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Literature Review

Curcumin induces tumor suppression in ameloblastoma by promoting apoptotic mechanism via MiR-9 expression: A narrative review

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ABSTRACT

Background: Ameloblastoma is a neoplastic odontogenic tumor that has a local invasive characteristic. The current treatment for ameloblastoma requires a precise surgical resection and chemotherapy. It requires a different approach to diminish the therapy drawbacks. Curcumin, as one of the most common well-described compounds, remarkably has a potential antitumor agent. **Method:** Our findings and opinions are based on a comprehensive search through scientific resources and correspondingly relating all the keywords using the Boolean technique and Medical Subject Headings (MeSH) term search to find the interest study. **Review:** By understanding curcumin and its target genes, curcumin itself can induce regulation of tumor suppression and oncogenic microRNA. MiR-9 has proven to be expressed for modulating the mutation genes causing tumorogenesis in ameloblastoma. Curcumin also upregulates miR-9, causing cytotoxic activity against cancers in many proven studies. **Conclusion:** The highly expressed miR-9 curcumin-mediated ameloblastoma inhibition will be the new insight and adjunct cancer therapy.

Keywords: Curcumin; Ameloblastoma; Non-Communicable Disease; Cancer; Medicine

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INTRODUCTION

Ameloblastoma is an odontogenic benign neoplasm constructed from tooth-forming tissue (dental lamina) arising within the jaw. Its characteristic is being locally invasive, causing inflammation and massive bone resorption as the clinical signs and symptoms. Ameloblastoma constitutes 13–15% of all odontogenic tumors, positioning it as the second most common tumor in the jaw. An analysis retrospective study of 188 cases of ameloblastoma observed in Dr. Cipto Mangunkusumo National Central Public Hospital, with the majority of the cases observed having ameloblastoma affected into the mandible. In Yogyakarta, there's an increased number of ameloblastoma cases, from 26 in 2012 to 69 cases in 2016.[1,2] The complications arose of the conservative surgical approach alone, such as failure of reconstruction, wound dehiscence, post-operative infection, paresthesia, facial asymmetry, development of bone sequestrum, and failure of flap joint.[3–7] With the possibility of recurrency and poor prognosis due to malignancy potency after the surgical resection, it is a required approach for improving the health quality of the patients.

Turmeric, scientifically known as *Curcuma longa*, is a multifaceted botanical species that holds significant economic worth and may be readily acquired. *Curcoma longa* is used as a culinary spice, medicinal herb, and decorative plant, primarily found in Southeast Asia and South Asia. Curcumin constitutes the predominant bioactive compound in *C. longa*, comprising up to 15% of its dry weight. The amount of curcumin produced by *C. longa* can vary depending on hybridization with other *Curcuma* species. However, the purebred *C. longa* found in Indonesia contains a high concentration of curcumin.[6] Curcumin is a naturally occurring compound obtained from the kingdom plantae of *the Zingiberaceae* family, specifically the *C. longa* species. Curcumin possesses a molecular weight of 368.4 and has a molecular structure represented by the chemical formula $C_{21}H_{20}O_{6.}$[8] Curcumin, which also works as an antioxidant, antiinflammatory, and antiviral effect, is also known for inhibiting thrombin and reducing the viscosity of blood. As a polyphenol component substance plant, this traditional medicine originated from *Curcuma longa, which* for so long had been used in Indonesia, commonly as an alternative with the use of 8 genera of curcumin of 15 species that can grow in Indonesia.[9] The use of herbs as a formula traditional and alternative medicine in Indonesia a total of 49% of Indonesian households are planting and using the herbs, especially *Curcuma longa.*[10]

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Curcumin has been recognized because of its modulation effects on suppressing tumors, inhibiting malignancy, and promoting survival of healthy cells by apoptotic of cancer cells. A phytochemical-proven dietary that curcumin upregulates microRNA-9/miR-9, tumor suppressor microRNA. MicroRNA-9 is one of the non-coding conserved RNAs with 22 nucleotides in length that regulates the mRNA of a specific gene by binding to its 3'-untranslated region (3UTR). MiR-9 has been found as a useful miRNA for downregulating many cancer types. MiR-9 is also found expressed in Ameloblastoma.[11] MiR-9 has a target gene by binding the sequence of Nuclear Factor Kappa Light Chain Enhancer B Cells (NF-κB) messenger RNA (mRNA).[12] NF-κB plays an important role for tumor cell survival, elimination, and differentiation of tumorogenesis in ameloblastoma.

