A REVIEW ON ASPECTS OF DIABETES MELLITUS CAUSED BY OXIDATIVE STRESS

By

Md. Rasshiq Amin Bhuiyan

17146042

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
December 2022

© 2022. Brac University

All rights reserved.

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Md. Rasshiq Amin Bhuiyan
ID: 17146042

Approval

The thesis titled "A review on aspects of diabetes mellitus caused by oxidative stress" submitted by Md. Rasshiq Amin Bhuiyan (17146042), of Spring, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

Sania Ashrafi
Lecturer
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

As a result of constant exposure to various stimuli, the human body produces reactive species known as free radicals (ROS/RNS), which oxidize cellular components through the transfer of their free unpaired electrons. The body possesses endogenous antioxidant systems, or it acquires exogenous antioxidants from the diet to combat the harmful effects of such species. These antioxidants neutralize the harmful species and maintain the body's homeostasis. Any imbalance between RS and antioxidants causes oxidative stress, which in turn causes the emergence of pathological conditions, one of which is diabetes. The majority of research suggest that oxidative stress plays a role in the pathogenesis of diabetes through changes in enzymatic systems, lipid peroxidation, poor glutathione metabolism, and decreased levels of vitamin C. Different biomarkers of oxidative stress in diabetes mellitus include lipids, proteins, DNA damage, glutathione, catalase, and superoxide dismutase. Diabetes complications brought on by oxidative stress can include stroke, neuropathy, retinopathy, and nephropathy. This review's main goal was to briefly summarize the fundamentals of oxidative stress in diabetes mellitus and propose some natural remedies.

Keywords: Diabetes mellitus, Oxidative stress, Antioxidant, Biomarkers.

Acknowledgement

First and foremost, I'd want to express my profound appreciation to Allah (SWT) for bestowing great benefits on me and enabling me to complete the thesis.

I would like to convey my heartfelt gratitude to my academic supervisor for her guidance and enthusiasm throughout the project, Sania Ashrafi (Lecturer, School of Pharmacy, Brac University).

I'd also want to thank Dr. Eva Rahman Kabir (Professor and Dean, School of Pharmacy, Brac University) for her devotion, contribution, and direction to both students and the department.

I would want to thank my parents for always motivating me to push myself beyond my comfort zone. I would not have gotten this far without their unending prayers and love. I would also want to thank all of the faculty members in the School of Pharmacy, as well as everyone who has assisted me to the best of their ability whenever I've needed it.

I would also like to express gratitude to everyone for their advice and support.

Contents

List of Table

List of Figures

List of Acronyms

DM	Diabetes mellitus
ROS	Reactive oxygen species
AGE	Advanced glycation end-product
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
IDDM	Insulin-dependent diabetes mellitus
NIDDM	Noninsulin-dependent diabetes mellitus
GDM	Gestational diabetes mellitus
DCM	Diabetic Cardiomyopathy
SOD	Superoxide oxide dismutase
GSF	Glutathione
DN	Diabetic Nephropathy
GPX	Glutathione peroxidase
IRe	Insulin resistance
PPAR	Peroxisome proliferator-activated receptor
AMPK 50	Adenosine monophosphate-activated protein kinase
PGC-1	Peroxisome proliferator-activated receptor-gamma coactivator 1
mPTP	Mitochondrial permeability transition pore
FAO	Fatty acid oxidation

1 Introduction

1.1 Overview

When it comes to diabetes mellitus oxidative stress is linked in so many ways. Diabetes and complications associated with it are developed and progressed by the involvement of oxidative stress. Oxidative stress is the outcome of alteration of the cell's redox balance DNA, protein and lipid biomolecules which are vital gets damaged as a result. A chronic endocrine and metabolic illness called diabetes mellitus (DM) is defined by hyperglycemia and vascular consequences and is highlighted by insulin insufficiency, insulin sensitivity, or both (Pizzino et al., 2017). Oxidative stress has been strongly associated with the prevalence of diabetes mellitus, as well as a number of other health issues like cancer and neurological diseases. It has been demonstrated that oxidative stress weakens the two main processes that are involved with diabetes, insulin secretion and insulin action. It might be said that oxidative stress has a dual function in diabetes. Not only does oxidative stress encourage the development of diabetes, but it also makes the condition of the illness and its related consequences worse (Yang, Jin, Kei Lam, et al., 2011). According to experimental data, type 1 diabetes is accompanied by altered beta-cell activity driven by autoimmune responses, cytokines, and inflammatory proteins. Additionally, it has been observed that hyperglycemia increases oxidative stress by generating free radicals from de novo and the defense system of antioxidant gets suppressed. Sustained formation of reactive oxygen species (ROS) in chronic hyperglycaemia, causes intense suppression of the antioxidant enzymes and non-enzymatic antioxidants which occurs in different tissues' and promote oxidative stress (Kuyvenhoven & Meinders, 1999).

1.2 Objective of Study

The study was done to build a concise review based on findings from the previous and recent studies done on diabetes mellitus and oxidative stress. Oxidative stress may play a significant role in the development of diabetes and related complications. The project focuses on the diabetes mellitus and its connection to oxidative stress and some therapeutic approaches based on natural products.

1.3 Oxidative Stress

It is crucial and crucially important to understand how oxidative stress contributes to the onset and progression of diabetes mellitus. Pro-oxidative processes have been observed in a number of molecular event cascades in several metabolic pathways, including the glycolytic, hexosamine, protein kinase C, polyol, and advanced glycation end-product (AGE) pathways. And in diabetics it is often up regulated. The primary cause of the oxidative stress associated with diabetes appears to be the inhibition of glyceraldehyde 3-P dehydrogenase by poly-ADP-ribose polymerase 1 and the resultant buildup of the enzyme substrate (Gly-3-P) When free radicals and antioxidants are not balanced in the body, it causes oxidative stress. Oxidative stress also occurs because of the variation in the generation of reactive oxygen species (ROS) and its accumulation. Oxidative stress develops when there are too many free radicals in the cells of the body. (Yaribeygi et al., 2020).

2 Methodology

Databases with bibliography such as PubMed, Google Scholar, Science Direct, Springer link, and Scopus were investigated strenuously and information like oxidative stress, biomarkers of oxidative stress, diabetes mellitus, and oxidative stress induces diabetes mellitus were assembled. Mendeley desktop version 1.19.8 was used to cite and reference the information sources.

3 Diabetes Mellitus

The word "diabetes mellitus" refers to a metabolic illness in which the body's insulin hormone is insufficiently generated or used to turn carbohydrates into energy. This disorder was also referred as the "black death" in the 14th century. A hyperglycemic condition called hyperglycemia may occur as a result of flaws in the production or activity of the insulin hormone. These flaws may result in certain metabolic abnormalities. Juvenile onset and adult onset have been used to describe the two most common diabetes syndromes throughout the majority of this century. The initial age range, however, was never sufficient since both adult and juvenile diabetes can develop at a young age. In 1979, a system of insulin tolerance categorization was developed. T1DM, T2DM, and GDM have been accepted by the National Diabetes Committee (Yang, Jin, Kei Lam, et al., 2011). It makes the costliest diabetic complication when the renal system is impacted by the microvascular risks with prolonged failure of kidney (nephropathy) and injury of nerve

(neuropathy) results into the raising the risk of diabetic foot ulcers and/or amputations. Different types of serious health problems will start to make place in the body by the effects of diabetes if it is not treated and left as it is as well as complications related to microvascular and macrovascular will arise as it effects smaller and larger vessels. Furthermore, macrovascular disorders including coronary heart failure, peripheral artery disease, and stroke, as well as the eye illness retinopathy, can all lead to blindness (Kuyvenhoven & Meinders, 1999). Poor digestion of electrolytes, sugars and protein results in the problem such as unstable vascular system of body and hyperglycemic disease. Grandiose endothelial cells are the retina, glomerulus, middle, and peripheral nerves in this condition as a result of excessive or less glucose accumulation in certain cells, failure of lipid metabolism, and increased reactive development. (CURCHOD & DAEPPEN, 1959)

3.1 Types of DM

3.1.1 Type I: Insulin-Dependent Diabetes Mellitus

Type I diabetes, also known as insulin-dependent diabetes mellitus (IDDM), is the earliest subtype of the disease and is clinically distinguished by the sudden onset of symptoms, insulinopenia, the need for administered insulin to maintain life, and propensity for ketosis. Young people typically get affected by this type of illness thus the name "Juvenile diabetes" was used to define it. However, at any age it can exhibit symptoms and can be diagnosed for the first time. As a result, based on the patient's age making a diagnosis will not provide correct diagnosis. IDDM is heterogeneous when it comes to the genetics of the disease and the environmental factors that cause it. (Buchanan & Xiang, 2005)

3.1.2 Type II: Noninsulin-Dependent Diabetes Mellitus

The type II diabetes, also known as noninsulin-dependent diabetes mellitus (NIDDM), is the second subtype of diabetes and metabolic abnormalities related to this type of diabetes typically exhibit little or no symptoms. NIDDM patients are not at risk for ketosis and they do not rely or need insulin to avoid ketonuria. For the treatment of symptomatic or chronic fasting hyperglycemia the administration of insulin might require if it cannot be done with diet or oral medications. There is a possibility of NIDDM patients not exhibiting any symptoms for years or even decades, and the condition merely slowly advances. Moreover, this kind can also exhibit the common chronic connections and consequences of diabetes, such as macroangiopathy,

microangiopathy, neuropathy, and cataracts. Weight loss frequently helps with hyperglycemia and glucose intolerance. (Buchanan & Xiang, 2005)

3.1.3 Other Types of Diabetes

Diabetes belongs to this subclass along with a few additional illnesses and various of clinical traits that aren't typically connected to the diabetic state can be seen as syndrome. The etiologic connections that are known or hypothesized have been used to divide this subclass. Diabetes can be secondary to diseases related pancreas or pancreatic tissue removal. Acromegaly, cushing's syndrome, pheochromocytoma, glucagonoma, somatostatinoma, primary aldosteronism, which are examples of endocrine diseases. Drugs, chemicals and hormones that can cause hyperglycemia after administration can also cause diabetes.

