DOI: https://doi.org/10.36094/sc.v91.2025.The_Mechanistic_Insights_of_Sitagliptin.Nag.603

Sci. and Cult. 91 (11–12) : 603-607 (2025)

The Mechanistic Insights of Sitagliptin in Ameliorating Colorectal Carcinoma

***Abstract*: Sitagliptin is a well known drug, widely used in the market against Type II diabetes to inhibit DPP4 and has shown good results in human with a few adverse effects. This review focuses on the efficacy of sitagliptin to inhibit colorectal cancer. It has been seen that Sitagliptin prevents the development of acryptic foci, and growth of tumor cells by reducing ROS levels, lowering IL6 expression, enhancing CD8+T cell infiltration and by modulating CD24, SOX4 and β catenin levels.**

Keywords: Sitagliptin, Colon cancer, mechanism of action, DPPIV inhibition

As one of the most common cancers worldwide, colon cancer is regarded as one of the major causes of death, along with lung, prostate, and breast cancer. The treatment of this common disease has made significant strides in recent years[1]. Colon cancer continues to rank among the leading causes of death globally for both men and women, despite years of research. Furthermore, tumour recurrence is observed in almost 50% of individuals with colorectal cancer. Colon cancer stem cells (CCSCs) have been linked to chemoresistance and cancer recurrence, according to recent studies. By continuously overexpressing their capacity for self-renewal, CSCs provide a sizable protumorigenic environment. Additionally, CSCs interact with immunological infiltrates, stromal cells, and cytokine-chemokines through cross-network, all of which enhance their capacity for aggressive proliferation[2]. Many considerations need to be made for patients with early-stage colon cancer who are thinking about adjuvant chemotherapy, including the chance of disease repetition, the chemotherapy's lifespan advantages, treatment toxic exposure, and the patient's coexisting medical problems. Chemotherapy, targeted therapy, immunotherapy, and microsatellite instability score are among the biomarkers that oncologists might use to customise systemic treatment regimens for metastatic colon cancer patients based on their unique needs[3]. Hence treatment strategies with drugs that show long term usage in patients with least toxicity and greater efficacy against the cancer is the requirement. Patients with type 2 diabetes mellitus are more likely to develop various cancers, including hepatocellular, colon, and pancreatic cancer.

The gastrointestinal incretin hormone glucagon-like peptide-1 (GLP-1) is released by enteroendocrine cells in response to food consumption. GLP-1 has three primary actions in blood glucose homeostasis: it decreases stomach emptying, boosts pancreatic production of insulin, and restricts pancreatic glucagon secretion [4]. DPP-4 inhibitors, such as sitagliptin (STG), have recently attracted interest as therapeutic possibilities for the the control of type 2 diabetes because DPP-4 efficiently degrades and eliminates GLP-1[5]. Dipeptidyl peptidase-4 (DPP-4) inhibitors have been used as a novel class of treatment for type 2 diabetes.

Dipeptidyl peptidase 4 (DPP4, sometimes referred to as CD26), has recently been linked to distant metastases and is identified as a hallmark of stemness (CSCs) in a variety of cancers. DPP4 is a multifunctional membrane molecule that has been associated with multiple cancer types, including colorectal cancer, due to its relationship with the tumour microenvironment and its extensive expression in T cells[6-8]. It has been shown that increasing DPP4 in colorectal cancer (CRC) enhances cancer expansion, progression, and metastasis, making it a potentially effective and unique treatment target. Thus, researchers have focused on DPP4's function in combating colon cancer.

For the treatment of adult patients with type 2 diabetes (T2D), the dipeptidyl peptidase-4 inhibitor sitagliptin is approved in more than 130 countries worldwide, both as solo and in conjunction with other antihyperglycemic medications. The glycaemic efficacy of oral sitagliptin (and other antihyperglycaemic medications) has been solidly proven by extensive clinical experience in a wide range of T2D patients, including those who are obese, elderly, or have impaired kidney function, as well as those who already have cardiovascular disease (CVD). Sitagliptin is usually well tolerated; the majority of side effects are mild to moderate in severity, and very few individuals stop taking the medication as a result of these occurrences[9]. Also sitagliptin showed protective effects on the cardiovascular events in diabetes patients[10] and it did not effect kidney outcomes in the patients with 5 years follow-up with sitagliptin[11]. This review focuses on the

efficacy of sitagliptin in colon carcinoma and studying its mechanism of action.

