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Original Article

Baneh Gum Essential Oil Enhances Doxorubicin Cytotoxicity and Downregulates hsa-mir-181a-5p in Human Gastric Adenocarcinoma Cells

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Abstract

Introduction: Current treatments for gastric cancer (GC) involve chemotherapy, radiotherapy, and surgery, with chemotherapy being the primary method despite its side effects and potential for drug resistance. Some plants are recognized as valuable sources for anticancer drug development, providing therapeutic benefits and reducing side effects economically. This study aims to investigate the anticancer effects of Baneh gum essential oil (BGEO) alone and combination with doxorubicin on hsa-mir-181a-5p expression in AGS cells as a GC cell line, addressing the significant burden of late-diagnosed gastric cancer.

Materials and Methods: After culturing the AGS cells as a GC cell model, they were treated with different concentrations of BGEO (1, 2, 4, 6, 8, 10, 12, 14, and 16 µl) to determine the IC_{50} over a period of 72 hours, with the initial concentration held constant at 25 µg/ml. Subsequently, cell viability, apoptosis, and the expression of the hsa-mir-181a-5p gene were investigated alone and in combination with doxorubicin (0.025 µM).

Results: Our results showed that treatment with BGEO causes a significant decrease in cell viability and a significant increase in the apoptosis of AGS cells compared to the control group ($p < 0.05$). Also, the results showed that the expression level of hsa-mir-181a-5p was significantly decreased in combination to the control group ($p < 0.05$). The results of investigating the simultaneous effects of BGEO in combination with doxorubicin (DXR) showed that both agents in combination have more effects than single treatment ($p < 0.05$).

Conclusions: In summary, BGEO significantly reduces cell viability and increases apoptosis in AGS cells, suggesting its potential as a therapeutic agent. The notable decrease in hsa-mir-181a-5p expression indicates its influence on key regulatory pathways in GC. Additionally, this activity was enhanced in combination with DXR. These findings underscore the promise of BGEO in cancer treatment and call for further research into its mechanisms and clinical applications.

Keywords: Gastric Cancer, Baneh Gum Essential Oil, Cell Viability, Apoptosis, MicroRNA

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Introduction

Cancer cells are characterized by their unchecked growth and proliferation, which result from the malfunction of genes and proteins that regulate growth and the cell cycle. Although there has been a gradual decline in the incidence of GC over the past 50 years, it remains the fourth most prevalent cancer globally and the second leading cause of cancer-related deaths worldwide.[1] In Iran, a significant number of prevalent cancers are linked to the digestive system, with GC being one of the most common. Additionally, as life expectancy rises, there is a growing concern that the incidence and mortality rates of this deadly disease will increase rapidly in the near future.[2] GC is often diagnosed at advanced stages due to the absence of clinical symptoms. The standard treatments for this disease typically include surgery and chemotherapy.[3] The primary reasons for the failure of chemotherapy in GC are its relatively low effectiveness, considerable toxicity, and the development of drug resistance. In terms of surgery, the most significant challenge is the recurrence of GC, often with metastasis to the lymph nodes, occurring in about 50% of cases. Like all cancers, GC is a complex disease influenced by numerous genetic and epigenetic factors that contribute to its development.[4,5] MicroRNAs are significant epigenetic factors involved in the clinical processes of GC, acting as

