International Journal of Pharmacology and Toxicology, 12 (1) (2024) 1-7

International Journal of Pharmacology and Toxicology

Website: www.sciencepubco.com/index.php/IJPT

Review

Uncaria-derived alkaloids: A review on the mechanism in inducing apoptosis in oral squamous cell carcinoma

Fiki Muhammad Ridho [1] *, Kamailiya Ulfah [2], Iren Angelia Aruan [3], Naurah Nabilah Pramaztri [1], Eko Puji Laksono [4], Aurellia Nuraini Anindito Putri [5]

[1] *Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia*
[2] *Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia*
[3] *Faculty of Pharmacy, National Institute of Science and Technology, Jakarta, Indonesia*
[4] *Department of Intensive Care Unit, Tarakan General Hospital, Jakarta, Indonesia*
[5] *Faculty of Medicine, Universitas Jember, Jember, Indonesia*
**Corresponding author E-mail: fikimuhammadridho@gmail.com*

Abstract

Alkaloids, the major secondary metabolite compounds identified in the genus *Uncaria*, exhibit the ability to induce apoptosis in oral squamous cell carcinoma (OSCC). Various potential alkaloids in herbal medicine have been explored and provided promising results, one of which is the potential to induce apoptosis. This study aims to provide a more comprehensive review of the mechanism of alkaloids derived from *Uncaria* in inducing apoptosis in OSCC. In the systematic search conducted, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were adhered to conduct this review through the databases, including PubMed, ScienceDirect, Wiley and a manual search using Google Scholar. According to the findings, this review states that several types of alkaloids derived from *Uncaria* that have been reviewed, such as hirsutine, rhynchophylline, isorhynchophylline, and hirsuteine, have different mechanisms in inducing apoptosis in OSCC, both through intrinsic and extrinsic pathways. The evidence presented in the present study provides an opportunity for future research to determine the appropriate therapeutic dose based on the specific alkaloid, duration of therapeutic administration, and in vivo and/or in human testing.

Keywords: *Alkaloids; Apoptosis; Herbal; Oral Cancer; Oral Squamous Cell Carcinoma; Uncaria.*

1. Introduction

Cancer is a pathological condition characterized by the dysregulation of cellular processes involved in cell survival, proliferation, and differentiation [1]. Squamous cell carcinoma is the dominant type of cancer found in the head and neck, with oral squamous cell carcinoma (OSCC) representing the predominant subtype, comprising approximately 90% of all oral cancer cases [2 - 4]. OSCC is a common type of cancer that is widely observed across worldwide, with an annual occurrence of over 350,000 new cases and resulting in over 177,000 mortality [5], and is often found in low-income communities with 90% occurring among people aged over 45 years who are exposed to risk factors [6]. The etiology of OSCC is multifactorial and many widely studied risk factors have been associated with oral cancer. The most studied risk factors for OSCC are tobacco or betel use and regular consumption of alcoholic beverages [3]. Additionally, several risk factors that also increase the incidence of OSCC include human papillovirus (HPV) infection, radiation exposure [7], immune defects such as in transplant patients, chronic immune disorders or HIV/AIDS, drugs such as marijuana, Li Fraumeni syndrome, dyskeratosis congenita, Fanconi anemia, xeroderma pigmentosum, discoid lupus erythematosus, scleroderma, diabetes [2], and consumption of low amounts of fruits and vegetables which can be associated to an unhealthy lifestyle characterized by excessive intake of fat and/or sugar [8].

The pathogenesis of OSCC is a complex and progressive process involving the accumulation of multiple genetic mutations and subsequent changes in cellular function, commonly referred to as oncogenesis, and is impacted by both the patient's genetic predisposition and the impact of various risk factors [9]. The aforementioned alterations might manifest as mutations or modifications in the sequence of the DNA code, removal of specific segments of the DNA, amplification of DNA, or as epigenetic changes [10]. Tumorigenic genetic changes encompass two primary categories, specifically tumor suppressor genes that facilitate tumor progression upon inactivation, and oncogenes that facilitate tumor progression upon activation [11]. The initiation of cancer cell growth commences with the occurrence of DNA damage, leading to the subsequent failure of DNA repair and consequent genomic changes in somatic cells, leading to the oncogene growth trigger activation, tumor suppressor genes inactivation, and alteration in genes regulating apoptosis, resulting in uncontrolled cell proliferation and reduced apoptotic activity [12]. Apoptosis is defined as a programmed cell death mechanism, wherein cells with DNA damage undergo elimination, is distinguished by three primary biochemical characteristics associated with apoptosis, including activation of caspase, fragmentation of DNA and proteins, and alteration in the cell membrane. Consequently, cells experiencing DNA damage can be identified and engulfed by phagocytic cells [13]. Nevertheless, cancer cells possess the capability to evade the apoptotic mechanism, hence enabling uncontrolled proliferation [14].

The primary therapeutic approach for OSCC depends on various factors, including disease stage, disease location, and the patient's overall health status, but surgical intervention remains the mainstay of multimodal treatment, despite the existence of other therapies such as radiotherapy and chemotherapy [15], [16]. Post-surgical treatment, in general, is radiotherapy approximately six weeks following surgery with a total dose usually around 60 Gy because it is difficult to remove radiated tissue surgically, because the tissue becomes fibrous and exhibits delayed healing abilities [16]. In addition, chemotherapy is also used as an additional modality for the treatment of advanced OSCC [17]. However, the utilization of chemotherapy and radiotherapy can result to the developing adverse effects, which greatly decrease the overall well-being of patients, as a result, there has been a growing interest in exploring the potential of natural products containing bioactive components and pure compounds derived from plants and herbal formulations, in order to explore their efficacy in both preventing and treating cancer. Several studies have indicated that natural products had the potential to reduce many adverse effects such as oral mucositis resulting from chemotherapy and radiotherapy, gastrointestinal toxicity, nephrotoxicity, hematological system injury, neurotoxicity, mobility abnormalities, hepatotoxicity, cardiotoxicity, and cognitive impairments [18], [19]. Therefore, currently, there is an increasing demand for the concept or approach of herbal medicines as a supplementary and alternative modality to modern medicine in the treatment of cancer [20]. Several strong lines of evidence from studies suggest the importance of plant-derived compounds, phytochemicals, to inhibit the tumors progression and spread in pre-clinical studies [21].

