

Insights on antioxidant therapeutic strategies in type 2 diabetes mellitus: A narrative review of randomized control trials

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Specialty type: Biochemistry and molecular biology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Lee KS, South Korea; Nasrallah O, Lebanon

Received: December 19, 2022

Peer-review started: December 19, 2022

First decision: January 5, 2023

Revised: January 11, 2023

Accepted: May 11, 2023

Article in press: May 11, 2023

Published online: June 15, 2023



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Abstract

BACKGROUND

Type 2 diabetes mellitus (T2DM) is a metabolic disease of impaired glucose utilization. Imbalance in generation and elimination of free radicals generate oxidative stress which modulates glucose metabolism and insulin regulation, resulting in the occurrence and progression of diabetes and associated complications. Antioxidant supplements in T2DM can be seen as a potential preventive and effective therapeutic strategy.

AIM

To compare randomized controlled trials (RCTs) in which antioxidants have been shown to have a therapeutic effect in T2DM patients.

METHODS

We systematically searched the electronic database PubMed by keywords. RCTs evaluating the effect of antioxidant therapy on glycaemic control as well as oxidant and antioxidant status as primary outcomes were included. The outcomes considered were: A reduction in blood glucose; changes in oxidative stress and antioxidant markers. Full-length papers of the shortlisted articles were assessed for the eligibility criteria and 17 RCTs were included.

RESULTS

The administration of fixed-dose antioxidants significantly reduces fasting blood sugar and glycated hemoglobin and is associated with decreased malondialdehyde, advanced oxidation protein products, and increased total antioxidant capacity.

CONCLUSION

Antioxidant supplements can be a beneficial approach for the treatment of T2DM.

Key Words: Diabetes; Antioxidants; Oxidative stress; Malondialdehyde; Polyphenols; Antioxidant therapy

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Core Tip: Antioxidant supplementation reduces oxidative stress in diabetes. Antioxidant supplementation is a potential therapeutic approach for type 2 diabetes mellitus.

Citation: Shrivastav D, Dabla PK, Sharma J, Viswas A, Mir R. Insights on antioxidant therapeutic strategies in type 2 diabetes mellitus: A narrative review of randomized control trials. *World J Diabetes* 2023; 14(6): 919-929

URL: <https://www.wjgnet.com/1948-9358/full/v14/i6/919.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v14.i6.919>

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycaemia which arises from resistance or deficiency of insulin secreted from pancreatic beta cells[1]. Obesity and physical inactivity are general well-known risk factors for T2DM as well as its micro (nephropathy and retinopathy) and macrovascular (atherosclerotic cardiovascular disease) complications[2]. According to the World Health Organization, the prevalence and death rate was 470 million and 1.37 million in 2017, respectively, and expected to increase continuously, and the estimated prevalence and death rate in 2025 will be 570.9 million and 1.59 million, respectively[3]. In India, the prevalence of T2DM and impaired fasting glucose was 9.3% and 24.5%, respectively, in 2022. Approximately 45.8% of T2DM patients are aware of their diabetes, 6.1% are taking diabetes medication, and 15.1% have diabetes under control.

Oxidative stress

Oxidative stress is the excess production or insufficient clearance of highly reactive molecules like reactive oxygen species (ROS) and reactive nitrogen species. In physiological conditions, it is generated in the non-enzymatic, enzymatic, and mitochondrial processes. Enzymes of respiratory chain, phagocytosis, prostaglandin synthesis, and mitochondrial cytochrome P450 system and purine degradation produce free radicals[4]. In diabetes, due to hyperglycaemia, the formation of free radicals is increased, resulting in an increase in oxidative stress which promotes the rate of protein glycation (non-enzymatic), oxidation of glucose, lipid peroxidation, and ultimately impairment of cellular machinery, enzymes, and insulin pathways[5].

Oxidative stress targeted molecular pathways in T2DM pathogenesis

In T2DM, the prolonged exposure to high glucose and free fatty acid levels significantly contributes to the dysfunction of beta cells. These beta cells are highly sensitive to free radicals (due to low quenching and antioxidant activity). Consequently, the oxidative stress can harm mitochondria and significantly decrease insulin secretion and may cause insulin resistance (Figure 1). Under physiological conditions, cellular metabolic processes like glucose oxidation, generate superoxide anion radical [O₂(-)] inside the mitochondria which is combated by the antioxidant defence system of the body at a certain level[6]. However, in hyperglycaemic conditions, the production of O₂(-) is elevated, which decreases the body's antioxidant capacity and consequently generates oxidative stress and damage to several biomolecules including DNA[7]. DNA damage activates poly-ADP-ribose polymerase-1 (PARP-1) (DNA damage repair enzyme). Since this PARP-1 enzyme is a potent inhibitor of glyceraldehyde 3-phosphate dehydrogenase of the glycolysis pathway, the intracellular concentration of glycolytic intermediates including glyceraldehyde 3-phosphate, fructose-6-phosphate, and glucose-6-phosphate increases[8]. As a result, glycolytic intermediates accumulate inside the cell and promote some other pro-oxidant pathways like protein kinase C and the advanced glycation end products hexosamine and polyol related pathways[9].