important post-transcriptional regulators. Their unique characteristics, including tissue and cellular specificity, stability in various biological fluids, and their upregulation during tumorigenesis, make them promising candidates for potential biomarkers and therapeutic targets in cancer treatment.[6] Recent studies have demonstrated that microRNAs can function as both oncogenes and tumor suppressors in the development and progression of cancer. GC, being a prevalent malignancy, has a notably low survival rate. In 2018 alone, over 1 million new cases of GC were reported, resulting in approximately 783,000 deaths.[7] Identifying and characterizing new biomarkers for the treatment of GC is crucial. One such multifaceted microRNA is miR-181, which plays a significant role in various cellular processes, particularly in determining cell fate and promoting cell invasion. This makes miR-181 a potential target for therapeutic strategies in GC.[8] miR-181 is often found to be aberrantly expressed in human tumors, and it exhibits contrasting functions depending on the type of cancer. In some cancers, it may act as an oncogene, promoting tumor growth and invasion, while in others, it may function as a tumor suppressor, inhibiting cancer progression.[9] Various studies have indicated that miRNA-181a is overexpressed in GC tissues. Clinical and pathological analyses have revealed that the expression of miR-181 is linked to tumor size, lymph node metastasis, and distant metastasis. Furthermore, Kaplan-Meier analysis has demonstrated that the overexpression of miR-181 is associated with poor overall survival in patients with gastric cancer. This suggests that miR-181a could serve as a potential biomarker for prognosis and a target for therapeutic intervention in GC.[10] In addition, miR-181 is overexpressed in GC cells, and reducing its levels can induce cell apoptosis while suppressing the proliferation, invasion, and metastasis of GC cells both *in vitro* and in clinical settings. This indicates that targeting miR-181 could be a promising strategy for developing therapies aimed at inhibiting GC progression and improving patient outcomes.[11] *Pistachios* belong to the *Pistacia* genus in the *Anacardiaceae* family, with 11 species worldwide. In Iran, three wild species grow, including *Pistacia atlantica*, *Pistacia vera*, and *Pistacia khinjuk*, mainly in central and western regions. *P. khinjuk* is often mistaken for Baneh due to its resemblance to *Pistacia atlantica*. It is a short shrub, 1 to 3 meters tall, featuring compound leaves, reddish-purple flowers, and small fruit shafts.[12] Baneh has been referenced in traditional medicine for cancer treatment. Recent studies indicate that various parts of the Baneh plant exhibit significant effects in controlling and inhibiting the proliferation of various cancer cell types.[13] The study aims to investigate the anticancer effects of BGEO alone and in combination with doxorubicin (DXR) on the cell viability and expression profile of hsa-miR-181a-5p in human gastric adenocarcinoma cells.

Materials and Methods

Reagents

RPMI-1640, fetal bovine serum (FBS), and penicillin-streptomycin, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium (MTT), dimethyl sulfoxide (DMSO), acridine orange (AO), and ethidium bromide (EtBr) were purchased from Bioidea, Iran. The RNA extraction kit and DNase I enzyme were purchased from Sinaclon, Iran. The cDNA synthesis kit was purchased from AddBio, Korea. 2X Prime Q-Master Mix with SYBR Green I was purchased from Parstous, Iran. Baneh essential oil was purchased from Saghez Sazi Kurdistan (Van) Co., Iran.

Cell Culture and Experimental Design

AGS cells, a human GC cell line, were obtained from the Pasteur Institute of Iran in Tehran. The cells were cultured at 37 °C in a humidified atmosphere of 95% air and 5% CO_2 using a culture medium that included heat-inactivated FBS, glutamine, penicillin, and streptomycin (1%). Subsequently, the cells were divided into four groups: Control without treatment, treated with different concentrations of BGEO (1, 2, 4, 6, 8, 10, 12, 14, and 16 µl), treated with doxorubicin (0.025 µM), and combined treatment (BGEO at IC_{50} and doxorubicin). Cells were treated in different groups for a total of 72 hours, and then evaluations were conducted.

Cell Viability

The cell viability was assessed using the MTT assay, in which the reduction of MTT by live and proliferating cells leads to the formation of formazan crystals. In this study, MTT was used both to determine the IC_{50} and to assess the final cell viability. In each group, AGS cells were cultured in a 96-well plate and treated for 24, 48, and 72 hours. Then, 100 µl of MTT solution with a final concentration of 0.5 mg/ml was added to all wells and incubated for 4 hours at 37 °C. Finally, the formed formazan crystals were dissolved in 100 µl of dimethyl sulfoxide (DMSO) and incubated in the dark for 30 minutes. The optical absorbance of the wells was read using an ELISA reader (Thermo Scientific, USA) at a wavelength of 570 nanometers.

Apoptosis

To determine the level of apoptosis in cancer cells, AO and EtBr staining were used. After culturing the AGS cells in a 24-well plate, they were treated for 72 hours. Then, the wells were gently washed twice with PBS. A total of 250 µl of the AO/EtBr solution (5 µg/ml AO and 5 µg/ml EtBr in PBS) was added to all wells. After 2 minutes of incubation at room temperature, the supernatant was removed, and cellular apoptosis was examined under a fluorescence microscope.

