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Synergistic Cytotoxicity of β-Elemene and Cisplatin in Gingival Squamous Cell Carcinoma by Inhibition of STAT3 Signaling Pathway

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Cisplatin remains one of the most active agents and is the mainstay of combination chemotherapy regimens against gingival squamous cell carcinoma. However, the efficacy of cisplatin is limited by its high toxicity and the development of drug resistance. β-elemene, isolated from the Chinese herb *Rhizoma zedoariahas,* is highly effective against malignancies and has low toxicity, but the development of β-elemene sensitizing chemotherapy in targeting the STAT3 signaling pathway remains unexplored in gingival squamous cell carcinoma. The present study was conducted to assess the chemosensitizing effects of β-elemene for enhancing the cytotoxicity of cisplatin in gingival squamous cell carcinoma.

Material/Methods: The gingival squamous cell carcinoma YD-38 cell line was used. MTT assay, clonogenic assay, annexin V/PI apoptosis assay, Western blot analysis, and xenograft model treatment were carried out *in vitro* and *in vivo*.

Results: β-elemene significantly enhanced proliferative inhibition and cisplatin induced apoptosis in gingival squamous cell carcinoma. Cisplatin combined with β-elemene decreased the expressions of p-STAT3, p-JAK2, and Bcl-2, and increased the expressions of Bax and caspase-3 significantly compared to cisplatin only treatment, as well as in the xenograft model.

Conclusions: The results indicated that β-elemene promoted the anti-proliferative and apoptotic effect of cisplatin by inhibiting STAT3 and blocking the JAK2-STAT3 signaling pathway in GSCC *in vitro* and *in vivo*.

MeSH Keywords: Apoptosis • Drugs, Chinese Herbal • Mouth Neoplasms • STAT3 Transcription Factor

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Background

Oral squamous cell carcinoma is most common in oral malignancies, but gingival squamous cell carcinoma (GSCC) is a rare tumor which accounts for less than 10% of all oral malignancies [1]. GSCC occurs in either the maxilla or mandible [2,3]. GSCC typically resembles common periodontal lesion and has a high risk of metastasis and bone invasion with delayed diagnosis [4,5]. Chemotherapy is the main treatment for malignancies. Cisplatin is a DNA-damaging agent that is commonly used in the treatment of numerous types of cancer, including lung cancer, ovarian cancer, and head and neck carcinomas, especially oral squamous cell carcinoma [6]. Although cisplatin inhibits GSCC growth, it leads to severe adverse effects. Therefore, more effective strategies with less toxic treatments are needed. Anti-tumor agents from natural products are suitable alternatives as sensitizers for chemotherapy of malignancies [7–13].

β-elemene [(1S,2S,4R)-2,4-diisopropenyl-1-methyl-1-vinylcyclohexane, $C_{15}H_{24}$)], isolated from the Chinese herb *Rhizoma zedoariae*, is approved to be effective against a variety of cancers, including glioblastoma, renal-cell carcinoma, esophageal carcinoma, bladder cancer, breast cancer, ovarian cancer, and lung cancer [14–23]. As a natural plant extract, β-elemene has fewer adverse effects and is widely used in combination with chemotherapy and radiotherapy. Its mechanism involves inducing apoptosis, cell cycle arrest, reversing multidrug resistance, inhibition of ATM, ERK and Phosphoinositol 3-kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR) signaling pathways and activation of ERK12 and AMPKα signaling pathways [14–23]. But the mechanism underlying its anti-tumor effects in GSCC and how to obtain optimum therapeutic modality is unclear. Therefore, the aim of the present study was to investigate the synergism between β-elemene and cisplatin in GSCC and to elucidate the underlying molecular mechanism. β-elemene has been approved by the State Food and Drug Administration of China for decades and it is well-tolerated by patients with numerous cancer types. The results of our study suggest that β-elemene serves as an anti-tumor agent to sensitize GSCC cells and xenograft model to cisplatin, and the novel combination therapy may be beneficial for GSCC patients.

