



A narrative review of the antitumor studies of solanine

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Abstract: Cancer is a major worldwide public health problem. With the popularity of medical examinations, the improvement of surgical procedures and the application of antitumor drugs, the mortality rate of cancer has declined in recent years, but the quantity remains extremely high. At the same time, with the emergence of tumor drug resistance, it is particularly urgent to seek new and effective drugs for tumor treatment. Solanine, a type of steroidal alkaloid, is the main extract of *Solanum nigrum* L. Because of its wide biological activity, it has attracted increasing attention, specifically, towards the empirical study of its antitumor activity. This article summarizes the research progress of the antitumor effect and mechanism of solanine over the past 20 years, to provide a reference for workers in the field of cancer research. Studies from 2000 to 2020 were reviewed from PubMed, Springer Link and the Web of Science using the keywords *Solanum nigrum* L., solanine, α -solanine, β -solanine, γ -solanine, tumor, cancer and their combinations. Exclude research articles of extraction mixture. Language is limited to English. Solanine shows antitumor ability against different tumors by targeting different proteins. Although there is a lack of clinical large-scale studies, a large number of basic pharmacological and toxicological studies have confirmed that solanine may be a new effective cancer drug or adjuvant therapy. Solanine preparations and solanine derivative preparations have broad economic and scientific research prospects.

Keywords: *Solanum nigrum* L.; solanine; tumor

Submitted Oct 19, 2020. Accepted for publication Jan 22, 2021.

doi: 10.21037/tcr-20-3094

View this article at: <http://dx.doi.org/10.21037/tcr-20-3094>

Introduction

Cancer is a major worldwide public health problem. With the popularity of medical examinations, the improvement of surgical procedures and the application of antitumor drugs, the mortality rate of cancer has declined in recent years, but the quantity remains extremely high (1,2). In particular, early diagnosis of some tumors, such as pancreatic cancer, is difficult, and patients often lose the chance of surgery by the time they are diagnosed. At the same time, with the emergence of tumor drug resistance, it is particularly urgent to seek new and effective drugs for tumor treatment.

Solanum nigrum L. is a traditional medicinal plant.

A large number of studies have confirmed that *Solanum nigrum* extract has significant antitumor activity (3-5). With further purification and analysis, it was found that solanine was one of the most important bioactive components. Solanine is a natural steroidal alkaloid, first discovered in 1820, and was later found to be ubiquitous in plants, such as potatoes and tomatoes. Solanine is divided into α -solanine, β -solanine, and γ -solanine, of which the α -solanine content is the highest (6). Therefore, an increasing number of scholars have begun to study the treatment of tumors with solanine or its component α -solanine (7,8).

This review collects the latest research on the different roles of solanine in the treatment of cancer and suggests

that solanine is a promising drug candidate that can be used alone or in combination with other drugs as an effective antitumor drug. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-3094>).

Methods

Studies from 2000 to 2020 were reviewed from PubMed, Springer Link and the Web of Science using the keywords *Solanum nigrum* L., solanine, α -solanine, β -solanine, γ -solanine, tumor, cancer and their combinations. Exclude research articles of extraction mixture. Language is limited to English.

Discussion

Anti-cell proliferation

Due to genetic and epigenetic mutations, a rapid cell proliferation rate has become one of the basic characteristics of cancer. Growing tumors not only promote the production of cachexia, but also exert pressure on local organs. Some studies indicate that α -solanine downregulates S100 calcium binding protein P (S100P) expression in colorectal cancer cells in a dose- and time-dependent manner, while blocking the cell cycle at G0/G1 phase, and inhibiting the expression level of cyclin D1 and CDK2, thereby inhibiting the proliferation of human colorectal cancer cells (9,10). Solanine also inhibits the proliferation of human prostate cancer xenografts in nude mice by significantly inhibiting the mRNA and protein expression of cyclin D1, cyclin E1, cyclin dependent kinase 2 (CDK2), CDK4 and CDK6 *in vivo* (11,12). A number of studies have confirmed that solanine has strong anti-cell proliferation effects on leukemia (13,14), endometrial cancer (15), liver cancer (16,17), esophageal cancer (18), pancreatic cancer (19) and so on (20).

