Review of Literature

2.0 REVIEW OF LITERATURE

The review of literature pertaining to the present study entitled "**Antidiabetic and Antioxidant effect of *Aristolochia bracteolata* in Streptozotocin induced Diabetic rats**" is discussed under the following headings.

2.1. Oxidative stress

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2.2.1 Reactive Oxygen species

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2.4.1. Enzymic antioxidants

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- **Superoxide dismutase**
- **Glutathione-S-transferase**

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- **Ascorbic acid**
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- **Reduced Glutathione**

2.5 Phytochemical screening of Medicinal plants

2.6 Medicinal plant selected for the study *Aristolochia bracteolata*

Let food be thy medicine and medicine be thy food." The desire for a long and healthy life has been a catalyst for the public's increasing interest in dietary antioxidants. **"...prevention, prevention, prevention' is the nutrition mantra for successful aging** (www.kraftnutrition.com , 2008). Various components of foods have clearly established strong links with human health and it is learnt that their deficiencies provoke diseases. The natural products releasing such superb active components are known as nutraceutical foods. Each day, we encounter multiple environmental exposures, such as certain chemicals, ultraviolet rays and/or air pollution, which can potentially cause damage to healthy cells through the process of oxidation (Ali *et al.*, 2009).

Excessive generation of oxidants, induced by various stimuli and which exceed the antioxidant capacity of the organism, leads to a variety of pathophysiological processes such as inflammation, diabetes, genotoxicity, and cancer. In diabetes, there is an increased oxidative stress which co-exist with reduction in the antioxidant status (Adedapo *et al.*, 2009). Free radicals which have one or more unpaired electrons are produced in normal or pathological cell metabolism and are overproduced in pathological conditions, causing oxidative stress. An adequate intake of natural antioxidants could protect macromolecules against oxidative damage in cells (Khanavi, *et al.*, 2009).The potentially toxic and beneficial properties of prooxidant and antioxidants have made them the focus of many studies. Pro-oxidants may represent a threat to health, whereas antioxidants may counteract these effects by scavenging pro-oxidants (Kool *et al.*, 2007).

2.1 Oxidative stress

Oxidative stress is defined as a significant imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses. Oxidative stress is associated with the peroxidation of cellular lipids, which is determined by measurement of TBA-reactive substances. Lipid peroxidation in biological systems has long been thought to be a toxicological phenomenon, resulting in pathological consequences (Wu *et al.*, 2004).

Oxidative stress induced DNA damage

The oxidative damage to mitochondrial DNA is well known to occur in all aerobic cells, ROS induces DNAdamage in the form of modification of all bases (primarily guanine via lipid peroxyl or alkoxyl radicals), production of base-free sites, deletions, frame shifts, DNA cross-links through covalent binding to MDA, and chromosomal rearrangements. Oxidative stress has also been associated with high frequencies of single and double DNA strand breaks (Maneesh *et al.*, 2006).

2.2 Free Radicals

An ideal "**golden triangle**" of oxidative balance, in which oxidants, antioxidants and biomolecules are placed. In a normal situation, a balanced-equilibrium exists among these three elements. Excess generation of free radicals may overwhelm natural cellular antioxidant defenses leading to oxidation and further contributing to cellular functional impairment (Fusco *et al.*, 2007).Free radicals and oxidants play a dual role as both toxic and beneficial compounds, since they can be either harmful or helpful to the body. The term "free radicals" designates a family of compounds characterized by great reactivity due to the unpaired electron in the outer orbital. To this group belong reactive oxygen species (ROS) and reactive nitrogen species (RNS). (Huy *et al.*, 2008).

2.2.1 Reactive oxygen species

ROS are continuously produced during normal physiologic events and can easily initiate the peroxidation of membrane lipids, leading to the accumulation of lipid peroxides. ROS are also capable of damaging crucial biomolecules such as nucleic acids, lipids, proteins and carbohydrates and may cause DNA damage that can lead to mutations (Ak *et al.*, 2008). Reactive oxygen species (ROS) react easily with free radicals to become radicals themselves. ROS are

various forms of activated oxygen, which include free radicals such as superoxide anion radicals (O_2) and hydroxyl radicals (OH), as well as non-free radical species (H_2O_2) and the singled oxygen (Ceriello, 2005). ROS may directly lead to lipid peroxidation, and the production of highly reactive aldehyde species exerts further detrimental effects. Most free radicals are highly reactive and short lived. Free radical mediated lipid peroxidation has recently been proposed as a basic mechanism of injury responsible for a wide variety of diseases (Khanna *et al.*, 2005).

