

# The Role of Antioxidants in the Pathophysiology, Complications, and Management of Diabetes Mellitus

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## ABSTRAK

*Diabetes melitus (DM) merupakan gangguan metabolik yang tetap menjadi masalah kesehatan terbesar di dunia. Penyakit ini dikarakteristikan dengan defisiensi relatif atau absolut dari sekresi insulin dan/atau resistensi insulin yang menyebabkan hiperglikemia kronik dan gangguan metabolisme karbohidrat, lipid, dan protein. Diabetes telah diketahui sebagai gangguan stres oksidatif yang terjadi akibat ketidakseimbangan antara pembentukan radikal bebas dengan kemampuan antioksidan alami dari tubuh. Banyak penelitian telah menyatakan bahwa stres oksidatif berperan pada inflamasi sistemik, disfungsi endotel, gangguan sekresi sel  $\beta$  pankreas dan gangguan utilisasi glukosa pada jaringan perifer. Pada penderita diabetes melitus tipe 2 (DMT2) yang berisiko, intervensi intensif dengan kombinasi obat multipel dan modifikasi gaya hidup menunjukkan efek yang bermanfaat terhadap komplikasi vaskular dan menurunkan jumlah kematian akibat penyakit kardiovaskular dan penyebab lainnya. Selain itu juga telah diperlihatkan bahwa netralisasi molekul reaktif secara signifikan dapat menghambat perkembangan disfungsi endotel, kardiomiopati, retinopati, nefropati, dan neuropati pada penderita DM.*

*Sampai saat ini penggunaan antioksidan masih tetap menjadi kontroversi, namun penggunaannya sebagai terapi DM dapat dipertimbangkan karena antioksidan telah menunjukkan efektivitasnya dalam menurunkan risiko perkembangan DM dan komplikasinya. Berbagai macam antioksidan telah dikembangkan saat ini dalam penanganan stres oksidatif pada DM, antara lain penggunaan vitamin dan suplemen, juga penggunaan beberapa komponen dari tanaman dan buah-buahan segar yang memiliki manfaat antioksidan pada DM. Dalam beberapa penelitian terakhir dinyatakan juga bahwa beberapa obat yang rutin digunakan dalam terapi DM ternyata juga memiliki manfaat antioksidan.*

**Kata kunci:** diabetes melitus, diabetes melitus tipe 2, antioksidan.

## ABSTRACT

*Diabetes mellitus (DM) is a metabolic disorder that remains a major health problem in the world. It is characterized by relative or absolute deficiency of insulin secretion and/or insulin resistance that causes chronic hyperglycemia and impaired carbohydrates, lipids, and proteins metabolism. Diabetes has been known as an oxidative stress disorder caused by imbalance between free radical formation and the ability of the body's natural antioxidants. Many studies have suggested that oxidative stress play a role in systemic inflammation, endothelial dysfunction, impaired secretion of pancreatic  $\beta$  cells and impaired glucose utilization in peripheral tissues. In patients with type 2 diabetes mellitus (T2DM) who are at risk, intensive intervention with multiple drug combinations and lifestyle modifications showed a beneficial effect on vascular complications and reduce*

mortality rate due to cardiovascular disease and other causes. There has also been shown that neutralization of reactive molecules can significantly inhibit the development of endothelial dysfunction, cardiomyopathy, retinopathy, nephropathy, and neuropathy in patients with DM.

Recently the use of antioxidants still remains a controversy, but its use as a therapy for DM can be considered because its demonstrated effectiveness in lowering the risk of developing diabetes and its complications. Various antioxidants have been developed for oxidative stress treatment in DM, including the use of vitamins and supplements as well as the use of some components of plants and fresh fruits which have demonstrated antioxidant effect in DM patients. In some recent studies, some drugs routinely used in the treatment of DM also demonstrated antioxidant effects.

