagen type 1 levels in the liver [41-43].

Further in vitro experiments demonstrated that silymarin or its main constituent, silybin, significantly inhibits hydroxyl and hydroxyethyl radical generation induced by ethanol metabolism. This activity inhibits the activation of CYP2E1 and hence helps to avoid the generation of ROS. Silymarin has also been demonstrated to reduce the proliferation of liver cancer cells, revealing its liver protection potential [44-46].

Evidence suggests that in the presence of metal ions, such as iron, silymarin can exhibit pro-oxidant behavior by promoting the formation of ROS. This effect is largely attributed to iron-catalyzed oxidation processes, which result in the production of hydroxyl radicals and other reactive intermediates associated with oxidative damage. The pro-oxidant potential of silymarin appears to be most significant at higher concentrations and in conditions where metal ion levels are elevated.[47].

Fig. 3 *Silybum marianum*

Betaine

This substance, also known by other names such as trimethylglycine (TMG), is found in Betaine, also known as trimethylglycine, an antioxidant produced from choline in the body, and is found in foods and plants such as *Beta vulgaris*, Spinacia oleracea, *Avena sativa* (Fig. 4), and *Triticum aestivum [48]*.

In animal studies, this compound exerts significant hepatoprotective effects, especially in ethanol-induced hepatic injury. According to research, betaine supplementation can reduce hepatotoxicity by boosting liver levels of vitamin A and GSH, decreasing malondialdehyde content in liver tissue, and lowering serum aminotransferase levels when compared to animals treated with ethanol alone [49].

It has benefits in lowering hepatic lipid levels, homocysteine concentrations, endoplasmic reticulum stress, and apoptosis. Lowering homocysteine levels promotes the migration of triglycerides away from the liver, reducing endoplasmic reticulum stress [50]. Betaine has been found to decrease ethanol-induced elevations in liver lipid peroxides, liver triglycerides, and serum aminotransferase levels in animal models of guinea pigs. Moreover, betaine prevents ethanol-induced hepatic GSH depletion, an observation that further supports its involvement in protecting the liver from oxidative stress and in maintaining cellular health [51].

Fig. 4 *Beta vulgaris*

Vitamin A

Vitamin A is found in many foods, including *Daucus, Cucurbita maxima* (Fig. 5), *Pomoea batatas, Capsicum annuum, Ice cream, and beef liver [52]*. Several studies support the point that vitamin A possesses crucial roles in the regulation of fat and energy balance. For instance, the administration of vitamin A resulted in weight loss for mice [53]. Additionally, genetic variation in enzymes involved in vitamin A metabolism in mice has been associated with obesity alterations [54, 55]. It has also been demonstrated that vitamin A or its active derivative, retinoic acid, treatment impacts the expression of genes associated with lipid metabolism, which is relevant to the control of energy homeostasis [53, 56]. Despite these discoveries, the particular molecular pathways behind these effects remain unclear. Vitamin A acts as a natural ligand for peroxisome proliferator-activated receptor beta/delta (PPARβ/δ) beyond the classic actions on nuclear receptors, like retinoic acid receptors (RARs) [57-59]. This higher-than-expected biological activity might suggest that vitamin

A does more physiological tasks than those currently perceived. One of the major functions described for the RA receptor PPARβ/δ is the modulation of glucose and lipid balance in adipose tissue and other tissues, thus ensuring its importance for metabolic regulation [60-62].

PPARβ/δ agonists have been proposed as therapeutic candidates for the management of metabolic syndrome [3]. The finding that retinoic acid (RA) binds to PPARβ/δ raises the intriguing prospect that this hormone is essential for controlling glucose and lipid metabolism. Classical RARs can control energy and fat homeostasis. Based on the existing data, RARs and PPARβ/δ may stimulate critical proteins such as apolipoprotein A1 (apo A1), necessary for the transportation of lipids like plasma cholesterol, and uncoupling protein 1 (UCP1), dealing with energy dissipation. Administration of RA improved glucose tolerance and reduced fat mass in obese mice, as observed in earlier studies. These advantageous effects can be ascribed to the simultaneous activation of RARs and PPARβ/δ in a variety of tissues, such as the adipose tissue, muscle, and liver. Due to its dual activation, RA may be especially useful in lowering insulin resistance and obesity, underscoring its special potential as a therapeutic agent that targets both nuclear receptors [63-65].

PPARβ/δ is an essential regulator of energy balance; its biological activities also include direct control of genes related to glucose and lipid metabolism. Such activation of PPARβ/δ has been reported to enhance lipid catabolism in skeletal muscle and adipose tissue, contributing to the prevention and treatment of obesity.

Research indicates that vitamin A can act as a pro-oxidant, primarily due to its ability to generate ROS through pathways involving xanthine oxidase. In vitro studies have shown that this enzyme catalyzes the conversion of retinol to retinoic acid, a reaction that concurrently produces superoxide radicals. This ROS production is stimulated by the presence of NADH and can be effectively suppressed by allopurinol, a known inhibitor of xanthine oxidase. In Sertoli cells, exposure to retinol has been associated with increased xanthine oxidase activity, leading to elevated ROS levels, protein damage, and cellular toxicity. Notably, inhibiting the oxidation of retinol to retinoic acid may further amplify these pro-oxidant effects [66].