MicroRNA-9 has proven to induce the apoptosis by binding the ubiquitin-like containing PHD and RING finger domains 1 (UHRF1) for the apoptosis mechanism. UHRF1 is functionally for maintaining the DNA an oncogene, which is expressed in late G1 and G2/M phases. This serves as oncogene in many cancers. MiR-9 has interference for UHRF1 expression in A549 lung cancer cell lines.[13] The B-type RAF Kinase(BRAF) mutation in Ameloblastoma has a correlation with the apoptosis mechanism through NF- κB which regulated by miR-9 expression.[14]

The properties exhibited by curcumin are proven as anti-inflammatory and anti-cancer effects. Curcumin disrupts various cellular signaling pathways, such as the cyclin family in the cell cycle, apoptosis for cancer cell and inhibition of cell growth through specific receptors.[8]

This study is mainly focusing how the new approach of phytochemical substance may bring a novel therapeutic strategy for inhibiting the tumorogenesis by inducing apoptosis mechanism modulated with the high expression of microRNA-9 and producing good prognosis for Ameloblastoma treatment, while curcumin has major effect on many cancers through its apoptosis ability but the scant result in Ameloblastoma. This novelty of curcumin compounds can potentially be the new treatment option for ameloblastoma. With this background, this review would like to deliver the new insight of curcumin potential in Ameloblastoma by targeting the oncogene for inhibiting the proliferation of tumor cells via miR-9 expression exerted by curcumin intake.

METHOD

To do the literature search, PubMed, Scopus, and Google Scholar databases were used by using the exploration strategical method as described criteria met. Initially, the search found many articles, which were then reviewed accordingly for suitable review. A comprehensive search done by combining the keywords of "Ameloblastoma", "Apoptosis", "Curcumin", and "MicroRNA". All keywords have been searched at once with the boolean operators technique with mesh terms. "Ameloblastoma" AND "Apoptosis" AND "Curcumin" ANR "MicroRNA" OR "miR-9"; "Ameloblastoma" AND "Curcumin"; "Ameloblastoma" AND "Apoptosis" AND "MicroRNA" OR "miR-9"; "Curcmin" AND "MicroRNA" OR "miR-9"; "Curcumin" AND "Apoptosis"; and "Apoptosis" AND "MicroRNA" OR "miR-9." The findings are related to curcumin-mediated miR-9 upregulation and its molecular inducement for inhibition of tumorogenesis in ameloblastoma.

REVIEW

Curcumin induces various types of molecular signaling and pathways and works as an antitumor for ameloblastoma. Curcumin, the active compound in turmeric, exhibits a biological function and medical purposes that contribute to its potential as a promising therapeutic agent. Some of the key properties include: (1) Anti-inflammatory Activity: Curcumin has been understood for anti-inflammatory potency. It can help reduce inflammation by inhibiting various inflammatory pathways and mediators. (2) Antioxidant Activity: Curcumin possesses a strong antioxidant effect; by that, curcumin enables neutralizing the free radicals so cells can be protected from oxidative damage phenomena. (3) Immunomodulatory Effects: Curcumin has been shown to modulate the immune response, enhancing immune function and promoting overall immune health. (4) Anti-cancer Potential: Curcumin exhibits anti-cancer properties by targeting various pathways involved in the development of cancer and its progression. Curcumin has also been studied for its inhibitory effect on tumor growth, modulating the apoptosis process, and preventing metastasis. (5) Neuroprotective Effects: Studies suggest that curcumin has neuroprotective properties and can alleviate conditions such as Alzheimer's disease, Parkinson's disease, and other neurological disorders. (6) Antimicrobial Activity: Curcumin has shown antimicrobial properties against various pathogens, making it a potential natural agent for combating infections. (7) Anti-diabetic Effects: Research indicates that curcumin may help the body prevent diabetic conditions by regulating the blood sugar levels, enhancing the sensitivity of insulin, and preventing diabetes complications. (8) Antiviral Activity: Curcumin has been investigated for its potential antiviral effects, including against viruses like HSV-2, and its role in reducing the severity of infections. These diverse biological properties of curcumin highlight its versatility as a therapeutic agent with potential applications in various health conditions.[15]

