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Harnessing Phytomedicines: Anticancer Strategies Against Osteosarcoma- A Review

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Abstract

Osteosarcoma (OS), the most common primary bone malignancy, predominantly affects children and adolescents, with poor prognosis in advanced or metastatic cases. Originating from osteoblasts, OS is characterized by rapid proliferation, local invasion, and a high propensity for lung metastasis. It is classified as primary (central or surface) or secondary when arising from preexisting conditions. Despite advances in chemotherapy and surgery, the long-term survival rate for patients with metastatic or recurrent OS remains poor, emphasizing the need for novel therapeutic approaches. Phytomedicine, derived from plant-based compounds, has garnered attention for its potential in targeting OS molecular pathways. Phytochemicals such as curcumin, resveratrol, and epigallocatechin gallate (EGCG) exhibit therapeutic effects by modulating key pathways, including Wnt/β-catenin, PI3K/AKT/mTOR, and MAPK/ERK, which are crucial for OS cell migration, proliferation, and survival. These compounds inhibit angiogenesis, promote apoptosis, and reduce metastasis by regulating the epithelial-to-mesenchymal transition (EMT). Additionally, they induce reactive oxygen species (ROS), trigger autophagy, and disrupt cellular signaling, effectively killing OS cells. Emerging studies highlight the potential of phytomedicines to enhance current treatments and improve patient outcomes by offering less harmful and more effective options. This review explores the molecular mechanisms underlying OS and evaluates phytomedicine's role in developing innovative therapies. By integrating genetic, molecular, and clinical profiles, these findings provide valuable insights for advancing OS diagnosis and management, offering hope for more sustainable and effective treatment strategies.

Keywords: *Osteosarcoma, Classification, Signalling pathways, Medicinal plants, Phytomedicines.*

Introduction

Osteosarcoma

Sarcomas of soft tissues and bones are a rare and diverse class of tumours. These tumours constitute 15% of paediatric cancers and less than 1% of all adult cancers, despite the fact that soft tissues and bone comprise about 75% of the typical body weight [1]. Skeletal system malignancies account for just 0.2 percent of all newly diagnosed cases of cancer. The two most prevalent bone tumours, Osteosarcoma and Ewing's sarcoma, mostly emerge in Children and Adolescents [2]. Osteosarcoma, chondrosarcoma, and the Ewing sarcoma/primitive neuroectodermal tumour (PNET) family of tumours are the most prevalent malignant tumours of bone. Just under five percent of all primary malignant bone tumours are malignant fibrous histiocytoma, fibrosarcoma, chordoma, and giant cell tumour of bone. While osteosarcoma

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has a biphasic pattern of incidence that peaks in adolescents with the growth of long bones and in the elderly with tumours arising in association with Paget disease or previously radiated tissues, Ewing sarcoma/PNET family tumours tend to occur more frequently in children and adolescents. Patients with chondrosarcomas typically have tumours with a higher grade of malignancy and are diagnosed after the fifth decade of life, while they can also develop in younger patients [3]. Mesenchymal cells which generate osteoid and immature bone make up Osteosarcomas (OS), referred to as malignant bone tumours. Osteosarcoma is the most prevalent primary malignant bone tumour that is not haematologic [4]. Although further clinical research is required to maximize their use, miRNAs are important in OPMDs and have the potential to be both therapeutic targets and diagnostic indicators [5].

