

Anti-Cancer Effect of Solanum Nigrum on Colorectal Cancer

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Abstract

Colorectal cancer is the third most occurring cancer in the world. The major causes of colorectal cancer are obesity, poor nutritional habits and eating patterns, smoking, and the progressive aging of the population. The Solanum nigrum is a shrub-like plant traditionally used for curing many diseases, using the various parts of Solanum nigrum. Solanum nigrum is therapeutically used for gouty joints, anti-tuberculosis, cough, inflammation, skin diseases, digestive issues, asthma, rheumatic arthritis, nausea, cardiogenic, and various nerve disorder, and for depressing and calming the Central nervous system (CNS) and spinal cord. Solanum nigrum also shows the anti-cancer effect on liver cancer, lung cancer, prostate cancer, and breast cancer. The glycoproteins constituents and glycoalkaloids like alpha-solanine of Solanum nigrum have an anti-cancer effect on colorectal cancer. Glycoproteins and alpha-solanine can target and cause apoptosis, control the Reactive oxygen species (ROS) mechanism and inhibit the expression of various mutated genes making possible therapeutic solutions for colorectal cancer. Further, research on Solanum nigrum will open many other therapeutic targets like other apoptotic genes B-cell lymphoma (BCL) and BCL-2 associated x (BAX) proteins in colorectal cancer. This review aims to understand the effect of Solanum nigrum on Colorectal cancer.

Keywords

Colorectal cancer, glycoproteins, solanine, apoptosis.

Introduction

Colorectal cancer is the most occurring cancer after lung cancer and breast cancer in cancer pathology.^{1,3} In current times, colorectal cancer is the most common cancer in the gastrointestinal tract. Colorectal cancer is the most occurring type of cancer after breast cancer in women and the third most occurring type of cancer in men after lung and prostate cancer.¹ Across the world, 1.8 million cases are observed per year. A high rate of occurrence of colorectal cancer cases is seen in countries like Hungary, South Korea, Slovakia, the United States across the world.¹ The major causes of colorectal cancer are obesity, poor nutritional habits and eating patterns, smoking, and the progressive aging of the population.³ The rise of colorectal cancer is also seen in the younger generation due to lifestyle changes. People aged above 65 and having a genetic history of colorectal cancer are at high risk of occurring of colorectal cancer.^{3,15}

Poor nutrition, poor lifestyle choices, and genetics may cause mutation in various genes in the gastric canal cells. The major genes involved in colorectal cancer are Adenomatous polyposis coli (APC), Deleted in colorectal carcinoma (DCC), B-raf protein (BRAF), Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA), Protein B kinase (AKT), Tumor protein-53 (TP53), K-ras proteins (K-RAS), and Catenin B protein (CTNNB).³ These genes and proteins play important role in the cell cycle, cell progression, and cell proliferation in both normal cells and cancer cells, which makes potential therapeutic targets for cancer. In colorectal cancer treatment, K-RAS mutation is considered a bad prognosis but it is also considered to be a biomarker that predicts the response to the treatment.³

The current curative treatments for colorectal cancer across the world are surgery, chemotherapy, and radiation therapy.⁴ These current treatments are having many side effects on the patient. Although surgery is currently the most effective treatment but recurrence of cancer is observed in many patients. Similarly, for chemotherapy there are many side effects such as neutropenia, nausea, vomiting, hepatorenal toxicity, and also may show low efficacy in many patients.⁴ Due to these side effects, alternative herbal medicine is being studied for a few decades. Many compounds originating from plants are evaluated for potential chemopreventive activity and also, these plant compounds are used to prevent the development of cancer.⁴ According to traditional Chinese medicine, *Solanum nigrum* can be used

therapeutically for various types of cancer specifically, colorectal cancer.⁴ This review aims to understand the effect of *Solanum nigrum* on Colorectal cancer.

***Solanum nigrum* – The plant:**

The *Solanum nigrum* also commonly known as black nightshade belongs to the Solanaceae family of plants. *Solanum nigrum* is a shrub-like plant that grows in various countries around the world. It grows wildly as a weed in the field, building areas, under trees, and wasteland.⁵ Some African and North American countries do semi-cultivate for many purposes.⁵ *Solanum nigrum* is therapeutically used for various diseases condition. *Solanum nigrum* and many species of the same family are used as traditional medicine in various Asian countries for many diseases condition.⁵ Various parts of *Solanum nigrum* are used for many disease conditions such as gouty joints, anti-tuberculosis, cough, inflammation, skin diseases, digestive issues, asthma, rheumatoid arthritis, nausea, cardiogenic, for various nerve disorders and for depressing and calming the Central nervous system (CNS) and spinal cord.^{5,6}