Material and Methods

Cell culture and chemicals

Gingival squamous cell carcinoma YD-38 cell line was obtained from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). The cells were cultured in RPMI-1640 containing 10% FBS (Gibco-BRL, Carlsbad, CA, USA) and 1% penicillin and streptavidin at 37°C in an atmosphere of 5% CO_2. β-elemene (C15H24) was obtained from Dalian Holley Kingkong Pharmaceutical Co., Ltd. (cat. no. 081152; Dalian, China). Cisplatin and MTT reagent were purchased from Sigma-Aldrich (St. Louis, MO, USA). The Annexin V Apoptosis Detection kit was purchased from BD Biosciences (NJ, USA). Antibodies against STAT3, p-STAT3, JAK2, p-JAK2, caspase-3, Bcl-2, and Bax were purchased from Cell Signaling Technology (Danvers, MA, USA). Anti-GAPDH was obtained from Abcam (Cambridge, UK).

Cell proliferation assay

The anti-proliferative effects of β-elemene and cisplatin were assessed by MTT assay. YD-38 cells were seeded into 96-well plates at a density of 1×10^4 cells/ml and cultured overnight, then treated with β-elemene (20–100 μg/ml). Further, YD-38 cells were treated with cisplatin (from 1 to 64 μM) and β-elemene (40 and 80 μg/ml). Absorbances at a wavelength of 490 nm were detected and dose-dependent curves were generated.

Clonogenic assay

YD-38 cells were seeded into 6-well plates at a density of 1×10^4 cells/ml and cultured, then treated with cisplatin (1 to 64 μM) with or without β-elemene (40 μg/ml) for 48 h. Then the cells were trypsinized, counted, and seeded into a flask (1000 cells/well) and cultured for 2 weeks. The colonies were then fixed and stained. Colonies (>50 cells) were counted under a microscope (Olympus Co., Tokyo, Japan).

Cell apoptosis assay

Annexin V/PI method was performed to quantify cell apoptosis. YD-38 cells were placed into 6-well plates at a density of 1×10^4 cells/ml and cultured, then treated with cisplatin (1 to 64 μM) with or without β-elemene (40 μg/ml) for 48 h. Cells were then harvested, trypsinized, and washed with PBS. An Annexin V Apoptosis Detection kit was used to stain the cells and then the apoptotic cells were detected by flow cytometry (Beckman Coulter, Inc., Brea, CA, USA).

Western blot analysis

YD-38 cells were placed into 6-well plates at a density of 1×10^4 cells/ml and cultured, then treated with cisplatin (8 μM) with or without β-elemene (40 μg/ml) for 48 h. Cells were lysed and then total proteins were separated by SDS-polyacrylamide gel electrophoresis. Proteins were transferred to a polyvinylidene difluoride (PVDF) membrane and then the membrane was blocked for 1 h at room temperature. The membranes were incubated overnight with primary antibodies (STAT3, p-STAT3, JAK2, p-JAK2, caspase-3, Bcl-2, and Bax) at 1: 1000 dilution at 4°C. The membranes were then incubated for 2 h with

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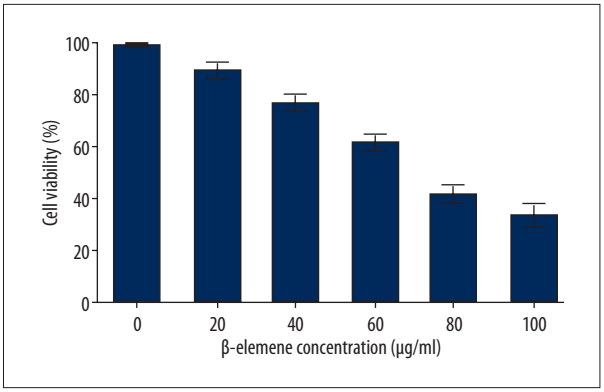

Figure 1. Anti-proliferative effect of β-elemene with increasing concentrations in GSCC cell line YD-38.

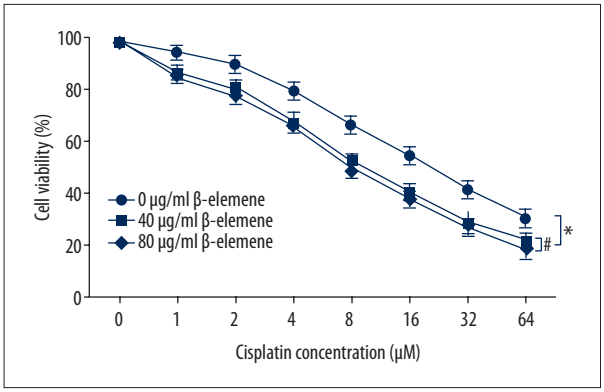

Figure 2. β-elemene promoted cisplatin sensitivity in GSCC cell line YD-38 with increasing doses. * Statistically significant difference between the cisplatin+β-elemene groups and the cisplatin treatment only group (P<0.01, by ANOVA). # No statistically significant difference between the low dose and high dose of β-elemene with cisplatin (P>0.05, by t-test).

