CHAPTER I

INTRODUCTION

THE BURDEN OF NON-COMMUNICABLE DISEASES IN SOUTH EAST ASIA

Non-communicable diseases (NCDs) are globally the leading cause of mortality (Alwan et al., 2010) the burden of which constitutes a major public health challenge that undermines social and economic development worldwide (WHO, 2013). The global mortality owing to NCDs are sky rocketing and the future trends aren't bright either (WHO, 2014). NCDs kill more individuals than the figure of all the other causes put together. Not surprisingly, they strike the middle and the low income countries (Alwan et al., 2010) accounting for nearly 80% of NCD mortalities there (WHO, 2008). Over 14 million deaths from NCDs occur in those aged between 30-70 years, of which 85% are in developing countries. Thirty eight million people die due to NCDs each year primarily due to; cardiovascular disease (CVD), cancers, diabetes and chronic lung diseases (WHO, 2014). Interventions channelized at early detection and timely treatment can save many a lives from the burden of NCDs (IDF, 2013). However, the challenge remains to deliver appropriate care, access to technologies and medicines in the middle and low income countries where there is a dearth of resources (WHO, 2011).

The global prevalence of type 2 diabetes is on a rise, posing a public health challenge. It is estimated that by 2035 the proportion of diabetics will increase by 55% (IDF, 2013). As per the WHO projections, diabetes will become the 7^{th} leading cause of mortality by 2030 (WHO, 2011). Worldwide, there are about 347 million individuals who have diabetes (Danaei et al., 2011) and the prevalence is expected to double in the next two decades. Alarmingly, the greatest contributor to this escalation in prevalence will be from Asia and the Indian subcontinent in specific, with more than 130 million individuals going to be affected by the said metabolic derangement (Zimmet et al., 2001). Close to one-fifth of all adults with diabetes in the world live in the South-East Asia (SEA) region. Of the 72.1 million people who have diabetes in SEA, 65.1 million are from India. Diabetes from India, Bangladesh, and Sri Lanka make up 98.8% of the Region's total diabetes population. India also happens to be the

largest contributor to regional mortality, with 1.1 million deaths attributable to diabetes in 2013 and is also estimated to have spent the largest proportion on diabetes health care in the SEA region (IDF, 2013).

THE SECONDARY COMPLICATIONS ASSOCIATED WITH TYPE 2 DIABETES

Diabetics are predisposed to developing a number of disabling and life-threatening health complications (IDF, 2013). Mortality rates are double amongst the diabetics compared to their healthy counterparts (Roglic et al., 2005). Hence, diabetics should be regularly monitored for complications (IDF, 2013). Listed below are some of the common complications that diabetics develop.

Cardiovascular disease (CVD): It is the most common cause of disability and accounts for 50% mortality amongst the diabetics (Morrish et al., 2001). It manifests in the form of angina, myocardial infarction, stroke, peripheral artery disease and congestive heart failure. Hypertension, hypercholesterolemia and hyperglycemia contribute to the development of cardiovascular complications (IDF, 2013). Diabetes increases the risk of heart disease and stroke by two-fold (Boden-Albala et al., 2008).

Kidney disease: Nephropathy is more prevalent amongst the diabetics than the non-diabetics; and diabetes is one of the leading causes of chronic kidney disease and kidney failure (WHO, 2011). Owing to damage to small blood vessels, the kidneys become less efficient or fail altogether (IDF, 2013).

Eye disease: Persistent hyperglycemia, hypertension and hypercholesterolemia give rise to retinopathy. In retinopathy, the small blood vessels to the retina become blocked and damaged that may lead to vision impairment (IDF, 2013). Infact, diabetic retinopathy is an important cause of blindness and accounts for one percent of global blindness (WHO, 2012).

Nerve damage: In conditions of hyperglycemia and hypertension, neuropathy can set in. It can lead to a multitude of physiological problems such as; difficulty in digestion, urination and erectile dysfunction. Peripheral neuropathy can cause pain, tingling and loss of feeling. This maybe detrimental as injuries may go unnoticed, causing

infections, ulceration, diabetic foot and amputations in the worst scenario (IDF, 2013; WHO, 2014).