Defects in insulin receptor can be one of the causes that is related to diabetes. Insulin receptor deficiencies can be linked to diabetes, and it is caused by abnormal number of insulin receptors or effectiveness of insulin receptors or antibodies to receptors, whether or not they are accompanied by immunological conditions. (Diabetes & Group, 1997) In gestational diabetes mellitus (GDM) a hormone produced by the placenta interferes with the body's ability to use insulin. As opposed to being taken in by the cells, glucose accumulates in the blood. (Buchanan & Xiang, 2005)

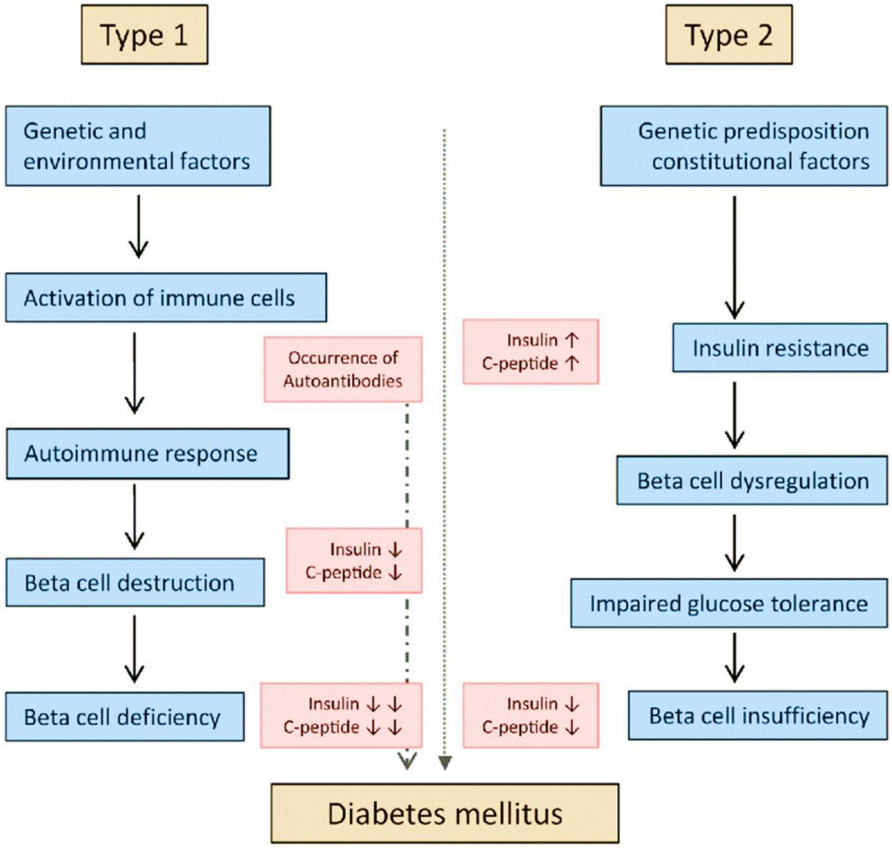


Figure 1: Difference between Type 1 and Type 2 diabetes mellitus (Hörber et al., 2020)

3.2 Pathophysiology of DM

3.2.1 Pathophysiology of Type 2 Diabetes

In those who are at risk for type 2 diabetes, skeletal muscle insulin resistance is the first anomaly that might be seen. Throughout many groups, it has been shown that reduced insulin-stimulated glucose elimination, as shown by testing of glucose tolerance through intravenous, can be used to determine the onset of diabetes in people on high-risk. Additionally in high-risk individuals' activation of signal transduction of insulin is weakened, certain genes are not always able to give modified expressions, stimulation of the synthesis of muscle glycogen is not strong. Possible mediator of insulin resistance, formation and storage of intramyocellular lipid has been identified as a source. Adipose tissue, liver, beta cells, and the brain have all been shown to play significant roles in the etiology of diabetes in recent studies using both human and animal models. Clinical evidence shows that adipose tissue excess (obesity) or deficiency (lipodystrophy) can lead to insulin resistance and diabetes supports this idea. In addition, some aspects of the insulin resistance

and insulin secretory dysfunction defining type 2 diabetes are produced by abnormalities in insulin and IGF-1 signaling in liver, cells, and neurons. (Patti, 2004)

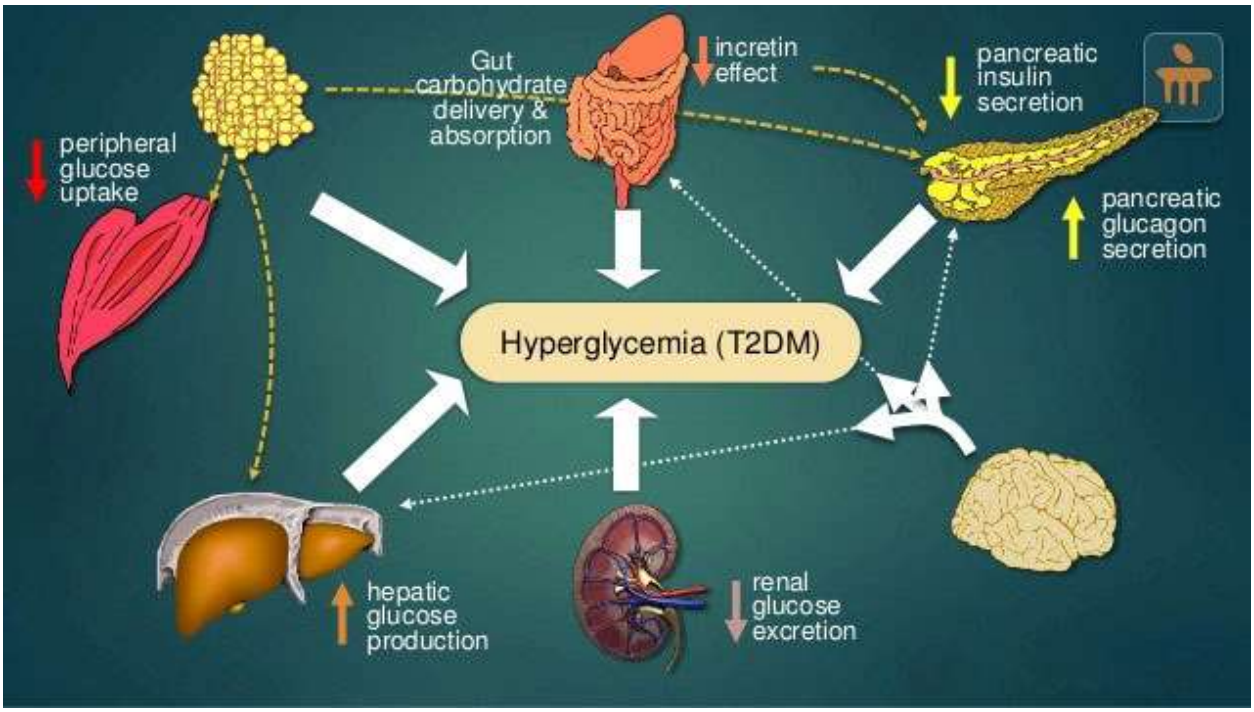
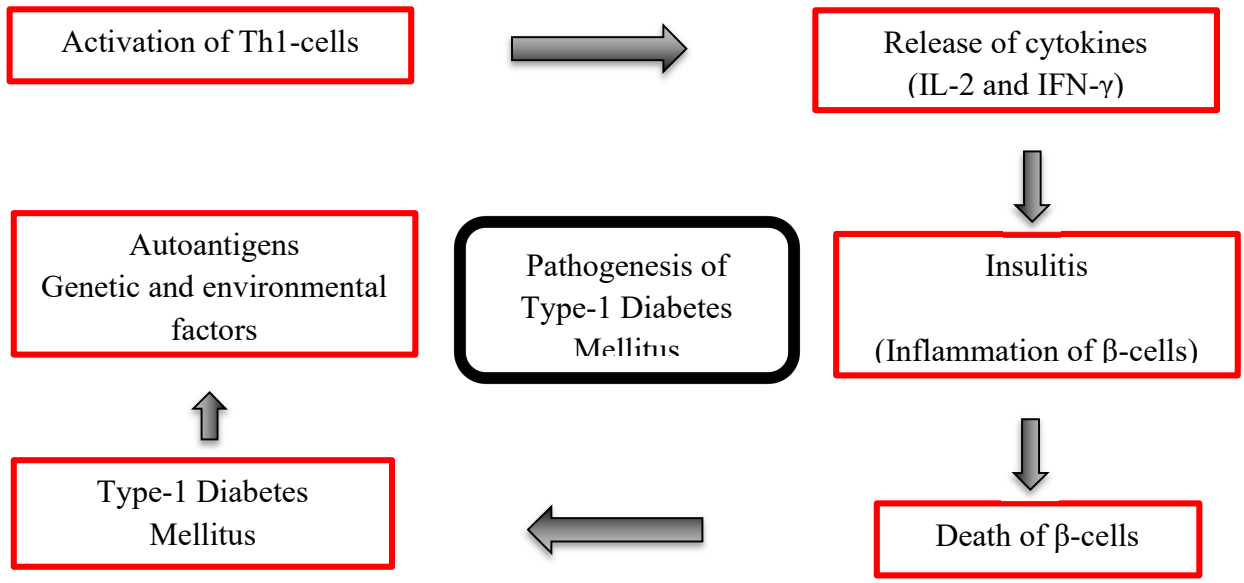


Figure 2: Pathophysiology of T2DM (Galicia-Garcia et al., 2020)

3.2.2 Pathogenesis of Type-I Diabetes

A lack of endogenous insulin release from the pancreatic β-cells (often because of cell death) causes Type 1 diabetes mellitus (T1DM), a significant chronic condition. Although T1DM is recognized to have autoimmune processes that target beta cells and malfunctioning of beta cells, still much unknown are the exact etiology and pathogenic processes. Though it can emerge at any age, T1DM often develops in kids or young adults. (Ilonen et al., 2019)



Abbreviations: Th1, T helper cells; IL-2, Interleukin-2; IFN-γ, Interferon-gamma.