Endogenous sources and characteristics of oxygen radicals

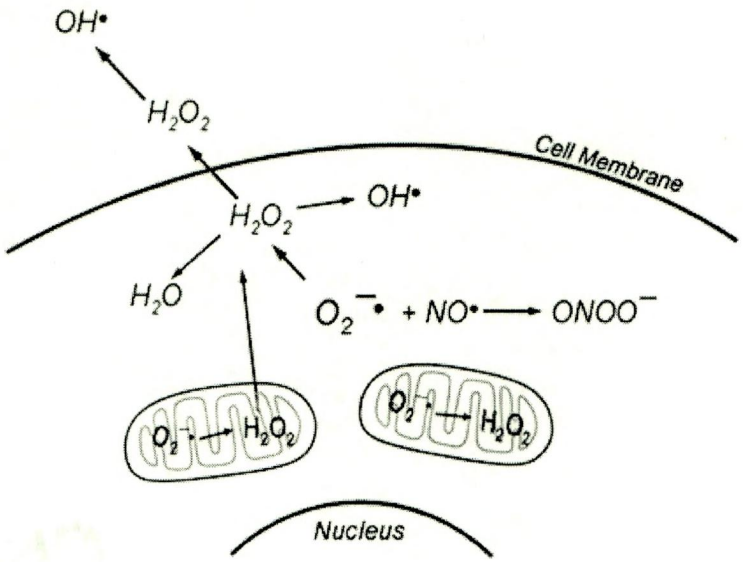
Exposure to radiation from the environment and manmade sources is the exogenous source for the formation of oxidants. Other than the exogenous sources, enzymatically or non-enzymatically mediated electron transfer reactions are the endogenous source of free radicals produced in the cells

- Consumption of O_2 by mitochondria during normal aerobic respiration to produce H_2O. Oxidants such as oxygen free radical, H_2O_2 and hydroxyl radical are the byproducts of this process
- Destroying of bacteria and virus infected cells by phagogytic cells releases nitric oxide, hydrogen peroxide and oxygen free radical.
- Degradation of fatty acids and other molecules by peroxisomes, the organelles produce hydrogen peroxide as byproduct, which is then degraded by catalase. Oxidants produced during the course of p. 450 degradation of natural toxins (Krishnaiah *et al* 2007).

Physiologic and Pathologic ROS production

Under normal circumstances, cells are able to balance the production of oxidants and antioxidants, resulting in redo equilibrium. Oxidative stress occurs when cells are subjected to excess levels of ROS or as a result of depletion of antioxidant defenses. Over-production of ROS may induce the opening of the membrane permeability transition pore in mitochondria with

the release of cytochrome c and other apoptogenic factors, which ultimately lead the cell into dysfunction, apoptosis, and/or necrosis (Korkmaz *et al.,* 2008).



Formation of intracellular reactive Oxygen and Nitrogen species.

Mitochondria are particularly vulnerable to oxidative damage because they are constantly exposed to high levels of ROS Mitochondrial DNA has been shown to undergo oxidative damage. In addition to lipid peroxidation, protein oxidation and nitration results in altered function of many metabolic enzymes in the mitochondrial matrix as well as those comprising the electron transport chain (Szeto *et al.,* 2006).

