CHAPTER 2.0 REVIEW OF LITERATURE

2.1 Adverse effects of fructose

With the available literature, high fructose intake leads to the many disease conditions like obesity, all kinds of complications related to diabetes mellitus, accelerated aging, etc. (Gaby, 2005). Earlier study stated that high fructose intake induce insulin resistance, a significant factor involved in increasing the level of ROS, lipid peroxidation which causes exhaustion of the antioxidants in various tissues (Reddy et al. 2009). Excess of fructose in diet brings metabolic dysfunction which leads to alterations in lipid metabolism with a rapid elevation of serum triglycerides (TGs), and very low-density lipoprotein (VLDL) secretion (Botezelli et al. 2010). Similarly, the increased intake of fructose is a key contributor of metabolic syndrome, as a result of hyperinsulinemia, insulin resistance, and hypertriacylglycerolaemia (Suwannaphet et al. 2010) and increase the risk of diabetes and cardiovascular diseases. Due to modern life trend and high consumption of sugar / caloric food, the prevalence of metabolic syndrome has increased worldwide (Misra et al. 2009) which inturn causes an increase the rate of morbidity and mortality.

![Diagram of the effect of excess fructose diet](Toit and donner, 2012)

Figure 2.1 Effect of excess fructose diet (Toit and donner, 2012)
2.2 Insulin resistance

Insulin resistance (IR) is a metabolic condition where the cells become resistant to the action of insulin. It is defined as a state in which the normal or elevated level of insulin produces a reduced biological response which is referred to impairment in the insulin sensitivity to dispose glucose. The insulin resistance leads to a variety of clinical manifestations includes obesity, glucose intolerance as well as diabetes and are associated with various endocrine, metabolic, immunological and genetic conditions.

Figure 2.2 The consumption of fructose and metabolic syndrome (Simopoulos, 2013)

Insulin sensitivity and secretion are interrelated in a wavy or hyperbolic manner in order to balance between normal glucose and lipid levels. The insulin resistance results in increased insulin secretion. The pancreatic β cells receive signals from several intermediaries such as glucose and fatty acids in order to respond insulin resistance. The impairment of the signals causes improper
insulin levels, impaired fasting glucose, glucose tolerance, and T2DM (Olatunbosun, 2015). The high fructose diet consumption induced insulin resistance is referred to cluster of abnormalities and strongly contributes to the alteration in circulating lipids. The fructose metabolism in liver is different from glucose metabolism which promotes the deposition of triglycerides in adipose tissue and contributes to dyslipidaemia and insulin resistance.

A highly lipogenic pathway: Liver has the capacity to rapidly metabolize the fructose from the diet and the metabolites are involved in the de novo lipogenesis. Fructose in high concentration stimulates triglyceride synthesis which lead to hepatic accumulation thereby reduces hepatic insulin sensitivity and increase synthesis of VLDL particles (Basciano et al. 2005).

Figure 2.3 Hepatic fructose metabolism (Basciano et al. 2005)
2.3 Curcumin

Curcumin is the prime compound found in turmeric (Curcuma longa Linn), a popular spice in Asian food. It is valuable for human health. It contains anti-inflammatory and antidiabetic properties. It delay development of T2DM, enhance β-cell functions, inhibit β-cell death, and decreases insulin resistance in animals. Thus, due to their effectiveness in the regulation of various targets, polyphenols have received considerable attention as potential therapeutic agents for the prevention and treatment of diabetes.

The active substance of turmeric, curcumin has gained scientific consideration as a therapeutic agent for the diabetes and its related complication due to effective in decreases the glycemia and reduces the hyperlipidemia and it is inexpensive and safe.

This review seeks to briefly summarize the ample scientific literatures regarding curcumin as a potential treatment for diabetes and its associated complications.

2.3.1 Biological activities of curcumin

Turmeric (Curcuma longa rhizomes), a spice is well recognized for its medicinal properties in Indian and Chinese systems of medicine and has been commonly used for the improvement of a number of diseases. Epidemiological studies indicated that utilization of turmeric reduces the risk of cancers and other protective biological effects in humans as well as in animals. These effects attributed to curcumin generally considered as anti-inflammatory, anti-angiogenic, free radical scavenger, anti-oxidant, chemoprotective agent, wound curing and anti-cancer effects (Masuda et al. 2001; Maheshwari et al. 2006; Menon and Sudheer 2007; Alrawaiq and Abdulla 2014).

Gupta et al. (2012) discussed about the several miraculous activities of curcumin and reported to modulate the biological signaling molecules such as inflammatory molecules, transcription factors, activates or inhibits enzymes like protein kinases, reductases, carrier proteins, the cell survival proteins, drug resistance proteins, adhesion molecules, growth factors, receptors, cell cycle
regulatory proteins, chemokines, DNA, RNA and metal ions. Similarly, curcumin acts as a natural antimicrobial agent on bacteria, viruses, fungi and parasites and it enhance the inhibitory effect through synergism (Moghadamtousi et al. 2014).

