Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

Evaluation of the effect of sclareol on endoplasmic reticulum stress in the KATO III human gastric carcinoma cell line

Mojtaba Ghaffarian Gabalou [1], Seyed Ali Rahmani [1*], Changiz Ahmadizadeh [2], Rasoul Sharifi [3]

1. Department of Molecular Genetics, Ah.C., Islamic Azad University, Ahar, Iran
2. Department of Microbiology, Ah.C., Islamic Azad University, Ahar, Iran
3. Department of Biochemistry, Ah.C., Islamic Azad University, Ahar, Iran

* Correspondence: Seyed Ali Rahmani. Department of Molecular Genetics, Ah.C., Islamic Azad University, Ahar, Iran.
Email: rahmaniseyedali@yahoo.com

Abstract

Background: The main goals of chemotherapy are to induce apoptosis (Cell death) and arrest the cell cycle in cancer cells. An important factor in inducing apoptosis in cancer cells is increased endoplasmic reticulum stress. This study investigated the effect of Sclareol on the ATF6 pathway, as well as its effects on two other genes, VEGF and E2F1, associated with the UPR pathways.

Methods: The target population comprised KATO III human gastric carcinoma cells purchased from the Pasteur Institute of Iran. The cells were cultured in the cell culture laboratory until their number reached at least 100,000 cells/well. They were treated with 0, 20, 40, 60, 80 and 100 µM Sclareol for 5 hours. The expression of the genes specified in the research objectives was analyzed in gastric cancer cells before and after Sclareol treatment using quantitative real-time PCR on cell-line spheroids cultured in suspension. SPSS Software was used for statistical analysis.

Results: ATF-6 gene expression increased significantly at Sclareol doses of 20, 40 and 60 µM ($P<0.0001$). In contrast, VEGF gene expression decreased significantly at Sclareol doses of 20, 40 and 60 µM ($P<0.001$). E2F1 gene expression also increased significantly at Sclareol doses of 20, 40 and 60 µM ($P<0.003$).

Conclusion: The findings of the present study suggest that Sclareol may reduce VEGF gene expression and increase the expression of ATF-6 and E2F1, which are responsible for increasing endoplasmic reticulum stress in KATO III human gastric cancer cells. Sclareol doses of 40 and 60 µM were considered effective.

Article Type: Research Article

Article History

Received: 13 November 2024
Received in revised form: 9 May 2025
Accepted: 8 June 2025
Available online: 30 August 2026
DOI: 10.29252/mlj.20.4.38

Keywords

Gastric Cancer
Endoplasmic Reticulum Stress
Sclareol
KATO III Gastric Cancer Cells

OPEN ACCESS
© The author(s)

Introduction

Stomach cancer results from the uncontrolled growth of malignant cells in the stomach. It develops slowly over several years but, unfortunately, causes no symptoms in its early stages, which may explain why it is difficult to diagnose (1).

Stomach cancer progresses slowly over several years. Before cancer develops, precancerous changes often occur in the inner lining (Mucosa) of the stomach. These initial changes can cause substantial symptoms (1,2).

Approximately 90 to 95 percent of stomach cancers are adenocarcinomas. This type of stomach cancer develops from the innermost layer of the stomach (Mucosa). Other types of stomach cancer include lymphoma, stromal tumors, and carcinoid tumors (3,4). Helicobacter pylori infection, smoking, a high-salt diet, and insufficient antioxidant intake have been reported as causes of this disease (5,6).

One of the main causes of stomach cancer is Helicobacter infection, which causes stomach ulcers and gastritis; however, not everyone with Helicobacter infection develops stomach cancer. Otherwise, more than 55% of the world's population would have died from stomach cancer because more than half of the global population is infected with Helicobacter, whereas only 3% of infected individuals may develop stomach cancer (1).

This cancer may spread from the stomach to other parts of the body, particularly the liver, lungs, bones, abdominal wall, and lymph nodes (1,2).

Cancer arising in different parts of the stomach may cause different symptoms, and its location can affect treatment options. Factors such as ethnicity, living environment, nutrition, gene mutations, pernicious anemia, stomach polyps, low socioeconomic status, and obesity may contribute to the development of stomach cancer (1).

In the 20th century, stomach cancer was the most common cause of cancer-related death worldwide. More recently, lung cancer has become the leading cause of cancer-related death, and stomach cancer has fallen to second place. In Iran, cancer is reported to be the third leading cause of death, and between 30 and 40 thousand Iranians die from it each year (7).

This disease is diagnosed using endoscopy and medical imaging, and its most common treatments are surgery, chemotherapy, and radiation therapy (8).

Chemotherapy is one of the most effective treatments for metastatic tumors. The simultaneous resistance of cancer cells to structurally and functionally unrelated drugs, known as multidrug resistance, remains a major obstacle to successful chemotherapy. Three decades of research on drug resistance have identified various approaches to overcoming this problem. However, studies indicate that resistance also develops to each new effective treatment. Therefore, the ability to predict and overcome drug resistance will probably contribute substantially to improving chemotherapy (9).