horseradish peroxidase-labeled secondary antibodies (1: 5,000; affinity purified goat anti-mouse IgG and goat anti-rabbit IgG, Santa Cruz Biotech) at room temperature. The immunostained protein bands were developed using the enhanced chemiluminescence system (Immun-Star™AP Chemiluminescence kit; Bio-Rad Laboratories) and X-ray films (Santa Cruz Biotechnology Inc.). The blots were analyzed using Quantity One software, version 4.6 (Bio-Rad Laboratories).

Xenograft treatment

BALB/c nude mice were obtained from the Laboratory Animal Center of Zhejiang University (Hangzhou, China). The animal experimental protocols were carried out according to the NIH guidelines and approved by the Hangzhou Cancer Hospital Research Ethics Committee. YD-38 cells were injected subcutaneously into the left flank of nude mice. Twenty tumor-bearing nude mice (male, aged 4–6 weeks, weighing 18±2 g) were randomly divided into 4 groups when the tumor reached 500 mm^3 in size. The control group was intraperitoneally injected with 0.1 ml 0.9% saline once daily for 4 weeks. The β-elemene group was treated by intraperitoneally injection with 0.1 ml β-elemene (45 mg/kg) once daily for 4 weeks. The cisplatin group was intraperitoneally injected with cisplatin (5 mg/kg) once weekly for 4 weeks. The cisplatin + β-elemene group received the above administration. Tumor volumes were evaluated every week and mice were sacrificed after 4 weeks. Tumor samples were obtained for Western blot analysis.

Statistical analysis

Data are expressed by mean ±SD (standard deviation). The statistical analysis was performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). The t-test and one-way analysis of variance (ANOVA) were used with P<0.05 as statistical significance. All experiments were performed in triplicate.

Results

β-elemene enhances proliferative inhibition effect of cisplatin in GSCC cells

The YD-38 cells were treated with 20, 40, 60, 80, and 100 μg/ml β-elemene for 48 h. The results showed that β-elemene inhibited the viability of YD-38 cells in a dose-dependent manner (Figure 1). Then the cells were treated by a low dose and a high dose of β-elemene (40 and 80 μg/ml) combined with cisplatin. The results showed that cisplatin inhibited the viability of YD-38 cells with the increasing concentration (from 1 to 64 μM). When combined with β-elemene, the inhibitory effect of cisplatin was significantly enhanced. Moreover, the synergistic cytotoxicity of low dose (40 μg/ml) and high dose (80 μg/ml) of β-elemene to cisplatin had no significant difference (Figure 2). Further, clonogenic assay was performed and the result showed that colony formation of cisplatin combined with low dose of β-elemene group was inhibited significantly when compared to the cisplatin treatment only group (Figure 3).

β-elemene enhances apoptosis induced by cisplatin on GSCC cells

Annexin V-FITC assay was used to evaluate the effect of β-elemene on apoptosis induced by cisplatin in GSCC cells. YD-38 cells were treated with cisplatin (1 to 64 μM) and β-elemene (40 μg/ml) for 48 h. The results showed that cisplatin induced a significant apoptosis compared to the control group, and a significant increasing apoptosis rate induced by cisplatin was observed when combined with β-elemene (Figure 4).

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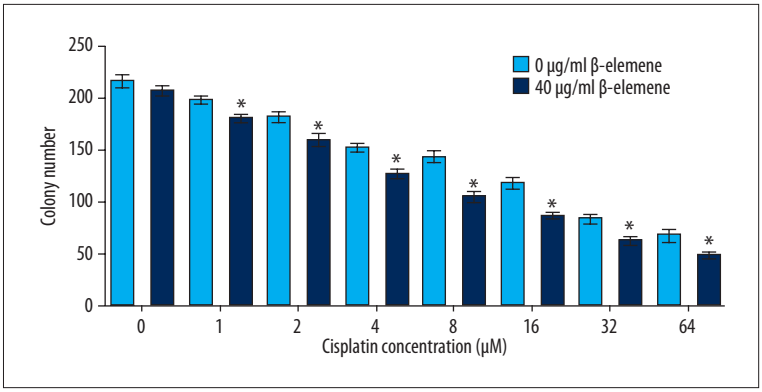

Figure 3. Low dose of β-elemene promoted cytotoxicity of cisplatin in a dose-dependent manner in GSCC cell line YD-38, as determined by clonogenic assay. * Statistically significant difference between the cisplatin+β-elemene groups and the cisplatin treatment only group (P<0.01, by t-test).

