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**PhD Dissertation Defense**

Entitled

*NOVEL INSIGHTS INTO THE ANTI-DIABETIC MECHANISM(S) OF WITHANIA COAGULANS AND ITS ACTIVE CONSTITUENT, COAGULANSIN-A*

by

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Abstract

Type 2 diabetes mellitus has become a serious medical challenge of the 21st century with a dramatic surge in diabetes cases since the last decade. It accounts for 90-95% of all cases of diabetes mellitus. The interplay between insulin resistance and beta cells dysfunction plays a crucial role in the pathophysiology of diabetes mellitus. Type 2 diabetes mellitus is characterized by peripheral insulin resistance in skeletal muscles that leads to a constellation of metabolic disorders, and exhaustion of pancreatic beta cells to maintain euglycemia. The inability of pancreatic beta cells to compensate insulin demand in an insulin-resistant state, result in the persistent prolonged hyperglycemia that leads to the production of advanced glycation end products. The toxic effects of advanced glycation end products, oxidative stress, inflammation, glucotoxicity, and lipotoxicity in an insulin-resistant state are attributed to the induction of signaling cascades responsible for the pathophysiology of type 2 diabetes mellitus. The complications associated with diabetes mellitus make this disease more susceptible to morbidity, mortality and increases the risk of other diseases. Despite multiple therapeutic approaches, diabetic patients still exhibit poor glycemic control and suffer from drug-related undesirable side effects. The purpose of the present study was to investigate strategic interventions that can target multiple pathophysiological mechanisms associated with this disease. Several studies showed the beneficial effect of medicinal plants with anti-inflammatory potential in type 2 diabetes mellitus due to the presence of multiple pharmacologically active compounds. *Withania Coagulans* is known for its anti-hyperglycemic and anti-inflammatory properties, but the mechanism by which *Withania Coagulans* ameliorates the pathological hyperglycemic condition in type 2 diabetes mellitus still needs to be evaluated. To address this, we evaluated the beneficial effects of the aqueous extract of *Withania Coagulans* in both in-vivo and in-vitro models, using a variety of biochemical, morphological, and cell biology techniques. For in-vivo analysis, streptozotocin-induced eight months diabetic male Wistar rats were used. The results in our study revealed that forty days of *Withania Coagulans* administration helped to combat the AGEs-RAGE-NFκB axis, lipotoxicity, inflammation, and oxidative stress. For in-vitro analysis, the human type 2 diabetic skeletal muscle myoblasts were used. The results exhibited that *Withania Coagulans* significantly ameliorated glucose uptake in human type 2 diabetic skeletal muscle myoblast. Overall, our results demonstrated that *Withania Coagulans* treatment ameliorates streptozotocin-induced chronic diabetes. Hence, *Withania Coagulans* offers a novel approach for the management of type 2 diabetes mellitus.

**Keywords:** Type 2 diabetes mellitus, insulin resistance, hyperglycemia, pancreatic beta cells, advanced glycation end products, inflammation, oxidative stress, *Withania Coagulans*.