ROS and other pro-oxidants

ROS and other pro-oxidants can interact with virtually any macromolecule of biological interest. ROS and reactive pro-oxidants can elicit peroxidation of lipids and their subsequent degradation and fragmentation. When interacting with proteins, ROS may lead to:

(a) oxidation of critical amino acid residues, for example, the thiol group of cysteine;

(b) formation of intramolecular disulfide bonds (-S-S-);

(c) thiol/disulfide changes leading to either formation or disruption of inter-molecular disulfide bonds between homo- or hetero-dimers;

(d) formation of di-tyrosine and protein cross-linking; (www.healthchecksystems.com)

ROS and RNS can react with cellular lipids directly or indirectly, generating a spectrum of products, many of which contain functional groups capable of modifying proteins. Oxidized lipids can activate cell-signalling pathways in three different ways:

- by non-covalent mechanisms involving binding to a protein receptor;
- covalent pathways leading to direct protein modification by the oxidized lipids
- the activation of pathways leading to calcium influx and intracellular ROS/RNS formation (Zmijewski *et al.*, 2005).

Hydrogen peroxide (H_2O_2)

H_2O_2 represents a two-electron reduction state of molecular oxygen and originates mainly from enzymatic dismutation catalysed by superoxide dismutase (SOD) isoforms.

$$2\ O_2.- + 2H \rightarrow H_2O_2 + O_2$$

H_2O_2 can also originate from non-enzymic dismutation of O_2•- as well as from direct reduction of O_2. Major features of H_2O_2 include: it can easily diffuse across biological membranes; it is a non-radical potent oxidizing agent; in aqueous solutions it can oxidize or reduce several inorganic ions; it can usually be removed by either catalase or glutathione peroxidase; it can give rise to the very reactive and damaging •OH when interacting with O_2• (Novo and Parola, 2008).

Singlet oxygen

Singlet oxygen is generated in the skin by ultraviolet radiation. It is a high energy form of oxygen and is known as one of the ROS. Singlet oxygen induces hyperoxidation and oxygen cytotoxicity and decreases antioxidant activity (Hazara *et al.*, 2008).

Superoxide

Superoxide anion, arising either through metabolic processes or following oxygen "activation" by physical irradiation, is considered the "primary" ROS, and can further interact with other molecules to generate "secondary" ROS, either directly or prevalently through enzyme- or metal-catalyzed processes. The production of superoxide occurs mostly within the mitochondria of a cell (Valko *et al.*, 2006).

Hydroxyl radical

Hydroxyl radical has a very short half-life (10^{-9} s) and high reactivity. As such, in biological systems it does not diffuse from the site of generation and can rapidly damage any surrounding macromolecules. $OH^{\bullet}$ is widely implicated as the most potent oxidant and the major damaging species in free radical pathology (Kosem *et al.*, 2007).

Lipid peroxidation

LPO is broadly defined as "oxidative deterioration of PUFA" which are fattyacids that contain more than two carbon carbon double bonds. Lipids are highly prone to free radical damage resulting in lipid peroxidation that can lead to adverse alterations. This reaction leads to the formation of lipid radicals (L•) that, in turn, can react with available O_2 to generate lipid peroxyl radicals (LOO•). Among these, Malondialdehyde is an important reactive carbon compound which is used commonly as an indicator of lipid peroxidation (Karatas *et al.*, 2006).

2.2.2 Reactive Nitrogen Species

Reactive Nitrogen Species include free radicals like nitric oxide ($NO^{\cdot}$) and nitrogen dioxide ($^{\cdot}NO_2^{-}$). Of these reactive molecules superoxide, nitric oxide and nitrogen dioxide are the most widely studied species (Selvi *et al.*, 2007).

Nitric oxide and reactive nitrogen species

Nitric oxide (NO) is a potent pleiotropic mediator of physiological processes such as smooth muscle relaxation, neuronal signaling, inhibition of platelet aggregation and regulation of cell mediated toxicity (Sunil Kumar *et al.*, 2008). It is a diffusible free radical which plays many roles as an effectors molecule in diverse biological systems. Moreover in the pathological conditions, nitric oxide reacts with superoxide anion and form potentially cytotoxic molecules, peroxynitrite (Nagulendran., 2007).

Peroxynitrite

Peroxynitrite (ONOO-) is a strong oxidant able to react directly with thiol groups, iron-sulphurcentres and the active site -SH groups in tyrosine phosphatases. In pathological conditions, ONOO- can act either as a direct oxidizing species or indirectly by decomposing into highly reactive radicals. ONOO- can also interact with mitochondria, reaching them from extra-mitochondrial compartments or being locally produced through the interaction of NO and O_2•-. (Punitha *et al.*, 2005).