Diabetic foot: Diabetics may develop different types of foot problems owing to damaged nerves and blood vessels, which can give rise to infections, ulcerations and increase the risk of amputation. There is a 25 times greater risk of amputation in individuals with diabetes compared to those without diabetes (International Consensus on the Diabetic Foot, 1999).

NON-ALCOHOLIC FATTY LIVER DISEASE: A GROSSLY NEGLECTED DIABETIC COMPLICATION

Non-alcoholic fatty liver disease (NAFLD) is a condition characterised by deposition of triglycerides in the hepatocytes, which exceeds 5% of the liver weight (Ratziu et al., 2010; Angulo, 2007) in the absence of alcohol intake (Sanyal, 2002), but resembles the histological changes observed in alcoholic liver disease (Chalasani et al., 2012). It defines the entire spectrum of the disease that can be histologically categorised into two phenotypes; non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) (Matteoni et al., 1999). NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury and NASH is defined as the presence of hepatic steatosis and inflammation with evidence of hepatocyte ballooning with or without fibrosis (Chalasani et al., 2012; Puri and Sanyal, 2012; Rinella et al., 2014).

Globally, NAFLD is now the most common hepatic disease (Mavrogiannaki and Migdalis, 2013), with an assumed 6% to 33% prevalence in the general population (Vernon et al., 2011). In the West, the prevalence of NAFLD ranges from 20-30% (Everhart and Bambha, 2010) and in the East from 10-20% (Loomba and Sanyal, 2013). Alarmingly, during the last couple of decades, the prevalence of NAFLD has gone up whereas that of the other chronic liver diseases has either stabilised or decreased (WGO, 2014). Inspite of being a common condition, NAFLD remains under-recognised and under-diagnosed (Mcavoy et al., 2006), hence most cases go unrecognised (Bhatia et al., 2012). NAFLD and NASH are pandemic global public health problems that will impact all economies alike (WGO, 2014) by posing huge burden on the public health systems (Bhatia et al., 2012).

Type 2 diabetes patients are at a higher risk of developing NAFLD and NASH compared to the non-diabetics (Angulo et al., 1999; Ong et al., 2005; Younossi et al., 2004). Its presence in type 2 diabetics is taken to be a predictor for the development of fibrosis, cirrhosis and eventual liver complications (Neuschwander-Tetri and Caldwell, 2003; Oprea-Călin et al., 2014). Moreover, majority of the cases of cryptogenic cirrhosis are diabetics (Maheshwari and Paul, 2006; Caldwell and Lee, 2008). Liver failure is also a potent threat that is unrealised and neglected in type 2 diabetics (Bugianesi et al., 2007; Younossi et al., 2004). Type 2 diabetics with NAFLD have a 22 fold higher risk of liver related mortality and 3.3 relative risk for overall mortality (Younossi et al., 2004), independent of the classical risk factors (Söderberg et al., 2010).

In type 2 diabetes, the amount of hepatic fat influences the severity of insulin resistance (IR). Type 2 diabetics with NAFLD have higher hepatic and peripheral IR and poor glycemic control (Perseghin, 2009). Moreover, the quantum of hepatic fat is an important determinant of the amount of insulin required to achieve normal metabolic levels of glucose in type 2 diabetics, thus the insulin requirement correlates with the hepatic fat content (Ryysy et al., 2000; Juurinen et al., 2007).

PREVALENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE AMONG TYPE 2 DIABETES PATIENTS

Recent findings report NAFLD prevalence up to 70% in type 2 diabetics (Chalasani et al., 2012). The prevalence of NAFLD among the diabetics is more than twice that of the prevalence observed amongst the non-diabetics (Targher et al., 2007; Leite et al., 2009).

The prevalence of NAFLD was 69.5% among type 2 diabetics in a study held in a large outpatient clinic in Italy (Targher et al., 2007). An increase in the prevalence of NAFLD was observed with an increase in age. The study found NAFLD to be associated with prevalent CVD independent of classical risk factors, glycemic control, medications and the features of metabolic syndrome (MS).

