CHAPTER II
LITERATURE REVIEWS

1. Diabetes Mellitus (DM)

Diabetes mellitus (DM) is a lifelong progressive metabolic disease characterized by the high levels of blood glucose. It occurs as the result of the incapability to produce insulin or inefficiently use insulin at the maximum potential. It has been reported that diabetes mellitus, one of the challenges in this decade, affects more than 230 million people worldwide and this number is expected to reach 350 million by 2025. It has been regarded as the fourth leading cause of death by disease globally and every 10 seconds a person dies from diabetes-related causes (Kowluru and Chan, 2007). There are two main types of diabetes; 1) insulin-dependent diabetes mellitus (IDDM) or type 1 DM and 2) noninsulin-dependent diabetes mellitus (NIDDM) or type 2 DM.

1.1 Insulin-dependent diabetes mellitus (IDDM) or type 1 diabetes

Insulin-dependent diabetes mellitus (IDDM) or type 1 DM is an inflammatory-autoimmune disease resulting from a specific destruction of the insulin-producing β-cells of the islets of Langerhans of the pancreas. It has two distinct phases including 1) insulitis: in this phase, islets are invaded by a mixed population of leukocytes 2) diabetes: in this phase, most β-cells have been destroyed until they can no longer produce sufficient insulin to regulate blood glucose levels resulting in hyperglycemia. The time which requires for the progression of insulitis to diabetes mellitus depends on species. The required time for the progression in human (years) is longer than that in rodent (months). IDDM, a T-cell mediated autoimmune, is determined in part by genes in major histocompatibility complex (MHC) class II. It has been reported that MHC regulates cell-mediated adaptive immune response. MHC genes encode for the human leukocyte antigens (HLAs) on the cell surface. It helps immune cells to discriminate between normal antigens on the surface of all cells, and those that are foreign and potentially dangerous. Defects of MHC genes lead to autoimmune disorders in which the body fails to recognize self-antigens such as diabetes mellitus. It has been reported that both the defects of MHC and environmental factors such as viruses, toxins and diet can increase the genetic susceptibility which in turn triggers the release of autoantigen from β-cells.

Autoantigens released from β-cells are processed by antigen-presenting cells (APCs) are presented to helper T cells (Th cells) in association with MHC class II molecules This event induces the release of interleukin-12 (IL-12) from APCs which in turn activates TH1- type CD4+ T cells giving rise to the breakdown of immune balance between effector and regulatory cells. TH1 cells produce IL-2, which activates β-cell –specific precytotoxic T cells (Pre CTL) to become cytotoxic (CTL), and IFN-γ, which may induce the conversion of macrophages (MØ) to cytotoxic macrophages. These cytotoxic macrophages release b cell–cytotoxic cytokines including IL-1b, TNF-a, and IFN-γ, and free radicals. TH1 cells also secrete cytokines which directly induce cytotoxicit to β-cells. The β-cell antigenspecific CD8+ cytotoxic T cells (CTL) recognize antigens expressed on β-cells in association with MHC class I molecules. These CTLs release granzyme and perforin (cytolysin), which are toxic to β-cells. Fas- and TNFR-mediated apoptosis are also involved in β-cell destruction. Therefore, macrophages, T cells, and cytokines synergistically act to destroy β-cells as shown in figure 2-1.

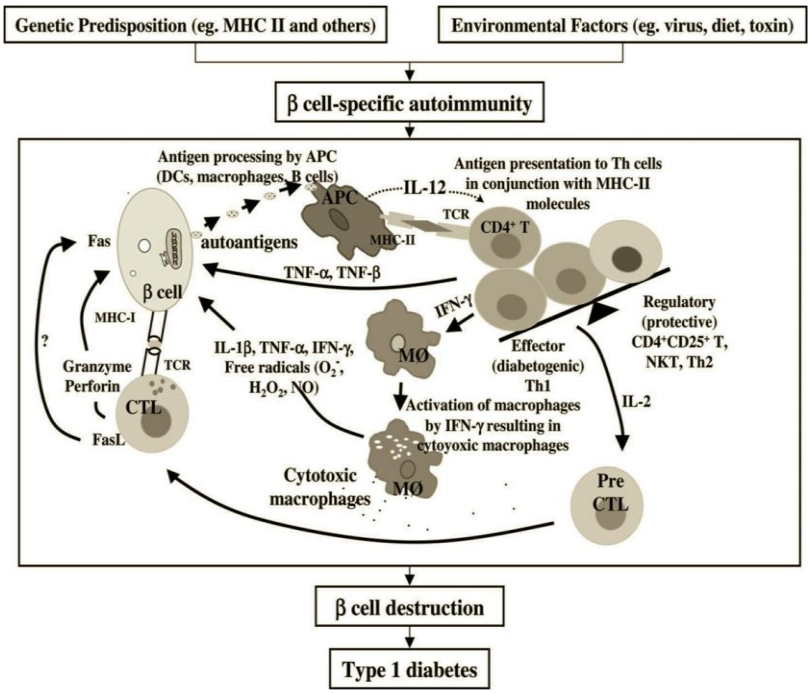

Figure 2-1 Schematic diagram illustrating underlying mechanism of β-cell destruction in IDDM (Yoon and Jun, 2005)

1.2 Noninsulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes

Noninsulin-dependent diabetes mellitus (NIDDM) or type 2 DM is characterized by the following three disorders: 1) peripheral resistance to insulin, especially in muscle cells; 2) increased production of glucose by the liver; and, 3) altered pancreatic insulin secretion. Firstly, the insulin resistance of tissue occurs and follows by the impairment of insulin secretion. Although pancreas still produces insulin, the released insulin cannot be used properly at the cellular level. Due to the insulin resistance, glucose cannot enter the target cells leading to the accumulation of glucose in the blood stream or hyperglycemic condition. Since the elevation of blood glucose is a key factor to stimulate an increase in insulin production by the pancreas the excessive insulin production (hyperinsulinemia) is observed in type 2 DM.