The *Uncaria* genus has around 34 species that are geographically spread in tropical regions, specifically Asia, Africa and Southeast America [20], [22]. Recently, many studies have been conducted regarding the genus *Uncaria* and reported that plants of the genus *Uncaria* have various pharmacological effects [23], such as treating wounds and ulcers, fever, asthma, rheumatism, hyperpyrexia, anti-inflammatory, hypertension, antioxidant, gastrointestinal diseases, antibacterial, antifungal, antiprotozoal, antiviral, anticancer, anticonvulsant, antidepressant, antithrombotic, antidiabetic, stroke, epilepsy and neurodegenerative diseases [24 - 30]. Based on phytochemical studies carried out, alkaloids are secondary metabolite compounds that are proven to be the most common and found in the genus *Uncaria* [26], [31 - 34]. Alkaloids have been reported to offer anticancer activity by suppressing tumorigenesis, initiating apoptosis, inhibiting cancer cell differentiation, inhibiting angiogenesis, and impeding metastasis through the modulation of various signaling pathways [25], [35 - 39], consequently, alkaloids naturally have promising activity against various cancer cells, including OSCC, as well as drug-sensitive and drug-resistant cancer cells [40], [41]. The aforementioned findings provide essential information for future research regarding the mechanism of apoptosis induction in OSCC. Hence, the primary aim of this study is to conduct a review of the *Uncaria*-derived alkaloids which have anticancer bioactivity, as well as the mechanism of alkaloids in inducing apoptosis in OSCC.

2. Methods

The review of published research was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A comprehensive literature search was conducted on PubMed, ScienceDirect, Wiley, and a manual search using Google Scholar until October 2023 using combination keywords in the form of ("alkaloids" OR "secondary metabolites" OR "Uncaria") AND ("apoptosis" OR "oral cancer" OR "oral squamous cell carcinoma"). This process was conducted by three independent researchers: FMR, KU, and IAA. We identified relevant scientific publications in the database and all literature search results using a combination of keywords, then articles that met the criteria were grouped and any duplicate literature was removed. In this process, we limited the search using inclusion criteria, including articles published in English and published in the last 10 years. The remaining studies were then screened at a final stage according to their full text, and articles that did not meet the established inclusion criteria were excluded. In this process, we document using Microsoft Excel.

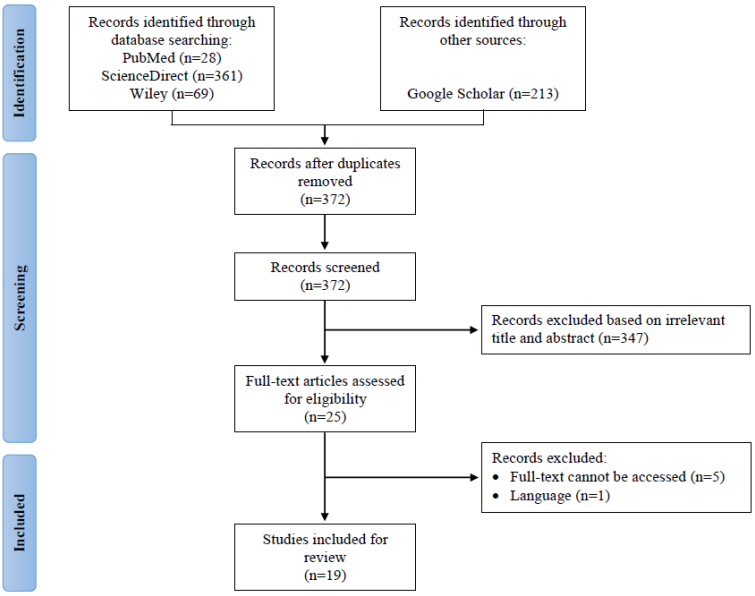

Fig. 1: PRISMA Flow Chart for the Study Selection Procedure.

3. Discussion

Alkaloids are mostly in solid form and are commonly present in many plant species belonging to families such as *Rubiaceae*, *Apocynaceae*, *Piperaceae*, *Amaryllidaceae*, *Ranunculaceae*, *Annonaceae*, *Boraginaceae*, *Lauraceae*, *Berberidaceae*, *Papaveraceae*, *Loganiaceae*, *Gnetaceae*, *Liliaceae*, *Leguminoceae*, *Magnoliaceae*, *Menispermaceae*, *Rutaceae*, *Solanaceae*, etc. [42]. Alkaloids, which are very prevalent, have been identified as the major compounds in the genus *Uncaria*. Basically, alkaloids are a collection of natural chemical composites usually consisting of basic nitrogen atoms, which may also contain some neutral compounds or weak acids [43], [44]. The alkaloid

compounds, the major secondary metabolite of the genus *Uncaria*, is most prevalent in hook stems with an average concentration of 0.22% and is classified into monoterpenoid type alkaloids, indole monoterpenoid type alkaloids, isoechinulin type alkaloids, and other types of alkaloids [28], [45]. Various studies reported the effectiveness of *Uncaria*-derived alkaloids in inhibiting the developing of cancer cells through various pathways, one of which is through the apoptosis mechanism.

Apoptosis is a programmed cell death process through three main pathways, namely extrinsic, intrinsic and granzyme B (GrB) [46]. These three pathways will trigger a proteolytic cascade involving caspase effectors and are responsible for the execution phase of apoptosis. This results in progressive dismantling of cellular structures and eventual engulfment by phagocytic cells [47], [48]. This process is an important component in eliminating unwanted cells as well as homeostasis of the immune system which acts as a barrier to the development of cancer [49]. All antiapoptotic which include B-cell lymphoma-2 (BCL-2), BCL-extra (BCL-x), BCL-extra-large (BCL-xL), BCL-2-related protein A1 (BCL2A1), BCL-2-associated athano-gene 1 (BAG1), survivin, and proapoptotic which include BCL-2-antagonist/killer (BAK), BCL-2-associated X (BAX), BCL-2 interacting mediator of cell death (BIM), BCL-2-associated death promoter (BAD), BH3 interacting-domain death agonist (BID), p53 upregulated modulator of apoptosis (PUMA), apoptotic protease activating factor-1 (APAF-1), caspase-2, -3, -6, -7, -8, -9, -10, second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI (Smac/DIABLO), and cytochrome C (CytC) were expressed in OSCC samples [50].