Factors involved in cancer-cell resistance to anticancer drugs are divided into two general categories:

1- Factors that affect the exposure of tumor cells to anticancer drugs: Interference with drug delivery to cells may result from poor absorption of the administered drugs, increased drug metabolism or excretion, and, ultimately, reduced drug levels in the blood and decreased diffusion from the blood into the tumor mass (6-8).

2- Factors that influence the sensitivity of cancer cells to drugs because of genetic and epigenetic changes.

Environmental factors, such as the extracellular matrix and tumor location, also contribute to drug resistance (6,9).

The main goals of chemotherapy are to induce apoptosis, or cell death, and arrest the cell cycle in cancer cells. One of the most important factors that induce apoptosis in cancer cells is increased endoplasmic reticulum stress.

The endoplasmic reticulum (ER) is a cellular organelle and the largest intracellular organelle involved in intracellular communication. It consists of numerous membrane-bound folds, and the space within the ER is known as the lumen. The endoplasmic reticulum also transports proteins and carbohydrates to the Golgi apparatus, cell membrane, lysosomes, and other sites where they are needed (10).

With the assistance of chaperones in the lumen, the endoplasmic reticulum folds secretory proteins and subsequently transfers them to the Golgi apparatus. Chaperones are three-dimensional molecules in the organic acid group that facilitate the folding of proteins synthesized in cells (10,11).

Under various physiological conditions, excessive increases in metabolic factors such as glucose, lipids, unsaturated fatty acids, cholesterol, and neurotransmitters increase the cellular demand for protein synthesis. If chaperones do not function properly, unfolded proteins accumulate in the endoplasmic reticulum network and induce stress, thereby stimulating apoptosis or repair (11,12). Disruption of endoplasmic reticulum (ER) homeostasis creates stress conditions. Cells respond to disturbances caused by unfolded or misfolded proteins through a cascade of reactions known as the Unfolded Protein Response (UPR*) (11,12).

Therefore, endoplasmic reticulum stress may result from nutrient deprivation, hypoxia, and calcium depletion, among other factors, and initiates responses through three main pathways and other secondary pathways.

Under normal conditions, three integral endoplasmic reticulum proteins are bound to the BiP/GRP78 chaperone; under stress conditions, they dissociate from it and become activated (13).

The three pathways described above attempt to restore endoplasmic reticulum homeostasis by attenuating translation; inducing the transcription of proteins located in the endoplasmic reticulum; activating the endoplasmic reticulum-associated degradation system; and expanding the endoplasmic reticulum in response to pressure from unfolded proteins. If homeostasis cannot be restored, these responses lead to apoptosis (11,12).

The use of natural food-derived chemicals such as Sclareol as cancer chemopreventive and therapeutic agents is attractive because these compounds are generally inexpensive and readily available, are easily metabolized in the human body, and usually cause no substantial harm to normal cells. Accordingly, at the interface of cell biology and biochemistry, using food-derived chemicals to activate endoplasmic reticulum stress signaling and apoptosis in cancer cells represents a potential strategy for combating cancer.

This study investigated the effect of Sclareol on the ATF6 pathway and on two other genes related to the UPR pathways, VEGF and E2F1. Sclareol from sage, scientifically known as "Salvia officinalis," has been reported to induce apoptosis in many cancer-cell types. Sclareol is an aromatic compound found in and obtained from "Salvia Sclarea." It is classified as a bicyclic diterpene alcohol and is an orange-colored solid with a sweet, safflower-like odor.

Sclareol is used as a fragrance in cosmetics and as a flavoring in food.

Recent studies have demonstrated that intratumoral Sclareol injection exerts antitumor effects, modulates immune responses by reducing Treg cells, and inhibits tumor growth in vivo (13,14).

Sclareol has been reported to be a nontoxic compound capable of inducing apoptosis in a leukemia cell line in a time- and concentration-dependent manner. Research findings indicate that plant-derived diterpenes present in sage (Sclareol) have anticancer properties in vitro (15,16).

Previous studies indicate that Sclareol has the potential to act as a chemotherapeutic agent and exert cytostatic activity in cancer cells. It may therefore have potential for drug development. Further molecular pathways must be investigated to clarify the compound's molecular mechanisms (17,18).

Methods

This experimental study analyzed laboratory findings, and its target population comprised human gastric cancer cells from the cell line.

The target population comprised KATO III human gastric cancer cells purchased from the Pasteur Institute of Iran. The cells were cultured in the cell culture laboratory until their number reached at least 100,000 cells/well. Accordingly, the sample size was set at a minimum of 100,000 cells in each flask, divided into six groups treated with six different concentrations of Sclareol.