Osteosarcoma is a type of primary bone cancer which most often originates in the metaphases of the most rapidly developing bones during the pubescent growth spurt (15–19 years of age) [6]. The hallmark of osteosarcoma is an elevated cell division, that is essential for bone elongation. Throughout this process, cells may experience several alterations, including a deletion of tumour suppressor gene activity, which ultimately leads them to develop into cancer. In addition, certain conditions have been reported to predispose paediatric patients towards osteosarcoma, which includes retinoblastoma, Li-Fraumeni, and Rothmund-Thomson syndromes. Additionally, sarcomatous transformation, an uncommon consequence seen in older people with Paget's disease of the bone, can lead to Osteosarcoma. The tumour no longer primarily affects the long bones in this patient group. Rather, the most severely affected regions are the jaw and pelvis [7-10]. Modifications in TP53, Rb, and RecQ Like helicase 4 signalling pathways, as well as Bloom Syndrome RecQ Like helicase and Werner syndrome RecQ helicase are contributing factors in the genesis of Osteosarcoma. Therefore, Osteosarcoma is more likely to develop in children and adolescents having genetic diseases including Li-Fraumeni, hereditary retinoblastoma, Rothmund-Thomson, Bloom, or Werner syndrome [11-13]. By causing apoptosis, preventing glycolysis, and lowering migration and invasion in HSC-3 oral cancer cells, calotropin demonstrates anti-cancer potential [14]. Higher risk of Paget's disease of bone (PDB) and greater bone resorption by osteoclasts are linked to a further peak of osteosarcoma in older patients. Also, environmental exposures to substances like radium, beryllium, and chromium during lifespan or a history of radiation exposure (such as prior radiation therapy episodes) are factors that influence the risk of Osteosarcoma in elderly individuals [13, 15-20]. Higher caries severity, higher DMFT scores, and a plaque ecology that favors Streptococcus mutans are all associated with *H. pylori* in cavitated carious lesions [21].

Classification of Osteosarcoma

Osteogenic Sarcoma (OS) is a synonym for Osteosarcoma. In addition to less frequent locations which involve the skull, mouth, and pelvis, Osteosarcoma typically develops close to the metaphysis of the long bones, such as the proximal tibia, proximal humerus, and distal femur. The location of the tumour, its histology, and genetic profile are all valid criteria to categorise Osteosarcoma into different subtypes. The World Health Organisation (WHO) emphasises that Osteosarcoma can be histologically classified into two groups: Surface (Peripheral) and Central (Medullary) tumours, each of which has a number of subgroups. The Surface (Peripheral) Osteosarcoma subtypes are parosteal, periosteal and high-grade surface, whereas the Central (Medullary) Osteosarcoma subtypes are conventional, telangiectatic, low-grade, and small-cell [22]. There are two types of Osteosarcomas which are Primary and

Secondary. According to WHO classification, Primary are further subtyped as Intramedullary/Central and Surface Osteosarcomas. Primary osteosarcomas are further subtyped as Conventional-Intramedullary/Central high grade (most common), Small cell, Telangiectatic, Low grade central, Surface osteosarcomas. Conventional-intramedullary/central high grade (most common) further sub-typed as Osteoblastic (50%), Chondroblastic (25%), Fibroblastic (25%) and Surface osteosarcomas are further sub-typed as: Parosteal, Periosteal, High grade surface. Secondary osteosarcomas can occur after radiation exposure and in Paget's disease. In addition to their analogous biological actions, atypical kinds of osteosarcoma outlined below are regarded as subgroups of conventional osteosarcoma., they are Osteoblastic osteosarcoma-sclerosing type, Osteosarcoma resembling osteoblastoma, Chondromyxoid fibroma-like osteosarcoma, Chondroblastoma-like osteosarcoma, Clear-cell osteosarcoma, Malignant fibrous histiocytoma-like osteosarcoma, Giant cell rich osteosarcoma, Epithelioid osteosarcoma [23].

