

RETRACTED ARTICLE: Solasodine, Isolated from *Solanum sisymbriifolium* Fruits, Has a Potent Anti-Tumor Activity Against Pancreatic Cancer

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Background: Increasing evidences have revealed that solasodine isolated from *Solanum sisymbriifolium* fruits, has multiple functions such as anti-oxidant, anti-tumor and anti-infection. However, its role in pancreatic cancer has not been well studied.

Methods: To explore the role of solasodine in pancreatic cancer, human pancreatic cell lines including SW1990 and PANC1 were treated with different concentrations of solasodine for 48 h, and cell viability was evaluated by MTT assay, cell invasion and migration were evaluated by Transwell assay. The effect of solasodine on the apoptosis of SW1990 and PANC1 cells was detected by flow cytometry. To further explore the antitumor effect of solasodine in vivo, an SW1990 tumor-bearing mouse model was constructed. The effects of solasodine on cytokines in the serum of SW1990 tumor-bearing mice were also evaluated by ELISA assay.

Results: Specifically, in vitro, solasodine could significantly inhibit the proliferation of pancreatic cancer cell lines SW1990 and PANC1 cells. Flow cytometric analysis indicated that solasodine could induce apoptosis of SW1990 and PANC1 cells. Western blot assay indicated that solasodine could significantly inhibit the activation of Cox-2/Akt/GSK3 β signaling pathway. Meanwhile, the release of Cytochrome c from mitochondria to cytoplasm which can raise the caspases cascade (C-caspase 3 and C-caspase 9) was significantly enhanced by solasodine. In vivo, the results showed that solasodine had potent anti-tumor activities with a lower cytotoxicity. In addition, the serum TNF- α , IL-2 and IFN- γ levels in SW1990 tumor-bearing mice after the treatment of solasodine was significantly increased.

Conclusion: Taken together, our results suggested that the solasodine could prevent the progression of pancreatic cancer by inhibiting proliferation and promoting apoptosis, as well as stimulating immunity, suggesting that solasodine might be a potential therapeutic strategy for pancreatic cancer.

Keywords: pancreatic cancer, solasodine, Cox-2/Akt/GSK3 β signal pathway, apoptosis, apoptosis

Introduction

Pancreatic cancer ranks the fourth leading cause of cancer-related deaths in the western world with the increasing incidence every year.¹ And a large number of pancreatic cancer patients are diagnosed with either locally advanced unresectable disease due to an extensive vascular infiltration, or metastatic disease.² Pancreatic cancer is difficult to treat because many patients are diagnosed at a later stage in which the tumor has spread.³ However, a lot of patients with later-stage diagnoses when surgery is not possible, chemotherapy and radiation therapy are available

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treatment options.⁴ Despite many advantages on the various therapies in pancreatic cancer and its serious effects in healthy human health, the identification and development of specific, efficient and low toxicity therapeutic drugs for pancreatic cancer is still an urgent need.

Recently, several potential chemotherapy drugs and better action mechanisms against pancreatic cancer have been developed and studied. Gemcitabine has been considered as the standard treatment and has been widely utilized as a first-line drug for advanced pancreatic cancer.⁵ Two combination regimens for metastatic pancreatic cancer turned out to be gold standards in recent years: 5-fluorouracil (5-FU)/leucovorin with irinotecan and oxaliplatin (FOLFIRINOX).⁶ In addition, a recent study showed that adjuvant therapy with a modified FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and fluorouracil) regimen brought a profoundly longer survival than gemcitabine among resected pancreatic cancer patients.⁷ Despite many advantages in the treatment, the fundamental reasons for these frustrating outcomes are related to the development of chemical resistance,⁸ it is necessary to identify more effective treatment agents for preventing pancreatic cancer progression.

Solasodine is isolated from *Solanum sisymbriifolium* fruits,⁹ which has been identified to exhibit a series of functions including anti-oxidant, antitumor and anti-infection.^{10–12} In the last decades, solasodine has also been demonstrated that can play potent anticancer activities through inducing cancer cells apoptosis and cell cycle arrest in breast cancer, oral epidermal carcinoma, chronic myelogenous leukemia, prostate cancer and basal cell carcinoma.^{13–15} Based on its wide antitumor effect in various human cancers, the effects and specific mechanisms of solasodine in pancreatic cancer remains unclear and attracted us to further focus on it.

Recent studies have been demonstrated that the activation of Cox-2/p-Akt/p-GSK3 β /signaling pathway can lead to tumor progression.¹⁶ And many treatment drugs targeting Cox-2/p-Akt/p-GSK3 β /signaling pathway to prevent the progression of various cancers such as gastric cancer, breast cancer and colon cancer have been identified. For instance, Compound Wumei Powder (CWP) has been reported to inhibit invasion and metastasis of gastric cancer through activating the Cox-2/PGE2-PI3K/AKT/GSK3 β / β -catenin pathway.¹⁷ Coagulation factor VIIa-mediated activation of protease-activated receptor 2 can result in β -catenin accumulation via the AKT/GSK3 β pathway and contributes to the development of breast cancer.¹⁸ Piroxicam, a traditional

NSAID and c-phycocyanin, a newly discovered COX-2 selective inhibitor, constitutes remarkable chemopreventive targets in mediating apoptosis in the DMH (1,2-dimethylhydrazine) induced early rat colon carcinogenesis via regulating PI3-K/Akt/GSK-3 β /PTEN signaling pathways.¹⁹ Meanwhile, an earlier study showed that caspase 3 can promote tumor growth by providing a pro-angiogenic microenvironment.²⁰ Cytochrome C normally functions its role via the association with other molecules to form a caspase-9-activating complex which plays a key role in the caspase-dependent apoptotic pathway.²¹ Cytokines such as TNF- α , IL-2 and IFN- γ are molecular messengers of the innate and adaptive immunity that enable cells of the immune system to recognize and destroy cancer cells, and have been considerably interest in harnessing cytokines for the treatment of cancer over the past decades.²²