RNA Extraction

To extract RNA, we incubated a sample with 10^6 cells at

room temperature for 5 minutes after adding RNX-plus TM. We then centrifuged the mixture at 12,000g for 2 minutes at 4 °C after shaking it with chloroform and letting it incubate for 3 minutes. After combining the aqueous phase with isopropanol, we centrifuged it once again for 20 minutes at 12,000g. Following the discarding of the supernatant, we applied ethanol to the residual pellet. After another round of centrifugation, we reconstituted the pellet in RNase-free water. To remove genomic DNA from the RNA, we added DNase I enzyme and its buffer. After adding EDTA acid solution and allowing the mixture to sit, we used a NanoDrop (Thermo Scientific, USA) to measure the RNA quantity.

cDNA Synthesis

We need to mix RNA with a specific primer that has a stem-loop structure to create microRNA cDNA. After mixing, add DEPC water until the volume reaches 7 µl. Next, incubate the mixture for 10 minutes at 70 °C using a heat cycler. Then, mix the mixture with 10 µl of 2X reaction buffer, 2 µl of dNTP (10 mM), and 1 µl of 20X RT. After that, incubate the synthesis for 10 minutes at 25 °C and 60 minutes at 50 °C in a 20 µl volume. Incubate the mixture at 80°C for 5 minutes to deactivate the reverse transcriptase (RT). For later use, the generated cDNA can be stored frozen at -70 °C.

Primer Design

Considering that microRNAs are short sequences (about 18 to 23 nucleotides), primer design for cDNA synthesis and amplification is done in special and different ways from other genes. We used the stem-loop primer method for cDNA synthesis. The design of primers was done using the online OligoAnalyzer software at https://www.idtdna.com/pages/tools/oligoanalyzer. The sequence of the primers is given as follows in Table 1.

Table 1. Sequence of hsa-miR-181a-5p and U48 Primers

miRNA	Sequence	Primer sequence
hsa-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	Stem-loop primer: GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATAGACACTCAC Forward primer: GCATAACATTCAACGCTGTCG Reverse primer: GTCGTATCCAGTGCAGGGT
U48	AGTGATGATGACCCCAGGTAACTCTTGAGTGTG TCGCTGATGCCATCACCGCAGCGCTCTGACC	Stem-loop primer: GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACGGTCAG Forward: CTCTGAGTGTGTCGCTGATGCC Reverse: CCAGTGCAGGGTCCGAGGTA

hsa-miR-181a-5p Expression

After RNA extraction and DNase treatment, cDNA was synthesized using primer synthesis. To confirm the expression changes of hsa-miR-181a-5p, real-time PCR was performed using the SYBR Green method following the Pars Tous kit protocol. Initially, 10 µl of Master Mix Cyber Green was added to a specialized microtube for real-time PCR. Then, 1 µl of the forward and reverse primer mixture for the target gene was added, followed by 1 µl of the cDNA prepared in the previous step, which was diluted with distilled water.

Statistical Analysis

We used SPSS 23 software to analyze the data, and Tukey's test method was used to determine the significance of differences by comparing the means between groups of different treatments. It should also be noted that, in all investigations, a *p*-value of less than 0.05 was considered a significant level. The figures were drawn using GraphPad software, and the data were reported as mean ± SEM. To analyze the Real-Time PCR results, REST software was used.

Results

IC_{50} Concentration of the BGEO

Figure 1 shows the cell viability of AGS cells after treatment with different concentrations of BGEO. According to Figure 1, to calculate the IC50, we need to consider that the volumes indicated in the graph were poured into wells of a 96-well plate and diluted with culture media to reach a maximum volume of 100 µl. Therefore, to calculate the IC_{50}, we need to divide the initial concentration (25 µg/ml) by the amount that the volume changed. With this explanation, the IC50 for 24, 48, and 72 hours can be calculated as 4.159, 2.049, and 0.845 µl, respectively.

Cell Viability

According to Figure 2, BGEO and doxorubicin significantly decreased the viability of AGS cells compared to the control group ($p < 0.05$). It was also observed that the cytotoxic effects of BGEO are significant and lower than those in the doxorubicin-treated group ($p < 0.05$). The results of investigating the simultaneous effects of BGEO in combination with doxorubicin showed that both agents in combination have more cytotoxic effects than single-agent treatment ($p < 0.001$).