The KATO III cell line was cultured as an adherent monolayer in complete RPMI-1640 (Roswell Park Memorial Institute) culture medium containing heat-inactivated fetal bovine serum at 100 ml/l, penicillin and streptomycin at 100 mg/l each, and glutamine at 2 mmol/l liter. The cells were maintained at 37 degrees in a humidified atmosphere containing CO2 gas at a relative pressure of 50 ml/liter. After reaching a suitable density of at least 100,000 cells per plate, the cells were detached from the bottom of the flask using trypsin and then passaged.

The cells were treated with 0, 20, 40, 60, 80, and 100 µM Sclareol for 5 hours. In accordance with the research objectives, gene expression in gastric cancer cells before and after Sclareol treatment was analyzed using quantitative real-time PCR on cell-line spheroids cultured in suspension. Total RNA was extracted from cultured cells using Trizol solution according to the kit protocol and was analyzed quantitatively and qualitatively by agarose gel electrophoresis and spectrophotometry at 260 nm.

cDNA was synthesized from an RNA template using reverse transcriptase. Like other DNA-synthesizing enzymes, this enzyme requires a primer. Therefore, two types of primers, random hexamers and oligo dT, were used to synthesize cDNA. Oligo dT binds to the polyadenine tail of mRNA, whereas random hexamers bind randomly to different regions of mRNA. After primer binding, reverse transcriptase synthesizes DNA (cDNA) from the RNA template. The PrimeScript™ 1st Strand cDNA Synthesis Kit (Takara) was used to synthesize cDNA.

Specific primers and probes for the target genes were designed using Primer-3 and Primer Express® software based on sequences retrieved from the GenBank database. The final selected oligonucleotide sequences are presented in Table 1.

In this study, real-time PCR was used to examine gene expression with a Corbett Rotor-Gene 6000. All samples were analyzed three times. After the reaction was completed and the threshold line was established, the threshold cycle (CT) was determined for each sample. Relative gene expression was calculated using the $2^{-\Delta\Delta CT}$ method, with the threshold cycle of the gene of interest normalized to that of the housekeeping gene β-Actin.

Table 1. Sequences of the primers designed for the E2F1, VEGF, ATF-6 and β-Actin genes

Gene name	Primer type	Primer sequence (5' → 3')	Accession No.
E2F1	Forward	TACCTTTTCCTGGATGGCGG	NC_000020.11
	Reverse	TCCTGGTTACTGGGCATCCT	
VEGF	Forward	TGCAGATTATGCGGATCAAACC	NM_001287044.1
	Reverse	TGCATTCACATTTGTTGTGCTGTAG	
ATF-6	Forward	GATTGGGGTGAGTGGGATCTG	NC_000001.11
	Reverse	GCCGAACGATACTCCCAGAC	
β-Actin	Forward	GGTGAGCTGCGAGAATAGCC	NC_000007.14
	Reverse	CTCCGACCAGTGTTTGCCTT	

Descriptive data were presented as the mean, median, standard deviation, minimum, and maximum. Data normality was then assessed using the Kolmogorov-Smirnov test. Finally, the research hypotheses were examined using one-way analysis of variance and SPSS 22 statistics.

Results

To assess the quality of the extracted RNA, the 18S rRNA and 28S rRNA bands were examined on a 2% agarose gel. For this purpose, 1.5 microliters of four randomly selected RNA samples treated with 4 microliters of loading buffer were electrophoresed on a 2% agarose gel for 20 minutes. The relevant bands were observed as shown in Figure 1.

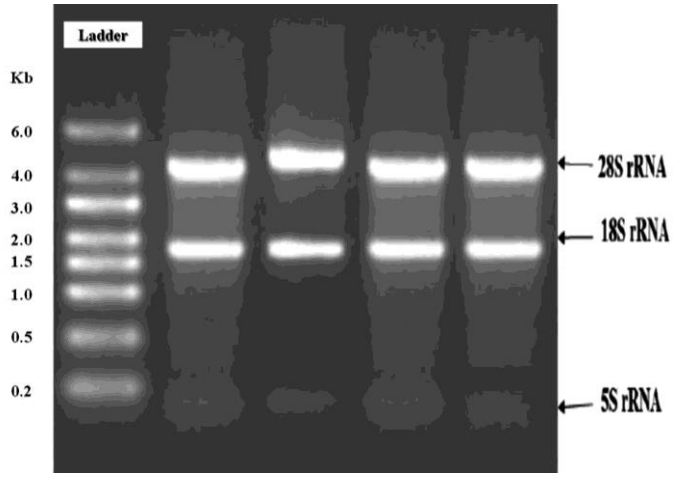

Figure 1. 18s rRNA and 28s rRNA electrophoresis bands from RNA samples extracted from culture media

Assessment of primer quality using a PCR gradient reaction

To assess primer quality, a PCR gradient reaction was performed for the β-Actin gene primer.