Epidemiology and Incidence of Osteosarcoma

OS has an estimated yearly incidence of 5.6 cases per million children under the age of 15, making it the third most frequent cancer in adolescence, after brain tumours and lymphomas [24-26]. Incidence spikes in the second decade of life [27, 28]. OS is uncommon before age five [29]. About 70% of tumour tissues have a chromosomal aberration, but OS emerges sporadically and is rarely associated to known hereditary disorders in cell cycle regulation. These generally entail mutations in DNA helicases or tumor-suppressor genes [30, 31]. The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review reported that the age-adjusted incidence rate for all types of bone and joint cancers, throughout all ages and races, is 0.9 per 100,000 annually, with a 5-year overall survival rate of 67.9%. The mortality rate is 0.4 per 100,000. The majority of bone and joint cancer cases (28.7%) occur before the age of 20, with a median diagnosis age of 39 years. The annual incidence rate for all bone and joint malignancies in children (ages 0–14) is 0.7 per 100,000 individuals for both sexes, while the annual fatality rate is 0.1 per 100,000. All bone and joint malignancies have an annual incidence rate of 0.9 per 100,000 people for children and adolescents (ages 0–19), and a mortality rate of 0.4 per 100,000. With an average yearly incidence rate of 8.7 per million children and adolescents below the age of 20, bone and joint malignancies account for roughly 6% of childhood and adolescent cancers [32-34]. South Europe, Africa, Asia, South America, and the Pacific Islands seem to have higher rates of juvenile osteosarcoma diagnosis, whereas Northern Europe, the US, and Australia seem to have higher rates of late tumour onset. Mirabello et al. hypothesised that malignant transformation of Paget's disease could be the cause of osteosarcoma in elderly individuals. The authors' discussion of a notable regional difference in Paget's disease prevalence served to bolster this claim. North America, Australia, and the United Kingdom have been found to have high rates of the disease, while Asia and the Middle East have lower rates. This distribution aligns with the diagnosis of osteosarcoma in the older individual’s population [35-37]. Numerous investigations, especially those conducted on the African population, have shown a greater correlation between osteosarcoma and gender in males than in females. Additionally, it has been noted that compared to men in the same age range, women under the age of 15 had somewhat higher cancer rates. Incidence peaks later in adolescence and is higher in males (age 15–19, peak rate of 9–15 cases/million population) than in females (age 10–14, peak rate of 6–10 cases/million population). This suggests that the aetiology of osteosarcoma

may involve bone growth, hormonal changes, as well as puberty-related development [38-52]. Osteosarcoma has a complicated and poorly known aetiology. Numerous genetic risk factors, such as Li Fraumeni syndrome, Rothmund-Thomson syndrome, and hereditary retinoblastoma (Rb), have been revealed through studies [53-57]. Rb gene mutations are strongly correlated with osteosarcoma predispositions, and a lack of heterogeneity in the Rb gene may be a sign of an adverse clinical outcome. Additionally, 10–39% of osteosarcoma cases were found to have changed p53 loci. Mutations in p53 and Rb together exhibit synergistic carcinogenic effects [58-66].

Role of Phytomedicines in the Treatment of Osteosarcoma

Chemotherapy is frequently employed for the treatment of cancer. Nevertheless, chemotherapy therapies can occasionally result in a variety of undesirable side effects and toxicities. Phytocompounds derived from medicinal herbs are becoming more widely acknowledged as effective supplemental therapy for many cancer categories. Plants have been utilised for centuries to treat cancer and have been a significant source of potent anticancer drugs. Of the 92 anticancer medications that were licensed globally between 1983 and 1994 and that were commercially available in the US prior to 1983, over 62% have natural origins. As the world's largest producer of medicinal plants, India is justifiably referred to as the "Botanical Garden of the World." Numerous studies on these plants have been completed, and certain plant extracts have been sold as anticancer medications based on scientific reports and traditional applications. According to the World Health Organisation, around 75% of people worldwide today utilise herbal remedies and other traditional treatments to cure illnesses [67-71]. Different genetic alterations found in oral squamous cell carcinoma grades are revealed by NGS analysis, which helps with individualized therapy planning and advances minimal intervention techniques [72].