Antioxidants

To counteract the oxidative stress, the human body produce antioxidants at a low concentration which significantly delay or inhibit cellular damage[4]. Humans have extremely complex antioxidant systems that protect the body's cells and organ systems from free radicals. Antioxidants can be categorized as antioxidant enzymes and substrates[10], natural substances[11], combination medications[12], synthetic

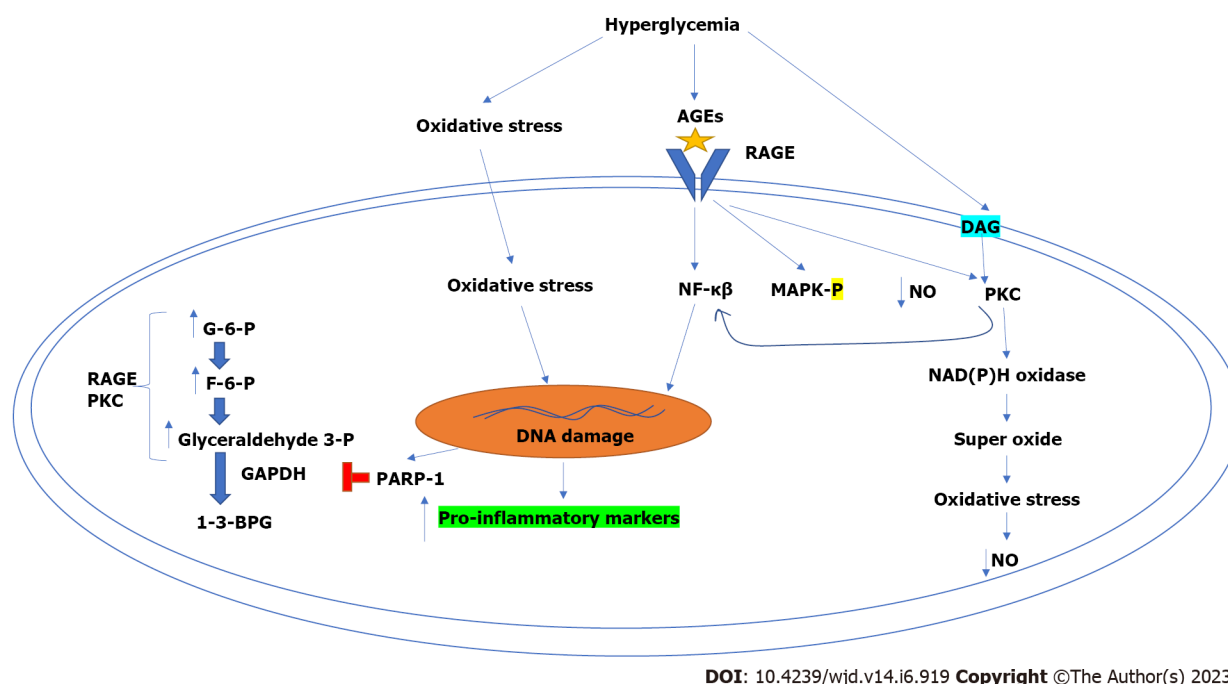


Figure 1 Systematic representation of metabolic pathways affected by hyperglycaemic and oxidative stress. Hyperglycaemia causes cell damage in three ways: (1) By directly increasing oxidative stress which affects glycolytic enzymes; (2) by forming advanced glycation end products which activate NF- κ B and increase DNA damage; and (3) by affecting diacylglycerol enzyme and ultimately reducing nitric oxide levels.

antioxidants[13], and pharmaceuticals[14]. In the antioxidant enzyme and substrate system, superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, and catalase can combat the oxidative stress either directly or sequentially and abolish its excessive development of deleterious effects[15]. The non-enzymatic antioxidant system is endogenously produced and scavenges free radicals. It includes vitamin C, vitamin D, vitamin E, carotenoids, lipoic acid, selenium, and other dietary derivatives such as glutathione and ubiquinol[16].

