CHAPTER 1: INTRODUCTION

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Diabetes mellitus is a prevalent metabolic disorder characterized with elevated blood sugar level and improper primary metabolism. According to the classical definition, it is a disorder due to genetic predisposition and environmental factors, and characterized by alterations in the carbohydrate, protein and fat metabolism due to deficit of insulin secretion or different levels of insulin resistance\(^1\). Patients with long-standing diabetes develop complications consisting of alteration in the physiology and failure of organs. Long-standing diabetes can leads to retinopathy, nephropathy, neuropathy and cardiovascular, cerebrovascular and peripheral vascular complications\(^1\).

Symptoms of hyperglycemia include weight loss, polydipsis, polyurea, polyphagia and blurred vision. Chronic hyperglycemia can also results in impairment of growth and increase the propensity to certain infections\(^2\). The number of diabetic patients is increasing due to increase in number of population, obesity, aging and physical inability. As per the recent estimate/report, India will be the country with greatest number of diabetes patients. The total number of diabetes patients is anticipated or projected to increase from 31.70 million in 2000 to 79.40 million in 2030 and in the entire world the total number of diabetes patients is anticipated or projected to increase from 171 million in 2000 to 366 million in 2030. Globally the prevalence of diabetes was estimated 2.80% in 2000 and 4.40% in 2030. Thus, the world population appears to be in the hub of an epidemic of diabetes\(^3\).

Regardless of immense march that have been made to understand the pathogenesis of diabetes mellitus and complications secondary to diabetes mellitus, the disease and its related complications are rising incessantly. Parallel to this, recent research in understanding in the pathogenesis of the disease have opened up many new avenues to identify and develop novel therapies to fight the diabetic plague. Oral hypoglycaemic agents are available for the treatment of diabetes, but these drugs have many side effects and fail to treat the diabetic complications.

Oxidative stress occur mainly due to increase in the formation of reactive oxygen species (ROS) and decrease antioxidant defence capacity in the biological system and it is one of the main mechanisms to cause diabetes and complications due to diabetes mellitus\(^4\). A number of mechanisms are involved in the generation of oxidative stress such as, auto-oxidation of glucose, glycation of protein, generation of advanced glycation end products (AGEs), and the polyol pathway\(^5\). Increase ROS results in damage of cell membrane, genetic materials, and different cellular enzymes. Moreover, generation of ROS also causes
microvascular and macrovascular complications leads to retinopathy, nephropathy and cardiovascular problem.

In allopathy, there are five classes of oral drugs; namely, sulphonylurea, repaglinide, biguanides, thiazolidinediones and alpha-glucosidase inhibitors are used in the management of diabetes mellitus. Although, these drugs are highly effective but they are expensive and have characteristic profile of adverse effects, such as hypoglycaemia, hepatotoxicity, dyslipidemia, hypertension, hypercoagulability and lactic acidosis. On the other hand, in ayurvedic and other traditional systems of medicine there are several relatively inexpensive herbs that are claimed to have safe antidiabetic potentials. However, efficacy of many of these has not been scientifically proven. In addition, recent studies also suggest that both forms (Type I and II) diabetes mellitus are characterized by expression of certain proinflammatory cytokines, which induce apoptotic pathway in β-cells results in loss of β-cells, and diabetes.

The word inflammation is derived from “inflammare”. Inflammare is a latin word which means to burn. Inflammation plays a very important role in the defence of an organism against local injury and infections. However it often progress to painful or chronically harmful diseases requiring pharmacologically treatment. Inflammatory response is a series of well coordinated dynamic mechanisms such as vascular, humoral, and cellular events. These events are characterized by movement of fluids, plasma, and inflammatory cells like neutrophils, eosinophils, basophils, and macrophages to the site of inflammation. An array of chemical mediators like histamine, serotonin, leukotrine, prostaglandins, and free radicals are produced by inflammatory cells participates in onset of inflammation.

