

# Anticancer effects of dietary administration of secoisolariciresinol diglucoside in a patient of gastrointestinal stromal tumor: a case report

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**Introduction:** Gastrointestinal stromal tumor (GIST) is among the leading malignancies of the digestive system. GIST is not susceptible to chemotherapies and is prone to recurrence or metastasis after surgical operation. Secoisolariciresinol diglucoside (SDG) was suggested to have potential anticancer effects, but no clinical evidence had been available. Here we report successful treatment of a postoperative GIST case with dietary SDG.

**Presentation of Case:** The patient was a 58-year-old man. He had GIST and received resection of small intestinal lesions 1 year before. He was diagnosed with postoperation of GIST and presented with high level of serum carbohydrate antigen 72-4 (CA72-4). The patient was then treated with dietary administration of SDG with his voluntary acceptance for 5 months, and underwent 2 serum CA72-4 measurements during this period. CA72-4 level of the patient was restored to normal range after treatment with dietary SDG for 1 month. There was no aberrant CA72-4 level, recurrence or metastasis after the treatment with dietary SDG.

**Discussion:** This is to our knowledge the first report on application of dietary SDG on a postoperative GIST patient with aberrant level of serum CA72-4. SDG can be transformed into active substances with antitumor effects by human gut bacteria. Dietary SDG might inhibit tumorigenicity and malignant behavior of GIST cells.

**Conclusion:** The excellent effects suggest dietary SDG to be a potential therapy for GIST, especially against recurrence or metastasis.

**Keywords:** GIST, CA72-4, Dietary SDG, Recurrence, Metastasis, Case report

## Key points

- (1) Dietary secoisolariciresinol diglucoside (SDG) shows potent anticancer effect reflected by complete patient recovery.
- (2) Carbohydrate antigen 72-4 (CA72-4) level becoming normal correlated very well with the recovery of the patient.
- (3) SDG is easily edible and may be used widely for cancer prevention and treatment.

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## Introduction

Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal malignancies in the gastrointestinal tract, with no specific clinical manifestations to be used for diagnosis at early stages<sup>[1]</sup>. The incidence rate of GIST is ~0.001%–0.0015% but a trend of increase is obvious in recent years<sup>[2]</sup>. GIST is mostly seen in men over 50 years old, occurring in the stomach (60%–70%), the small intestine (25%–36%), colon (5%) or esophagus (5%)<sup>[3]</sup>. About 10%–30% of the GIST patients develop metastasis<sup>[4]</sup>, most commonly in the liver (65%), followed by the peritoneum (21%), the bone (10%), and lung (10%)<sup>[5]</sup>. The treatment for GIST is quite challenging, as GIST is not susceptible to radiotherapy or chemotherapy. As a result, surgical resection is almost the only method left to treat the disease. However, over half of the patients would face recurrence or metastasis after the surgical operation<sup>[6]</sup>. Multiple genetic changes have been identified for their associations with GIST, including C-KIT mutations in 70%–80% and PDGFR- $\alpha$  mutations in 5%–10% of the examined cases. The downstream signaling pathways of C-KIT include PI3K/ART, Src family kinases, RAS-ERK, and JAK-STAT6<sup>[7]</sup>.

Currently, tyrosine kinase inhibitors (TKIs) as routine targeted drugs<sup>[8]</sup>, with Imatinib as a representative, are often used after GIST surgery. Imatinib can inhibit the activities of both C-KIT

and PDGFR- $\alpha$ <sup>[9]</sup>. However, C-KIT/PDGFR- $\alpha$  gene mutations may lead to drug resistance and cause increasing relapse rate of GIST. Most GIST patients treated with Imatinib may develop drug resistance within 2 years<sup>[10,11]</sup>, complicating the situations that about 14% of the patients with GISTs have primary resistance to Imatinib<sup>[12]</sup>. Sunitinib and Regorafenib are second-line and third-line drugs for the treatment of Imatinib-resistant patients, respectively, but patients are still prone to drug resistance after treatment for a few months<sup>[13,14]</sup>. In addition, a type of GIST, called wild-type GIST, does not have mutations in the C-KIT or PDGFR- $\alpha$  gene<sup>[15]</sup> and so is naturally resistant to the imatinib treatment. While long-term use of imatinib may be accompanied with side effects such as fatigue, diarrhea, nausea, periorbital edema, muscle cramps, and skin rash, etc<sup>[16]</sup>, the emergence of drug resistance and the high cost of treatment are even more problematic<sup>[13]</sup>. This situation calls for novel therapeutics to minimize the adverse reactions and maximize treatment effects.