Fig. 5 *Cucurbita maxima*

Carotenoids

Carotenoids are plant pigments that are responsible for the bright red, yellow, and orange colors of many fruits and vegetables, especially *Lycopersicon esculentum* Mill. (Fig. 6) [67]. Studies have indicated that carotenoids can scavenge ROS and interact with transcription factors, including NRF2 and NF-κB, that are implicated in inflammation and oxidative stress [68].

It is becoming more widely acknowledged that the state of obesity and high amounts of fat storage are associated with high levels of systemic oxidative stress and inflammation. A greater Dietary Antioxidant Index (DAI) is protective against obesity, whereas a greater Dietary Inflammatory Index (DII) diet is associated with increased obesity risks [69-71].

The role of carotenoids in regulating adipocyte function is becoming important. These substances interact with important transcription factors, including retinoid X receptors (RXR), RARs, and peroxisome proliferator-activated receptors (PPARs), together with their metabolites known as apocarotenoids. These interactions control adipocyte growth and function by influencing lipid oxidation, storage mechanisms, differentiation of adipose tissue, inflammation, and oxidative stress [72].

Research on commonly studied carotenoids like β-carotene, phytoene, and phytofluene has increased as a result of multiple studies showing a positive correlation between carotenoids and body composition [73]. Because of their potential value in dietary assessment, blood-stream carotenoids have also been employed as indicators of fruit and vegetable consumption [74]. The markers of inflammation, such as CRP, IL-6, and TNF-α, declined significantly with carotenoid supplements, especially astaxanthin and lutein/zeaxanthin [75]. In addition, carotenoids induce antioxidant enzyme activity, such as CAT, superoxide dismutase, and glutathione peroxidase, which aid in the body's intrinsic antioxidant mechanisms. Additionally, they interact with transcription factors that are essential to cellular antioxidant responses, such as NRF2 [76]. It has been postulated that carotenoids exert their protective actions by inducing the expression of vitagenes, which are genes responsible for maintaining cellular homeostasis [77].

Carotenoids are widely recognized for their antioxidant capabilities; however, their activity can shift depending on the cellular environment, allowing them to function as either antioxidants or pro-oxidants. Under normal physiological conditions, compounds such as β-carotene, lycopene, and astaxanthin serve as effective antioxidants by neutralizing ROS and reducing oxidative stress. In contrast, within cancer cells, which naturally exhibit elevated ROS levels, carotenoids may exert pro-oxidant effects, promoting ROS-induced

apoptosis as a potential anticancer mechanism [28]. Additionally, even carotenoids typically regarded as robust antioxidants, such as astaxanthin, have demonstrated pro-oxidant behavior under certain conditions, highlighting the context-dependent nature of their redox activity [78].

Fig. 6 *Lycopersicon esculentum Mill*

Lycopene

Lycopene is a natural pigment that gives certain fruits and vegetables their red color. This substance, which is abundant in tomatoes (Fig. 7), is a powerful antioxidant [79]. Anti-obesity products have employed a variety of plant metabolites as substitutes for traditional methods of managing obesity [80, 81]. Lycopene (LYC), which mainly exists in tomatoes, grapefruit, watermelon, and apricots, stands out due to its high antioxidant capacity [82]. LYC is one of the carotenoids having the utmost antioxidant potential and elicits potent anti-inflammatory and antioxidant actions. These characteristics imply that LYC might aid in lowering the risk of obesity and associated disorders connected to oxidative stress and inflammation [83, 84].

Several research studies have proven that LYC has an outstanding effect on obese patients who have high levels of HDL, which lowers atherosclerosis risks. The ability to accumulate in the liver contributes to its efficacy in preventing fat accumulation [85]. Therefore, LYC supplementation can reduce serum TG, TC, and LDL-c levels but increase the HDL-c levels in obese rat models. These findings are in agreement with previous reports that LYC supplementation improved serum biomarkers associated with lipid metabolism [85-87].

High plasma LYC levels are associated with a decrease in body weight, obesity, and changes in serum lipid profile, especially in adolescents [88]. It has been demonstrated that LYC metabolites, including apo-12'-lycopene, improve adiponectin secretion, boost glucose absorption, and facilitate adipocyte differentiation [89]. Also, administering LYC and resveratrol together can lessen the production of lipid droplets in human white adipocytes in vitro [90].

Other than the transportation of lipids, HDL is important because it exerts anti-inflammatory, antithrombotic, and vasodilator activities. For such features, HDL represents an intervening factor in preventing obesity-associated cardiovascular diseases. As such, drug and nutrition strategies to increase HDL levels are employed for the treatment of obesity and its etiology [91].

Lycopene supplementation has been demonstrated to reduce levels of Apo-A1 and Apo-B; the latter is the major apolipoprotein associated with LDL-C. A significant reduction in levels of TC follows this reduction in Apo-B. This result agrees with other research where supplementation with a high dose of lycopene significantly reduced the levels of leptin in rats, a hormone involved in the regulation of appetite and fat storage [92, 93].

The remarkable antioxidant properties of lycopene might be due to its potential to induce the NRF2. In the process of inducing the production of the cytoprotective genes, NRF2 plays an important role in regulating the antioxidant cellular defense system. Important antioxidant enzymes, including GPx, SOD, and CAT, are more readily synthesized as a result of this activation. These enzymes take part in the detoxification of the excess electrophilic molecules produced in conjugation procedures, such as ROS, which protect cells against oxidative damage [94, 95].

