INTRODUCTION

Diabetes mellitus

Diabetes mellitus (DM) is one of the major global public health problems. Recently, a survey estimated that there will be more than 439 million people suffering from diabetes in nearly all countries by the year 2030[(1)].

DM is a disease marked by high levels of blood glucose resulting from a defect in insulin production, insulin action or both, that can lead to macro and micro vascular complications and is a chronic, life threatening condition that depends on medication, diet and life style modification to prevent long term complications [(2)]. These results primarily in elevated fasting and postprandial blood glucose levels. If this imbalanced homeostasis does not return to normal and continues for a protracted period of time, it leads to hyperglycemia that in due course turns into a syndrome called DM [(3)].

Insulin reduces the blood glucose levels by increasing glycogen synthesis, lipogenesis, glucose transport and decreasing the lipolysis, gluconeogenesis, glycogenolysis. Other hormones that elevate the blood glucose levels comprise of growth hormone, catecholamines, cortisol and glucagons by increasing the glycogen break down, lipolysis and gluconeogenesis [(4)] (Figure 1).

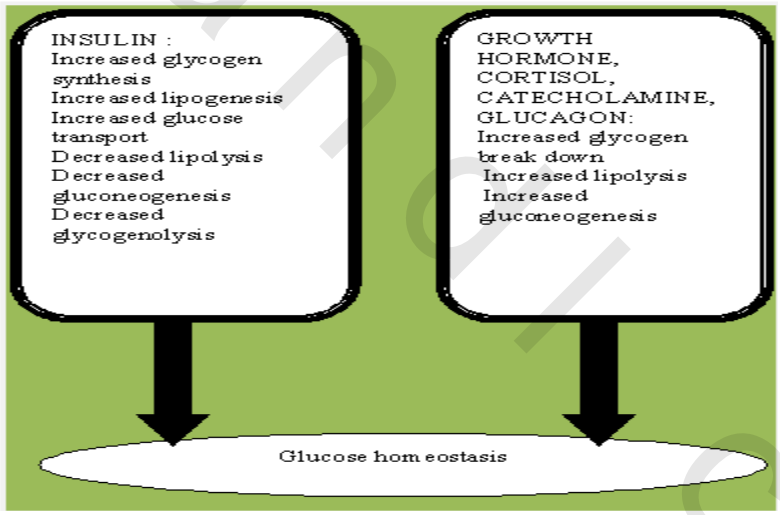


Figure 1: Glucose homeostasis [(4)]

Insulin resistance:

Insulin resistance is defined as diminished tissue responses to insulin at one or more sites in the complex pathways of the hormone action, which is associated with hyperinsulinemia [(5)] (Figure 2).

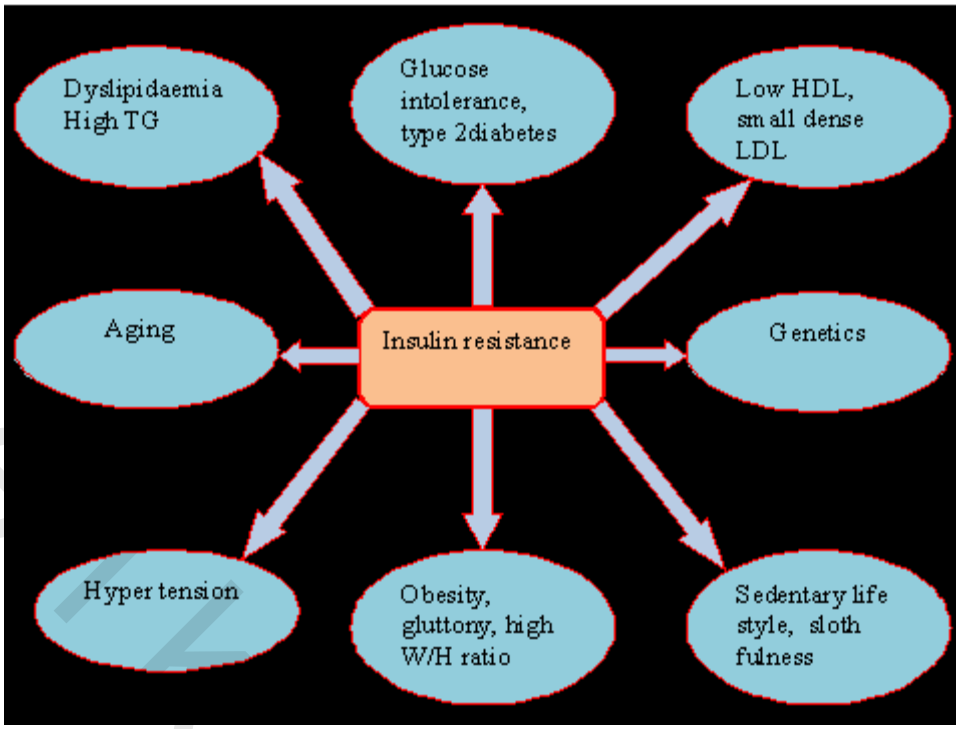


Figure 2: Factors leading to insulin resistance [5]

Classification of Diabetes:

DM is mainly divided into four main types:

1. Type 1: (type1A, type 1B): Beta cell (β-cell) destruction with little or no endogenous insulin secretory capacity.
   - Autoimmune (type1A)
   - Idiopathic (type 1B)
2. Type 2: Ranges from relative insulin deficiency to disorders of insulin secretion and insulin resistance.
3. Gestational diabetes
4. Other specific types:
   - Genetic defects of β-cell function.
   - Genetic defects in insulin secretion.
   - Diseases of the exocrine pancreas.
   - Endocrinopathies.
   - Drug-induced or chemical-induced infections (congenital rubella, cytomegalovirus and others).
   - Uncommon forms of immune mediated diabetes.
   - Other genetic syndromes sometimes associated with diabetes [6].

1-Type 1 Diabetes Mellitus (T1D):

T1D is also known as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. In this type of diabetes, the pancreas produces little or no insulin [7].This type of diabetes represents around 10–15% of all cases of diabetes [8].T1D develops as a result of the synergistic effects of genetic, environmental and immunologic factors that ultimately destroy the pancreatic β-cells. T1D results from autoimmune β-cell destruction, which leads to insulin deficiency [9].

T1D is further sub classified into two types:

Type 1A (autoimmune) which is associated with the presence of islet cell autoantibodies and Type 1B (idiopathic) characterized by the absence of such antibodies [10].

Pathophysiology of T1D:

Hyperglycaemia and ketonaemia constitute the most important sequale of insulin deficiency in T1D. Hyperglycaemia is essentially due to varying combination of lack of glucose utilization and over production of glucose through accelerated gluconeogenesis. Ketonaemia is a result of impaired lipogenesis and enhanced lipolysis leading to a release of free fatty acids (FFA) into the circulation. The synthesis of triglycerides (TG) from FFA is regulated by the molar ratio of insulin and glucagon in the liver. There is a secondary hyperglucoagonaemia in DM leading to a reduced activity of malonyl CoA, thereby affecting TG synthesis. In addition, enhanced activity of carnitine acyl transferase facilitates FFA entry into mitochondria, where through beta oxidation excessive amounts of acetyl CoA are generated, leading to the formation of large amounts of ketone bodies which are utilized only in muscle and other peripheral tissues [11].

2-Type 2 Diabetes Mellitus (T2D):

T2D is also known as non-insulin-dependent diabetes mellitus (NIDDM) or adult onset diabetes [7]. It accounts for 85–90% of all cases of diabetes [12]. The incidence of T2D is increasing worldwide [13]. It is a heterogeneous condition characterized by the presence of both impaired insulin secretion and insulin resistance [14]. It is a complex multifactorial disease involving genetic predisposition and various environmental factors [15], affecting the length and quality of life of an affected individual [16]. Although the genetic basis of T2D has yet to be identified, there is strong evidence that modifiable risk factors such as obesity and physical inactivity are the main nongenetic determinants of the disease [10]. T2D is a common disease with substantial associated morbidity and mortality. Up to 80% of patients with T2D will develop or die of macrovascular disease [17].

Pathophysiology of T2D:

This type of diabetes is characterized by 2 major pathophysiologic defects: insulin resistance, which results in increased hepatic glucose production (HGP) and decreased glucose disposal, and impaired β-cell secretory function (both basal and glucose stimulated) [18].