In this study, we selected the CTX treatment as the control to compare the antitumor effect of solasodine in pancreatic cancer. CTX has been identified to have effective anticancer activities against pancreatic cancer.²³ Our results demonstrated that solasodine could efficiently inhibit cell growth of pancreatic cancer cell lines (SW1990 and PANC1 cells) by promoting apoptosis in vitro and partially through inhibiting the activation of Cox-2/p-Akt/p-GSK3 β /signaling pathway. Further, the results in vivo indicated that solasodine could efficiently inhibit tumor growth than CTX treatment in the SW1990 tumor-bearing mouse model. Our data contributed to understand the complex mechanism in the progression of pancreatic cancer and provided that solasodine might be an efficient therapeutic drug for pancreatic cancer.

Materials and Methods

Materials

Solasodine (purity >98%) was purchased from Wuhan doctoral Bioengineering Co., Ltd (Wuhan, China) and used for subsequent experiments. All of the other chemicals and solvents were commercially available and used as received. The chemical structural of solasodine is shown in Figure 1.

Cell Culture

Human pancreatic cancer cell lines (SW1990 and PANC1) were purchased from the American Type Tissue Culture Collection (ATCC). Cells were cultured with RPMI-1640 medium containing 10% FBS, 100 U/mL penicillin and 0.1 mg/mL streptomycin at 37 °C with 5% CO₂.

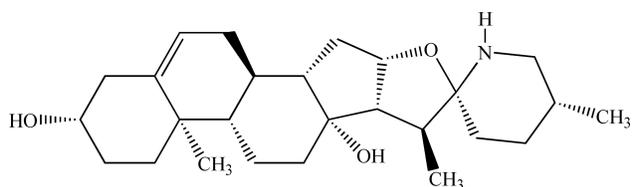


Figure 1 The structural formula of solasodine.

Cell Viability Assay

The antiproliferative and cytotoxic roles of solasodine in SW1990 and PANC1 cells were examined by MTT assay.²⁴ Briefly, approximately 2×10^4 SW1990 and PANC1 cells were plated into 96-well microplates and cultured for 12 h. Cells were treated with various concentrations of solasodine (0, 2.5, 5, 10, 20 and 40 $\mu\text{g}/\text{mL}$) for 24 h. After treatment, 10 μL 5mg/mL MTT solution was added to each well and incubated for 10 min, and 150 μL dimethylsulfoxide (DMSO) was added and the absorbance (570 nm) was detected using an ELISA reader.

Colony Formation Assay

Colony formation assay was performed as previously described with minor modifications.²⁵ Cells were seeded into 6-well plates and incubated with DMEM medium containing 10% FBS and the number of colonies in each well was approximately 1000/well. After treated with different 0, 2.5, 5, 10, 20 and 40 $\mu\text{g}/\text{mL}$ for 2 weeks, cells were washed with PBS, fixed in methanol and stained with 1% crystal violet dye, then the numbers of colonies were counted under a light microscope.

Cell Invasion and Migration Assay

Cell invasion and migration was performed by using Transwell assay as previously described.²⁶ Briefly, 1×10^5 cells were plated into the upper chambers with serum-free medium. The lower chambers were filled with medium containing 20% FBS. After incubation for 24 h with different concentration of solasodine (0, 10, 20 and 40 $\mu\text{g}/\text{mL}$), cells were fixed by 4% paraformaldehyde and stained with crystal violet. The migration assay was performed similarly without coating the membranes with Matrigel™. The number of invasion and migration cells were photographed and counted under a microscope.

Analysis of Apoptosis

Apoptosis-mediated cell death of cells was examined using Annexin V-FITC/PI apoptosis detection kit

according to the manufacturer's instructions. Flow cytometric analysis was performed using a FACSCalibur flow cytometer within 1 h after supravital staining.

Western Blot

Total protein of cultured cells was extracted using the RIPA Lysis Buffer according to the manufacturer's instructions. Approximately 50 μg of protein was separated by SDS-PAGE and then transferred to PVDF membranes. After blocking with 3% BSA, the membranes were incubated with primary antibodies (1:1000, Cambridge, MA) for Cox-2, p-Akt, Akt, GSK3 β , p-GSK3 β , C-caspase-9, C-caspase-3, Bcl-2, Bax, Cyto C and overnight at 4°C, with β -actin as internal reference. Finally, the membranes were exposed to horseradish peroxidase-labeled IgG for 1 h, and the bands were visualized by a Bio-Rad imaging system.

Animal Experiments

The SW1990 tumor-bearing mouse model was constructed as previously described with minor modification.²⁷ SW1990 cells were intraperitoneally injected into BALB/c nude mice, the ascites was taken from mice and diluted to 1×10^7 cells/mL with physiological saline. Then, 0.2 mL of diluted cells was subcutaneously injected into the right armpit of mice. This study was approved by the Animal Ethics Committee of Shidong Hospital affiliated to the University of Shanghai For Science and Technology. When tumors reached approximately $\sim 50 \text{ mm}^3$, 60 BALB/c mice (sex in half. Male; 6-weeks old; $20.0 \pm 2.0 \text{ g}$) were randomly divided into six groups (n=10): PBS group, low-dose group (solasodine, 10 mg/kg), medium-dose group (solasodine, 20 mg/kg), high-dose group (solasodine, 40 mg/kg) and positive control group (CTX, 25 mg/kg) by peritoneal injection; 10 days after treatment, mice were sacrificed through by cervical dislocation, and the tumors from different groups were also removed and weighed, tumor volume was calculated every one week for 5 weeks according to the following formula: tumor volume = length \times width²/2.