In the Valpolicella Heart Study, a cohort of 2103 type 2 diabetics who were free of CVD at baseline, the prevalence of NAFLD was as high as 75% among the type 2 diabetics (Targher et al., 2005). The study highlighted an independent association

between NAFLD and the increased risk of future occurrence of CVD in these patients independent of the classical risk factors, liver enzymes and the MS.

In Iran, of the 172 type 2 diabetic patients enrolled from a tertiary referral centre, 55.8% were diagnosed as having NAFLD, with BMI and triglycerides being significantly higher in the NAFLD group as compared to the normal liver group (Merat et al., 2009).

A high prevalence of 82.9% of ultrasonography diagnosed NAFLD was reported in type 2 diabetic patients in Iran. BMI was found to be the only predictor variable for NAFLD in type 2 diabetics (Hosseinpanah et al., 2007).

A study conducted on type 2 diabetics (72 with NAFLD and 29 without NAFLD) concluded that NAFLD is associated with visceral obesity and low HDL-C. Overweight and obesity was significantly higher amongst those with NAFLD, along with ALT and low HDL-C. NAFLD was positively associated with above normal waist circumference (WC) and above normal ALT. BMI was found to be a significant predictor of NAFLD (Trojak et al., 2013).

In the Edinburgh type 2 diabetes study, a sample of type 2 diabetics, aged between 61-76 years, 56.9% prevalence of hepatic steatosis was observed. After ruling out the secondary causes of NAFLD, the final prevalence arrived at was 42.6%. BMI, glycated hemoglobin and triglycerides were found to be the independent predictors of NAFLD. The authors had concluded that association with features of the MS could be used to target screening for NAFLD in the type 2 diabetics (Williamson et al., 2011).

In a study involving 180 type 2 diabetic patients, the prevalence of NAFLD was 69.4% based on ultrasonographic diagnosis. Abdominal obesity, hypertriglyceridemia were found to be associated with NAFLD. The study concluded that NAFLD's progression is independent of diabetes progression (Leite et al., 2009).

In another study involving type 2 diabetic patients, a prevalence of 78% NASH was diagnosed based on histology. Hypertriglyceridemia, low HDL-C and increased ALT were independently associated with a higher risk NASH. High serum GGT levels, old age and the male gender correlated independently with the presence of NASH (Leite et al., 2011).

INDIAN SCENARIO OF NON-ALCOHOLIC FATTY LIVER DISEASE AMONG TYPE 2 DIABETES PATIENTS

In India, the data on NAFLD is sparse owing to the fact that the disease was recognised by the medical fraternity just a couple of decades ago and it was thought to be of a benign nature and viral hepatitis shadowed NAFLD (Duseja, 2010).

In a prospective study conducted in India on type 2 diabetics attending an outpatient diabetic clinic, 54.11% were found to have NAFLD on histology, of which 38.9% had steatohepatitis and 23.2% had fibrosis. The risk factors such as age, duration of diabetes, glycemic control, BMI, WC and family history of diabetes did not predict the presence or the severity of NAFLD or fibrosis. Low HDL-C was found to be the only factor which was independently associated with fibrosis. The research concluded with a piece of anecdote that it is necessary to identify type 2 diabetics who happen to be at the highest risk (Prashanth et al., 2009).

In a study from Mumbai involving type 2 diabetics, a 49% prevalence of NAFLD based on ultrasound was diagnosed. However, no significant differences were observed in BMI, transaminase levels, cholesterol and triglycerides of those with and without NAFLD. A sub-sample of them underwent liver biopsy and 66% had mild NASH, 13% moderate NASH, 9% severe NASH and 22% had fibrosis (Gupte et al., 2004).

To determine the anthropometric and metabolic profile of type 2 diabetes patients with NAFLD, 44 type 2 diabetics were enrolled from a diabetic clinic, 30 of them had NAFLD whereas the remainder 14 had a normal liver. A significantly higher BMI, waist hip ratio (WHR), AST/ALT >1 were observed amongst those with a fatty liver as compared to the ones with a normal liver (Pai et al., 2012).

