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Caspase-3/-9 as tongue cancer cell apoptosis target induced by ibuprofen

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ABSTRACT

Background: *Tongue carcinoma is different from oral cancer in other areas because it has a high amount of cell growth, localized migration, and a higher rate of spreading to cervical lymphatic nodes. Therapeutic alternatives, particularly concerning recurrent malignancies, are notably constrained. Nevertheless, it is imperative to explore novel methodologies for refractory neoplasms, one of which may involve the application of ibuprofen.* ***Purpose:*** *The goal of this study was to look at how well caspase-3 and -9 break down proteins as possible targets for apoptosis in tongue cancer cells that were caused by ibuprofen.* ***Methods:*** *A controlled laboratory experiment employing a post-test-only design was executed. We used a colorimetric test for caspase-3 and -9 to check for the induction of apoptosis. The suppression of cellular invasion was verified through the Boyden chamber assay. Western blot analysis was utilized to identify the presence of caspase-3 and -9 proteins. The administered doses of ibuprofen were calibrated at 0, 5, 10, 25, 50, and 100 µg/mL. Data were subjected to analysis using two-way ANOVA followed by post-hoc Least Significant Different (LSD), with a significance threshold set at 95%.* ***Results:*** *It was established that ibuprofen at dosages ranging from 25 to 100 µg/mL significantly facilitated apoptosis in cells through an augmentation of the proteolytic activity of caspase-3 and -9. Notably, caspase-9 exhibited a superior proteolytic activity (1.85-fold) compared to caspase-3 (1.30-fold) (P = 0.038) at the 100 µg/mL concentration. The upregulation of caspase-3 and -9 proteins was observed in cells treated with ibuprofen. Ultimately, ibuprofen demonstrated an ability to inhibit the invasion of tongue carcinoma cells across various dosages.* ***Conclusion:*** *Ibuprofen has been shown to induce the proteolytic activities of caspase-3 and -9 in tongue carcinoma cells. However, the proteolytic activity of caspase-9 surpassed that of caspase-3, suggesting that targeting this protein may constitute a promising novel therapeutic strategy for this cancer variant.*

Keywords: *apoptosis; caspases; ibuprofen; invasion; tongue cancer cell*
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INTRODUCTION

Human tongue carcinoma is distinguished by accelerated cellular proliferation, significant invasiveness, and a propensity for metastasis, and is classified as a malignancy with a pronounced tendency for recurrence.[1,2] There is an observable escalation in the incidence of tongue carcinoma, especially within the anterior two-thirds of the lingual structure, accompanied by an increased prevalence of tongue carcinoma among younger individuals (those under the fifth decade of life). Tongue carcinoma represents the most prevalent form of malignancy within the oral cavity and is notable for its rapidly aggressive biological characteristics. The documented five-year survival rate for patients diagnosed with tongue carcinoma has consistently been reported to be less than 50% over the preceding four decades.[3,4]

Ibuprofen is categorized as a non-steroidal anti-inflammatory drug (NSAID) that manifests its pharmacological effects by inhibiting the biosynthesis of hormones implicated in the processes of inflammation and nociception within the organism.[5] It is chemically designated as (2RS)-1[4-(2-methyl propyl) phenyl] propionic acid, which was the pioneering compound among derivatives of propionic acid to be introduced in 1969 as a more efficacious substitute for Aspirin.[6]