Under normal conditions, insulin binds to insulin receptors (IRs) on target cells, resulting in cellular cascades that promote intracellular glucose transport and metabolism. Insulin resistance in target tissues (muscle and liver) is observed early in the disease process and is rapidly followed by decreased insulin secretion as a result of progressive pancreatic β-cell dysfunction. This combination leads to overt diabetes with fasting and postprandial hyperglycemia. Insulin resistance is a common defect in T2D, with the liver continuing to produce glucose and the uptake of glucose into muscle being impaired [(19)]. Loss of the acute insulin response to a carbohydrate load, a prototypical defect that occurs early in the natural course of the disease, generally when fasting plasma glucose (FPG) levels reach 115 mg/dL, leads to postprandial hyperglycemia [(18)].

Insulin resistance in the hepatocyte and peripheral tissues, particularly skeletal muscle, leads to unrestrained HGP and diminished insulin-stimulated glucose uptake and utilization. The underlying mechanism may be related to defects in IR binding, decreased numbers of IRs, or post receptor attenuation of insulin action. Hyperglycemia itself further impairs insulin secretion and increases insulin resistance, in part by down regulation of the glucose transport system in β-cells and insulin-sensitive tissues. These effects of chronically elevated blood glucose levels are referred to as glucose toxicity. In addition, the high circulating FFA levels associated with diabetes further aggravate insulin resistance and may adversely affect β-cell secretion, a phenomenon known as lipotoxicity [(18)]. A complex interaction between genetic and environmental factors leads to insulin resistance resulting in impaired glucose tolerance (IGT) due to obesity, high FFA, high glucose which also acts on β-cells causing failure of β-cells leading to T2D [(4)] (Figure 3).

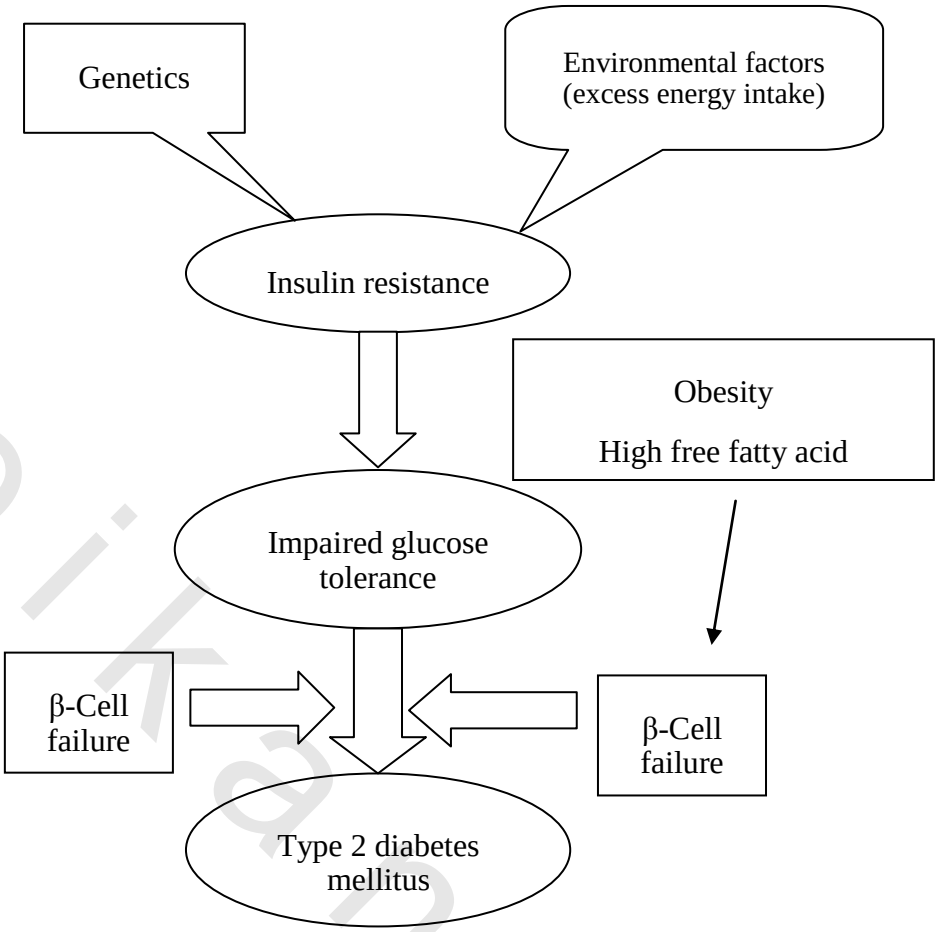


Figure 3: Type 2 diabetes mellitus [4]

3- Gestational diabetes:

Gestational diabetes mellitus (GDM) is defined as a state of carbohydrate intolerance of variable severity and evolution, which develops or is first detected during pregnancy [20] and is present in approximately 4–7% of pregnancies [21]. Classically, it is associated with an increase in perinatal morbidity and mortality, as well as a greater frequency of long-term complications in the mother and her offspring [20].

Pathophysiology of GDM:

Pregnancy is normally attended by progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to levels that approximate the insulin resistance seen in T2D. The insulin resistance of pregnancy may result from a combination of increased maternal adiposity and the insulin-desensitizing effects of hormones made by the placenta [22].

4- Other specific types

- **Genetic defects of the β-cell:**

These conditions are associated with monogenetic defects in β-cell function. They are referred to as maturity-onset diabetes of the young and are characterized by impaired insulin secretion with minimal or no defects in insulin action [23].

- **Genetic defects in insulin action:**

These are abnormalities associated with mutations of the IRs and may range from hyperinsulinemia and modest hyperglycemia to severe diabetes [(4)].

- **Diseases of the exocrine pancreas:**

Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy and pancreatic carcinoma [(4)].

- **Endocrinopathies:**

Acromegaly, Cushing's syndrome, glucagonoma and pheochromocytoma can all cause diabetes [(4)].

- **Drug or chemical-induced diabetes:**

This form of diabetes occurs with drugs or chemicals that affect insulin secretion, increase insulin resistance or permanently damage pancreatic β-cells, as is seen with the administration of high dose of steroids [(24)]. Corticosteroids have profound effects on carbohydrate metabolism: stimulating liver to form glucose from amino acids and glycerol. In the periphery, corticoids decrease glucose utilization, increase protein breakdown and activate lipolysis, thereby providing amino acids and glycerol for gluconeogenesis. The net result is increase in blood glucose levels [(25)].

- **Infections:**

Viral infections that may cause β-cell destruction include coxsackie virus B, cytomegalovirus, adenovirus and mumps.Genetic syndromes sometimes associated with diabetes are Down's syndrome, Klinefelter's syndrome, Turner's syndrome and Wolfram syndrome [(4)].

Diagnostic criteria and evaluation of glycemic control:

In 1998, the World Health Organization adopted the diagnostic parameters for diabetes established by the American Diabetes Association [(26)]. Currently, there are three ways to diagnose diabetes [(27)]. Because a single abnormal laboratory test is not sufficient to establish a diagnosis, any positive laboratory value must be confirmed on a different day: (1) symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl. Casual is defined as any time of day without regard to the time since the last meal, (2) FPG ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 hours and (3) 2-hour post load glucose (PG) ≥200 mg/dl during an oral glucose tolerance test. The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. The normal FPG level is <100 mg/dl. Impaired fasting glucose (IFG) is diagnosed when the FPG level is ≥100 mg/dl but ≤125 mg/dl. Impaired glucose tolerance (IGT) can only be diagnosed after an oral glucose tolerance test. A normal 2-hour PG level is <140 mg/dl. IGT is diagnosed when the 2-hour PG concentration is ≥ 140 mg/dl but ≤199 mg/dl (Table 1).

Table (1) : 2005 American Diabetes Association Criteria for the diagnosis of DM, IGT and IFG [27].

	Normal	Diabetes	IGT	IFG
FPG (mg/dl)	<100	≥ 126		100 to 125
Casual plasma glucose (mg/dl)			≥ 200 plus symptoms of diabetes	
2-hour PG (mg/dl)	<140	≥ 200	140 to 199	

In a patient with diagnosed diabetes, the hemoglobin A1c test (HbA1c) is used to monitor the patient's overall glycemic control. It is not recommended for diagnosis because there is not a gold standard assay for the HbA1c and because many countries do not have ready access to the test. Glycohemoglobin is formed continuously in erythrocytes as the product of a nonenzymatic reaction between glucose and the hemoglobin protein, which carries oxygen. The binding of glucose to hemoglobin is highly stable; therefore, hemoglobin remains glycated for the life span of the erythrocyte, ~123±23 days [28]. The HbA1c test is used to measure glycohemoglobin levels and provides an estimate of the average blood glucose level over the preceding 30 to 90 days period. Higher average blood glucose levels are reflected in higher HbA1c values [29] (Table 2).The normal HbA1c is <6 % [27] (Table 3). HbA1c levels correlate well with the development of diabetic complications and may become established as a test for the diagnosis of diabetes at some time in the future [30].