In a study conducted on type 2 diabetics at Nagpur, 56.6% were having ultrasonography diagnosed NAFLD. Elevated WC, BMI, SBP, DBP, HbA1c, AST, ALT, TC, TG and decreased HDL-C were observed in those with a fatty liver compared to those without fatty liver. The independent predictors of NAFLD were BMI, HbA1c, triglycerides and the presence of coronary artery disease (Somalwar and Raut, 2014).

From the meagre literature that is available, it seems that the Indian scenario of NAFLD from the type 2 diabetic perspective does not differ much in terms of prevalence and risk factors from their Western counterparts. However, the question whether NAFLD in India in type 2 diabetics share an association metabolic syndrome needs much clarity.

TREATMENT AND GOALS OF NON-ALCOHOLIC FATTY LIVER DISEASE

The treatment of NAFLD suffers a huge set back in the light of absence of evidence based guidelines for its treatment (WGO, 2014). However, for reversing NAFLD and NASH, incorporation of lifestyle changes becomes essential (WGO, 2014). Infact, recent reviews are of the opinion that weight loss and lifestyle modification should be propagated as the first line therapy for the treatment of NAFLD (Schwenger and Allard, 2014; Mavrogiannaki and Migdalis, 2013). As of now, the current treatment and management modalities revolve around correcting the underlying metabolic abnormalities associated with NAFLD through insulin sensitizing agents, dyslipidemic agents and discontinuing hepatotoxic drugs, if any (Lewis and Mohanty, 2010; WGO, 2014). As the goals of treating type 2 diabetic NAFLD patient are to improve on their quality of life and prolong their survival (Shams et al., 2011), the concept of lifestyle modification through behavioural methods appropriately fits in as a treatment modality of NAFLD.

LIFESTYLE MODIFICATION IN THE MANAGEMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE

Targeting behavioural methods to impart nutrition education is an effective and useful way of dealing with a health problem (Yasutake et al., 2014). The theory of behaviourism propagates that positive changes in behaviours can be only achieved by modifying the environmental cues and reinforcements of these behaviours (Wing, 2002). Lifestyle interventions are considered as the cornerstone of management of NAFLD (Bacchi et al., 2013), which is a combination of diet, exercise and positive behaviours (Wadden et al., 2004). Its fundamental goals are weight loss, increase in muscle mass, peripheral insulin sensitivity and improvement in lipemic status (Colak et al., 2012). For weight loss; weight management, dietary macronutrient

composition, physical activity and behaviour therapy are the key elements (McCarthy and Rinella, 2012).

Counselling programs with a cognitive behavioural therapy approach are effective in NAFLD/NASH as they improve insulin sensitivity (Kim and Younossi, 2008), liver enzymes, hepatic fat content as well as the grade and stage of hepatic inflammation and fibrosis (Bellentani et al., 2008; Huang et al., 2005). Studies have proven that lifestyle modification through behavioural therapy helps to reduce aminotransferases and improve hepatic steatosis as confirmed by ultrasound (Park et al., 1995; Ueno et al., 1997; Kugelmas et al., 2003; Sreenivasa et al., 2006; Hickman et al., 2004; Suzuki et al., 2005).

Lifestyle modification brings about a reduction in hepatic fat and improves glucose control and insulin sensitivity (Conlon et al., 2013; Bhat et al., 2012), improves liver histology (Bhat et al., 2012) and delays the progression of NAFLD to more advanced stages (McCarthy and Rinella, 2012). Thus, lifestyle modification should be used as a first step in clinical setting (Schwenger and Allard, 2014).

The data is extremely scarce on the impact of lifestyle modification therapy in the management of NAFLD in type 2 diabetics, with respect to India. Studies with the diabetic population with NAFLD outcomes will provide the scientific base for the formation of evidence based guidelines (Conlon et al., 2013). The research may provide a glimpse about whether lifestyle modification as a treatment modality holds scope with the Indian NAFLD patients or not.