Induction of apoptosis

Apoptosis is a type of programmed cell death controlled by gene regulation. Maintaining homeostasis of cell numbers requires a balance between the effects of proliferation and apoptosis. Inducing apoptosis has become a new model for the study of cancer therapy. In-depth study of the regulatory mechanism of drug-induced apoptosis provides new ideas and methods for the development of cancer drugs. One study found that solanine opened the

permeability transition channel in the membrane, which led to an increase in Ca (2+) concentration, thus causing membrane rupture and releasing caspase-activating factors (21). Additionally, solanine induces apoptosis of cells by regulating the ROS and Bax/Bcl-2 pathway (11,14). The combination of multiple studies illustrates that apoptosis is another important mechanism by which solanine exerts its antitumor effects (22,23).

Induction of autophagy

Autophagy is the self-digestion of cells. What distinguishes autophagy from cell necrosis is that autophagy breaks down organelles and cellular proteins through lysosomes. Under normal conditions, cell autophagy is maintained at a low basal level, but increasing studies have found that inducing autophagy in tumor cells may be an important direction for the development of new antitumor drugs. Experiments such as electron microscopy observation, western blotting detection of autophagy markers, and immunofluorescence detection of microtubule-associated proteins 1A/1B light chain 3B (LC3) found that α -solanine increases levels of intracellular oxygen free radicals and induces autophagy through the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway (24). Thus, α -solanine can be used as a potential inducer of autophagy.

Restrained migration and invasion

Tumor recurrence and metastasis are the main causes of death of most cancer patients. The epithelial-mesenchymal transition (EMT) plays an important role and gives cells a greater ability to move and invade. Matrix metalloproteinases (MMPs) are the main proteases involved in tumor cell metastasis, spread and invasion (25). The expression of MMP-2 and MMP-9 decreases in cancer cells treated with α -solanine (26,27). While the expression level of E-cadherin is significantly higher (18). Lv (19) also found that solanine inhibits the migration and invasion of the human pancreatic cancer cell lines PANC-1, SW1990, and MIA PACA-2 in a dose-dependent manner by inhibiting the expression of MMP-2/MMP-9 and reducing E-cadherin loss (23).

Inhibition of angiogenesis

Angiogenesis plays an important role in the growth and development of tumors. Vascular endothelial growth factor (VEGF) is currently the most effective angiogenic

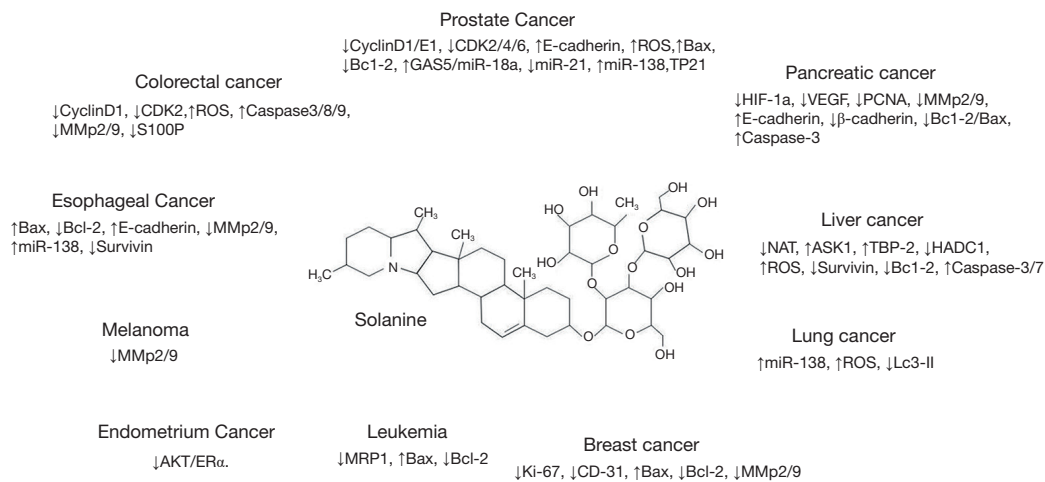


Figure 1 The main proteins targeted by solanine in different cancers. ↓ Downregulation/inhibition; ↑ upregulation/activation.

