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The Anticancer Effect of Piperine on Tongue Squamous Cell Carcinoma Cell Line

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Aim: The purpose of this study was to investigate the impact of piperine (PP) on tongue squamous cell carcinoma cell line.
Materials and Methods: In this research, cultured tongue carcinoma cells were separated into two groups: a control group, and PP treated group. The cytotoxicity assay was utilized to measure cell viability. Flow cytometry was employed to examine and assess the cell cycle and apoptosis phases.
Results: Piperine induced cytotoxicity on tongue carcinoma cells, reducing the mean percentage of cell viability in a concentration-dependent manner, with an IC_{50} of 21.2 µM. Moreover, PP treatment induced a rise in the percentage of cells in the G1 to S phases of the cell cycle and a reduction in the percentage of cancer cells in the G2/M phase. Exposure of tongue carcinoma cells to PP led to a decrease in the number of viable cells, along with a rise in the combined proportion of apoptotic and necrotic cells to 31.14%.
Conclusion: Piperine reduced the viability, caused cell cycle changes, and induced cell death of tongue squamous cell carcinoma cell line suggesting that PP has a potential as a therapeutic agent.

Keywords: Piperine, Carcinoma, Cell cycle analysis, Tongue

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Introduction

Oral squamous cell carcinoma (OSCC) is ranked as the predominant type of head and neck squamous cell carcinoma, typically showing a 5-year overall survival rate of about 50%.[1] It is characterized by an aggressive pathology and often has a poor prognosis due to its late diagnosis, typically at stages III or IV. This results in more radical treatment options and adversely affects patients' quality of life.[1]

Many well-established etiological factors contribute to oral cancer, with risks increasing primarily due to age, alcohol and tobacco consumption, unhealthy diet, lack of physical activity, and exposure to atmospheric pollutants.[2] The International Agency for Research on Cancer (IARC) categorizes tobacco as a Group I carcinogen when it comes to its impact on the oral cavity.[3, 4]

Conventional cancer treatments, such as radiation and chemotherapy, are often linked to severe health issues because they affect vital structures, cause significant side effects, and sometimes lead to therapeutic resistance. Therefore, there is a pressing necessity for new and alternative treatments.[5] Exploring herbal medicine as a potential alternative, adjunctive, or supplementary approach in OSCC treatment is worthwhile, as natural compounds could potentially mitigate the negative adverse effects of conventional chemotherapy.[6, 7]

Black pepper, scientifically known as Piper nigrum L., earns the title "King of Spices" and hails from the Piperaceae family. Originating in southern India, its name "pepper" can be traced back to the Sanskrit word "Pipali." This spice contains a chemical called piperine, which exhibits various effects within the body.[8]

Piperine stands out as a simple, crystalline alkaloid compound with a yellow color and no discernible odor, known for its sharp-tasting that can be extracted from several plants of the Piperaceae family.[9]

Piperine has a diverse set of biological and pharmacological effects, like reducing fever, anti-apoptotic, anti-inflammatory, anti-mutagenic, anti-metastatic[10], anticonvulsive activity, antioxidant activity,[8] liver protective, neuroprotective, hepatoprotective activities and displaying antimicrobial activity.[9]

Piperine's effects have been observed in several types of cancer. In lung cancer cells, it triggers apoptosis through p53 signaling [11]. It also inhibits proliferation and metastasis of breast cancer cells in both experimental and animal models.[12] PP initiates arrest of cell cycle, triggers autophagy and inhibits proliferation in prostate cancer cell lines.[13] Additionally, in rectal cancer, PP enhances the generation of reactive oxygen species (ROS) in rectal cancer cells, leading to apoptosis.[11]

Piperine demonstrates strong chemopreventive properties. Its effects are observed in various ways, including enhancing the antioxidant defenses, elevating the levels and efficacy of detoxifying enzymes, and reducing stem cell renewal. Furthermore, PP has proven to hinder the growth and viability of numerous malignant cell lines by influencing the cell cycle and displaying anti-apoptotic properties.[14]

Several anticancer actions were observed when the oral cancer cells were treated with PP, including nuclear condensation, intracellular ROS generation, mitochondrial membrane potential depolarization, arrest of the cell cycle, and increased caspase activity. These actions collectively contribute to the inhibition of oral cancer growth and suggest that PP could be a valuable candidate for future anticancer therapies.[11, 15]

The objective of this research was to assess piperine's cytotoxic, and apoptotic properties, in addition to detect its effect on

cell cycle on tongue squamous cell carcinoma cell line.

Material and Methods

The research protocol received approval from the Faculty of Dentistry's research ethics committee at Minia University (approval number: 89/2022).

Material

Piperine (> 97% purity) was sourced from Sigma-Aldrich, USA. The MTT assay kit (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyltetrazolium bromide) and Dimethyl sulfoxide (DMSO) were also acquired from Sigma (Saint Louis, Missouri, USA). PP (molecular weight 285.34 g/mol) was solubilized in DMSO. Moreover, streptomycin and penicillin antibiotics, and fetal bovine serum were employed in the experiments.

Cell Line and Cell Culture Protocol

The tongue carcinoma cell line (HNO-97) was acquired from NAWAH scientific in Cairo, Egypt. The cell line, originally acquired as frozen vials from the American Type Culture Collection (ATCC), was cultured in Dulbecco's Modified Eagle's Medium (DMEM) sourced from Sigma-Aldrich. The pH of the medium was set to 7.2, and it was supplemented with 10% fetal bovine serum (FBS), sodium bicarbonate, and 2 mM glutamine. For experimentation, cells were placed into either 6-well or 96-well plates for seeding.

Cell Viability and Cytotoxicity Assay (MTT Assay)

The tongue carcinoma cells were placed in 96-well culture plates and subjected to varying doses of piperine (0.25-500 µM) for 24 hours. Following this, each well received 10 µL of MTT solution (0.5 mg/ml), followed by a 4-hour incubation at 37°C. After removal of the culture medium, the resulting purple Formazan crystals were gently dissolved in 100 µL of DMSO. The absorbance of the resulting solution was assessed spectrophotometrically at 570 nm using a Master Plex Reader spectrophotometer.[16]

The MTT assay results were processed with the Master Plex Reader Fit software to establish the IC_{50} value of the tested drug for use in subsequent assays.

Grouping

Tongue carcinoma cells were separated into two groups: group I acted as the control group (untreated), while PP treated group: the cells were treated with IC_{50} dose after 24 h.

Cell Cycle and Apoptosis Analysis by Flow Cytometry

The impact of examined PP on cell proliferation and quantitative detection of apoptosis were determined by analyzing the distribution of cell cycle phases.

Tongue carcinoma cells were first grown in 25 cm^3 cell culture flasks and exposed to piperine at an IC_{50} concentration of 21.2 µM for 24 hours in a DMEM-based medium. After this incubation period, the cells were separated using trypsin, centrifuged at 2000 rpm, at 4°C for 10 minutes, and then rinsed twice with chilled PBS.

Subsequently, the cells were fixed by immersion in 70% ethanol at 4°C for a minimum of 1 hour, and left overnight for complete fixation. Following fixation, the cells underwent staining with 50 µl of Annexin V-FITC and 50 µl of propidium iodide (PI) staining solution. The final mixture was diluted to volume of 500 µl with binding buffer and then analyzed using flow cytometry at 4°C. Prior to analysis, the cells were resuspended in PBS with an addition of 0.1 mg/ml RNase and incubated in darkness for 15 minutes. The analysis was conducted by a Becton Dickinson (BD) fluorescence-activated cell sorting (FACS) Calibur flow

cytometer, and the results presented in dot plots and frequency histograms.[17]

Statistical Analysis

The experimental data were gathered, organized into tables, and subjected to statistical analysis using Statistical Package for Social Sciences (SPSS) version 20.

The Z test of proportion was indicated to evaluate the outcome of the studied parameters. The P value of significance was <0.05.

Results

Cell Viability and Cytotoxicity Assay (MTT Assay)

Exposure to PP demonstrated concentration-dependent cytotoxic effects on a tongue carcinoma cell line (Table 1).

With increasing drug concentrations from 0.25 µM/ml to 500 µM/ml, the treated cells exhibited a reduced mean viability percentage compared to the control cells (Figure 1).

Table (1): The average cell viability percentage of tongue carcinoma cells following treatment with varying concentrations of piperine for 24 hours.

Piperine Concentration (µg/ml)	500	250	125	62.5	31.25	15.6	7.8	3.9	2	1	0.5	0.25
%Viability	12.92	16.73	22.49	24.61	73.61	79.09	82.99	92.94	94.26	95.07	96.64	98.11

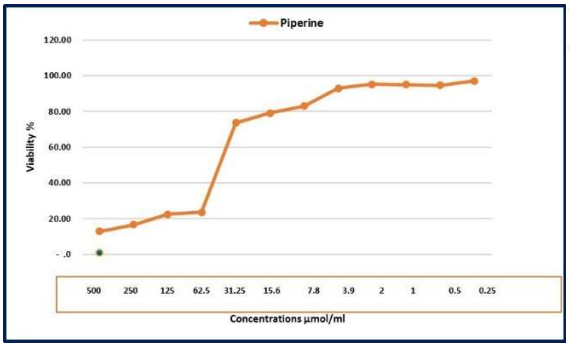

Figure (1): A graph showing the viability percentage of tongue carcinoma cells following treatment with varying doses of piperine for 24 hours.

Significant statistical differences were observed between the control group and varying concentrations of PP.

Cell Cycle Analysis by Flow cytometry

The PP treated group demonstrated a decrease in DNA content in cancer cells progressing through the cell cycle, particularly in G1 phase (53.29%). Regarding S phase, there was an increase in the percentage of cells in the PP treated group (30.56%) when compared to the control group. Additionally, the proportion of cancer cells decreased in the G2/M phase (16.15%) (Figure 2).

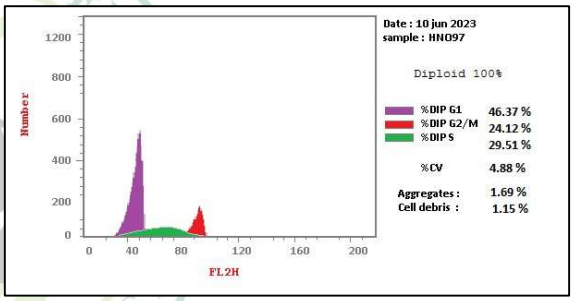

Figure (2): (A) The DNA histogram of the control group revealed the highest cell population peak (46.37%) in the G1 phase, (B) The DNA histogram of tongue carcinoma cells treated with piperine showed the highest cell population peak (53.29%) in the G1 phase.

Regarding the G1, S, and G2 phases, there were no statistically significant differences among the control group and the PP group at the IC_{50} concentration.

The Z test of proportion indicated no statistically significant difference between the groups (Table 2).

Table (2): Descriptive Statistics for comparison between cell cycle analysis in control group and piperine group.

DNA content	Groups		P value	95% CI
	Control	Piperine		
G0-G1%	46.37	53.29	0.624	-13.89% to 27.08
S%	29.51	30.56	0.832	17.57% to 20.38%
G2/M%	24.12	16.15	0.216	-5.7% to 24.55%

P, P value; CI, confidence interval

Apoptosis Phase

The early apoptosis rate in tongue carcinoma cells exposed to PP was 22.69%, and the late apoptosis rate was 4.25%.
Exposure of tongue carcinoma cells to PP resulted in a decrease in the number of living cells, alongside an increase in the combined percentage of apoptotic and necrotic cells to 31.14% (Figure 3).

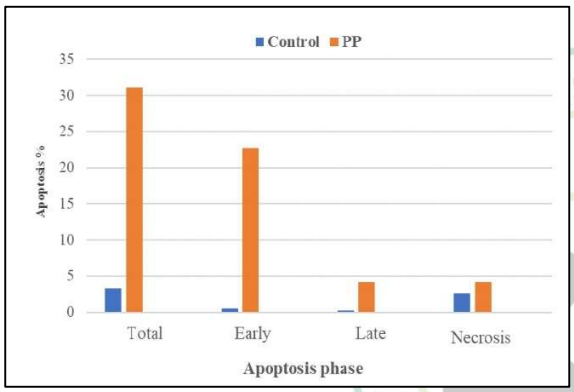

Figure (3): Bar chart showing the apoptosis phase of tongue carcinoma cells of the control group and piperine treated group.

The group treated with PP experienced a continuous rise in apoptotic cell count. In contrast, the control group showed minimal apoptosis, while the PP treated group recorded the highest percentage at 26.94%.
The Z test of proportion revealed a statistically significant difference between the groups (P<0.0001) (Table 3)
.

Table (3): Descriptive Statistics for comparison between apoptosis phase percentage in control group and piperine group.

Apoptosis phase		Groups		P value	95% CI
		Control	Piperine		
Apoptosis	Total	3.37%	31.14 %	<0.0001	11.824% to 46.388%
	Early	0.52%	22.69 %	<0.0001	8.834% to 40.041%
	Late	0.23%	4.25 %	0.364	-1.518% to 17.386%
Necrosis		2.62 %	4.2%	0.899	-5.063% to 15.093%

P, P value; CI, confidence interval

PP treated group demonstrated a higher statistically significant prevalence of early apoptosis, than the control group.

Moreover, PP treated group revealed a higher statistically significant rate of total apoptosis, than the control group.

Discussion

Oral Squamous Cell Carcinoma stands as a highly prevalent form of malignancy, comprising 95% of head and neck cancers, with high mortality and morbidity rates. In many countries worldwide, the survival rate for OSCC typically falls between 45% and 50%, and there has been little notable improvement in these rates over the past few decades.[18]

Traditional medicine relies on natural products sourced from the environment for therapeutic purposes, and it is prevalent in several countries, including China, Japan, India, Iran, and Saudi Arabia.[19]

Numerous natural substances, including phytochemicals and dietary compounds, have been discovered to reduce the severity of oral cancer by influencing processes like cell growth, differentiation, blood vessel formation, cell death, and cellular communication pathways.[20, 21]
PP has attracted interest due to its observed capability to suppress cell proliferation and combat neoplastic growth in human cancer cells such as those found in ovarian cancer,[22] breast cancer,[23] and OSCC, with minimal side effects.[24]

In this research, assessments of cell viability, cytotoxicity, cell cycle analysis, and apoptosis were conducted to determine how the investigated drug induce cytotoxic effects, inhibits growth, and promotes apoptosis.

The current study's findings indicated that PP exhibited potential cytotoxic effects on OSCC cell line in concentration-dependent manner. It decreased the percentage of viable and proliferating cells as its dosage increased, while increasing the percentage of apoptotic cells. These effects are probably attributable to PP 's abilities to

inhibit cell proliferation, reduce inflammation, and act as an antioxidant. These results align with those of Siddiqui et al [15], who also observed PP 's anticancer effects on OSCC cell line, demonstrating concentration-dependent inhibition of cell growth and viability.

Similar to our findings, Fattah et al [25] demonstrated that naturally extracted PP exhibits cytotoxic effects and inhibits cell viability in a breast cancer cell line. They suggest that PP could potentially be used as a more effective and potent anticancer agent requiring lower dosages in cancer therapy.

Siddiqui et al [15] made a noteworthy discovery regarding PP 's effects on OSCC. PP 's effects were found to be dependent on the dosage applied, exhibiting a dose-dependent manner. We demonstrated that higher concentrations of PP caused a notable reduction in the average viability of tongue carcinoma cells to 12.92%. This result aligns with similar observations by Anitha et al [26] on osteosarcoma, Ahmadi et al [23] and Fattah et al [25] study on breast cancer. Additionally, Siddiqui et al [15] noted that exposure to varying concentrations (25–300 μM) of PP led to decreased cell viability in OSCC cells. Flow cytometry and Annexin-V/PI staining assays were employed to validate the occurrence of apoptosis. Analyzing cell cycle distribution and proliferation is crucial for studying cell growth, differentiation, and apoptosis. These assessments are critical for evaluating the therapeutic effectiveness of anticancer agents.[27, 28]

In the current study, there was a mild nonsignificant shift to the G1 and S phases in comparison to the control revealing a cell cycle arrest at G1 and S phases, suggesting alterations in DNA content among the cycling cells. This could lead to a dysregulation in the cell cycle, hindering the growth and proliferation of cancer cells in PP treated group.

Previously, Singh et al [14] also demonstrated that PP exerts an inhibitory effect on OSCC by causing arrest of the cell cycle at the G2/M phase. Consequently, there was a subsequent rise in apoptotic cell numbers, suggesting that PP 's action on the cell cycle contributed to its pro-apoptotic effect.[14]

Fofaria et al [29] revealed that PP could cause cell cycle arrest at G1 phase on melanoma cell line.

In our current study, the analysis demonstrated that significant indicators of apoptosis and necrosis were shown after applying the IC_{50} dose of PP. Consequently, this suggests that in vitro setting, PP induced cell death through two distinct mechanisms, apoptosis and necrosis.

Regarding apoptosis phase, in the present research, there was a notable rise in overall cell mortality (including apoptosis and necrosis) when the IC_{50} dose of PP was added, reaching 31.14% compared to the control group 3.37%. These findings align with Siddiqui et al [15] study, which proposed that PP effectively induces cell death by reducing ROS release, subsequently activating caspase-3 and causing cell cycle arrest.

Chaudhari et al [30] examined the impact of various doses of PP on OSCC cells and discovered that PP triggered cellular senescence. Additionally, they noted that this phenomenon was both preceded and accompanied by apoptosis, autophagy, and a rise in ROS accumulation.[30]

Based on the research conducted by Yoo et al [31], it was validated that PP regulates the proapoptotic pathway in melanoma cells. Umapathy et al [32] found that PP's intrinsically active apoptotic-inducing abilities have been demonstrated in diverse types of cancer cell lines. PP controls a lot of proteins in the Bcl-2 family, including Bax and Bcl-2.

Similar to our study results, the observed response to PP treatment was

characterized by apoptosis, not necrosis, which was supported by evidence such as nuclear condensation, increased caspase-3 activity, and activation of cell cycle checkpoints.[15]

Piperine demonstrated an anticancer effect with increasing doses. This study highlights the potential of using PP as an adjunct treatment with traditional cytotoxic drugs.

Limitations and Recommendations

The present study only examined cell cycle and apoptosis by using flow cytometry and it is recommended to detect the different gene expressions of apoptosis and cell cycle after treatment with PP.

Conclusions

Piperine has cytotoxic effects, and decreased the viability in the OSCC cell line in concentration-depentent manner. PP arrested the cell cycle of tongue carcinoma cells at the G0-G1 and S phases and induced cell death. PP might show a promising effect as an adjunctive treatment to the traditional cytotoxic drugs.

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Data availability: Data is available upon request.

Declarations: The research is a part of PhD thesis that will be submitted to Faculty of Dentistry, Minia University. Publishing a paper is a prerequisite for thesis defense. It is approved by supervisors, Prof. Sherif Farouk El-Gayar and Ass. Prof. Enas Alaa Eldin Abd Elaziz.

Ethics approval and consent to participate: the research ethical committee of the Faculty of Dentistry, Minia University approved the protocol of the study (approval number: 89/2022).

Competing interests: None.

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