Type 2 DM, a multifactorial disease, is under the influence of genetic factors associating with the impaired insulin secretion and insulin resistance and environmental factors such as obesity, overeating, lack of exercise and stress, as well as aging. It has been reported that the genetic abnormality in the molecules related to the regulatory system of glucose metabolism plays the important role. Numerous genes such as glucokinase genes, mitochondrial genes, and insulin receptor genes are proposed to be the cause of Type 2 DM. Aging, obesity, insufficient energy consumption, alcohol drinking, smoking, etc. are independent risk factors of pathogenesis of obesity which in turn gives rise to a decrease in muscle mass and induces insulin resistance (Kaku, 2010).

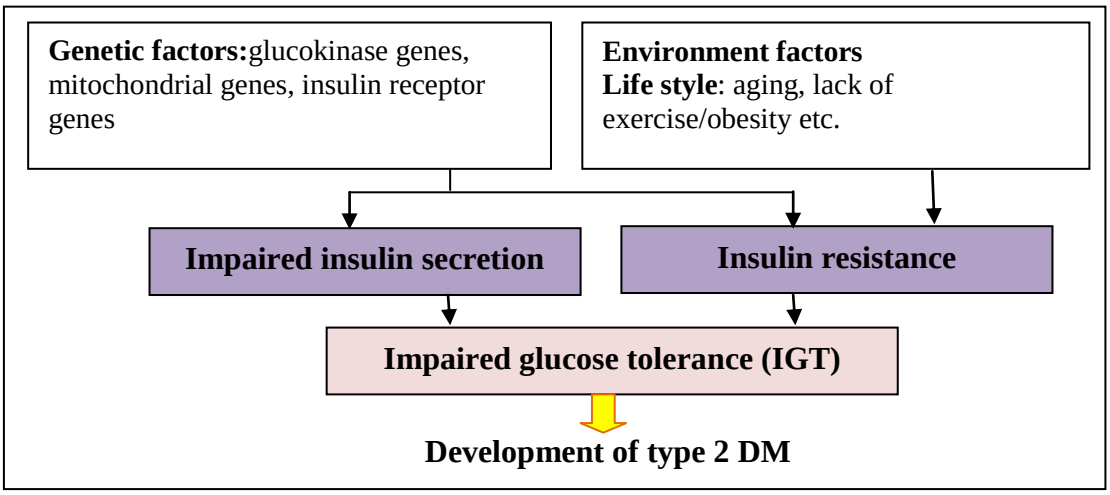

Figure 2-2 Pathophysiology of Type 2 diabetes mellitus

2. Diabetic Complications

2.1 Diabetic neuropathy

Diabetic neuropathy (DN) is a chronic diabetes complication commonly found in both Type 1DM and Type 2DM. It is a chronic microvascular complication affecting both somatic and autonomic peripheral nerves. DN has been defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes (Boulton *et al.*, 1998). DN often presents as an insidious and progressive disorder which begins with a long asymptomatic stage. Regarding to the morphological changes, the primary segmental demyelination of long axons,an axonal degeneration, a decrease density of small unmyelinated fibers, a paranodal anarchic regeneration processes, and Waller's degeneration are observed (Boulton, 2007). There are many types of neuropathy with varying clinical presentations. Peripheral neuropathy can manifest either with painful or painless symptoms or both. The two most common types of diabetic neuropathies associated with pain are acute sensory neuropathy and chronic sensorimotor neuropathy. Acute sensory neuropathy presents with either acute or subacute onset characterized by severe sensory symptoms, usually with a few, if any, clinical signs. It is usually associated with hyperglycemia or intensification of glycemic control and may gradually lessen as euglycemia is obtained. Chronic sensory-motor neuropathy is the most common form of diabetic peripheral neuropathy, associated with symptomatic pain and clinical signs of neuropathy.

2.2 Diabetic cataract

Cataract is a major cause of blindness in the world. Over 25 million adults and children suffer from cataract induced blindness. Approximate 90% of these patients are from the developing countries. The number of people with cataracts is expected to be double by the year 2020 both by the increased population and the by the increased population over 65 in the developing countries (Obrosova *et al.*, 2010). Cataract is the cloudy of the natural lens, which are the part of the eye playing an important role on the focusing activity of light in order to produce a clear and sharp image. There are 3 main types of cataract in diabetic patients including 1) Nuclear cataract, the most commonly found age-related cataract, which shows a gradual yellow cloudiness and hardening of the central part of the lens called the nucleus.

2) Cortical cataract which shows the cloudy opacity in the cortex of the lens which consists of the peripheral, or outer part, of the lens. This type of cataract is the most common form of senile cataract. It usually begins as whitish, wedge-shaped opacities or streaks on the outer edge of the lens cortex. As it slowly progresses, the streaks extend to the center and interfere with light passing through the center of the lens. Thus, the light is scattering when it hits the spoke-like opacities. 3) Posterior subcapsular cataract, an opacity started to develop on the back surface of the lens, directly underneath the lens capsular bag that houses the lens. This type of cataract induces light sensitivity, blurred near vision, glare and halos around lights at night.