Antioxidant therapy in diabetes

Exogenous antioxidant supplementation may reduce oxidative stress in T2DM by increasing antioxidant levels and decreasing free radical formation[17]. This supplementation potentially improves the metabolic pathways including nitric oxide (NO) production, endothelial dysfunction, mitochondrial function, and vascular NAD(P)H oxidase activity[18,19]. According to recent clinical data in diabetic patients, supplementation of antioxidants improves glycaemic status [glycated hemoglobin (HbA1c) and random blood sugar], reduces oxidative stress biomarkers [malondialdehyde (MDA)], and increases serum levels of antioxidant enzymes including SOD, catalase, and glutathione peroxidase[5]. Golbidi *et al*[20] investigated the therapeutic use of antioxidants as an adjuvant to standard diabetes treatment. Those authors searched the clinical trial studies over the last ten years using terms vitamin E, vitamin C, coenzyme Q10 (CoQ10), alpha lipoic acid, L-carnitine, ruboxistaurin, or LY 333531 and diabetes and concluded that vitamin supplementation is not beneficial for managing diabetes complications. In this study, we tried to compare interventional randomized control trials (RCTs) in which antioxidants have been shown to have a therapeutic effect in the treatment of T2DM.

MATERIALS AND METHODS

Search methodology: The literature search was carried out in the PubMed NCBI database. The search strategy was carried out by combination of ("Diabetes Mellitus, Type 2"[MeSH]) AND "Antioxidants"[MeSH]) AND "Oxidative Stress"[MeSH]) using Boolean operators. The fixed dose of antioxidant was the inclusion criterion for eligibility.

At the beginning of the literature search, the NCBI PubMed database showed 726 articles. After applying filters and limiting the search with "full text", "five years" (2017 to 2022), and "human randomized controlled trials", 23 RCTs were obtained. Full-length papers of the shortlisted articles were assessed for the eligibility criteria and 17 RCTs that fulfilled the inclusion criteria were finally included in the study (Figure 2 and Table 1).

Table 1 Basic characteristics of included studies

No.	Study design	Setting	Population	Sample size	Intervention	Duration	Effect of treatment	Ref.
1	Randomized controlled trial	Primary Health Care Centre in Podgorica	T2DM patients	Total: <i>n</i> = 130; Group I: <i>n</i> = 65; Group II: <i>n</i> = 65	Group I: 14000 IU vitamin D + metformin; Group II: Metformin only	First for 3 mo and later on for 6 mo	Improves blood HbA1c and reduces advanced oxidation protein products	Cojic <i>et al</i> [22], 2021
2	Randomized controlled trial	Prince of Wales Hospital, the Teaching Hospital of The Chinese University of Hong Kong, Shatin, Hong Kong	T2DM patients	Total: <i>n</i> = 20; Group I: <i>n</i> = 10; Group II: <i>n</i> = 10	Group I: 1.4 g/d bilberry (<i>Vaccinium myrtillus</i> L.); Group II: Placebo	3 wk	Reduces serum HbA1c level by 4.6% and ascorbic acid by 14%	Chan <i>et al</i> [43], 2021
3	Randomized controlled trial	Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan	T2DM patients	Total: <i>n</i> = 54; Group I: <i>n</i> = 27; Group II: <i>n</i> = 27	Group I: Three-gram citrulline daily; Group II: Placebo	2 mo	Reduces serum fasting blood glucose and MDA level by 16% and 25%, respectively; Increases serum levels of NOx, SOD, and GPx by 27%, 2%, and 2.2%, respectively	Azizi <i>et al</i> [45], 2021
4	Randomized controlled trial	Khon Kaen University, China	T2DM patients	Total: <i>n</i> = 24; Group I: <i>n</i> = 12; Group II: <i>n</i> = 12	Group I: 1000 mg vitamin C; Group II: Placebo daily	6 wk	Improves blood pressure regulation, increases NO release, and significantly lowers serum MDA and F2-IsoPs levels	Boonthongkaew <i>et al</i> [23], 2021
5	Randomized controlled trial	Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad, India	T2DM patents	Total: <i>n</i> = 60 patients; Group I: <i>n</i> = 20; Group II: <i>n</i> = 20; Group III: <i>n</i> = 20	Group I: One capsule of <i>T. chebula</i> 250 mg twice daily; Group II: One capsule of <i>T. chebula</i> 500 mg twice daily; Group III: Placebo	12 wk	Improves serum NO level and reduces oxidative stress markers (GSH and MDA)	Pingali <i>et al</i> [31], 2020
6	Randomized controlled trial	Endocrinology and Metabolism Clinics of Golestan Hospital at Ahvaz Jundishapur University of Medical Science, Iran (IRCT registration number: IRCT20120704010181N12)	T2DM patients	Total: <i>n</i> = 42; Group I: <i>n</i> = 21; Group II: <i>n</i> = 21	Group I: One-gram <i>Anethum graveolens</i> (dill) powder; Group II: Placebo	8 wk	Decreases serum insulin, HOMA-IR, LDL-C, TC, and MDA and increases serum level of HDL and total antioxidant level	Haidari <i>et al</i> [33], 2020
7	Randomized controlled trial	Tan Tock Seng Hospital, Singapore (registration number: NCT02776397)	T2DM	Total: <i>n</i> = 187; Group I: Type 2 diabetes individuals with haptoglobin 2-2 (Hp 2-2); Group II: Type 2 diabetes individuals without haptoglobin 2-2 (Hp 2-2)	Group I: Total 400 IU of vitamin E daily; Group II: Placebo	24 wk	Increases reactive hyperaemia index, LDL, and ox-LDL concentrations	Dalan <i>et al</i> [24], 2020
8	Randomized controlled trial	Isfahan University Endocrine and Metabolism Research Centre, Isfahan, Iran (IRCT registration number: IRCT20180818040827N1)	T2DM	Total: <i>n</i> = 80; Group I: <i>n</i> = 40; Group II: <i>n</i> = 40	Group I: 20 g wheat germ; Group II: Placebo	12 wk	Significant change in serum TC level	Mohammadi <i>et al</i> [47], 2020
9	Randomized controlled trial	Velayat Hospital of Qazvin University of Medical Sciences, Qazvin, Iran (IRCT registration number: IRCT2017041019669N4)	T2DM	Total: <i>n</i> = 62; Group I: <i>n</i> = 31; Group II: <i>n</i> = 31	Group I: 500 mg of propolis 3 times in a day; Group II: Placebo	8 wk	Decreases FBS, 2-hp, insulin, HbA1c, and HOMA-IR and upregulates TAC, SOD, and GSH	Afsharpour <i>et al</i> [40], 2019