Solanum nigrum has shown the anti-cancer effect on liver cancer, lung cancer, prostate cancer, and breast cancer through various cellular mechanisms like apoptosis, control Reactive oxygen species (ROS) production.^{5,9,10,11,12,13}

Solanum nigrum contains secondary metabolites like alkaloids, glycoalkaloids, flavonoids, tannins, glycosides, coumarins, glycoproteins, steroids, and saponins. *Solanum nigrum* contain macromolecule like carbohydrate, proteins, lipids.⁵ These secondary metabolites are non-essential molecules produced by plants as their defense mechanism against the various pathogens in nature. These secondary metabolites exhibit anti-oxidant, anti-inflammatory, radical scavenging, and anti-tumor properties which makes them highly therapeutic for many diseases and cancer conditions in animals and humans.^{5,6,7,8}

Current research based on the effect of *solanum nigrum* on colorectal cancer:

The anti-cancer of *Solanum nigrum* and its components are studied and understood mostly in in-vitro studies and also in vivo studies. The in-vitro studies are done on carcinoma cell lines like HCT-116, HT-29, and RKO, microfluid system, and tissue culture, whereas in-vivo studies are done on rats and zebra fishes. The cell lines like HCT-116, HT-29, and RKO are human colorectal carcinoma cell lines extensively used for colorectal cancer

research. The anti-cancer effect of *Solanum nigrum* was studied and examined by targeting various genes, transcriptional factors, and cellular mechanisms found in colorectal cancer.

Effect of *Solanum nigrum* on the proliferation of colorectal cancer cells:

Cell proliferation is one of the prominent characteristics of colorectal cancer. Cell proliferation along disturbed balance in cell loss and cell gain may lead to metastasis and invasion in colorectal cancer development.¹⁴

To study cell proliferation, 4,5- dimethyl thiazol-2-yl (MTT) assay is performed on the cancerous cells. MTT assay is the colorimetric method used to check viability (cytotoxicity) and proliferation of cells. This assay helps to understand dead and live cells based on the treatment of *solanum nigrum*.

Solanum nigrum shows a strong cytotoxic and anti-proliferative effect on various colorectal cancer cells (cell lines). Alpha – solanine are glycoalkaloids, extracted from *Solanum nigrum* have shown an anti-proliferative effect in the dose and time-dependent manner on RKO cells.²⁰ The glycoproteins of *Solanum nigrum* have also shown anti-proliferative effect in the dose and time-dependent manner on HT-29 and HCT-116 cells through MTT assay.^{17,18,19} These anti-proliferative effects of phytochemicals of *Solanum nigrum* show the potential anti-cancer activities on colorectal cancer.

Anti-oxidative effect of *solanum nigrum* on the production of reactive oxygen species in colorectal cancer cells:

Reactive oxygen species (ROS), also called free radicals are products of a cellular mechanism having a specific role in normal cells to maintain normal cellular function.¹⁵ ROS increases in cancer cells which activate various signaling pathways during tumor progression leading high proliferation rate. So, the need for potent antioxidants in our diet and drug supplements is very necessary for Colorectal cancer.¹⁵

Solanum nigrum glycoproteins showed dose-dependent radical scavenging activities including 1, 1-diphenyl-2-picrylhydrazyl radicals (DPPH), superoxide radicals (O_2^-) & hydroxyl radicals (OH). The antioxidant properties of *solanum nigrum* glycoprotein may induce apoptosis by reducing oxidative stress in HT-29 cells. The ethanol extract of the whole plant of *Solanum nigrum* shows hydroxyl radical activity through increasing the concentration

of the solutes in cells. The glycoproteins also showed a significant reduction in nitric oxide radicals' production.¹⁷

Alpha – solanine of *Solanum nigrum* increased the ROS production in RKO cells which causes apoptosis (cell death) of cells. High levels of ROS production in cancer cells may cause apoptosis.²⁰ Different components of *Solanum nigrum* may show anti-cancer activities through a different mechanism. An increase or decrease of ROS can cause cell death depending on treatment, cells, and cell conditions

Apoptotic effect of solanum nigrum on colorectal cancer cells:

Apoptosis is programmed cell death, in which a highly complex cascade of cellular events that results in chromatin condensation, DNA fragmentation, cytoplasmic membrane breaking, and cell shrinkage. Caspase cascade is a group of cysteine proteases that trigger apoptosis in the cells. Caspase -3 and caspase -9 are therapeutic targets for colorectal cancer. Apoptosis is an important cancer therapeutic target, the assessment of molecular mechanisms and targeting of apoptosis-related genes lead to a new therapeutic target in curing cancer.¹⁷

The glycoproteins cause DNA fragmentation in the HCT-116 and HT-29 cell lines in a dose-dependent manner, studied through the Electrophoresis technique.^{16,17,18,19} In many studies, the fluorescence technique is used to study DNA fragmentation quantitatively.