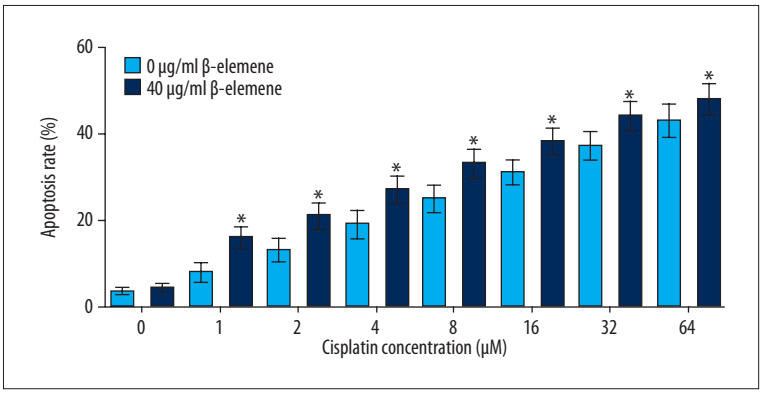

Figure 4. β-elemene promoted cisplatin-induced apoptosis in GSCC cell line YD-38. * Statistically significant difference between the cisplatin+β-elemene groups and the cisplatin treatment only group (P<0.01, by t-test).

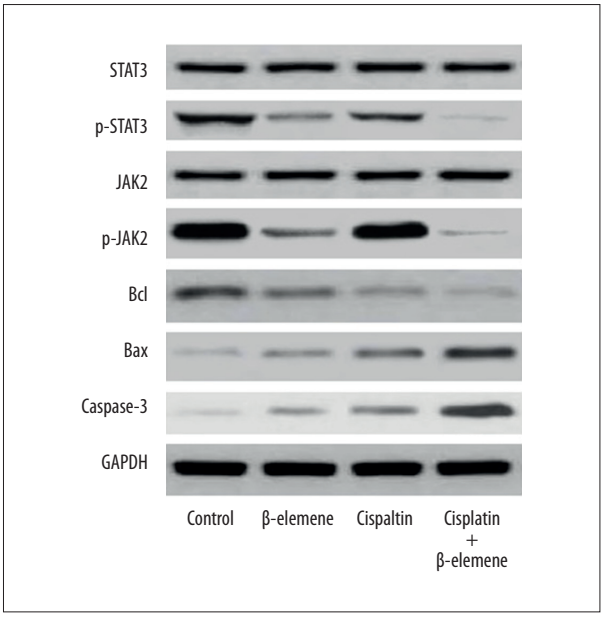

Figure 5. β-elemene enhanced cisplatin-induced protein expressions of STAT3, JAK2, Caspase-3, Bcl-2, and Bax on GSCC cell line YD-38. Cisplatin combined with β-elemene decreased the expressions of p-STAT3, p-JAK2, and Bcl-2, and increased the expressions of Bax and caspase-3 significantly compared to the cisplatin group, as determined by Western blotting analysis.

β-elemene enhances proliferative inhibition and apoptosis effects of cisplatin by inhibition of STAT3 signaling pathway

Western blotting analysis was performed to detect the levels of key proteins in the STAT3 pathway, including STAT3, JAK2, caspase-3, Bcl-2, and Bax in GSCC cells treated by cisplatin combined with β-elemene for 48 h. The results showed that cisplatin combined with β-elemene decreased the expressions of p-STAT3, p-JAK2, and Bcl-2, but significantly increased the expressions of Bax and caspase-3 compared to the cisplatin treatment only group (Figure 5).