Extrinsic pathway apoptosis begins with the release of a signal, a ligand, which will bind to the death receptor located on the target cell transmembrane which induces apoptosis [13]. The death receptors, which is located on the cell surface, are the tumor necrosis factor (TNF) receptor family, consisting of TNF receptor 1 (TNF-R1), Fas/cluster of differentiation 95 (Fas/CD95), and TNF-related apoptosis inducing ligand receptor 1 (TRAIL-R1) and receptor 2 (TRAIL-R2). Activation of these receptors will cause trimerization of the death domain containing Fas-associated death domain (FADD) and TNF-R1-associated death domain (TRADD) proteins into the receptor complex. The complex formed between the ligand-receptor and the death receptor FADD is named death-inducing signaling complex (DISC). The DISC signal complex will activate the protease caspase-8 to activate the executor. The working system of caspase-8 is to cut the BCL-2 family members, namely BID. The downstream of the BID fragment will induce the insertion of BAX into the mitochondrial membrane and release pro-apoptotic molecules such as CytC, Smac/DIABLO, apoptosis-inducing factor (AIF), and Omi/high temperature requirement protein A2 (Omi/HtrA2) [13], [51]. The formation of a complex between CytC, APAF-1, and caspase-9 is called the apoptosomes. Caspase-9 activates the caspase-3 protein to become caspase-3 which is an effector caspase for apoptosis [13], [52].

The intrinsic pathway of apoptosis is alternatively referred to as the mitochondrial pathway. Mitochondria stress will induce apoptosis in the intrinsic pathway caused by chemical compounds, causing disruption in the mitochondria which will result in the release of CytC from the mitochondrial intermembrane and binding to the cytoplasmic protein, namely APAF-1. Release of CytC by mitochondrial outer membrane permeabilization (MOMP) stimulation and proteins release from the intermembrane mitochondrial space (IMS) along with the BCL-2 protein family, namely proapoptotic BAX and BAK and anti-apoptotic BCL-2 [53], [54]. These proteins will activate the initiator caspase-9 in the cytoplasm and activate caspase-3. Caspase-3 acts as a cell executor by proteolyzing cellular proteins [53], [54], [55]. Caspase-3 will breakdown various substrates such as poly (ADP-ribose) polymerase (PARP), a DNA repair enzyme, and DNA protein kinase, a cellular and nuclear structural protein, including the nuclear mitotic apparatus, nuclear lamina, actin, and endonucleases such as inhibitor of caspase-activated DNase (ICAD) and other components. Later, AIF and caspase-activated DNase (CAD) will be released from the mitochondrial intermembrane and move to the nucleus and degrade chromatin to form a DNA ladder. The activation of caspase-3 can result in the dissociation of the complex formed by CAD and ICAD, thus allowing CAD to translocate into the nucleus of cancer cells and initiate the degradation of DNA. The cellular entities undergoing degradation are referred to as apoptotic bodies, subsequently identified by macrophages through the phagocytic process [13], [56].

Apoptosis can be initiated through the perforin or GrB pathway, which is facilitated by antibodies produced by cytotoxic T lymphocytes and natural killer (NK) cells. The oligomerization of perforin on the membrane of the target cell facilitates the activation of caspase-3 and BID, similar to caspase-8 [46], while GrB will enter target cells where it plays an important role in cell apoptosis. GrB can trigger caspase activation indirectly, which is achieved by activating the pro-apoptotic BCL-2 family member BH3, just like BID. The interaction of BID with members of the BAX and/or BAK family leads to the release of pro-apoptotic mitochondrial mediators, such as CytC, into the cytosol. The pro-caspase-9 activation occurs with the release of CytC, and by binding to APAF-1, pro-caspase-9 becomes caspase-9 which continues to form apoptosomes and activates caspase-3 downstream. Activated caspase-3 exhibits the capability to enzymatically cleave particular substrates, such as ICAD, hence facilitating the translocation of CAD to the nucleus for the purpose of DNA fragmentation. Apart from BID, GrB can deactivate myeloid leukemia-1 (MCL-1), a member of the anti-apoptotic BCL-2 family to release the BIM protein, which is a pro-anti-apoptotic BCL-2 family member on the outer mitochondrial membrane [57], [58].

The potential of several types of *Uncaria*-derived alkaloids in inducing in OSCC is demonstrated by several evidences in Table 1. below.

Table 1: Summary of the Mechanisms of *Uncaria*-Derived Alkaloids in Apoptosis

Compound	Mechanism in Inducing Apoptosis	Reference
Unidentified Alkaloids (*Uncaria tomentosa*)	Inactivates c-Jun, JunB, RelB, p65, and p50 subunits	[59]
	Increases activation of caspase-8 and caspase-3	[60], [61]
	Blocks AKT	[62], [63], [64]
Hirsutine	Decreases BCL-2 expression	[45], [65], [66], [67]
	Releases CytC	[45], [64], [65], [66], [67]
	Activates caspase-9 and -3	[45], [64], [65], [66], [67]
	Increases ROCK1/PTEN/PI3K/AKT signaling pathways	[64]
	Downregulates expression of p-p65	[63]
	Decreases BCL-xL expression	[64]
	Increases BAX expression	[67]
Rhynchophylline	Affects the MAPK signaling pathway	[45]
	Inhibits CREB, AKT, and STAT3	[45]
	Increases p53 expression	[38]
	Suppresses the PI3K/AKT pathway	[68]
	Decreases CXCR4 expression	[69]
	Decreases BCL-2 and BCL-xL expression	[70]
	Increases BAX and p21 expression	[71]
Isorhynchophylline	Activates caspase-3 and PARP	[71]
	Inhibits CREB, AKT, and STAT3	[39], [71]
	Affects the MAPK signaling pathway	[39], [71]
Hirsuteine	Increases p-p53 signaling	[39]
	Downregulates BCL-2 expression	[72], [73], [74]

Compound	Mechanism in Inducing Apoptosis	Reference
	Upregulates CytC, BAX, and APAF-1	[72], [73]
	Activates caspase-3, -8, and -9	[72], [73]
	Involves sending AIF factor	[73]
	Induces PARP cleavage	[74]
	Decreases BCL-2 expression	[73], [74]

Alkaloids extracted from *Uncaria tomentosa* exhibit the activity in decreasing and inactivating several subunits, including c-Jun, JunB, p65, RelB, and p50 [59]. Inactivation of c-Jun by alkaloids has an impact on disrupting the development of OSCC which is correlated with increasing p53 protein levels [75]. Decreased expression of p65 and p50 in OSCC leads to a decrease the activity of nuclear factor-kappa B (NF-κB) [76], thereby activating cell death pathways such as apoptosis and necroptosis [77] (Krishnan et al., 2023). Meanwhile, oxindole alkaloids derived from *Uncaria tomentosa* have the ability to increase the activity of caspase-8 and -3 [60], [61]. Activation of caspase-8 will cleave the BID and cBID proteins which will then activate the effector proteins BAX and BAK, thus allowing the executioner caspase to induce apoptosis [78]. In addition, activation of caspase-8 will trigger the formation of DISC which will then activate caspase-3 [46].