Apoptosis Assessment

According to Figure 3, the results showed that compared to the control group, BGEO and DXR caused a significant increase in the apoptosis of AGS cancer cells ($p < 0.01$). It

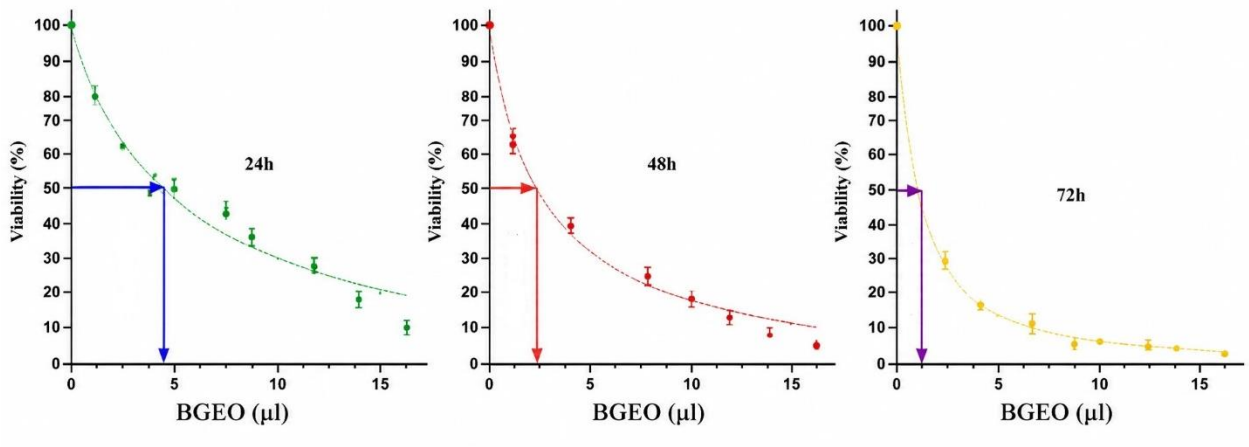

Figure 1. IC_{50} Concentration of the BGEO in 24, 48, and 72 Hours after Treatment.

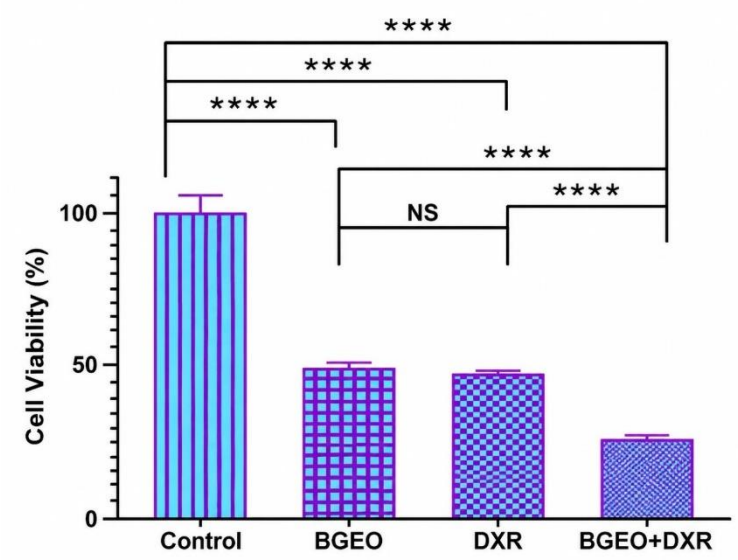

Figure 2. Cell Viability of AGS Cells after Treated with BGEO and DXR and Combine Group. The level of statistical significance was also considered as symbols *(p <0.05), **(p <0.01), ***(p <0.001) and ****(p <0.0001) and non-significance with NS.