Ameloblastoma is highly expressed with proliferating cell nuclear antigen (PCNA) for differentiation of the tumor origin in oral cavity hard tissue.[16] Ameloblastoma is also being regulated by the signal transducer and activator of transcription 3 (STAT3). In ameloblastoma, STAT3 will inhibit the enzymatic activity of protein kinase R in the cytoplasm and be responsible for cell migration.[17] These genes were proven to be regulated by curcumin intake in a previous study did an experiment by applying

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4-nitroquinoline 1-oxide (4-NQO) for the carcinogenesis of oral squamous cell carcinoma in rats, then were given curcumin, which had an effect on decreasing the expression of several genes, by consuming a dosage of 100 mg/kg for a duration of 12 weeks. Curcumin has proven decreasing in the expression of signal transducer and activator of transcription 3 (STAT3), suppressor of cytokine signaling (SOCS)-1, B-cell lymphoma (Bcl-2), and proliferating cell nuclear antigen (PCNA).[18] In mouth cancer, curcumin also successfully inhibits the cancer cell formation in animal models such as hamsters. It is stated that curcumin, whether administered alone or in conjunction with green tea, inhibited cell growth, triggered apoptosis, and hindered the angiogenesis. These effects were ascribed to the anticancer characteristics of curcumin and its capacity to impede the development of blood vessels that sustain tumor growth.[19]

Curcumin has been discovered to exhibit AKT/mTOR-dependent anticancer action.[20] Curcumin effectively prevents the excessive production and activation of proteins related to these pathways, including cyclin, Bcl-2, and other cancer-causing proteins. This clearly demonstrates the anticancer properties of curcumin.[21] Furthermore, curcumin has been shown induct the cell cycle arrest through the EGFR signaling pathway, which interferes at the G2/M phase. This causes the suppression of oral squamous carcinoma cell proliferation.[22] Curcumin upregulates the pro-apoptotic Bcl-2 family (Bax, Bik, Bim), apoptotic protease activating factor-1 (Apaf-1), and cytochrome-c and downregulates B-cell lymphoma-2 (Bcl-2). Those apoptotic factors have proven to cause the death of oral cancer cells induction by curcumin utilization.[21]

The invasion of tumor cells is widely recognized to depend on the disruption between cellular interaction and the extracellular matrix (ECM). Proteolytic enzymes, specifically matrix metalloproteinases (MMPs) and plasminogen activators (PAs), are believed to have a role in the invasion and spread of cancer cells.[23] The observed impact of curcumin on cell invasion may be largely attributed to its ability to reduce the activity of extracellular matrix proteases, specifically MMP-2 and MMP-9, which are crucial for local invasion and are regulated by Wnt signaling. Metalloproteinases in ameloblastoma are responsible for bone resorption.[24]

Ameloblastoma is associated with a higher Notch-1 gene mutation related to the vascularization and fibrosis in the tumor environment. The alterations of NOTCH1 protein due to gene mutation affecting the plasminogen inhibitor protein serpin perptidase inhibitor clade E member 1 (SERP1NE1) are highly expressed and then bind to the urokinase-type plasminogen activator receptor (uPAR) for initiating the signal for proliferation, cell survival, and migration promotion in tumor cells.[25] A study proved elevated expression of uPA/uPAR in OSCC with tumor invasion and metastasis treated with curcumin. The findings demonstrated that curcumin has the ability to suppress the movement of the SCC-25 cell line. This effect is attributed to its capacity to decrease the levels of uPA/uPAR and MMP2/9.[22] Curcumin also mainly acts as an inhibitor as part of a natural compound that is found to directly bind as an antagonist in the Notch signaling pathway. Curcumin suppressed the Notch signaling and all the downstream targets, such as Bcl2, cyclin D1, VEGF, and MMP-9.[25,26]

The alteration and mutation of the B-Rapidly Accelerated Fibrosarcoma (BRAF) gene in ameloblastoma tumorogenesis confers the poor prognosis. The mutational state of this gene led to EGFR and continuous tumor proliferation. Curcumin has proven both *in vitro* and *in vivo* of the colorectal cancer, targeting the BRAF upstream by inhibition of EGFR and MAPK. Initiated suppressing AKT and c-Jun N-terminal kinase (JNK) pathways, curcumin induced the apoptosis of the cancer.[27]

Current combination of natural compounds and surgical approach for ameloblastoma treatment