DIABETIC DYSLIPIDEMIA AS A RISK FACTOR FOR NON-ALCOHOLIC FATTY LIVER DISEASE

An atherogenic profile; elevated triglycerides, small and dense LDL-C, apo B, low HDL-C is frequently seen in cases of hepatic steatosis with type 2 diabetes (Caceaune, 2012). Dyslipidemia is commonly reported in patients with NAFLD with a prevalence ranging from 20 – 92% with hypertriglyceridemia as a major abnormality (Angulo, 2002). Metabolically, there are four possible pathways through which the triglycerides or the free fatty acids may meet different fates, they are; metabolization by beta oxidation in the mitochondria, esterification and storage as triglycerides in lipid droplets, utilization to form other lipids or packaging with apoB into VLDL (Hooper

et al., 2011). However, hepatic insulin resistance IR holds the key to determine its metabolic fate (Bugianesi et al., 2010). Thus, any dysregulation in this metabolism or a disturbance in the homeostasis leads to excessive accumulation of lipids and retarded excretion of lipids out of the liver giving rise to hepatic steatosis (Cohen, 2011; Bugianesi et al., 2010; Enjoji et al., 2012). Liver responds to the elevated free fatty acids in the liver by enhancing cholesterol ester synthesis, VLDL production, and *de novo* lipogenesis that further promotes dyslipidemia (Sniderman et al., 2001; Rector et al., 2008). Correction of dyslipidemia is necessary for NAFLD patients to reduce the risk of cardiovascular disease (Dyson et al., 2014).

MANAGEMENT OF DIABETIC DYSLIPIDEMIA WITH TRADITIONAL MEDICINE FOR PREVENTION OF NON-ALCOHOLIC FATTY LIVER DISEASE

WHO states that 80% of the Asia's population relies on traditional medicine for their primary health care. Traditional medicinal plants scores over the modern medicine owing to lesser side effects and lesser drug reactions (Pandey et al., 2013; Malviya et al., 2010). Infact, many a times they are found to be more effective and needless to say, are affordable and acceptable by the community at large (Kumar et al., 2013). Additionally, they are taken to be powerful health promoting nutritional agents (Kavishankar et al., 2011). The biological modes of action of the medicinal plants with anti-diabetic potential require further elucidation. There is a need for in-depth investigations to evaluate the mechanism of action of medicinal plants with antidiabetic effect (Mamun-or-Rashid et al., 2014; Malviya et al., 2010). However, the presence of phytochemicals such as glycosides, alkaloids, terpenoids, flavonoids are thought to impart the said biological antidiabetic effect (Malviya et al., 2010; Grover et al., 2002).

There are some 800 plant species that have been identified as having anti-diabetic potential (Mentreddy et al., 2005). Some of the commonly used medicinal plants are; bitter gourd for imparting anti-diabetic effect (Saeed et al., 2010) and also impacting beneficially in other diseased conditions, fenugreek for hypoglycemic (Mullaicharam et al., 2013) as well as hypocholesterolemic effect (Srinivasan, 2006), gymnema imparts anti-diabetic (Dey et al., 2002) as well as anti-obesity effect (Bunyapraphatsara

et al., 1996), curry leaves favourably impact diabetes in association with lipid and cardiac abnormalities (Dineshkumar et al., 2010), insulin plant improves glycemic control (Shetty et al., 2010), indian gooseberry kernels impart hypoglycemic effect (Bhowmik et al., 2013), ivy gourd having hypoglycemic impact (Kurpad and Raj, 2002), cinnamon aids in improving glycemic and lipemic profile (Crawford, 2009) and improving blood pressure in metabolic syndrome (Ziegenfuss et al., 2006), garlic (Cefalu et al., 2011) and onion (Joseph and Jini, 2011) have a host of other properties other than being anti-diabetic and hypolipedemic and barley serves as a good hypolipedemic (Shimizu et al., 2008) and hypoglycemic agent (Hinata et al., 2007).

Though the traditional system of medicine may have established the antidiabetic properties of many of these medicinal plants, they are yet to get their recognition as modern medicine (Wadkar et al., 2008). This is largely due to dearth of clinical studies that would establish the efficacy of the traditional medicine on scientific grounds (Konda et al., 2013). Amongst the vast library of hypoglycemic and hypolipedemic plants, Tinospora cordifolia remains under-explored, found effective if, can be used as an adjunct therapy in the management of diabetic dyslipidemia and dysglycemia.