Figure 3: Pathogenesis of Type-I diabetes mellitus (Jansari et al., 2014)

3.3 Complication of DM

3.3.1 The Microvascular Complication of Diabetes

Retinopathy

Diabetic retinopathy, a microvascular disorder that can damage the macula, peripheral retina, or both, it causes significant vision loss and blindness in diabetics. A complete or partial loss of vision may be brought on by vitreous hemorrhage or retinal objectivity. Endothelial cell and pericyte retinal capillary degeneration caused by ischemia and micro-aneurysms is a hallmark of the diabetic retinopathy condition. Proangiogenic mediators, vascular endothelial growth factor particularly, are enhanced at an advanced stage of the illness, leading to pathological retinal vessel proliferation. Vision loss may be brought on by alterations in the retinal microvasculature, increased retinal vascular leakage can be another reason. (Fujimoto, 2000)

Neuropathy

The most significant and least well-known consequence affects more than 15% of chronic diabetes is diabetic neuropathy. The cumulative effects of these harmful events may cause neuronal death through the production of reactive oxygen species and mitochondrial malfunction, according to recent research (Fujimoto, 2000).

Nephropathy

In both types of diabetes mellitus, T1DM and T2DM, nephropathy is a chronic complication that is identified by elevated urine albumin excretion (proteinuria) or decreased kidney glomerular filtration rate (GFR). About 30% of people with type 1 diabetes (T1D) and 40% of those with type 2 diabetes have proteinuria (T2D). (Fujimoto, 2000)

3.3.2 The Macrovascular Complication of Diabetes

Coronary artery disease, cerebrovascular disease, and peripheral artery disease are all lifetime medical conditions that require continuous medical therapy as these diseases are part of diabetic mellitus. Patients are at a significant risk of developing these conditions as well as several complications related to macrovascular problems. Chronic hyperglycemia has been established as the key contributing component to the incidence of diabetic vascular problems. Hyperglycemia, which is the primary initiating factor in diabetic vascular pathogenesis, which also causes endothelial dysfunction. (Fujimoto, 2000)

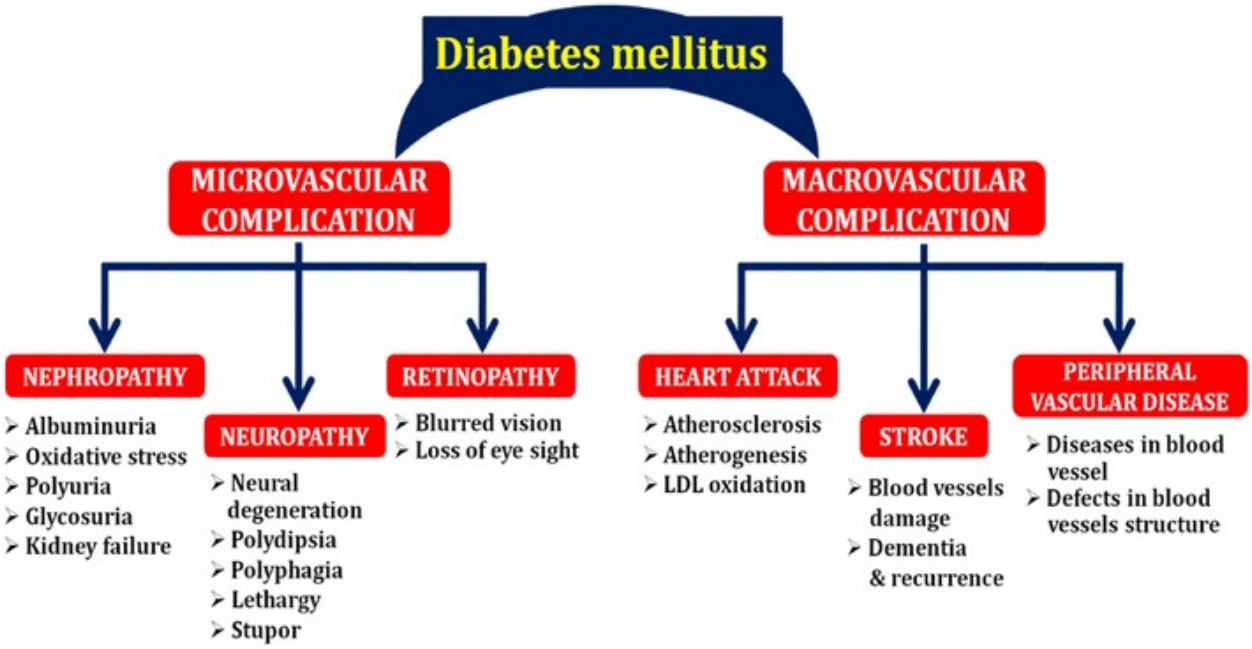


Figure 4: Diabetes mellitus complication *(Naveen & Baskaran, 2018)*

Diabetic Cardiomyopathy

When there are no additional cardiac risk factors present, such as significant valve dysfunction, coronary artery disease, or hypertension, diabetic cardiomyopathy is referred to as a diseased heart type. Cardiac diabetic cardiomyopathy (DCM) is classed as compromised heart structure and manifestations, and severe volvuli disease, hypertension, and coronary artery disease are some of the examples. Clinical studies indicate that 19 to 26% of diabetes people have cardiac insufficiency. According to the Framingham Heart Study, both male and female diabetes patients had an increased risk of heart failure relative to their age ranges. Obesity was not a factor in this connection. The pathophysiologic mechanisms behind DCM are still not completely understood. Insulin resistance, microvascular failure, subcellular component defects, metabolic disorders, autonomic cardiac dysfunction, renin-angiotensin system changes, and maladaptive immune response are some of the potential reasons behind the DCM occurrence. (Fujimoto, 2000)

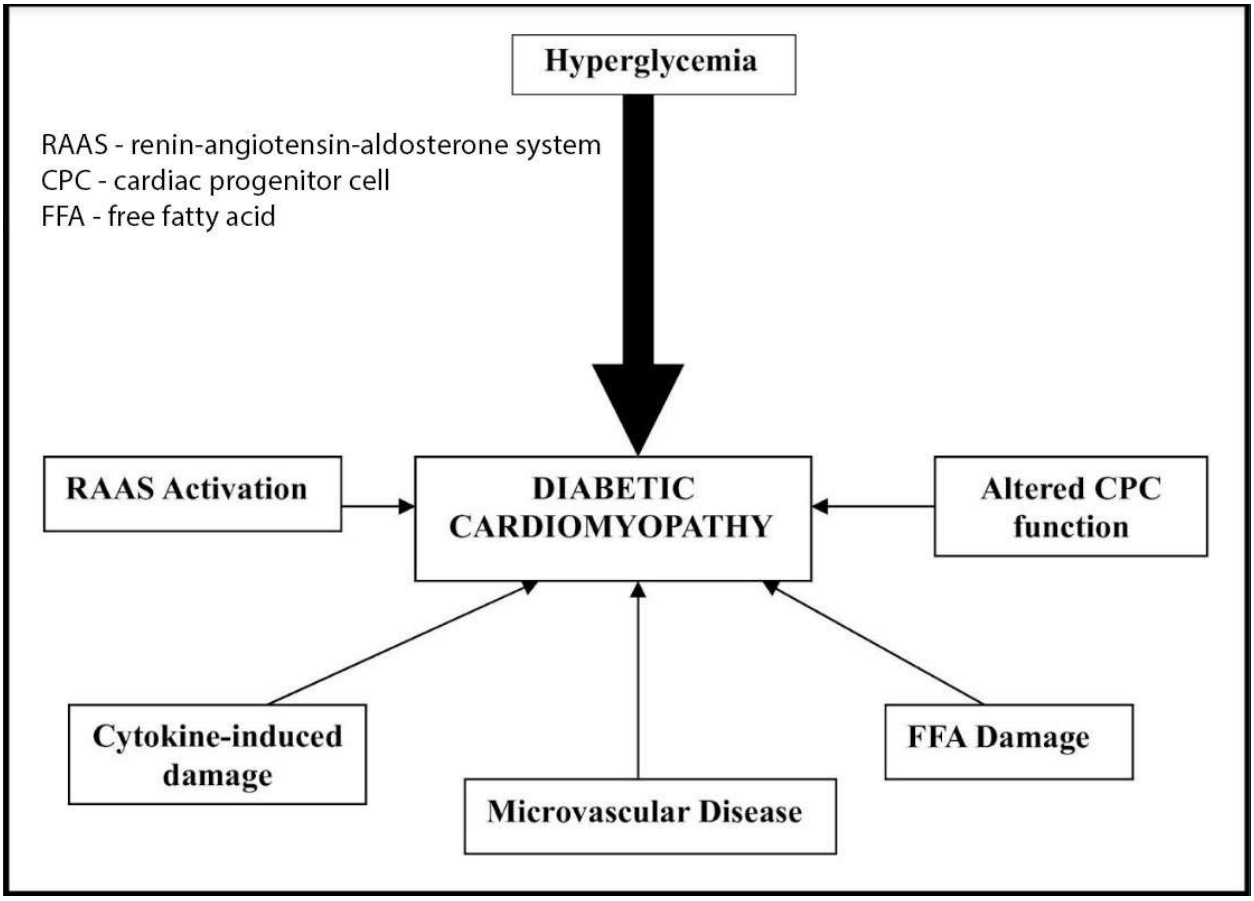


Figure 5: Diabetic Cardiomyopathy (Aneja et al., 2008)

4 Free Radical

4.1 Free Radical

Any molecular species with an unpaired electron in an atomic orbital and the ability to sustain its own existence is referred to as a free radical. Most radicals exhibit a few similar characteristics when an unpaired electron is present. There are numerous radicals that are not stable and shows a great reactive nature. They act as oxidants or reductants depending on whether they give or take an electron from other molecules. In various disease conditions, the hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical are very significant oxygen-containing free radicals. These are very reactive species that can harm biologically important components including DNA, proteins, carbohydrates, and lipids in cell membranes and the nucleus. Important macromolecules are attacked by free

radicals, which damages cells and disrupts homeostasis. Free radicals may attack every type of molecule in the body. They mainly target lipids, nucleic acids, and proteins. (Lobo et al., 2010)

4.2 Types of Free Radical

4.2.1 Reactive oxygen species (ROS)

Superoxide (O2), hydroxyl (OH), peroxyl (RO2), and hydroperoxyl (HO2) radicals are just a few examples of oxygen radicals that fall under the category of reactive oxygen species (ROS). Other nonradical oxidizing agents that fall under this category include hydrogen peroxide (H2O2), hypochlorous acid (HOCl), and ozone (O3). (Bayir, 2005)

4.2.2 Reactive Nitrogen species (RNS)

Reactive nitrogen species are oxidants that include nitrogen, such as nitric oxide (NO), peroxynitrite (ONOO), and nitrogen dioxide (NO2) (RNS) (Ozcan & Ogun, 2015)

