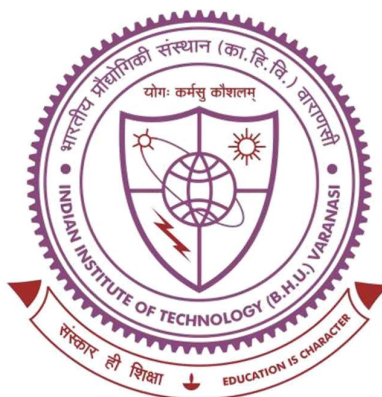


**PROTECTIVE ROLE OF SITAGLIPTIN IN THE  
TREATMENT OF OBESITY AND ASSOCIATED  
METABOLIC COMPLICATIONS IN ANIMAL  
MODEL OF HIGH-FAT DIET-INDUCED OBESITY**



**Thesis submitted in partial fulfilment for the  
Award of Degree**

**Doctor of Philosophy**

**By**

***Swati Prakash***

**DEPARTMENT OF PHARMACEUTICAL  
ENGINEERING & TECHNOLOGY  
INDIAN INSTITUTE OF TECHNOLOGY  
(BANARAS HINDU UNIVERSITY)  
VARANASI – 221005  
INDIA**

**Roll No- 14161011**

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## *CONCLUSION*

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- ❖ **The intake of 60% high-fat diet and 20% fructose water for sixteen weeks successfully developed obesity, metabolic syndrome, fatty liver, and oxidative stress in the mice model.**
- ❖ **The anti-obesity effect of sitagliptin was observed with the higher doses of sitagliptin (20 and 30 mg/kg/day). It ameliorated insulin resistance, metabolic syndrome, and improved the serum adipokine levels in HFFW-fed obese mice.**
- ❖ **Sitagliptin treatment ameliorated fatty liver by up-regulating the hepatic adiponectin and AMPK expression and reducing hepatic oxidative stress and white adipose tissue inflammation.**
- ❖ **Sitagliptin treatment up-regulated the mitochondrial biogenesis markers in the brown and white adipose tissues in obese mice, possibly through up-regulating P-AMPK.**
- ❖ **Among the three doses of sitagliptin, 30mg/kg was more successful in improving the metabolic complications of obesity.**

### **Implications of the present study**

Obesity accounts for 80-85% of the risk of developing DM, where the management of obesity prevents the future risk of obesity-associated metabolic complications. In this regard, the possible mechanisms for the management of obesity involve either decreasing energy consumption or increasing energy expenditure. The AMPK pathway is involved in the regulation of obesity and diabetes both, suggesting a

common link between them. Thus, AMPK targeting can be of therapeutic advantage in metabolic complications. It is being suggested that the repurposing of the approved drugs, such as topiramate for obesity, raloxifene for breast cancer, and aspirin for colorectal cancer, involves lower developmental costs and short timelines.

In this perspective, the present study suggests that the US-FDA approved anti-diabetic agent sitagliptin is capable of reducing the body weight without affecting the food intake. Moreover, a marked improvement was observed in the serum lipid profile, free fatty acid, uric acid, and GLP-1 levels. The ALT and AST levels were also restored along with diminished hepatic triglyceride levels. Also, the level of pro-inflammatory cytokines in white adipose tissue was reduced, and the level of leptin and adiponectin were improved. In addition to this, the adiponectin expression was improved in liver and white adipose tissues. Sitagliptin improved the metabolic complications of obesity, including the fatty liver and metabolic syndrome, by up-regulating AMPK in the metabolic tissues, including liver and white and brown adipose tissues. This activation, in turn, up-regulated the mitochondrial biogenesis markers and reduced the oxidative stress in the metabolic tissues.

Our findings suggest the experimental basis for the treatment of obesity and related metabolic complications with sitagliptin. However, further studies should be designed along with the approved anti-obesity agents to conclude the anti-obesity effect of sitagliptin. Also, the DPP-IV enzyme plays a crucial role in the adipose tissues and liver, and recent studies suggest its over-expression in the metabolic organs in animal models of obesity and fatty liver. Being a DPP-IV inhibitor, future studies need to be

conducted to evaluate the role of sitagliptin in regulating the DPP-IV activity in the metabolic organs.