Table (2): Correlation between HbA1c levels and mean plasma glucose levels [27].

HbA1c (%)	Mean Plasma Glucose (mg/dl)
6	135
7	170
8	205
9	240
10	275
11	310
12	345

The HbA1c test provides an estimate of the average glucose level over the 30 to 90 days preceding the test. It does not account for short-term fluctuations in plasma glucose levels.

Table(3): American Diabetes Association Recommendations for HbA1c Levels [27].

HbA1c (%)	Interpretation
<6	Normal value
<7	Treatment goal for patient with diabetes; diet, exercise, and/or medications should control glucose levels well enough to maintain HbA1c values <7%
>8	Physician intervention in diabetes management Regimen is recommended

DM effects on endocrine system:

DM is a disorder of carbohydrate, protein and lipid metabolism associated with an absolute or relative insufficiency of insulin secretion accompanied by various degrees of insulin resistance [31]. Defects in carbohydrate metabolizing machinery and consistent efforts of the physiological systems to correct the imbalance in carbohydrate metabolism place an overexertion on the endocrine system, which leads to the deterioration of endocrine control. Continuing deterioration of endocrine control exacerbates the metabolic disturbances and leads primarily to hyperglycemia [32].

Symptoms of DM:

Thirst, polyuria, fatigue, general malaise, infections and blurred vision [32]. It is also characterized by hyperglycaemia, glycosuria, negative nitrogen balance and sometimes ketonaemia [33]. Over time patients with DM also develop symptoms related to major microvascular (i.e. retinopathy, nephropathy, neuropathy and diabetic foot problems) and macrovascular (i.e. cardiovascular disease, cerebra-vascular disease and peripheral vascular disease) complications [34].

Biochemical markers estimated in diabetes:

Glucose, cholesterol, TG, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol levels are estimated in the diagnosis of DM. Elevated blood pressure, elevated serum concentrations of glucose, total cholesterol, LDL cholesterol and TG are seen in diabetic conditions [15].

Streptozotocin – induced diabetes:

Streptozotocin **(**STZ) is a nitrosurea derivative of D-glucosamine compound that isolated from *Streptomyces achromogenes* [35]. STZ has a structure similar to glucose and N-acetyl glucosamine (GlcNAc) [36,37] (Figure: 4)

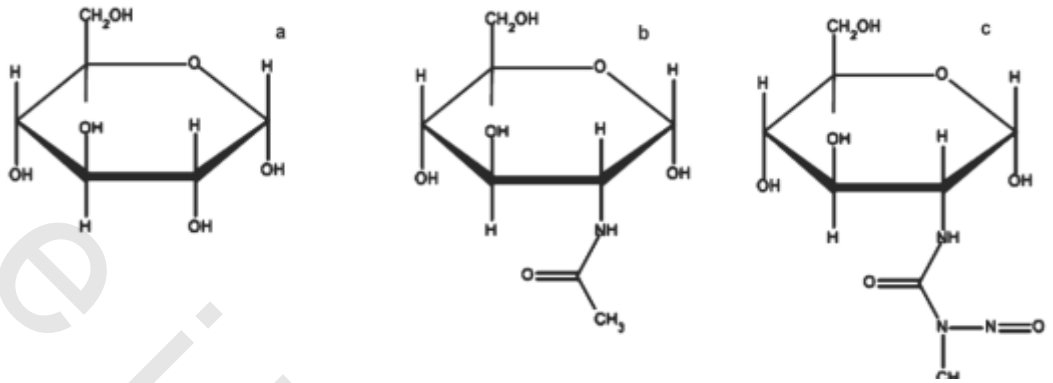


Figure 4: Chemical structures of (a) glucose, (b) N-acetyl glucosamine and (c) STZ [36, 37].

It is a broad spectrum antibiotic and alkylating genotoxic agent which possesses antibacterial, tumoricidal, carcinogenic and diabetogenic properties [38-40]. However, STZ is not a drug of choice for treatment of cancers due to development of resistance to its genotoxic effects [41]. Moreover, severe toxicities were observed in different cancer patients when STZ was used alone or in combination with other antineoplastic drugs [42]. More specifically, STZ exhibits pancreatic β-cells toxicity and is often used to induce diabetes in experimental animals [43,44].

β-cells toxicity and diabetogenic properties of STZ are mediated through uptaking of STZ in β-cells by glucose transporter 2 (GLUT2) receptors [45] and increased oxidative stress due to nitric oxide (NO) release and reactive oxygen species (ROS) production [46–50]. STZ induces β-cell dysfunction and apoptosis at lower doses while causing β-cell necrosis at higher doses. Insulin-secretory cells also develop resistance on repeated exposures to STZ through a wide spectrum of toxin tolerance mechanisms [51].

In adult rats, 60 mg/kg is the most common dose of STZ to induce T1D, but higher doses are also used. STZ is also efficacious after intraperitoneal administration of a similar or higher dose, but single doses below 40 mg/kg may be ineffective. In general, rats are considered diabetic if tail blood glucose concentrations in fed animals are greater than 200–300 mg/dl, 2 days after STZ injection [52]. In mice, however, multiple low doses (40 mg/kg) are the most effective at maintaining mouse viability and inducing pancreatic dysfunction in part through immune destruction [35].

Disadvantages of diabetes induction by STZ:

There are some disadvantages to STZ use in chronic experiments, especially - spontaneous recovery from high blood glucose levels by the development of functioning insulinoma and high incidence of kidney and liver tumors [53].

DM and oxidative stress:

Diabetes is the world's largest endocrine disease with deranged carbohydrate, fat and protein metabolisms [(54)]. There is considerable evidence suggesting that oxidative stress plays a role in tissue damage associated with diabetes [(55)]. Oxidative stress is a condition in which the cellular production of ROS (sometimes referred to as 'free radicals') exceeds the physiological capacity of the antioxidant defense system to render ROS inactivates [(56)]. Oxidative stress may be increased in diabetic patients since persistent hyperglycemia causes an increased production of oxygen free radicals (OFRs) through auto oxidation of glucose and nonenzymatic protein glycation [(57)] and activation of polyol pathway [(58)]. Increased levels of the products of oxidative damage to lipids and protein have been detected in the serum of diabetic patients and their presence correlates with the development of complications [(59)]. Oxidants are counteracted by antioxidant enzyme systems such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) and by nonenzymatic antioxidant systems in the organism [(60)]. The efficiency of this defense mechanism is altered in diabetes [(61)]. The term antioxidant has been defined as "any substance exogenous or endogenous in nature that delays or inhibits oxidative damage to a target molecule [(62)]. It protects biologically important molecules such as deoxyribonucleic acid (DNA), proteins and lipids from oxidative damage and consequently reduces the risk of several chronic disease [(63)]

During diabetes, persistent hyperglycemia causes increased production of free radicals especially ROS, for all tissues from glucose auto-oxidation and protein glycosylation. Free radicals are generated as byproducts of normal cellular metabolism; however, several conditions are known to disturb the balance between ROS production and cellular defense mechanisms, which causes cell dysfunction and destruction resulting in tissue injury. The increase in the level of ROS in diabetes could be due to their increased production and / or decreased destruction by nonenzymatic and enzymatic antioxidants CAT, GPx and SOD. The level of these antioxidant enzymes critically influences the susceptibility of various tissues to oxidative stress and is associated with the development of complications in diabetes. Diabetes produces disturbances of lipid profiles, especially an increased susceptibility to lipid peroxidation, which is responsible for increased incidence of atherosclerosis, a major complication of DM [(64)].

β-cells are very sensitive to cytotoxic stress because they express very little of the antioxidant enzymes. Hence, β-cell is at greater risk of oxidative damage than other tissues with higher levels of antioxidant protection. During pathogenesis of DM, oxidative and nitrosative stresses contribute to the destruction of insulin-producing β-cells. Moreover, it is believed that increased oxidative stress is one of the main factors in the etiology and complications of DM [(65)].

Treatment of DM:

These are classified as pharmacological treatment (oral hypoglycemic drugs Table (4) and insulin injection), non-pharmacological treatment (Exercise and Diet) and medicinal plants used in treatment of DM [(4)].