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This pharmaceutical compound is also utilized to mitigate postoperative pain, dysmenorrhea, discomfort associated with osteoarthritis, and pain resulting from nephrolithiasis. This agent functions by hindering the enzyme responsible for the synthesis of prostaglandins (hormone-like molecules that play a role in various physiological processes), consequently leading to reduced concentrations of prostaglandins within the organism.[7] Reduced concentrations of prostaglandins serve to alleviate pain, inflammation, and febrile responses. In general, ibuprofen is prescribed for the management of ailments and conditions that induce pain, fever, and mild to moderate inflammation. For the aforementioned indications, the efficacy of ibuprofen has been assessed as being comparable to or exceeding that of other available nonprescription analgesics. The use of ibuprofen for self-treatment is not advised in individuals under the age of 12 years.[8] Ibuprofen represents the pioneering compound among non-aspirin NSAID agents to receive approval for over-the-counter (OTC) distribution and is widely recognized as the most well-tolerated medication within its pharmacological class. Low-dose, over-the-counter ibuprofen has been administered for analgesic purposes for over three decades without any discernible significant health complications.[9,10] Furthermore, ibuprofen has received Food and Drug Administration (FDA) endorsement for addressing mild to moderate pain. It is accessible as an OTC therapeutic agent for pain, typically of a mild nature. Common OTC applications for ibuprofen include alleviation of muscle sprains or strains, joint discomfort, pain associated with migraines, sore throat, and pain resulting from cold or influenza. Contemporary research investigating the application of ibuprofen as a therapeutic modality for various pain sources predominantly centers on evaluating treatment efficacy in relation to other NSAIDs, with particular focus on cyclooxygenase-2 (COX-2) inhibitors or innovative therapeutic approaches. A comparative study of COX-2 inhibitors and ibuprofen post third molar extraction revealed no statistically significant disparities in pain alleviation at 6, 8, and 12 hours; however, there was a marked increase in the use of rescue analgesia within the ibuprofen cohort at the 24-hour mark.[11] It has been reported that ibuprofen may impede the survival of bladder cancer cells through the induction of the p75NTR tumor-suppressor protein.[12]

Research conducted by Rayburn et al.[13] identified a significant correlation between inflammatory processes and oncogenesis, highlighting that a multitude of anti-cancer therapeutics are simultaneously utilized in the therapeutic approach to inflammatory disorders, including rheumatoid arthritis. Additionally, persistent inflammation amplifies the susceptibility to an array of neoplasms, indicating that the reduction of inflammatory responses may represent a plausible approach for the prevention and treatment of cancer. Additionally, ibuprofen is frequently utilized as an analgesic for oral cancer due to its efficacy as an NSAID in attenuating inflammation and pain. The primary rationales for the application of ibuprofen (National Cancer Institute US)[14] include, first, its anti-inflammatory properties: ibuprofen functions by inhibiting the enzyme cyclooxygenase, which assumes an essential function in the biosynthesis of prostaglandins, which are biochemical entities that instigate inflammatory responses. By attenuating inflammation in the vicinity of oral malignancies, ibuprofen may subsequently mitigate the associated nociceptive sensations. Second, its analgesic properties: in addition to its anti-inflammatory effects, ibuprofen manifests a direct analgesic action, reducing the subjective experience of pain in individuals diagnosed with oral cancer. A recent investigation revealed that the utilization of topically administered non-steroidal anti-inflammatory medications was adopted for the chemoprevention of oral malignancies.[15]

Apoptosis constitutes a distinct biological process of programmed cellular death that is regulated by the Bcl-2 protein family in conjunction with caspase enzymes. The phenomenon of programmed cell death exhibits unique morphological features and energy-dependent biochemical processes. Apoptosis is regarded as an essential element in various biological functions, including routine cellular turnover, development and regulation of the immune system, hormone-mediated atrophy, embryogenesis, and chemically induced cellular death.[16] The caspase cascade, which is integral to the execution of cell death following the release of cytochrome c, has been extensively characterized; however, the specific functions of individual caspases, particularly caspase-3 and -9, during the apoptotic pathway remain ambiguous.[17] In the present study, the proteolytic functions of caspase-3 and -9 were assessed as molecular targets associated with apoptosis in human tongue carcinoma provoked by ibuprofen.