TINOSPORA CORDIFOLIA: A MEDICINAL PLANT WITH ANTI-DIABETIC AND ANTI-DYSLIPIDEMIC PROPERTY

Tinospora cordifolia belongs to the family *Menispermaceae* (Sankhala et al., 2012) which consists of about 70 genera and 450 species that primarily thrive in tropical lowland regions (Sharma et al., 2010). It is an important medicinal plant of the Indian Systems of Medicine and has been used right from the Vedic era (Sinha et al., 2004) for a stronger immune system (Khare, 2007; Srivastava, 2011). In modern medicine, tinospora cordifolia is called ‘the magical rejuvenating herb’ (Singh et al., 2003) owing to its properties to cure many diseases (Srivastava, 2011). It is a deciduous climbing shrub that is widely distributed in India (Sinha et al., 2004) and also in neighbouring tropical countries such as Pakistan, Sri Lanka, Myanmar, Bangladesh and China (Sharma et al., 2010; Sankhala et al., 2012) and also in Malaysia, Indonesia, Philippines and Thailand (Sharma et al., 2010).

PHYTOCHEMICAL PROFILE AND PHYSIOLOGICAL FUNCTIONS

A variety of chemical constituents/bioactive compounds have been isolated from tinospora cordifolia such as; alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoids, phenolics, aliphatic compounds and polysaccharides (Sankhala et al., 2012; Upadhyay et al., 2010; Grover and Bansal, 2012; Singh et al., 2003; Yadav and Agarwala, 2011) lignans (Grover and Bansal, 2012), proteins, flavanoids, saponins (Yadav and Agarwala, 2011) that contain medicinal properties (Sharma et al., 2010; Singh et al., 2003; Upadhyay et al., 2010; Saha and Ghosh, 2012; Sharma et al., 2012).

ETHNOBIOLOGIC USE OF TINOSPORA CORDIFOLIA

Spanning across India, ethnobiologically, tinospora cordifolia has been used to treat many ailments. Traditionally, the plant has been in use as an anti-spasmodic, anti-inflammatory, jaundice, diabetes, seminal weakness, urinary tract infections, fever, general debility, skin diseases, expectorant, digestive, anti-stress and aphrodisiac (Farooqi et al., 2001). Tinospora cordifolia stem is bitter, stomachic, stimulates bile secretion, enriches the blood and cures jaundice, urinary disease and upper respiratory tract infection (Vedavathy, 1991). The stem of tinospora cordifolia has been used in the treatment of fever (Singh and Maheshwari, 1983; Bhatt and Sabnis, 1987), skin diseases (Raghunathan and Mittra, 1982; Shah et al., 1983), rheumatoid arthritis (Pendse et al., 1977), enhancing immunity (Manjrekar et al., 2000; Dikshit et al., 2000), cancer (Bhatt and Sabnis, 1987), general debility (Shah et al., 1983) and asthma (Sinha et al., 2004).

TINOSPORA CORDIFOLIA IN MODERN MEDICINE ERA

A double blind, randomized placebo controlled trial on healthy volunteers reported beneficial impact on learning and memory activities owing to tinospora cordifolia (Bairy et al., 2004). A randomized controlled study also established its efficacy on ulcer healing in case of a diabetic foot (Purandare and Supe, 2007). A clinical trial established the plant's efficacy as a useful adjunct in the management of HIV/AIDS (Kalikar et al., 2008). It has also shown to have anti-osteoporotic effect

(Abiramasundari et al., 2012). It has shown to benefit patients with infective hepatitis by relieving the symptoms and correcting the altered liver enzymes profile (Prakash and Rai, 1996). In post menopausal women, tinospora cordifolia supplementation turned out to be a better sustained therapy with no side effects and also proved to be cost effective than hormone therapy (Nandaa, 1997). The plant has been utilised in various diseased conditions, however, its potential as a hypolipedemic agent remains untapped.