4.2.3 Reactive chlorine species (RCS)

Similar to •OH, reactive chlorine species (RCS) have increased levels of oxidation rate for organic pollutants, including the chlorine radical (Cl•) and its secondary radicals (e.g., Cl2•-). (Wang et al., 2020)

4.3 Biological Role of Free Radical

It has been shown that oxidative stress, or an imbalance between reactive oxygen species and defense and repair antioxidant mechanisms, contributes to the onset of chronic illnesses in biological systems. In order to avoid and assess aging-related disorders, it may be helpful to determine the antioxidant state of biological systems. It is important to assess how much food actually contributes to the antioxidant status in biological systems and how much dietary antioxidants should be consumed, alongside organism defences. (Sánchez-Moreno, 2002) Some genes may increase the formation of free radicals and regulate antioxidant levels in the body are advantageous in the early years of life, allowing for survival and reproduction, although it can become harmful later on. (Halliwell, 2009)

4.4 Production and Scavenging of Free Radical

ROS may be generated by a wide range of cellular systems. The mitochondrial respiratory chain, which uses between 80 and 90 percent of the oxygen a person takes in, is the primary source of ROS generation in the cell. Neutrophils and macrophages, two immune cell types that aid in the body's defense against invaders like microbes, are additional producers of ROS in the body. (Bachur, 1982) Antioxidants that are strong and natural with free radical scavenging action include phytochemicals including carotenoids, tocopherols, ascorbates, lipoic acids, and polyphenols. Free radicals are scavenged by endogenous antioxidant enzymes such superoxide oxide dismutase (SOD), catalase, glutathione peroxidase, and glutathione reductase, as well as minerals like selenium, manganese, copper, and zinc and several vitamins. (Prakash et al., 2011) A variety of polypeptides and enzymes that are encoded in the genome control the rates of free radical synthesis and eradication of a healthy cell. Numerous research have examined how free radical-related parameters vary with age in animal tissues, and some have demonstrated how antioxidants influence mean life expectancy through various experimental methods. (Perez-Campo et al., 1998) As a producer of free radicals and a potential victim of oxidative damage, the red blood cell has been the subject of substantial research in both fields. Hemolytic anemia and red cell death can occur because of the oxidation-reduction reactions performed by xenobiotics and several medications. (Winterbourn, 1985)

5 Oxidative Stress

Reactive oxygen intermediates including superoxide anion (O2•(-)), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH) may harm proteins, nucleic acids, and cell membranes, which is what causes the occurrence of oxidative stress. Reactive oxygen species have been linked to a number of illnesses, according to growing data. (Storz & Imlay, n.d.)

Oxidative stress contributes to cellular harm actively and it can occur before many diabetic problems manifest themselves and it is one of the main factors in that develops diabetes. Cellular oxidative stress is a also significant contributor to both insulin resistance and diabetic cell damage. Oxidative stress may be facilitated by glucose fluctuations abruptly. Reactive oxygen species can be produced more often in cells with increased cellular glucose levels. Additionally, reduction of insulin sensitivity and elimination of the insulin-producing cells in the pancreas can

cause oxidative stress to encourage the development of DM. ROS production could be done because of free fatty acids in addition to harming the mitochondrial DNA and affecting pancreatic beta-cell activity. The mechanisms that regulate oxidative stress are directly involved in the pathogenic effects of these illnesses. (Yang, Jin, Lam, et al., 2011)

The development of diabetic complications, both microvascular and cardiovascular, is significantly influenced by oxidative stress. Diabetes-related metabolic problems lead to an overproduction of mitochondrial superoxide in the heart, small and large vessel endothelial cells. (Giacco & Brownlee, 2010) A major factor in the pathophysiology of diabetic problems is high oxidative stress. It is hypothesized that if oxidative stress in diabetes is in elevated level it favors the onset of retinopathy, cardiac damage, nephropathy, and neuropathy. Autooxidation of glucose, changes in redox balances, lower tissue concentrations of low molecular weight antioxidants like reduced glutathione (GSH) and vitamin E, and reduced activity of antioxidant defense enzymes like superoxide dismutase (SOD) and catalase are some potential causes of oxidative stress in diabetes. A causal relationship is thought to exist between higher glucose and other metabolic abnormalities crucial to the emergence of diabetes complications. ROS are produced by high glucose. (Kowluru & Chan, 2007)

Diabetes and its accompanying problems have been linked to oxidative stress as a factor in their development and onset. The development of insulin resistance, β - cell dysfunction, decreased glucose tolerance, and mitochondrial dysfunction are some effects of an oxidative environment that might ultimately result in the diabetes. The factor behind the incident are dysfunction of beta cell, glucose tolerance becomes less, mitochondrial dysfunction. Occurrences of ketosis, lack of sleep, and excessive food consumption are only a few examples of the various lifestyle factors and illness states that can cause oxidative stress. The family of serine/threonine kinases is involved in a number of stress pathways that are activated by oxidative stress and which, in turn, negatively impact insulin signaling. (Rains & Jain, 2011)

5.1 Pro-oxidative and Antioxidant Systems of ROS

Oxidative stress caused by endobiotic or xenobiotic that is either produced because of ROS production or by blocking antioxidant mechanisms is referred to as a prooxidant. Any reactive, free radical-containing molecule found in cells or tissues may fall under this category. Several of

the well-known antioxidant flavonoids have also been observed that in the presence of transitional metal to behave as prooxidants. These flavonoids' structures affect both their antioxidant and copper-induced prooxidant properties. ROS transforms into water and O2, more stable molecules because of reactions that are conducted by several widely distributed major antioxidant enzymes in eukaryotic organisms, including SOD, catalase, and other peroxidases.

As direct scavengers of ROS, small molecular-weight nonenzymic antioxidants like as GSH, NADPH, thioredoxin, vitamins E and C, and trace metals like selenium also perform this role. By preserving a delicate intracellular redox equilibrium and limiting unfavorable cellular damage brought on by ROS, these enzymatic and nonenzymatic antioxidant mechanisms are essential for supporting life. (Rahal et al., 2014)

5.2 Biomarkers of Oxidative Stress

Biomarkers are substances whose fluctuation can reveal a change in a physiological process and be employed as a preventative measure against subsequent disease. Due to their unpaired electron, free radicals are very reactive, and their reactivity dictates their extremely short half-life. Additionally useful indicators of oxidative stress are the byproducts of radical damage to cells, such as DNA, lipids, and proteins. Oxidative stress can be tracked by assessing the presence of such beneficial species because against these toxic compounds cell evolved a variety of defense mechanism. (Chikezie et al., 2015) Urinary 8-oxo-7,8-dihydro-2-deoxyguanosine (8oHdG) is a common illustration of a biomarker of oxidative stress. This marker, which is formed as a result of oxidative DNA damage, shows up in the urine unmetabolized. Because people who excrete the biomarker more frequently in their urine than those who do not or very slightly excrete it have been found to have a considerable rate of diabetic nephropathy (DN) progression, urinary 8oHdG is a useful clinical marker for the prediction of the development of DN in diabetic patients. (Samuel, 2017)

5.2.1 DNA

DNA may undergo oxidative alterations in a variety of ways, such as by generating crosslinks or altering the bases or sugars of the nucleotides. There is a possibility of cellular aging, death, and mutations due to these alterations. Damaged DNA undergoes alterations in vivo, such as deamination. (Chikezie et al., 2015)

5.2.2 Nitrotyrosine

Nitrotyrosine is a reliable indicator of oxidative stress and protein oxidative stress. Nitric oxide and superoxide can spontaneously combine to generate the potent oxidant peroxynitrite when they are present in close vicinity to one another. The main outcome of the peroxynitrite impact on proteins is nitration at the 3-position (ortho) of tyrosine. Peroxynitrite-induced protein tyrosine nitration changes protein function through interfering with signaling pathways for phosphorylation and dephosphorylation. HPLC, GC-MS, or ELISA method are most commonly used for detecting nitrotyrosine. (Chikezie et al., 2015)

5.2.3 Proteins

An amino acid may be converted to another or to a changed residue by oxidation of the amino acid side chain as a consequence of alterations to proteins, along with crosslinking, peptide fragmentation, and other effects. A protein's secondary and tertiary structures may change as a result of these modifications, and the modifications can reveal the areas that are protected to more oxidation or to other forms of spontaneous antioxidant vitamins, stop the production of new free radical species, or newly created free radicals are eliminated prior to the initiation of a chain reaction. These enzymes may either repair cell structures harmed by free radical attack or they stop the chain reaction. (Chikezie et al., 2015)

5.2.4 Lipids

The process caused by free radicals called lipid peroxidation has most likely been studied in depth. At the membrane level, where the majority of reactive radicals, particularly reactive oxygen species, are produced, these chemicals are prominent. A chain reaction that starts as a result of lipid peroxidation may also continue on its own, as a result a large number of lipid peroxide radicals is produced and the ROS impact is increased. (Chikezie et al., 2015)

5.2.5 Antioxidant Enzymes

Peroxisomes contain the enzyme catalase, which produces water and oxygen by breaking down hydrogen peroxide. Superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase

(CAT) are three of these biomarkers that are crucial for maintaining homeostasis which aids in the continuation of activity of normal cell. (Begum et al., 2014)

5.2.6 Vitamins

Dietary sources of vitamins A, C, and E detoxify free radicals. Additionally, production of vitamins is done when these vitamins during recycling procedures. Ascorbic acid recycles the tocopherol radical, regenerating α-tocopherol, while glutathione recycles the dihydroascorbic acid that is produced. By the creation of prooxidants under some circumstances, these vitamins can promote toxicity. In direct interactions with peroxyl, superoxide, and singlet oxygen, vitamin E, a component of the system that traps peroxyl radicals, shields membranes against lipid peroxidation. Increased peroxides and aldehydes in several tissues occur along with a vitamin E deficit. (Maritim et al., 2003)

5.2.7 Glutathione

A direct free-radical scavenger, co-substrate for glutathione peroxidase activity, cofactor for several enzymes, and a form of conjugates in endo- and xenobiotic processes, glutathione serves a variety of roles in the body. Chemically induced diabetic animals had lower levels of glutathione in their liver, kidney, pancreas, plasma, red blood cells, nerve, and precataractous lens. (Maritim et al., 2003)