Mechanism of Action of Sitagliptin in Colon Cancer Cells

A preliminary study on colon cancer cell lines with Sitagliptin showed that using the MTT assay, it was discovered that it exhibits anticancer activity ranging from low to high concentrations when compared against the control. Sitagliptin was discovered to have an IC 50 value of 32.1 ìg/ml. Similar research has demonstrated that when sitagliptin is given to rats at a therapeutic dosage for humans, it also lowers blood ROS levels and colon carcinogenesis in rats[12]. Another report stated the role of sitagliptin on murine colorectal carcinoma murine model with type 2 diabetes mellitus. Individuals diagnosed with type 2 diabetes are recognised to possess a heightened vulnerability to colorectal neoplasia. DPP-4 inhibitors may raise the risk of colorectal tumours since the substrates for DPP-4 include chemokines like GLP-2 and stromal cell-derived factor-1 (SDF-1) and intestinotrophic hormones, which are linked to the development of tumours. It was observed that the long term administration of sitagliptin reduced the risk of colon cancer. Through the incretin effect, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1, two incretin hormones inactivated by dipeptidyl peptidase-4 (DPP-4), promote insulin secretion following an oral glucose load. This process may be slowed or missing in type 2 diabetes; however, insulin excretion can be revived by using pharmaceutical amounts of GLP-1. GLP-1 receptor agonists can increase the proliferation of pancreatic beta cells while reducing their death[13]. Proglucagon-derived peptide glucagon-like peptide 2 (GLP2) is generated by intestinal enteroendocrine L-cells and a specific subset of neurons in the brainstem, primarily projecting to the hypothalamus. At least in the animal model, GLP2 has positive effects on glucose metabolism, particularly in situations like obesity that are associated with increased energy absorption. In fact, proopiomelanocortin-expressing hypothalamic neurons in mice lacking the GLP2 receptor specifically exhibit decreased postprandial glucose tolerance as well as hepatic insulin resistance (due to increased gluconeogenesis)[14]. GLP-2 is a prospective target for the creation of innovative therapies for intestinal disorders since it has strong anti-apoptotic effects in the gastrointestinal system. Since DPP-4 quickly breaks down and deactivates GLP-2, DPP-4 inhibitors are also thought to be cutting edge methods for treating intestinal inflammation. In this experiment the administration of sitagliptin did not enhance the body weight in the leptin deficient colon cancer mice, however it increased the survivability rate in the mouse. It also lowered the mean number of tumors in the leptin deficient colon cancer mice. When comparing ob/ob animals to WT mice, there was a substantial increase in mucosal and plasma GLPs. On the other hand, STG had very little influence on the GLP concentrations in the mucosa and plasma of ob/ob mice. It appears that chronic STG treatment does not considerably change the metabolic status in ob/ob mice because the administration of STG did not significantly lower the plasma levels of resistin. The treatment of STG dramatically lowered the colonic mucosal IL-6 mRNA expression, which was significantly elevated in ob/ob mice compared to WT mice, according to real-time PCR analysis. However, the expression of TNF-á and IGF-1 was not changed in the mucosa. Thus in obese mutant mouse which continuously fed on food showed inhibition of colon tumorigenesis in a GLP independent manner and without effecting the metabolic pathways upon administration of Sitagliptin[4].

Another report of sitagliptin in colon cancer utilized the immunotherapy mechanisms to alleviate colon cancer. Tumour cells produce PD-L1, which attaches to PD-1 on T cells to disable these cells in order to evade detection and eradication by T cells. Consequently, T cell-mediated tumour cell death results from inhibiting this connection with monoclonal antibodies (mAbs) that target either PD-1 or PD-L1[15]. Sitagliptin monotherapy effectively decreased the growth of subcutaneously transplanted MC38 cells in WT C57BL/6 mice, according to a research conducted with a syngeneic mouse colon cancer model. In WT Balb/c mice, sitagliptin monotherapy dramatically reduced the proliferation of subcutaneously implanted CT26 cells, correspondingly. The number of tumoral infiltrating CD8+ T cells was significantly raised by sitagliptin according to immunohistological analysis of the MC38 and CT26 tumours. Sitagliptin was the first DPP4 inhibitor approved in 2006 for its use and have previously shown good results to prevent the proliferation of breast cancer cells. A recent study revealed that sitagliptin promotes CXCL10 and eosinophil infiltration to boost CD8+ T lymphocyte invasion and works in concert with anti-PD1 treatment for hepatcellular carcinoma[16]. Henceforth sitagliptin alleviated colon cancer by increasing the amount of tumoral infiltrated CD8+ T cells and improved the therapeutic impact of anti-PD1 on colorectal tumours[17].