Table (4): Oral hypoglycemic agents with mechanism of action and side effects [4]

No	Oral antidiabetics	Mechanism of action	Side effects
1	Sulfonylureas Glimiperide, Glipizide, Glipizide-gits, Glyburide, Glyburide micronized, Tolbutamide, Chlorpropamide, Tolazamide, Acetoheximide	Stimulate first-phase insulin secretion by blocking K+ channel in β-cells.	Late hyperinsulinemia, and hypoglycemia, Weight gain
2	Meglitinides Repaglinide, Nateglinid	Stimulate first-phase insulin secretion by blocking K+ channel in β-cells	Hypoglycemia Weight gain
3	Biguanides Metformin, Metformin-XR	Decrease hepatic glucose production Increase muscle glucose uptake and utilization	Nausea, Diarrhea Anorexia, Lactic acidosis
4	Thiazolidinedinediones Rosiglitazone, Pioglitazone	Increase insulin sensitivity via activation of PPAR-γ Receptors	Fluid retention and weight gain
5	α-Glucoside Inhibitors Acarbose, Miglitol	Decrease hepatic glucose production Delays glucose absorption	Flatulence Abdominal bloating

Traditional medicines and extracts from medicinal plants have been extensively used as alternative medicine for better control and management of DM. Medicinal plants are continued to be a powerful source for new drugs, now contributing about 90% of the newly discovered pharmaceuticals. Traditional medicines provide better health coverage for 80% of the world population, especially in the developing countries [66].

One of the most widely used herbs is *Panax ginseng*; it is valuable in traditional medicine in many countries [67]. It is the most efficacious for immune stimulation and the prevention of diabetes [68]. It has been used to treat a wide variety of diseases including anemia, gastritis, blood pressure abnormalities together with its role to decrease blood coagulation, cholesterol and sugar levels [69].

Ginseng

Plant Profile:

Plant taxonomy [70]

Kingdom	: Plantae
Division	: Angiosperms
Sub division	: Eudicots
Class	: Asterids
Order	: Apiales
Family	: Araliaceae
Subfamily	: Aralioideae
Genus	: Panax
Species	: Ginseng

A 

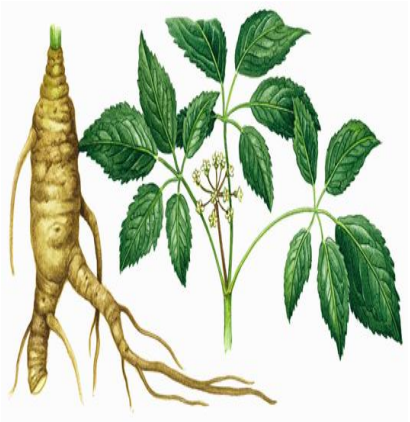
B 

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Figure 5 : (A) Root of *panax ginseng* (B) Leaves, flowers and root of *panax ginseng* (C) Fruit of *panax ginseng*[71].

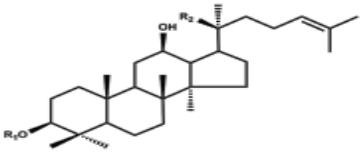
Common Names:

Asian ginseng, Asiatic ginseng, Chinese ginseng, ginseng, ginseng asiatique, *Ginseng radix*,ginseng root, guigai, hong shen, Japanese ginseng, jen-shen, jinsao, jintsam, insam, Korean ginseng, Korean *panax ginseng*, Korean red ginseng, ninjin, Oriental ginseng, *Panax ginseng*, Radix ginseng rubra, red ginseng, renshen, renxian, sang, seng, sheng shai shen and white ginseng [72].

There are five main species of ginseng: American, Chinese, Korean, Japanese and Siberian (or Russian) and it is important to be able to distinguish between them. The commercially available product 'ginseng' usually refers to the dried root of *Panax ginseng*, commonly known as Korean or Asian ginseng [73]. Traditionally, ginseng has been processed to make white ginseng (air-drying after harvest) and red ginseng (steaming or heat process) to enhance its preservation and efficacy. Red ginseng is more common as a herbal medicine than white ginseng because steaming induces changes in the chemical constituents and enhances the biological activities of ginseng [74,75].

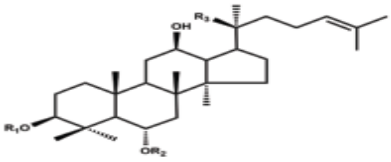
Panax ginseng is a popular herbal remedy that has been used for thousands of years. It has been an important part of the pharmacopoeia of Traditional Chinese Medicine and is classified as an adaptogen that is thought to increase the body's overall resistance to stress and infection [76]. This herb has a wide base of application and is considered the most popular herbal medicine worldwide [77]. It has been used to treat a variety of disorders including: anaemia, insomnia, dyspnea, memory impairment, confusion, decreased libido, chronic fatigue, angina and DM [78-80].

The pharmacological properties of ginseng are mainly attributed to ginseng saponins, commonly called ginsenosides, the major and bioactive constituents [81, 82]. Ginsenosides can be classified as dammarane-type, ocotillol-type, oleanane-type oligoglycosides (Figure 6) and polysaccharides [83]. Furthermore, the dammarane type saponins are classified into protopanaxadiol (PPD) and protopanaxatriol (PPT) types. The PPD type has sugar moieties attached to OH at C-3 and/or C-20, and the PPT type has sugar moieties attached to OH at C-3, C-6 and/or C-20. The ocotillol-type has a five membered epoxy ring at C-20 and the Oleanane-type has a modified C-20 side chain. With the development of instrumental analysis, minor constituents are constantly being isolated from these ginsengs [84].



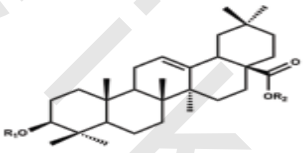
PPD

	R1	R2
Ginsenoside Rb_1	Glc-glc-	Glc-glc-O-
Ginsenoside Rd	Glc-glc-	Glc-O-
Ginsenoside Rg_3		HO-
Ginsenoside Ra_3	Glc-glc-	Xyl-glc-glc-
Ginsenoside Rh_2	Glc-	HO-
Compound K	H	Glc-O-
20S-protopanaxadiol	H	HO-



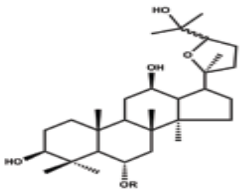
PPT

	R1	R2	R3
Ginsenoside Re	H		
Ginsenoside Rg_1	H	Glc-	Glc-O-
Ginsenoside Rf	H	Glc-glc-	HO-
Ginsenoside Rh_1	H	Glc-	HO-
Notoginsenoside R1	H	Xyl-glc-	Glc-O-
Gisnenosdie F1	H	H	Glc-O-
20S-protopanaxatriol	H	H	OH



Oleanane

	R1	R2
Ginsenoside Ro	GlcA-glc-	Glc-
Chikusetsusaponin IVa	GlcA-	Glc-



Octotillol

	R
Majonoside R2	Xyl-glc-
Pseudogiinsenoside RTt5	Glc-

Modified PPD and PPT

	R1	R2		R1	R2
Ginsenoside Rk_1	Glc-glc-	H-	Ginsenoside Rg_5	Glc-glc-	H
Ginsenoside Rk_2	Glc-	H	Ginsenoside Rh_3	Glc-	H
Ginsenoside Rk_3	H	Glc-O-	Ginsenoside Rh_4	H	Glc-O-

Modified ginsenoside

	R1	R2		R1	R2
Quinquinoside IV	Glc-glc-	Glc-glc-	Vina-ginsenoside R3	Glc-glc-	Glc-
Notoginsenoside G	Glc-glc	Glc-			

Figure 6: The structures of representative ginseng saponins [(84)].

Chemical constituents:

Panax ginseng contains triterpene glycosides or saponins. Many active compounds can be found in all parts of the plant, including amino acids, alkaloids, phenols, proteins, polypeptides,vitamins B1 and B2 [85]. Up to 40 distinct ginsenosides have been identified by thin layer chromatography (TLC) and methanol extraction experiments [85,86], the nomenclature of ginsenosides is by the designation Rx, where x represents the retention factor value from the sequence of spots on TLC from bottom to top. The two major sub-types of ginsenosides, PPD and PPT are classified according to the arrangement and number of sugar residues glucose, rhamnose, xylose and arabinose on the ginsenoside. Rb1, Rb2, Rc and Rd are examples of PPD ginsenosides. Re, Rf, Rg1 and Rg2 are examples of PPT [85-87]. These ginsenosides have varying concentrations in red and white *Panax ginseng* extracts due to different processing methods that affect deacetylating enzymes within the raw plant material [88].