The PCR products were examined by electrophoresis on a 2% agarose gel, and a sharp single band was obtained at 57.8 degrees. The band was detected and recorded under UV light, as shown in Figure 2.

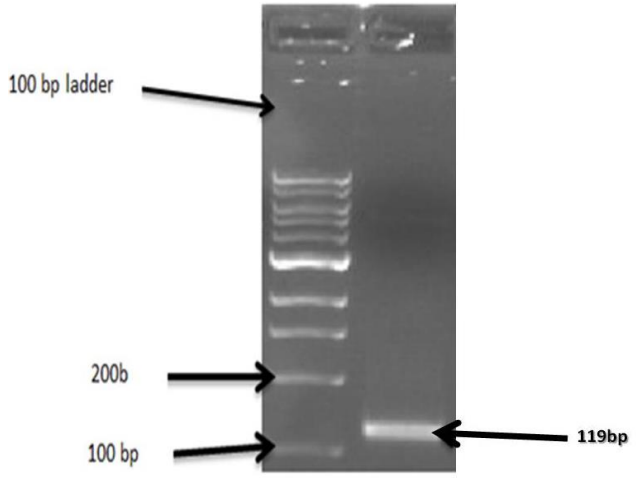

Figure 2. Electrophoresis gel image of the β-Actin gene, showing a band for the 119bp product at 57.8°C.

Assessment of synthesized cDNA quality using a positive PCR control

To assess the quality of the synthesized cDNA, PCR was performed for the housekeeping gene β-Actin. In this reaction, cDNA served as the template, and Smar Taq DNA polymerase was used.

The PCR products were examined by electrophoresis on a 2% agarose gel, and a sharp single band was obtained at 58.5 degrees. The PCR products were stained with ethidium bromide, observed, and recorded. They were then visualized under UV light, as shown in Figure 3.

Figure 3. Electrophoresis gel image of the β-Actin gene, showing a band for the 218 bp products at 58.5°C.

Analysis of melting curves obtained using real-time PCR to identify specific and nonspecific products

Figures 4 and 5 show the melting-curve diagrams obtained after the PCR reaction for the β-Actin and ATF6 genes. As shown, nonspecific products were minimized in this study.

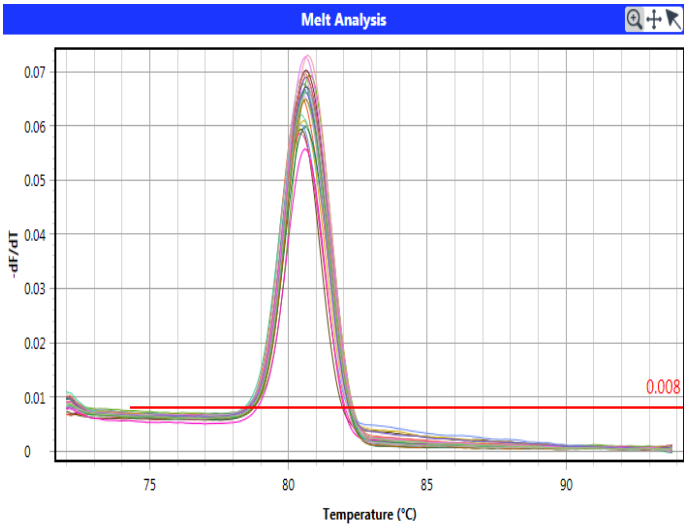

Figure 4. Melting-curve diagram obtained using real-time PCR for the β-Actin gene

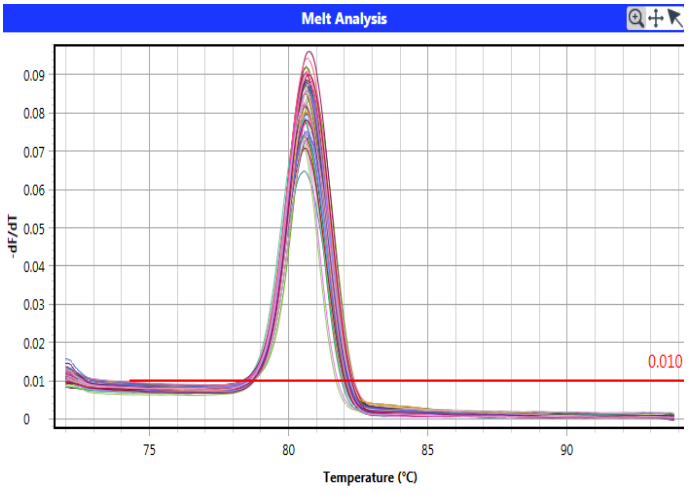

Figure 5. Melting-curve diagram obtained using real-time PCR for the ATF6 gene

ATF-6 gene expression increased significantly at Sclareol doses of 20, 40 and 60 µM. ATF-6 gene expression at a Sclareol dose of 20 µM was 0.21 ($2^{-\Delta\Delta CT}$); at a dose of 40 µM, it was 0.45 ($2^{-\Delta\Delta CT}$); and at a dose of 60 µM, it was 0.98 ($2^{-\Delta\Delta CT}$). In contrast, expression decreased at doses of 80 and 100 µM. ATF-6 gene expression at a Sclareol dose of 80 µM was 0.56 ($2^{-\Delta\Delta CT}$), and at a dose of 100 µM, it was 0.23 ($2^{-\Delta\Delta CT}$) ($p<0.0001$). Figure 6 shows the effects of different Sclareol concentrations on ATF-6 gene expression in cancer cells.