Statistical Analysis

The data are presented with means \pm SD method and analyzed by the SPSS software (version 18.0). Difference was tested using unpaired *t*-test (two groups) or ANOVA method (multiple groups) followed by a post hoc test. With $P < 0.05$ as the significant threshold.

Results

Solasodine Inhibited the Cell Viability of SW1990 and PANC1 Cells in vitro

The chemical structure of solasodine is shown in Figure 1. We first explored the effect of different concentrations of solasodine (0, 2.5, 5, 10, 20 and 40 $\mu\text{g}/\text{mL}$) in the pancreatic cancer cell lines (SW1990 and PANC1) for 24 h, and the results indicated that 10, 20 and 40 $\mu\text{g}/\text{mL}$ solasodine significantly inhibited the cell viability of SW1990 (Figure 2A) and PANC1 (Figure 2B). In addition, we found that 20 and 40 $\mu\text{g}/\text{mL}$

solasodine could significantly inhibit the colony formation of SW1990 cells (Figure 2C) and PANC1 cells (Figure 2D). These results suggested that solasodine could efficiently inhibit the growth of pancreatic cancer cells in vitro.

Solasodine Inhibited the Invasion and Migration of SW1990 and PANC1 Cells in vitro

To explore the effect of solasodine on migration and invasion of pancreatic cancer cells, SW1990 and PANC1 cells

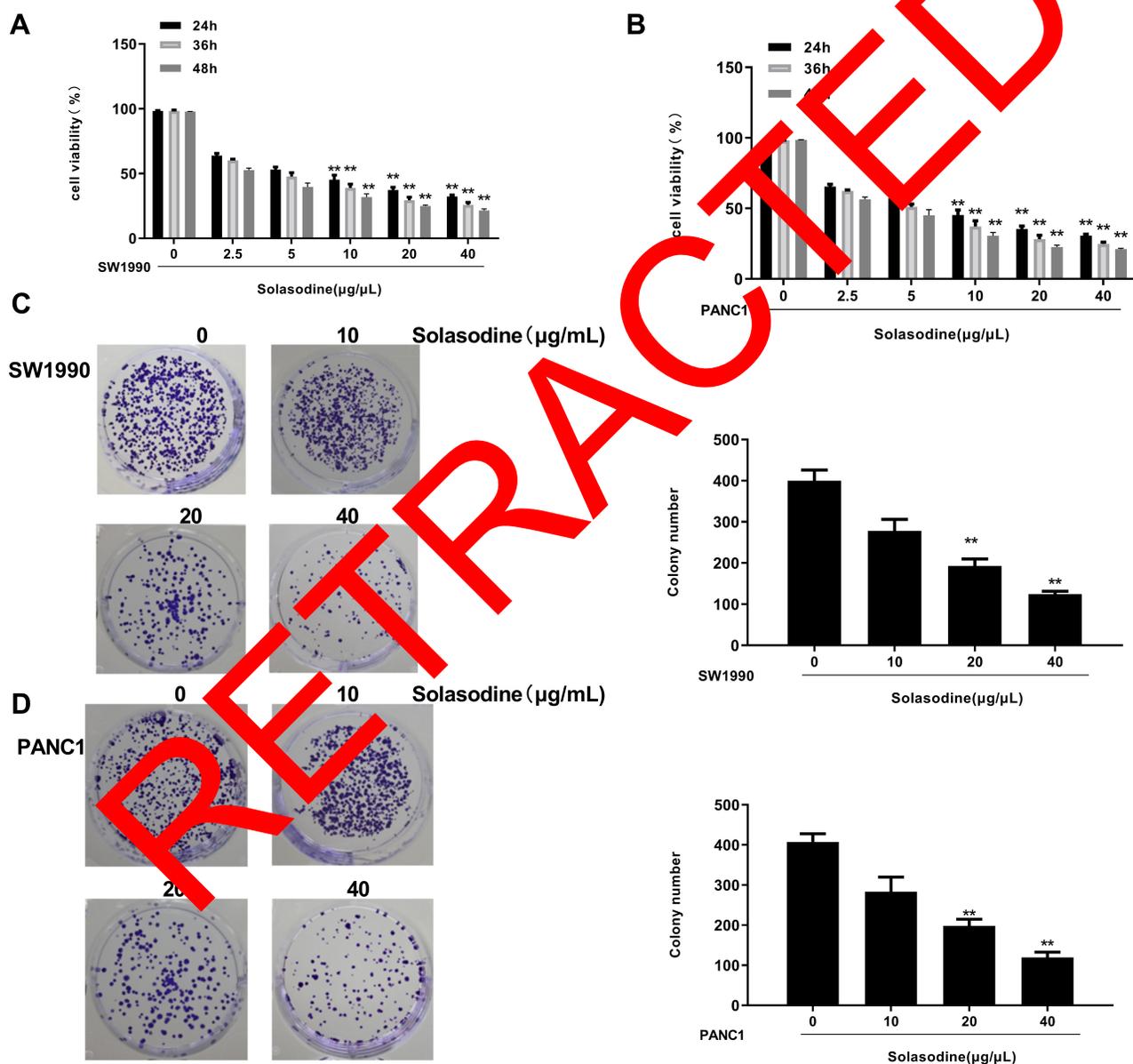


Figure 2 Solasodine inhibited the cell viability of SW1990 and PANC1 cells. (A and B) SW1990 and PANC1 cells were treated with different concentrations of solasodine for indicated times, and the cell viability was detected by MTT assay. (A) The cell viability of SW1990 cells. (B) The cell viability of PANC1 cells. (C and D) SW1990 and PANC1 cells were induced by different concentrations of solasodine for 48 h, and the colony formation was detected. (C) The colony formation and colony numbers of SW1990 cells. (D) The colony formation and colony numbers of PANC1 cells. N = 3, **P < 0.01.

were treated with different concentrations of solasodine for 24 h. The results demonstrated that 20 and 40 $\mu\text{g}/\text{mL}$ solasodine could significantly inhibit invasion (Figure 3A) and migration (Figure 3B) of both SW1990 and PANC1 cells. These results suggested that solasodine could efficiently restrain the migration and invasion of pancreatic cancer cells in vitro.