Laboratory investigations have revealed that lycopene can exhibit pro-oxidant behavior under certain oxidative conditions. For example, at a concentration of 20 μM, lycopene significantly increased lipid peroxidation triggered by a lipid-soluble radical initiator (AMVN). In contrast, it was found to reduce lipid peroxidation induced by ferric nitrilotriacetate (Fe/NTA), indicating a context-dependent response [96]. Furthermore, lycopene has been shown to promote the formation of hydroperoxides in triglyceride oxidation models, reinforcing its potential pro-oxidant role. Interestingly, this effect was reversed in the presence of α-tocopherol, suggesting that the pro-oxidant activity of lycopene may be influenced by its interaction with other antioxidants [97].

Fig. 7 *Solanum lycopersicum*

Flavonoids

Flavonols are the major group of flavonoids, and they include kaempferol, quercetin, and myrcene. These three flavonols are found in significant amounts in tea (Fig. 8) and fruits [98]. Plants' yellow, orange, and red coloring is caused by a broad class of polyphenols called flavonoids, which are prevalent in diets derived from plants [99]. Flavonoids are known for their excellent antioxidant activities [100]. In abundance in citrus fruits, one of the common flavonoids is hesperidin, known to exert potent antioxidant properties that prevent oxidative stress and peroxidation of lipids and cholesterol [101]. Additionally, flavonoids have been linked to reducing blood cholesterol levels [102, 103]. These substances decrease the activity of malondialdehyde (MDA) while enhancing some important antioxidant enzymes like Glutathione reductase (GR), glutathione (GSH, glutathione peroxidase (GPx, and glutathione S-transferase (GST). SOD activity is not impacted by dietary hesperidin, although it has been demonstrated that supplementing with quercetin increases SOD activity. Of these flavonoids, quercetin is effective at increasing the activity of antioxidant enzymes [104]. Studies have revealed that flavonoids dramatically reduce blood levels of TG, LDL-C, and TC. Furthermore, consumption of flavonoids is associated with lower serum concentrations of important indicators of liver function, such as ALP, ALT, and AST. Histopathological examinations of liver tissue in the flavonoid-treated hamsters revealed that there was a significant improvement in the damaged areas compared to the animals in the high-fat diet HFD group. It was reported that flavonoid treatment restored the levels of the essential enzyme CYP7A1, or cholesterol 7-alpha hydroxylase. Subsequent research has shown that flavonoids reduce MDA levels in response to tissue damage and inflammation by altering the activity of SOD and mitigating oxidative stress and free radical damage. Flavonoids also exert their protective effects against oxidative and inflammatory damage by participating in reducing pro-inflammatory cytokines such as IL-6 and TNF-α. Furthermore, flavonoids increase RNA levels and protein expression of peroxisome proliferator-activated receptors such as PPAR-α and PPAR-γ in hyperlipidemic hamsters' liver, adipose tissue, and skeletal muscle. This boost helps to reduce serum cholesterol levels in these hamsters by increasing liver function, which is mostly due to the antioxidant and anti-inflammatory characteristics of flavonoids. These benefits probably occur through processes that activate PPARα and PPARγ pathways, which are key modulators of lipid metabolism and general metabolic health [105-107].

Flavonoids, while widely recognized for their antioxidant properties, can also exhibit pro-oxidant behavior, particularly in the presence of transition metals such as copper (Cu^{2+}) and iron (Fe^{2+}). This pro-oxidant activity is linked to their ability to chelate metal ions, which can subsequently catalyze the generation of ROS through mechanisms similar to Fenton reactions. A key aspect of this process involves the redox cycling of flavonoids, during which they may generate free radicals capable of damaging critical biological macromolecules, including lipids, proteins, and DNA [108, 109].

Fig. 8 *Camellia sinensis*

Vitamins E, A, and D

Vitamins A and E are known for their ability to act as antioxidants [110]. As a result of its conjugated diene link, vitamin A binds to peroxidized free radicals, which, in turn, reduces the damage caused by free radicals and, therefore, lipid peroxidation [111]. Vitamin E is an effective free radical scavenger, helping to prevent lipid peroxidation. Lacferrol, a hydrolysis product of vitamin E, has potent antioxidant and anti-inflammatory activities [112]. Numerous studies have shown that vitamin A/TG and vitamin E/TG levels are higher in people with coronary heart disease (CHD) than in controls, indicating a strong connection. The data showed that low levels of vitamin A were related to an increased risk of CHD. In addition, vitamin E plays an important role in lipid metabolism, contributing to the breakdown and metabolism of fats, thus reducing the chances of developing atherosclerosis. [113, 114].

Fat-soluble vitamins reduce inflammation by turning on the receptor, the so-called retinoid-related receptor α (RORα). RORα regulates macrophage polarization, plaque stability, and intraplaque inflammation, leading to vascular protection and a lower risk of inflammatory illnesses [115, 116]. Furthermore, vitamin E has been found to slow the narrowing of artery walls by reducing smooth muscle cell proliferation [117]. It also helps to reduce platelet release, accumulation, and adhesion, preventing atherosclerosis [118].

Vitamin D (VD) is largely found in two active forms: VD2 and VD3, with 25-hydroxyvitamin D [25(OH)D], particularly VD3, serving as a good marker for VD levels [119]. Plasma VD3/TG levels were found to be inversely correlated with TC, TG, and LDL levels. Wang S. found that VD3 increased the expression of LDL receptors on hepatocytes, which improves their activity and lowers blood LDL content. Furthermore, VD3 promotes timely lipid breakdown while inhibiting lipid synthesis, returning lipid levels to normal during disturbed lipid metabolism [120].

Despite earlier findings suggesting that vitamin E may help lower the risk of cardiovascular disease, these benefits have not been consistently supported by randomized controlled trials. For example, the HOPE study found no significant reduction in cardiovascular events following vitamin E supplementation. Moreover, high doses of vitamin E have been associated with an increased risk of bleeding and other adverse effects, particularly in individuals with underlying health conditions or those taking anticoagulant therapies [121, 122].

There are a lot of medicinal plants, such as *Cannabis sativa*, that exhibit potent antioxidant and vasorelaxant activity, along with immunomodulatory effects, which together support the broader role of plant-derived compounds in vascular protection and mitigating oxidative stress, concepts that parallel the mechanisms attributed to vitamins A and E (e.g., free radical scavenging, vascular dilation, inflammation reduction) [123].

Selenium

Selenium is an essential element for the body. Selenium is present in many plants and foods, including fruits, vegetables, grains, fish, nuts, and dairy products (Fig. 9) [124]. Selenium (Se), a trace element, has been shown in both experimental and clinical tests to be an effective antioxidant, protecting tissues against damage [125]. Se has been recognized for its preventive and restorative effects on diabetic endothelium dysfunction, principally by increasing nitric oxide (NO) bioavailability [126-128].

Oztürk et al. showed Se effects on the dysfunction of endothelial cells and NO bioavailability in mouse models with type 2 diabetes fed on a high-fat diet (HFD) and low-dose STZ and found that Se was effective in restoring blood glucose, lipid profiles, and MDA levels to normal in type 2 diabetic rats whose diabetes was induced by hypoglycemia. Additionally, Se treatment increased the levels of GPx in rats with diabetes, while the levels of SOD remained unchanged [129]. Se has been demonstrated to decrease oxidative stress, which improves endothelial dysfunction associated with diabetes and dyslipidemia. Hyperglycemia and dyslipidemia are known to cause an overproduction of ROS, such as superoxide. NADPH oxidase is a crucial enzyme that generates superoxide, which leads to NO breakdown in blood vessels. The reaction between superoxide and NO leads to peroxynitrite production and reduces NO bioavailability, which is essential for vasorelaxation, which is dependent on the endothelium. In animal models of diabetes and dyslipidemia, there was a marked increase in mRNA expression and activity of NADPH oxidase, leading to an increased generation of superoxide [130].

Studies have shown that upregulated NOX-4 mRNA expression increases the levels of NO and decreases endothelial dysfunction. Dyslipidemia triggers PKC, which further triggers NOX. This process finally leads to ROS production. ROS levels are regulated by the activation of the signaling complex PKC/NOX. This regulation could trigger proapoptotic signals via the MAPK pathway or anti-apoptotic signals through NF-κB pathway activation [131, 132].

Selenium plays a dual role in biological systems, acting as either an antioxidant or a pro-oxidant depending on its concentration and chemical form. At appropriate physiological levels, selenium supports antioxidant defenses by working synergistically with selenoenzymes such as glutathione peroxidase, which help neutralize ROS and reduce oxidative stress. However, when administered at high or supranutritional doses, selenium can exhibit pro-oxidant properties, potentially contributing to cellular oxidative damage [133]. For instance, inorganic selenium compounds, such as selenite, have been observed to react with thiol-containing molecules, including glutathione, to form selenotrisulfides. This redox interaction also results in the generation of superoxide anions and other ROS, thereby promoting oxidative stress through a self-sustaining cycle [134].

Fig. 9 *Cicer arietinum*

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a fat-soluble compound that resembles a vitamin. Fruits, seeds, legumes, vegetables, and Fish are full of Q10 [135]. The damage induced by free radicals is proposed to play an important role in endothelial dysfunction and atherogenesis. Coenzyme Q10 (CoQ10) is an intracellular antioxidant that prevents senescence and dysfunction caused by oxidative stress [136]. CoQ10 is commonly used to treat cardiomyopathy, and heart function has been remarkably improved following CoQ10 supplementation [137]. CoQ10 deficiency, which usually occurs with aging, has been shown to increase the risk of type 2 diabetes mellitus (T2DM) [138] and CVD On the other hand, there are trials evaluating the effects of CoQ10 on lipid profiles with inconclusive results. We have previously shown in a meta-analysis that taking CoQ10 by patients with metabolic disorders significantly reduced serum triglyceride levels, yet did not affect other lipid profiles [139]. In another meta-analysis conducted by Sahebkar et al [140]. CoQ10 supplementation significantly decreased lipoprotein (a) [Lp(a)] levels among patients with obesity, T2DM, and CVD, mainly in those with $Lp(a) \geq 30$ mg/dL. However, in another meta-analysis conducted by Suksomboon et al [141]. CoQ10 supplementation had no beneficial effects on lipid profiles or blood pressures among diabetic patients.

Under certain conditions, particularly at elevated concentrations or in the presence of metals such as zinc (Zn), CoQ10 has been shown to exhibit pro-oxidant behavior. For example, when CoQ10 is combined with zinc, its antioxidant capacity may be diminished, potentially leading to increased production of ROS and consequent cellular damage. This dual nature of CoQ10 highlights the complexity of its role in maintaining redox homeostasis; depending on the environmental context and dosage, it can either mitigate or contribute to oxidative stress.

In summary, although CoQ10 is predominantly regarded as an antioxidant, its potential to act as a pro-oxidant under specific conditions necessitates careful evaluation of its therapeutic application, especially in contexts characterized by oxidative stress and metal ion interactions [142, 143].

Epicatechin

Epicatechin is a bioactive plant phytochemical found in certain plants, such as grapes, tea, and cocoa (Fig. 10). Studies have indicated that consuming products with high levels of epicatechin may offer numerous health benefits [144]. Epicatechin has been demonstrated to exert a substantial effect in reducing markers associated with oxidative stress and inflammation in obese animals. A notable finding was the significant reduction in serum levels of IL-6 and 8-isoprostane in WKY-HFHC rats. In agreement with current knowledge [145]. The findings of this study suggest that the administration of epicatechin at a dose of 5 mg/kg/d is efficacious in the attenuation of inflammation and oxidative stress in states of obesity and metabolic distress.

In accordance with the extant literature, epicatechin treatment resulted in a significant decrease in serum TAG levels by over 50% in WKY-HFHC rats. The study demonstrated a significant decrease in LDL concentrations, with a 45.9% reduction observed in WKY-HFHC rats. Serum HDL levels were increased by 27·9 % in WKY-HFHC rats. The prevailing hypothesis concerning the mechanism by which epicatechin exerts its effect on plasma lipid concentrations is that it does so by enhancing oxidative metabolism, thereby promoting the structure and function of mitochondria [146].

Catechins have also been demonstrated to be effective in improving lipid peroxidation by reducing the levels of lipid peroxidation products such as MDA, 4-hydroxynonenal (4-HNE), and F2 isoprostane (PGF-2α). It has been demonstrated through experimental means that catechins have the capacity to reduce levels in a manner that is effective in the alleviation of lipid metabolism disorders arising from oxidative stress. The process of free radical oxidation modifies lipids, and the final product of lipid peroxidation is MDA [147].

While epicatechin is known for its beneficial effects, it also has the potential to act as a pro-oxidant, particularly when transition metal ions like copper and iron are present. In such conditions, epicatechin can catalyze the formation of hydroxyl radicals and superoxide anions, leading to oxidative stress and damage to cellular components, including DNA, proteins, and lipids. The pro-oxidant activity of epicatechin is particularly pronounced in the presence of metal ions, which facilitate its oxidation and conversion into polymerized polyphenols, thereby amplifying its pro-oxidant effects [148].

Fig. 10 *Theobroma cacao*

Adverse Effects of Antioxidants

The most prevalent forms of antioxidants encompass vitamins (A, C, and E), β-carotene, minerals such as selenium, and natural polyphenols. The effects of these substances on body cells are known to vary. It is evident that vitamins, in conjunction with β-carotene, are equipped with conjugated double bonds and functional groups, which collectively contribute to their capacity as antioxidants and the pigmentation exhibited in various fruits and vegetables. Whilst the medical community acknowledges the potential adverse effects of these substances, members of the general population frequently overestimate the toxicity of the substances. Czernichow conducted a study over a period of 7.5 years to examine the impact of antioxidant supplementation on the incidence of metabolic syndrome (MetS). The present study examined the correlation between baseline serum antioxidant levels and the future likelihood of developing metabolic syndrome (MetS) [149]. The investigation revealed that antioxidant supplementation did not yield any advantageous outcomes in a population with adequate nutrition. However, baseline serum antioxidant concentrations of β-carotene and vitamin C exhibited a negative correlation with the risk of MetS. Baseline serum zinc concentrations were positively associated with the risk of developing MetS [149, 150]. The analysis of data from a total of thirteen prospective cohort studies revealed no clear evidence of a direct correlation between the intake of vitamins A, C, and E and the risk of developing colorectal cancer. However, a higher overall intake of these nutrients was observed to be associated with a reduced risk of colorectal cancer. Furthermore, the utilization of multivitamins, particularly those comprising individual vitamins, has been demonstrated to exhibit an inverse correlation with the risk of developing colon cancer. A deficiency in antioxidant vitamins and minerals has been demonstrated to be a contributing factor to the development of cardiovascular diseases and cancer. Following a period of 7.5 years, the ingestion of low-dose antioxidant supplements resulted in a reduction of total cancer incidence and all-cause mortality among male subjects. However, no such effect was observed among female subjects, a phenomenon that may be attributed to the lower baseline levels of certain antioxidants, such as β-carotene, in female subjects [151].

Prooxidant Effects of Antioxidants

It has been reported that certain well-known antioxidants may, in fact, exhibit prooxidant properties. It is evident that a minimum of three factors have the capacity to influence the functionality of an antioxidant, thereby inducing its conversion into a pro-oxidant. These pivotal factors encompass the presence of metal ions, the antioxidant's concentration within its matrix environment, and its inherent redox potential [152, 153]. Vitamin C is a highly efficacious antioxidant; however, its capacity to act as a prooxidant is contingent upon the dosage. The substance has been demonstrated to exhibit an antioxidant effect at low dosages (30-100 mg/kg body weight) and a prooxidant effect at high dosages (1000 mg/kg body weight) [154, 155]. The prooxidant effect of vitamin C has been observed to occur in the presence of iron, resulting in the reduction of Fe^{3+} to Fe^{2+}. In addition, the presence of copper has been shown to induce the reduction of Cu^{2+} to Cu [156]. It has been established that a decline in transition metals results in a reduction of hydrogen peroxide to hydroxyl radicals via the Fenton reaction [157, 158]. α-Tocopherol, a compound that has been studied for its antioxidant properties, is also capable of acting as a prooxidant when present in high concentrations. Upon exposure to ROS, the subject undergoes a transformation, becoming a radical itself. In the absence of adequate vitamin C for its regeneration, it perpetually remains in a reactive state [159]. The antioxidant activity of β-carotene is contingent upon its interaction with biological membranes and the concomitant presence of co-antioxidants, such as ascorbic acid (Vitamin C). It has been demonstrated that at elevated levels of oxygen tension, the effectiveness of β-carotene as an antioxidant is diminished. A systematic review and meta-analysis revealed an elevated mortality rate in subjects who had used supplements containing β-carotene, vitamin A, and vitamin E for a prolonged duration [160]. It has been documented that flavonoids exhibit prooxidant properties in systems that contain transition metals. [161]. Flavonoids, including quercetin and kaempferol, have been observed to induce DNA damage and lipid peroxidation in the presence of a transition metal. Phenolics have the capacity to exhibit prooxidant effects, particularly within systems comprising redox-active metals. The presence of iron or copper has been shown to catalyze their redox cycling. This catalyzing process may result in the formation of phenolic radicals, which have been demonstrated to cause damage to lipids and DNA [162, 163].

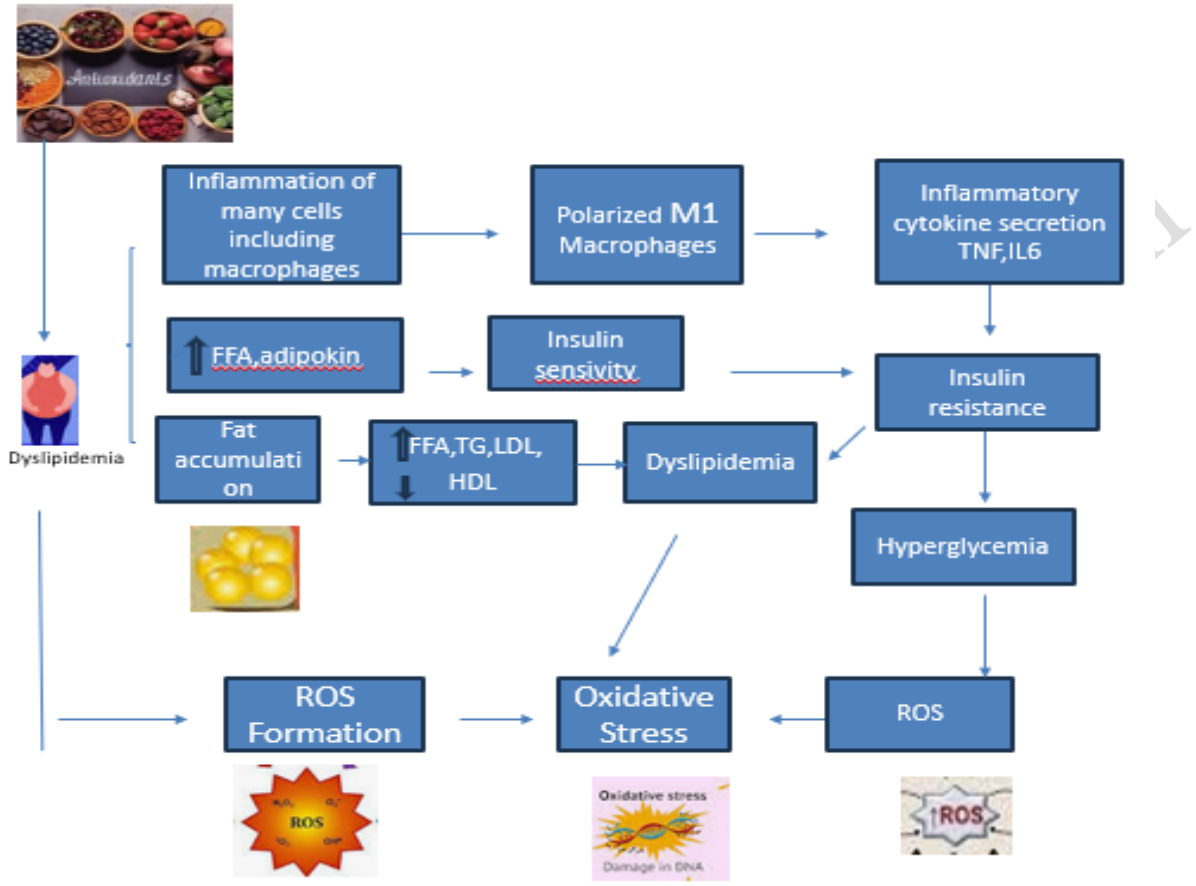

Fig. 11 Graphic abstract: Obesity and dyslipidemia activate the macrophage cells and polarize them into M1 macrophages, which eventually leads to inflammatory cytokine secretion, such as TNFα and IL-6. These cytokines can induce dysfunction of pancreatic cells that finally results in insulin resistance. Hyperglycemia, a result of insulin resistance, can increase ROS and lead to oxidative stress. ROS can be generated by obesity through superoxide formation, oxidative phosphorylation, and auto-oxidation of glyceraldehyde. ROS generation finally leads to oxidative stress. Obesity can also raise free fatty acids (FFA) and adipokines, reducing insulin sensitivity and leading to type 2 diabetes and dyslipidemia. Obesity can also impact fat storage, increasing FFA, TG, and LDL while decreasing HDL, resulting in dyslipidemia.

DISCUSSION

Our study has pointed out that antioxidants are vital in fighting free radicals, which are known to cause damage to the cells. Free radicals can trigger various diseases, which include metabolic disorders, cardiovascular diseases, premature aging, cancer, and digestive conditions. Furthermore, the body's defenses against antioxidants weaken with aging. Hence, it is recommended that one consume more antioxidants in order to prevent diseases and maintain good health. Fruits and vegetables have valuable antioxidant sources, such as β-carotene, vitamins A, C, E, phenols, curcumin, quercetin, and anthocyanin. They also contain some essential minerals, including selenium and zinc. These nutrients have been shown to prevent obesity, dyslipidemia, diabetes, and vascular diseases [164]. In a laboratory investigation, Huang et al. found that giving anthocyanins at a dosage of 200 g/ml resulted in a 60% decrease in fat content. Also, a dosage of 10 g/ml of anthocyanins was found to reduce ROS levels but significantly increase the CAT and SOD enzymes [165]. Swantavi et al. reported that cyanidin, an anthocyanin, at a dose of 1–300 μM had the potential to potentiate insulin production from INS-1 cells [166]. However, concentrations of 60, 100, and 300 μM were most efficient in increasing insulin secretion [167]. Furthermore, in vivo experiments on rats with obesity showed that providing 200 mg/kg of blackberry anthocyanins (BLA) and blueberry anthocyanins (BBA) for 12 weeks avoided a 40.5% and 55.4% rise in body weight, respectively [168].

Zhang et al. conducted a clinical experiment on dyslipidemic individuals, which included anthocyanin supplementation. The study showed that anthocyanin supplementation could raise total levels of SOD in comparison to the placebo group, indicating a dose-response link between oxidative stress and inflammation ($P < 0.05$). It lowered serum IL-6, TNF-α, and urine 8-PGF2α levels significantly compared to the placebo group ($P < 0.05$) dose dependently [169].

Quercetin, a well-studied flavonol present in apples, berries, cauliflower, cabbage, and beans, has been shown to have important biological activities such as antioxidant, anti-dyslipidemic, anti-diabetic, and anti-inflammatory properties [170]. An in vivo study in HFD-fed Wistar rats, 0.04% g/g PMQ for 17 weeks, caused a marked reduction in glucose, LDL, TG, and TC, and levels [171].

Curcumin, found in turmeric roots (*Curcuma longa* L.), is well-known for its antioxidant, anti-obesity, anti-inflammatory, anti-dyslipidemic, and anti-diabetic activities [172]. Zhao et al. examined the action of curcumin on 3T3-L1 preadipocytes. They have reported that the treatment of 20, 10, and 35 μM of curcumin for 8 days induced the differentiation of adipocytes and the formation of lipid droplets. Curcumin induced a decrease of about 55.0% and 74.7% in viability at the doses of 50 and 75 μM, respectively, in comparison with the control group. Curcumin has been proven in vivo, in vitro, and in clinical investigations to have powerful effects on metabolic disorders such as obesity, dyslipidemia, and diabetes. However, additional research is required to evaluate suitable dosage forms, long-term safety, and potential side effects [173, 174].

Polyphenols administered at doses ranging from 125 to 500 mg over 8 days to 3T3-F442A cells enhance fat development by triggering adipogenic genes and modulating GLUT-4 (translocate glucose transporter 4) and PI3K [175]. Also, green tea prevented weight gain and showed anti-obesity and anti-dyslipidemic effects, particularly in individuals under 50 years old [176].

An in vivo study of Wistar rats fed a diet containing the strawberry antioxidant ellagitannin (ET) at 0.24% of the total diet for four weeks showed that it was helpful in preventing and curing obesity-related metabolic abnormalities, dyslipidemia, and inflammation [177]. In an in vivo research, Sosa et al. delivered 50 mg/kg of α-Int. terpineol to male Sprague-Dawley rats on a high-fat diet. Results demonstrated better insulin sensitivity and lower serum levels of pro-inflammatory cytokines, TNF-α, and IL-1β, relative to the control group [178].

Research showed antioxidants are important in preventing the oxidation of unsaturated fatty acids connected to LDL-C, blocking the formation of foam cells and atherosclerotic plaques. Dietary antioxidants, mainly vitamins A, C, and E, zinc, selenium, phenols, flavonoids, and anthocyanins, have key roles to play. Vitamin E efficiently inhibits the oxidation of cell membrane lipids [179]. Vitamin C increases LDL-C's resistance to oxidation while decreasing oxidative stress from active radicals [180]. Vitamin A stimulates cell differentiation, inhibits cell adhesion, and controls the antioxidant defense system [181]. Zinc functions as an oxygen-free radical receptor and controls the production of the vitamin A nuclear receptor gene [182]. Selenium detoxifies oxygen-free radicals, which helps to improve health and boost the antioxidant defense system [١٨١]. A lack of these antioxidants can endanger the antioxidant defense system's integrity by decreasing the efficacy of other active antioxidant compounds [183]. As a result, simultaneous antioxidant supplementation is critical for lowering oxidative stress and preventing vascular and associated disorders.

Excessive free radical generation and oxidative damage are thought to lead to dyslipidemia and other disorders. Multiple studies have shown that natural antioxidant molecules can help manage difficulties linked with an HFD. In this context, researchers investigated the role of dietary lycopene supplementation in reducing oxidative stress induced by obesity, inflammation, and aspartic acid-related complications. According to earlier studies, lycopene dramatically reduced body weight increase and abdominal fat buildup caused by prolonged HFD consumption [92, 184].

The lycopene capacity to quench singlet oxygen is much higher than that of β-carotene and α-tocopherol. LDL oxidation is considered a critical step in the atherogenic process, and LDL-associated antioxidants defend against it. Laboratory studies have suggested that lycopene, along with other carotenoids, can prevent LDL oxidation [185].

Hu et al. discovered that a 10 ng/ml decrease in plasma VD3 levels corresponded to a 0.84-fold increased chance of having dyslipidemia. A rise in dyslipidemia can harm vascular endothelial cells, potentially accelerating the evolution of CHD [186]. Su et al. reported that VD3 up-regulates the expression of LDL receptors on hepatocytes, thereby enhancing their activity and reducing blood levels of LDLs [187]. Besides, Zhao et al. demonstrated that VD3 regulates lipid synthesis and degradation [120].

A pioneering study demonstrated very influential evidence of the effects of lutein supplementation on body composition and the lipid profile among obese middle-aged adults. The study found that those on a low-calorie diet supplemented with lutein lost much more body fat than those on a low-calorie diet alone. Furthermore, lutein supplementation maintained lean mass during calorie restriction, and visceral fat was significantly reduced only in the lutein-supplemented group [188].

Pourrajab's study in 2023 indicated that elevated concentrations of carotenoids in plasma are associated with a favorable lipid profile. The aforementioned factors encompass a reduction in serum triglyceride levels, a decrease in saturated fatty acid consumption, and an augmentation in levels of HDL cholesterol. The carotenoid astaxanthin, in particular, has attracted significant interest due to its capacity to enhance blood lipid profiles through a reduction in LDL cholesterol and triglycerides, concurrent with an increase in HDL cholesterol [189].

The findings of the present systematic review and meta-analysis demonstrated that supplementation with CoQ10 led to a significant improvement in lipid profiles. The study revealed that a decrease in total cholesterol was accompanied by an increase in HDL-cholesterol levels. However, no alterations were observed in triglyceride, LDL-cholesterol, and Lp(a) levels in patients diagnosed with coronary artery disease (CAD). These findings were derived from a meta-analysis conducted by Susomboon *et al*. [141]. The anti-hyperlipidemic efficacy of fenofibrate has been well-documented. Notwithstanding, the synergistic impact of the combination with CoQ10 is encouraging. A substantial decline in serum triglyceride levels was documented subsequent to supplementation with CoQ10 in conjunction with fenofibrate [12]. However, Sahebkar et al. [140]. As demonstrated in their meta-analysis, CoQ10 supplementation has been shown to have a significant effect on reducing plasma Lp(a) levels in individuals with a Lp(a) level of ≥30 mg/dL. Notwithstanding, the remaining lipid profile parameters remained constant. [141].

A substantial body of research has repeatedly demonstrated that epicatechin has a considerable capacity to decrease total cholesterol and LDL cholesterol levels. For instance, in hypolipidemic mouse models, epicatechin administration resulted in a reduction in LDL cholesterol and total cholesterol [190]. It is evident that epicatechin exerts a regulatory function over the metabolic pathways associated with lipid metabolism. This property is believed to underpin its hepatoprotective effect against non-alcoholic fatty liver disease (NAFLD), characterized by the accumulation of fat in the liver [191].

Suggestions for Future Work

The antioxidant paradox may suggest that supplementation with high doses of antioxidants may even worsen oxidative status due to tightly regulated endogenous defenses. Hence, future studies should explore this duality under various physiological and pathophysiological conditions. Exploring how varying doses of specific plant-based antioxidants may switch their role from protective to harmful by mapping the precise points at which antioxidant benefits give way to pro-oxidant effects addresses the so-called 'antioxidant paradox' and calls for further investigation across different physiological and disease contexts.

CONCLUSION

Antioxidants protect tissues from free radicals by blocking, neutralizing, and eliminating them. These protective benefits are critical for avoiding cardiovascular diseases such as CVD, heart failure, atherosclerosis, and metabolic disorders. Antioxidants accomplish this by inhibiting LDL oxidation, increasing HDL levels, lowering inflammatory factors and interleukins, reducing oxidative stress, increasing nitric oxide levels and vasodilation, improving anti-apoptotic activity, increasing antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase, and improving endothelial function and mitochondrial mitophagy properties.

While antioxidants generally mitigate oxidative stress, certain compounds may exhibit pro-oxidant behavior depending on dosage and physiological conditions, potentially exacerbating atherosclerotic processes. These findings underscore the necessity for personalized antioxidant therapy in cardiovascular disease management.

Highlight

- Fruits and vegetables have valuable antioxidant sources, such as beta-carotene, vitamins A, C, E, phenols, curcumin, quercetin, and anthocyanin. They also contain some essential minerals, including selenium and zinc. These nutrients have been shown to prevent obesity, dyslipidemia, diabetes, and vascular diseases
- Antioxidants safeguard tissues from free radicals, playing a vital role in preventing cardiovascular diseases, heart failure, and metabolic disorders.
- Antioxidants are believed to raise HDL levels, reduce LDL oxidation, and consequently lower oxidative stress related to atherosclerotic issues, cardiovascular disease, blood pressure, and lipids.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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