β-elemene enhances the anti-tumor effects of cisplatin in GSCC xenograft model

The anti-proliferative activity of cisplatin combined with β-elemene was further determined in the nude mice xenograft model *in vivo*. The results showed that tumor volumes and weight in the cisplatin combined with β-elemene group were reduced significantly compared to the cisplatin treatment only group (Figure 6). Western blotting analysis verified the molecular mechanism of β-elemene in sensitizing the anti-tumor activity of cisplatin through inhibition of the STAT3 signaling pathway *in vivo*. The expressions of p-STAT3, p-JAK2, and Bcl-2 decreased, but Bax and caspase-3 expressions increased

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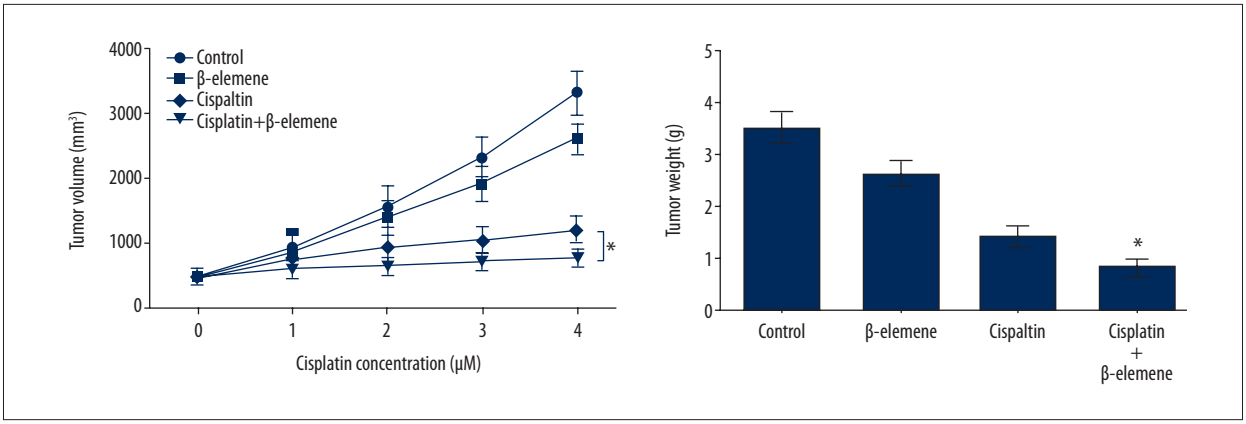

Figure 6. β-elemene promotes cisplatin sensitivity on tumor volumes and weight of mice in a YD-38 xenograft mouse model. * Statistically significant difference between the cisplatin+β-elemene groups and the cisplatin treatment only group (P<0.01, by t-test).

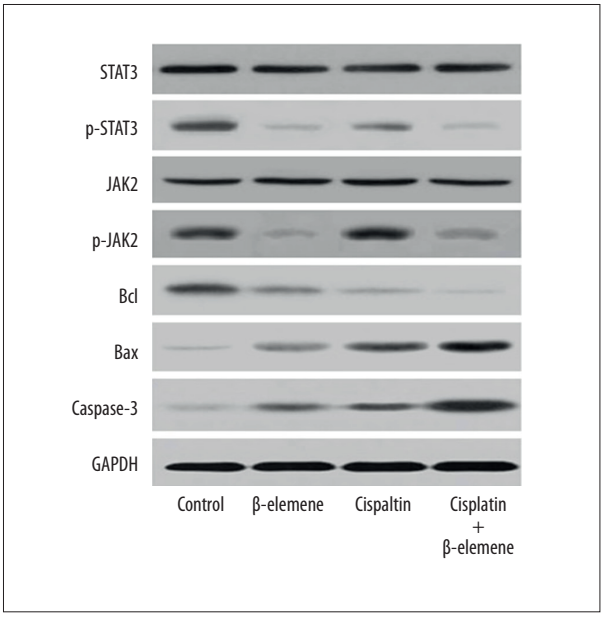

Figure 7. β-elemene enhanced cisplatin-induced protein expressions of STAT3, JAK2, caspase-3, Bcl-2, and Bax in tumor tissues. Cisplatin combined with β-elemene decreased the expressions of p-STAT3, p-JAK2, and Bcl-2, and increased the expressions of Bax and caspase-3 significantly compared to the cisplatin group, as determined by Western blotting analysis.

significantly in the cisplatin combined with β-elemene group compared to the cisplatin treatment only group (Figure 7).

Discussion

There has been slow but steady progress in chemotherapy for the management of GSCC in the past decades. Nevertheless, combination chemotherapy regimens confer only a modest survival benefit, and recurrent or metastatic disease remains essentially incurable. Currently, cisplatin remains one of the most active agents and is the mainstay of combination chemotherapy regimens against GSCC. However, the efficacy of cisplatin is limited by its high toxicity and the development of drug resistance [24,25].