Hirsutine dan hirsuteine are types of alkaloids that can be found in *Uncaria rhynchophylla*, *Uncaria tomentosa*, *Uncaria attenuata*, *Uncaria guianensis*, *Uncaria sinensis*, *Uncaria sessilifructus*, *Uncaria nervosa*, and *Uncaria kunstleri* [25], [45]. Hirsutine has bioactivity in inducing apoptosis in OSCC through blocking protein kinase B (PKB/AKT) [62], [63], decreasing the ratio of BCL-2 to BAX and activating caspase-9 and -3 [45], [65], [66], increasing Rho-associated coiled-coil containing protein kinase 1/phosphatase and tensin homolog/phosphatidylinositol 3-kinase/AKT (ROCK1/PTEN/PI3K/AKT) signaling pathways [64], downregulating expression of p-p65 [63], increasing BAX expression, cleavage of caspase-3 and -9, CytC, and decreasing BCL-2 protein expression [67]. Meanwhile, hirsuteine has the potential to induce OSCC apoptosis by downregulating BCL-2 and upregulating CytC, BAX, APAF-1, cleavage of caspase-9 and -3 [72 - 74], reducing BCL-2 expression [73], [74], and inducing cleavage of PARP [74]. Inhibition of AKT results in the activation of proapoptotic proteins, namely BAD and BAX, and subsequently triggers the activation of caspases, which are directly involved in apoptosis and forkhead box protein O1 (FOXO-1) which act as a transcription factor and regulate the proapoptotic genes expression, including BIM and Fas ligand (FasL) [79], [80]. Decreased BCL-2 expression and increased BAX expression led to a decrease in the ratio of BCL-2/BAX and increased apoptosis in OSCC [46], [81], [82]. This will produce MOMP and the release of proapoptotic proteins, including CytC which will then activate caspase-9. Activation of caspase-9 is also supported by hirsutine which will continue to cleave and activate caspase-3 and -7 [83]. Hirsutine results in activation of ROCK1 through cleavage via caspase and Ras homolog family member A (RhoA) during apoptosis, leading to phosphorylation and activation of PTEN. PTEN inactivates PI3K/AKT, so that by suppressing AKT, the p38 and Jun N-terminal kinases (JNK) signaling pathways can be activated and can induce apoptosis [64], [84], [85]. Increased ROCK1 signaling is involved in regulating dynamin-related protein 1 (DRP1) mitochondrial translocation [86]. Upon activation, DRP1 is translocated to the outer mitochondrial membrane where it forms a ring structure around the mitochondria, which triggers mitochondrial fission, subsequently leading to the release of CytC and caspase activation, ultimately leading in apoptosis [87], [88].

Rhynchophylline, a type of alkaloids found in *Uncaria tomentosa*, *Uncaria attenuata*, *Uncarua macrophylla*, *Uncaria rhynchophylla*, *Uncaria borneensis*, *Uncaria longiflora* var. *pteropoda*, *Uncaria acida*, *Uncaria africana*, *Ucnaria bernaysii*, *Uncaria cordata*, *Uncaria elliptica*, *Uncaria kunstleri*, *Uncaria guianensis*, *Uncaria sessilifructus*, *Uncaria sterrophylla*, and *Uncaria sinensis* [25], [45], provides an impact on p38, extracellular signal-regulated kinases (ERK), JNK, cyclic adenosine monophosphate response element-binding protein (CREB), AKT and signal transducer and activator of transcription 3 (STAT3) signaling and augmenting the phosphorylation of p53 [38], [45], decreases C-X-C chemokine receptor 4 (CXCR4) expression [69], and activates the PI3K/AKT signaling pathway [70]. The mitogen-activated protein kinase (MAPK) pathway, which includes p38, ERK, and JNK, is influenced by rhynchophylline by activating p38 and JNK and inhibiting ERK, thereby inducing apoptosis [89], [90]. Furthermore, activation of p38 and JNK will release CytC and continue caspase activation [91]. STAT3, a potential cytoplasmic transcription factor, is overexpressed in OSCC and plays an essential role on the aggressiveness of OSCC [92], [93], therefore, STAT3 inhibition is carried out in order to promote apoptosis in OSCC by reducing the target genes expression, including BCL-2 and BCL-xL [94]. Blocking CREB by rhynchophylline leads to cell cycle arrest and apoptosis by activating caspase-3 and decreasing BCL-2 protein expression [95]. Rhynchophylline-induced p53 activation targets p21, PUMA, NOXA, and BAX. PUMA and NOXA are members of the BH3-only family, which play the essential function of triggering the apoptotic process. Meanwhile, BAX and BAK are involved in mediating the release of CytC which then binds to APAF-1, thereby initiating the caspase activation cascade and apoptosis [96], [97]. Inhibition of CXCR4 expression promotes apoptosis of OSCC cells [98], through inhibiting PI3K/AKT/NF-κB signaling [99].

Isorhynchophylline is a type of alkaloid that can be found in *Uncaria tomentosa*, *Uncaria attenuata*, *Uncaria macrophylla*, *Uncaria rhynchophylla*, *Uncaria borneensis*, *Uncaria longiflora* var. *pteropoda*, *Uncaria acida*, *Uncaria africana*, *Ucnaria bernaysii*, *Uncaria cordata*, *Uncaria elliptica*, *Uncaria kunstleri*, *Uncaria guianensis*, *Uncaria sessilifructus*, *Uncaria sterrophylla*, and *Uncaria sinensis* [25], [45]. Isorhynchophylline has activity in inducing apoptosis in OSCC by reducing the expression of BCL-2 and BCL-xL [70], increasing the cleavage of procaspase-8 and -9, caspase-3 and PARP, decreasing the level of phosphorylation such as phosphorylated STAT3, JNK, p38, ERK, c-Jun, CREB, and AKT [39], [71], as well as decreasing p-p38 signal and increasing p-p53 signal [39]. During apoptosis, PARP undergoes cleavage by caspase-3, leading to DNA damage and the induction of apoptosis [100], [101], [102]. In this process, isorhynchophylline exhibits activity in enhancing the activation of caspase-3 and PARP, which are indications of apoptosis in OSCC. Therefore, it may be concluded that the anticancer activity of some alkaloids, as stated in this review, is attributed to their ability to induce apoptosis. However, additional research is required to evaluate the bioactivity of different alkaloid types derived from *Uncaria* that remain unidentified.

4. Conclusion

In conclusion, we can say that alkaloids derived from the genus *Uncaria* possess promising anticancer potential through the induction of apoptosis in OSCC. The mechanism by which apoptosis is induced varies depending on the type of alkaloid. The findings presented in this study offer an opportunity for future research aimed at determining the optimal therapeutic dose according to the type of alkaloid, duration of therapeutic administration, and in vivo and/or human testing.

Acknowledgement

The authors would like to acknowledge that no external assistance or funding was received for this research.

References

[1] G. G. Dark, Oncology at a Glance. Oxford: John Wiley & Sons, 2013.
[2] C. Scully and J. Bagan, "Oral squamous cell carcinoma overview," Oral Oncol, vol. 45, no. 4–5, pp. 301–308, Apr. 2009, https://doi.org/10.1016/j.oraloncology.2009.01.004.
[3] M. Miloro, G. E. Ghali, P. E. Larsen, and P. D. Waite, Peterson's Principles of Oral and Maxillofacial Surgery, 3rd ed. Connecti-cut: People's Medical Publishing House, 2011.
[4] R. D. Coletta, W. A. Yeudall, and T. Salo, "Grand Challenges in Oral Cancers," Frontiers in Oral Health, vol. 1, no. 3, Jun. 2020, https://doi.org/10.3389/froh.2020.00003.
[5] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN esti-mates of incidence and mortality worldwide for 36 cancers in 185 countries," CA Cancer J Clin, vol. 68, no. 6, pp. 394–424, Nov. 2018, https://doi.org/10.3322/caac.21492.
[6] C. Scully and J. Bagan, "Oral squamous cell carcinoma: overview of current understanding of aetiopathogenesis and clinical impli-cations," Oral Dis, vol. 15, no. 6, pp. 388–399, Sep. 2009, https://doi.org/10.1111/j.1601-0825.2009.01563.x.
[7] L. Feller and J. Lemmer, "Oral Squamous Cell Carcinoma: Epidemiology, Clinical Presentation and Treatment," J Cancer Ther, vol. 03, no. 04, pp. 263–268, 2012, https://doi.org/10.4236/jct.2012.34037.
[8] S. Petti, "Lifestyle risk factors for oral cancer," Oral Oncol, vol. 45, no. 4–5, pp. 340–350, Apr. 2009, https://doi.org/10.1016/j.oraloncol-ogy.2008.05.018.
[9] S. H. Hassanpour and M. Dehghani, "Review of cancer from perspective of molecular," Journal of Cancer Research and Practice, vol. 4, no. 4, pp. 127–129, Dec. 2017, https://doi.org/10.1016/j.jcrpr.2017.07.001.
[10] G. H. Lyman, J. Cassidy, D. Bisset, and R. A. J. Spence, Oxford American Handbook of Oncology, 2nd ed. Oxford: Oxford Uni-versity Press, 2015. https://doi.org/10.1093/med/9780199689842.001.0001.
[11] S. Choi and J. N. Myers, "Molecular Pathogenesis of Oral Squamous Cell Carcinoma: Implications for Therapy," J Dent Res, vol. 87, no. 1, pp. 14–32, Jan. 2008, https://doi.org/10.1177/154405910808700104.
[12] R. Sjamsuhidajat and W. De Jong, Buku Ajar Ilmu Bedah, 3rd ed. Jakarta: EGC, 2017.
[13] L. M. Sari, "Apoptosis: mekanisme molekuler kematian sel," Cakradonya Dent J, vol. 10, no. 2, pp. 65–70, 2018. https://doi.org/10.24815/cdj.v10i2.11701.
[14] K. Matsuura, K. Canfield, W. Feng, and M. Kurokawa, "Metabolic regulation of apoptosis in cancer," Int Rev Cell Mol Biol, vol. 327, pp. 43–87, 2016, https://doi.org/10.1016/bs.ircmb.2016.06.006.
[15] S. A. Gharat, M. M. Momin, and C. Bhavsar, "Oral squamous cell carcinoma: current treatment strategies and nanotechnology-based approaches for prevention and therapy," Crit Rev Ther Drug Carrier Syst, vol. 33, no. 4, 2016. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2016016272.
[16] K. Omura, "Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma," Int J Clin Oncol, vol. 19, no. 3, pp. 423–430, Jun. 2014, https://doi.org/10.1007/s10147-014-0689-z.
[17] U. J. Moore, Principles of Oral and Maxillofacial Surgery, 6th ed. West Sussex: Wiley-Blackwell, 2011.
[18] Q.-Y. Zhang, F.-X. Wang, K.-K. Jia, and L.-D. Kong, "Natural Product Interventions for Chemotherapy and Radiotherapy-Induced Side Effects," Front Pharmacol, vol. 9, Nov. 2018, https://doi.org/10.3389/fphar.2018.01253.
[19] J. Fernando and R. Jones, "The principles of cancer treatment by chemotherapy," Surgery (Oxford), vol. 33, no. 3, pp. 131–135, Mar. 2015, https://doi.org/10.1016/j.mpsur.2015.01.005.
[20] R. Abdul, M.-R. Wang, C.-J. Zhong, Y.-Y. Liu, W. Hou, and H.-R. Xiong, "An updated review on the antimicrobial and pharma-cological properties of Uncaria (Rubiaceae)," J Herb Med, vol. 34, p. 100573, Jul. 2022, https://doi.org/10.1016/j.hermed.2022.100573.
[21] F. Ciani et al., "Anti-proliferative and pro-apoptotic effects of Uncaria tomentosa aqueous extract in squamous carcinoma cells," J Ethnopharmacol, vol. 211, pp. 285–294, Jan. 2018, https://doi.org/10.1016/j.jep.2017.09.031.
[22] Erwin, "Review kandungan metabolit sekunder beberapa tumbuhan Uncaria yang terdapat di Kalimantan Timur," Jurnal Atomik, vol. 05, no. 1, pp. 18–24, 2020.
[23] M. Almeida et al., "The Potency of the Genus Uncaria from East Borneo for Herbal Medicine Purposes: A Mini-review," Journal of Tropical Phar-macy and Chemistry, vol. 6, no. 2, pp. 167–176, Oct. 2022, https://doi.org/10.25026/jtpc.v6i2.457.
[24] A. S. Ravipati, N. Reddy, and S. R. Koyyalamudi, "Biologically active compounds from the genus Uncaria (Rubiaceae)," Studies in Natural Products Chemistry, vol. 43, pp. 381–408, 2014, https://doi.org/10.1016/B978-0-444-63430-6.00013-8.
[25] Q. Zhang, J. J. Zhao, J. Xu, F. Feng, and W. Qu, "Medicinal uses, phytochemistry and pharmacology of the genus Uncaria," J Ethnopharmacol, vol. 173, pp. 48–80, Sep. 2015, https://doi.org/10.1016/j.jep.2015.06.011.
[26] W. Yang, S.-P. Ip, L. Liu, Y.-F. Xian, and Z.-X. Lin, "Uncaria rhynchophylla and its Major Constituents on Central Nervous System: A Review on Their Pharmacological Actions," Curr Vasc Pharmacol, vol. 18, no. 4, pp. 346–357, Jun. 2020, https://doi.org/10.2174/1570161117666190704092841.
[27] F. M. Ridho, "Mechanism of Alkaloids and Flavonoids in Bajakah (Uncaria nervosa Elmer) as Antidiabetic Agents," Jurnal Ilmu Medis Indonesia, vol. 3, no. 1, pp. 9–16, 2023.
[28] J.-H. Liang et al., "The genus Uncaria: A review on phytochemical metabolites and biological aspects," Fitoterapia, vol. 147, p. 104772, Nov. 2020, https://doi.org/10.1016/j.fitote.2020.104772.
[29] K. J. Aprely, S. Misfadhila, and R. A. Asra, "Review: The Phytochemistry, Pharmacology and Traditional Use of Gambir (Un-caria gambir (Hunter) Roxb.)," EAS J. Pharm. Pharmacol, vol. 3, pp. 21–25, 2021.
[30] K. M. M. Koriem, "Cortex Uncariae: A Review on Pharmacology, Toxicology, Precautions, and Dosage," Biointerface Res Appl Chem, vol. 13, no. 4, p. 334, Sep. 2022, https://doi.org/10.33263/BRIAC134.334.
[31] F. M. Ridho, "Kandungan Metabolit Sekunder dari Ekstrak Kayu Bajakah (Uncaria nervosa Elmer) dan Bioaktivitasnya Sebagai Antikanker," Uni-versitas Airlangga, Surabaya, 2020. Accessed: Jul. 24, 2023. [Online]. Available: http://lib.unair.ac.id
[32] S. Sultan, K. A. Mohd Ali, N. D. Mohamed Akram, K. Ashraf, M. Ashraf, and G. K. Surindar Singh, "Antimicrobial Activity of Secondary Metab-olites Isolated from Endophytic Fungi Associated with Rubiaceae Species," International Journal of Pharmaceu-ticals, Nutraceuticals and Cosmetic Science, vol. 5, no. 1, pp. 33–47, Jun. 2022.
[33] M. Yang, B. Yao, and R. Lin, "Profiles of Metabolic Genes in Uncaria rhynchophylla and Characterization of the Critical Enzyme Involved in the Biosynthesis of Bioactive Compounds-(iso)Rhynchophylline," Biomolecules, vol. 12, no. 12, p. 1790, Nov. 2022.
[34] D. Martins and C. Nunez, "Secondary Metabolites from Rubiaceae Species," Molecules, vol. 20, no. 7, pp. 13422–13495, Jul. 2015.
[35] J. Song, B. Zhang, M. Li, and J. Zhang, "The current scenario of naturally occurring indole alkaloids with anticancer potential," Fitoterapia, vol. 165, p. 105430, Mar. 2023.
[36] A. Dhiman, R. Sharma, and R. K. Singh, "Target-based anticancer indole derivatives and insight into structure–activity relationship: A mechanistic review update (2018–2021)," Acta Pharm Sin B, vol. 12, no. 7, pp. 3006–3027, Jul. 2022.

[37] M.-L. Luo, W. Huang, H.-P. Zhu, C. Peng, Q. Zhao, and B. Han, "Advances in indole-containing alkaloids as potential anticancer agents by regulating autophagy," Biomedicine & Pharmacotherapy, vol. 149, p. 112827, May 2022.
[38] N. Qin et al., "Recent research progress of Uncaria spp. based on alkaloids: phytochemistry, pharmacology and structural chemis-try," Eur J Med Chem, Oct. 2020.
[39] H. Lee et al., "Isorhynchophylline, a Potent Plant Alkaloid, Induces Apoptotic and Anti-Metastatic Effects in Human Hepatocellu-lar Carcinoma Cells through the Modulation of Diverse Cell Signaling Cascades," Int J Mol Sci, vol. 18, no. 5, p. 1095, May 2017.
[40] F. Song et al., "Indole Alkaloids, Synthetic Dimers and Hybrids with Potential In Vivo Anticancer Activity," Curr Top Med Chem, vol. 21, no. 5, pp. 377–403, Mar. 2021.
[41] Y. Jia, X. Wen, Y. Gong, and X. Wang, "Current scenario of indole derivatives with potential anti-drug-resistant cancer activity," Eur J Med Chem, vol. 200, p. 112359, Aug. 2020.
[42] P. Dey et al., "Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids)," in Recent Advances in Natural Products Analysis, Elsevier, 2020, pp. 505–567.
[43] A. S. Saroya, Herbalism, Phytochemistry and Ethnopharmacology. New Hampshire: Science Publisher, 2011.
[44] N. Bribi, "Pharmacological activity of Alkaloids: A Review," Asian Journal of Botany, vol. 1, no. 1, pp. 1–6, 2018.
[45] N. Qin et al., "Recent research progress of Uncaria spp. based on alkaloids: phytochemistry, pharmacology and structural chemis-try," Eur J Med Chem, vol. 210, p. 112960, Jan. 2021.
[46] S. He, R. Chakraborty, and S. Ranganathan, "Proliferation and Apoptosis Pathways and Factors in Oral Squamous Cell Carcino-ma," Int J Mol Sci, vol. 23, no. 3, p. 1562, Jan. 2022.
[47] C. Pfeffer and A. Singh, "Apoptosis: A Target for Anticancer Therapy," Int J Mol Sci, vol. 19, no. 2, p. 448, Feb. 2018.
[48] L. Villanova, S. Careccia, R. De Maria, and M. Fiori, "Micro-Economics of Apoptosis in Cancer: ncRNAs Modulation of BCL-2 Family Members," Int J Mol Sci, vol. 19, no. 4, p. 958, Mar. 2018.
[49] D. Hanahan and R. A. Weinberg, "Hallmarks of cancer: the next generation," Cell, vol. 144, no. 5, pp. 646–674, Mar. 2011.
[50] C. M. Coutinho-Camillo et al., "Profile of apoptotic proteins in oral squamous cell carcinoma: A cluster analysis of 171 cases," Applied Cancer Research, vol. 37, no. 1, p. 2, Dec. 2017.
[51] S. Lin, J. Pan, X. Huang, Z. Wang, X. Zhao, and S.-K. Sun, "Near-infrared-inducible Bcl-2-associated X protein system for apop-tosis regulation in vivo," Chemical Engineering Journal, vol. 461, p. 141771, Apr. 2023.
[52] R. Singh, A. Letai, and K. Sarosiek, "Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins," Nat Rev Mol Cell Biol, vol. 20, no. 3, pp. 175–193, Mar. 2019.
[53] S. Elmore, "Apoptosis: A Review of Programmed Cell Death," Toxicol Pathol, vol. 35, no. 4, pp. 495–516, Jun. 2007.
[54] V. T. DeVita, T. S. Lawrence, and S. A. Rosenberg, Cancer: principles & practice of oncology: primer of the molecular biology of cancer. Lippincott Williams & Wilkins, 2012.
[55] E. Dirican, H. Özcan, S. Karabulut Uzunçakmak, and U. Takım, "Evaluation Expression of the Caspase-3 and Caspase-9 Apoptot-ic Genes in Schiz-ophrenia Patients," Clinical Psychopharmacology and Neuroscience, vol. 21, no. 1, pp. 171–178, Feb. 2023.
[56] B. Alberts, Molecular biology of the cell. Garland science, 2017.
[57] D. B. Kiselevsky, "Granzymes and Mitochondria," Biochemistry (Moscow), vol. 85, no. 2, pp. 131–139, Feb. 2020.
[58] F. Velotti, I. Barchetta, F. A. Cimini, and M. G. Cavallo, "Granzyme B in Inflammatory Diseases: Apoptosis, Inflammation, Ex-tracellular Matrix Remodeling, Epithelial-to-Mesenchymal Transition and Fibrosis," Front Immunol, vol. 11, Nov. 2020.
[59] R. Pilarski et al., "Enhanced proapoptotic response of the promyelocytic leukemia HL-60 cells treated with an Uncaria tomentosa alkaloid prepara-tion," J Herb Med, vol. 3, no. 4, pp. 149–156, Dec. 2013.
[60] L. Z. de Oliveira et al., "Effect of Uncaria tomentosa Extract on Apoptosis Triggered by Oxaliplatin Exposure on HT29 Cells," Evidence-Based Complementary and Alternative Medicine, vol. 2014, pp. 1–10, 2014.