In a different study, the growth impact of sitagliptin was observed in the colon and small intestine of mice, and it was investigated if sitagliptin encouraged colonic neoplasia in mice treated with carcinogens. No changes in body weight or colon weight was observed upon treatment

with Sitagliptin, although slight increase in intestinal weight was observed after 30 days of treatment. The DPP4 inhibition was more than 80% after 4 hours of administration of Sitagliptin. It was confirmed by the methylene blue staining of the colonic mucosa that no increase in count of acryptic foci or adenomas or mucin depleted foci was observed upon treatment with Sitagliptin. No significant increase in crypt depth or mucosal area was seen with Sitagliptin treatment, henceforth nullifying the possibility of causing colon neoplasia[18].

Another study reported the protective effects of Sitagliptin in 1,2-dimethylhydrazine-induced colon carcinogenesis in male F344 rats. Body weight or food consumption by rats were not affected by the treatment with Sitagliptin however the concentration of reactive oxygen species in the blood of rats were significantly lowered upon treatment with Sitagliptin. SITA treatment was associated with a substantial reduction in the number of MDF(mucin-depleted foci) precancerous lesions in the colorectum compared to control rats, suggesting that SITA may have a preventive effect against carcinogenesis. Sitagliptin, however, had little effect on the quantity of crypts that made up each focus. Additionally, morphometric measures of the small intestine revealed no change in response to Sitagliptin treatments. Rats administered with Sitagliptin had significantly less DPP4 activity in ileal mucosa homogenates than did the control group. In contrast, it did not significantly alter DPP4 activity in the serum. This report counteracted the tumorigenesis from the very beginning of the induction of the disease as compared to the previous report[18] which administered sitagliptin for a much shorter duration, allowing it to act on the disease only at the end of injecting DMH in mice. However apart from preventing tumorigenesis, this study did not see any change in metabolism, body weight or blood glucose levels upon treatment with sitagliptin thus suggesting that sitagliptin might control colon cancer but not reduce the blood glucose levels in colon cancer patients[19].

The ability to divide and replenish cells indefinitely is the property of cancer stem cells. They are identified by the expression of CD24, CD44, CD133, OCT4, aldehyde dehydrogenase 1 (ALDH1), and CXC-chemokine receptor 4 (CXCR4). Approximately 70% of CRC patients had high levels of CD24 expression, which has also been proven to have CSC characteristics, according to several studies. SOX4, a molecular marker controls the transcriptional level of the β-catenin/TCF4 pathway, which has been linked to the initiation of cancer recently. A greater number of van der Waals forces, salt bridges, pi-pi stacked, pi-pi shaped, pi-alkyl, and—most importantly—two typical hydrogen bonds and their minimal distance limitations were revealed by molecular docking interactions between sitagliptin and DPP4 and CD24. Sitagliptin was shown to have a higher affinity for CD24 than for DPP4 itself as binding energy with DPP4 was -7.4Kcal/mol and that with CD24 was -9.6Kcal/mol. Sitagliptin was also found to have strong binding energies for β-catenin and SOX4 with a binding affinity of -7.4 Kcal/mol and -9.1 Kcal/mol. Sitagliptin and β-catenin and SOX4 were shown to be interacting through conventional hydrogen bonds as well as amino acids, van der Waals forces, carbon-hydrogen bonds, halogens, and pi-pi stacking. Additionally, sitagliptin reduced the cell viability of DLD1 and HCT116 cells with IC50 values of 140 ìM and 270 ìM. The drug also showed considerable inhibition on the migration, sphere and colony formation for the DLD1 and HCT116 cells as confirmed by the in-vitro studies. Furthermore, the effect of sitagliptin with 5 fluorouracil decreased the colony formation or the sphere-forming ability much more as compared to treatment with only 5 fluorouracil. Western Blot studies showed that combination of sitagliptin with 5 fluorouracil showed greater inhibition on DPP4, CD24, SOX4 and β-catenin. Another study has also reported the prevention of colon cancer metastasis upon treatment with sitagliptin in animal models. A component of CD26-positive CRC cell lines' promotion of cell invasion, motility, and aggregation is the cell membrane glycoprotein CD26 with peptidase activity (DPP4). Assays measuring invasion and motility, which rely on the collagen matrix, exhibited a reduction following administration of sitagliptin, a DPP4 inhibitor[20]. A graphical abstract

