CHAPTER 1
INTRODUCTION

1.1 Obesity

Obesity is defined as a condition of abnormal or excessive fat accumulation in the adipose tissue, to the extent that health is impaired (Ofei, 2007). Obesity is characterised by excess body fat accumulation (Hawkesworth, 2013). It has now become an epidemic in developing and developed countries worldwide (Pi-Sunyer, 2009). Global scenario shows rising rates; increased rapidly over the past 50 years. Recent World Health Organisation (WHO) estimates follow that, in 2014 over 600 million were obese (11% of men and 15% of women). Both societal and environmental factors contribute to this upsurge (Farooqi, 2014).

1.2 Obesity and BMI

The current classification of obesity is based on the Body Mass Index (BMI), which is the weight (in kilograms), divided by the square of height (in metres). WHO defines obesity as having BMI greater than 30.0 kg/ m² as an international standard for all ethnic groups. A BMI of 25 kg/m² and ≤ 30 kg/m² is the index of obesity for Asian and Caucasian populations respectively (O’Neill and O’Driscoll, 2015).

BMI has limitations as it does not distinguish between lean mass and fat; it may overestimate body fat in well-trained body builders and underestimate body fat in older persons; moreover, BMI does not identify fat distribution. It is
now well recognised that abdominal fat is a major risk for obesity-related diseases; indeed, visceral fat accumulation contributes to pro-oxidant and pro-inflammatory states, as well as to alterations in glucose and lipid metabolisms and also associated with cardiovascular risks (Piva et al., 2013 and Wonisch et al., 2012). Waist Circumference (WC) or Waist-to-Hip Ratio (WHR) are useful indicators of visceral fat distribution: WC equal to or more than 80 cm (in women) or 94 cm (in men) and WHR above 0.90 for males and 0.85 for females are associated to high cardiometabolic risk in Europeans. Asian population has lower WC and WHR compared to the European and Caucasian populations (85 cm and 80 cm WC values and WHR above 0.90 and 0.80 for males and females respectively) (Nishida et al., 2010; O’Neill and O’Driscoll, 2015).

1.3 Obesity and Energy imbalance

Excessive body fat accumulation is a consequence of energy imbalance i.e., increased energy intake (intake of energy dense food deficient in micronutrients and bioactive compounds) and decreased energy expenditure (Sarvottam and Yadav, 2014; Farooqi, 2014; Hill et al., 2012) and also from interaction of several factors such as decreased physical activity (sedentary lifestyle), nutritional and hormonal status in early life, as well as genetic, environmental, cultural, and economic factors.

Greater consumption of energy leads to an increase in fat mass (adiposity) and fat-cell enlargement (hypertrophy), producing the characteristic pathology of obesity. Energy homeostasis (regulation of food intake and energy expenditure) is controlled by brain (hypothalamus, especially the arcuate nucleus) (Schwartz et al., 2003) which receives sensory input from the body in the form of circulating hormones (leptin, ghrelin), fuels (glucose, fatty acids) and vagal efferent’s from the gut (Shah et al., 2011).
1.4 Comorbidities of obesity

Obesity is a major causative factor for metabolic syndrome and cardiometabolic dysfunction. It is associated with a number of pathologies including dyslipidemia, glucose intolerance, insulin resistance and type 2 diabetes mellitus (Brown and Kuk, 2015; O’Neill and O’Driscoll, 2015). High fat deposition is closely associated with metabolic dysfunction (in particular insulin sensitivity) (Oliverosa et al., 2014 and De Lorenzo et al., 2006; Karelis et al., 2004; Dvorak et al., 1999. Strong correlations are evident among high fat content, metabolic dysregulation and cardiovascular risk indexes (e.g., High Total Cholesterol/HDL ratio, LDL- cholesterol, triglycerides etc.) (De Lorenzo et al., 2006).

1.5 Treatment strategies for obesity- Synthetic vs Natural therapy

Many drugs for anti-obesity treatment are currently available in the market. One of these is Orlistat (Chaput et al., 2007), which reduces intestinal fat absorption through inhibition of pancreatic lipase (Drew et al., 2007; Thurairajah et al., 2005). The other is Sibutramine (Reductil) (Chaput et al., 2007), which is an anorectic, or appetite suppressant (Lean, 2001; Poston and Foreyt, 2004). Both the drugs have side-effects, including increased blood pressure, dry mouth, constipation, headache, insomnia etc. (De Simone and D’Addeo, 2008; Thurairajah et al., 2005).

A number of anti-obesity drugs are currently undergoing clinical trials, including centrally-acting drugs (e.g., Radafaxine and Oleoyl-estrone), drugs targeting peripheral episodic satiety signals (e.g., Rimonabant and APD356), drugs blocking fat absorption (e.g., Cetilistat and AOD9604) and human growth hormone fragments (Halford, 2006). At present, because of dissatisfaction with high costs and potentially hazardous side-effects, the potential of natural products
for treating obesity is under exploration, and this may be an excellent alternative treatment strategy for developing future effective, safe antiobesity drugs (Mayer et al., 2009 and Nakayama et al., 2007).