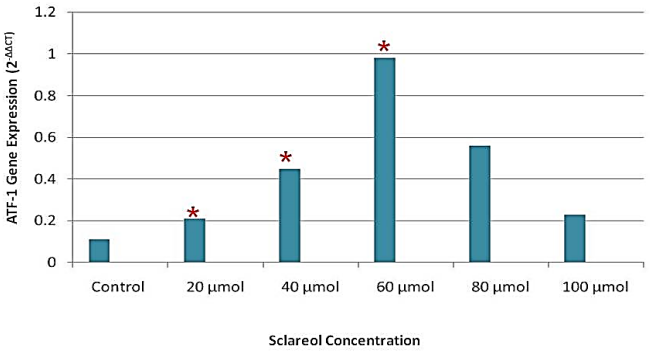

Figure 6. Effect of Sclareol concentrations on ATF-6 gene expression in cancer cells

In the present study, VEGF gene expression decreased significantly at Sclareol doses of 20, 40 and 60 µM. VEGF gene expression at a Sclareol dose of 20 µM was 0.59 ($2^{-\Delta\Delta CT}$); at a dose of 40 µM, it was 0.39 ($2^{-\Delta\Delta CT}$); and it was 0.21 ($2^{-\Delta\Delta CT}$) at a dose of 60 µM. However, expression increased again at doses of 80 and 100 µM. VEGF gene expression at a Sclareol dose of 80 µM was 0.61 ($2^{-\Delta\Delta CT}$), and at a dose of 100 µM, it was 0.77 ($2^{-\Delta\Delta CT}$) ($p<0.001$). Figure 7 shows the effects of Sclareol concentrations on VEGF gene expression in cancer cells.

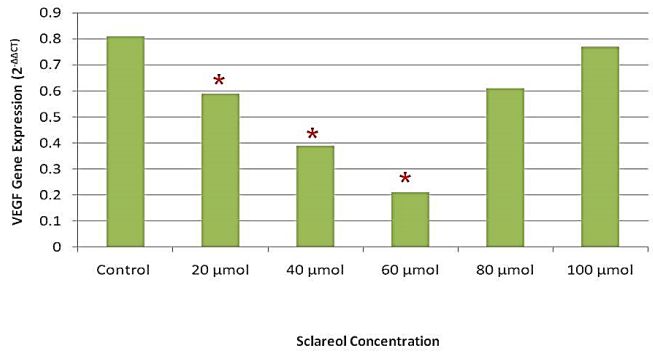

Figure 7. Effect of Sclareol concentrations on VEGF gene expression in cancer cells

E2F1 gene expression increased significantly at Sclareol doses of 20, 40 and 60 µmol. E2F1 gene expression at a Sclareol dose of 20 µM was 0.20 ($2^{-\Delta\Delta CT}$); at a dose of 40 µM, it was 0.31 ($2^{-\Delta\Delta CT}$); and at a dose of 60 µM, it was 0.41 ($2^{-\Delta\Delta CT}$). However, expression decreased at doses of 80 and 100 µM. E2F1 gene expression at a Sclareol dose of 80 µM was 0.51 ($2^{-\Delta\Delta CT}$), and at a dose of 100 µM, it was 0.26 ($2^{-\Delta\Delta CT}$) ($p<0.003$). Figure 8 shows the effects of Sclareol concentrations on E2F1 gene expression in cancer cells.

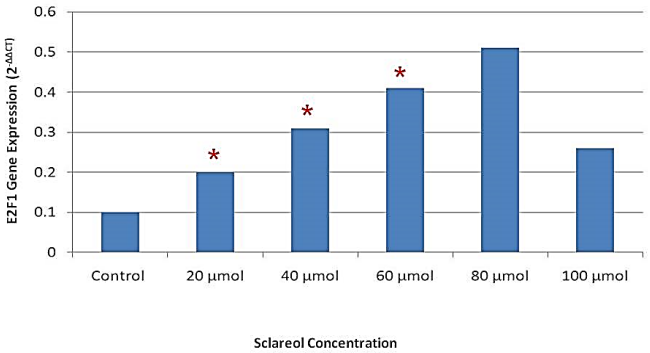

Figure 8. Effect of Sclareol concentrations on E2F1 gene expression in cancer cells

Discussion

As stated in the Introduction, the main objective of the present study was to investigate the effect of Sclareol on the expression of VEGF, E2F1 and ATF-6, which are key genes in the endoplasmic reticulum stress pathway in human gastric cancer cells.