Pharmacokinetics

Ginsenosides are activated by intestinal bacteria through deglycosylation and esterification [89]. PPD and PPT glycosides are absorbed into the blood or lymph and transported to target tissues for esterification with stearic, oleic or palmitic fatty acids. The transformation into ginsenoside metabolites, M1 (20S PPD 20-O-ß-D-glucopyranoside) and M4 (20S PPT) affect excretion and utilization of the metabolites [71].

Mechanism of action

Panax ginseng is often referred to as an adaptogen, which suggests it has varied actions and effects on the body that support non-specific resistance to biochemical and physical stressors, improve vitality, longevity and enhance mental capacity [90-92]. Some reviews suggest that *Panax ginseng* has immuno-modulating activity by affecting the hypothalamic-pituitary-adrenal (HPA) axis [85,93]. *In vitro* experiments reveal enhanced natural killer (NK) cell activity, increased immune cell phagocytosis enhances the production of interferon, improves physical and mental performance after ginsenoside exposure [85].

According to a 1999 World Health Organization review, ginseng saponins "are thought to decrease serum prolactin, thereby increasing libido" in male impotence [91].

The *Panax ginseng* has different pharmaceutical activities such as [71]:

- Anti sterility activity.
- Anti proliferative activity.
- Adaptogenic activity.
- Treatment for cold and flu.
- Memory power enhancing activity.
- Sports performance.
- Sense of well being effects.
- Anti diabetic activity.
- Anti inflammatory activity.

Anti diabetic activity

Eclectic medicine texts reference *Panax ginseng* for its beneficial use in blood sugar regulation [91,94]. In a double-blind randomized clinical trial (RCT), Sotaniemi et al. in (1995) examined the efficacy of *Panax ginseng* in newly diagnosed T2D [95]. By measuring included physical performance, mood, serum lipids, fasting blood glucose, HbA1c, amino terminal propeptide (PIIINP) concentration and body weight. PIIINP serum levels are associated with coronary artery disease and were used as a safety parameter in this study. The study participants (n=36) were given 100 mg ginseng extract, 200 mg ginseng extract, or placebo daily for eight weeks. Compared to the placebo group, the 200 mg ginseng group experienced elevated mood, improved physical performance and reduced fasting blood glucose. The authors concluded ginseng warrants further study as an adjuvant to diabetes.

A double-blind, 12-week RCT examined the effect of red *Panax ginseng* on HbA1c levels in 19 subjects with well-controlled T2D [96]. Study participants received 2 g ginseng or placebo three times daily before meals. Plasma glucose, insulin and oral glucose tolerance were secondary measures of efficacy, while blood pressure checks and liver and kidney function tests assessed safety. Although no change was seen in HbA1c levels with ginseng, the participants remained well controlled throughout the study without pharmaceutical intervention with average levels of HbA1c of 6.5 %. A significant 8-11 % decrease in glucose on the oral glucose tolerance test and 33% decrease in plasma insulin ($p<0.05$) was seen in the ginseng group compared to placebo. No change was reported in safety parameters throughout the study, which led the authors to conclude red *Panax ginseng* is safe to use in the treatment of T2D management.

Anti inflammatory activity

Previous paper proposed an anti-inflammatory role of *Panax ginseng* in the sequence of progression to promotion in a model of carcinogenesis [97]. *Panax ginseng* affects multiple points within the inflammatory cascade, including inhibition of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and nuclear factor kappaB (NFkB) [98,99]. Lee et al. in (2005) concluded that *Panax ginseng* has a radioprotective effect associated with antioxidant and immune modulation properties [86].

Drug Botanical Interactions

There are no known interactions between *Panax ginseng* and pharmaceuticals, as reported by the German Commission E [100,101]. Caution is advised with concomitant use with phenelzine, coumadin, oral hypoglycemics, insulin and caffeine, based on preclinical studies and proposed mechanisms of action. Seely et al. in (2008) suggests cautious use of *Panax ginseng* in pregnancy and lactation, although no specific teratogenic or hormone disrupting activity was noted [102].

Side Effects and Toxicity

Panax ginseng is associated with low toxicity; few adverse events have been reported with proper usage [85,100]. Adverse events have been associated with high doses and long-term usage, producing what has been cited in the literature as ginseng abuse syndrome[93,103] although case studies associated with ginseng abuse syndrome have been

discounted by several authors. Side effects such as hypertension, nausea, diarrhea, headache, mastalgia and insomnia and skin rash have been noted [93,103,104].

Cytochrome P450

The term 'cytochrome P450 (CYP450)' was coined in 1962 as a temporary name for a colored substance in the cell [105]. This pigment, when reduced and bound with carbon monoxide, produced an unusual absorption peak at a wavelength of 450 nm. Cytochrome is a misnomer given that the CYP450s are enzymes rather than true cytochromes. Despite this, the name 'CYP450' has stuck and is so widely accepted that any change would be impractical. At first, CYP450 was believed to represent a single enzyme. Today it seems likely that humans and other mammals have approximately 50 distinct CYP450 enzymes. The total number may be higher in plants, possibly as high as several hundred [106]. The name CYP450 derives from the fact that these proteins have a haem group and an unusual absorption spectrum range. The reason for CYP450 to absorb in this range is due to the unusual ligand haem iron. Four ligands are provided by nitrogen on the haem ring [107].

CYP450 enzymes are a super family of mono-oxygenases that are found in all kingdoms of life [108] and expressed in a variety of mammalian tissues including liver, kidney, lung, adrenal, gonads, brain, skin and others. These forms of CYP450 proteins are membrane bound and reside in the endoplasmic reticulum and in the mitochondrial membrane. Some other forms of CYP450 proteins are also observed in the outer nuclear membrane, different Golgi compartments, peroxisomes and other plasma membrane [109,110]. While most of the CYP450 enzymes have shown to be constitutively expressed, many are increased markedly in expression upon exposure to various inducers such as ethanol [111], polychlorinated biphenyls and polychlorinated dibenzo-ρ-dioxins [112,113].

The nomenclature of CYP450 is based on their amino acid sequence identity. The letters CYP are followed by a number indicating the CYP450 gene family (more than 40% identity), then a letter for the subfamily (more than 55% identity) and finally a number for each individual protein. Although, the amino acid sequence identity between different P450s may be very low, their secondary structure is highly conserved [114]. Humans have 57 CYP450 genes and 58 pseudogenes distributed in 18 CYP450 families, one fourth of the human CYP450s are not well-characterized and therefore considered 'orphans' [115]. The mouse genome has 102 CYP450 genes and nearly 90 pseudogenes [116].

The summary of the genes and proteins encoded is given in Table (5). Several of them have been identified as particularly important in oxidative metabolism. They are CYP3A4 (by far the most important), CYP2D6, CYP2C9 and CYP2C19. Other notable CYPs are CYP2E1, CYP2A6 and CYP1A2 [108].

Table (5): Classification of the CYP450 family on the basis of CYP450 isoform and function is given [108].

CYP Family	Function	Category	CYP Isoform
CYP1	Drug and steroid (especially estrogen) metabolism	3 subfamilies, 3 genes, 1 pseudogene	CYP1A1 CYP1A2 CYP1B1
CYP2	Drug and steroid metabolism	13 subfamilies, 16 genes, 16 pseudogenes	CYP2A6 CYP2A7 CYP2A13 CYP2B6 CYP2C8 CYP2C9 CYP2C18 CYP2C19 CYP2D6 CYP2E1 CYP2F1 CYP2J2 CYP2R1 CYP2S1 CYP2U1 CYP2W1
CYP3	Drug and steroid (including testosterone) metabolism	1 subfamily, 4 genes, 2 pseudogenes	CYP3A4 CYP3A5 CYP3A7 CYP3A43
CYP4	Arachidonic acid or fatty acid metabolism	6 subfamilies, 11 genes, 10 pseudogenes	CYP4A11 CYP4A22 CYP4B1 CYP4F2 CYP4F3 CYP4F8 CYP4F11 CYP4F12 CYP4F22 CYP4V2 CYP4X1 CYP4Z1
CYP5	Thromboxane A2 synthase	1 subfamily, 1 gene	CYP5A1
CYP7	Bile acid biosynthesis 7-alpha hydroxylase of steroid nucleus	2 subfamilies, 2 genes	CYP7A1 CYP7B1
CYP8	Varied	2 subfamilies, 2 genes	CYP8A1 (prostacyclin synthase), CYP8B1 (bile acid biosynthesis)
CYP11	Steroid biosynthesis	2 subfamilies, 3 genes	CYP11A1 CYP11B1 CYP11B2

Table (5): Classification of the CYP450 family on the basis of CYP450 isoform and function is given (cont.) [108].