**Key words:** diabetes mellitus, type 2 diabetes mellitus, antioxidant.

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that remains a major health problem in the world. It is characterized by relative or absolute deficiency of insulin secretion and/or insulin resistance that causes chronic hyperglycemia and impaired carbohydrates, lipids, and proteins metabolism.<sup>1</sup> Globally, the number of patients with DM is predicted to have two-fold increase in the next 30 years and consequently it will also increase the number of patients with vascular complication.<sup>2,3</sup>

Diabetes has been known as an oxidative stress disorder.<sup>4</sup> It occurs due to imbalance between free radical formation and the ability of the organism's natural antioxidants.<sup>3</sup> It further leads to oxidative disorder of cell components such as protein, lipid and nucleic acid which plays role in the development and progression of DM as well as the complications, both in type 1 and type 2 DM.<sup>1,3-5</sup> The number of macrovascular and microvascular complication still remains a problem. Antioxidant therapy may play great role for diabetic patients; therefore it can be considered for treatment of oxidative stress in DM.<sup>6</sup> However, there are many controversies nowadays on the role of antioxidant therapy for diabetic patients. Thus, this review will discuss about the role of antioxidant in DM.

## OXIDATIVE STRESS

Oxidative stress is defined generally as excessive formation and/or insufficient removal of highly reactive molecules such as ROS and RNS. Reactive oxygen species (ROS) include free radicals such as superoxide ( $\bullet\text{O}_2^-$ ),

hydroxyl ( $\bullet\text{OH}$ ), peroxy ( $\bullet\text{RO}_2^-$ ), hydroperoxyl ( $\bullet\text{HRO}_2^-$ ) as well as non-radical species such as hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) and hydrochlorous acid ( $\text{HOCl}$ ). Reactive nitrogen species (RNS) include free radicals like nitric oxide ( $\bullet\text{NO}$ ) and nitrogen dioxide ( $\bullet\text{NO}_2$ ), as well as non-radicals species such as peroxynitrite ( $\text{ONOO}^-$ ), nitrous oxide ( $\text{HNO}_2$ ), and alkyl peroxynitrates ( $\text{RONOO}$ ). Of those reactive molecules,  $\bullet\text{O}_2^-$ ,  $\bullet\text{NO}$ , and  $\text{ONOO}^-$  are the most widely studied species and play important role in cardiovascular complication of DM.<sup>7</sup>

## DIABETES MELLITUS AND OXIDATIVE STRESS

Oxidative stress plays an important role in developing complication of DM.<sup>8</sup> Excessive activity of oxidant is mechanically related to various etiologies of insulin resistance and the development of type 2 diabetes mellitus (T2DM).<sup>9</sup> There are many sources of oxidative stress in DM including enzymatic, non-enzymatic and mitochondrial pathways. Increasing oxidative stress in DM occurs due to multiple factors.<sup>7</sup> The most dominant factor is glucose auto-oxidation that results in the development of free radicals. Other factors are imbalance cellular reduction/oxidation and reduced antioxidant defenses (including reduced level of cellular antioxidant and reduced enzymes activity against free radicals).<sup>3</sup>

Increased extracellular glucose level is the main feature of DM, which will induce dysregulation of reactive oxygen and nitrogen generating pathways. The process will lead to disruption of vascular endothelium and

produce nitric oxide (NO). Superoxide, when combined with NO of the endothelial cells will result in formation of peroxynitrite, a cytotoxic antioxidant.<sup>10,11</sup>

The increased superoxide production causes activation of five pathways involved in the pathogenesis of DM complication, i.e. activation of polyol pathway flux, increased formation of advanced glycation end products (AGEs), increased expression of AGEs receptor and its activating ligands, activation of protein kinase C (PKC) and excessive activity of the hexoamine pathway.<sup>1,4,6,8</sup> The overproduction of superoxide through mitochondrial electron transport chain during hyperglycemia may become the initiating factor of the above mentioned process.<sup>4</sup>

### COMPLICATION OF DIABETES MELLITUS AND ITS CORRELATION TO OXIDATIVE STRESS

Hyperglycemia may induce oxidative stress that plays a role in complication of DM. In general, type 2 diabetes mellitus is characterized by increased development of morbidity and mortality for cardiovascular disease; therefore, DM is considered to be equal with cardiovascular disease. Moreover, DM is also characterized by microangiopathy complication such as retinopathy, nephropathy, and neuropathy.<sup>6</sup>

Several studies demonstrate that neutralization of reactive molecules has significantly been able to inhibit the development of endothelial dysfunction, cardiomyopathy, retinopathy, nephropathy, and neuropathy in patients with DM.<sup>10</sup> Complications of DM is correlated to oxidative stress are presented in **Figure 1**.<sup>3</sup>