MATERIALS AND METHODS

Dulbecco's modified Eagle medium (DMEM, Sigma-Aldrich, USA) was utilized for the cultivation of human tongue cancer cells (H357: ECACC General Cell Collection, UK). This medium was supplemented with 10% fetal calf serum (FCS, Moregate BioTech, Australia), 100 µg/mL of streptomycin, and 100 units/mL of penicillin (Invitrogen Corp., USA). The H357 cells were maintained at 37°C in an atmosphere of 5% CO2 and 95% humidity.[18] In a DMEM solution containing 10% FCS, a stock solution of 2.0 M ibuprofen was diluted to concentrations of 5, 10, 25, 50, and 100 µg/mL. A human tongue cancer cell line (H357) was incubated for 24 hours with the diluted solutions. To assess chemotaxis (directed invasion), a Boyden chamber instrument (Neuro Probe, Inc., Cabin John, MD, USA) was employed. Sub-confluent cells were harvested for 24 hours using 0.05% (w/v) trypsin (Invitrogen Corporation, USA) and 0.02% (w/v) ethylenediamine tetra-acetic acid (EDTA, Invitrogen Corporation, USA). The cells were then washed twice with phosphate buffer saline (PBS) and resuspended

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at a final concentration of 5x10^5 cells per mL in serum-free media containing 0.1% (w/v) bovine serum albumin fraction (BSA, Wako Pure Chemical Industries, Ltd). A polyvinylpyrrolidone (PVP) filter (Nuclepore Corp, Palo Alto, CA, USA) with an 8 µM pore size was coated with gelatin (Merck KGaA, Frankfurt, Darmstadt, Germany) at a concentration of 0.1 mg/ml and rinsed with sterile water. The bottom chamber was filled with 30 µL of DMEM 10% FCS and various concentrations of ibuprofen, then covered with a gelatin-coated polyvinylidene difluoride (PVDF) membrane. Furthermore, 50 µL of cell suspension (equivalent to 500 cells/mL) was introduced into the upper chamber. After a 24-hour incubation period, the membranes were stained with Giemsa's solution (Ted Pella Inc., Redding, CA, USA). The number of cells that passed through the filter was counted using a light microscope at 400x magnification. Calculations were conducted across 12 fields for each concentration.[19]

Caspase-3 and -9 activities were assessed utilizing the colorimetric assay kit following the guidelines provided by the manufacturer. In summary, equal volumes of cell extracts derived from the H357 cell line, which were treated with different doses of ibuprofen, were incubated with the substrates (DVED-pNA and LEHD-pNA; BioVision colorimetric assay kit, CA, USA) in the assay buffer for a duration of two hours at 37°C. The absorbance was recorded at 450 nm using a microplate reader (Bio-Rad Laboratories, Hercules, CA, USA). Each measurement was conducted in triplicate. Cell lysates were obtained from H357 cells that had been treated with ibuprofen at various doses in Falcon tissue culture dishes (Ø 10 cm) for 48 hours. Equal quantities of protein (70 µg) were subjected to electrophoresis on sodium dodecyl sulfate (SDS)-polyacrylamide gel and subsequently transferred to a PVDF membrane (BioRad, Hercules, CA, USA). The membranes were blocked in Tris-buffered saline (TBS) containing 5% non-fat milk powder at 37°C for one hour prior to being incubated with a 1:500 dilution of primary antibodies targeting caspase-3 (D3R6Y, Cell Signaling Technology, USA) and caspase-9 (Asp330, human-specific antibody, Cell Signaling Technology, USA). Horseradish peroxidase (HRP)-conjugated antibodies were visualized using the enhanced chemiluminescent plus kit (Amersham Pharmacia Biotech, UK). An anti-α tubulin monoclonal antibody (Zymed Labs, San Francisco, USA) was employed to normalize the western blot analysis.

Statistical differences in the mean proteolytic activity of caspase-3 and -9 were evaluated using Stat View 4.5 (Abacus Concepts, Berkeley, CA) and two-way ANOVA, followed by post-hoc Least Significant Different (LSD). The significance threshold was established at 95% for each analysis.

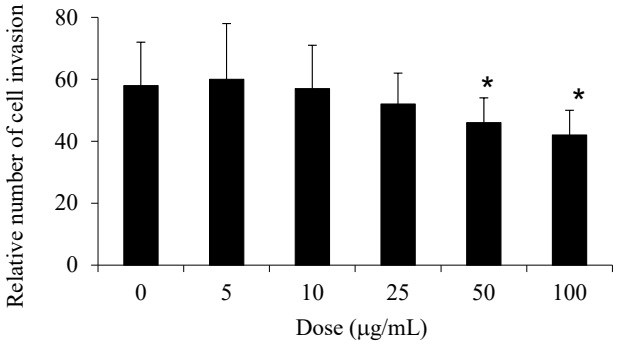

Figure 1. The relative frequency of H357 cell invasions after 24 hours of incubation with various dosages of ibuprofen. (* $p < 0.05$).

RESULTS

The cell migration assay is utilized to evaluate tumor invasion and metastasis. The migratory behavior of cells subjected to various concentrations of ibuprofen was analyzed using the Boyden chamber apparatus following a 24-hour incubation period. Figures 1 and 2 illustrate that H357-treated cells at concentrations of 0, 5, 10, 25, 50, and 100 µg/mL exhibited reduced cell invasion activity compared to the control group ($P < 0.05$; one-way ANOVA). Treatment with ibuprofen at concentrations ranging from 25 to 100 µg/mL resulted in a 10.3-27.6% inhibition of H357 cell invasion.

The activity levels of caspase-3 and -9 in H357 cells treated with varying dosages of ibuprofen were investigated. The incubation of H357 cells with 50 and

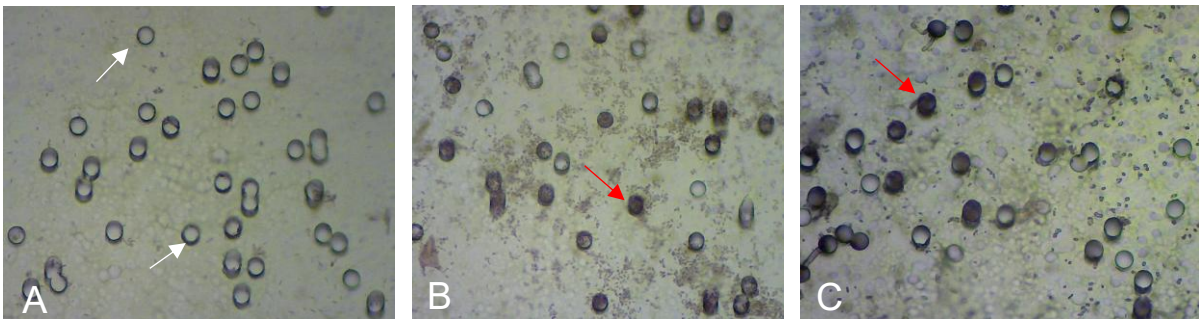

Figure 2. Chemotactic morphology of H357 cell invasion treated with different dosages of ibuprofen. A. Control (0). B. Dose: 50 µg/mL. C. Dose: 100 µg/mL. (White arrow indicates viable cell invasion; red arrow indicates apoptotic cells).

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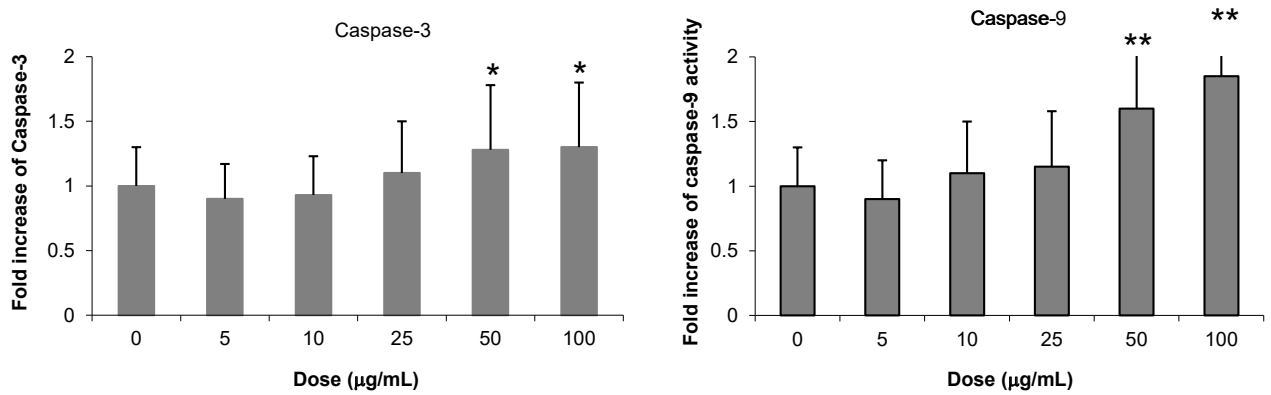