A variety of natural products, including crude extracts and isolated compounds from plants, can induce body weight reduction and prevent diet-induced obesity. Therefore, they have been widely used in treating obesity (Rayalam et al., 2008; Han et al., 2005). A wealth of information indicates numerous bioactive components from nature are potentially useful in obesity treatments such as the polyphenols which include apigenin, genistein and catechins (Rayalam et al., 2008; Thielecke and Boschmann, 2009).

The World Health Organisation defines traditional medicines as:

“The health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral-based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being”.

The natural products showing their efficacy for antiobesity action are based on the following mechanisms of action, such as less lipid absorption, decreased energy intake, increased energy expenditure, inhibition of pre-adipocyte differentiation/proliferation, regulation of appetite and lipid metabolism.

In the present scenario, chemical compounds and products derived from innumerable number of medicinal plants have become of great interest owing to their wide range of applications. Medicinal plants provide the richest source of drugs which form the basis for the different traditional systems of medicine, folk medicine, modern medicines, nutraceuticals, functional foods, pharmaceutical
intermediates and chemical entities for synthetic drugs (Vaidya and Devasagayam, 2007; Muhammad and Awaisu, 2008; Nishteswar, 2014). Herbal medicines are prepared from parts of herbs or whole herbs either as single or in combinations or as purified compounds such as phytochemicals (Yun, 2010). Synergistic effects using multiple products with similar targets or products that act on multiple targets are proved to achieve desirable therapeutic effects (Rayalam et al., 2008).

Most of the plants contain primary and secondary metabolites that form the active constituents. These phytoconstituents include phytosterols, polyphenols, flavonoids, phenolic acids, alkaloids, chlorophyll derivatives or carotenoids, tannins, organosulphur compounds, saponins, etc., that are being validated for their potential effects (Hall and Cuppett, 1997). The US Food and Drug Administration (FDA) recommend developing plant derived drugs which are excellent alternative to synthetic drugs as they can be developed at much faster rate and cheaper prices.

Because obesity is a serious problem, an effective and strategic solution is needed for its treatment and management. It is the need of the hour to develop products from natural sources that are more targeted, cost effective and provide a realistic alternative therapy to control obesity.

1.6 Objectives of the study

The present study focuses on antiobesity, antioxidant and cardioprotective effects of the new Poly Herbal Formulation (PHF) using animal models such as male and female Wistar rats.

The research objectives are stated as follows:

a) To develop a new Poly Herbal Formulation (PHF) for the control of obesity.
b) To validate the new PHF for its antioxidant potential by in vitro techniques.

c) To scientifically validate the PHF by in vivo studies for its antiobesity, antihyperlipidemic and cardioprotective activity.

1.7 Work Design

The research work was directed based on the above objectives.

The first step undertaken was the selection of herbals. Selection was based on the previous literature available to bring the plants in combination as a novel PHF. The finalised four plants were chosen after preliminary phytochemical analysis which was tested for the presence of active constituents. The authentication of the four herbals was determined by physicochemical parameters. After the quality of the individual herbals was assessed a unique combination of PHF was prepared. Different solvent extracts such as petroleum ether, chloroform, water and ethanol were quantitatively analysed for the screening of polyphenol content. Since ethanolic extracts of the PHF showed rich presence of polyphenols, biomarker (polyphenols) standardization was carried out using HPTLC technique. The ethanolic extract of the PHF was further used for detailed chemical investigation to characterise the polyphenolic compounds. This was done by analytical methods such as preparative HPTLC and IR.

Potential antioxidant activities of the aqueous and ethanolic extracts of PHF and its individual herbals were assayed in vitro conditions. Additionally, the total phenolic content and total flavonoid content were measured. Correlation matrix analysis was done to show significant linear correlation among the various antioxidant assays, total phenolic and flavonoid contents; to prove that all the methods are effective indicators of antioxidant properties of the PHF.
Pharmacological evaluation of the PHF for its antiobesity and in vivo antioxidant potential was carried out. Each of 6 male and female Wistar rats were fed a normal diet and 24 rats were fed High Fat Diet (HFD) to induce obesity for 6 weeks. After the induction of obesity, rats of the HFD group were equally divided into 4 subgroups. The first group received HFD, the 2nd group HFD+L-carnitine, 3rd group HFD+PHF (200 mg/kg) and 4th group HFD+PHF (400 mg/kg). L-Carnitine and PHF were administered at the 7th week (start time for treatments) for 4 weeks. Body weight, organ weights, lipid profile, AST and ALT activities, cardiac markers, renal function tests, oxidative stress markers, malondialdehyde activity in addition to glucose in serum and tissues were analyzed.

Evaluation of cardioprotective effect of PHF on isoproterenol (ISO)-induced Myocardial Infarction (MI) in male Wistar rats was also carried out. Five groups with six rats each were allocated for the study. The first two groups were maintained as untreated control and ISO control groups respectively. All the groups were administered 0.9% normal saline. ISO (85 mg/kg) was administered on 14th and 15th day at an interval of 24 hours. Atorvastatin (25 mg/kg) was orally administered to the healthy rats for 14 days (pretreatment) once daily to group III. Pretreatment with quercetin and PHF respectively was given to groups IV and V respectively for 15 days. MI was induced with a dose of ISO on 14th and 15th day to all the experimental animals (Group III – 13th and 14th day). Serum and heart tissues were collected and total cholesterol, phospholipids, triglycerides, malonialdehyde, superoxide dismutase, catalase, reduced glutathione were determined.