DECLARATION

I hereby declare that the work presented in the thesis entitled “Effect of Thiazolidinediones on the immune status in type 2 diabetes mellitus” has been carried out by me independently under the guidance of Dr. M. Ramalingam, Head(Retd), PG and Research Department of Chemistry, Rajah Serfoji Government College, Thanjavur - 613005 and the work has not been submitted either in whole or in part for any degree, diploma, fellowship, etc., at any other university or institute. In keeping with the general practice in reporting scientific observations, due acknowledgement has been made whenever the work described is based on the findings of other investigators.

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The prevalence of type 2 diabetes have soared in the past decades because of changing lifestyles and eating habits. Obesity associated with insulin resistance is one of the main determinants of the increase in occurrence of type 2 diabetes. Not surprisingly, the major long-term complications of type 2 diabetes are an increased risk of myocardial infarction, stroke and peripheral vascular disease. Although microvascular complications cause considerable morbidity in patients with type 2 diabetes, up to 80% of patients die from macrovascular pathology.

Treatment of individual risk factors has been shown to reduce cardiovascular events in type 2 diabetes. Therefore, targeting the underlying pathophysiological mechanisms of the insulin resistance syndrome may be a more logical and beneficial strategy for reduction of cardiovascular morbidity and mortality. Pharmacological modulation of the insulin resistance syndrome will not only improve glycaemic control, but may also have beneficial effects on inflammation, dyslipidemia and possibly other components of the syndrome independently from improvements in glucose metabolism.

The discovery of nuclear peroxisome proliferator-activated receptors (PPARS) and subsequent insight into their role in general metabolic pathways was a major breakthrough in the understanding of pathophysiological mechanisms underlying the insulin resistance syndrome.

PPARS are ligand-activated transcription factors belonging to the nuclear receptor superfamily. As transcription factors, PPARS regulate the expression of numerous genes and affect glycaemic control, lipid metabolism, vascular tone and inflammation. Activation of the subtype PPAR-γ improves insulin sensitivity. Expression of PPAR-γ is present in general cell types involved in the process of atherosclerosis. Thus, modulation of PPAR-γ activity is an interesting therapeutic approach to reduce cardiovascular events.

Thiazolidinediones are PPAR-γ agonists and constitute a new class of pharmacological agents for the treatment of type 2 (non-insulin-dependent) diabetes mellitus. Two such components are currently available for clinical use: rosiglitazone and pioglitazone. Thiazolidinediones improve insulin sensitivity and glycaemic control in patients with type 2 diabetes. In addition, improvement in endothelial
function, a decrease in inflammatory conditions, a decrease in plasma level of free fatty acids and lower blood pressure have been observed, which may have important beneficial effects on the vasculature.

The aim of this research work is to focus on the potential role of thiazolidinediones on immune status in type 2 diabetes mellitus. Thus, studying the above effects of thiazolidinediones may shed more light on the mechanisms involved in the insulin resistance syndrome. Furthermore, thiazolidinediones could have specific, direct effects on processes involved in the development of vascular abnormalities.