5.2.8 Glutathione Peroxidase and Glutathione Reductase

The cytoplasm, mitochondria, and nucleus all contain the enzymes glutathione peroxidase and reductase. By employing reduced glutathione as a hydrogen donor, glutathione peroxidase breaks down hydrogen peroxide into water. Glucose 6-phosphate dehydrogenase, produces the cofactor NADPH and it is used in the process where glutathione reductase converts glutathione disulfide back to glutathione. (Maritim et al., 2003)

5.3 Antioxidant

Different molecules are involved in the antioxidant cell defenses; some of these molecules, such SOD, glutathione peroxidase, and antioxidant vitamins. Prior to the initiation of chain reaction the removal of newly produced free radicals or the prevention of the creation of new free radical

species are done by this system. These enzymes may either repair cell structures harmed by free radical assault or help to stop the chain reaction, DNA-repairing enzymes is one of the example. Increased ROS production has damaged a cell's or an organism's antioxidant defenses when a specific antioxidant molecules concentration is reduced or when there is a general drop in antioxidant status. Hydrogen peroxide and molecular oxygen (glutathione peroxidase, glutathione reductase) are converted by superoxide radical by the help of the enzymes glutathione (GSH), glutathione transferase (GST), and SODs. It is a crucial antioxidant system which removes peroxides and aldehydes that are harmful and help to maintain reduced functional forms of vitamins C and E. (Chikezie et al., 2015)

5.3.1 Origin and Sources of Antioxidants

In colored fruits Beta carotene is the most biologically active antioxidants like squash, potatoes, apricots, pumpkin, mangoes and orange. Natural food, leafy vegetables and fruit sources are the richest source of antioxidants. Besides, lemon, amla, ashwagandha also contains antioxidants. Beta carotene is also found in green leafy vegetables such as spinach, kale, and coloured greens. For healthy eyes Lutein is best green leafy vegetable. In most of developing countries wheat and rice are the main dietary source of selenium having major antioxidant enzymes. Carrots, milk, sweet potatoes, mozzarella and egg yolks consist of retinol, 3 hydroxyretinol and didehydroretinol. Poultry, beef, cereals and fish contains vitamin C. Flavonoids, diterpenes, cinnamic acid, phenylpropanoids contains phytoconstituents with antioxidants. (Khan et al., 2020)

6 Oxidative Stress in Diabetes Mellitus

Specifically in type 2 diabetes, oxidative stress is thought to have a significant role in the development of vascular problems. (Pham-Huy et al., 2008) The autooxidation of glucose in diabetes typically results in high energy particle production, which contributes to the imbalance in antioxidant-prooxidant activity. Increased synthesis of ROS by catalase (CAT—enzymatic/non-enzymatic), superoxide dismutase (SOD), and glutathione peroxidase (GSH–Px) may contribute to elevated ROS levels in diabetes. The tissues become vulnerable to oxidative stress due to variations in these enzyme levels, which results in the development of diabetes complications. (Lipinski, 2001) The relationship between diabetes mellitus and oxidative stress is further supported by the fact that free radicals gradually grow, and antioxidant defense mechanisms

become less effective. The formation of free radicals and reactive oxygen species is directly enhanced by hyperglycemia in the case of oxidative stress brought on by non-enzymatic sources. (Khan et al., 2020)

6.1 Pathophysiology of Oxidative Stress in Diabetes

There is currently evidence to suggest that oxidative stress has a role in the etiology of both type 1 and type 2 diabetes. Due to oxidative stress, free radical generation in diabetes causes damage to enzymes, and cellular machinery, and an increase in insulin resistance by producing non-enzymatic glycation of proteins, glucose oxidation, and enhanced lipid peroxidation.(Maritim et al., 2003) Recent studies have shown that oxidative damage in diabetes complications is caused by lipid and the apolipoprotein component of LDL, which forms insoluble aggregates as a result of hydroxyl radical-induced cross-linkage between apo-B monomers.(Pham-Huy et al., 2008) The mitochondria are the principal sources of oxidative stress in diabetes mellitus. The oxygen used during oxidative metabolism in mitochondria is partially reduced to water, and the remaining oxygen is changed into oxygen free radical (•O), a major ROS that is converted to other reactive species (RS) like $ONOO^-$, OH, and H_2O_2 (Moussa, 2008) Additionally, high glucose level has the potential to play a significant role in the emergence of late-stage diabetic issues. Furthermore, the development of cell dysfunction and IRe is significantly influenced by oxidative stress. (Collins et al., 1998)

6.2 Evidence of Oxidative Stress in Diabetes

Numerous experimental findings have demonstrated a connection between oxidative stress and diabetes by assessing a variety of biomarkers, including those for DNA damage and lipid peroxidation products. Free radicals are thought to have a significant role in the development of late diabetes complications as a result of their capacity to damage lipids, proteins, and DNA. (R. et al., 2014) Diabetic complications caused by free radicals and oxidative stress include coronary artery disease, neuropathy, nephropathy, and retinopathy. (Phillips et al., 2004) In-vivo studies indicate the role of hyperglycemia in the formation of oxidative stress, which leads to endothelial dysfunction in diabetes patients' blood vessels. (Ceriello, 2006) As determined by in vivo ESR monitoring, streptozotocin-induced diabetic rats showed elevated oxidative stress. This in vivo ESR approach was created to assess noninvasive oxidative stress in living animals. (Sonta et al., 2004). Diabetes patients with high glucose and insulin levels, as well as dyslipidemia, develop

macroangiopathies, which produce oxidative stress and lead to atherosclerosis. (Giugliano et al., 1995)Studies have shown that type 2 diabetes individuals had greater urinary 8-OHdG excretion than control subjects. A number of harmful consequences on the kidney is linked to the reactive oxygen species and because of this certain glomerular or tubulointerstitial diseases development are also linked with oxidative stress (Kanauchi et al., 2002) It is commonly recognized that people with diabetes are more likely to develop atherosclerosis. This can be caused by lipoprotein oxidative modification and other free-radical reactions according to the available data. One theory is that post-synthetic chemical alteration of lipoprotein by oxidation, glycosylation, or both may occur more often in diabetics. (Mori et al., 1999)

6.3 Oxidative Stress and Insulin Resistance

Oxidative stress has been demonstrated to contribute to insulin resistance and in the endothelium specifically. Furthermore, there is a strong correlation between elevated oxidative stress indicators and decreased insulin receptor activation. Increased generation of superoxide by the mitochondrial electron transport chain as a result of increased free fatty acid oxidation in endothelial cells causes insulin signaling to become inappropriate. Insulin resistance can be accelerated by elevated insulin levels, which can also enhance the generation of reactive oxygen species and oxidative stress. It is

possible to increase insulin sensitivity by consuming antioxidants including alpha-lipoic acid, vitamin E, ascorbate, and glutathione. (Banks & Rhea, 2021)

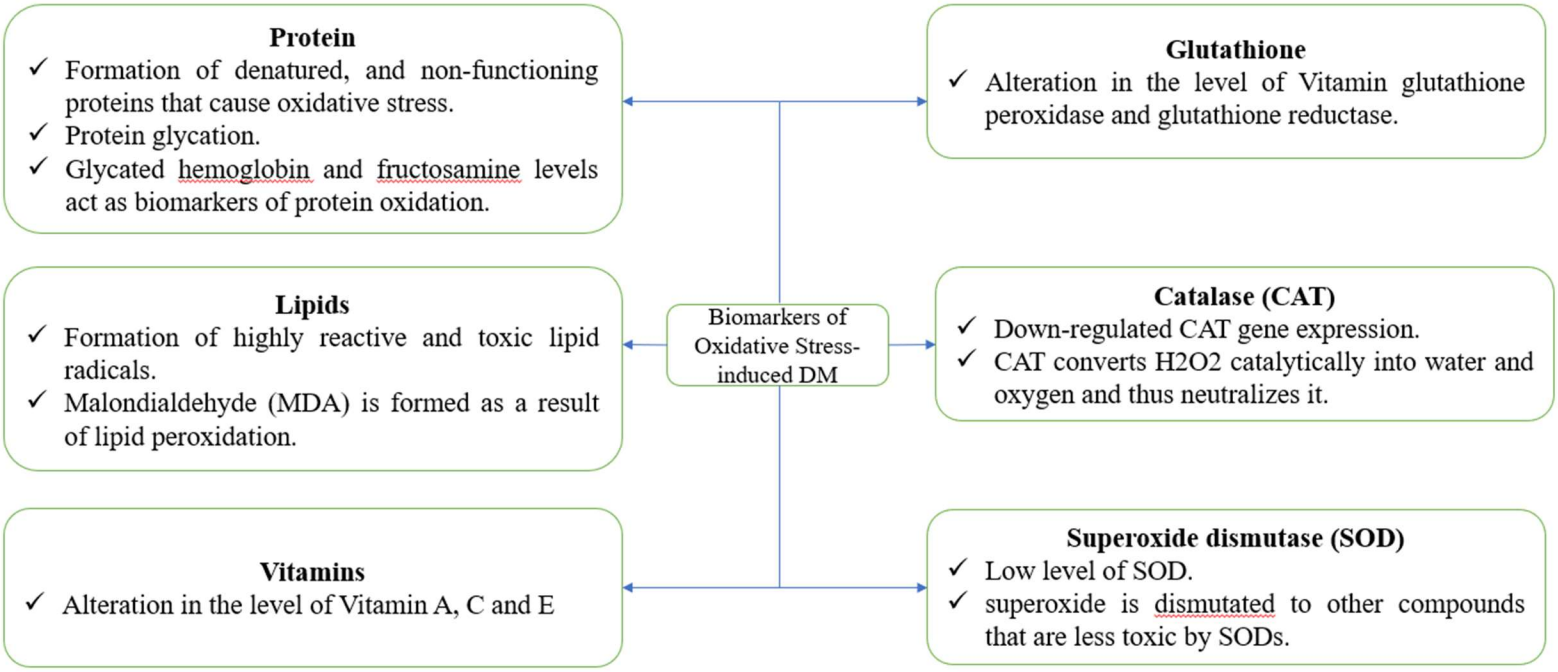


Figure 6: Biomarkers of Oxidative Stress induced Diabetes (Asmat et al., 2016)