Considerable information is now available on the mechanisms of drug resistance in cancer cells. Despite advances in chemotherapy, cellular defense mechanisms against cytotoxic compounds remain a major obstacle to successful cancer treatment. A better understanding of drug-resistance mechanisms may support the development of new chemotherapy strategies that are less susceptible to resistance (19).

In recent decades, research on Sclareol has shifted from its role as a plant-derived substance to its potential to prevent disease and reduce disease risk when used at appropriate levels. Studies have demonstrated the beneficial effects of Sclareol in various cancers. Reports indicate that the plant extract inhibits cancer-cell growth and increases the cytotoxic effects of chemotherapy on cancer cells. Nevertheless, the precise mechanism through which Sclareol affects cancer cells remains unknown. Different studies have proposed several mechanisms for its anticancer effects (20).

Hassan and colleagues in 2003 (21) suggested that Sclareol could provide an interesting alternative to conventional routes of intratumoral administration. In the study by Noori et al. (2010) (14), Sclareol was extracted from the S. Sclarea plant, and its effectiveness was evaluated following direct injection into the tumor. In this study, Sclareol produced effective results at low doses (Between 20-60 mmol), consistent with the findings of the present study. Although gastric cancer is a common solid tumor, the effects of Sclareol at doses above 80% on gastric tumor cells have not been reported. A limitation of the present study was the inability to analyze the effect of Sclareol on healthy stomach cells; this issue should be addressed in future studies. Moreover, because similar studies in human stomach cancer samples have not been reported, no general conclusion can be drawn from the present findings.

Cancer cells induce the UPR to alleviate ER stress as a survival strategy (22). The UPR has also been reported to play a significant role in resistance to chemotherapy or radiation in cancer (23). Therefore, one therapeutic rationale for cancer suppression is to promote the accumulation of unfolded proteins by inhibiting UPR components involved in the survival response, ultimately leading to apoptosis (24).

Karayiannakis et al. (25) reported that serum VEGF levels were higher in patients with gastric cancer than in the control group. Serum VEGF levels were significantly associated with disease stage, tumor-invasion depth, and the presence of distant metastases. Serum VEGF levels decreased significantly after radical resection of the primary tumor and increased in patients with unresectable tumors. Multivariate regression analysis showed that the serum VEGF level was an independent prognostic factor for survival. The present study demonstrated that Sclareol can reduce VEGF gene expression, a finding consistent with the results reported by Amirchaghmaghi et al. in 2015 (26).

Morishima et al. in 2011 (27) concluded that ER stress caused by oxidized derivatives of various substances may promote apoptosis. The present study showed that ATF6 gene expression increased significantly in the study group. In other words, Sclareol increased the expression of genes in the endoplasmic reticulum stress pathway.

As noted earlier, after the induction of endoplasmic reticulum stress, a cAMP response element-binding protein promotes the dissociation of ATF6 from BiP/GRP78. ATF6 then enters the Golgi apparatus, where it is cleaved, and subsequently enters the nucleus as a transcription factor to activate genes involved in chaperone synthesis. Increased chaperone levels promote the folding of linear proteins and their transport to the cytosol or their ubiquitination and delivery to the proteasome for degradation. These processes can reduce ER stress. Therefore, the observed Sclareol-induced increase in ATF6 gene expression suggests that Sclareol may affect factors that facilitate ATF6 synthesis. For example, it may increase cAMP synthesis or act through other mechanisms (28,29).

Few studies have examined the E2F1 gene, and little is known about the effects of Sclareol on its function or expression (30). Montecillo-Aguado et al. (In 2023) (31) conducted a study showing that high consumption of polyunsaturated fatty acids (PUFAs) reduces cancer risk and increases sensitivity to chemotherapy by arresting the G2 cell cycle

and reducing E2F1 transcription in cancer cells. However, the present study showed increased E2F1 expression. This discrepancy may reflect the effect of Sclareol, which was not examined in the previous study, on the continuation of the cell-cycle process or on apoptotic-protein pathways, potentially causing their dysfunction. Further studies are needed to clarify the reasons for this discrepancy.

Conclusion

The results of this study suggest that Sclareol reduces VEGF gene expression and increases the expression of ATF-6 and E2F1, genes responsible for increasing endoplasmic reticulum stress in KATO III human gastric cancer cells. Sclareol doses between 40 and 60 µM were considered effective, whereas doses above 60 µM did not produce the same effect. These findings may provide a basis for reducing drug resistance in patients with stomach cancer.

Acknowledgement

The authors thank Shahin Rashedi for support in maintaining the cell lines and for technical assistance with the laboratory assays.

Funding Sources

This research received no external funding.

Ethical Statement

This study was approved by the Ethics Committee of the Islamic Azad University, Tabriz Branch (Approval Code: IR.IAU.TABRIZ.REC.1403.399).