[61] S. Kaiser et al., "Cat's Claw Oxindole Alkaloid Isomerization Induced by Cell Incubation and Cytotoxic Activity against T24 and RT4 Human Bladder Cancer Cell Lines," Planta Med, vol. 79, no. 15, pp. 1413–1420, Aug. 2013.
[62] P. Katyal and S. Sharma, "Emerging Alkaloids Against Cancer: A Peep into Factors, Regulation, and Molecular Mechanisms," in Bioactive Natural Products for the Management of Cancer: from Bench to Bedside, Singapore: Springer Singapore, 2019, pp. 37–60.
[63] C. Lou, S. Yokoyama, I. Saiki, and Y. Hayakawa, "Selective anticancer activity of hirsutine against HER2-positive breast cancer cells by inducing DNA damage," Oncol Rep, vol. 33, no. 4, pp. 2072–2076, Apr. 2015.
[64] R. Zhang et al., "Hirsutine induces mPTP-dependent apoptosis through ROCK1/PTEN/PI3K/GSK3β pathway in human lung cancer cells," Cell Death Dis, vol. 9, no. 6, p. 598, May 2018.
[65] Md. S. Bhuia et al., "Hirsutine, an Emerging Natural Product with Promising Therapeutic Benefits: A Systematic Review," Mole-cules, vol. 28, no. 16, p. 6141, Aug. 2023.
[66] Q.-W. Huang, N.-N. Zhai, T. Huang, and D.-M. Li, "Hirsutine induces apoptosis of human breast cancer MDA-MB-231 cells through mitochondrial pathway," Acta Physiologica Sinica, vol. 70, no. 1, pp. 40–46, Feb. 2018.
[67] J. Meng, R. Su, L. Wang, B. Yuan, and L. Li, "Inhibitory effect and mechanism of action (MOA) of hirsutine on the proliferation of T-cell leukemia Jurkat clone E6-1 cells," PeerJ, vol. 9, p. e10692, Feb. 2021.
[68] M. Zheng et al., "Protection by rhynchophylline against MPTP/MPP+-induced neurotoxicity via regulating PI3K/Akt pathway," J Ethnopharmacol, vol. 268, p. 113568, Mar. 2021.
[69] Z. Zhang, Y. Li, G. Wu, Y.-M. Li, D. Zhang, and R. Wang, "A comprehensive review of phytochemistry, pharmacology and clin-ical applications of Uncariae Ramulus Cum Uncis," Arabian Journal of Chemistry, vol. 16, no. 5, p. 104638, May 2023.
[70] R. Qin et al., "Naturally derived indole alkaloids targeting regulated cell death (RCD) for cancer therapy: from molecular mecha-nisms to potential therapeutic targets," J Hematol Oncol, vol. 15, no. 1, p. 133, Sep. 2022.
[71] C. Liu et al., "Alkaloids from Traditional Chinese Medicine against hepatocellular carcinoma," Biomedicine & Pharmacotherapy, vol. 120, p. 109543, Dec. 2019.
[72] J. Meng, Y. Yuan, Y. Li, and B. Yuan, "Effects of hirsuteine on MDA MB 453 breast cancer cell proliferation," Oncol Lett, vol. 25, no. 1, p. 4, Nov. 2022.
[73] X. Yun et al., "Inhibitory effect and mechanism of hirsuteine on NCI H1299 lung cancer cell lines," Oncol Lett, vol. 25, no. 5, p. 202, Apr. 2023.
[74] S. Gao et al., "Growth Inhibitory and Pro-Apoptotic Effects of Hirsuteine in Chronic Myeloid Leukemia Cells through Targeting Sphingosine Kinase 1," Biomol Ther (Seoul), vol. 30, no. 6, pp. 553–561, Nov. 2022.
[75] S. Wang et al., "Combined Expression of c-jun, c-fos, and p53 Improves Estimation of Prognosis in Oral Squamous Cell Carci-noma," Cancer Invest, vol. 34, no. 8, pp. 393–400, Sep. 2016.
[76] Z. Gao, Y. Zhang, H. Zhou, and J. Lv, "Baicalein inhibits the growth of oral squamous cell carcinoma cells by downregulating the expression of transcription factor Sp1," Int J Oncol, vol. 56, no. 1, pp. 273–282, Oct. 2019.
[77] R. P. Krishnan, D. Pandiar, P. Ramani, and S. Jayaraman, "Necroptosis in human cancers with special emphasis on oral squamous cell carcinoma," J Stomatol Oral Maxillofac Surg, p. 101565, Jul. 2023.
[78] B. Tummers and D. R. Green, "Caspase-8: regulating life and death," Immunol Rev, vol. 277, no. 1, pp. 76–89, May 2017.
[79] C. Harsha et al., "Targeting AKT/mTOR in Oral Cancer: Mechanisms and Advances in Clinical Trials.," Int J Mol Sci, vol. 21, no. 9, May 2020.
[80] H.-M. Yun, Y.-J. Kwon, E. Kim, H.-J. Chung, and K.-R. Park, "Machilin D Promotes Apoptosis and Autophagy, and Inhibits Necroptosis in Human Oral Squamous Cell Carcinoma Cells," Int J Mol Sci, vol. 24, no. 5, p. 4576, Feb. 2023.
[81] L. L. Loro, A. C. Johannessen, and O. K. Vintermyr, "Loss of BCL-2 in the progression of oral cancer is not attributable to muta-tions.," J Clin Pathol, vol. 58, no. 11, pp. 1157–62, Nov. 2005.