#### Cardiovascular Disease

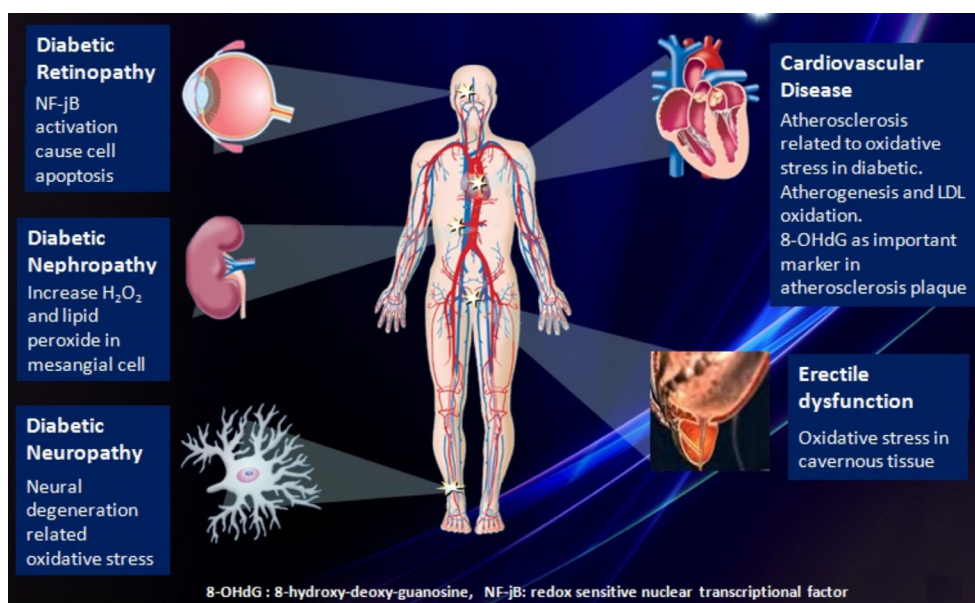
One of the major diabetes complication is cardiovascular disease. The potential mechanism that can mediate the process is oxidative stress, which plays a very important role in atherogenesis and may result in LDL oxidation.<sup>3</sup>

#### Diabetic Nephropathy

Diabetic nephropathy is one of important microvascular complications of DM. High glucose levels will directly increase the production of hydrogen peroxides of mesangial cells and lipid peroxidation of glomerular mesangial cells.<sup>3</sup>

#### Diabetic Neuropathy

Hyperglycemia plays a major role in the development and progression of diabetic neuropathy. In one of its mechanisms, hyperglycemia causes neural degeneration through increased oxidative stress induced by DM. Metabolic and oxidative disorders sometimes cause incredibly rapid changes of glia cells.<sup>3</sup>



**Figure 1.** Complication of diabetes and its association with oxidative stress

### Diabetic Retinopathy

Retinopathy is another complication of DM. In the pathogenesis of diabetic retinopathy, the pericytes and endothelial cells lose their selectivity before any histopathology can be detected. Apoptosis is assumed as one of possible mechanisms of cell death. One of important regulator of antioxidant enzymes is redox-sensitive nuclear transcriptional factor (NF- $\kappa$ B). Activation of NF- $\kappa$ B is regarded as important signaling pathway of endothelial cells apoptosis caused by high glucose levels. In the retina, NF- $\kappa$ B is localized in sub-retinal membranes and microvessels and early activated in the development of diabetic retinopathy.<sup>3</sup>

### Erectile Dysfunction

Erectile dysfunction is usually associated with DM and commonly occurs in young-aged diabetic patients. Oxidative stress in cavernous tissue may be an important factor of erectile dysfunction in patients with DM.<sup>3</sup>

### ANTIOXIDANT IN DIABETES MELLITUS

Some large-scale studies have demonstrated that earlier intensive glucose control will reduce the risk of DM complications, both micro- and macrovascular complications. Epidemiological studies and some prospective data also support that there are long-term effects on clinical outcome by practicing early metabolic control.<sup>6</sup> Antioxidant in DM patients