Solasodine Promoted Apoptosis of SW1990 and PANC1 Cells in vitro

Next, the effect of solasodine on the apoptosis of SW1990 and PANC1 cells was detected by flow cytometry. And the results indicated that the apoptosis rates of both SW1990 and PANC1 cells were significantly increased by 20 and 40 $\mu\text{g}/\text{mL}$ solasodine (Figure 4). These data indicated that solasodine-induced cell death was principally due to apoptosis induction.

Solasodine Inhibited the Activation of Cox-2/Akt/GSK3 β Signaling Pathway in SW1990 Cells

Further, solasodine could significantly downregulated the protein expression level of the Cox-2, and the phosphorylation

level of p-Akt and p-GSK3 β in SW1990 cells ($p < 0.01$), while showed no obvious effect on Akt and GSK3 β expression (Figure 5). These results suggested that solasodine could inhibit the activation of Cox-2/Akt/GSK3 β signal pathway in pancreatic cancer cells.

Solasodine Promoted the Release of Cytochrome C Expression and the Activities of Caspase-Related Proteins in SW1990 Cells

Next, the expression of cytochrome C in the cytoplasm and apoptosis related proteins in SW1990 cells after the treatment of solasodine was evaluated by Western blot. The results indicated that cytochrome C, c-caspase-9 and c-caspase-3 were significantly increased by different concentrations of solasodine in a dose dependent manner (Figure 6A). Meanwhile, the expression of Bcl-2 was also decreased, while the expression of Bax was increased in a dose dependent manner after the treatment of solasodine (Figure 6B). These data were consistent of that solasodine could significantly promote cell apoptosis.

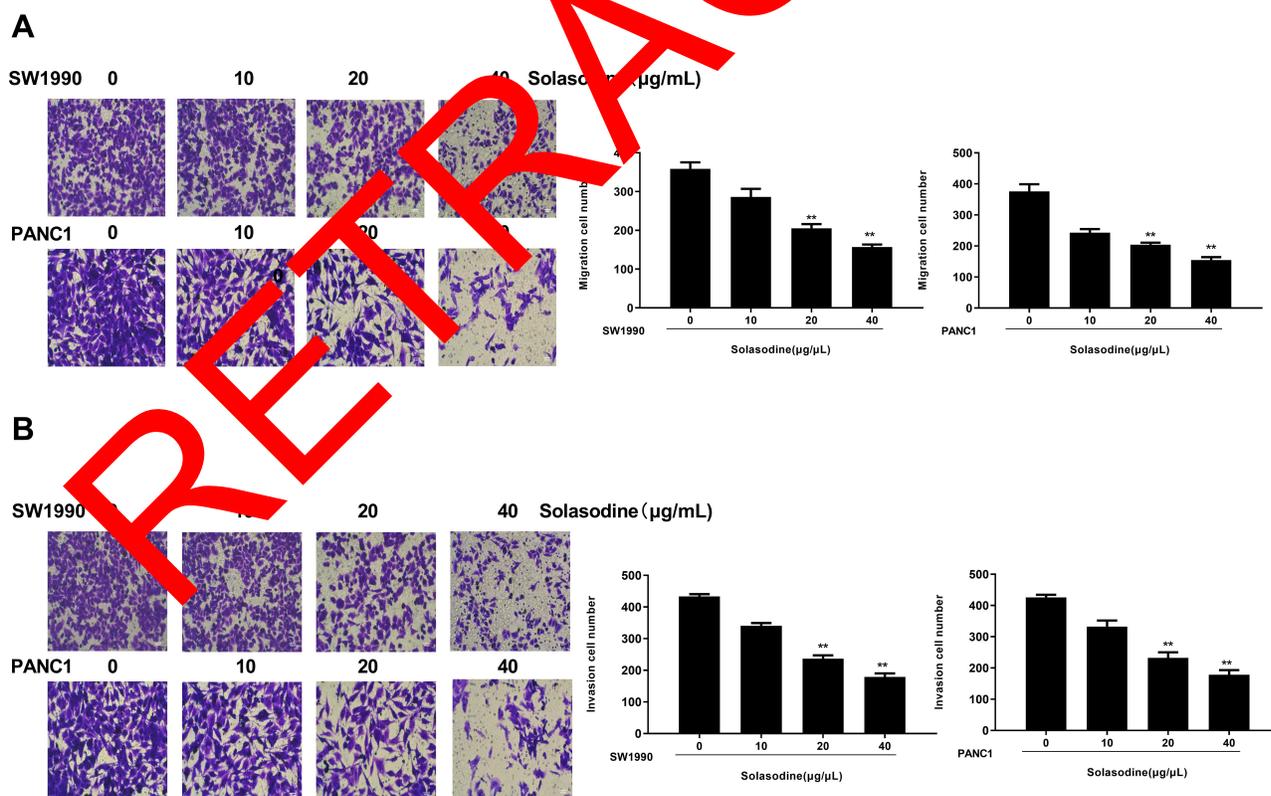


Figure 3 Solasodine inhibited the migration and invasion of SW1990 and PANC1 cells. SW1990 and PANC1 cells were treated with different concentrations of solasodine for 48 h, and the cell migration and invasion were analyzed by transwell assay. (A) The migration ability of SW1990 and PANC1 cells induced by solasodine. (B) The invasion ability of SW1990 and PANC1 cells induced by solasodine. N = 3, **P < 0.01.