CYP Family	Function	Category	CYP Isoform
CYP17	Steroid biosynthesis, 17-alpha hydroxylase	1 subfamily, 1 gene	CYP17A1
CYP19	Steroid biosynthesis: aromatase synthesizes estrogen	1 subfamily, 1 gene	CYP19A1
CYP20	Unknown function	1 subfamily, 1 gene	CYP20A1
CYP21	Steroid biosynthesis	2 subfamilies, 2 genes, 1 pseudogene	CYP21A2
CYP24	Vitamin d degradation	1 subfamily, 1 gene	CYP24A1
CYP26	Retinoic acid hydroxylase	3 Subfamilies, 3 genes	CYP26A1 CYP26B1 CYP26C1
CYP27	Varied	3 subfamilies, 3 genes	CYP27A1 (bile acid biosynthesis), CYP27B1 (vitamin D3 1-alpha hydroxylase, activates vitamin D3) CYP27C1 (unknown function)
CYP39	7-alpha hydroxylation of 24-hydroxycholesterol	1 subfamily, 1 gene	CYP39A1
CYP46	Cholesterol 24-hydroxylase	1 subfamily, 1 gene	CYP46A1
CYP51	Cholesterol biosynthesis	1 subfamily, 1 gene, 3 pseudogenes	CYP51A1 (lanosterol 14-alpha demethylase)

Function of CYP450

Functionally, CYP450 enzymes may be broadly divided into three groups, those:

- involved in the metabolism of drugs and other foreign chemicals;
- functioning during steroidogenesis; and
- participating in other important endogenous functions [106].

CYP450s involved in the metabolism of a broad range of substrates and catalyzes a variety of interesting chemicals reactions [117]. They catalyze both endogenous and exogenous compounds, converting them to more soluble hydrophilic metabolites that can be removed readily from the body [115]. However, in some situations, the metabolism of chemicals by the CYP450 enzymes may be undesirable or detrimental to the body and can lead to toxic or reactive intermediates resulting in target organ toxicity and/or carcinogenic insult [118-120].

CYP450 enzymes are important in the production of compounds such as cholesterol, corticosteroids and fatty acids. The most important feature of the CYP450 enzymes is its unique ability to activate molecular oxygen and to subsequently insert a single oxygen atom stereo-specifically into inert chemical bonds. CYP450 enzymes catalyses the insertion of oxygen into activated carbon – hydrogen bonds to yield alcohol (e.g $RH + O_2 + 2H^+ + 2e^- \rightarrow ROH + H_2O$). However, they can also carry out plethora of other reactions including epoxidation, dealkylation and heteroatom oxidation [107].

Ginseng and ginsenoside may have selectively inhibitory effects on CYP450 activities. In a previous animal study, ginseng was found to inhibit specially benzo [alpha] pyrene-induced CYP1A1 activation by down regulation of the gene expression [121].

Cytochrome P450 2E1

Cytochrome P450 2E1 (CYP2E1) is a member of the CYP450 super family and primarily involved in Phase I metabolism where its major role is detoxification and bioactivation of drugs and xenobiotics [122].

The CYP2E1 isoform is responsible for the metabolism of many small compounds and molecules including ethanol, carbon tetrachloride, chloroform, tetrachloroethylene, styrene and benzene [123,124]. Assessing the CYP2E1 phenotype in subject exposed to industrial chemicals and environmental pollutants may be useful either to predict their susceptibility to or to detect early effects from exposure to those chemicals. CYP2E1 metabolizes some endogenous physiological substrates; these include acetone and fatty acids such as linoleic and arachidonic acids [124]. CYP2E1 involved in the metabolism of ethanol and generate ROS such as superoxide anion, hydrogen peroxide (H_2O_2) and 1-hydroxyethyl free radicals. These ROS are known to react with cell membrane and initiate lipid peroxidation, resulting in the formation of protein adducts and increases collagen synthesis, which ultimately leads to alcoholic liver disease including liver cirrhosis [118]. Also CYP2E1 is involved in the etiology and pathology of many diseases including diabetes [125].

Biomarker of oxidative stress

Malondialdehyde

The role of free radical injury in the pathogenesis of some clinical conditions is now widely studied all over the world [126]. Free radical attack on polyunsaturated membrane lipid gives malondialdehyde (MDA) in the course of its reactions. Therefore, measurement of MDA is widely used in determining the level of attack on polyunsaturated membrane lipid by free radicals [127]. This is frequently measured because of the unstable nature of free radical in the system [128].

MDA is a late-stage lipid oxidation byproduct that can be formed nonenzymatically or as a byproduct of cyclooxygenase activity (Figure 7) [129]. MDA is a volatile molecule that reacts, via Schiff base formation, with free amino groups of protein, lipid and DNA. It is estimated that up to 80% of MDA is protein bound [129]. In addition, accumulation of MDA affects membrane organization by increasing phosphatidyl serine (PS) externalization [130]. Accumulation of MDA and MDA adducts is correlated with many disease states, such as hepatitis C [131], Down syndrome [132], cancer [133], liver injury [134], neurodegenerative diseases [135] and DM [129].

MDA levels are increased in mesangial cells [136], proximal tubule cells [137], vascular smooth muscle cells [138,140], erythrocytes [137,140,141] and mononuclear leukocytes treated with high concentrations of glucose [142]. MDA is also increased in plasma [143], the renal cortex [144] and the aorta [145] of STZ induced diabetic rats. Finally, MDA formation is stimulated in the plasma of IDDM patients [146,147], in reticulocytes [148], erythrocytes [148, 149] and plasma [149] from NIDDM patients and in the plasma of obese patients [150]. In addition, there is a positive correlation between plasma and erythrocyte MDA accumulation and the duration of diabetes in IDDM patients [149]. Underscoring its nonenzymatic production by oxidants, increased MDA levels can be suppressed by antioxidant treatment of diabetic animals, humans and in glucose treated cells [138,144,151].

Interestingly, MDA accumulation has been linked to hyperketonemia in IDDM patients, as well as to elevated glucose levels [151,152]. These data are supported by the fact that MDA also accumulates in endothelial cells exposed to acetoacetate [153].