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

SAR and CA contributed to the study design and manuscript preparation. MGG and RS contributed to data collection and analysis. All authors read and approved the final version of the manuscript.

Data Availability Statement

All data relevant to this study are included in the article.

Use of Artificial Intelligence

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) solely for language editing and to improve the manuscript's clarity and readability. The authors reviewed and revised all AI-assisted content and take full responsibility for the accuracy, originality, and integrity of the final manuscript. AI was not used for the study design, data collection, data analysis, interpretation of the results, or generation of scientific findings.

References

1. Conti CB, Agnesi S, Scaravaglio M, Masseria P, Dinelli ME, Oldani M, et al. Early gastric cancer: update on prevention, diagnosis and treatment. Int J Environ Res Public Health. 2023;20(3):2149. [View at Publisher] [DOI] [PMID] [Google Scholar]
2. Gullo I, Grillo F, Mastracci L, Vanoli A, Carneiro F, Saragoni L, et al. Precancerous lesions of the stomach, gastric cancer and hereditary gastric cancer syndromes. Pathologica. 2020;112(3):166-85. [View at Publisher] [DOI] [PMID] [Google Scholar]
3. Ilic M, Ilic I. Epidemiology of stomach cancer. World J Gastroenterol. 2022;28(12):1187-203. [View at Publisher] [DOI] [PMID] [Google Scholar]
4. Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. Ann Surg. 2005;241(1):27-39. [View at Publisher] [DOI] [PMID] [Google Scholar]
5. Ebrahimi Z, Shateri Z, Nouri M, Sikaroudi MK, Masoodi M, Shidfar F, et al. Ultra-processed food intake and risk of Helicobacter pylori infection: a case-control study. Food Sci Nutr. 2024;12(7):5019-26. [View at Publisher] [DOI] [PMID] [Google Scholar]
6. Dolatkhah H, Movahedian A, Somi M-H, Aghaei M, Samadi N, Mirza-Aghazade A, et al. Effect of PUFAs oral administration on the amount of apoptotic caspases enzymes in gastric cancer patients undergoing chemotherapy. Anticancer Agents Med Chem. 2017;17(1):93-101. [View at Publisher] [DOI] [PMID] [Google Scholar]
7. Farhood B, Geraily G, Alizadeh A. Incidence and mortality of various cancers in Iran and compare to other countries: a review article. Iran J Public Health. 2018;47(3):309-16. [View at Publisher] [PMID] [Google Scholar]
8. Tringali A, Giannetti A, Adler DG. Endoscopic management of gastric outlet obstruction disease. Ann Gastroenterol. 2019;32(4):330-7. [View at Publisher] [DOI] [PMID] [Google Scholar]
9. Garg P, Malhotra J, Kulkarni P, Horne D, Salgia R, Singhal SS. Emerging therapeutic strategies to overcome drug resistance in cancer cells. Cancers (Basel). 2024;16(13):2478. [View at Publisher] [DOI] [PMID] [Google Scholar]
10. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Chapter 13: Intracellular vesicular traffic. In: Molecular biology of the cell. 4th ed. New York: Garland Science; 2002. [View at Publisher] [Google Scholar]
11. Adams BM, Canniff NP, Guay KP, Hebert DN. The role of endoplasmic reticulum chaperones in protein folding and quality control. Prog Mol Subcell Biol. 2021;59:27-50. [View at Publisher] [DOI] [PMID] [Google Scholar]
12. Zhang K, Kaufman RJ. From endoplasmic-reticulum stress to the inflammatory response. Nature. 2008;454(7203):455-62. [View at Publisher] [DOI] [PMID] [Google Scholar]
13. Ni M, Zhang Y, Lee AS. Beyond the endoplasmic reticulum: atypical GRP78 in cell viability, signalling and therapeutic targeting. Biochem J. 2011;434(2):181-8. [View at Publisher] [DOI] [PMID] [Google Scholar]
14. Noori S, Hassan ZM, Mohammadi M, Habibi Z, Sohrabi N, Bayanolahgh S. Sclareol modulates the Treg intra-tumoral infiltrated cell and inhibits tumor growth in vivo. Cell Immunol. 2010;263(2):148-53. [View at Publisher] [DOI] [PMID] [Google Scholar]
15. Afshari H, Nourbakhsh M, Salehi N, Mahboubi-Rabbani M, Zarghi A, Noori S. STAT3-mediated apoptotic-enhancing function of sclareol against breast cancer cells and cell sensitization to cyclophosphamide. Iran J Pharm Res. 2020;19(1):398-412. [View at Publisher] [DOI] [PMID] [Google Scholar]
16. Vandghanooni S, Farajzadeh Vahid Z, Nakhlband A, Bahadori MB, Eskandani M. Sclareol inhibits hypoxia-inducible factor-1α accumulation and induces apoptosis in hypoxic cancer cells. Adv Pharm Bull. 2022;12(3):593-602. [View at Publisher] [DOI] [PMID] [Google Scholar]
17. Talib WH, Alsayed AR, Barakat M, Abu-Taha MI, Mahmod AI, Ismail Mahmod A. Targeting drug chemo-resistance in cancer using natural products. Biomedicines. 2021;9(10):1353. [View at Publisher] [DOI] [PMID] [Google Scholar]
18. Aboutalebi E, Sakhinia E, Beilanokhi V, Dolatkhah H. Investigating the effect of sclareol on IRE-1 and PERK genes in the pathway of endoplasmic reticulum stress in gastric cancer cells MKN-45. J Res Appl Basic Med Sci. 2020;6(1):32-44. [View at Publisher] [Google Scholar]
19. Pisa R, Kapoor TM. Chemical strategies to overcome resistance against targeted anticancer therapeutics. Nat Chem Biol. 2020;16(8):817-25. [View at Publisher] [DOI] [PMID] [Google Scholar]
20. Zhou J, Xie X, Tang H, Peng C, Peng F. The bioactivities of sclareol: a mini review. Front Pharmacol. 2022;13:1014105. [View at Publisher] [DOI] [PMID] [Google Scholar]
21. Hassan ZM, Yaraee R, Zare N, Ghazanfari T, Sarraf Nejad AH, Nazori B. Immunomodulatory effect of R10 fraction of garlic extract on natural killer activity. Int Immunopharmacol. 2003;3(10-11):1483-9. [View at Publisher] [DOI] [PMID] [Google Scholar]
22. Yuan S, She D, Jiang S, Deng N, Peng J, Ma L. Endoplasmic reticulum stress and therapeutic strategies in metabolic, neurodegenerative diseases and cancer. Mol Med. 2024;30(1):40. [View at Publisher] [DOI] [PMID] [Google Scholar]