SDG, a kind of phytolignans existing in a broad range of plants, with the seed of flax (*Linum usitatissimum* L) being among the richest sources, has strong bioactivities, including antioxidant, antidepressant, and anticancer effects, and may also affect lipid regulation and cholesterol metabolism<sup>[17–21]</sup>. Here we report a GIST case treated with plant materials containing SDG after surgical removal of the tumor, because the patient refused to accept any chemotherapy. The patient achieved remarkable treatment effects as reflected by rapid recovery of his general health status and drastically lowered CA72-4 level ( $> 300$  U/mL before the use of the dietary SDG and 3.99 U/mL after the use of the dietary SDG), suggesting that the dietary SDG had potent suppressive activities on GIST.

## Case presentation

### Medical records

The patient was a 56-year-old man, who complained of intermittent hematochezia lasting for over 1 month. He was born in Inner Mongolia Autonomous Region, China. He is of Han ethnic group

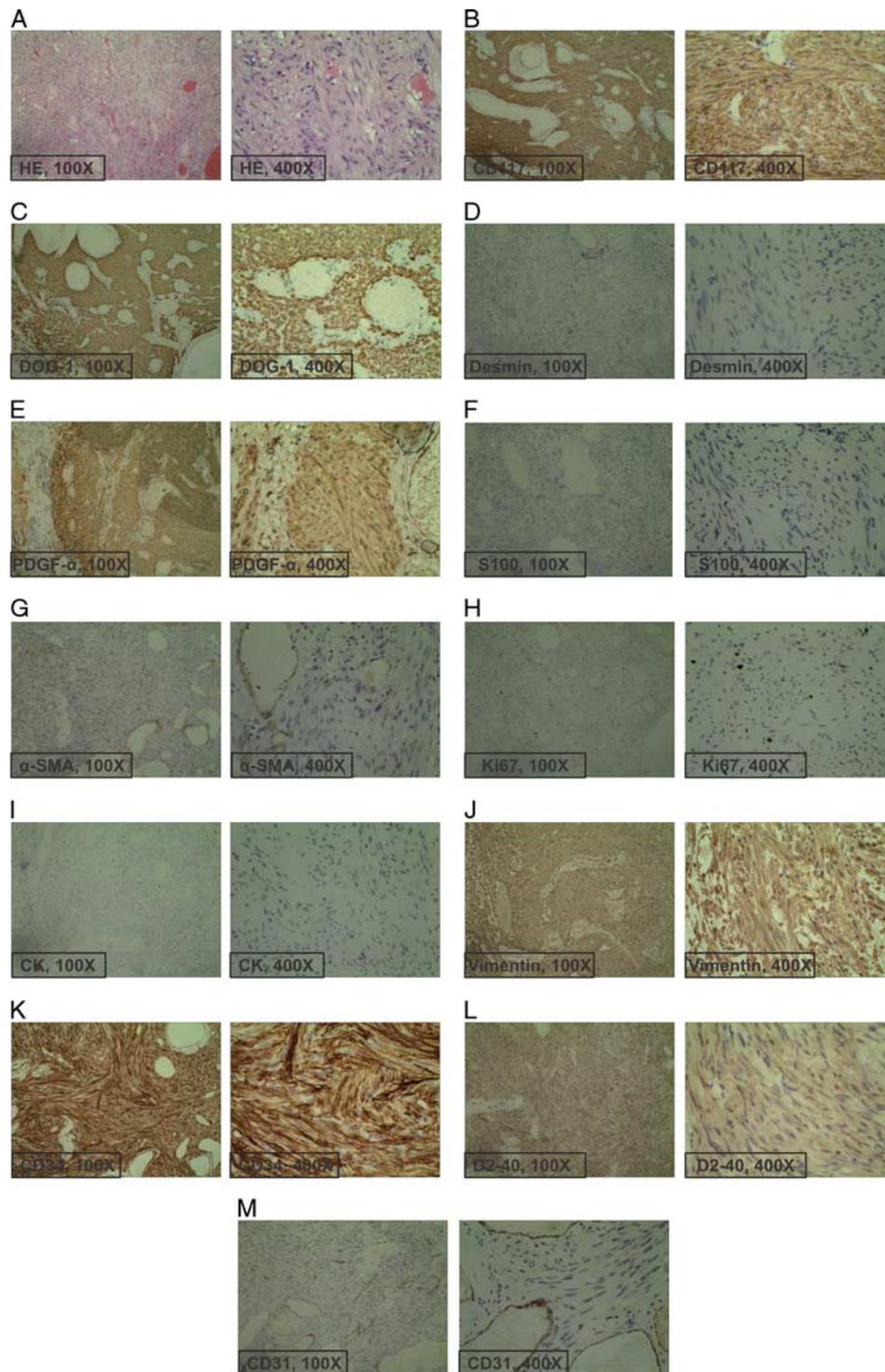


**Figure 1.** Abdominal enhancement computed tomography showed that there was a jejunal mass (red arrow, high-density) in region of the left abdomen.

and retired. The patient's medical history included gastric bleeding and he underwent subtotal gastrectomy 35 years before. He had no history of hypertension, diabetes, cardiovascular or mental diseases and no history of allergy, smoking, drinking or drug use. His spouse was healthy. He denied a history of familial hereditary diseases. The physical examination of the patient showed that the abdomen was flat and soft, the abdominal breathing and intestinal sound were normal. Percussion of the abdomen was a drum sound. No abnormality was found on anal examination. There was no abdominal mass, subcutaneous varicose vein of abdominal wall, gastrointestinal type, peristaltic wave, rebound pain, muscle tension, shifting dullness, gurgling or Murphy sign. Liver and spleen were impalpable. The patient's general conditions, including the mental, diet, sleep, and urination states, were normal. No nausea or vomiting was observed. The abdominal enhancement computed tomography (CT) showed that there was a jejunal mass in the left abdomen, suggesting neoplastic lesions (Fig. 1). The patient underwent laparoscopic exploration and was then treated with small intestinal tumor resection operation. The operation was