CHAPTER NO. 1

Introduction
1. **Introduction:**

The metabolic syndrome is a clustering of factors associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD) and diabetes. The core ‘metabolic risk factors’ are atherogenic dyslipidaemia, elevated blood pressure, elevated plasma glucose, a prothrombotic state and a pro-inflammatory state, and each of these ‘risk factors’ has several components. This is called clustering and is associated with several other conditions, including fatty liver, polycystic ovary disease, sleep apnoea, cholesterol gallstones, and some forms of cancer. Metabolic syndrome is becoming increasingly common, largely because of the increase in the prevalence of obesity.

Excess body fat, particularly when present in the upper body, is one contributing cause of the metabolic syndrome. In abnormally obese individuals with the metabolic syndrome, weight reduction will reduce all of the metabolic risk factors, which is unique among available therapeutic strategies. This documented efficacy accounts largely for the great interest in the development of drugs to treat obesity.

The term diabetes mellitus a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. (Definition, Diagnosis and Classification of Diabetes Mellitus and its complications- report of a WHO Consultation-WHO/NCD/NCS/992)

Diabetes has been recognized since ancient times, and diagnostic and therapeutic methods have been investigated for many years. As the oral hypoglycemic agents, sulfonylureas (for example, tolbutamide, chlorpropamide and glibenclamide), biguanides (for example, metformin and buformin) and alpha-glucosidase inhibitors (for example, acarbose and voglibose) can be listed. In addition, recently the agents for insulin-resistance amelioration (for example, rosiglitazone and pioglitazone) have been developed and marketed. Thus, currently there are various types of therapeutic agents; however, still the patient number has been continuously increasing. Thus, the development of more efficient agents is anticipated.
Hyperlipidaemia is mentioned as one of the life-style-related diseases as much as so for diabetes. Hyperlipidemia means status in which levels of lipids in plasma are increased over normal ranges. Coronary heart disease (CHD) is the leading cause of death and disability worldwide. It is a complex condition resulting from numerous gene-gene and gene-environment interaction. (Stephen 2003).

According to WHO, 16.6 million people around the globe die of CHD each year. WHO also estimates that low and lower-middle income countries contributed more than 70 percent to the global distribution of chronic disease death in 2005, and the projected death rates from CVD in countries like India and Pakistan would be much higher than the death rates from HIV/AIDS, tuberculosis and malaria. In India, CHD prevalence in urban population rose from 3.5% in 1965 to 9% in 1990. Rates appear to be higher in southern India with highest in Kerala. (Ens, 1998)

Most persons with atherogenic dyslipidemia have the metabolic syndrome. Several drugs currently available do not affect other metabolic risk factors and none of them have considerable potential to reduce the risk for ASCVD. Key agents to treat atherogenic dyslipidaemia are HMG CoA reductase inhibitors (statins), cholesterol-absorption blockers, bile acid sequestrants, nicotinic acid, and PPAR α agonists (fibrates).

Nicotinic acid seems to decrease risk for ASCVD. However, it has little effect on other components of the metabolic syndrome. Nicotinic acid worsens the insulin resistance and can exacerbate hyperglycemia in patients with diabetes. It is not a candidate as a drug to use to modify non-lipid risk factors of the metabolic syndrome. Nicotinic acid is an effective hypolipidaemic drug and is inexpensive; but tends to produce hepatotoxicity, hyperglycemia, and hyperuricaemia.

Fibric acid derivatives (gemfibrozil, fenofibrate and bezafibrate) have lower efficacy for reducing cardiovascular events compared to statins. Because of the inferior efficacy of fibrates compared with statins, their use as single agents in patients with the metabolic syndrome is not attractive. The current fibric acid derivatives (fibrates) are all weak PPAR α agonists and require high doses for their clinical activity. All of the current fibrates require multiple daily doses except a micronized formulation of fenofibrate.
In general, the currently used lipid lowering agents are also not without any shortcomings. Statins are found to produce hepatotoxicity and myopathy with rhabdomyolysis, whereas nicotinic acid produces hyperglycemia, liver toxicity, flushing and dyspepsia. Fibric acid derivatives are found to have side effects such as rashes, myalgia etc.

Therefore, now there is an all time need of intense research and newer therapeutic options for CHD risk factors due to their rising prevalence, increasing aging population, and a huge economic burden by these disorders. Moreover, long-term administration of the current agents either causes serious side effects or fails to produce adequate responses. Because of these, an obvious need exists for newer therapeutic options, which are patient-friendly, safe, and effective for these complications. Above all, in CHD, a pharmacotherapeutic agent is largely awaited with potent hypolipidaemic, hypoglycemic and antioxidant properties.

The chemistry of thiazolidin-4-one was reviewed in detail by Brown (1961). The history of thiazolidinones can be traced back to the late nineteenth century. Hantzsch, who prepared a number of simple compounds containing thiazole rings, did the pioneering work in the field of thiazoles. Soon many other researchers picked up the lead resulting in a series of thiazolidinones and related compounds. A number of naturally occurring substances have the thiazolidine nucleus in their structures. Williams et al in 1935 demonstrated the existence of a thiazole nucleus in thiamine (Vitamin B\textsubscript{1}). Penicillins, which form an important group of antibiotics have a thiazole moiety fused with a β-lactam ring. Actithiazic acid is an antibiotic obtained from Streptomyces and is a thiazolidinone derivative (Sobin et.al, 1952).

Literature survey reveals that various thiazolidinones have attracted considerable attention as they are endowed with wide range of pharmacological activities. A study on the influence of structure on activity shows that sometimes a minor change in heterocyclic nuclei enhances the pharmacological profile many fold than its parent nuclei. The search for new, effective and safe nuclei lead to an improvement in the existing drugs by increasing their potency, duration of action and decreasing toxic side effects as well as creating new biologically active agents by molecular modifications.
IMPORTANCE OF PROPOSED RESEARCH INVESTIGATION:
Presently available drugs although potent and effective, have limitations. These potentially useful medicines, due to lack of tissue specificity, oral absorption have failed to fulfill their therapeutic promise. Some of the compounds have complications like congestive disturbances, weight gain, hepatotoxicity, flatulence, myopathy with rhabdomyolysis, hyperglycemia, hyperuricaemia, flushing etc. Hence, better and safe drugs are required.

In an early paper, the thiazolidinone compounds with highly hindered phenolic groups exhibited antioxidant properties. (Kato et al. 1998). Thiazolidin-4-one compounds with nicotinoyl moiety through amide linkage and having a potential antioxidant, para methoxy moiety was reported to possess hypoglycemic and hypolipidemic activity (Jacob & Kutty, 2004). So extensive research and studies in these areas may give a breakthrough and may produce a potent hypolipidemic and antidiabetic class of agents with negligible side effects.

Strategy for therapy of the metabolic syndrome

1. Keep the total number of drugs as low as possible
2. Compound drugs into single formulations
3. Development of multifunctional drugs

This prompted many scientists, researchers at various universities including pharmaceutical industries for the designing of drugs that can target the metabolic syndrome as a whole, which could mitigate polypharmacy.

In this aspect, the proposed study may lead to the synthesis and evaluation of number of such new series of thiazolidin-4- one therapeutic compounds, which may be useful in the management of metabolic syndrome with good efficacy, fewer side effects, inexpensive, better tissue specificity and to emerge as “potential drugs in the future”. If the new molecules are potent and safe, they will have positive implications for the treatment of dyslipidaemia and diabetes.