Anticancer chemotherapy medications can often be replaced with natural drugs that are safer, more affordable, and more effective. Natural remedies can help lessen negative side effects. For example, most cancer treatments include components derived from plants. Medicinal herbs' anticancer properties are attributed to their antioxidant content, according to multiple investigations. In actuality, therapeutic plants are more readily accessible, less expensive, and non-toxic than contemporary (allopathic) medications. In numerous studies, secondary metabolites like polyphenols, terpenes, and alkaloids have been proposed to have antimutagenic and anticancer effects. Many therapeutically effective anticancer drugs have been created from chemicals found in plants. In the prevention and treatment of cancer, natural phenolic chemicals are crucial. Phenolic compounds have a variety of biological properties that give them chemopreventive qualities, such as anti-inflammatory, anticarcinogenic, or antimutagenic actions [67, 71, 73-74]. During orthodontic treatment stages, there is a negative correlation between salivary 1-25dihydroxycholecalciferol and IL-17A levels, indicating that vitamin D administration may hasten tooth movement while minimizing tissue injury [75].

The new alkaloid medication Aloperine (ALO), which is derived from *S. alopecuroides*, has antiviral, anticancer, anti-inflammatory, and antiallergenic properties. DAPI assays and flow cytometry demonstrated that ALO caused OS cells to undergo apoptosis. Additionally, the results of quantitative real-time polymerase chain reaction and western blotting showed that ALO downregulated Bcl-2 and elevated the protein and mRNA of Bax and cleaved caspase-3. Furthermore, by suppressing the OS cells' PI3K/AKT signalling pathway, ALO prevented the invasion of MG-63 and U2OS cells [76].

A component of some Chinese herbs, such as *Huang lian*, includes berberine (BBR), an isoquinoline alkaloid with antimicrobial, anti-inflammatory, anti-diabetic, anti-angiogenesis, and cholesterol-lowering properties. The MTT assay was used to assess the proliferation impact of U20S, and flow cytometric analysis was used to figure out the proportion of apoptotic cells. By suppressing the PI3K/AKT signalling pathway, this therapy produced dose-structured inhibition of U20S cell growth and induced apoptosis. This led to an upregulation of PARP and Bax expression and a downregulation of Bcl-2 and caspase3 expression. As a result, the study suggests that BBR might be a useful substitute treatment for OS in clinical environments [77].

The natural polyphenol component resveratrol (3,5,4′-trihydroxy-trans-stilbene) is present in many plants, including peanuts, cranberries, blueberries, raspberries, mulberries, and grape skin. It has been well shown to have anticancer properties. It has anti-aging, antiviral, antioxidative, anti-inflammatory, and anticancer effects. By altering a number of crucial processes, it also demonstrates some tumor-suppressing properties in bone cancer. It has also been shown to be highly successful in preventing HOS cell proliferation by reducing β-catenin signalling and triggering apoptosis [78].

A remarkable plant-derived member of the triterpenoid family, cucurbitacin E (CuE) has been shown to be an anticancer drug by preventing the growth, migration, and metastasis of a variety of cancers. CuE's ability to prevent OS cell growth and invasion while tracking its underlying molecular process was the goal of the current investigation. The cell counting Kit-8 assay was used to evaluate the anti-proliferative impact of CuE following treatment with varying doses. The distribution of cell cycles was examined using propidium iodide staining. The expression of cell growth, cell cycle, and cell apoptosis regulators were altered by CuE, which also prevented cell invasion and growth, caused a cell cycle halt, and induced apoptosis. By suppressing the PI3K/AKT/mTOR pathway and the epithelial-mesenchymal transition, CuE prevented OS invasion and metastasis. The study conducted revealed that CuE might stop the development and invasion of OS tumours by blocking the PI3K/AKT/mTOR signalling pathway. CuE may be a viable anticancer drug for OS, according published data [79].

The main bioactive component of the medicinal spice *Nigella sativa*, commonly referred to as black cumin, is thymoquinone (TQ), which in a dose-dependent manner increased the percentage of growth inhibition and apoptosis in the HOS cell line SaOS-2 when compared to the control. In SaOS-2 cells, the TQ significantly reduced NF-κB DNA-binding activity, XIAP, surviving, and VEGF, according to the EMSA assay and western blot evaluation. It also suppresses NF-κB and its regulated molecules on SaOS-2 cells, which prevents tumour angiogenesis and tumour growth [80].