performed by the chief physician of the General Surgery Department and the procedure went smoothly. Postoperative pathology showed that the tumor of the small intestine was spindle cell type, consistent with the diagnosis of GIST according to immunohistochemistry (IHC). The volume of the tumor was  $3.4 \times 3.2 \times 2.8$  cm. The mitosis counts were  $< 5/50$  HPF. There was extensive hemorrhage and necrosis in the tissue. The IHC results of some key molecules were as follows: CD117 (+), DOG-1 (+), Desmin (-), PDGFR- $\alpha$  (+), S-100 (-),  $\alpha$ -SMA (-), Ki67 (MIB-1) (2%+), CK (AE1/AE3) (-), vimentin (+), CD34 (+), D2-40 (+), and CD31 (-) (Figs. 2A–M). The patient recovered well after the operation. The discharge diagnosis of the patient was gastrointestinal bleeding and GIST.

### Postoperative reexamination and dietary administration of SDG

The patient did not receive any other treatment after the surgical operation. He had another examination of serum tumor markers and a CT scan of the abdomen 1 year after GIST resection. The CT results showed no abnormalities around the abdomen. Serum levels of detected biomarkers were as follows: AFP, 2.68 ng/mL (reference value: 0–7.00 ng/mL); CEA, 1.60 ng/mL (reference value: 0–5 ng/mL); CA125, 19.70 U/mL (reference value: 0–35 U/mL); CA-199, 6.50 U/mL (reference value: 0–27 U/mL); and CA-153, 10.12 U/mL (reference value: 0–25 U/mL). However, the serum level of carbohydrate antigen (CA72-4) was  $> 300$  U/mL (the upper limit of detection; reference value: 0–6.9 U/mL) (Supplement Fig. 1, Supplemental Digital Content 1, <http://links.lww.com/IJSO/A14>), indicating possible recurrence or metastasis of postoperative GIST or other gastrointestinal tumors. As the patient refused to receive any chemotherapy, we treated him with dietary SDG, 15 g a dose twice a day, in the morning and at night. He was told to pay attention to his general condition and to have CA72-4 reexamined on a monthly basis. The patient continued this treatment and did not receive any other medical intervention. He had CA72-4 re-checked after one month. Remarkably, the level was 1.39 U/mL (Supplement Fig. 2, Supplemental Digital Content 1, <http://links.lww.com/IJSO/A14>). He continued to take dietary SDG and had CA72-4 tested again 3 months after the previous reexamination and it was 3.99 U/mL (Supplement Fig. 3, Supplemental Digital Content 1, <http://links.lww.com/IJSO/A14>).