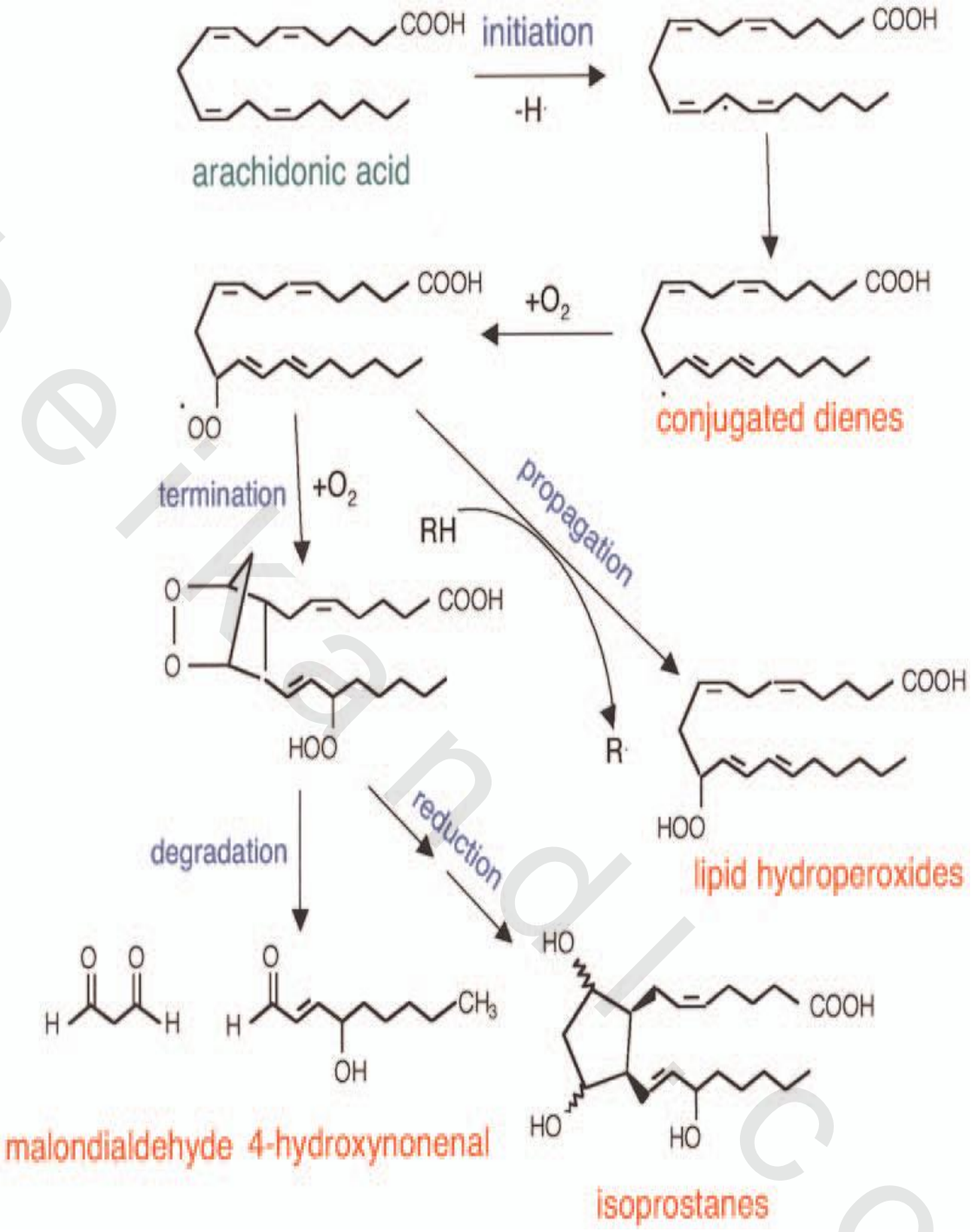


Figure 7: Polyunsaturated fatty acids can be nonenzymatically oxidized to produce lipid oxidation byproducts. The process is initiated by extraction of a hydrogen radical from a fatty acid. Molecular oxygen reacts with the fatty acid radicals to form a variety of products, including lipid hydroperoxides, isoprostanes and MDA. These molecules are generally reactive and some, such as isoprostanes, possess biological activity. Many have been measured as markers of oxidative stress in diabetes [(129)].

Antioxidant parameters

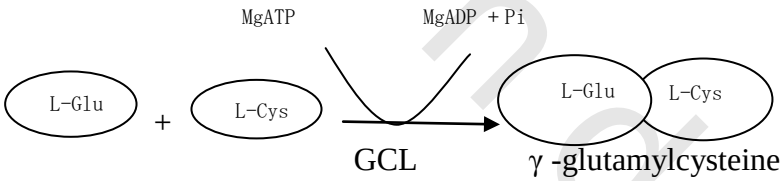
1-Glutathione

Gluthatione (GSH) is an important endogenous antioxidant which can scavange ROS and maintain the intracellular redox equilibrium and protect tissues from oxidative stress. GSH scavange the toxic effect of ROS catalyzed by GPx [154-156]. There are two forms of glutathione, the active reduced form (GSH) and the inactive oxidized form (GSSG). The oxidized form of glutathione can be recycled into reduced form, catalyzed by glutathione reductase and supported by the nicotinamide adenine dinucleotide phosphate reduced (NADPH) from the hexose monophosphate (HMP) shunt [156]. Liver is an organ with highest concentration of GSH compared to other tissues. High concentration of GSH also supported by the high activity of HMP shunt in liver tissue [156,157].

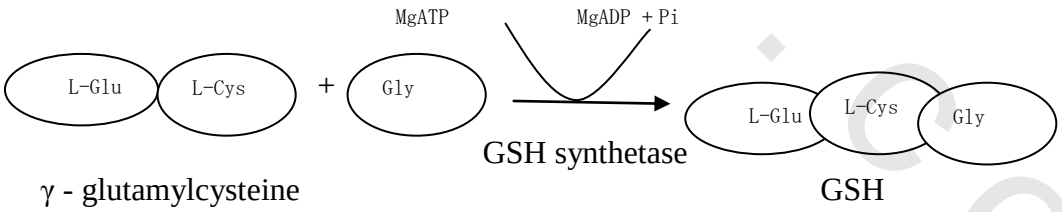
GSH Biosynthesis

GSH is a tripeptide formed by glutamic acidic, cysteine and glycine. The glutamic acid forms a particular gamma-peptic bond with cysteine by its γ-glutamyl group [158]. The synthesis of GSH from its constituent amino acids involves two Adenosine triphosphate (ATP) requiring enzymatic steps:

(1) The first step is rate-limiting and catalyzed by γ-glutamylcysteine ligase (GCL) which is composed of two subunits: one catalytic (GCLC) and one modifier (GCLM):



(2) The second step is catalyzed by GSH synthetase [159]:



However, under normal physiological conditions, the rate of GSH synthesis is largely determined by two factors that are, cysteine availability and GCL activity. Cysteine is normally derived from diet, protein breakdown and in the liver, from methionine via transsulfuration (conversion of homocysteine to cysteine). Cysteine differs from other amino acids because its sulfhydryl form cysteine is predominant inside the cell whereas its disulfide form cystine is predominant outside the cell [160].

GSH Functions

The chemical structure of GSH determines its potential functions and its broad distribution among all living organisms reflects its important biological role. A major function of GSH is the detoxification of xenobiotics and some endogenous compounds. These substances are electrophiles and form conjugates with GSH, either spontaneously or enzymatically, in reactions catalyzed by glutathione-*S*-transferases (GST) [161]. Human GSTs are divided into two distinct family members: the membrane-bound microsomal and cytosolic family members. The conjugates formed are usually excreted in the bile, but can also undergo modification to mercapturic acid.

Another important GSH function is the maintenance of the intracellular redox balance and the essential thiol status of proteins [160].

The reaction with the protein is as follows:

$$\text{Protein-SSG} + \text{GSH} \longleftrightarrow \text{Protein-SH} + \text{GSSG}. \quad (1)$$

The equilibrium of this reaction depends on the concentrations of GSH and GSSG. The reversible thiolation of proteins is known to regulate several metabolic processes including enzyme activity, transport activity, signal transduction and gene expression through redox-sensitive nuclear transcription factors such as AP-1, NFkB and p53 [160, 162]. In fact, DNA-binding activity of transcription factors often involves critical cysteine residues and the maintenance of these residues in a reduced form, at least in the nuclear compartment, is necessary [163]. AP-1 is a transcription factor related to tumor promotion [164], and its DNA-binding activity can be diminished if cysteine-252 is oxidized [165]. Tumor suppressor p53, known as the "guardian of the genome" contains 12 cysteine residues in its amino acid sequence [166] and oxidation of some of these inhibits p53 function [167].

Moreover, GSH performs an antioxidant function, The H_2O_2 produced during the aerobic metabolism, can be metabolized in the cytosol by GPx and CAT in peroxisomes. In order to prevent oxidative damage, the GSSG is reduced to GSH by GSSG reductase at the expense of NADPH forming a redox cycle [158]. Organic peroxides can be reduced both by GPx and GST. In extreme conditions of oxidative stress, the ability of the cell to reduce GSSG to GSH may be less, inducing the accumulation of GSSG within the cytosol. In order to avoid a shift in the redox equilibrium, the GSSG can be actively transported out of the cell or react with protein sulfhydryl groups and form mixed disulfides (Figure 8).

