Genotoxic and Cytotoxic Assessment of Sitagliptin and Simvastatin Alone and in Combination

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Background: Type 2 Diabetes Mellitus (T2DM) patients are at high risk of Coronary Heart Disease (CHD) and thus, need a global therapeutic intervention (Zafar, Sharif et al. 2020)**.** Type 2 diabetic(T2DM) patients at greater chances of cardiovascular disease and require global therapeutic strategy (Scheen 2012)**.** The Food and Drug Administration (FDA) has approved a fixed-dose combination tablet consisting of simvastatin and sitagliptin. It is the first registered product in which a drug treating type 2 diabetes is present in combination with cholesterol lowering drug (Ramadan and Kabbara 2015). Sitagliptin at (1000µg/mL) was found to be genotoxic when comet assay was carried out on isolated human peripheral lymphocytes *in vitro* (Deniz Yuzbasioglu et al, 2018).

Objectives: Research was conducted to evaluate the cytotoxic and genotoxic potential of Simvastatin and Sitagliptin alone and in combinations by using *in vitro* MTT and Comet assays in a dose dependent fashion

Methodology: Different dilutions of Sitagliptin (31.25, 62.5, 125, 250, 500 and 1000µg/mL, Simvastatin(31.25, 62.5, 125, 250, 500µg/mL), and their combinations (31.25:31.25, 62.5:62.5, 125:125, 250:250, 500:500 and 1000:500 µg/mL) were used to identify the potential of genotoxicity and cytotoxicity. The Ethics Committee of the Institute of Pharmacy Faculty of Pharmaceutical and Allied Health Sciences, Lahore College for Women University (LCWU), Lahore approved the study prior to start of experimentation. Vero cell line was used for the MTT assay. Isolated Human lymphocytes were used for the comet assay.

Results: No significant change in proliferative activity upon treatment with simvastatin was observed**.** However, combination of both drugs exhibited a better survival percentage except highest dose combination (1000:500µg/mL). Simvastatin produced non-significant DNA damage with the threshold concentration of 500 µg/ml in lymphocytes. Sitagliptin produced significant DNA damage above the concentration of 250 µg/mL. DNA damage or DNA tail protrusions by combinations of both drugs were less than what was observed with Sitagliptin alone.

Conclusion: Current study provided evidence that the combination of sitagliptin/simvastatin (1000:500 µg/mL) is non cytotoxic. It is worth to mention that Cmax reported for the sitagliptin was 950 nM whereas present study concluded that combination was safe even at sitaglpitin/simvastatin (1000:500 µg/mL) concentration. Our findings suggest the safe use of the combination both in T2DM and CHD.