To this date, surgery remains the established method for treating ameloblastomas. Resection is the preferred surgical approach due to the unsatisfactory recurrence rate associated with conservative treatments like enucleation.[28] Palliative care for ameloblastoma treatment now includes chemotherapy, radiation, and extensive surgeries. Due to the absence of a consistent association between signaling pathways in the development of ameloblastoma, chemotherapy was not recommended or extensively investigated. Although chemotherapy does not provide a cure, various combinations of Cisplatin, Adriamycin, Cyclophosphamide, Doxorubicin, Vinblastine, and Bleomycin have been documented to cause tumor shrinkage and relieve symptoms.[29] The treatment of both benign and malignant ameloblastoma has been predominantly surgical, including sufficient resection of the primary lesion and the metastasis.[30] Curettage and numerous surgeries enhance the chance of metastases, especially to nearby tissues. Neoadjuvant targeted therapy should be evaluated as a means to decrease the need for extensive or repetitive procedures.[31]

A conservative surgical strategy, such as curettage and enucleation, is commonly employed for managing unicystic ameloblastoma, except for cases of the mural variant characterized by epithelial invasion of the cyst wall. The efficacy of curettage or enucleation may be limited to completely eradicating tumor tissue located deep within cancellous bone, extending beyond what is visible macroscopically or on radiographs. To enhance the effectiveness of these procedures, adjunctive measures such as cryotherapy, electrocautery, or the use of cauterizing agents like Carnoy's solution can be considered. Conservative resection techniques involving enucleation or marginal resection offer the advantage of enabling a restricted form of reconstruction, ranging from no reconstruction to bone graft reconstruction. Within this context, both autologous and alloplastic options exist, each capable of filling the resection defect and providing structural support or rigidity to the remaining facial skeleton.[32] In order to treat conventional ameloblastomas in the mandible and maxilla, a segmental excision is frequently performed, and either immediate or delayed bone rebuilding follows.[28,30] Resection reduces the possibility of tumor recurrence, but it also has negative

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effects on the functional and aesthetic outcomes, leading to a diminished quality of life for the affected persons after treatment.[29]

Medicinal plants have been utilized over an extensive period for the purpose of averting and managing a variety of illnesses. In recent times, researchers have been drawn to plant-food-derived natural chemicals due to their exceptional anticancer properties. The National Cancer Institute has recognized around 35 plant-derived foods that exhibit preventive characteristics against numerous oral ailments, such as garlic, onion, ginger, umbelliferous vegetables, turmeric, cruciferous vegetables, whole wheat, oats, and additional botanicals like thyme and mint**.** Moreover, the utilization of these bioactive components alongside cytotoxic drugs appears to amplify their efficacy without causing any harm to healthy cells.[33]

The plant known as green tea (*Camellia sinensis L. Kuntze*) is known for its appealing scent, flavor, and potential health benefits, which are mostly attributed to its polyphenol content.[34] Studies conducted in laboratories and on animals have demonstrated that polyphenols obtained from tea have the ability to hinder the growth of malignant cells and trigger apoptosis. Similarly, catechins generated from tea hinder the angiogenesis and tumor cell invasion. Furthermore, research has demonstrated that green tea stimulates variety of enzymes in biological processes such as detoxification, for example glutathione S-transferase and quinone reductase. This activation of enzymes may contribute to the prevention of tumor growth.[19,35] Garcinol, identified alternatively as camboginol, represents a bioactive compound that has undergone examination due to its potential in inhibiting the expression of phosphorylated-signal transducer and activator of transcription (STAT)-3, p65, Ki-67, and CD31 in the treated groups, as compared to the control group.[36]

Diets high in vegetables, namely those comprising the genus Brassica, belonging to the Cruciferae family, including vegetables like broccoli, cabbage, and cauliflower, harbor bioactive compounds known for their potent anticancer properties. The presence of high concentrations of glucosinolates primarily contributes to these attributes, with isothiocyanates (ITCs) standing out as the most efficacious among them. Isothiocyanates have the ability to trigger programmed cell death and hinder the NF-κB signaling pathway through various methods.[37] Furthermore, by diminishing EGFR signaling, they have the ability to decrease the production and functionality of matrix metalloprotease-2 (MMP-2) and MMP-9 enzymes, leading to the prevention of metastasis.[19]

Azadirachta indica, usually referred to as neem, is a widely recognized plant species. Neem possesses pharmacological effects such as working as an antihelminthic, showing antibacterial potency, being antimycotic, regulating blood sugar, and having anti-inflammatory, antiviral, and anti-tumor activities. Their antitumor activities are due to the chemopreventive potential of neem, ascribed to their anti-lipid peroxidative and antioxidant capabilities in the prevention of oral carcinogenesis.[38]

Curcumin inhibits NF-KB/RANKL in ameloblastoma tumorogenesis.