10	Double-blind randomized, placebo-controlled clinical trial	Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Kermanshah University of Medical Sciences, Tehran, Iran (IRCT registration number: IRCT20140413017254N5)	T2DM	Total: $n = 80$; Group I: $n = 40$; Group II: $n = 40$	Group I: 80 mg Nano curcumin capsules once a day; Group II: Placebo	8 wk	Improves serum HbA1c, RBS, total neuropathy score, and total reflex score	Asadi <i>et al</i> [35], 2019
11	Double-blind, randomized, parallel, placebo-controlled trial	Yeh, Chung Shan Medical University Taiwan (registration number: NCT02622672)	T2DM	Total: $n = 50$; Group I: $n = 25$; Group II: $n = 25$	Group I: Liquid ubiquinol (100 mg/d); Group II: Placebo	12 wk	Reductions in blood HbA1c and fasting glucose, and increase in SOD activity	Yen <i>et al</i> [29], 2018
12	Single-blinded randomized controlled clinical trial	Medical Laboratories of the Central Blood Bank Society, and the Medical Relief Society, Gaza Strip, Palestine	T2DM	Total: $n = 40$ patients; Group I: $n = 10$; Group II: $n = 10$; Group III: $n = 10$; Group IV: $n = 10$	Group I: 500 mg of metformin + placebo twice daily; Group II: 500 mg of metformin + 500 mg of vitamin C twice daily; Group III: 500 mg of metformin + 400 mg of vitamin E twice daily; Group IV: 500 mg of metformin + 500 mg of vitamin C + 400 mg of vitamin E twice daily	90 d	Regulates FBS, HbA1c, HOMA-IR, and QISCI and improves GST, MDA, G6PD, GSH-PX, GSHE, and GSHW	El-Aal <i>et al</i> [25], 2018
13	Randomized double-blind placebo-controlled trial	Baqiyatallah University of Medical Sciences, Iran (IRCT registration number: IRCT201505301165N4)	T2DM	Total: $n = 100$; Group I: $n = 50$; Group II: $n = 50$	Group I: 500 mg curcumin + 5 mg piperine/day; Group II: Placebo	3 mo	Controls insulin, HbA1c, and HOMA-IR index	Panahi <i>et al</i> [36], 2018
14	Randomized, double blind, parallel group design	Clinics Hospital of Porto Alegre	T2DM	Total: $n = 30$; Group I: $n = 15$; Group II: $n = 15$	Group I: n -3 PUFAs (capsules containing 180 mg of eicosapentaenoic acid and 120 mg of docosahexaenoic acid; Group II: Placebo	8 wk	Reduces serum level of TBARS, F2-isoprostanes, and triglycerides	Fayh <i>et al</i> [27], 2018
15	Randomized double-blind placebo-controlled trial	Tehran University of Medical Sciences (IRCT registration number: IRCT2015072523336N1)	T2DM	Total: $n = 48$; Group I: $n = 24$; Group II: $n = 24$	Group I: 800 mg/d resveratrol daily; Group II: Placebo	2 mo	Decreases MDA and carbonyl protein and increases total thiol, NOS, and catalase	Seyyedebrahimi <i>et al</i> [49], 2018
16	Randomized double-blind placebo-controlled clinical trial	Diabetic Clinic of Golestan Hospital, Jundishapur University of Medical Science, in Ahvaz, Iran (IRCT registration number: IRCT2015081810181N6)	T2DM	Total: $n = 64$; Group I: $n = 32$; Group II: $n = 32$	Group I: 500 mg hesperidin/ daily; Group II: Placebo	6 wk	Increases total antioxidant concentration and reduces serum concentrations of fructosamine, 8-OHdG, and MDA	Homayouni <i>et al</i> [38], 2017
17	Randomized double-blind placebo-controlled clinical trial	Toho University Medical Center	T2DM	Total: $n = 50$; Group I: $n = 25$; Group II: $n = 25$	Group I: Resveratrol oligo-stilbene 27.97 mg/100 mg/d; Group II: Placebo	12 wk	Decreases SBP and reactive oxygen metabolite significantly and also reduces risk of atherosclerosis in T2DM patients	Imamura <i>et al</i> [50], 2017