23. Bonsignore G, Martinotti S, Ranzato E. Endoplasmic reticulum stress and cancer: could unfolded protein response be a druggable target for cancer therapy? Int J Mol Sci. 2023;24(2):1566. [View at Publisher] [DOI] [PMID] [Google Scholar]
24. Kim C, Kim B. Anti-cancer natural products and their bioactive compounds inducing ER stress-mediated apoptosis: a review. Nutrients. 2018;10(8):1021. [View at Publisher] [DOI] [PMID] [Google Scholar]
25. Karayiannakis AJ, Syrigos KN, Polychronidis A, Zbar A, Kouraklis G, Simopoulos C, et al. Circulating VEGF levels in the serum of gastric cancer patients: correlation with pathological variables, patient survival, and tumor surgery. Ann Surg. 2002;236(1):37-42. [View at Publisher] [DOI] [PMID] [Google Scholar]
26. Amirchaghmaghi E, Rezaei A, Moini A, Roghaei MA, Hafezi M, Aflatoonian R. Gene expression analysis of VEGF and its receptors and assessment of its serum level in unexplained recurrent spontaneous abortion. Cell J. 2015;16(4):538-45. [View at Publisher] [DOI] [PMID] [Google Scholar]
27. Morishima N, Nakanishi K, Nakano A. Activating transcription factor-6 (ATF6) mediates apoptosis with reduction of myeloid cell leukemia sequence 1 (Mcl-1) protein via induction of WW domain binding protein 1. J Biol Chem. 2011;286(40):35227-35. [View at Publisher] [DOI] [PMID] [Google Scholar]
28. Lei Y, Yu H, Ding S, Liu H, Liu C, Fu R. Molecular mechanism of ATF6 in unfolded protein response and its role in disease. Heliyon. 2024;10(5):e25937. [View at Publisher] [DOI] [PMID] [Google Scholar]
29. Sano R, Reed JC. ER stress-induced cell death mechanisms. Biochim Biophys Acta. 2013;1833(12):3460-70. [View at Publisher] [DOI] [PMID] [Google Scholar]
30. Fang Z, Lin M, Li C, Liu H, Gong C. A comprehensive review of the roles of E2F1 in colon cancer. Am J Cancer Res. 2020;10(3):757-68. [View at Publisher] [PMID] [Google Scholar]
31. Montecillo-Aguado M, Tirado-Rodriguez B, Huerta-Yepez S. The involvement of polyunsaturated fatty acids in apoptosis mechanisms and their implications in cancer. Int J Mol Sci. 2023;24(14):11691. [View at Publisher] [DOI] [PMID] [Google Scholar]

Cite this article as:

Ghaffarian Gabalou M, Rahmani SA, Ahmadizadeh Ch, Sharifi R. Evaluation of the effect of sclareol on endoplasmic reticulum stress in the KATO III human gastric carcinoma cell line. *Med Lab J.* 2026;20(4):38-43. http://dx.doi.org/10.29252/mlj.20.4.38