[82] L. L. Loro, O. K. Vintermyr, P. G. Liavaag, R. Jonsson, and A. C. Johannessen, "Oral squamous cell carcinoma is associated with decreased bcl-2/bax expression ratio and increased apoptosis.," Hum Pathol, vol. 30, no. 9, pp. 1097–105, Sep. 1999.
[83] M. Brentnall, L. Rodriguez-Menocal, R. L. De Guevara, E. Cepero, and L. H. Boise, "Caspase-9, caspase-3 and caspase-7 have distinct roles during intrinsic apoptosis," BMC Cell Biol, vol. 14, no. 1, p. 32, Dec. 2013.
[84] R. Aikin, D. Maysinger, and L. Rosenberg, "Cross-Talk between Phosphatidylinositol 3-Kinase/AKT and c-Jun NH2-Terminal Kinase Mediates Survival of Isolated Human Islets," Endocrinology, vol. 145, no. 10, pp. 4522–4531, Oct. 2004.
[85] R. Fragoso and J. T. Barata, "Kinases, tails and more: Regulation of PTEN function by phosphorylation," Methods, vol. 77–78, pp. 75–81, May 2015.
[86] G. Li et al., "Mitochondrial translocation and interaction of cofilin and Drp1 are required for erucin-induced mitochondrial fission and apoptosis," Oncotarget, vol. 6, no. 3, pp. 1834–1849, Jan. 2015.
[87] Q. Zhang et al., "ROCK1 induces dopaminergic nerve cell apoptosis via the activation of Drp1-mediated aberrant mitochondrial fission in Parkinson's disease," Exp Mol Med, vol. 51, no. 10, pp. 1–13, Oct. 2019.
[88] J. Hu et al., "ROCK1 activation-mediated mitochondrial translocation of Drp1 and cofilin are required for arnidiol-induced mito-chondrial fission and apoptosis," Journal of Experimental & Clinical Cancer Research, vol. 39, no. 1, p. 37, Dec. 2020.
[89] Y. Cheng, J. Chen, Y. Shi, X. Fang, and Z. Tang, "MAPK Signaling Pathway in Oral Squamous Cell Carcinoma: Biological Function and Targeted Therapy," Cancers (Basel), vol. 14, no. 19, p. 4625, Sep. 2022.
[90] J.-H. Seo, G. Yoon, S. Park, J.-H. Shim, J.-I. Chae, and Y.-J. Jeon, "Deoxypodophyllotoxin Induces ROS-Mediated Apoptosis by Modulating the PI3K/AKT and p38 MAPK-Dependent Signaling in Oral Squamous Cell Carcinoma," J Microbiol Biotechnol, vol. 32, no. 9, pp. 1103–1109, Sep. 2022.
[91] J. Yue and J. M. López, "Understanding MAPK Signaling Pathways in Apoptosis," Int J Mol Sci, vol. 21, no. 7, p. 2346, Mar. 2020.
[92] I. Gkouveris, N. Nikitakis, D. Avgoustidis, M. Karanikou, G. Rassidakis, and A. Sklavounou, "ERK1/2, JNK and STAT3 activa-tion and correlation with tumor differentiation in oral SCC.," Histol Histopathol, vol. 32, no. 10, pp. 1065–1076, Oct. 2017.
[93] X. Huang et al., "IL-6/STAT3 Axis Activates Glut5 to Regulate Fructose Metabolism and Tumorigenesis.," Int J Biol Sci, vol. 18, no. 9, pp. 3668–3675, 2022.
[94] M. Jiang and B. Li, "STAT3 and Its Targeting Inhibitors in Oral Squamous Cell Carcinoma," Cells, vol. 11, no. 19, p. 3131, Oct. 2022.
[95] A. Steven et al., "What turns CREB on? And off? And why does it matter?," Cellular and Molecular Life Sciences, vol. 77, no. 20, pp. 4049–4067, Oct. 2020.
[96] R.-W. Lin et al., "P53 enhances apoptosis induced by doxorubicin only under conditions of severe DNA damage," Cell Cycle, vol. 17, no. 17, pp. 2175–2186, Sep. 2018.
[97] B. J. Aubrey, G. L. Kelly, A. Janic, M. J. Herold, and A. Strasser, "How does p53 induce apoptosis and how does this relate to p53-mediated tumour suppression?," Cell Death Differ, vol. 25, no. 1, pp. 104–113, Jan. 2018.
[98] Y. Duan et al., "Targeted silencing of CXCR4 inhibits epithelial-mesenchymal transition in oral squamous cell carcinoma," Oncol Lett, vol. 12, no. 3, pp. 2055–2061, Sep. 2016.
[99] C. Jiang et al., "Effect of CXCR4 on Apoptosis in Osteosarcoma Cells via the PI3K/Akt/NF-κβ Signaling Pathway," Cellular Physiology and Biochemistry, vol. 46, no. 6, pp. 2250–2260, 2018.
[100] C.-D. Kim, J.-D. Cha, S. Li, and I.-H. Cha, "The mechanism of acacetin-induced apoptosis on oral squamous cell carcinoma," Arch Oral Biol, vol. 60, no. 9, pp. 1283–1298, Sep. 2015.
[101] L. Zhao et al., "Hydrogen peroxide induces programmed necrosis in rat nucleus pulposus cells through the RIP1/RIP3-PARP-AIF pathway," Journal of Orthopaedic Research, vol. 36, no. 4, pp. 1269–1282, Apr. 2018.
[102] N. B. Madungwe et al., "Mitochondrial inner membrane protein (mitofilin) knockdown induces cell death by apoptosis via an AIF-PARP-dependent mechanism and cell cycle arrest," American Journal of Physiology-Cell Physiology, vol. 315, no. 1, pp. C28–C43, Jul. 2018.