The Chinese plant *Solanum incanum* yielded the steroidal glycoalkaloid known as solamargine (SM). It caused OS U2OS cells to undergo apoptosis and significantly decreased cell viability. Therefore, raises the expression of p53 and Bax in both mRNA and protein. Additionally, the expression of the anti-apoptotic protein Bcl-2 was decreased. Furthermore, SM caused apoptosis, cytochrome c release, activation of caspase-9 and -3, loss of mitochondrial membrane capacity, and p53 translocation in the mitochondria. Thus, the study proposed that SM may be used as a possible treatment drug for OS as it is a strong apoptosis inducer through p53 activation [81].

The plant's rhizome contains an active ingredient called curcumin, which has anti-inflammatory, anti-cancer, and antioxidant effects. Curcumin significantly induced G1 arrest and death in U2OS cells, confirming the development of inhibitory effects on U2OS

cells in a dose- and time-structured manner. In U2OS cells, curcumin-induced apoptosis was followed by downregulation of Bcl-2 and upregulation of Bax, Bak, and p-Bad; Bcl-XL and Bad protein levels were unaffected. Moreover, curcumin administration raised the levels of mitochondrial cytochrome C and caspase-3 and significantly decreased the ability of the mitochondrial membrane [82].

Withania somnifera is a medicinally significant plant that contains the well-known steroidal lactone withaferin A (WA). It has been claimed that they have anticancer effects. WA caused cell cycle arrest at the G2/M phase, according to flow cytometric analysis. This was linked to the suppression of cyclin B1, cyclin A, CDK2, and p-Cdc2 (Tyr15) expression, the rise in p-Chk1 (Ser345) and p-Chk2 (Thr68) levels, and the reduction of G2/M checkpoint protein expression levels. Based on this, the results showed that WA had strong anti-proliferative effects on MG-63, U2OS, and HOS cell lines [83]. The potential of salivary MMP-9 as a marker for malignant transformation is suggested by the markedly higher levels observed in OSCC and severe oral epithelial dysplasia [84].

The majority of cancer chemoprevention research make extensive use of sodium selenite (Na2SeO3, or SSE), an inorganic Se compound. Reactive oxygen species (ROS) production, apoptotic body formation, and cell accumulation at a certain stage of the advanced phase of apoptosis are all indications that SSE also suppressed cell viability through apoptosis. P53 and PTEN overexpression, Bcl-2 downregulation, and CASP 3 activation were all associated with SSE-induced apoptosis in U2OS cells. Thus, according to the investigations, SSE is a potential anticancer component that might be utilised in OS treatments in the future [85].

It has been demonstrated that the active ingredient shikonin (SK), which is taken from the Chinese medicinal plant *Lithospermum erythrorhizon*, has anticancer properties. When SK and ADM were administered to U2OS and MG63 cells, Western blot examination showed elevated expression levels of Bax, caspase-3, caspase-8, and PARP. The combination treatment of SK and ADM dramatically accelerated apoptosis, according to flow cytometric analysis. This was likely caused by triggering caspase-3 and caspase-8 dependent apoptosis in the OS cells, which may have been an enhancer for the treatment of drug-resistant primary OS [86, 87].

Role of Phytomedicines in Signalling Pathways of Progression in Osteosarcoma

PI3K/AKT/MTOR PATHWAY

A novel signalling mechanism that was closely linked to the viral oncogene's tyrosine kinase activity was discovered in 1984. The virus-associated tyrosine kinase, known as PI3K, was identified by Cantley and Downes' lab in 1988. It produces PI3K by phosphorylating the 3-OH group on the inhibitor.Lipid kinases were engaged in this signalling system, which was later dubbed the PI3K signalling pathway. Subsequent investigations revealed the presence of AKT, mTOR, and other genes downstream of the PI3K signalling pathway. As a result, this route was later dubbed the PI3K/AKT/mTOR signalling pathway. It controls cellular biological processes such cellular differentiation, proliferation, and migration and is one of the most important intracellular signalling pathways [88-91]. By causing cytotoxic effects and controlling apoptotic signals, β-sitosterol shows promise as a treatment for oral cancer [92].