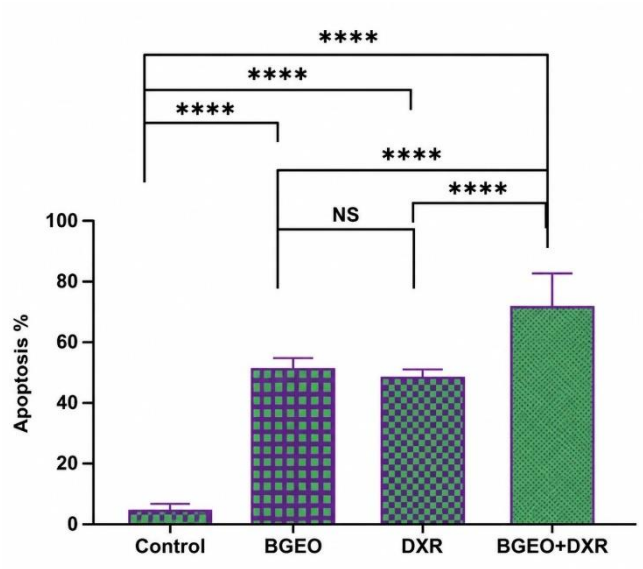

Figure 3. Apoptosis Percent of AGS Cells after Treated with BGEO and DXR and Combine Group. The level of statistical significance was also considered as symbols *(p <0.05), **(p <0.01), ***(p <0.001) and ****(p <0.0001) and non-significance with NS.

was also observed that the apoptotic effect of BGEO compared to the group treated with DXR is not significan. The results of investigating the simultaneous effects of BGEO in combination with DXR showed that both agents in combination have more apoptotic effects than single-agent treatment ($p < 0.05$).

hsa-mir-181a-5p Expression

According to Figure 4, the expression level of the hsa-miR-181a-5p gene in the treatment group has significantly decreased compared to the control group (-3.597-fold for BGEO and -8.771-fold for DXR).

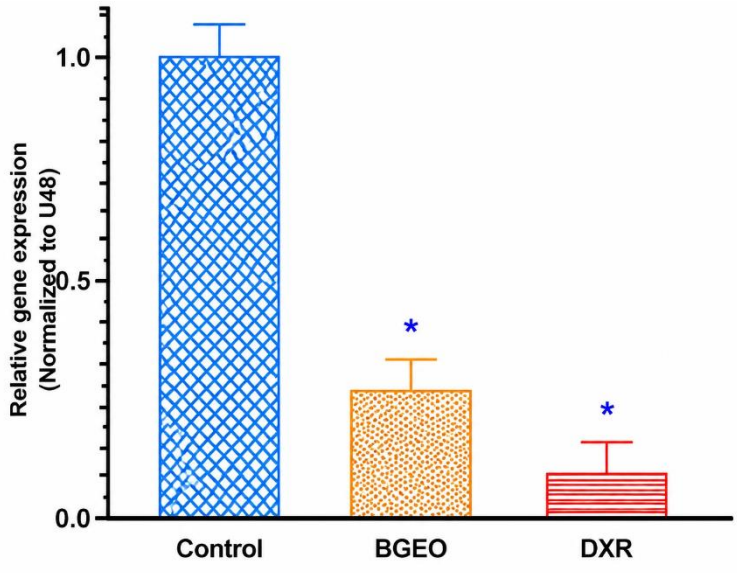

Figure 4. Expression of hsa-miR-181a-5p in AGS Cells in Different Treatment Groups. The level of expression in BGEO and DXR groups shows a decrease of 3.597 and 8.771 times, respectively, compared to the control group (*$p < 0.05$).

Discussion

The aim of this study was to investigate the cytotoxic effects of BGEO and determine the expression profile of hsa-miR-181a-5p in AGS cells. The results of the study showed that treatment with BGEO caused a significant increase in cytotoxicity and a significant decrease in the cell viability of AGS cells compared to the control group. Additionally, the results showed that the expression level of hsa-miR-181a-5p significantly decreased compared to the control group. Thus, we can confirm some or all of the related statements from other studies with similar contexts included at the end of this section. The burden of cancer and cancer risk factors (e.g., smoking) is increasing worldwide. Most of these deaths occur in developing countries, and in many cases, they can be prevented through knowledge, awareness, and control programs based on existing data.[14] In terms of the incidence of GC, it is the fourth most common cancer and the second leading cause of death in the world. In Iran, this cancer is very important and is one of the major health problems.[15] Fortunately, the occurrence of this cancer in the world (especially in developed countries) has a decreasing trend. In America, the incidence of this cancer has been decreasing in recent decades. This situation has also been observed in Canada, and from 1984 to 2013, the incidence rate of this cancer decreased from 18.4 to 9.5 per 100 thousand people.[16] Additionally, this cancer is not common in European countries, while it is increasing in Asian and developing countries.