6.4 Natural Remedies to Limiting Oxidation-Associated Damage in Diabetes

Herbal remedies are one method that can be used to cure and prevent diabetes as well as its secondary issues. One of the aims of this review was to focus on herbal and natural treatments that are used to treat or prevent the morbid illness of diabetes, including the underlying mechanisms underpinning their ability to lower blood sugar levels A key component of the therapy of diabetes mellitus is the use of traditional remedies made from plant sources. Due to the unsatisfactory results of conventional therapies, higher treatment costs, and increasing side effects of modern medications, many patients choose herbal medicine over conventional therapies. Apoptosis that is generated by oxidative stress and is a key component of the pathological process of diabetes mellitus is one area in which medicinal plants are most frequently assessed for their therapeutic efficacy. Phytochemicals exert their effects by way of a number of different metabolic pathways. (Panigrahy et al., 2017)

1. Ginseng, a plant-derived ginsenoside, prevents cytokine-induced apoptosis of cells by reducing the generation of nitric oxide (NO), reactive oxygen species (ROS), inhibiting the expression of the genes p53 and p21, and inhibiting caspases and Poly (ADP-ribose) polymerase (PARP). (Panigrahy et al., 2017)

2. By lowering oxidative stress and regulating the polyol pathway, the intragastric injection of berberine from Coptidis rhizoma (CR) and Cortex phellodendri to streptozotocin-induced diabetic rats demonstrated regulated blood glucose. (Panigrahy et al., 2017)

3. In rats with diabetes caused by streptozotocin (STZ), fenugreek leaf powder lowers oxidative stress. By enhancing the antioxidant system in diabetic rats, it lowers blood glucose. (Panigrahy et al., 2017)

4. Amla inhibited the development of AGE Products, lowered glycosylated protein (an indication of oxidative stress), and decreased blood creatinine levels when administered orally to streptozotocin-induced diabetic mice for 20 days. Oxidative stress was reduced, and thus enhanced glucose metabolism. (Panigrahy et al., 2017)

5. By lowering endoplasmic reticulum (ER) stress in cells, 4-phenyl butyric acid and taurine-conjugated ursodeoxycholic acid (chemical chaperones) were used to treat oxidative stress induced obesity and diabetes. By stabilization of hyperglycemia, improvement of insulin action in liver, muscle, and adipose tissues, and restoration of systemic insulin sensitivity in mice. (Panigrahy et al., 2017)

6. In vitro, animal, and/or human studies have shown that cinnamon extracts enhance insulin sensitivity and glucose transport, boost antioxidant activity, and reduce protein glycation. (Panigrahy et al., 2017)

7. In diabetic rats, the hydroalcoholic extract of mature Diospyros peregrine fruits boosted the activity of antioxidant enzymes and restored normal levels of lipid peroxidation. Through an antioxidant defense mechanism, they exhibited hypoglycemic and hypolipidemic action. (Panigrahy et al., 2017)

8. C57BL/KsJ-db/db mice's blood glucose levels were dramatically reduced by. Eucommia ulmoides Oliver (Du-zhong) leaf extract. According to the findings, Du-zhong extract supplements reduce blood sugar levels by boosting the body's antioxidant defenses and lowering lipid peroxidation. (Panigrahy et al., 2017)

9. In rats with alloxan-induced diabetes, an aqueous extract of A. campestris leaf reduced blood glucose levels, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-c), increased high-density lipoprotein cholesterol (HDL-c) levels, and antioxidant enzymes.This finding shows that the antioxidant capacity of A. campestris leaf extracts in rat pancreas tissue, which may be advantageous for protection against diabetes and its consequences, by the hypoglycemic and hypolipidemic effects of the extracts. (Panigrahy et al., 2017)

10. Diabetic rats were given an oral dose of an ethanolic extract of aloe vera gel, which lowered blood glucose levels and raised hemoglobin and glycosylated hemoglobin. The decrease in blood glucose also lessens the possibility of the enzymes becoming glycated and inhibits the excessive production of free radicals through several metabolic pathways. (Panigrahy et al., 2017)

11. In Sprague-Dawley rats, leaves of Beta vulgaris L. var. cicla demonstrated a reduction in oxidative stress and an increase in antioxidant defense. Through Akt2, the extracts stimulate GLUT2 production in hepatocytes. (Panigrahy et al., 2017)

12. Thiazolidones, statins, Angiotensin-converting enzyme (ACE) inhibitors, and Gluten and Amylase Trypsin Inhibitors (ATI) inhibitors have all recently demonstrated their effectiveness, occasionally causing pleiotropic effects that may be related to their antioxidant action. While statins increase NO bioavailability, lower superoxide generation, prevent the synthesis of nitrotyrosine and reduce the creation of free radicals brought on by angiotensin II, thiazolidones are efficient in reducing the action of peroxynitrite. An enhanced endothelial function is anticipated as a result of such activities. (Panigrahy et al., 2017)

13. In a recent study, it was shown that cardiac manganese superoxide dismutase (MnSOD) was boosted by luteolin therapy at a dosage of 100 mg/kg and endothelial nitric oxide synthase (eNOS) production as well as inhibit Ca2+-induced mPTP opening. (Sapian et al., 2021)

14. In vitro research has also demonstrated that the flavone myricitrin, which is abundant in berries and teas, inhibits high glucose-induced superoxide generation in mitochondria, depolarization of mitochondrial membrane potential, and restoration of mPTP formation in diabetic cardiomyopathy. (Sapian et al., 2021)

15. According to a different research, rutin-rich flavonoids in a leaf extract from the malvaceous plant Abroma augusta L. increased the levels of coenzyme Q9 and Q10 in the mitochondria by acting as antioxidants and scavenging free radicals, which in turn prevented the oxidation of lipids. (Sapian et al., 2021)

16. According to previous research, flavanols present in the Abroma augusta L. family of Malvaceae, such as rutin, myricetin, and quercetin, have been shown to revive the activity of ubiquinones (co-enzyme Q), which is crucial for the distribution of electron carriers inside cell organelles in particular and lowers ROS generation in cardiac mitochondria of T2DM. (Sapian et al., 2021)

17. The activation of the genes AMPK2, PPAR, and PCG-1, which are essential in altered energy metabolism pathways, was discovered to be another method by which quercetin regulates free fatty acid oxidation (FAO) in a different cardiac research model. (Sapian et al., 2021)

Table 1: Antidiabetic Effects of Phytochemicals

Phytochemical	Extract	Observation	Mechanims of action (MoA)	Reference
Ginseng	——	Lowers ROS and NO generation	1.Inhibits expression of gene p53/p21 2. Inhibits caspases and Poly (ADP-ribose) polymerase	(Xiang et al., 2008)
Berberine	——	Lowers oxidative stress	Regulation of blood glucose	(Kuyvenhoven & Meinders, 1999)
——	Fenugreek	Lowers oxidative stress	Enhances antioxidant system	(Annida & Prince, 2005)

——	Amla	Oxidative stress reduced	1.Inhibits AGE Products 2.Loweres glycosylated protein 3.Decreases blood creatinine levels	(Rao et al., 2005)
4-phenyl butyric acid	——	Lowers endoplasmic reticulum (ER) stress in cells	1.Stabilization of hyperglycemia 2.Improves insulin action in liver, muscle, and adipose tissues 3.Restores systemic insulin sensitivity	(Özcan et al., 2006)
——	Cinnamon	Boost antioxidant activity, and reduce protein glycation	Enhance insulin sensitivity and glucose transport	(Qin et al., 2010)
——	*Diospyros peregrine*	Exhibits hypoglycemic and hypolipidemic action	1.Boosts the activity of antioxidant enzymes. 2.Restores normal levels of lipid peroxidation.	(Dewanjee et al., 2011)

——	*Eucommia ulmoides* Oliver	Reduces blood glucose levels	1.Boosts the body's antioxidant defenses. 2.Lowers lipid peroxidation.	(Sefi et al., 2010)
——	*A. campestris*	Hypoglycemic and Hypolipidemic effects	1.ReduceS blood glucose levels, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-c), 2. Increases high-density lipoprotein cholesterol (HDL-c) levels, and antioxidant enzymes.	(Özcan et al., 2006)
——	Aloe Vera	Lowers blood glucose levels and raises hemoglobin and glycosylated hemoglobin	1.Lessens the possibility of the enzymes becoming glycated. 2.Inhibits the excessive production of free radicals through several metabolic pathways.	(Sefi et al., 2010)
——	*Beta vulgaris* L. var. cicla	1.Reduces oxidative stress. 2.Increases antioxidant defense	Stimulates GLUT2 production in hepatocytes.	(Gezginci-Oktayoglu et al., 2014)

Statins	——	pleiotropic effects	1.Increases NO bioavailability 2.Lowers superoxide generation 3.Prevents the synthesis of nitrotyrosine 4.Reduces the creation of free radicals brought on by angiotensin II	(Piconi et al., 2003a; Shiojiri et al., 2002a)
Thiazolidones	——	pleiotropic effects	Reduces the action of peroxynitrite	(Piconi et al., 2003b; Shiojiri et al., 2002b; Takemoto et al., 2001)
Luteolin therapy	——	Boosts Manganese superoxide dismutase (MnSOD)	1.Produces endothelial nitric oxide synthase (eNOS) 2.Inhibits Ca2+-induced mPTP opening	(Takemoto et al., 2001)
Flavone myricitrin	——	Inhibits high glucose-induced superoxide	1.Depolarization of mitochondrial membrane potential 2. Restoration of mPTP formation in diabetic cardiomyopathy.	(Zhang et al., 2016a)

		generation in mitochondria		
——	Malvaceous plant	Increases the levels of coenzyme Q9 and Q10 in the mitochondria	Acts as antioxidants and scavenging free radicals, which in turn prevents the oxidation of lipids	(Zhang et al., 2016b)
——	Abroma augusta L.	Rutin, myricetin, and quercetin, have been shown to revive the activity of ubiquinones (co-enzyme Q)		(Khanra et al., 2015)
Quercetin	——	Activation of the genes AMPK2, PPAR, and PCG-1	regulates free fatty acid oxidation (FAO) in cardiac system	(Sanderson et al., 2014)

7 Discussion and Future Prospect

Over the course of the following 25 years, DM is anticipated to change at least 366 million people's lives globally. It is commonly acknowledged that oxidative stress brought on by hyperglycemia contributes to the malfunctioning of cells and tissues in diabetes. Drug development should not just concentrate on glucose-centric targets, such as antioxidant defense of the β-cell, but also on targets that are insulin-centric. This could make it easier for the β-cells to recover from oxidative stress damage brought on by persistent hyperglycemia. The use of antioxidant agents in treatment, such as trace elements and other antioxidants, has been shown in recent years to be effective in preventing cardiovascular system dysfunction brought on by diabetes, according to various studies. Antioxidants reduce oxidant-induced cell damage in both direct and indirect ways by functioning through a variety of processes. Their function includes, scavenging of ROS, decreasing of ROS production, or interfering with the changes brought on by ROS.