Figure 3. Colorimetric assessment of caspase-3 and -9 for the induction of apoptosis in oral tongue cancer (H357) cells subjected to ibuprofen treatment at different dosages over a period of 48 hours. (*, P < 0.05; **, P < 0.01 in comparison to control, analyzed using one-way ANOVA and post-hoc test).

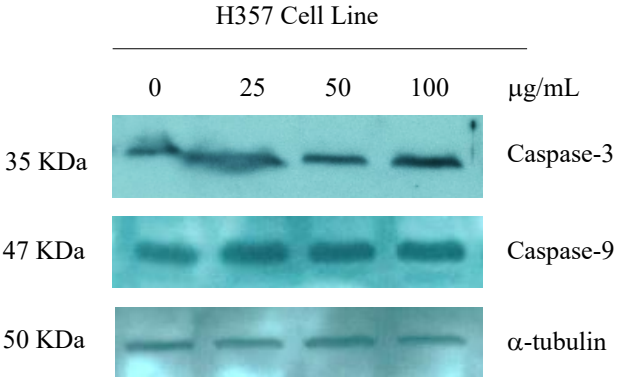

Figure 4. Western blot analysis. Human oral tongue carcinoma (H357) cell expressed caspase-3, caspase-9, and α-tubulin.

100 µg/mL ibuprofen led to an increase in caspase-3 and -9 activity when compared to the control group (Figure 3). Notably, caspase-9 exhibited greater proteolytic activity in H357 cells than caspase-3. Specifically, the incubation of H357 cells with 100 µg/mL ibuprofen resulted in a 1.30 and 1.85-fold increase in caspase-3 and caspase-9 activity, respectively.

Western blotting was employed to assess the expression levels of caspase-3, caspase-9, and α-tubulin. Cells treated with 50 and 100 µg/mL ibuprofen demonstrated elevated levels of caspase-3 protein and an upregulation of caspase-9 in comparison to the untreated group. The expression of α-tubulin remained consistent across all ibuprofen dosages analyzed (Figure 4).

DISCUSSION

Current studies on oral cancer are centered around enhancing the inhibition of cell growth, chemotactic migration, cell invasion, metastasis, and the induction of apoptosis.[20] The proliferation, invasion, and metastasis of cancer cells, along with their resistance to therapy, represent critical factors in the malignancy and progression of cancer cells.[2,21] The abnormal regulation of cell cycle proteins and the imbalance between apoptotic and viable cells are two contributing factors to the malignancy and aggressiveness of cancer cells.[22] Presently, conventional treatments for oral cancer, including radiotherapy, chemotherapy, surgery, and their combinations, continue to yield poor results.[23] Similarly, research on the prevention of chemotactic cell migration, proliferation, invasion, metastasis, and death in human tongue cancer using a non-steroid anti-inflammatory medicine, such as ibuprofen, has not yet been published. An increasing number of epidemiological, clinical, and laboratory investigations have revealed that NSAIDs may be able to prevent the beginning and spread of certain cancers.[24] However, the precise mechanism(s) of NSAID activity to reduce neoplasia remains unknown.