Curcumin inhibits the NF-κB pathway in cervical cancer cells through various mechanisms. Studies have shown that curcumin can suppress NF-κB activation induced by different stimuli, such as cigarette smoke, in lung epithelial cells. By preventing the activation of upstream kinases of the NF-κB pathway, such as IKKβ and IKKα, curcumin effectively downregulates NF-κB activation. This inhibition of NF-κB activity by curcumin leads to reduced expression of NF-κB target genes involved in inflammation and cancer progression (MMP9, Pro-MMP2, cyclin D1, and COX-2). Furthermore, curcumin has been observed to prevent multiple myeloma, head and neck cancer, and mantle cell lymphoma by inhibiting the constitutive activation of NF-κB. Via NF-κB signaling targeting, curcumin can modulate the expression of genes associated with cell proliferation, invasion, and inflammation, thereby exerting its anti-cancer effects in cervical cancer cells. Curcumin inhibits the NFκB pathway in cancer cells by suppressing NNFκB activation, downregulating NF-κB target genes, and interfering with upstream kinases involved in NFκB signaling. These actions contribute to the anti-proliferative and anti-inflammatory effects of curcumin in cervical cancer therapy.[39] NF-κB also induces the proapoptotic mechanism through MAPK phosphorylation in cancer cells.[40]

The process of macrophages transforming into osteoclasts is primarily influenced by the release of signaling factors from osteoblasts or bone marrow stromal cells (BMSCs). Bone marrow stromal cells (BMSCs) or osteoblasts secrete signaling molecules that primarily regulate the differentiation of macrophages into osteoclasts. For osteoclasts to grow, macrophage colony-stimulating factor (M-CSF) and nuclear factor receptor activator kappa B ligand (RANKL) are very important.[28] The receptor activator of nuclear factor kappa B (RANK), which is found on the surface of osteoclast precursor cells, binds to RANKL. The interaction of this substance triggers the activation of pathways involved in osteoclast formation, such as mitogen-activated protein kinase pass (MAPK), protein kinase B (Akt), and nuclear transcription factor-κB (NF-κB). RANKL also stimulates the production of other factors involved in osteoclast formation, including the c-fos and nuclear factor of activated T cells 1 (NFATc1).[41]

Curcumin controls the process of osteoclast differentiation, hence impacting bone resorption. Curcumin decreased the proportion of M1-type macrophages and promoted macrophage conversion from the M1-type to the M2-type phenotype.[42] The M2 macrophages suppress osteoclast differentiation and production, release anti-inflammatory molecules, and encourage the creation of an anti-inflammatory microenvironment.[41] Curcumin, as believed, stimulated the transformation of macrophages from the M1-type to the M2-type phenotype and reduced the activation of the NF-κB and Akt pathways. This had a beneficial impact on RANKL-induced osteoclastogenesis, providing protection. However, the precise mechanisms by which curcumin triggers this change in the functional

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state of macrophages remain unknown. The results suggest that curcumin enhanced the differentiation, fusion, and maturation of osteoclasts through the action of RANKL.[42] Curcumin inhibits the formation of osteoclasts by decreasing the expression of RANKL in bone marrow stromal cells.[43] Curcumin at a concentration of 15 μM demonstrated a suppressive impact on the autophagic activity of osteoclast precursors (OCPs) produced by RANKL. This effect may be counteracted by the overexpression of Beclin1. The observed outcomes may be attributed to a reduction in the activity of RANKL following the injection of curcumin.[44] Curcumin can inhibit the development of osteoclasts by decreasing the downstream signaling pathways activated by RANKL.[45] Curcumin inhibited the development of osteoclasts by downregulating the activity of RANKL signaling and upregulating the expression of the antioxidant enzyme glutathione peroxidase 4 (GPX4). Curcumin also impairs MAPK activation and reduces NFAT2 expression, which results in aberrant RANKL signaling.[46] However, curcumin is not suitable for clinical applications since it has low solubility in water, degrades quickly at physiological pH, and undergoes photodegradation in organic solvents. β-cyclodextrin can be utilized as solubilizing and stabilizing agents for curcumin by forming inclusion complexes, which enhance its water solubility, stability, and bioavailability.[45] RANKL is known to promote cancer cell proliferation by suppressing tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Blocking RANKL and TRAIL expression proven in cancer cell apoptosis.[47]

Cur-induced miR-9 potencies as novel therapeutic strategies for ameloblastoma

Many studies have proven and revealed the natural compound of turmeric, curcumin, shown in various tumor suppression microRNA expression. Mainly the apoptosis effect, possibly a direct target of Cur-induced microRNA to the cancer cells. Osteoarthritis patients and received curcumin as the treatment and showed the trend of expression of microRNA for regulating immune response.[48] As curcumin modulates microRNA expression of epigenetic function, it inhibits DNA methyltransferase I (DNMT1), induces hypomethylation of global genomic DNA, and modulates histone deacetylases (HDACs) and histone acetyltransferase (HATs).[49]

Curcumin has been investigated in oral cancer, especially oral squamous cell carcinoma, by inhibition of AKT and knockdown of CCAAT/enhancer binding protein beta (C/EBPb) expression, causing several microRNAs to be expected to be expressed. Curcumin profoundly attenuates AKT and diminished C/EBPb. C/EBPb is responsible for certain gene expression, possibly the pre-microRNA genes.[50] MiRNA experiments in two types of ameloblastoma (Solid and Unicystic), which showed miR-9 is lowly expressed. The expression of miR-9 negatively correlated and significantly ini ameloblastoma proliferation, migration, and invasion.[51] MiR-9 is responsible for suppressing malignant tumor cells binding to target genes of CDK6 and cyclin D1, so the cells will stay in cycle arrest of G0/G1 phase.[52]

Curcumin has been shown to upregulate the microRNA-9 expression, which was studied in *vitro* in ovarian cancer cells. This miR-9 upregulation induced by curcumin may have therapeutic implications in cancer treatment. MiR-9 expression is responsible for cellular processes, regulating cancer cell proliferation, the migration of cancer, invasiveness, and the apoptosis process. By modulating miR-9 expression, curcumin may influence these processes in cancer cells. Furthermore, the upregulation of miR-9 by curcumin could potentially inhibit cancer progression and promote ovarian cancer cell degradation through apoptosis. MicroRNA-9 upregulation induced by curcumin may contribute to its anti-cancer properties by influencing key cellular processes involved in cancer progression.[53] In a experiment with the effect curcumin exerts on upregulating microRNA-9 expression in ovarian cancer study, in vitro.[54] MicroRNA-9 is highly expressed and induced by curcumin, demonstrating the suppression of ovarian cancer cells. They also performed an overexpression of miR-9, causing significant apoptosis of ovarian cancer cells via caspase-3 activation and degradation of poly ADP-ribose polymerase/PARP. Curcumin is also found to inhibit oral squamous cell carcinoma cell proliferation and colony formation via miR-9 expression.[55] The expression of miR-9 is induced by curcumin, upregulating miR-9 and concomitantly the higher expression of glycogen synthase kinase 3β (GSK-3b) and decreasing cyclin D1 level. The GSK-3b enzyme works as cancer therapy by interacting with much more than 100 functional proteins.[56]

Curcumin exertion will allow miR-9 to be overexpressed in ameloblastoma. miR-9 itself is responsible for several target genes that regulate ameloblastoma tumorogenesis. miR-9 is found to bind with NF-κB, and NF-κB plays a crucial role for inflammation response, immortalization, survival, angiogenesis, proliferation, tumor promotion, and metastasis of ameloblastoma. It's possible that curcumin will impede the tumorogenesis of ameloblastoma through these pathways. The proliferation ameloblastoma cells of Cyclin D1 are also negatively expressed with miR-9. As curcumin enables miR-9 to express, cyclin D1 will be repressed, allowing cell tumor growth to no longer function. The BRAF-V600E mutation in ameloblastoma also regulated the cancer growth, showing a negative correlation to mir-9 expression. miR-9 may have inhibition activity by directly targeting BRAF.[14] Along with that, miR-9 also targets NF-κB to induce a negative feedback loop for suppressing the tumor progression.[57]

An active compound in natural substances within curcumin has proven to modulate miR-9 expression. As many molecular signaling pathways and transcription factors contributed to Ameloblastoma tumorogensis by inducing apoptosis mechanisms, they were also proven to be regulated by curcumins and miR-9. Both miR-9 and curcumin combined as neoadjuvant therapy with the current surgical approach may deepen the study for obtaining a good prognosis of ameloblastoma.

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