Glycoproteins also induce apoptosis by inhibiting the expression and signaling of Nuclear factor-kappa B (NF-kB) in the colorectal cancer cell. NF-kB is a nuclear factor, also a protein complex that controls the transcription of DNA and cell survival. The inhibition of expression and signaling of the NF-kB pathway in the cells may cause apoptosis of cells. Glycoproteins also induce apoptosis through activation of caspase -3, Prolactin receptor-associated protein (PRAP), and inhibiting the production of Nitric Oxide.¹⁹ *Solanum nigrum* is one of the agents that's blocks 12-o-tetradecanoyl-phorbol-13-acetate (TPA) -induced signal responses in the cancer-tumor cells.⁵

Alpha-solanine also induces apoptosis through DNA fragmentation in a dose-dependent manner in RKO cells, studied through flow cytometry technique and fluorescence

techniques.²⁰ Alpha-solanine affects the caspase mechanism by targeting caspase 3, caspase 6, and caspase 9 and inducing apoptosis in RKO cells.²⁰

Effect of Solanum nigrum on metastasis, invasion & tumor growth in colorectal cancer cells:

Metastasis is a biological process, which includes tumor cells diffusing from the group of primary abnormal cells (lesion), adhering to blood/lymphatic vessels, entering the blood/lymphatic circulation, adhering to the vascular endothelium, invading into target organs, and then proliferating to form metastatic condition. Metastasis and invasion are major characteristics of colorectal cancer and they may lead to liver and lung cancer. Alpha-solanine inhibits migration and invasion in HCT-116 cell lines in a dose-dependent manner.²⁰

Alpha-solanine inhibits tumor growth in tumor weight and tumor volume in the nude mice. Alpha solanine targets and inhibits the Ki-67 proliferation marker in the cells of tumorous mice. Ki-67 is a nuclear protein, also used as a marker and therapeutically associated with cell proliferation and cells cycle. Alpha-solanine induces apoptosis in tumorous cells of mice through DNA fragmentation and activation of the caspase cascade.²⁰

Conclusion

Solanum nigrum has been used as a folk therapeutic agent for many years. In previous studies, glycoproteins and solanine steroids isolated from Solanum nigrum had shown anti-cancer on various cancer like liver cancer, prostate cancer, breast cancer, and stomach cancer. This review demonstrates the anti-cancer effect of glycoproteins and solanine of Solanum nigrum on colorectal cancer in in-vitro and in vivo conditions.

Glycoproteins and solanine show the cytotoxic effect on HT-29 and HCT-116 cells, studied through MTT assay. MTT assay is used to study cytotoxicity/proliferation in normal cells and cancer cells.

Apoptosis is the event of cascade reaction mediated by caspase complex and it is an important mechanism for cancer therapy. In the present review, after the treatment of glycoproteins and solanine, the carcinoma colorectal cells showed apoptotic cell morphology like fragmented nuclei and these cells are densely stained with fluorescence stains due to DNA

fragmentation. The glycoproteins and solanine induce apoptosis by activation of caspase complex and inhibition of NF-kB in colorectal cells.

Reactive oxygen species (ROS) are products of cellular metabolism. The increase and decrease levels of ROS compared to the normal range of ROS in cells can cause apoptosis. Induction of ROS levels is crucial for tumor therapy. The present review shows glycoproteins have anti-oxidant properties, which lowers the level of ROS in the cells causing the apoptosis of the cells whereas solanine caused the apoptosis of cells by increasing the production of ROS in the cells.

Tumor metastasis is a multiple-step biological process, starting from tumor cells diffusing from the primary lesions, adhering to the vascular endothelium, invading into target organs, and then proliferating to form a metastatic condition. In the present reviews, alpha-solanine inhibits the metastasis, invasion, and adhesion of colorectal cancer. Alpha-solanine may have an inhibitory effect on Mycophenolate mofetil (MMF) genes. MMF- 2 and MMF -9 are metastatic genes that play a key role in the metastasis of cancer cells.

In conclusion, the present review shows glycoprotein and alpha-solanine of *Solanum nigrum* have an anti-cancerous effect on colorectal cancer through apoptosis, ROS mechanism, and inhibiting various genes and metastasis.

Future aspects of research of *Solanum nigrum*:

In the future, other phytochemicals of *Solanum nigrum* should be studied for anti-cancer activity on colorectal cancer and as well as other cancers. Glycoproteins and alpha-solanine can be studied on many other apoptotic genes like B-cell lymphoma (BCL) genes, angiogenesis genes like MMF -3 and MMF -9 and also should research in an in-vitro system.

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