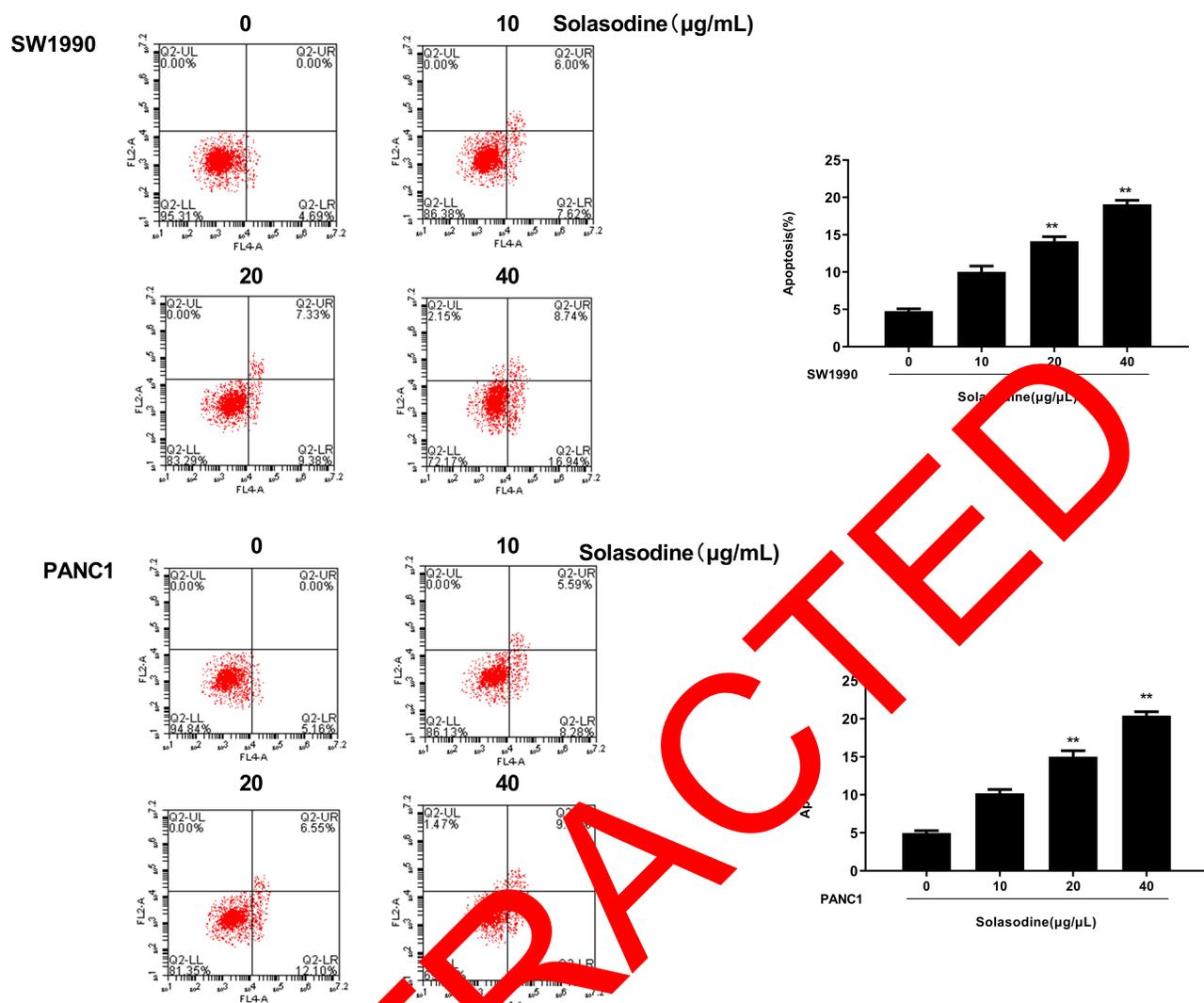


Figure 4 Solasodine-induced apoptosis of SW1990 and PANC1 cells. SW1990 and PANC1 cells were treated with different concentrations of solasodine, then cell apoptosis was analyzed by flow cytometer and apoptosis rate was calculated. N = 3, **P < 0.01.

Solasodine Inhibited Tumor Growth in vivo

To further confirm the inhibitory effect of solasodine in pancreatic cancer in vivo, the SW1990 tumor-bearing mouse model was established. Compared with CTX group, the body weight of mice in each group treated with solasodine showed a significant increase ($p < 0.01$), suggesting that solasodine had a lower toxicity than CTX; While, the tumor inhibition in the solasodine group and CTX group were all effective, meanwhile, low-, medium- and high-dose solasodine could significantly inhibit the growth of tumor in W1990 tumor-bearing mice (Table 1). Meanwhile, we found that different concentrations of solasodine all obviously decreased tumor volume compared with CTX group ($p < 0.05$), while low-dose solasodine exhibited

a better inhibitory effect compared with medium- and high-dose group (Figure 7A). In addition, the acute toxicity pretest was also performed, and the results showed that: after the administration of solasodine, mice were subjected to gastric stress induced by dilatation for 1–3 min, and then returned to normal. Mice in each group were continuously observed for 14 days, and there were no abnormalities in eating, drinking water, activity and mental state, smooth fur and normal excreta. None of the mice in each group died, the LD50 in each group was all greater than 5 g/kg (BW), and the maximum dose was 15.7 g/kg (BW). The size, appearance, color, congestion, bleeding and edema of the main organs were not changed by naked eyes (data not shown). According to the classification standard of relative toxicity of chemical substances, LD50 >5 g/kg (BW) indicates that the tested