In Iran, the incidence of stomach cancer is increasing, especially in the west of the country, which is considered a significant problem. The variation in the disease's incidence in different regions may be due to genetic differences and diet.[17] Today, chemotherapy and surgery are commonly used to treat cancer, but they often have side effects and limited effectiveness.[18] The use of medicinal plants in cancer treatment has gained attention from researchers. Secondary metabolites in plants possess therapeutic properties that can prevent diseases caused by free radicals and reduce oxidative stress.

Plants such as thyme, gourd, thistle, saffron, and rose, which contain secondary metabolites such as phenolic compounds, flavonoids, alkaloids, terpenoids, and steroids, play an important role in the treatment of various diseases, including cancer.[19] One of the important molecules that play a key role in cancer is microRNAs. MicroRNAs are non-coding RNA molecules that are typically 18–25 nucleotides long. They have been conserved throughout evolution and work by inhibiting translation of a gene or causing mRNA to be degraded after transcription to control the expression of that gene.[20] These molecules play a critical role in regulating cell activity and have the ability to prevent or delay the development of cancer. Cancer can result from mutations in specific regions of these molecules. The discovery of microRNAs and the molecules they influence by researchers

provides insight into the pathogenesis of cancer. These microRNAs have the potential to diagnose, predict, and treat cancer.[21] According to Yu et al. (2018), in GC cell lines, miR-181a decreases the expression of the *Bax* while increasing the expression of *cyclin A2*, *CDC25A*, and *Bcl-2*. Additionally, the research indicated that miR-181a could directly interact with RASSF1A to contribute to the development of GC.[10] Ahmadirad et al (2020) showed that the IC_{50} value for MCF-7 cells and L929 after 48 h of treatment with *Pistacia atlantica* extract was 250 mg/ml and 400 mg/ml, respectively. Morphological analysis and DNA fragmentation assay confirmed the occurrence of apoptosis in both L929 and MCF-7 cells after treatment with *Pistacia atlantica* extract at the IC_{50} concentration. This idea suggests that increasing the expression of *caspase-8*, *caspase-3*, *p53*, and *Bax* genes leads to a decrease in *Bcl-2* gene expression, indicating that the *Pistacia atlantica* extract induces apoptosis in MCF-7 cells through both intrinsic and extrinsic pathways of programmed cell death.[22] Rahman et al. (2018) demonstrated that gum resin of *Pistacia atlantica*, in concentrations ranging from 0.01 to 100 µM, induces cancer cell death in a dose- and time-dependent manner. Flow cytometry results indicated that mastic gum resin significantly halted COLO205 cell proliferation in the G2/M phase of the cell cycle.[23] Ben et al. (2021) showed that crude extracts and compounds isolated from *Pistacia atlantica* have a wide range of medicinal properties such as antimicrobial, antifungal, anti-inflammatory, analgesic, wound healing, anti-cancer, cytotoxic, anti-cholinesterase, anti-diabetic, liver protection, urea inhibition, anti-hypertensive, improvement of nipple gap, anti-leishmanial, and anti-plasmodial activities.[24] Rahbar et al. (2016) showed that the resin has significant cytotoxic effects on cancerous and non-cancerous cell lines. These results indicate that apoptosis and necrosis are the dominant mechanisms by which the resin affects the cell lines.[13] Tilkat et al. (2021) showed that *Pistacia khinjuk* Stocks had apoptotic effects against MCF-7 (breast cancer) and HT-29 (colon cancer) cell lines.[25]

Conclusion

This study demonstrates that BGEO exerts significant cytotoxic and pro-apoptotic effects on AGS gastric cancer cells, as evidenced by reduced cell viability and increased apoptosis. Notably, BGEO treatment downregulates hsa-miR-181a-5p expression, a microRNA implicated in gastric cancer progression. The combination of BGEO with doxorubicin enhances these anticancer effects compared to either agent alone, suggesting a synergistic potential. These findings highlight BGEO as a promising complementary therapeutic agent for gastric cancer, warranting further mechanistic studies and *in vivo* investigations to assess its clinical applicability.

Authors' Contributions

All authors contribution equally to this study.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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