Recently, β-elemene has been used clinically to treat solid tumors without adverse effects, and has been used in combination with radiotherapy or chemotherapy with its high efficiency towards malignancies and low toxicity to normal tissues. But the exact molecular mechanism of β-elemene in combination regimens still remains unclear. Previous studies showed that β-elemene enhanced both radiosensitivity and chemosensitivity of glioblastoma cells through the inhibition of the ATM signaling pathway [14]. Another study demonstrated that β-elemene induced caspase-dependent apoptosis through the upregulation of Bax and Fas FasL and downregulation of Bcl-2 in glioma [15]. In lung carcinoma, β-elemene inhibited expression of DNA methyltransferase 1 through activation of ERK1/2 and AMPKα signaling pathways [16]. In esophageal carcinoma, β-Elemene inhibited cell proliferation by regulating long noncoding RNA-mediated inhibition of hTERT expression [17]. In renal-cell carcinoma, β-elemene induced apoptosis through inhibition of MAPKERK and PI3K/Akt/mTOR signaling pathways [18]. In breast cancer, β-elemene reversed chemoresistance by reducing resistance transmission via exosomes [19]. In ovarian cancer, β-elemene sensitized chemoresistant ovarian carcinoma cells to cisplatin-induced apoptosis through a mitochondria- and caspase-dependent cell death pathway [20].

In the present study, the synergistic cytotoxicity of β-elemene and cisplatin was evaluated in GSCC *in vitro* and *in vivo*. The results demonstrated the pharmacologic advantage of β-elemene in promoting the cytotoxicity of cisplatin and the mechanisms by which β-elemene increases cisplatin sensitivity in GSCC. β-elemene promoted the cytotoxic effect of cisplatin

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by significantly inducing apoptosis and inactivating the STAT3 signaling pathway. The family of signal transducer and activator of transcription (STAT) proteins plays an important role in cancer cell proliferation, apoptosis, invasion, and survival [26]. Among them, STAT3 is constitutively active in various carcinomas. STAT3 undergoes tyrosine phosphorylation and then transcription after activation [27,28]. Janus-activated kinases (JAKs), including JAK1, JAK2, and JAK3, mediate the phosphorylation process of STAT3 [29]. The downstream signaling of STAT3 includes various proteins, such as c-Myc, Mcl-1, cyclin D1, survivin, caspases, and Bcl-2 family, that are required for cell cycle, apoptosis, and survival [30,31]. The apoptosis process is mediated by caspases, mainly caspase-3 and caspase-9. The apoptosis pathway can be triggered through the cleavage of caspase-3. Bcl-2 and Bax play important roles in caspase-dependent apoptosis. Bcl-2 is an anti-apoptotic protein, while Bax promotes apoptosis. Therefore, inhibition of STAT3 activation has potential in cancer treatment. STAT3 activation is related to the induction of apoptosis resistance, probably by increasing the expression of Bcl-2 [32]. In the present study, β-elemene promoted cisplatin-induced apoptosis of GSCC cells, likely via downregulation of Bcl-2 expression and upregulation of Bax and caspase-3 expression. The results of the present study show that β-elemene induces inhibition of JAK2-STAT3 signaling in GSCC. Although the mechanisms of JAK2-STAT3 signaling-mediated apoptosis are well known, the development of β-elemene sensitizing chemotherapy in targeting this pathway remains unexplored. The present *in vitro* and *in vivo* study shows that β-elemene can inhibit JAK2-STAT3 signaling, and subsequently modulates cell survival and apoptotic downstream proteins of STAT3, including Bcl-2, Bax, and caspase-3. These results suggest that inactivation of STAT3 might be a critical mechanism by which β-elemene suppresses cell proliferation and induces apoptosis in GSCC.

Conclusions

Current systemic chemotherapy regimens have led to limited outcomes with low response rates and high toxicity. However, the present study found that β-elemene promoted the anti-proliferative and apoptotic effect of cisplatin by inhibiting STAT3 and blocking the JAK2-STAT3 signaling pathway in GSCC *in vitro* and *in vivo*. This therapeutically effective combination is a potential strategy for clinical GSCC treatment and needs further preclinical study preceding human trials.

Conflicts of interest

The authors declare no conflict of interest.

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