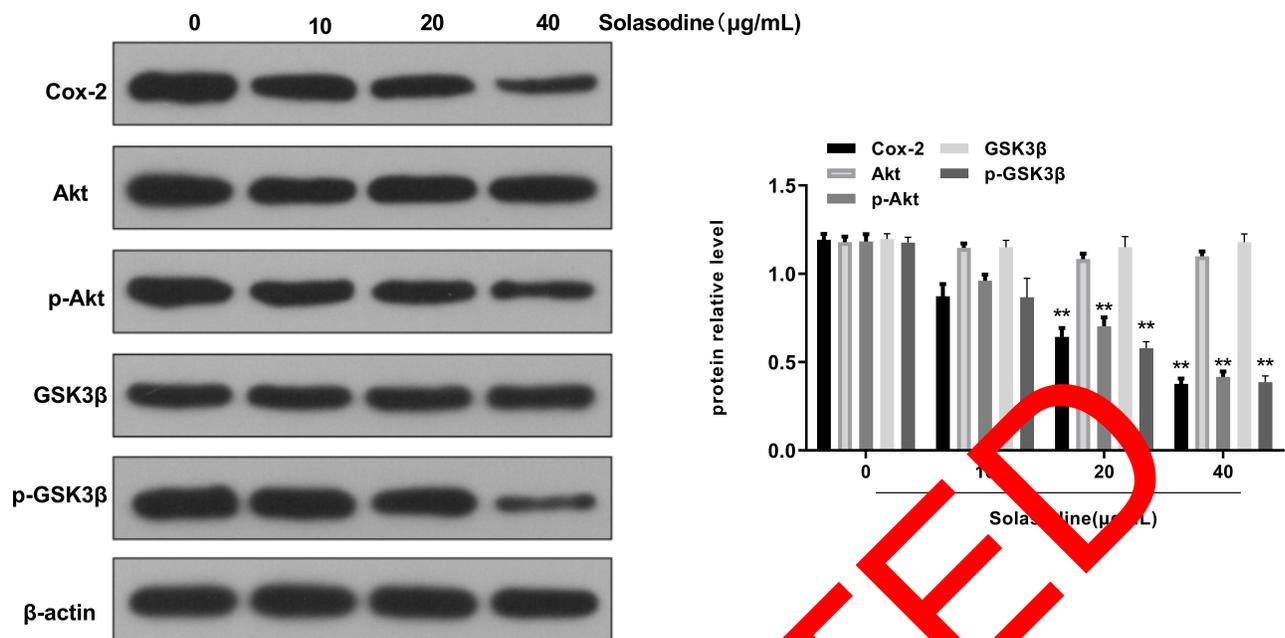


Figure 5 Solasodine inhibited Cox-2/Akt/GSK3 β pathway in SW1990 cells. SW1990 cells were treated with solasodine for the indicated time periods, and the protein level of Cox-2, Akt, p-Akt, GSK3 β , p-GSK3 β was detected by Western blot. β -Actin was used as the equal reference. The quantitative analysis of interesting genes was performed by ImageJ. N = 3, **P < 0.01.

material is actually non-toxic, and LD50 >15 g/kg (BW) indicates that the tested substance is non-toxic.²⁸ Hence, solasodine might be considered as a non-toxic agent. These results indicated that solasodine could efficiently inhibit the tumor growth with a lower toxicity in vivo.

Solasodine Enhanced the Levels of Serum TNF- α , IL-2 and IFN- γ in SW1990 Tumor-Bearing Mice

Finally, the effects of solasodine on cytokines production in tumor tissues of SW1990 tumor-bearing mice were also evaluated. The results showed that solasodine could significantly elevate the levels of serum TNF- α , IL-2 and IFN- γ (p < 0.01) in SW1990 tumor-bearing mice, further suggesting that the antitumor effect of solasodine might through increasing the levels of serum cytokines including TNF- α , IL-2 and IFN- γ to stimulate immunity in SW1990 tumor-bearing mice (Figure 7B).

Discussion

Pancreatic cancer is the fifth leading cause of cancer death in western countries and is also the second in incidence among gastrointestinal tumors.²⁹ Pancreatic cancer has become the worst prognosis among all gastrointestinal malignancies.³⁰ During pancreatic cancer, tumors are highly invasive with potential for early metastasis and

therapeutic options are limited.³¹ Despite that extensive treatment strategies have been made to improve the detection rate and survival rate of pancreatic cancer in recent decades, and the 5-year survival rate of pancreatic cancer (less than 5%) has not improved significantly. Recently, a series of therapeutic targets have been identified to potentially apply to the treatment of pancreatic cancer. For example, long non-coding RNA H19 might act as a sponger of miR-675 to promote pancreatic ductal adenocarcinoma cell proliferation by enhancing E2F-1 expression.³² Keratin 17 (KRT17) knockdown can significantly inhibit cell growth, colony formation, migration and tumor growth through affecting ERK1/2/Bad signaling in pancreatic cancer.³³ Overexpression of stanniocalcin 2 (STC2) in pancreatic cancer contributes to the metastasis through the promotion of epithelial-mesenchymal transition (EMT) process, suggesting that STC2 is a potential prognostic biomarker and therapeutic target for pancreatic cancer.³⁴ However, taken into consideration drugs resistance and other cytotoxicity, it is more necessary to identify new and potent therapeutic drugs for the treatment of pancreatic cancer.

Solasodine has been reported that can be potentially applied to the treatment of various cancers through different manners. For example, solasodine can inhibit the invasion of human lung cancer cell via downregulating miR-21

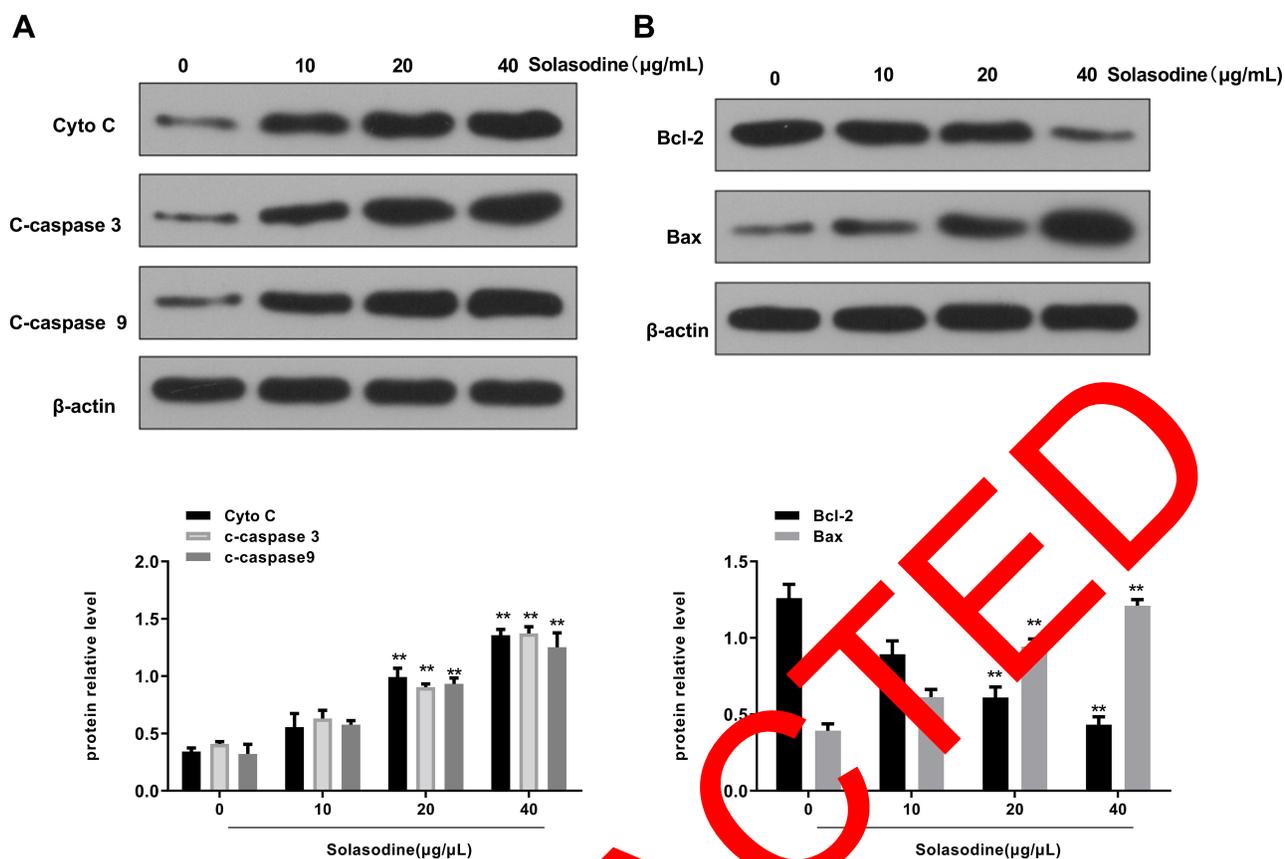


Figure 6 Solasodine regulated the expression of apoptosis-associated genes. SW1990 cells were treated with solasodine for indicated time periods, and the protein level of cytochrome C, c-caspases-9, c-caspase-3, Bcl-2 and Bax was evaluated by Western blot with β -actin as internal reference. Meanwhile, the quantitative analysis of interesting genes was performed by ImageJ. **(A)** The protein expression of cytochrome C, c-caspase-9 and c-caspase-3 was detected. **(B)** The protein expression of Bcl-2 and Bax was detected. N = 3, **P < 0.01.

and (tissue inhibitor of metalloproteinase) MMPs expression.³⁵ Solasodine attenuates TGF- β -induced EMT and decreases MMPs expression and prevents the invasion and migration of human colorectal cancer cells.³⁶ Solasodine has been also identified to possess antiproliferation, apoptosis-inducing, autophagy-modifying, and antimetastatic activities in ovarian cancer cells.⁹ In addition, solasodine also can protect the brain from ischemia/reperfusion injury through its antioxidant activity.¹⁰ Despite its wide uses, the effect of solasodine in pancreatic cancer has not been well studied. In this study, we

demonstrated that solasodine could significantly inhibit the growth of pancreatic cancer cells through inducing cell apoptosis in vitro.

Cox-2/Akt/GSK3 β signaling pathway has been reported to participate in the progression of most human cancers.^{37,38} Cyclooxygenase 2 (Cox-2) has been identified to promote the tumorigenicity of pancreatic cancer cells.³⁹ AKT can be activated by PI3K, and the prolonged activation is closely related to the occurrence and development of tumor. Through phosphorylation, AKT is able to activate a variety of downstream target genes and regulates cell proliferation,

Table 1 Effects of Solasodine on Body Weight and Tumor Growth in SW1990 Tumor-Bearing Mice

Group	Initial Weight (g)	Final Weight (g)	Tumor Weight (g)	Tumor Inhibitory Rate (%)
PBS	21.35 \pm 0.57	25.47 \pm 1.45	1.72 \pm 0.29	0
CTX	21.39 \pm 0.67	26.02 \pm 1.11 [#]	0.51 \pm 0.20 ^{###}	66.42
Solasodine/L	21.37 \pm 0.69	26.23 \pm 1.08 ^{**}	1.17 \pm 0.17 ^{**}	33.79
Solasodine/M	21.32 \pm 0.64	27.45 \pm 1.45 ^{**}	0.75 \pm 0.15 ^{**}	47.59
Solasodine/H	21.42 \pm 0.47	28.42 \pm 1.61 ^{**}	0.62 \pm 0.21 ^{**}	56.83

Notes: Data are expressed as mean \pm SD. n=10, **p < 0.01 vs CTX group, [#]p < 0.05, ^{###}p < 0.01 vs PBS group.