Through the integration of many extracellular signals, the PI3K/AKT/mTOR pathway controls a variety of cellular processes. A vital part of the cell membrane, PI3K is an intracellular phosphatidylinositol kinase. It possesses both serine/threonine (Ser/Thr) kinase and phosphatidylinositol kinase activity. Type I PI3K, a heterodimer composed of the

catalytic subunit p11031 and the regulatory subunit p85, is specifically involved in the PI3K/AKT pathway and is most strongly associated with cancer. Target proteins with matching binding sites may interact with the structural domains SH2 and SH3 present in the regulatory subunit [93-94].

The PI3K/AKT/mTOR pathway commonly undergoes modifications in OS. One important mechanism of OS proliferation and metastasis is the high frequency of PI3K mutations and/or their enhanced catalytic activity in tumour cells [98].

Multiple downstream signalling pathways are accessible through mTOR, which can be activated by a range of upstream regulatory factors. At the conclusion of the PI3K/AKT/mTOR signalling pathway is mTOR, one of the PI3K axis's most autonomous elements. Mutations in upstream regulatory components from several axes, including PTEN, PI3K, and endothelial growth factor receptor, may cause excessive mTOR activation. Any disruption in the control of mTOR activity can change how OS cell proliferation and differentiation are regulated [99, 83, 100-104]. Leukoplakia, OSMF, and OSCC patients at high risk of malignant transformation may be identified using circulating exosomal miRNAs miRNA 21, miRNA 184, and miRNA 145 as plasma biomarkers [105].

A semisynthetic derivative of cantharidin hydrolysed by sodium hydroxide is sodium cantharidinate. Sodium cantharidinate stimulates the PI3K/AKT pathway in MG63 cells, which leads to p53/p21 activation, cyclin D1 expression levels and activity inhibition, and cell block in the G0/G1 phase and reduction of human OSMG63 cell growth [106, 107].

Conclusion

Compounds produced from phytomedicine provide a possible therapy option for osteosarcoma by modifying important signalling pathways implicated in tumour resistance and development. To improve the prognosis of patients with osteosarcoma, further research is necessary to get these natural substances from the laboratory to the bedside.

Conflict of Interest

There is no conflict of interest as expressed by the authors.

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References

[1]. Malawer, M., Sugarbaker, P. H., Shmookler, B., Bickels, J., Jelinek, J., Sugarbaker, P., & Malawer, M., 2001, Bone and soft-tissue sarcomas: epidemiology, radiology, pathology and fundamentals of surgical treatment. *Musculoskeletal Cancer Surgery: Treatment of Sarcomas and Allied Diseases*, 3-35.

[2]. DeVita, V., Lawrence, T., Rosenberg, S., Weinberg, R. A., & DePinho, R. A. 2008, Cancer: Principles and Practice of Oncology Vols 1 and 2. Philadelphia, PA, USA: *Lippincott Williams & Wilkins.*

[3]. Kantarjian, H., Wolff, R. A., & Koller, C. A. 2011, The MD Anderson manual of medical oncology.

[4]. Alessio, B., Massimiliano, D. P., & Nikolin, A., 2014, Osteosarcoma symptoms, diagnosis and treatment options. Edwin Choy. Library of congress cataloging-in-publication data.

[5]. Jayaraman, S., Natarajan, S. R., Veeraraghavan, V. P., & Jasmine, S., 2023, Unveiling the anti-cancer mechanisms of calotropin: Insights into cell growth inhibition, cell cycle arrest, and metabolic regulation in human oral squamous carcinoma cells (HSC-3). *Journal Of Oral Biology And Craniofacial*

Research, 13(6), 704–713. https://doi.org/10.1016/j.jobcr.2023.09.00.

[6]. Jame, A., James, L., Gulley., Carmen, J., 2014, Allegra. Bethesda handbook of clinical oncology - Fourth edition © 2014 by Lippincott Williams & