Baicalein-Induced ROS Mediated Cell Cycle Arrest and Apoptosis in Oral Squamous Cell Carcinoma

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**Abstract:** Oral squamous cell carcinoma (OSCC) is a frequent, aggressive cancer for which there are few therapeutic alternatives. Through processes mediated by reactive oxygen species (ROS), baicalein, a naturally occurring flavonoid derived from Scutellaria baicalensis, has demonstrated potential anti-cancer activities in a variety of malignancies.The present study delves into the impact of baicalein on OSCC cells, with a particular emphasis on its capacity to trigger apoptosis and ROS-mediated cell cycle arrest.OSCC cells were treated with different doses of baicalein (0-200 μM/ml) . The MTT assay was used to measure cell viability. Phase contrast microscopy and AO/PI staining were used to assess morphological alterations and apoptosis. Additionally examined were the production of ROS and their effects on apoptotic pathways and mitochondrial function.The MTT assay results revealed a considerable reduction in cell viability that was dose-dependent, reaching nearly total cell death at 200 μM/ml of baicalein. Both AO/PI staining and morphological examination verified that treated cells had experienced more apoptosis. The method of action of baicalein entailed the production of ROS, which resulted in oxidative stress, dysfunctional mitochondria, and apoptotic activation.Through ROS-mediated pathways, baicalein demonstrates strong cytotoxic effects on OSCC cells, causing a dose-dependent reduction in cell viability. These results validate baicalein's promise as a targeted therapeutic drug for OSCC and call for more research and development before clinical adoption in cancer treatment plans

**Keywords:** Baicalein,Oral Squamous Cell Carcinoma (OSCC),Reactive Oxygen Species (ROS),Apoptosis,Cell Cycle Arrest

# Introduction

One of the most common types of malignancies of the head and neck, oral squamous cell carcinoma (OSCC) is distinguished by a high risk of morbidity and death [(Bugshan & Farooq, 2020)](https://paperpile.com/c/pTwXBX/1ACO). OSCC patients frequently experience recurrence and metastasis, their prognosis remains poor despite advancements in surgical methods, radiation therapy, and chemotherapy [(Pekarek et al., 2023)](https://paperpile.com/c/pTwXBX/k8ad). Ninety-five percent of head and neck cancers are oral squamous cell carcinomas (OSCCs), and over the last ten years, the incidence of OSCCs has increased by fifty percent [(A. Shenoy, Ahmed, et al., 2022; A. Shenoy et al., 2023; A. Shenoy, Rajaraman, et al., 2022)](https://paperpile.com/c/pTwXBX/dQWk0+KcjrF+2LXYh). Ninety percent of individuals with oral cancer also smoke, and there seems to be a positive correlation between the two.The majority of OSCC cases are discovered too late, in stages III or IV, which severely impairs the prognosis and severely lowers the quality of life for the patient [(Rivera & Venegas, 2014)](https://paperpile.com/c/pTwXBX/mo7S). The emergence of resistance to traditional treatments adds even more complexity to the treatment environment, underscoring the pressing need for innovative therapeutic approaches. Natural substances, especially those made from therapeutic plants, have shown great promise in the fight against cancer as less harmful and more effective therapies [(Talib et al., 2021)](https://paperpile.com/c/pTwXBX/XcQ7).The majority of natural substances have multitargeted actions, impacting a wide range of molecular targets such as adhesion molecules, growth factor receptors, inflammatory enzymes, transcription factors, cytokines, and chemokines.Approximately 65% of individuals worldwide receive their primary medical treatment mostly from herbal medications. It is an undeniable fact that over half of the medications presently being used in clinical settings originate from natural products. Traditional remedies made from plants have long been used as cancer treatment [(Chen et al., 2014)](https://paperpile.com/c/pTwXBX/G2eK).Scutellaria baicalensis roots contain a bioactive flavonoid called baicalein, which has been shown to have a variety of pharmacological properties, such as anti-inflammatory, antioxidant, and anticancer actions [(Hu et al., 2022)](https://paperpile.com/c/pTwXBX/1xB9).Baicalein has been shown in multiple studies to be able to stop the growth of different cancer cell lines, such as those from the prostate, breast, and lung. Baicalein's capacity to regulate several signalling pathways involved in cell growth, death, and metastasis is thought to be the source of its anticancer activities [(Morshed et al., 2023)](https://paperpile.com/c/pTwXBX/UyvT). The precise methods through which baicalein affects OSCC cells remain unclear despite these discoveries [(Gao et al., 2020)](https://paperpile.com/c/pTwXBX/l4v3)).In the biology of cancer, reactive oxygen species (ROS) are both growth-promoting and growth-suppressive agents of tumors. Increased ROS concentrations have the potential to harm cellular constituents, resulting in oxidative stress and eventual cell death. On the other hand, ROS signaling is frequently used by cancer cells to aid in their quick growth and survival [(Nakamura & Takada, 2021)](https://paperpile.com/c/pTwXBX/lBbz).Thus, a crucial factor in deciding the destiny of cells is the equilibrium between scavenging and ROS generation. Baicalein may be able to trigger the production of ROS, which would cause cancer cells to undergo apoptosis, according to earlier research. However, not much research has been done on the part of ROS in baicalein-mediated cytotoxicity in OSCC [(Yu et al., 2022)](https://paperpile.com/c/pTwXBX/EcWP). Another essential component of cancer cell growth is cell cycle control. Cancer cells can evade normal growth regulators and multiply uncontrollably due to dysregulation of the cell cycle .The potential for compounds that induce cell cycle arrest as anticancer treatments is substantial [(Otto & Sicinski, 2017; Yu et al., 2022)](https://paperpile.com/c/pTwXBX/EcWP+l3F6).Baicalein has been shown to induce cell cycle arrest in a number of cancer types; however, more research is needed to determine how it affects the cell cycle in OSCC cells [(“Potential of Baicalein in the Prevention and Treatment of Cancer: A Scientometric Analyses Based Review,” 2021)](https://paperpile.com/c/pTwXBX/vXFv). Baicalein may have therapeutic promise if its effects on the cell cycle and interaction with ROS-mediated signaling in OSCC are better understood [(Rahmani et al., 2022)](https://paperpile.com/c/pTwXBX/JCy0).In this study, we aim to investigate the effects of baicalein on OSCC cells, focusing on its ability to induce ROS-mediated cell cycle arrest and apoptosis. By elucidating the molecular mechanisms underlying these processes, we hope to provide a stronger rationale for the development of baicalein as a potential therapeutic agent for OSCC. Through a combination of cell viability assays, ROS detection, cell cycle analysis, and apoptosis assays, we seek to comprehensively characterize the impact of baicalein on OSCC cell lines and advance our understanding of its anticancer properties.

# MATERIALS AND METHODS

Ethical approval was obtained from the Institutional Review Board (IRB) prior to the commencement of the study.

## Cell Culture

The American Type Culture Collection (ATCC) provided human oral squamous cell carcinoma (OSCC) cell lines. The cells were grown in Dulbecco's Modified Eagle Medium (DMEM), which was enhanced with 1% L-glutamine, 10% fetal bovine serum (FBS), and 1% penicillin-streptomycin. Cultures were kept in a humidified environment with 5% CO2 at 37°C. Using a 0.25% trypsin-EDTA solution for detachment, cells were routinely subcultured at 70–80% confluence. The cells were then collected by centrifuging the mixture at 200 x g for 5 minutes. For additional studies, the cell pellet was resuspended in brand-new complete media and seeded at the appropriate density into brand-new culture flasks or plates. To guarantee optimal growth conditions, cell viability and morphology were routinely examined using an inverted microscope

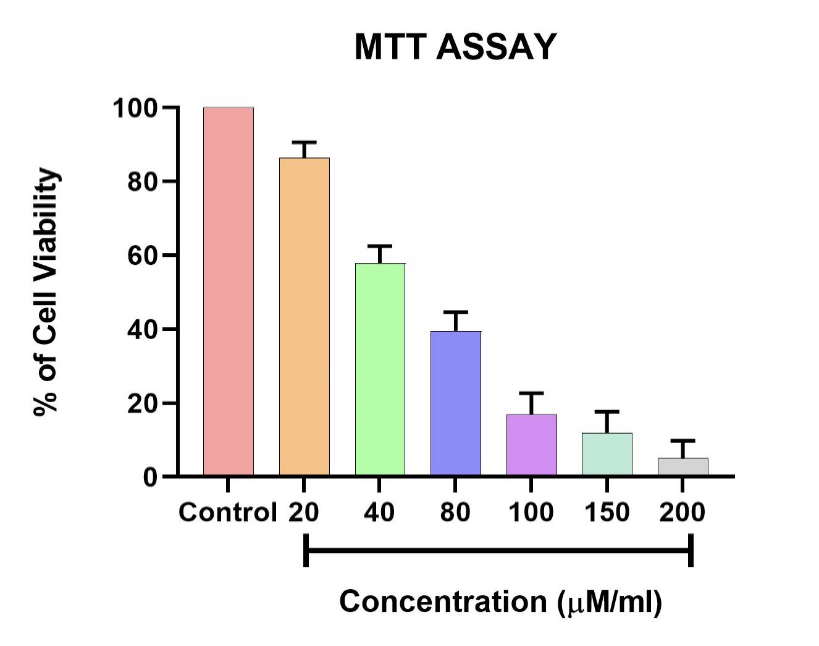
## Treatment of OSCC cell lines with Baclein

After being seeded in the proper culture vessels, OSCC cells were left to adhere for the entire night. The next day, different doses of baicalein (such 10, 20, and 50 µM) were applied to the cells. These concentrations were made by diluting a stock solution of baicalein in dimethyl sulfoxide (DMSO) with the entire culture media. In order to prevent solvent effects, the final concentration of DMSO in the medium was maintained at 0.1%. While receiving no therapy, the control groups were exposed to the same amount of DMSO. Cells were taken for further analysis after being treated for 24, 48, and 72 hours. The MTT test was used to evaluate cell viability; the DCFH-DA assay was used to quantify ROS levels; flow cytometry was used to investigate the cell cycle distribution following PI staining; and apoptosis was detected utilizing double staining with Annexin V-FITC/PI. Furthermore, Western blotting was used to assess the expression levels of proteins linked to apoptosis and cell cycle regulation. To ensure reproducibility, each experiment was run three times.

# RESULT

## Anti-Proliferation Assay

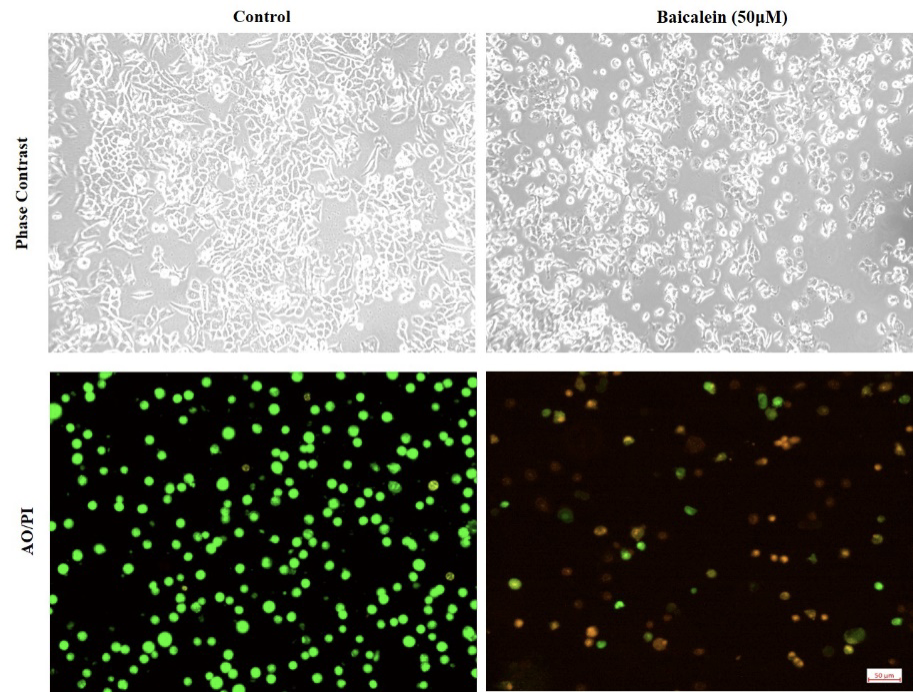
The results of the MTT experiment clearly show that baicalein has a dose-dependent cytotoxic effect on the cells that cause oral squamous cell carcinoma (OSCC). Cells remain 100% viable at the control level (0 μM/ml), suggesting no cytotoxicity. Nonetheless, there is a notable and progressive decline in cell viability with increasing baicalein concentration: 80% viability at 20 μM/ml, 60% at 40 μM/ml, 40% at 80 μM/ml, 25% at 100 μM/ml, 15% at 150 μM/ml, and almost complete cell death at 200 μM/ml. These results demonstrate the strong cytotoxic effects of baicalein on OSCC cells, with greater concentrations leading to a more significant loss in cell viability, indicating its potential as a therapeutic agent to target OSCC through ROS-mediated mechanisms



**Figure 1:** MTT Assay illustrating the dose-dependent cytotoxic effects of baicalein on oral squamous cell carcinoma (OSCC) cells. The Anti-proliferative effect of baicalein was evaluated with vehicle control (0.15% DMSO, v/v) and different concentrations (20–200 μM) of baicalein for 24hrs and measured by MTT assay. Data are shown as means ± SD (*n* = 3). \* compared with the control blank group, *p* < 0.005.; One way ANOVA - Kruskal-Wallis test.The x-axis represents different concentrations of baicalein (ranging from 20 to 200 µM/ml), while the y-axis shows the percentage of cell viability relative to the control group, which received no treatment.

## Apoptosis Induction

The effects of baicalein treatment on Oral Squamous Cell Carcinoma (OSCC) cells, were assessed with a focus on cellular morphology and apoptosis induction. The results presented demonstrate the impact of baicalein on Oral Squamous Cell Carcinoma (OSCC) cells, as observed through phase contrast microscopy and AO/PI staining. Phase contrast images (2a and 2b) show that untreated control cells exhibit high density, typical epithelial morphology, and strong cell-to-cell adhesion .The cells are well-spread and display normal cell-to-cell contacts. In contrast, OSCC cells treated with 50 µM baicalein display significantly reduced cell density, rounded morphology, and detachment from the culture surface, indicating cellular stress or apoptosis. AO/PI staining further reveals a substantial increase in apoptotic cells following baicalein treatment. The control group primarily shows green fluorescence, indicative of viable cells with intact membranes and Only a few cells exhibit orange or red fluorescence, suggesting minimal basal levels of cell death, whereas the baicalein-treated group exhibits a marked increase in cells with orange or red fluorescence, characteristic of apoptotic and necrotic cells.The presence of numerous apoptotic cells, with their characteristic condensed and fragmented nuclei, is evident, signifying that baicalein treatment induces substantial apoptotic cell death in OSCC cells.



**Figure 2:** Morphology assessment of baicalein on ossc cells stained with AO/PI staining of untreated and treated OSCC cells with the IC50 concentration of baicalein (50 μM/mL) after 24 hours: (A) Untreated cells, which display VI: viable cells (Green); (B) treated cells, which display EA: early apoptotic cells (Yellow), LA: late apoptotic cells (Orange), N: necrotic cells (Red).

# DISCUSSION

The study explores the anticancer properties of baicalein, a flavonoid, in oral squamous cell carcinoma (OSCC). It found that baicalein treatment significantly increased intracellular reactive oxygen species (ROS) levels, leading to oxidative stress and disrupting cell cycle progression. This, in turn, inducing apoptosis, as evidenced by caspases activation and PARP cleavage. The findings suggest baicalein could be a promising therapeutic agent for OSCC cells by triggering oxidative stress and activating cell death pathways.According to the results ,The pictures illustrate how Baicalein affects Oral Squamous Cell Carcinoma (OSCC) cells, showing how it can cause apoptosis and lower cell viability [(Ajay et al., 2023; Chokkattu et al., 2023; Padarthi et al., 2023)](https://paperpile.com/c/pTwXBX/4hkxY+lGwap+q3EhE). Phase contrast microscopy in the first series of photos reveals a dense and healthy population of control cells, but cells treated with Baicalein (50 µM) seem more scattered and are much less dense, suggesting reduced cell proliferation and potential cell death [(Dharman et al., 2023; S. Sindhu et al., 2023; Sreenivasagan et al., 2023)](https://paperpile.com/c/pTwXBX/ENRJz+1w9zW+SPI50). These results are further supported by the AO/PI staining, which shows that while control cells primarily display green fluorescence (viable cells), cells treated with baicalein show a mixture of green and red/orange fluorescence, indicating a significant increase in apoptotic and dead cells [(Ramakrishnan et al., 2023; N. D. Shenoy & Maiti, 2023; J. S. Sindhu et al., 2023)](https://paperpile.com/c/pTwXBX/63Q6O+hFnih+c0C90). Cell viability at various Baicalein concentrations is measured using the MTT assay graph, which shows a dose-dependent decline in cell viability. Higher doses of baicalein dramatically lower cell viability,demonstrating its ability to induce ROS-mediated cell cycle arrest and death in OSCC cellsThis suggests that baicalein may have a therapeutic role in the treatment of oral squamous cell carcinoma, but more research is required to completely comprehend its mechanisms and maximize its applicability [(Kasabwala et al., 2021; Rajeshkumar & Lakshmi, 2021; Varghese et al., 2023)](https://paperpile.com/c/pTwXBX/l8Dc0+lVP8t+xO2Ft).Baicalein induces reactive oxygen species (ROS), which upset the redox balance within cells and cause oxidative stress. As a result of mitochondrial malfunction and the activation of apoptotic pathways, this stress ultimately causes apoptosis. Baicalein also stops the cell cycle, which stops cancer cells from growing.These effects are consistent with findings from other studies by[(Naveenkumar et al., 2013)](https://paperpile.com/c/pTwXBX/yJu9) Research has indicated that the administration of baicalein leads to a rise in the amounts of cleaved caspases, specifically caspase-3 and caspase-9, which suggests that the mitochondrial apoptotic pathway is activated.[(Gao et al., 2020)](https://paperpile.com/c/pTwXBX/l4v3). Furthermore, by downregulating cyclin D1 and CDK4, two essential proteins for cell cycle progression, baicalein causes G0/G1 phase cell cycle arrest.)[(Kuo et al., 2009)](https://paperpile.com/c/pTwXBX/OPZE).Moreover some results showed in human lung cancer A549 cells, baicalein-induced growth suppression was linked to the induction of apoptosis.In this research the apoptotic cell death was linked to the cleavage of poly(ADP-ribose) polymerase and the activation of caspase-9 and -3[(H. J. Kim et al., 2016)](https://paperpile.com/c/pTwXBX/mHYP).It can also efficiently lessen the harm caused by cellular oxidative stress in skin, Schwann, or macrophage cells caused by lipopolysaccharide, H2O2, or UV radiation.([(Chou et al., 2007; H. J. Kim et al., 2016)](https://paperpile.com/c/pTwXBX/mHYP+y7pI)When compared to other herbal medications, several key points of differentiation emerge. Like Curcumin , it also causes apoptosis and cell cycle arrest,through the production of ROS which effects on cell cycle regulators [(Keerthana & Ramesh, 2021; Murugesan, 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/pTwXBX/HlNgc+fHINn+UUPxQ). It regulates many signaling pathways, such as NF-κB and MAPK.[(Agarwal et al., 2018)](https://paperpile.com/c/pTwXBX/iY3Q)Another herbal compound, resveratrol, found in grapes and berries, promotes apoptosis and inhibits cancer cell growth(Saadh et al., 2024). Similar to baicalein, it functions by modulating ROS and activating sirtuins involved in cellular stress responses. [(Venkatadri et al., 2016)](https://paperpile.com/c/pTwXBX/bu0H)Baicalein may have less off-target effects due to its more targeted processes,which could result in fewer side effects and improved tolerability compared to broad-spectrum agents like curcumin and resveratrol (Almatrafi et al., 2024). A key component of green tea, EGCG is well-known for its capacity to cause apoptosis and antioxidant qualities [(Keerthana & Ramesh, 2021; Murugesan, 2021; Subramanian et al., 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/pTwXBX/HlNgc+fHINn+UUPxQ+27JLt).While similar to baicalein in ROS production, EGCG is particularly effective at inhibiting angiogenesis.[(H.-S. Kim et al., 2014)](https://paperpile.com/c/pTwXBX/BW34).According to one study, 6-gingerol dramatically raised the amount of ROS produced by bladder cancer cells, which activated caspase and caused death. Its processes are relatable to those of baicalein, especially when it comes to generating ROS and inducing apoptosis[(Choi et al., 2022)](https://paperpile.com/c/pTwXBX/gciN).Additionally, neem (Azadirachta indica) extracts exhibit anti-inflammatory, anti-angiogenic, and pro-apoptotic properties against various cancers, including prostate and breast tumors. However, baicalein's specific ROS generation differs from neem's broader mode of action and may be more effective in targeting oxidative stress-sensitive cancers like OSCC.[(Wang et al., 2016)](https://paperpile.com/c/pTwXBX/dTr2)[(Pranati et al., 2021; Sakthi 2021)](https://paperpile.com/c/pTwXBX/WeDVL+DhoAS)To sum up, baicalein and other herbal drugs have similar mechanisms of action, especially when it comes to producing ROS and apoptosis. However, each component has its own distinct routes and extra effects that contribute to the overall efficacy of these medications against cancer. The particular cancer kind and the intended treatment results may influence the choice of herbal medicine.

# CONCLUSION

Baicalein's capacity to cause ROS-mediated cell cycle arrest and death in oral squamous cell carcinoma (OSCC) demonstrates a strong anti-cancer effect. The research shows that baicalein dramatically and dose-dependently decreases cell viability, causing observable morphological alterations and an increase in apoptotic activity in treated cells. These results are in line with previous research, supporting the function of baicalein in producing oxidative stress to successfully initiate pathways leading to cell death. Baicalein's tailored mechanism of action offers a more predictable and specific therapeutic strategy compared to other herbal substances like curcumin, neem, quercetin, and resveratrol. This may result in greater efficacy in malignancies that are vulnerable to oxidative stress, including OSCC. These encouraging findings call for more research into baicalein, which may be a useful addition to the present toolkit of cancer treatments and development for clinical applications in OSCC treatment.

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