Studies done utilizing antioxidant as treatment therapy have been unsuccessful where the use of antioxidant was ensured, and clinical trials were also unsuccessful as the results were unsatisfactory as a result antioxidants are not yet favorite to use in the treatment of DM and its complications. The correction of glycemia and other therapies for diabetic complications should be used in conjunction with antioxidant therapy since it appears that oxidative stress is only one of the factors causing diabetic problems.

8 Limitation of the Study

- ✓ Biomarkers can indicate dietary antioxidant consumption and pro-oxidant exposure from the environment. Some oxidative stress biomarkers, however, could only turn out to be general markers of oxidative damage and have weak correlations with the development and prognosis of DM.
- ✓ The capacity of biomarkers to accurately evaluate important physiologic activities or correlate with recognized clinical indications should be the subject of new research investigations, with special emphasis on their accuracy, precision, and dependability.
- ✓ Finding out if particular biomarkers represent exposure to an antioxidant status or oxidative stress throughout the course of a short or extended period of time is a crucial research question.

- ✓ Herbal products already been marketed for the remedial action of diabetes have not been addressed in the study.

9 Conclusion

Reactive oxygen species have been shown to mediate or aggravate detrimental effects of hyperglycemia in various methods. Antioxidant enzyme defenses can be weakened by hyperglycemia, as a result reactive oxygen species also becomes able to harm structural proteins and other enzymes. During diabetes, among other things, insulin activity is impaired along with an increase in the incidence of complications. For both type 1 and type 2 diabetes utilizing antioxidants diabetic therapy has previously been demonstrated to be promising. an increase of oxygen level and other Lipid and nitrogen free radicals (ROS/RNS) have been connected to the oxidation of glucose, non-enzymatic protein glycation, and peroxidation are all contributors in diabetes mellitus and the problems it raises. The majority of research have revealed oxidative stress and diabetes link as well as heart, liver, renal, and eye problems related to it. Therefore, it appears that oxidative stress is more concerning in metabolic diseases, in particular type 2 diabetes.

Reference

Aneja, A., Tang, W. H. W., Bansilal, S., Garcia, M. J., & Farkouh, M. E. (2008). Diabetic Cardiomyopathy: Insights into Pathogenesis, Diagnostic Challenges, and Therapeutic Options. The American Journal of Medicine, 121(9), 748–757. https://doi.org/10.1016/j.amjmed.2008.03.046

Annida, B., & Prince, P. S. M. (2005). Supplementation of Fenugreek Leaves Reduces Oxidative Stress in Streptozotocin-Induced Diabetic Rats. Journal of Medicinal Food, 8(3), 382–385. https://doi.org/10.1089/jmf.2005.8.382

Bachur, N. R. (1982). Free Radical Damage. Anthracycline Antibiotics in Cancer Therapy, 97–102. https://doi.org/10.1007/978-94-009-7630-6_8

Banks, W. A., & Rhea, E. M. (2021). The blood–brain barrier, oxidative stress, and insulin resistance. Antioxidants, 10(11). https://doi.org/10.3390/antiox10111695

Bayir, H. (2005). Reactive oxygen species. Critical Care Medicine, 33(12 SUPPL.). https://doi.org/10.1097/01.CCM.0000186787.64500.12

Begum, M. M., Sultana, Z., Ershad Ali, M., Jami, M. S. I., Khondkar, P., Khan, M. M., & Haque, M. M. (2014). Additive effect of lipid lowering drug (Simvastatin) in combination with antidiabetic drug (Glibenclamide) on alloxan induced diabetic rats with long term dyslipidemia. Indian Journal of Clinical Biochemistry, 29(4), 452–461. https://doi.org/10.1007/s12291-013-0393-1

Buchanan, T. A., & Xiang, A. H. (2005). Gestational diabetes mellitus. Journal of Clinical Investigation, 115(3), 485–491. https://doi.org/10.1172/JCI200524531

Chikezie, P. C., Ojiako, O. A., & Ogbuji, A. C. (2015). Oxidative stress in diabetes mellitus. International Journal of Biological Chemistry, 9(3), 92–109. https://doi.org/10.3923/ijbc.2015.92.109

Collins, A. R., Rašlová, K., Somorovská, M., Petrovská, H., Ondrušová, A., Vohnout, B., Fábry, R., & Dušinská, M. (1998). DNA damage in diabetes: Correlation with a clinical marker. Free Radical Biology and Medicine, 25(3), 373–377. https://doi.org/10.1016/S0891-5849(98)00053-7

CURCHOD, B., & DAEPPEN, J. P. (1959). Complications of diabetes mellitus. Praxis, 48(26), 602–603.

Dewanjee, S., Maiti, A., Sahu, R., Dua, T. K., & Mandal, V. (2011). Effective Control of Type 2 Diabetes through Antioxidant Defense by Edible Fruits of Diospyros peregrina. Evidence-Based Complementary and Alternative Medicine, 2011, 1–7. https://doi.org/10.1093/ecam/nep080

Diabetes, N., & Group, D. (1997). Guide to diagnosis and classification of diabetes mellitus and other categories of glucose intolerance. Diabetes Care, 20(1 SUPPL.), 1039–1057. https://doi.org/10.2337/diacare.20.1.s21

Fujimoto, W. Y. (2000). The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus. American Journal of Medicine, 108(6 SUPPL. 1), 9–14. https://doi.org/10.1016/s0002-9343(00)00337-5

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. International Journal of Molecular Sciences, 21(17), 6275. https://doi.org/10.3390/ijms21176275

Gezginci-Oktayoglu, S., Sacan, O., Bolkent, S., Ipci, Y., Kabasakal, L., Sener, G., & Yanardag, R. (2014). Chard (Beta vulgaris L. var. cicla) extract ameliorates hyperglycemia by increasing GLUT2 through Akt2 and antioxidant defense in the liver of rats. Acta Histochemica, 116(1), 32–39. https://doi.org/10.1016/j.acthis.2013.04.016

Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. Circulation Research, 107(9), 1058–1070. https://doi.org/10.1161/CIRCRESAHA.110.223545

Halliwell, B. (2009). The wanderings of a free radical. Free Radical Biology and Medicine, 46(5), 531–542. https://doi.org/10.1016/j.freeradbiomed.2008.11.008

Ilonen, J., Lempainen, J., & Veijola, R. (2019). The heterogeneous pathogenesis of type 1 diabetes mellitus. Nature Reviews Endocrinology, 15(11), 635–650. https://doi.org/10.1038/s41574-019-0254-y

Jansari, S., Devashri, N., Dhanani, A., & Chauhan, N. (2014). DIFFERENTIATION OF STEM CELLS INTO PANCREATIC β-CELLS: REGENERATIVE MEDICINE FOR DIABETES. International Journal of Biological & Pharmaceutical Research, 5, 901–909.

Kanauchi, M., Nishioka, H., & Hashimoto, T. (2002). Oxidative DNA damage and tubulointerstitial injury in diabetic nephropathy. Nephron, 91(2), 327–329. https://doi.org/10.1159/000058412

Khan, A. N., Khan, R. A., & Ahmad, M. (2020). Super Power of Antioxidant in Oxidative Stress and Diabetes Mellitus. Journal of Diabetes and Endocrinology Research, 3(6), 217–220. https://doi.org/10.47485/2693-2458/1009

Khanra, R., Dewanjee, S., K Dua, T., Sahu, R., Gangopadhyay, M., de Feo, V., & Zia-Ul-Haq, M. (2015). Abroma augusta L. (Malvaceae) leaf extract attenuates diabetes induced nephropathy and cardiomyopathy via inhibition of oxidative stress and inflammatory response. Journal of Translational Medicine, 13(1), 6. https://doi.org/10.1186/s12967-014-0364-1

Kowluru, R. A., & Chan, P. S. (2007). Oxidative stress and diabetic retinopathy. Experimental Diabesity Research, 2007. https://doi.org/10.1155/2007/43603

Kuyvenhoven, J. P., & Meinders, A. E. (1999). Oxidative stress and diabetes mellitus. European Journal of Internal Medicine, 10(1), 9–19. https://doi.org/10.1016/S0953-6205(99)00009-6

Lobo, V., Patil, A., Phatak, A., & Chandra, N. (2010). Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy Reviews, 4(8), 118–126. https://doi.org/10.4103/0973-7847.70902

Maritim, A. C., Sanders, R. A., & Watkins, J. B. (2003). Diabetes, oxidative stress, and antioxidants: A review. Journal of Biochemical and Molecular Toxicology, 17(1), 24–38. https://doi.org/10.1002/jbt.10058

Mori, T. A., Dunstan, D. W., Burke, V., Croft, K. D., Rivera, J. H., Beilin, L. J., & Puddey, I. B. (1999). Effect of dietary fish and exercise training on urinary F2-isoprostane excretion in non-insulin-dependent diabetic patients. Metabolism: Clinical and Experimental, 48(11), 1402–1408. https://doi.org/10.1016/S0026-0495(99)90150-6

Naveen, J., & Baskaran, V. (2018). Antidiabetic plant-derived nutraceuticals: a critical review. European Journal of Nutrition, 57(4), 1275–1299. https://doi.org/10.1007/s00394-017-1552-6

Ozcan, A., & Ogun, M. (2015). Biochemistry of Reactive Oxygen and Nitrogen Species. Basic Principles and Clinical Significance of Oxidative Stress. https://doi.org/10.5772/61193

Özcan, U., Yilmaz, E., Özcan, L., Furuhashi, M., Vaillancourt, E., Smith, R. O., Görgün, C. Z., & Hotamisligil, G. S. (2006). Chemical Chaperones Reduce ER Stress and Restore Glucose Homeostasis in a Mouse Model of Type 2 Diabetes. Science, 313(5790), 1137–1140. https://doi.org/10.1126/science.1128294