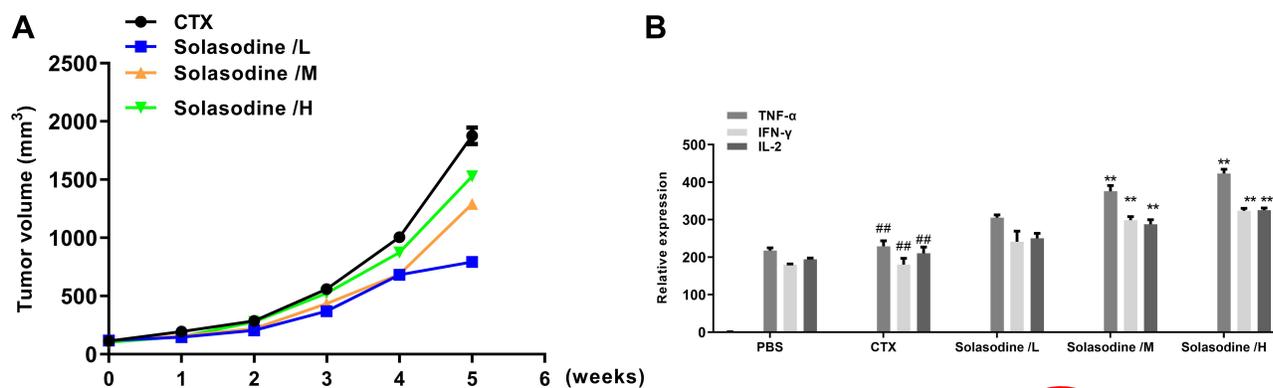


Figure 7 Solasodine inhibited tumor growth and enhanced serum cytokine levels in SW1990 tumor-bearing mice. The SW1990 tumor-bearing mice were treated with PBS, CTX, low-, medium- and high-dose solasodine. **(A)** Tumor volume. **(B)** The levels of TNF- α , IL-2 and IFN- γ in serum were detected by ELISA assay. [#] $P < 0.1$, ^{##} $P < 0.01$ vs PBS group; ^{**} $P < 0.01$ vs CTX group.

differentiation and apoptosis.⁴⁰ Glycogen synthase kinase-3 β (GSK3 β), one of the major components of the Wnt/ β -catenin signaling pathway, is the major target protein of AKT. GSK3 β can be phosphorylated by p-AKT and phosphorylated GSK3 β can inhibit the degradation of β -catenin.⁴¹ In this study, we demonstrated that solasodine could significantly downregulate the expression of Cox-2 and decrease the phosphorylation level of p-Akt and p-GSK3 β , suggesting that solasodine could remarkably inhibit the activation of Cox-2/Akt/GSK3 β signaling pathway.

Apoptosis or programmed cell death maintains the cell homeostasis in vivo, which is closely involved in the development and elimination of damaged cells.⁴² In mammalian cells, the release of cytochrome C from mitochondria can increase caspases activities and subsequent cell death. Bcl-2 family proteins which consist of negative bcl-2 and positive Bax regulators have been identified to be closely related to apoptosis in human cells, and Bcl-2 can inhibit apoptosis and Bax promote apoptosis. Here we demonstrated that solasodine could significantly inhibit the release of cytochrome C from cytoplasm and enhance caspase-3 and -9 expression levels, increase Bax protein expression while decrease Bcl-2 protein expression, and then induce cell apoptosis in human pancreatic cancer cell lines including SW1990 and PANC1 cells in vitro.

To further explore the antitumor effect of solasodine in mice in vivo, the SW1990 tumor-bearing mice model was constructed. Moreover, we found that solasodine could efficiently inhibit the growth of tumor with a lower toxicity. Meanwhile, we demonstrated that the expression of serum immune factors was significantly increased after solasodine treatment than that with CTX treatment, suggesting that solasodine could inhibit the growth of tumor by enhancing

immunity. All these data contributed to understand the complex mechanism of tumor progression in pancreatic cancer.

However, the transcription factor NF- κ B also plays an important role as an anti-apoptotic factor and the regulation of Cox-2 in the progression of various human cancers,^{45,46} it would be interesting to explore if solasodine could also affect NF- κ B activation in the subsequent experiments. In addition, CTX has been revealed to show certain antitumor activities in pancreatic cancer through downregulating Bcl-2 expression by inhibiting the activation of NF- κ B pathway.⁴⁷ Our study provided that the combined treatment with solasodine and CTX might be a novel therapeutic strategy to prevent against pancreatic cancer progression.

Conclusion

In summary, our results demonstrated that solasodine had potent antitumor activity in pancreatic cancer through inhibiting proliferation, invasion, migration and inducing apoptosis of pancreatic cancer cells by activating Cox-2/Akt/GSK3 β signaling pathway, as well as stimulating immunity in vitro and vivo, suggesting that solasodine might be a potential therapeutic strategy against pancreatic cancer.

Abbreviations

CWP, Compound Wumei Powder; KRT17, keratin 17; STC2, stanniocalcin 2; GSK3 β , glycogen synthase kinase-3 β ; Cox-2, cyclooxygenase 2.

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Disclosure

The authors declare that they have no competing interests.

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