FBS: Fasting blood sugar; GST: Glutathione S-transferase; G6PD: Glucose 6-phosphate dehydrogenase; GSH: Glutathione; GSHE: Glorisa superba hydroalcoholic extract; HbA1c: Glycated hemoglobin; HDL: High density lipoprotein; HOMA-IR: Homeostasis model assessment of insulin resistance; IsoPs: Isoprostanes; LDL: Low-density lipoprotein; LDL-C: Low-density lipoprotein cholesterol; MDA: Malondialdehyde; n -3 PUFA: Polyunsaturated fatty acid; NO: Nitric oxide; NOS: Nitric oxide synthase; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; ox-LDL: Oxidised low-density lipoprotein cholesterol; RBS: Random blood sugar; SBP: Systolic blood pressure; SOD: Superoxide dismutase; T2DM: Type 2 diabetes mellitus; TG: Triglyceride; TBARS: Thiobarbituric acid-reactive substances; TAC: Total antioxidant capacity; TC: Total cholesterol.

RESULTS

This study was performed to find the effect of antioxidants on oxidative stress in T2DM patients by



Figure 2 Flow chart of study selection process. Created from: <https://prisma-statement.org/prismastatement/flowdiagram.aspx>.

comparing RCT studies. After a literature search in the PubMed database, it was found that the antioxidants, including vitamins, free fatty acids, natural products, *etc.*, play diverse roles in combating oxidative stress in T2DM patients[21]. It is well known that non-enzymatic antioxidants like vitamins A, C, and E, glutathione, lipoic acid, mixed carotenoids, CoQ10, a number of bioflavonoids, antioxidant minerals like copper, zinc, manganese, and selenium, as well as cofactors like albumin, folic acid, uric acid, and vitamins B1, B2, B6, and B12 are involved in diverse biological functions. Antioxidants have shown promise as a potential therapy for the prevention and treatment of cancer, diabetic complications, and cardiovascular disease (CVD) since ROS have been linked to these diseases. In a study by Cojic *et al*[22], vitamin D supplements were given to proven T2DM patients with an average history of 4-6 years during a 6-mo follow-up period, and it was found that vitamin D supplementation (14000 IU weekly or 4 drops daily for 6 mo) improved blood HbA1c and reduced advanced oxidation protein products (AOPP). The triglyceride/thiobarbituric acid-reactive substances (TG/TBARS) index, homeostasis model assessment of insulin resistance (HOMA-IR) index, and MDA level were likewise affected by this vitamin D treatment. Boonthongkaew *et al*[23] studied the effect of vitamin C supplementation (1000 mg daily for 6 wk) on blood pressure (BP), oxidative stress, and NO release in T2DM patients and revealed that vitamin C supplementation improves blood pressure regulation, increases NO release, and significantly lowers serum MDA and F2-isoprostanes (IsoPs) levels. In another study, after supplementation of vitamin E (alpha-tocopherol-400 IU) in T2DM patients (duration of diabetes, 9-11 years), change in the reactive hyperaemia index (RHI) and augmentation index as the primary outcome, and pulse-wave velocity (PWV), carotid intima media thickness (CIMT), inflammation (hsCRP), derivatives of reactive-oxygen metabolites (dROMs), biological antioxidant potential (BAPs), HbA1c, low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and oxidised LDL-C (ox-LDL) as the secondary outcomes were measured. Dalan *et al*[24] concluded that vitamin E supplementation does not significantly improves RHI, PWV, CIMT, hsCRP, dROMs, BAPs, HDL-C, and HbA1c though a significant fall in ox-LDL levels was observed. Further in subgroup analysis, vitamin E supplementation can increase reactive hyperaemia index, LDL, and ox-LDL concentrations in the non-Hp-2-2 group. Similarly, El-Aal *et al*[25] revealed that supplementation of vitamin C and/or vitamins E for 90 consecutive days to T2DM patients regulates fasting blood sugar (FBS), HbA1c, HOMA-IR, and quantitative insulin sensitivity check index (QUICKI). Further, it also improves serum levels of glutathione-S-transferase, MDA, glucose-6-phosphate dehydrogenase, glutathione (GSH)-peroxidase, reduced glutathione in erythrocyte lysate, and reduced glutathione in whole blood. Polyunsaturated fatty acids (*n*-3 PUFAs) are long-chain polyunsaturated fatty acids that have antioxidant properties. Indeed, *n*-3 PUFA supplementation has been demonstrated to reduce oxidative stress-related mitochondrial dysfunction and endothelial cell mortality, with the benefit mediated by increased endogenous antioxidant enzyme activity[26]. In another study conducted by Fayh *et al*[27], supplementation of *n*-3 PUFAs (capsules containing 180 mg of eicosapentaenoic acid and 120 mg of docosahexaenoic acid) to T2DM patients (diabetes history of 6-8 years) non-significantly reduces serum levels of TBARS, F2-IsoPs, and triglycerides. CoQ10 is a powerful antioxidant found naturally in the mitochondria that is endogenously synthesised and fat soluble. Because of its antioxidant properties, it can effectively inhibit the oxidation of fat, protein, and DNA in the body. Deficiency in CoQ10, particularly ubiquinol (the reduced form of CoQ10), is common in T2DM patients[28]. Yen *et al*[29] revealed that supplementing T2DM patients with ubiquinol (100 mg/d for 12 wk) resulted in a significant reduction in blood HbA1c, fasting glucose, and anti-glycaemic agent use (thiazolidinediones by 25% to

83%), and increased SOD activity. However, there were no significant changes in the levels of serum MDA and ox-LDL. After 12 wk of supplementation, there was a further substantial association between the plasma CoQ10 level and the insulin level, HOMA-IR, and anti-hyperglycaemic medication effect scores.

Plant-based natural antioxidants are mostly composed of polyphenols (phenolic acids, flavonoids, anthocyanins, lignans, and stilbenes), carotenoids (xanthophylls and carotenes), and phenolic acids. These naturally occurring antioxidants, particularly polyphenols and carotenoids, have a variety of biological effects, including anti-inflammatory, antibacterial, antiviral, anti-aging, and anticancer properties[30]. *Terminalia chebula*, a traditional ayurvedic herb, is well-known for its antioxidant and antihyperlipidemic properties. Pingali *et al*[31] suggested that the supplementation of aqueous extract of *Terminalia chebula* (250 mg and 500 mg twice daily for 12 wk) to T2DM patients significantly improved endothelial function, serum NO level, lipid profile, hsCRP levels, and oxidative stress markers (GSH and MDA)[31]. Dill, also known as *Anethum graveolens* L. (*A. graveolens*), is a herb that is frequently used as a spice and a remedy. The oils of *A. graveolens* are also a source of antioxidants, have antibacterial and antispasmodic qualities, and are also a source of minerals, proteins, and fibres. According to research, *A. graveolens* exhibits anticancer, antibacterial, anti-gastric-irritation, anti-inflammatory, and antioxidant effects[32]. The interventional study of Haidari *et al*[33] suggested that the supplementation of *A. graveolens* (dill) powder (3 capsules per day, 1 g each daily) to T2DM patients (duration of diabetes, 8-9 years) significantly decreases serum insulin, HOMA-IR, LDL-C, total cholesterol (TC), and MDA and increases the serum level of HDL and total antioxidant level. However, a non-significant difference was observed in serum hsCRP (an inflammatory marker) level. Curcumin ($C_{21}H_{20}O_6$) is a lipophilic substance and polyphenol in nature. Due to its chemical structure and presence of hydroxyl and methoxy groups, it has many properties, in particular antioxidant, antimicrobial, anti-inflammatory, anti-angiogenic, and antimutagenic ones. Curcumin regulates cyclooxygenase-2, lipoxygenase, xanthine oxidase, and inducible nitric oxide synthase (NOS), and reduces serum level of MDA[34]. In another trial, Asadi *et al*[35] suggested that the supplementation of nano-curcumin (80 mg per day for 8 wk) to T2DM patients (diabetes history of 10-11 years) significantly improves serum HbA1c, random blood sugar, total neuropathy score, and total reflex score. Similarly, the administration of curcuminoids (daily dose of 500 mg/d) co-administered with piperine (5 mg/d for 3 mo) can control insulin, HbA1c, and HOMA-IR index. Further, it also reduces serum hsCRP and creatinine levels in T2DM patients[36]. Hesperidin (30,5,7-trihydroxy-40-methoxy-flavanone-7-rhamnoglucoside), a bioflavonoid, is a well-known antioxidant that can reduce risk of cardiovascular disease and T2DM[37]. The oral administration of hesperidin at 500 mg/d for 6 wk in T2DM patients (disease history of 3-11 years) increases total antioxidant concentration (mean percent change $13.35\% \pm 19.21\%$) and reduces the serum concentration of fructosamine (mean percent change $10.10\% \pm 16.84\%$), 8-hydroxy-2'-deoxyguanosine (mean percent change $25.11\% \pm 28.23\%$), and MDA (mean percent change $16.46\% \pm 18.04\%$)[38]. Various studies evidently prove that propolis (a resin like material synthesized by honey bee) has antioxidant properties and is sufficiently capable of scavenging free radicals[39]. The oral supplementation of propolis (500 mg, three times a day for 8 wk) to T2DM patients (disease history of 3-11 years) decreases FBS, 2-h postprandial glucose, insulin, HbA1c by 14%, and HOMA-IR by 25%, and upregulates total antioxidant capacity (TAC) by 19%, SOD by 3%, and GSH by 17%[40]. Anthocyanin is one of the major secondary metabolites which have antioxidant properties. Bilberry (*Vaccinium myrtillus* L.) is a natural and big source of anthocyanins[41]. Although bilberry is most typically used to improve vision, it has also been shown to lower blood sugar, have anti-inflammatory and lipid-lowering properties, increase antioxidant defense, and reduce oxidative stress. As a result, bilberry may be useful in the treatment or prevention of inflammation, dyslipidaemia, hyperglycaemia, and elevated oxidative stress, as well as CVD, cancer, diabetes, dementia, and other age-related disorders[42]. The oral supplementation of bilberry (1.4 g/d of extract) daily for 4 wk reduces serum HbA1c level by 4.6% and ascorbic acid by 14%. Further, it decreases serum level of lipid standardized vitamin E, allantoin, glutathione peroxidase, and superoxide dismutase non-significantly[43]. The non-essential α -amino acid L-citrulline plays a major role in liver and kidney regulations. L-citrulline is also beneficial for NO production and endothelial cell regulation[44]. The supplementation of L-citrulline (3 g daily for 2 mo) to T2DM patients (history of 3.5 years) significantly reduces serum fasting blood glucose and MDA levels by 16% and 25%, respectively. However, it significantly increases serum levels of NOx, SOD, and GPx level by 27%, 2% and 2.2%, respectively[45]. Wheat germ (WGEs) is a by-product of the wheat milling process that contains a variety of bioactive chemicals. Wheat germ extracts (WGEs) show potential as antioxidants since they include a variety of bioactive components. According to the findings of a previous study, bioactive compounds present in WGEs lower plasma lipid and oxidation levels[46]. Supplementation of WGEs (20 g per day for 8 wk) to T2DM patients results in a significant change in serum TC level, but it affects neither serum levels of FBS, HbA1c, TG, LDL-C, HDL-C, VLDL, MDA, and TAC, nor HOMA-IR, HOMA-B, QUICKI, TG/HDL ratio, LDL/HDL ratio, systolic blood pressure, and diastolic blood pressure[47].

Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a polyphenolic compound and a type of plant secondary metabolite, is a potent antioxidant which potentially scavenges the free radicals[48]. Oral supplementation of 800 mg/d resveratrol for 2 mo to T2DM patients decreases MDA by 8%, and carbonyl protein by 18.54%. However, it increases total thiol by 12%, NOS by 3%, and catalase 12%.

Further, it also upregulates the expression of nuclear factor erythroid 2-related factor 2 (oxidative stress responsive transcription factor)[49]. Similarly, administration of 100 mg resveratrol tablets (total resveratrol:oligo-stilbene 27.97 mg/100 mg/d) daily for 12 wk effectively regulates arterial stiffness. Resveratrol supplementation not only decreases systolic BP and reactive oxygen metabolite significantly but also reduces risk of atherosclerosis in T2DM patients[50]. In this study, we tried to analyze that how imbalance between the production and inactivation of ROS leads to the development of insulin resistance and metabolic syndrome. Therefore, preventing the damage caused by oxidation can prove to be an effective therapeutic strategy in diabetes. We conducted a comparison of RCTs comparison and performed a review of the available literature to summarize the evidence covering the pathophysiological impact of oxidative stress on type 2 diabetes. Despite these, this study has several limitations including the heterogeneity and lower sample size in RCTs lowering its generalizability. Further, large size randomized controlled trials in populations of different ethnicity and gender are needed to assess its therapeutic implications in T2DM.

DISCUSSION

The literature search revealed that non-enzymatic antioxidants such as vitamins A, C, and E, glutathione, lipoic acid, mixed carotenoids, CoQ10, and antioxidant minerals have diverse biological functions that can potentially prevent and treat cancer, diabetic complications, and cardiovascular diseases. The studies reviewed demonstrated that supplementation of vitamins D, C, and E, *n*-3 PUFAs, and CoQ10 can regulate FBS, HbA1c, and oxidative stress biomarkers such as AOPP, TBARS, and MDA. In particular, vitamin D supplementation significantly improved blood HbA1c and reduced AOPP, while vitamin C supplementation improved blood pressure regulation and significantly lowered serum MDA and F2-IsoPs levels. On the other hand, vitamin E supplementation did not significantly improve RHI, PWV, CIMT, hsCRP, dROMS, BAPs, HDL-C, and HbA1c, but it caused a significant decrease in ox-LDL levels. Furthermore, supplementation of *n*-3 PUFAs non-significantly reduced serum levels of TBARS, F2-IsoPs, and triglycerides, while ubiquinol supplementation resulted in a significant reduction in blood HbA1c, fasting glucose, and anti-glycaemic agent use, and increased SOD activity. However, there were no significant changes in the levels of serum MDA and ox-LDL. These studies highlight the potential benefits of antioxidant supplementation in managing T2DM and the importance of further research to establish optimal dosages, treatment durations, and patient populations.

CONCLUSION

The modern lifestyle, which includes an unhealthy diet, a lack of physical activity, and exposure to a variety of chemicals from various sources such as pesticides, heavy metals, food additives, and environmental pollution, can all influence the appearance of oxidative stress. Oxidative stress plays an important role in the pathogenesis of various metabolic disorders including pre-obesity, obesity, and T2DM. The production of ROS endogenously and/or exogenously is a significant contributor to the development of T2DM and its complications. Constant efforts have been made by researchers globally to develop the therapeutic model to treat T2DM which can ameliorate oxidative stress. In general, oxidative stress can be reduced by adopting a balanced lifestyle and healthy diet. Although nutrition plays a critical role, the supplementation of a diet with antioxidants like vitamins and natural products has the sufficient capacity to downregulate oxidative stress by quenching free radicals and enzymatic and non-enzymatic reactions. It is also suggested that these antioxidants may mitigate T2DM *via* various mechanisms like synchronizing or controlling insulin related cell signalling which can regulate gene replication, transcription, and translation and increase insulin secretion, and improve function of hepatic β cells and glucose reabsorption. Ideally, antioxidant rich food can be taken as part of life in early age. Further, it is also clear that antioxidants are sufficiently capable to reduce low grade inflammation with associated diseases. Also, antioxidant therapy might prove to be beneficial while being supplemented at the late stage of T2DM.

ARTICLE HIGHLIGHTS

Research background

Type 2 diabetes mellitus (T2DM) is a condition that affects how the glucose is metabolized for energy. When there is an imbalance between the creation and removal of free radicals, oxidative stress can occur, which affects how the body regulates glucose and insulin, leading to the development and worsening of diabetes and related complications. Taking antioxidant supplements may be a promising way to prevent and treat T2DM.

Research motivation

T2DM is a chronic metabolic disorder with increasing prevalence worldwide, and oxidative stress is implicated in its complications. Antioxidants may counteract this process and can help in improving the metabolic pathways.

Research objectives

To review the current evidence on the role of oxidative stress in the pathogenesis of T2DM and to evaluate the effectiveness of antioxidants as a potential therapy for managing diabetes and its complications.

Research methods

We systematically searched the electronic database PubMed by keywords. Randomized control trials (RCTs) evaluating the effect of antioxidant therapy on glycemic control and oxidant and antioxidant status as primary outcomes were included. The outcomes considered were: A reduction in blood glucose; changes in oxidative stress and antioxidant markers. Full-length papers of the shortlisted articles were assessed for the eligibility criteria and 17 RCTs were included.

Research results

The administration of fixed-dose antioxidants significantly reduced fasting blood sugar and glycated hemoglobin, and was associated with decreased malondialdehyde and advanced oxidation protein products and increased total antioxidant capacity.

Research conclusions

The modern lifestyle and environmental factors can contribute to oxidative stress, which plays a significant role in the development of metabolic disorders such as pre-obesity, obesity, and T2DM. The use of antioxidants through a balanced diet and/or supplementation can reduce oxidative stress, which may mitigate the development and complications of T2DM. Antioxidants can also reduce low-grade inflammation associated with various diseases. Further follow-up research is needed to determine the optimal timing and dosage of antioxidant therapy for diabetic patients.

Research perspectives

Future research should focus on identifying new antioxidants and their mechanisms of action in reducing oxidative stress and preventing or managing T2DM. Additionally, studies on the effectiveness of antioxidant supplementation in combination with other therapies, such as exercise and medication, should be conducted. Further investigation is also needed to determine the optimal timing and dosage of antioxidant supplementation for diabetes prevention and treatment.

FOOTNOTES

Author contributions: Shrivastav D conceptualized the study, retrieved the articles, analyzed the data, tabulated the findings, and drafted and proofread the manuscript; Dabla PK and Sharma J reviewed the data, analyzed the information, guided the inclusion of information, and drafted and proofread the manuscript; Viswas A helped in information retrieval and inclusion of findings; Mir R provided intellectual inputs and proofread the manuscript; Dabla PK conceived & guided the study, provided intellectual inputs, guided the inclusion of information, proofread at all steps, and approved the final version of the manuscript; and all authors contributed to and approved the submitted version.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

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S-Editor: Zhang H

L-Editor: Wang TQ

P-Editor: Chen YL

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