### 2.3.2 Pharmacological activities of curcumin

Turmeric, a gold-colored spicy substance of food also used as a yellow dye for textiles and for health care preparations. Since the period of Ayurveda (~1900 BC), turmeric has been known for its therapeutic action for a wide array of diseases and disorders. In the last few decades, extensive research demonstrated that most of these activities are due to the active phytoconstituents like curcumin which shown to exhibit antioxidant (Kuhad et al. 2007; Tokusoglu et al. 2015), anti-inflammatory (Aggarwal, et al. 2009; Ramadan et al. 2011), antiviral, antibacterial, antifungal and anticancer activities (Ireson et al. 2002; Smith et al. 2015; Nisar et al. 2015; Vallianou et al. 2015) and thus has a potential role against diabetes (Arun and Nalini, 2002). Curcumin directly acts on the genetic and transcriptional level, and inflammatory cytokines (Prasad et al. 2015). Considering the scientific research and demonstration as a therapeutic strategy for most chronic diseases, curcumin has been considered as an ideal "Spice for Life" (Krup et al. 2013; Amalraj et al. 2016; Mirmosayyeb et al. 2017).

### 2.3.3 Curcumin as a food additive

Turmeric is a natural pigment, supplemental ingredient of spice blends, commonly used in food industry as a curry powder (Ahmad et al. 2014). According to the Joint FAO / WHO Expert Committee on Food Additives (JECFA) establishment, the admissible daily recommended intake (ADI) is about 0–3 mg/kg body weight (Trujillo et al. 2013).
2.3.4 Curcumin in folk medicine

The consumption of curcuminoids as therapeutic infusions has been established over centuries worldwide. Curcumin possess a well documented therapeutic history for various respiratory conditions such as allergy, asthma, bronchial hyperactivity, running nose, cough, sinusitis as well as for liver disorders, rheumatism anorexia, and diabetic wounds (Maheshwari et al. 2006) in Ayurvedic medicine. Curcumin has been used for treating diseases associated with abdominal pain in traditional Chinese medicine apart from various other conditions mentioned above. It was also used to treat sprains and swelling in ancient Hindu medicine apart from the use as a remedy for intestinal parasites, poisoning of snakebites and various other complaints (Prasad and Aggarwal, 2011).

2.3.5 Beneficial effect of Curcumin on chronic diseases

Curcumin has been shown to possess anti-inflammatory, antioxidant, hypocholesterolemic and anti-diabetic properties. It is demonstrated that curcumin could delay development of Type 2 diabetes, protective against pancreatic injury (mostly on cells which secrete insulin), thereby prevent β-cell from destruction and lessen insulin resistance (Oh, 2015). Recent study revealed that curcumin not only protects the complications that are directly caused by diabetes, but also prevents the indirect complications (Mullaicharam and Maheswaran, 2012). For instance, the common complications of long-lasting diabetes like diabetic neuropathy, retinopathy, nephropathy, and cardiomyopathy were shown to be improved after curcumin administration (Khaliq et al. 2015). Gupta et al. (2013) demonstrated the therapeutic role of curcumin in human after multiple clinical trials. Either curcumin alone or various formulations like nanoparticles, liposomal encapsulation, emulsions, tablets, and powder have been evaluated and shown to have mechanistic protection against numerous diseases in human participants.
2.4 Rationale for choosing curcumin for the study

The research in the development of plant derived hypoglycemic drugs is on in a relentless manner and no such alternative drug candidate has been demonstrated to be economical and safe without any contraindications around the World. With the supportive epidemiological and experimental studies, it has been demonstrated that curcumin is a pleiotropic molecule and can acts against wide varieties of diseases as mentioned before. The Food and Drug Agency of USA (FDA) has stated that turmeric and its active compound curcumin as ‘Generally Regarded as Safe’ (GRAS) because of its safety and efficacy (Prasad and Tyagi, 2015).
As per the recommendation of expert committee on diabetes (WHO), the folk medicinal plants and plant derived compounds could be further investigated (Farzaei et al. 2015) for the prevention of DM due to the likelihood of higher benefits and largely free from adverse effects. Recently, several natural therapeutic substances and herbal extracts were used for the management of DM in various studies (Patel et al. 2012; Chawla et al. 2013). Studying and demonstrating the efficacy of various phytochemicals against experimental diabetes mellitus may be a valuable alternate for the hypoglycemic agents in practice in the near future (Kayarohanam and Kaviani, 2015).
In diabetic conditions, the insulin resistance leads to overload of hepatic and reduced utilization of glucose. Although several treatment modalities are available in management of diabetes, the economic burden and the development of adverse side effects limits its use (Saikia et al. 2011). So there is a large unmet area in the effective management of diabetes mellitus around the globe. Among many substances studied, one such phytochemical of turmeric, curcumin has a traditional use in Indian system of medicine. Curcumin, a polyphenol flavonoid extracted from the rhizome of the herb *Curcuma longa* possesses many pharmacological activities including anti-inflammatory, anti-cancer...
properties and is also a powerful anti-oxidant and an anti-diabetic agent (Prasad et al. 2015). Hence, the present investigation was focused on the protective effect of oral administration of curcumin against high fructose diet induced insulin resistance in rats (Vasanthi et al. 2016).