Inflammatory response occurs in two phases acute and chronic and each is apparently mediated by a different mechanisms. Acute inflammation lasts from few minutes to hours or one to two days. The cardinal sign of acute inflammation are those described by Celsus in the 1st century AD as rubor (redness), calor (heat), tumor (swelling) and dollar (pain). The events involved in acute inflammation can be divided into vascular and cellular events. Vascular event occur in micro vasculature 15-30 minutes after tissue injury. It occurs due to infection and in the presence of other inflammatory stimuli, which cause release of chemicals such as serotonin and histamine released from mast cells and leads to local vasodilation of venules and capillaries. In cellular event the infiltration of leukocytes from circulating blood is crucial in inflammatory reaction take place. A variety of chemotactic agents along with mediators of mast cell like histamine and leukotriene B4 (LTB₄) and platelets activating factor (PAF) elicit profound leukocytes (neutrophil) infiltration within 30-60 minutes.
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Chronic inflammation is characterized by infiltration of mononuclear cells (macrophages and lymphocytes), proliferation of fibroblasts, collagen fibres and formation of connective tissue, lead to formation of large granuloma (tumor like swelling). In chronic inflammation the degeneration of tissue is mediated by reactive oxygen species from infiltrate inflammatory cells. These reactive oxygen species also cause mutation by interacting with DNA in proliferation epithelium resulting in permanent genomic alteration such as point mutation, deletion or rearrangement.

The treatment or management of inflammatory diseases is mainly dependent on nonsteroidal anti-inflammatory drugs (NSAIDs). NSAID lessen the both pain and inflammation by blocking cyclooxygenase (COX) enzymes reduces which reduce the metabolism of arachidonic acid, which results in decrease prostaglandin synthesis. Prostaglandins are cytoprotective in nature. Long-term administration of NSAIDs results in gastrointestinal ulcer, gastrointestinal bleeding, and hepatic and kidney damage. These adverse effects of NSAIDs are due to non-selective antagonizing of both isoforms of COX enzyme (COX-1 and COX-2). Moreover, selective COX-2 inhibitors have less or no gastrointestinal toxicity but these drugs are leads to cardiac complications. Furthermore, steroidal anti-inflammatory drugs are also not safe because of multiple adverse effects.

Thus, developing of new drugs with potent antidiabetic or anti-inflammatory property with less adverse effect is at present great interest.

*Ipomoea staphylina* Roem and Schult. is a perennial, large climbing, woody and glabrous tree belonging to the family Convolvulaceae. This plant is commonly known as Onnankodi in Tamil and Lesser Glory in English. This plant is available in India, Sri Lanka, and China. Flowers are pink in colour with dark throat. Flowering starts from month of December and last up to month of March. Leaves are ovate with sub-cordate base. Leaves are approximately 7 cm long. Apex of the leaves is acute. Leaves also contain glabrescent, and petiole. Fruits are like subglobose capsule contain oblong seeds which are clothed with silky hairs. Fruiting time is the month of January onwards. A literature review reveals antiulcer, hepatoprotective, nephroprotective and analgesic activity of *Ipomoea staphylina*. The anti-inflammatory effect of other species of Ipomoea genus (*Ipomoea pes-caprae, Ipomoea imperati, Ipomoea involucrate and Ipomoea asarifolia*) has been reported by many researchers.

*Ipomoea batata* another species of genus Ipomoea has been reported for its antidiabetic activity in preclinical studies. Antidiabetic activity *Ipomoea batata* is also clinically proved by different studies.
Thus, based on the above context the present study was aimed to evaluate antidiabetic and anti-inflammatory activity of leaves of *Ipomoea staphylina*.

The main objectives of this study were:

✓ To perform the extraction of leaves of *Ipomoea staphylina*.

✓ To perform the fractionation and isolation of the active compound from the extract of leaves of *Ipomoea staphylina*.

✓ To evaluate the antidiabetic activity of ethanolic extract and its different fraction(s) and isolated compound(s) of leaves of *Ipomoea staphylina*.

✓ To evaluate the anti-inflammatory activity of ethanolic extract and its different fraction(s) and isolated compound(s) of leaves of *Ipomoea staphylina*.