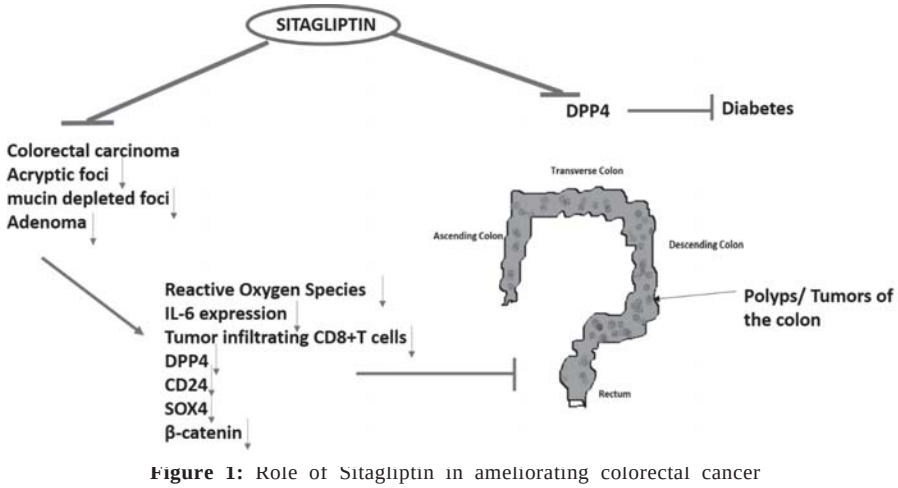

Figure 1: Role of Sitagliptin in ameliorating colorectal cancer

mentioning the mechanism of action of Sitagliptin on Colorectal Cancer has been illustrated in Fig 1.

Discussion

Sitagliptin a safe drug for combating diabetes mellitus has shown good results in ameliorating colon cancer in cell lines as well as in murine models. It reduces the mean number of tumors for colorectal carcinoma and reduced the number of mucin depleted foci in tumors by reducing the ROS levels in mouse blood, by inhibiting the expression of IL6 mRNA, increasing the number of tumoral infiltrating CD8+ T cells or eosinophils and by enhancing the therapeutic effect of anti-PD1 on tumor[17-19]. Increased counts of the acryptic foci,mucin depleted foci, adenomas or increase in crypt depth or mucosal area were not observed upon treatment with sitagliptin hence suggesting that it has no impact increasing the neoplastic lesion in colon cancer suggesting its safety. Although it did not enhance the body weight or the food consumption status in mice, it effectively increased the survivability of the mice induced with colon cancer, suggesting colon cancer patient longevity upon treatment with sitagliptin. Furthermore molecular docking has showed that sitagliptin reduces the growth or the metastatic potential of colorectal cancer stem cells by binding and inhibiting CD24 (cancer biomarker), SOX4 (cancer biomarker) and β-catenin/Wnt pathway. STGPT enhanced liver function, extended survival, and restored histological characteristics in hepatocellular carcinoma suggesting hepatoprotection[21]. Enhancing photodynamic tumour immunogenicity through regulating eosinophil chemotaxis and reviving T-cell immunity for activated cancer photo-immunotherapy is the goal of eosinophil-activating semiconducting polymer nanoparticles (SPNe). Through the use of a 1O2-cleavable thioketal linker, SPNe is made up of an amphiphilic semiconducting polymer and the dipeptidyl peptidase 4 (DPP4) inhibitor sitagliptin[22]. Sitagliptin nanoparticles also have the efficiency to kill breast cancer cells[23]. Hence it is suggestive that sitagliptin nanoparticles can combat colon cancer too.

Abdominal pain, diarrhoea were some clinical reports associated with sitagliptin administration, however it did not impact the body weight, blood pressure levels in

patients [24]. Also it did not show any adverse effects in kidney outcomes when administered for a period of 5 years[11]. Compared to patients receiving alternative diabetes medications, diabetic patients administered with the DPP4 antagonist sitagliptin had a higher overall survival rate following surgery for lung or colorectal cancer[22]. Although there are multiple reports of clinical study of sitagliptin on diabetes, there are no clinical trial reports of sitagliptin for the prevention of colon cancer.

Conclusion

The present study therefore repurposes sitagliptin for the inhibition of colon cancer progression and that it could be effective as a monotherapy or an adjuvant therapy with 5FU or other drugs. The study emphasizes that it could be administered in the form of nanoparticles to ameliorate the disease. According to our review, sitagliptin may be a useful adjuvant treatment for patients in between rounds of chemotherapy, offering a fresh way to boost immunity, maximise T-cell-mediated function, and extend overall survival for colon cancer. ❐

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Received: 22 July, 2024

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Letter to the Editor

Dr. Sanatan Koley <sanatankoley2017@gmail.com> Wed, Nov 19, 2025 at 5:39 PM

To: INDIAN SCIENCE NEWS ASSOCIATION <editorial.scienceandculture@gmail.com>, editor.scienceandculture@gmail.com

About the Editorial article on Gandhiji's Nobel snub

The Editorial article in the Sept-Oct '25 issue of The Science and Culture is an essential one which sheds light on Mahatma Gandhi's stature and impact as a world leader. We can only hope that his legacy drives mankind towards a peaceful and sustainable future in these trying times, when intolerance and violence are shamelessly politicised.

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