Tinospora Cordifolia in Management of Dyslipidemia and Dysglycemia

The tinospora cordifolia stem extract had demonstrated antidyslipidemic activity in alloxan-induced (150 mg/kg body wt.) diabetic rats. It has shown to be a better drug as a natural product to regress diabetic-dyslipidemia and oxidative stress in diabetes (Mahdi et al., 2013). The stem extract has normalized alterations in the lipid metabolism caused by diabetes mellitus in streptozotocin-induced diabetic rats indirectly benefiting the heart (Nagaraja et al., 2008). The extrapancreatic and intrapancreatic activities of tinospora cordifolia impart the anti-diabetic effect (Sharma et al., 2015). A significant effect on gluconeogenic enzymes Glucose-6-phosphatase and Fructose 1, 6- bisphosphatase activity in streptozotocin induced diabetic albino rats was observed following the administration of aqueous and alcoholic stem extracts at 200 and 400 mg/ kg b.w (Puranik et al., 2007). Streptozotocin diabetic albino rats benefited from different dosages (200 and 400 mg/kg b.w.) of tinospora cordifolia stem extracts (both aqueous and alcoholic) as it had significant anti-diabetic activity in diabetic animals and had an efficacy of 40% to 80% compared to insulin (Puranik et al., 2010). Further evidence comes from a study wherein hexane, ethyl acetate and methanol tinospora cordifolia stem extract at a dose of 250 mg/kg b.w. for a period of 100 days had an antidiabetic effect which reduced blood sugar level in streptozotocin induced diabetic rats (Rajalakshmi et al., 2009). Another study on diabetes induced Wistar rats demonstrated that alcoholic stem extract of tinospora cordifolia has antidiabetic and antihyperlipidemic potential (Selvaraj et al., 2012). Therefore, tinospora cordifolia stem extract holds potential in the management of dyslipidemia and dysglycemia.

To conclude, the data on NAFLD has been lacking in the Indian context especially with regard to type 2 diabetics. The cardio-metabolic derangements that occur with this diseased condition and its association with metabolic syndrome require further elucidation. While social health assessment still awaits inculcation in regular practice, quality of life of a type 2 diabetic NAFLD patient needs to be brought to light. In the absence of evidence based guidelines, delving into the dietary and physical activity profiles of the NAFLD patients may hold scope for introducing lifestyle modification, which has time and again proven to be the only efficacious treatment modality for NAFLD. On the prophylactic front, the underutilised traditional medicinal plant tinospora cordifolia that has never been tested may hold promise for the management of dyslipidemia in type 2 diabetics, which is implicated to be one of the risk factors for NAFLD.

Thus, to develop a broader understanding about the prevalence of NAFLD, its association with MS and the management of diabetic dyslipidemia with tinospora cordifolia, the following research objectives were framed:

1. To map the prevalence of NAFLD among type 2 diabetics attending an outpatient clinic in Baroda, Gujarat.
2. To map the prevalence of MS among type 2 diabetics with NAFLD and normal liver.
3. To assess the cardio-metabolic profile of type 2 diabetes patients with NAFLD and normal liver.
4. To study the dietary and physical activity profile of type 2 diabetes patients with NAFLD and normal liver.
5. To determine the predictor variables for NAFLD among type 2 diabetes patients.
6. To determine the quality of life of type 2 diabetes patients with NAFLD.
7. To assess the knowledge attitude and practices of type 2 diabetes patients with NAFLD.
8. To develop lifestyle modification therapy module for the management of NAFLD in type 2 diabetes.
9. To provide interpersonal counselling to type 2 diabetes patients with NAFLD for lifestyle modification for the management of NAFLD.

10. To assess the impact of interpersonal counselling in the management of NAFLD in type 2 diabetics.
11. To determine the impact of interpersonal counselling on knowledge attitude and practices of type 2 diabetes patients with NAFLD.
12. To analyse the qualitative phytochemical profile of tinospora cordifolia stem.
13. To assess the impact of tinospora cordifolia stem in the management of diabetic dyslipidemia.