factor. In addition to the effects on angiogenesis and vascular permeability, autocrine VEGF also promotes the dedifferentiation and the EMT of tumors through AKT and extracellular signal-regulated kinase (ERK) 1/2, further enhancing tumor invasion and viability, and plays an important role in the function and self-renewal of tumor stem cells. Several studies have confirmed that α -solanine significantly reduces the expression of VEGF in tumors and thus inhibits the survival of blood vessels (19,28). Hypoxia is one of the basic characteristics of tumors (29). α -Solanine inhibits VEGF expression by downregulating the ERK1/2-hypoxia-inducible factor-1 α and signal transducer and activator of transcription 3 signaling pathways under hypoxic conditions (30).

Improved sensitivity of chemoradiation

Radiotherapy and chemotherapy are currently the main treatment for patients who cannot surgically remove malignant tumors, and is used in all stages of tumor treatment. The different sensitivity of radiotherapy and chemotherapy leads to different efficacy. α -Solanine upregulates the expression of miR-138 in esophageal cancer cells to downregulate survivin expression and enhance the sensitivity of esophageal cancer cells to chemotherapy and radiotherapy (31,32). Zhang *et al.* demonstrated similar results in lung adenocarcinoma cells (33). At the same time, studies have pointed out that the growth arrest specific 5 (GAS5)/miR-18a axis is another important mechanism promoting the radiosensitivity of prostate cells (12). In the study of leukemia, solanine increases the chemical sensitivity

of acute lymphocytic leukemia to doxorubicin, and reverses multidrug resistance in chronic myelogenous leukemia cells by downregulating multidrug resistance protein 1 (MRP1) expression (13,14).

Inhibition of tumor immune escape

In tumor development and distant metastasis, immune dysfunction is an important influencing factor (34). Tumor immune escape refers to the phenomenon in which tumor cells escape recognition and attack by the body's immune system through a variety of mechanisms, so as to survive and proliferate in the body. It is reported that Solanine may enhance the antitumor immune response by downregulating the proportion of CD4+ CD25+ Treg and the expression of Foxp3 and TGF β in tumor tissues (35).

Summary and outlook

Nowadays, there is a growing concern for discovering drugs from plants which has been playing an increasingly important role in development of anti-tumor drugs. *Solanum nigrum* is known by the general public as a widely distributed medicinal material. It has advantages of easy acquisition, convenient processing and excellent curative effects; thus, it has good economic development and scientific research value. Solanine shows antitumor ability against different tumors by targeting different proteins (Figure 1). Although there is a lack of clinical large-scale studies on the efficacy of solanine, a large number of basic pharmacological and toxicological studies have confirmed

that solanine has good antitumor effects. The development of new solanine preparations or their derivative preparations is still one of the key concerns of solanine researchers (36). Indeed, the current research on solanine is in its infancy, and the detailed antitumor mechanism needs to be further explored. In addition, the reported research results need to be verified by other researchers. What is credible is that the development and research of solanine preparations and solanine derivative preparations have broad economic and scientific research prospects.

Acknowledgments

Funding: The present study was funded by the Wenzhou Municipal Science and Technology Bureau (No. Y20190194).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-20-3094>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-3094>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Luo S, Tian GJ, Yu FX, Wen ZD. A narrative review of the antitumor studies of solanine. *Transl Cancer Res* 2021;10(3):1578-1582. doi: 10.21037/tcr-20-3094