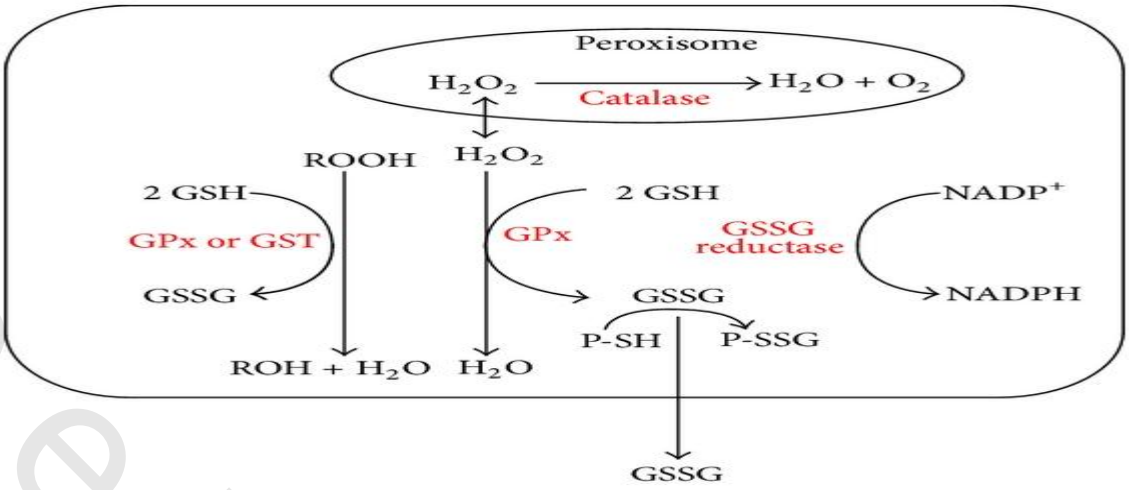


Figure 8: Antioxidant function of GSH.

In addition, storage of cysteine is one of the most important functions of GSH because cysteine is extremely unstable extra cellularly and rapidly autooxidizes to cystine in a process that produces potentially toxic OFRs [168]. The γ -glutamyl cycle allows GSH to be the main source of cysteine (Figure 9).

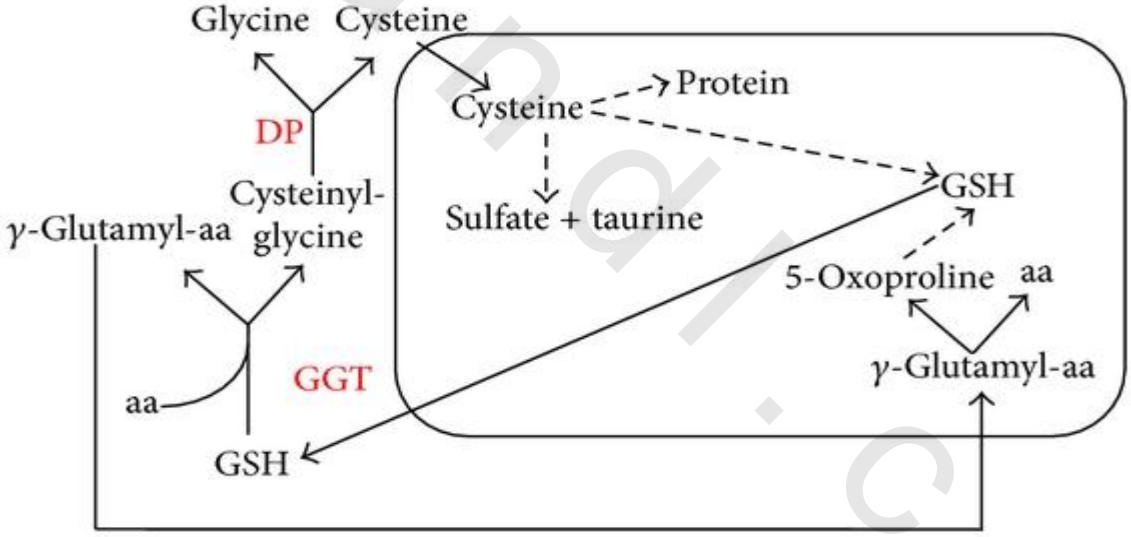


Figure 9: γ-Glutamyl cycle. In the γ -glutamyl cycle, GSH is released from the cell and the ectoenzyme GGT transfers the γ -glutamyl moiety of GSH to an amino acid (aa, the best acceptor being cysteine), forming γ -glutamyl-aa and cysteinyl-glycine. The γ-glutamyl-amino acid can then be transported back into the cell and once inside can be further metabolized to release the aa and 5-oxoproline, which can be converted to glutamate and used for GSH synthesis. Cysteinyl-glycine is broken down by dipeptidase to generate cysteine and glycine. Once inside the cell, the majority of cysteine is incorporated into GSH, some being incorporated into protein and some degraded into sulfate and taurine [169].

2-Glutathione Peroxidase

Glutathione Peroxidase (GPx) is a family of antioxidant enzymes. Their main function is to neutralize the H_2O_2 and organic hydroperoxides in the intracellular and extracellular compartments. In a recent review, Brigelius et al. in (2013) [170] summarized the latest knowledge on various aspects of GPx. There are eight forms of GPx which are characterized by similar features. They have different modes and sites of action and different chemical forms. They protect cells, in synergy with vitamin E, from the accumulation of H_2O_2 or organic hydroperoxides and they ensure the continued integrity of cell membranes. Their enzymatic activity is directly proportional to selenium intake, especially for forms 1 to 4 which are dependent on selenium, in order to perform neutralization. There is, therefore, a strong link between selenium deficiency and oxidative stress [171–173].

GPx-1 is widespread throughout the whole body. It is expressed at very high levels in erythrocytes, liver, kidneys and lungs [174]. Its main activity is antioxidant. It is the first enzyme to be affected in the case of selenium deficiency [175,176]. GPx-2 is localized predominantly in the gastrointestinal tissues and in the human liver. It protects against oxidative damages and presents 65% analogy with the GPx-1 [177]. GPx-3 is localized in extracellular fluid and plasma. It represents 10-30 % of selenium found in plasma. It is found in the liver, kidneys, heart, lungs, thyroid, gastrointestinal tract and breasts, and also in the placenta and the male reproductive system [178]. Its role is antioxidant in the plasma and it can also reduce lipid hydroperoxides.

GPx-4 is widely spread in the human body. Strong activity is observed in the testes. It is located in cells in the cytosol, mitochondria and nucleus [179]. Besides its antioxidant activity, it protects membranes from peroxidative degradation (an important role is suggested in the brain) [180]. It can convert cholesterol and cholesterol ester hydroperoxides into less toxic derivatives. It protects against DNA damages by oxidation. It plays a role in regulating the 15-lipoxygenase and 5-lipoxygenase pathways. GPx-4 is important for male fertility and maturation, function and sperm motility. GPx-5 is present in the embryo and the olfactory epithelium, its role remains unknown [175].

The GPx 6, 7 and 8 are less known. The GPx-6 is a selenoprotein found only in humans, it is a homologue of GPx-3 and its role remains unknown. There is an inverse relationship between GPx-7 and the proliferation of cancer cells. The GPx-7 is located in the lumen of the endoplasmic reticulum. It has an antioxidant function and it is probably involved in protein folding as well as the GPx-8 which is a membrane protein of the endoplasmic reticulum and the last of the family of GPx to be discovered [170].

Liver function enzymes

Alanine Aminotransferase (ALT): also called glutamate pyruvate transaminase (GPT) is an enzyme present in hepatocytes. When a cell is damaged, it leaks this enzyme into the blood, where it is measured. ALT rises dramatically in acute liver damage. ALT is a more reliable marker of liver integrity than aspartate aminotransferase (AST) [181].

Aspartate Aminotransferase (AST): also called glutamate oxaloacetate transaminase (GOT) is similar to ALT in that it is another enzyme associated with liver parenchymal cells. It is raised in acute liver damage, but is also present in red blood cells and cardiac and skeletal muscle and is therefore not specific to the liver. Increase in AST levels, however, can occur in connection with damages of heart or skeletal muscle as well as of liver parenchyma [(182)]. In medicine, the presence of elevated values of ALT and AST is indicative of liver damage [(183)].

Lipid profiles

Cholesterol is a sterol useful in cell membrane integrity and precursor for steroid hormones. Total cholesterol level is increased in diabetic rats when compared with control rats. DM leads with impaired carbohydrate metabolism and increased lipolysis causes accumulation of acetyl CoA. Increased availability of acetyl CoA leads to synthesis of cholesterol and causes hyperlipidemia [(184)]. Serum lipids increased by lipolysis due to insulin deficiency in diabetic rats [(185)]. Usually, insulin increases the lipogenesis and decreases lipolysis and ketogenesis. However in diabetic condition, insulin deficiency reverses the above said role in lipid metabolism [(186)].

Triglycerides (TG) are neutral fats, major energy reserve for the body stored at adipose tissue. Diabetic condition increases the lipolysis and produces more FFA. Increased release of FFA increases the production of ketone bodies and TG synthesis. Normally, insulin activates the enzyme lipoprotein lipase (LPL), which hydrolyses TG. But in diabetic state, LPL is not activated due to insulin deficiency, resulting in hypertriglyceridemia [(186)].