2.4 Diabetes Mellitus

Diabetes Mellitus is a complex and multifarious group of disorders that disturbs the metabolism of carbohydrates, fat and protein. It is a major endocrine disorder affecting nearly 10% of the population all over the world (Hossain *et al.*, 2007). Diabetes results from abnormal metabolism of insulin wherein insulin action is impaired or absolute insulin deficiency results in imbalance of glucose metabolism (Bhat *et al.*, 2009).

There are two types of diabetes, namely Type I and Type II. Type I diabetes accounts for 5-10% of diabetes. Type II is the most common form of the disease, accounting from 90-95% of diabetes. Type I diabetes is an autoimmune disease resulting from a specific destruction of insulin-producing ß-cells of the endocrine pancreas. Type II diabetes is non-autoimmune in

nature and is marked by insulin resistance associated with inadequate insulin secretion. Reduction in ß-cell glucose sensitivity after chronic exposure to hyperglycemia and/or islets death are the two causes of the reduction in insulin secretion in type 2 diabetes (Khalidi *et al.*, 2009).

Juvenile onset diabetes is also referred as Type I or Insulin dependent diabetes mellitus (IDDM) and ***Maturity onset diabetes*** is also referred as Type II /Non-insulin dependent diabetes mellitus (NIDDM) (Wadkar et *al.,* 2008).

Glucose as our primary fuel source

The most important factor in the excessive intracellular generation of ROS by hyperglycemia is the ability of individual cell types to process glucose. It is critical that cells are able to decrease the transport of glucose across the plasma membrane into the cytosol when exposed to hyperglycemia in order to maintain intracellular glucose homeostasis. The generation of ROS, specifically O_2^-, by damaged or dysfunctional mitochondria, has been postulated as the primary initiating event in the development of diabetes complications. Intramitochondrial O_2 production initiates a range of damaging reactions through the production of H_2O_2, ferrous iron, OH^-, and $ONOO^-$, which can then damage lipids, proteins, and nucleic acids (Forbes *et al.*, 2008).

Mechanisms of oxygen free radicals production by hyperglycemia

Hyperglycemia is a widely known cause of enhanced plasma free radical concentrations. Free radical production caused by hyperglycemia may occur via at least four different routes:

i) increased glycolysis
ii) intercellular activation of sorbitol (polyol) pathway
iii) auto oxidation of glucose and
iv) nonenzymatic protein glycation

Oxidative stress and insulin resistance: Possible mechanistic link

Oxidative stress in cells and tissues results from the increased generation of reactive oxygen species or from decreased antioxidant defense potential (Rajasekaran *et al.,* 2005). Insulin resistance most often precedes the onset of Type II diabetes by many years, is present in a large segment of the general population. In a variety of tissues, hyperglycemia and elevated free fatty acid result in the generation of ROS and RNS, leading to increased oxidative stress. In the absence of an appropriate compensatory response from the endogenous antioxidant network, the system becomes overwhelmed (redox imbalance), leading to the activation of stress-sensitive signaling pathways, that cause cellular damage, and are ultimately responsible for the long-term complications of diabetes (Rahman, 2007).

Oxygen free-radical can initiate peroxidation of lipids, which in turn stimulates glycation of protein, inactivation of enzymes and alteration in the structure and function of collagen basement and other membranes, and play a role in the long term complication of diabetes (Atawodi *et al.* 2005).

Increased superoxide production in endothelial cells

During hyperglycemic conditions there is an increased superoxide production seen in endothelial cells. The pathways suggested being involved in the development of diabetic complications are as follows:

- increased advanced glycosylation end product formation
- activation of protein kinase C and
- Increased hexosamine pathway flux (Poitout *et al.,* 2006).

Mechanisms of the toxic effects of AGEs

Advanced glycation end products (AGEs) is a class of complex products. They are the results of a reaction between carbohydrates and free amino group of proteins. Most of the AGEs

are very unstable, reactive compounds and the end products are difficult to completely analyze. AGEs are implicated in the basement membrane thickening through these alterations therefore modifies selective filtration properties of the basement membrane (Wautier *et al.,* 2001). Formation of advanced glycation end (AGE) products and their interaction with cellular targets, such as endothelial cells, may lead to oxidative stress and promote formation of oxidized LDL (Dusting *et al.,* 2005).

Oxidative stress in diabetes

Both radical and non-radical oxidants can induce lipid peroxidation particularly of those lipoproteins that contain unsaturated fatty acids. Antioxidant defenses may also be impaired in diabetes, thereby contributing to net oxidative stress. Increased oxidative stress may provide a plausible pathobiological basis for the direct association between hyperglycaemia and increased cardiovascular persuasive risk in diabetes mellitus (Ahmed *et al.,* 2005).

Streptozotocin (STZ)

Streptozotocin (STZ) is well known for its selective pancreatic islet cell toxicity and has been extensively used in induced diabetes mellitus in animals. STZ is taken up by the β cells via the glucose transporter GLUTZ and causes alkylation of DNA and reduction of ATP and NAD+ content. STZ induces severe and irreversible hyperglycemia in experimental animals. STZ was used to induced diabetes rather than alloxan. Since with STZ there is no incidence of spontaneous revision and greater of islets resulting in more than 90% of rats becoming diabetic (Prasad *et al.,* 2009).

STZ-induced Diabetes is characterized by severe loss of body weight and this reduction is due to loss of degradation of structural proteins (Veeramani *et al.,* 2008). It has been reported that chemically (STZ) induced diabetesproduces partial or total deficiency of insulin that results in decrease in the concentration of glycolytic enzymes. Insulin has been shown to be potentiator of hexokinse/glucokinase. The decreased levels of glycogen synthase,glucokinase, lactate

dehydrogenase, succinate dehydrogenase and malate dehydrogenase may be due to decreased insulin level in diabetic rats. Restoration of the concentration of glycolytic enzymes after oral administration aqueous *Ficus bengalensis* bark extract might be due to its normoglycemic activity (Gayathri *et al.*, 2008).

Pathogenesis of liver injury

Liver functions as a "glucostat" and plays a vital role in the maintanence of blood glucose level and hence it is of interest to examine the possible role of key enzymes of carbohydrate metabolism in liver. Liver is the candidate organ involved in glucose homeostatis. It is the main site for glycolysis, a process where glucose is degraded and gluconeogenesis, where glucose is synthesized from lactate,amino acids and glycerol (Reddy, 2006).

Hepatotoxicity has been viewed as liver injury associated with impaired liver function caused by exposure to drug or other noninfectious agents (Soetan *et al.*, 2009**).** The liver plays a significant role in the body as the organ responsible for metabolism of toxic substances that enter the body. The major functions of the liver can be detrimentally altered by liver injury resulting from acute or chronic exposure to toxicants or by situations affecting both ß-oxidation and the respiratory chain enzymes (Ali et al., 2009).

"Antioxidants are safe with no risks associated with their consumption in accordance with recommended daily allowances"

2.5 Antioxidant defense mechanism

Antioxidants are endogenous or exogenous compounds that either reduce the formation of free radicals or react with and neutralize them, thus potentially protecting the cell from oxidative injury. Individual antioxidants may have differential effects in protecting nucleic acids, proteins, and lipids from free radical damage, and some compounds may be preferentially localized within specific organelles (Delanty *et al.*, 2009).

Types of antioxidant defenses

- ***Primary or chain breaking antioxidants (scavenger antioxidants):*** These antioxidants can neutralize free radicals by donating one of their own electron, ending the electron "stealing" reaction

- ***Secondary or preventive antioxidants***: They act through numerous possible mechanisms like

  a) Sequestration of transition metal ions reactions.

  b) Removal of peroxides by catalases and glutathione peroxidase,

- ***Tertiary antioxidant defenses***: These are the repair processes, which remove damaged biomolecules before they can accumulate and before their presence results in altered cell metabolism and viability e.g. damaged DNA repaired by enzyme methionine sulphoxide reductase. (Thapa *et al.*,2005)

Mode of action of antioxidants

There are four routes:

1. Chain breaking reactions, e.g. alpha-tocopherol which acts in lipid phase to trap "ROD" radical.
2. Reducing the concentration of reactive oxygen species e.g. glutathione.
3. Scavenging initiating radicals e.g. superoxide dismutase which acts in aqueous phase to trap superoxide free radicals.
4. Chelating the transition metal catalysts: A group of compounds serves an antioxidant function by sequestration of transition metals that are well-established pro-oxidants. In this way, transferrin, lactoferrin, and ferritin function to keep iron induced oxidant stress in check and ceruloplasmin and albumin as copper sequestrants (http://www.doctorslounge.com/primary/articles/antioxidants/index.htm)

Antioxidant scavengers

The largest categories of antioxidants are those that are reactive toward ROS, and the product of the reaction results in a less-toxic species. The naturally occurring vitamins E and C are such examples. Both the ascorbate and α-tocopherol radicals are less reactive and can be recycled by cellular reductases. Glutathione is a thiol-containing tripeptide that readily reacts with peroxides and forms a less-toxic disulfide product that is recycled by glutathione reductase (Day., 2008).

2.4.1. Enzymic Antioxidants

Superoxide dismutase (SOD)

SOD convert superoxide to H_2O_2, a relatively stable molecule. Although it occurs spontaneously, the role of SOD is to increase the rate of the reaction to that of a diffusion-controlled process. In the cytosol and the inter-membrane space of mitochondria, superoxide is eliminated by CuZn-SOD, whereas in the matrix it is eliminated by MnSOD (Jyothi *et al.*, 2008).

Peroxidases

Peroxidases (EC 1.11.1.7) are referring to heme containing enzymes which are able to oxidise organic and inorganic compounds using hydrogen peroxide as co-substrate. The non-specificity of peroxidase makes the enzyme suitable to a broad range of electron donor substrates (Hakiman *et al.*, 2009).

Catalase (CAT)

Catalase is a heme protein which catalyses the reduction of hydrogen peroxides and protects the tissues from highly reactive hydroxyl radicals. This decrease in catalase activity could result from inactivation by glycation of enzyme (Pavana *et al.*, 2007).

Glutathione

GSH has a multifactorial role in antioxidant defense. It is a direct scavenger of free radicals as well as a co-substrate for peroxide detoxification by glutathione peroxidases (Lin *et al.,* 2000). Increased oxidative stress, resulting from significant increase in aldehydic products of lipid peroxidation has probably decreased hepatic GSH content. GSH has a higher ability to scavenge superoxide essential cofactor for a number of enzymes (Sathish *et al.,* 2008). .

Glutathione peroxidase

Glutathione peroxidases prevents the accumulation of oxidized lipids in mitochondrial cell membranes and also detoxifies H_2O_2 by utilizing reduced glutathione as a co-substrate. It has been reported that decreases in glutathione, a co-substrate of glutathione peroxidase, results in a greater susceptibility to oxidative stress (Vijayakumar *et al.*, 2006).

2.4.2 Nonenzymic antioxidants

Vitamin E

Vitamin E is one of the most important free radical scavenging chain-breaking antioxidant within biomembrane. Vitamin E present in the lipid residue reduces ferric ion to ferrous ions. Chain Breaking antioxidants such as α-tocopherol inhibit LPO in membranes by scavenging peroxyl (RO.) and alkoxyl (ROO.) radicals. (Maneesh *et al.,* 2006).

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble free radical scavenger. In the cell dehydroascorbic acid is formed on reduction of GSH, which cycles the tocopheroxyl radicals to tocopherol (Nair *et al.,* 2009).

Reduced Glutathione

A tripeptide glutathione (r- glutamylcysteinyl glycine) is abundant compound in plant tissues in all cell compartments and executes multiple functions. I act as potent detoxifier and serve as precursor of phytochelatins (Blokhina, *et al.*, 2003).

Allopathy vs homeopathy

The term Natural remedy refers to the ancient tradition of 'Herbalism'. In today's world Allopathy has become indispensable in achieving quick cure and relief. But even the greatest cure is not without side effects. If a person uses too much of allopathic medicine he is bound to face the harmful side effects that such medicines can cause.

Allopathic care refers to the idea of moving the patient in an opposite direction from the disease. It is known as 'treating the disease' since the approach has little to do with the patient as a whole. With homeopathic care, one treats relative to making the patient stronger so that their own biochemistry, their own health related mechanisms reacts to the 'imbalance' - which is the perspective of disease in these individuals.

Because nutritional medicine is non toxic in nature
we can layer treatments and attack from all sides in a
simultaneous assault on that which is dead set on taking our life

Natural Allopathic Medicine represents a new therapeutic principle that revolutionizes both allopathic and naturopathic medicine. Built on bedrock medical science and evidence based therapeutics, Natural Allopathic Medicine answers our need for a radical shift in medical thought and practice.

2.5 Phytochemical screening of medicinal Plants

The traditional use of plants can lead to the discovery of new potent pharmacological agents in the treatment of several diseases. The phylogenetic distance between families is a strong indication of the varied nature of the active constituents and mechanism of actions

(Khalidi *et al.*, 2009). Pharmacological treatment of Diabetes mellitus is based on oral hypoglycemic agents and insulin, but these approaches currently used in clinical practice either do not succeed in restoring normoglycaemia in most patients or fail after a variable period of time. Therefore, there is a need for discovering more effective and safe oral hypoglycemic gents (Zhou *et al.*, 2009).

Medicinal plants used to treat hyperglycemic conditions are of considerable interest for ethno-botanical community as they are recognized to contain valuable medicinal properties. Traditional plant medicines or herbal formulations might offer a natural key to unlock diabetic complications (Rout *et al.*, 2009).

Present status of herbal antidiabetic agents

Approximately 80% of the populations of third world countries are dependent on traditional therapies for their health care, and has been substantiated by the WHO recommendation to include traditional medicines in the primary health-care level of these countries. Most of the traditional therapies are constituted of plants. When tested using modern methods of evaluation, only 18% were found to exhibit some kind of pharmacological activity.

2.6 Medicinal plant selected for the study *Aristolochia bracteolata*

Aristolochia is a genus of evergreen and deciduous woody vines and herbaceous perennials. The smooth stem is erect or somewhat twining. The simple leaves are alternate and cordate, membranous, growing on leaf stalks. Aristolochia means "excellent birth" and refers to the traditional use of the fresh juice to induce labour. *Aristolochia bracteolata* is colloquially known as "Worm Killer" due to supposed antihelminthic activity (Muthu, 2006).

The Aristolochiaceae family contains about 400 species in 7 genera of cosmopolitan distribution, many of them of economic importance due to aristolochic acids and terpenoids. An unnamed alkaloid is reported present in the root and stem of Indian material.

Kingdom : Plantae

Family : Aristolochiaceae

Genus : Aristolochia

Species : bracteata, bracteolata

Tamil : Aduthinnapalai

Properties and Uses:

The roots and leaves are bitter, acrid thermogenic, antihelmintic.cathartic,anti-inflammatory,emmenagogue,vulnerary,apeptiser and are useful for inflammations, amenorrhoea, foul ulcers, boils, syphilis, skin diseases, eczema and intermittent.

Ethanol extract of the shade-dried leaves of Aristolochia bracteolata Lam. was studied for its effect on wound healing in rats. The plant showed a definite, positive effect on wound healing, with a significant increase of the level of two powerful antioxidant enzymes, super oxide dismutase and catalase, in the granuloma tissue (Shirwaikar *et al.*, 2003).

There are many ways to approach for getting new biologically active principles from higher plants.

- One can simply look for new chemical constituents.
- A second approach is random collection and broad screening, which means simply to collect every readily available plant, prepare extracts, and test each extract for one or more types of pharmacological activity.

The relation between free radicals, antioxidants and functioning of various organs and organ systems is highly complex and the discovery of 'redox signaling' is a milestone in this crucial relationship. Recent research centers on various strategies to protect crucial tissues and organs against oxidative damage induced by free radicals.