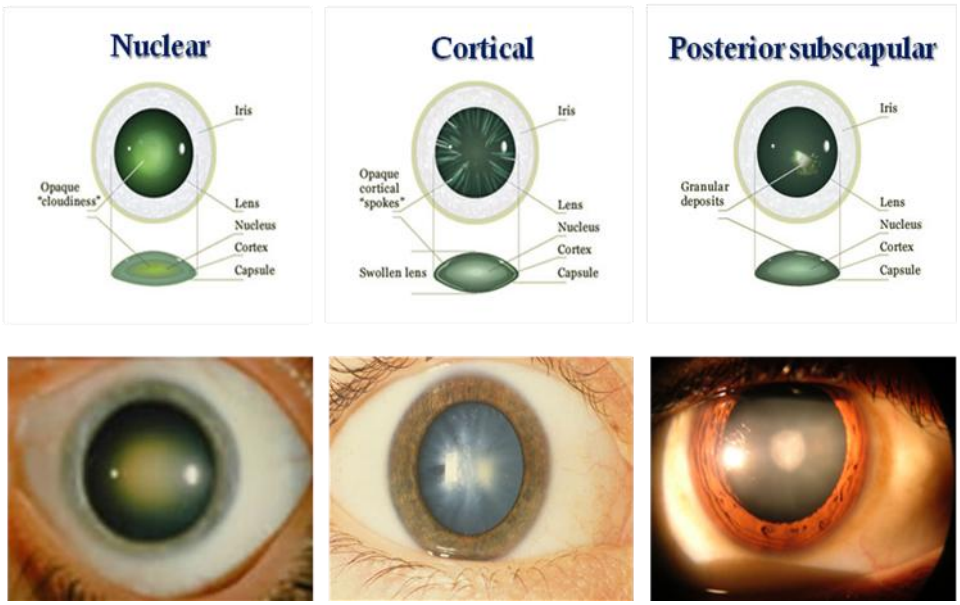

Figure 2-3 Classification of cataract according to the location of the opacity

3. Mechanisms and Pathophysiology of Diabetic Complications

Complications of diabetes are the major cause of morbidity and mortality in persons with type 1 and 2 diabetes. In both cases, the reduction of glucose uptake into muscle and adipose tissue gives rise to chronic extracellular hyperglycemia, which results in tissue damage and pathophysiological complications including retinopathy and cataract formation, nephropathy, peripheral nerve damage, heart disease and atherosclerosis. One of the most explored hypotheses to explain the onset of complications is a hyperglycemia-induced increase in oxidative stress. Oxidative

stress occurs when the rate of oxidant production (reactive oxygen species: ROS) exceeds the rate of oxidant scavenging. Increased glucose flux both enhances oxidant production and impairs antioxidant defenses by multiple interacting pathways including polyol pathway, advance glycation end products (AGE), glucose autoxidation, xanthine oxidase (XO) and nitric oxide synthase (NOS) as shown in figure 2-4

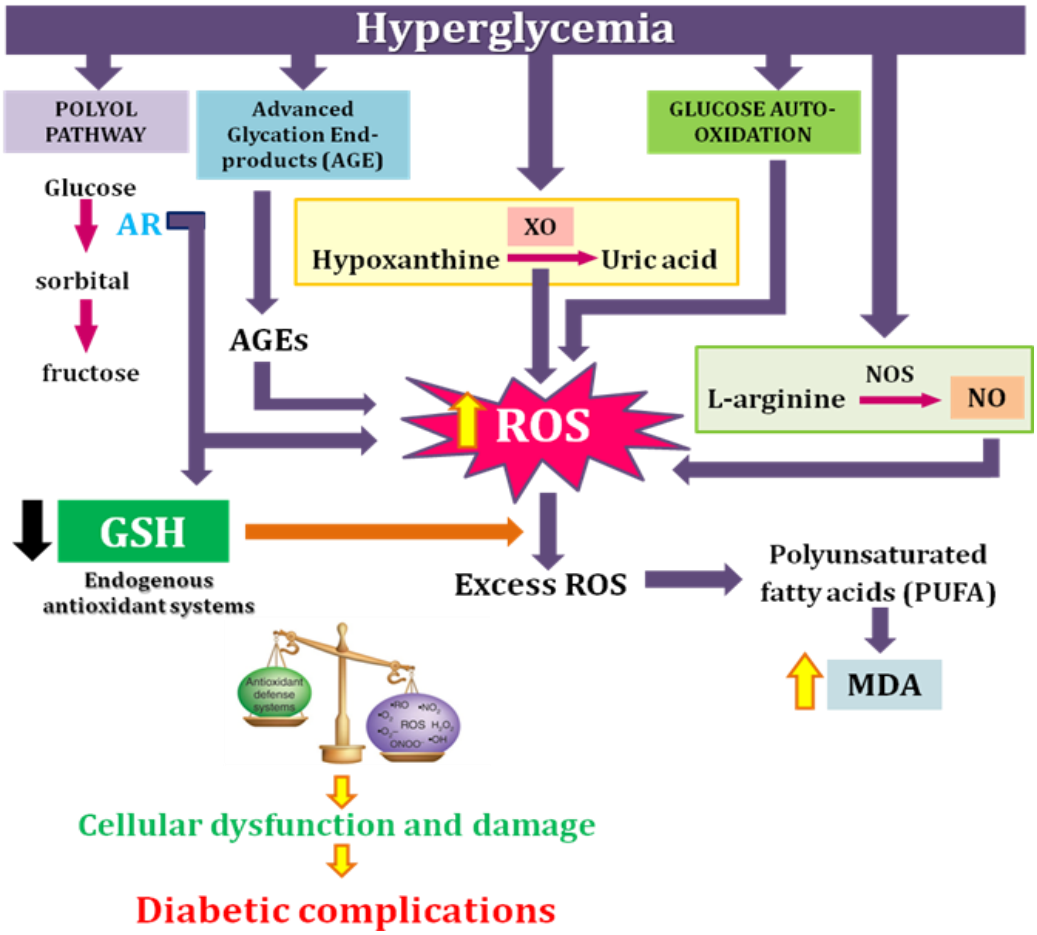

Figure 2-4 Schematic diagram illustrating multiple interacting pathways that resulting in the enhanced reactive oxygen species (ROS) which in turn induces the diabetic complications

3.1 Polyol pathway

The polyol pathway or sorbitol-aldose reductase pathway is a two-step metabolic pathway in which glucose is reduced to sorbitol and converted to fructose. This system usually becomes active when intracellular glucose levels are elevated.

Aldose reductase (AR), the first and rate-limiting enzyme in the pathway, reduces glucose to sorbitol using NADPH as a cofactor. Then sorbitol is metabolized to fructose by sorbitol dehydrogenase by using NAD^+as co-factor. The polyol pathway is the major source of diabetes-induced oxidative stress in lens and the nerve. Three potential mechanisms have been proposed to explain how the polyol pathway induces the excess oxidative stress as shown in figure 1-5. Firstly, the depletion of NADPH induced by the reaction via aldose reductase enzyme gives rise to the decreased glutathione reductase, an important antioxidant enzyme. Under hyperglycemic condition, approximate 30% of the glucose is channeled into the polyol pathway (Cheng and Gonzalez, 1986) causing a substantial depletion of NADPH and consequently induces a significant decrease in the GSH level. Thus, during hyperglycemia AR activity diminishes the cellular antioxidant capacity. Second, the elevation of NADH, a substrate for NADH oxidase to generate ROS, occurs during the oxidation of sorbitol to fructose by SDH.(Morre *et al.*, 2000). Thirdly, the increased oxidative formation via the enhanced advance glycation end products (AGE) formation in the polyol pathway.

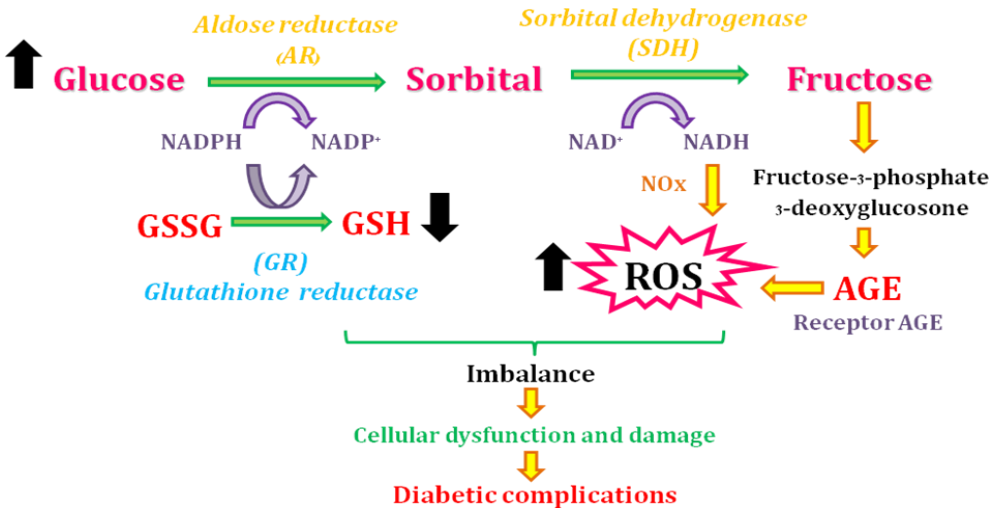

Figure 2-5 Schematic diagram illustrating polyol pathway-induced oxidative stress

3.2 Advance glycation end products (AGE)

Glucose can react directly with free amine groups on protein, DNA and lipids via Schiff base formation. The Schiff base is then reduced to an Amadori product. Then, the subsequent oxidations and crosslinking occur, Giving rise to the formation of advance glycation end products (AGE) (Singh *et al.*, 2001). AGE formation is dependent on oxidative processes (Chellan and Nagaraj, 2001; Jain and Palmer, 1997) and can create ROS (Akagawa *et al.*, 2002; Ortwerth *et al.*, 1998) through the Maillard reaction. In addition, glycated proteins also increased affinity for metals and increased the production of via Fenton reaction. AGEs can propagate oxidative stress in the cells and fluids in which they are produced. Extensively glycated proteins are also less susceptible to degradation by the multicatalytic proteasome leading to their intracellular accumulations. Data obtained from STZ-induced diabetic rats STZ-induced diabetic rats and patients with IDDM (Candiloros *et al.*, 1996) and NIDDM (Niwa *et al.*, 1997) IDDM (Candiloros *et al.*, 1996) and NIDDM (Niwa *et al*., 1997) showed that AGE are found in almost all tissues. Since AGE plays a pivotal role on the development of diabetic complications, AGE inhibitors have been tested clinically (Metz *et al*., 2003; Stitt *et al*., 2002). AGE inhibitor such as aminoguanidine and pyridoxamine, work to trap glycoxidation intermediates and impede crosslink formation. Many AGE inhibitors also possess antioxidant properties and can prevent lipid oxidation (Giardino *et al*., 1998; Ihm *et al*., 1999; Jakus *et al*., 1999; Kedziora-Kornatowska *et al*., 1998). AGE formed in plasma and on the surface of cells can bind to receptors known as RAGE (receptors for advanced glycation end products). These types of receptors are members of the immunoglobulin family of cell surface receptors and are pro-inflammatory found in the endothelium, retina, smooth muscle cells, monocytes, and neurons. After binding to RAGE, AGE stimulates signaling pathways that activate NADPH oxidase, which produces ROS (Wautier *et al*., 2001) and NFκB, a nuclear transcription factor.

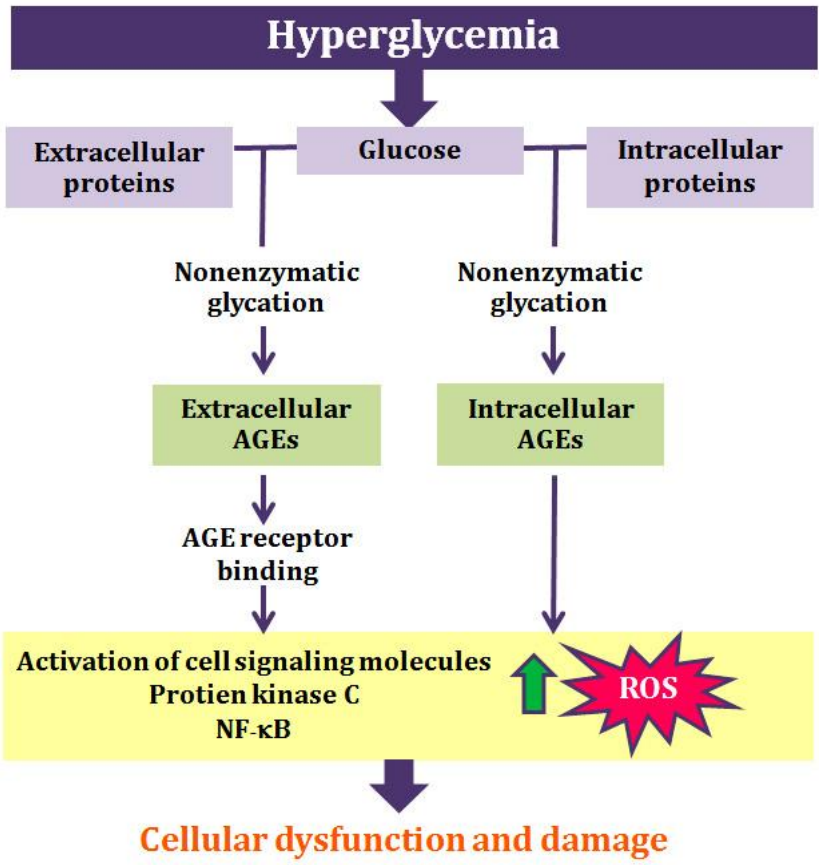

Figure 2-6 Schematic diagram illustrating advance glycation end products (AGE) pathway

3.3 Glucose autoxidation

The concept of glucose autoxidation and the consequent excess generation of ROS in relation to diabetes were proposed as early as 1987 by Wolff and Dean (Wolff and Dean, 1987). Although its relevance to defective β-cell function has not received a great deal of investigation. Glucose and many of its metabolites can react with hydrogen peroxide in the presence of transition metals such as Fe^{2+} and Cu^{2+} to form hydroxyl radical (•OH), the most reactive ROS (Robertson *et al.*, 2003; Wolff *et al.*, 1991). Most of the data supporting this hypothesis are indirect. For example, many studies demonstrate that metals are required for the induction of glucose-induced ROS production. Protein fragmentation induced by high concentrations of glucose is suppressed by metal chelators, such as diethylenetriaminepenta-acetic acid (Hunt and Wolff, 1991), whereas Cu^{2+} enhances the effect. Sorbitol, considered

an OH• scavenger, greatly reduces protein fragmentation in the presence of both glucose and Cu^{2+}. However, the most direct evidence in support of this hypothesis comes from the measurement of O_2 generation in endothelial cells. Both high glucose and 3-*O*-methylglucopyranose (3-OMG), a nonmetabolizable glucose manalog, cause an increase in O2•– production, indicating that metabolism of glucose is not necessary to induce oxidative stress. The increase in O2 •– from glucose is inhibited by iron chelation with desferral whereas the inhibition of enzymatic sources of RO such as cyclooxygenases, lipoxygenases, cytochrome P450, and nitric oxide synthase, have no impact. Because the effect of these inhibitors on O2 •– generation induced by 3-OMG was not examined, no conclusion can be made concerning to the source of ROS during treatment of this analog. These data support a role for metal-catalyzed glucose oxidation in the production of ROS (Wolff and Dean, 1987).

3.4 Xanthine oxidase (XO)

Xanthine dehydrogenase and xanthine oxidase are two molybdenum-containing flavoenzymes formed from the same gene product, the activity of which is collectively termed xanthine oxidoreductase. Xanthine dehydrogenase is an enzyme that catalyzes the oxidation of hypoxanthine to uric acid, using nicotinamide adenine dinucleotide (NAD+) as a cofactor. After the proteolytic cleavage and sulfhydryl oxidation of this enzyme, xanthine oxidase is formed. Xanthine oxidase catalyzes a similar reaction which substituting molecular oxygen as the electron acceptor. Superoxide, hydrogen peroxide, and hydroxyl radical are produced as byproducts of the xanthine oxidase reaction. Although xanthine oxidase activity is undetectable in normal endothelial cells (Paler-Martinez *et al*., 1994), it has been proposed to be a major source of ROS in atherosclerosis (Berman and Martin, 1993), ischemia-reperfusion injury (Friedl et al., 1990; Salas *et al*., 1999), and diabetes mellitus (Butler *et al*., 2000; Desco *et al*., 2002) Treatment of NIDDM patients with the xanthine oxidase inhibitor, allopurinol, reduces levels of lipid oxidation in plasma and improves blood flow and endothelial cell function (Butler *et al*., 2000). Increased xanthine oxidase activity has been demonstrated in the liver of STZ-treated rats (Desco *et al*., 2002) whereas allopurinol inhibits aortic ring O2 •- production and the oxidation of glutathione and lipid glutathione and lipid in the blood, liver, and heart. Atherosclerosis a major complication of diabetes mellitus complication of diabetes mellitus may probably develop via the same pathways.

3.5 Nitric oxide synthase (NOS)

Nitric oxide (NO) is an intracellular second messenger that modulates vascular tone and cardiac and neural function. It is produced by constitutive and inducible nitric oxide synthase (NOS), dimeric, zinc-cluster-containing enzymes. According to its function, O2 is incorporated into L-arginine and requires flavin, NADPH, heme, and tetrahydrobiopterin as cofactor (Massion *et al*., 2003; Zou *et al*., 2002). NOS are expressed in many tissues including cardiac and neuronal tissues and the endothelium. NOS has been shown to produce free radicals during the catalytic cycle that may leak from the active site due to enzyme uncoupling (Rosen *et al*., 2002). NOS can also transfer electrons directly to O2 to form O2 •–. In addition, NO can react with O2•– to form peroxynitrite, a highly reactive oxidant correlated with disease states such as sepsis, inflammation, atherosclerosis, and diabetes (Zou *et al*., 2002). Peroxynitrite has been shown to react with the zinc-cluster of NOS, dissociating the monomers and uncoupling enzyme function. Therefore, formation of peroxynitrite not only depletes existing NO, but also reduces a tissue's ability to produce more NO, resulting in defective tissue function Hyperglycemia contributes to regulation of NOS expression and the production of peroxynitrite.

4. Endogenous Antioxidant System

Under normal circumstance, the generated oxidative stress is buffered by endogenous antioxidant systems (EAS). EAS is divided in to 2 systems consisting of the enzymatic and non enzymatic systems. The enzymatic system comprises of the important enzymes including Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), Glutathione reductase (GR). The endogenous non-enzymatic antioxidants, which produced by metabolism in the body like lipoic acid, glutathione, L-ariginine, coenzyme Q10 or ubiquinone, melatonin, uric acid, bilirubin, metal-chelating proteins such as transferrin, vitamins E, C and beta-carotene (Panda, 2012). The imbalance between the oxidative stress formation and antioxidants will give rise to the pathophysiology of various conditions including diabetes mellitus**.**

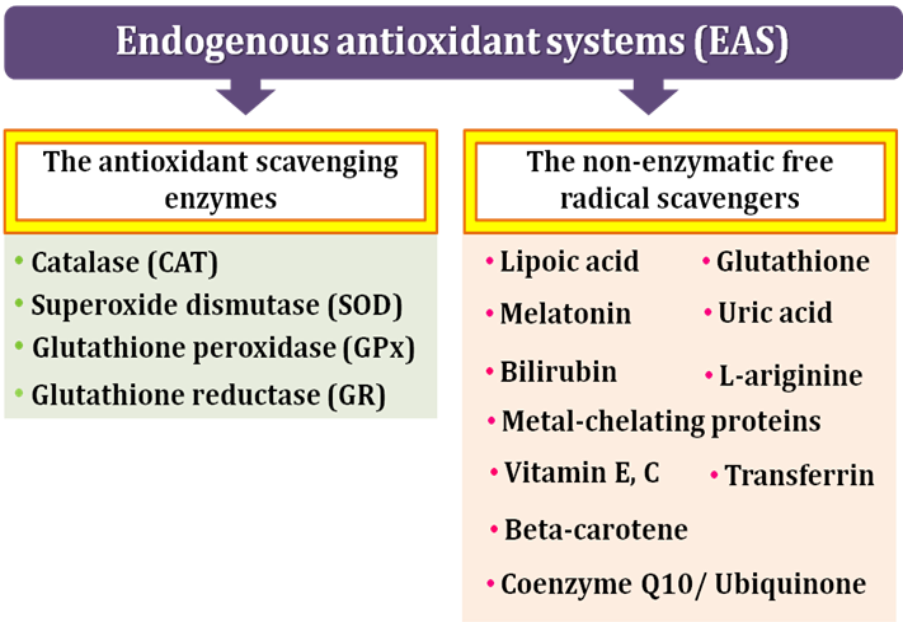

Figure 2-7 Endogenous antioxidant systems

5. Peripheral Nerve Injury

Peripheral nerve injury can occur at various sites (Campbell and Meyer, 2006) as shown in figure 2-8 as following 1) Spontaneous neural activity and ectopic sensitivity to mechanical stimuli develops at the site of nerve injury. 2) The expression of different molecules in the dorsal root ganglion of the injured nerve is up- or downregulated, reflecting the loss of trophic support from the periphery. Spontaneous neural activity develops in the dorsal root ganglia. 3) The distal part of the injured nerve undergoes Wallerian degeneration, exposing the surviving nerve fibers from uninjured portions of the nerve to a milieu of cytokines and growth factors. 4) Partial denervation of the peripheral tissues leads to an excess of trophic factors from the partail denervated tissue leading to the sensitization of primary afferent nociceptors. 5) The expression of different molecules in the dorsal root ganglion of the uninjured nerve is up- or downregulated, reflecting the enhanced trophic support from the periphery. 6) The development of sensitization of postsynaptic dorsal horn cells leading to an augmentation of the response to cutaneous stimuli. 7) Activated microglial cells contribute to the development of this dorsal horn sensitization. 8) Changes in descending modulation of dorsal horn neurons also may contribute to the enhanced responsiveness of dorsal horn neurons.

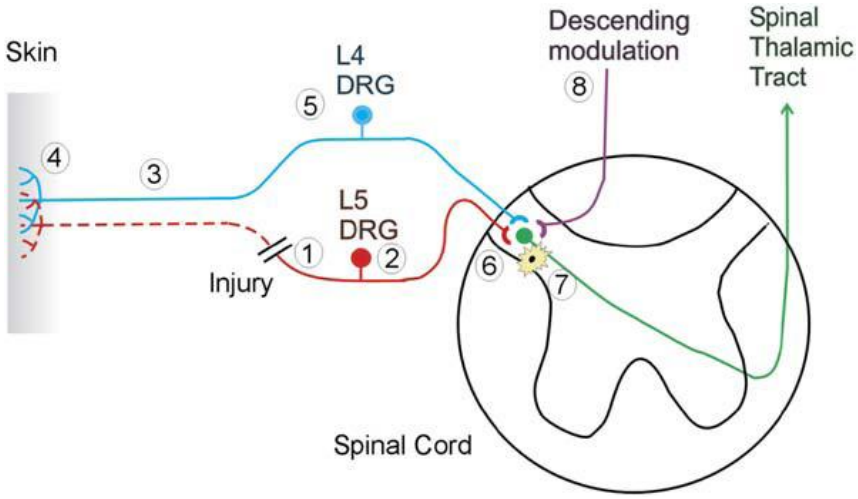

Figure 2-8 Schematic diagram showing the possible site of peripheral nerve injury (Campbell and Meyer, 2006)

6. Nerve Injury Classifications

The severity of the nerve injury is varied and can be classified according to Seddon's classification in three types: neuropraxia, axonotmesis, and neurotmesis as shown in figure 2-9. The lowest degree of nerve injury in which the nerve remains intact but signaling ability is damaged is called neurapraxia. The second degree in which the axon is damaged but the surrounding connecting tissue remains intact is called axonotmesis. The last degree in which both the axon and connective tissue are damaged is called neurotmesis. Some investigators also classified nerve injury further into five categories. A first-degree injury is neurapraxia and a second-degree injury is equivalent to axonotmesis. Third-degree nerve injuries occurs when there is a disruption of the axon (axonotmesis) and also partial injury to the endoneurium. This categorization places a third-degree between previous axonotmesis and neurotmesis. Depending on the extent of the endoneurial damage, functional recovery may be possible. Neurotmesis is divided into fourth and fifth degree injuries. In a fourth-degree injury, all portions of the nerve are disrupted except the epineurium. Recovery is not possible without surgical intervention. Similarly, a fifth-degree injury involves complete severance of the nerve.

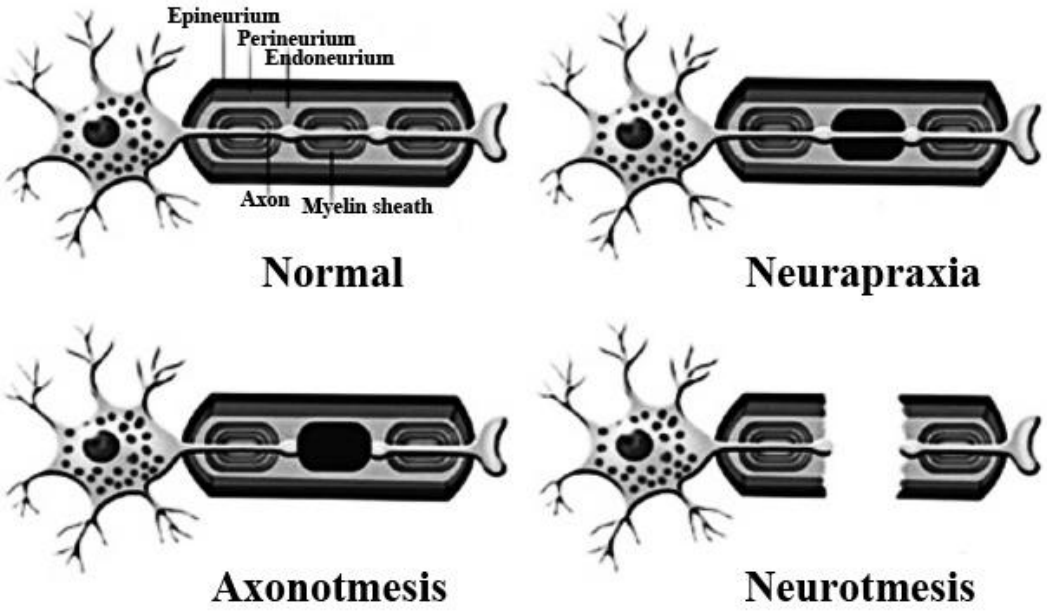

Figure 2-9 The classification of peripheral nerve injury according to Seddon's Classification (Martins *et al.*, 2013)

7. Neuropathic Pain

Neuropathic pain is a complex chronic unpleasant sensation and emotional experience associated with the damage to or dysfunction of the peripheral or central nervous system, rather than stimulation of pain receptors. Nerve injury usually produces a change in nerve function both at the site of injury and areas around the injury. The symptoms of neuropathic pain can manifested as hyperalgesia and allodynia as shown in figure 2-10. It has been well established that as hyperalgesia is an increased sensitivity to normally external painful stimuli (Ringkamp *et al.*, 1999) whereas allodynia is a painful response to stimulus which does not normally provoke pain (Merskey *et al.*, 1986).

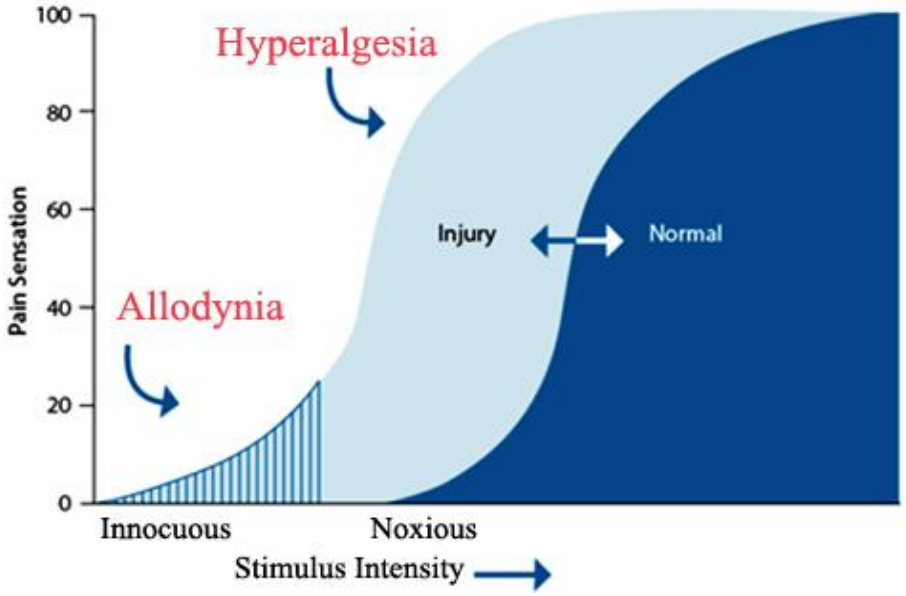

Figure 2-10 Common symptoms of painful diabetic neuropathy including hyperalgesia and allodynia

8. Plants and Nutritional Supplements

8.1 *Zea mays* Linn. var. *ceratina* Kulesh (Purple waxy corn)

Purple waxy corn, known as *Zea mays* L. is a plant in a family of Poaceae. Purple waxy corn is known as a significant source of natural colorant due to high anthocyanin concentration. The major anthocyanin was cyanidin 3-*O*-β-D-glucoside. The cyanidin derivatives constitute around 70% in purple corn seed. The average anthocyanin content of whole purple wax corn was 1640 mg/100g fresh weight (Cevallos-Casals and Cisneros-Zevallos, 2003). Recently, anthocyanins have been reported to have various biological activities, such as antioxidant (Solihah *et al.*, 2012)anti-microbial (Zhao *et al.*, 2009), anti-hypertensive (George *et al.*, 2013), anti-proliferation capacity (Zhao *et al.*, 2009) and anticancer activities (Tian *et al.*, 2013). In addition, purple waxy corn is reported to prevent diabetic (Kim *et al.*, 2013; Li *et al.*, 2012). No acute toxicity was found from purple corn extract following oral administration in male albino rats at doses of 446.43-3571.43 mg/kg. The oral LD50 of the purple corn extract in mice was estimated to be greater than 3571.43 mg/kg (Romina and Luis, 2007).

Figure 2-11 *Zea mays* Linn. var. *ceratina* Kulesh or Purple waxy corn

8.2 *Zingiber officinale* Roscoe (Ginger)

Ginger or *Zingiber officinale* Roscoe is a well known and widely used herb, especially in Asia. The main constituents of ginger are Gingerol, Shagaols, Zingerone and Paradol, however, the main constituents of ginger rhizome are 6-gingerol and 6-shogaol (Comell and McLachlan, 1972). It contains several interesting bioactive constituents and possesses health promoting properties. It has been reported that ginger has medicinal properties against digestive disorders, rheumatism and diabetes (Afzal *et al*., 2001). Ginger extract possesses antioxidative effect and can scavenge superoxide anion and hydroxyl radicals (Krishnakantha and Lokesh, 1993). In addition, it also possesses anti-hyperglycemic, anti-dyslipidemia effects (Akhani *et al*., 2004).

Figure 2-12 *Zingiber officinale* Roscoe or Ginger

8.3 *Morus alba* Linn (Mulberry)

Mulberry or *Morus alba* Linn is the most medicinally important plant which belongs to a family of Maraceae. It is one of conventional herbs which have been long-term used in medicine due to its chemical composition and pharmacological function. Most of the parts of mulberry plants are used as medicine in Chinese and Indian medicine. According to Zou and Chen (2003) (ZOU and Wu., 2003) mulberry leaves contain N-containing sugars, rutin, quercetin, volatile oil, amino acid, vitamins and microelements which exhibit many pharmacological activities such as hypoglycemic activity. In addition, mulberry plants also contains many active compounds possessing antioxidant activity such as polyphenols, carotenoids and vitamin A, C, E (Andallu *et al*., 2009). The mentioned compounds can increase the body's antioxidant status and regulate low-density lipoprotein (LDL) oxidation through different mechanisms. It is found that mulberry fruits strengthen the body protective system and decrease the oxidative stress in red blood cells (RBCs) of diabetic rats (Hong JH. et al., 2004). The main flavonol glycosides in the mulberry leaves are quercetin (6-malonylglucoside) and rutin (Katsube *et al*., 2006). It has been reported that these substances also exhibit potent antioxidative effect (Kim *et al*., 1999).

Figure 2-13 *Morus alba* Linn. or Mulberry

8.4 *Allium cepa* Linn. (Shallot or red onion)

Shallot or red onion or *Allium cepa* Linn is a versatile vegetable used as ingredient in many Asian dishes and also used as medicinal plants such as anti-diabetes (El-Demerdash *et al*., 2005). Onion consumption provides benefit for diabetic conditions. Its bulbs are a major source of quercetin, a strong antioxidant flavonoid (Zielinska *et al*., 2008) which alleviates oxidative stress induced by chemicals or drugs in diabetic rats induced by streptozotocin (Mahesh and VP., 2004). Consumption of 3% onion powder diet also reduced hyperglycemia, circulating lipid peroxides, and blood cholesterol (LDL-VLDL exclusively) (Suresh and K., 1997). Moreover, quercetin , the main component in red onion also significantly increases lymphocytes protects against DNA damage from hydrogen peroxide at the tissue level (Lean *et al*., 1999).

Figure 2-14 *Allium cepa* Linn. or Shallot or red onion

8.5 *Carica papaya* Linn (Papaya)

Papaya or *Carica papaya* Linn is a fruit bearing tree grown in a number of tropical regions, including Hawaii, Latin America, the West Indies, India, Indonesia, South Africa, Philippines and Thailand. Edible portions of the plant include the fruit and leaves, both of which contain variable amounts of carbohydrates, fiber, calcium, phosphorous, iron, carotene, thiamine, riboflavin, niacin, ascorbic acid, tryptophan, methionine, lysine, lycopene, magnesium, phosphoric acid, vitamins,

carotenoids, and proteolytic enzymes. Several lines of evidence have demonstrated the safety and antioxidative stress potential of the juice of *Carica papaya* (Mehdipour *et al*., 2006). It is found that the unripe papaya pulp could lower blood sugar in experimental animals. In addition, fermented papaya preparation which has been used as a food supplement also shows anti-inflammatory, antioxidant and immunostimulatory actions and has the potential to protect against cell damage in diabetic condition (Aruoma *et al*., 2010).

Figure 2-15 *Carica papaya* Linn. or Papaya