Panigrahy, S. K., Bhatt, R., & Kumar, A. (2017). Reactive oxygen species: sources, consequences and targeted therapy in type 2 diabetes. Journal of Drug Targeting, 25(2), 93–101. https://doi.org/10.1080/1061186X.2016.1207650

Patti, M. E. (2004). Gene expression in the pathophysiology of type 2 diabetes mellitus. Current Diabetes Reports, 4(3), 176–181. https://doi.org/10.1007/s11892-004-0020-x

Perez-Campo, R., López-Torres, M., Cadenas, S., Rojas, C., & Barja, G. (1998). The rate of free radical production as a determinant of the rate of aging: Evidence from the comparative approach. Journal of Comparative Physiology - B Biochemical, Systemic, and Environmental Physiology, 168(3), 149–158. https://doi.org/10.1007/s003600050131

Piconi, L., Quagliaro, L., & Ceriello, A. (2003a). Oxidative Stress in Diabetes. Clinical Chemistry and Laboratory Medicine, 41(9). https://doi.org/10.1515/CCLM.2003.177

Piconi, L., Quagliaro, L., & Ceriello, A. (2003b). Oxidative Stress in Diabetes. Clinical Chemistry and Laboratory Medicine, 41(9). https://doi.org/10.1515/CCLM.2003.177

Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., Squadrito, F., Altavilla, D., & Bitto, A. (2017). Oxidative Stress: Harms and Benefits for Human Health. Oxidative Medicine and Cellular Longevity, 2017, 1–13. https://doi.org/10.1155/2017/8416763

Prakash, D., Upadhyay, G., Pushpangadan, P., & Gupta, C. (2011). Antioxidant and free radical scavenging activities of some fruits. Journal of Complementary and Integrative Medicine, 8(1). https://doi.org/10.2202/1553-3840.1513

Qin, B., Panickar, K. S., & Anderson, R. A. (2010). Cinnamon: Potential Role in the Prevention of Insulin Resistance, Metabolic Syndrome, and Type 2 Diabetes. Journal of Diabetes Science and Technology, 4(3), 685–693. https://doi.org/10.1177/193229681000400324

Rahal, A., Kumar, A., Singh, V., Yadav, B., Tiwari, R., Chakraborty, S., & Dhama, K. (2014). Oxidative stress, prooxidants, and antioxidants: The interplay. BioMed Research International, 2014. https://doi.org/10.1155/2014/761264

Rains, J. L., & Jain, S. K. (2011). Oxidative stress, insulin signaling, and diabetes. Free Radical Biology and Medicine, 50(5), 567–575. https://doi.org/10.1016/j.freeradbiomed.2010.12.006

Rao, T. P., Sakaguchi, N., Juneja, L. R., Wada, E., & Yokozawa, T. (2005). Amla (Emblica officinalis Gaertn.) Extracts Reduce Oxidative Stress in Streptozotocin-Induced Diabetic Rats. Journal of Medicinal Food, 8(3), 362–368. https://doi.org/10.1089/jmf.2005.8.362

Samuel, U. (2017). The role of novel biomarkers in predicting diabetic nephropathy : a review. International Journal of Nephrology and Renovascular Disease, 10, 221–231.

Sánchez-Moreno, C. (2002). Methods Used to Evaluate the Free Radical Scavenging Activity in Foods and Biological Systems. Food Science and Technology International, 8(3), 121–137. https://doi.org/10.1106/108201302026770

Sanderson, M., Mazibuko, S. E., Joubert, E., de Beer, D., Johnson, R., Pheiffer, C., Louw, J., & Muller, C. J. F. (2014). Effects of fermented rooibos (Aspalathus linearis) on adipocyte differentiation. Phytomedicine, 21(2), 109–117. https://doi.org/10.1016/j.phymed.2013.08.011

Sapian, S., Taib, I. S., Latip, J., Katas, H., Chin, K. Y., Nor, N. A. M., Jubaidi, F. F., & Budin, S. B. (2021). Therapeutic approach of flavonoid in ameliorating diabetic cardiomyopathy by targeting mitochondrial-induced oxidative stress. International Journal of Molecular Sciences, 22(21). https://doi.org/10.3390/ijms222111616

Sefi, M., Fetoui, H., Makni, M., & Zeghal, N. (2010). Mitigating effects of antioxidant properties of Artemisia campestris leaf extract on hyperlipidemia, advanced glycation end products and oxidative stress in alloxan-induced diabetic rats. Food and Chemical Toxicology, 48(7), 1986–1993. https://doi.org/10.1016/j.fct.2010.05.005

Shiojiri, T., Wada, K., Nakajima, A., Katayama, K., Shibuya, A., Kudo, C., Kadowaki, T., Mayumi, T., Yura, Y., & Kamisaki, Y. (2002a). PPARγ ligands inhibit nitrotyrosine formation and inflammatory mediator expressions in adjuvant-induced rheumatoid arthritis mice. European Journal of Pharmacology, 448(2–3), 231–238. https://doi.org/10.1016/S0014-2999(02)01946-5

Shiojiri, T., Wada, K., Nakajima, A., Katayama, K., Shibuya, A., Kudo, C., Kadowaki, T., Mayumi, T., Yura, Y., & Kamisaki, Y. (2002b). PPARγ ligands inhibit nitrotyrosine formation and inflammatory mediator expressions in adjuvant-induced rheumatoid arthritis mice. European Journal of Pharmacology, 448(2–3), 231–238. https://doi.org/10.1016/S0014-2999(02)01946-5

Sonta, T., Inoguchi, T., Tsubouchi, H., Sekiguchi, N., Kobayashi, K., Matsumoto, S., Utsumi, H., & Nawata, H. (2004). Evidence for contribution of vascular NAD(P)H oxidase to increased oxidative stress in animal models of diabetes and obesity. Free Radical Biology and Medicine, 37(1), 115–123. https://doi.org/10.1016/j.freeradbiomed.2004.04.001

Storz, G., & Imlay, J. A. (n.d.). Oxidative stress Gisela Storz * and James A Imlay ? Current Opinion in Microbiology, 188–194.

Takemoto, M., Node, K., Nakagami, H., Liao, Y., Grimm, M., Takemoto, Y., Kitakaze, M., & Liao, J. K. (2001). Statins as antioxidant therapy for preventing cardiac myocyte hypertrophy. Journal of Clinical Investigation, 108(10), 1429–1437. https://doi.org/10.1172/JCI13350

Wang, X., Sun, M., Zhao, Y., Wang, C., Ma, W., Wong, M. S., & Elimelech, M. (2020). In Situ Electrochemical Generation of Reactive Chlorine Species for Efficient Ultrafiltration Membrane Self-Cleaning. Environmental Science and Technology, 54(11), 6997–7007. https://doi.org/10.1021/acs.est.0c01590

Winterbourn, C. C. (1985). Free-radical production and oxidative reactions of hemoglobin. Environmental Health Perspectives, VOL. 64(3), 321–330. https://doi.org/10.1289/ehp.8564321

Xiang, Y.-Z., Shang, H.-C., Gao, X.-M., & Zhang, B.-L. (2008). A Comparison of the ancient use of ginseng in traditional Chinese medicine with modern pharmacological experiments and clinical trials. Phytotherapy Research, 22(7), 851–858. https://doi.org/10.1002/ptr.2384

Yang, H., Jin, X., Kei Lam, C. W., & Yan, S.-K. (2011). Oxidative stress and diabetes mellitus. Clinical Chemistry and Laboratory Medicine, 49(11). https://doi.org/10.1515/cclm.2011.250

Yang, H., Jin, X., Lam, C. W. K., & Yan, S. K. (2011). Oxidative stress and diabetes mellitus. Clinical Chemistry and Laboratory Medicine, 49(11), 1773–1782. https://doi.org/10.1515/CCLM.2011.250

Yaribeygi, H., Sathyapalan, T., Atkin, S. L., & Sahebkar, A. (2020). Molecular Mechanisms Linking Oxidative Stress and Diabetes Mellitus. Oxidative Medicine and Cellular Longevity, 2020, 1–13. https://doi.org/10.1155/2020/8609213

Moussa, S. (2008) Oxidative Stress In Diabetes Mellitus 225-236

Zhang, B., Chen, Y., Shen, Q., Liu, G., Ye, J., Sun, G., & Sun, X. (2016a). Myricitrin Attenuates High Glucose-Induced Apoptosis through Activating Akt-Nrf2 Signaling in H9c2 Cardiomyocytes. Molecules, 21(7), 880. https://doi.org/10.3390/molecules21070880

Zhang, B., Chen, Y., Shen, Q., Liu, G., Ye, J., Sun, G., & Sun, X. (2016b). Myricitrin Attenuates High Glucose-Induced Apoptosis through Activating Akt-Nrf2 Signaling in H9c2 Cardiomyocytes. Molecules, 21(7), 880. https://doi.org/10.3390/molecules21070880

Ceriello, A. (2006). Oxidative Stress and Diabetes-Associated Complications. *12*(February),

2005–2007.

Giugliano, D., Ceriello, A., & Paolisso, G. (1995). Diabetes mellitus, hypertension, and cardiovascular disease: Which role for oxidative stress? Metabolism, *44*(3), 363–368. https://doi.org/10.1016/0026-0495(95)90167-1

Lipinski, B. (2001). Pathophysiology of oxidative stress in diabetes mellitus. Journal of Diabetes and Its Complications, *15*(4), 203–210. https://doi.org/10.1016/S1056-8727(01)00143-X

Maritim, A. C., Sanders, R. A., & Watkins, J. B. (2003). Diabetes, oxidative stress, and antioxidants: A review. Journal of Biochemical and Molecular Toxicology, *17*(1), 24–38. https://doi.org/10.1002/jbt.10058

Pham-Huy, L. A., He, H., & Pham-Huy, C. (2008). Free radicals, antioxidants in disease and health. International Journal of Biomedical Science, *4*(2), 89–96.

Phillips, M., Cataneo, R. N., Cheema, T., & Greenberg, J. (2004). Increased breath biomarkers of oxidative stress in diabetes mellitus. Clinica Chimica Acta, *344*(1–2), 189–194. https://doi.org/10.1016/j.cccn.2004.02.025

R., O., L., N., & O., O. (2014). Oxidative Stress and Diabetic Complications: The Role of Antioxidant Vitamins and Flavonoids. Antioxidant-Antidiabetic Agents and Human Health. https://doi.org/10.5772/57282