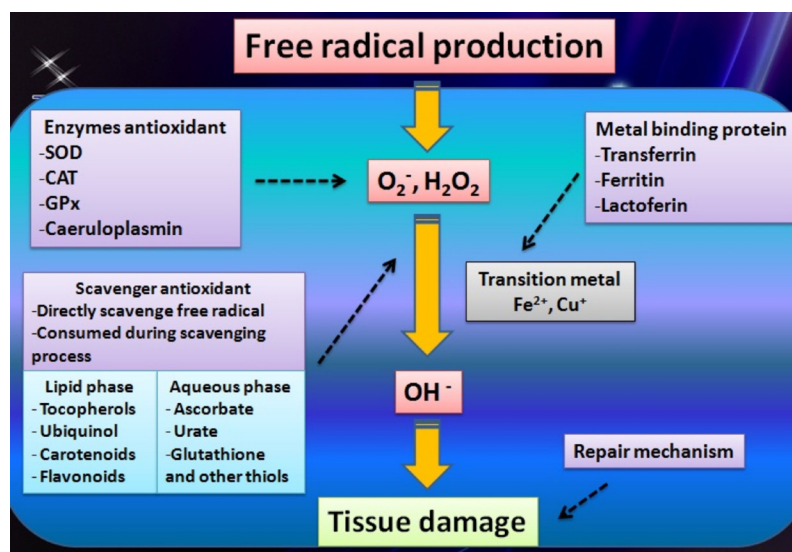
may inhibit the activity of free radicals through several mechanisms including its act as enzyme that destroys free radicals, its ability to bind metals which stimulate the production of free radicals and thus it can inhibit the formation of free radicals, as well as act as scavengers of free radicals. The mechanism of antioxidant in diabetes mellitus is shown in **Figure 2**.<sup>3</sup>

### ANTIOXIDANTS THAT HAVE ROLES IN DIABETES MELLITUS

#### Vitamin and Supplements

Antioxidants such as vitamin C, vitamin E and beta carotene have been considered as ideal supplements against oxidative stress and its complications.<sup>3</sup> Milman et al.<sup>12</sup> reported that reduced cardiovascular events after 1.5 years of vitamin E supplementation. Similar issue has also been reported by Blum et al.<sup>13</sup> who suggested that vitamin E supplementation in patients with DM may prevent myocardium infarction, stroke, and cardiovascular death.

A review by Akbar S.<sup>14</sup> who performed a meta-analysis of 14 studies indicate that antioxidant supplementation does not affect plasma glucose or insulin levels; however, the HbA1c level is significantly reduced by antioxidant supplementation (antioxidants possibly have a protective effect on DM complication). **Table 1** shows some studies that evaluate the effect of antioxidants such as vitamins and supplements on



**Figure 2.** Mechanism of antioxidant in diabetes mellitus



DM and its complications.<sup>4</sup>

### Plants and Their Active Substances

Data of various studies show that plants contain a range of substances with good antioxidant properties. The bioactive compounds in plants that have antioxidant effect are cinnamic acids, coumarins, diterpenes, flavonoid, lignin,

monoterpenes, phenylpropanoids, tannins and triterpenes. Natural antioxidants are found in almost all part of plants; therefore, plants with high antioxidant levels play an important role in disease recovery and is associated with oxidative stress as in DM.<sup>3</sup> **Table 2** shows some plants with positive effects in DM by their antioxidant properties.<sup>4</sup>

**Table 1.** Antioxidant efficacy of vitamins and supplements in diabetes and its complications<sup>4</sup>

Vitamin	Target	Efficacy
Vitamin C	Patients with type 2 Diabetes	Decreases fasting plasma insulin level, decreases HbA1c level, improves insulin action
Vitamin E (alpha tocopherol)	STZ-induced diabetic rats	Reduces LP, reduces the activity of GSH-Px and GST
	Diabetic patients	Reduces oxidative stress indicators, reduce protein glycosylation, reduces insulin resistance.
	Patients with type 2 Diabetes	Reduces retinal hemodynamic abnormalities, normalizes creatinine clearance
Vanadium	Patients with type 1 Diabetes	Scavengers of free radical, Reduces LP in pancreas
Zinc	STZ-induced diabetic rats	Induces synthesis of metallothionein, Reduces retinal LP
Selenium	Alloxane-induced diabetic rats	Increases GSH in liver and brain
Beta carotene	Alloxane-induced diabetic rats	Reduces oxidative LDL
	Patients with type 2 Diabetes	

STZ: Streptozocin, GSH-Px: Glutathione peroxidase, GST: Glutathione S-transferase, GSH: Glutathione, LDL: low density lipoprotein, LP: Lipid Peroxidation, Hb: Hemoglobin