In the current investigation, ibuprofen at various doses, particularly 25–100 µg/mL, reduced the invasion activity of human tongue cancer cells. This research demonstrated that ibuprofen has the capacity to boost intra- and intercellular proteins such as integrins, catenin, cadherin, and others, resulting in stronger cell attachment and inhibiting cell invasion to other locations.[22] It was previously established that ibuprofen at doses ranging from 25 to 100 µg/mL could reduce the invasion activity of human tongue cancer cells by 10.3 to 27.6% after 24 hours (Figure 1). Figure 2 shows the same results: tongue cancer cells died in large numbers after being incubated with ibuprofen concentrations of 50 and 100 µg/mL. The results of the cell invasion assay show that ibuprofen has the capacity to prevent the chemotactic migration of human tongue cancer cells. This data was consistent with that of Akrami et al.,[25] who found that ibuprofen has the potential to inhibit certain varieties of cancer cells, including prostate, colon, lung, breast, and gastric cancer, by increasing suppression of cell proliferation and chemotactic migration or invasion cell through the mechanism of disruption of the WNK1/GSK3β/SRPK1 protein complex. Recently, it was found that ibuprofen could lessen the malignant

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properties of adenocarcinoma gastric cells by inducing apoptosis, inhibiting cell proliferation, and inhibiting angiogenesis.[26,27] Another study found that ibuprofen affects the WNK1/GSK3β/SRPK1 protein complex, which is necessary for the production of the tumor-related splicing variation RAC1B in colorectal cells.[28] Infections and inflammation have historically been associated with cancer, and there are significant correlations between inflammation and the emergence of precancerous lesions at various anatomical locations. Chronic inflammation has been associated with heightened genomic damage, elevated DNA synthesis, increased cellular proliferation, disruption of DNA repair mechanisms, inhibition of apoptosis, as well as the promotion of angiogenesis and invasion.[29,30] All these processes are connected to the onset and advancement of cancer.

In the present study, we employed colorimetric assays for caspase-3 and caspase-9 to evaluate the apoptotic effects of ibuprofen at different dosages on tongue cancer cells. The observed rise in proteolytic activity in cells exposed to various concentrations of ibuprofen strongly indicates that apoptosis took place in those cultures. Caspase-3 and-9 proteolytic activity increased as ibuprofen doses increased (Figure 3). Cells treated with 25–100 µg/mL of ibuprofen induced apoptosis via the intrinsic route (caspase-9). At a dosage of 25 µg/mL, pro-apoptotic proteins in the mitochondrial membrane release Apaf-1, which activates pro-caspase-9, resulting in caspase-9. Ultimately, caspase-9 and caspase-3 are responsible for inducing cell death. A recent investigation revealed that activated caspase-8 can directly cleave and activate executioner caspases, such as caspase-3 through extrinsic pathways and caspase-9 through intrinsic routes. Alternatively, it may cleave a member of the Bcl-2 family (for instance, Bid) to facilitate the release of mitochondrial cytochrome-c, which in turn activates caspase-3 by forming an apoptosome that includes Apaf-1 and caspase-9. Moreover, the formation of apoptosomes and the activation of caspase-3, which functions as an executor caspase, will initiate cell death.[31] The activation of caspase-3 and -9 in tongue cancer cells treated with ibuprofen (25-100 µg/mL) resulted in apoptosis through both intrinsic and extrinsic mechanisms (see Figure 4). Nevertheless, the intrinsic mechanism, often referred to as chemical-induced apoptosis, exhibits greater proteolytic activity compared to the extrinsic pathway. This finding indicates that ibuprofen is more effective in enhancing caspase-9 activation.[20,31] Additionally, the most significant discovery from this research was that ibuprofen can induce apoptosis in oral cancer cells through two apoptotic mechanisms: intrinsic and extrinsic pathways.

In summary, ibuprofen has the capability to activate caspase-3 and -9 in tongue cancer cells. However, caspase-9 demonstrated greater proteolytic activity than caspase-3, implying that targeting this protein may represent a promising new therapeutic strategy for this type of cancer.

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