**Figure 2.** Representative hematoxylin and eosin (HE) and immunohistochemistry (IHC) images. A, Representative HE staining images. B, Representative IHC images of CD117. C, Representative IHC images of DOG-1. D, Representative IHC images of Desmin. E, Representative IHC images of PDGFR- $\alpha$ . F, Representative IHC images of S-100. G, Representative IHC images of  $\alpha$ -SMA. H, Representative IHC images of Ki67. I, Representative IHC images of CK. J, Representative IHC images of vimentin. K, Representative IHC images of CD34. L, Representative IHC images of D2-40. M, Representative IHC images of CD31.

During the period of dietary SDG administration, the patient kept reporting good physical conditions, indicating a good tolerability with dietary SDG intervention in addition to the excellent therapeutic effects. He felt much stronger and regained normal routine

activities including aerobics, better mood, and good sleep quality. This case is reported in accordance with the SCARE 2018 standard<sup>[22]</sup>, and additional details can be found in the full SCARE list.

## Discussion

Numerous mutations and high heterogeneity of GIST facilitate drug-resistance development during targeted therapy applications and therefore call for novel therapeutics<sup>[1]</sup>. CA72-4 is a glycoprotein antigen that is highly expressed in a variety of tumors including GIST<sup>[2,3,24]</sup>. We treated this postoperative GIST patient with dietary SDG and achieved general recovery of the patient from the malignancy, with greatly improved health status. Importantly, the drastically increased CA72-4 level suggests tumor recurrence or metastasis soon after the surgery and the rapid drop of the CA72-4 level to the normal range reflects effective suppression of the tumor recurrence or metastasis associated with the use of dietary SDG.

We gained several learning points in the treatment of this case with dietary SDG. First, no metastasis was found in the regional lymph node of the patient when he received surgery operation, indicating that he had a relatively low aggressive type of GIST. However, CA72-4 level increased abnormally one year after the operation, suggesting that even low-aggressive GIST may have the possibility of tumor recurrence or metastasis. Therefore, it seems improper to decide whether or not to carry out targeted treatment after operation based solely on the level of risk assessment. Second, considering the side effects of targeted drugs against GIST<sup>[16]</sup>, it is not appropriate to use them for prophylactic medication. This led to our way of thinking for preventing the recurrence or metastasis of a low-aggressive GIST patient that has no indication of targeted therapy after surgery operation. In this case, it is extremely intriguing that the CA72-4 level of this patient returned to normal level one month after the dietary SDG treatment and sustained a normal range with no recurrence or metastasis, demonstrating the promising use of dietary SDG against GIST. Furthermore, the patient did not show any side effects and regained active routine life.

The possible mechanism by which SDG exerts the anticancer effects seems to be through the biotransformation of SDG into enterodiol and enterolactone (ENL) by gut bacteria<sup>[18–20]</sup>. Our and others' previous work demonstrates that enterodiol and ENL reduce the metastasis of female malignant tumor cells by inhibiting the adhesion, invasion and motility and downregulate the expression of MMP-2, MMP-9 and MMP-14<sup>[25,26]</sup>. Moreover, treating mice with SDG or ENL inhibited the secretion of IL-1 $\beta$  in stroma around cancer tissues<sup>[27]</sup>. IL-1 $\beta$  has been proved to promote tumorigenicity and peripheral angiogenesis of tumor cells<sup>[28]</sup>. Therefore, we consider that dietary SDG may decrease the CA72-4 level of this patient through these mechanisms. Further investigation is needed to experimentally explore the inhibitory effects of SDG on GIST.

In short, this case suggests that dietary SDG is a potential anticancer therapy.

## Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying materials. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Ethical approval

Written informed consent for publication was obtained from the patient.

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## Author contribution

S.-L.L. and H.W.: conceptualization. H.W., Y.W., J.-T.C., and S.-L.L.: investigation. S.-L.L., L.-P.W., and G.-R.L.: project administration. L.-P.W.: resources. Y.W. and J.-T.C.: software. H.W. and S.-L.L.: validation.

## Conflict of interest disclosures

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Not applied.

## Guarantor

Shu-Lin Liu.

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