**Table 2.** Plants with positive effects in diabetes by their antioxidant properties<sup>4</sup>

Anoectochilus formosanus	STZ-induced diabetic rats	-	↓renal LP, ↑GSH, activation of renal catalase
Trifolium alexandrinum		Flavonoids	Free radicals scavengers, ↓ LP, ↑ hepatic GSH
Viburnum dilatatum		Cyaniding 3-sambubioside	Free radicals scavenger, ↓LP
Larrea divarita		Nordihydroguaiaretic acid	Inhibition of xanthine oxidase, ion chelation, free radicals scavenger, ↓systolic BP, prevent renal morphological changes, improves renal function
Aralia elata		-	Inhibition of aldose reductase, anticarcinogenic activity,
Viscum album		quercetin	↓oxidative stress biomarker, ↑ GSH in the heart and kidney
Fomes fomentarius		-	Ion chelation, free radicals scavenger, ↓LP, altered SOD, CAT and GSH Px activities, lower oxidative stress marker
Allium sativum		s-allyl cysteine sulfoxide	↑GSH, ↑SOD in the liver and kidney, ↓ LP
Eugenia jambolana		Flavonoids	Free radicals scavenger
Aloe vera		-	↑GSH, SOD, CAT, GSH-Px, and GST in the liver and kidney, ↓LP
Scoparia dulcis		-	↑GSH, SOD, CAT, GSH-Px and GST in the liver and kidney, ↓LP
Juglans regia	Type 2 diabetic mice	Pedunculagin	↑GSH, SOD, CAT, GSH-Px and GST in the liver and kidney, ↓LP Reduces oxidative stress biomarkers

**Table 2.** Plants with positive effects in diabetes by their antioxidant properties<sup>4</sup>

Ferula assa-foetida	STZ induced diabetic mice and KK-Ay mice	Ferulic acid	Free radicals scavenger, ↓LP
Vitis vinifera	Alloxan-induced diabetic rats	Proanthocyanidins	Free radicals scavenger, ↑ pancreatic GSH, ↓LP
Cassia fistula		-	↑SOD, CAT, GSH-Px and GR activity in the heart, ↓LP in the liver
Allium cepa		s-methyl cysteine sulfoxide	Free radicals scavenger
Allium sativum		s-methyl cysteine sulfoxide	Free radicals scavenger, ↓LP
Panax ginseng	Type 2 diabetic rats	-	Free radicals scavenger, prevent erectile dysfunction
Lycium barbarum	Alloxan-induced diabetic rats	-	Effect on lipid reduction

STZ: Streptozocin, LP: Lipid peroxidation, GSH-Px: Glutathione peroxidase, GR: Glutathione reductase, SOD: superoxide dismutase, CAT: catalase, BP: Blood pressure

**Table 3.** Drugs with antioxidant properties in diabetes<sup>4</sup>

Drugs	Mechanism of action	Benefits in diabetes
ACEI and ARB	Inhibition of angiotensin II and expression of NAD(P)H oxidase	Nephropathy
Melatonin	Free radicals scavenger	Nephropathy, neuropathy
α- lipoic acid	Free radicals scavenger, metal ion chelation, antioxidant recycling	Neuropathy, retinopathy
Glibenclamide	Free radical scavenger	
Allupurinol	Inhibit xanthine oxidase	
Metformin	↓ xanthine oxidase activity, metal ion chelation, free radicals scavenger, inhibit xanthine oxidase and phosphodiesterase, ↓ TNF-α production, inhibit AGEs	Cardiovascular disease
Repaglinide	↑ GR and GSH level	
Phosphodiesterase inhibitor	Inhibit phosphodiesterase, ↑ cAMP & cGMP	
Caffeic acid phenethyl ester	Free radicals scavenger	Cardiovascular disease
Carvedilol	Inhibit electrophile adduction, inhibit LP in myocardium cells, inhibit O <sub>2</sub> release through neutrophil, improve the body's natural antioxidant system, free radical scavengers	Cardiovascular disease

ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, NADPH: Nicotinamide adenine dinucleotide phosphate-oxidase, GSH: glutathione, GR: glutathione reductase, TNF: tumor necrosis factor, LP: lipid peroxidation, AGE: advanced glycation end product

### Drugs and Compounds with Antioxidant Properties

Some drugs with antioxidant properties which have antioxidant effect in patients with DM are shown in **Table 3**.<sup>4</sup>

### CONCLUSION

Antioxidant therapy has great effects on patients with diabetes based on novel ideas about mechanisms of oxidative stress formation in diabetic patients. Various antioxidants have

been developed recently to manage oxidative stress in DM; however, the application remains controversial.

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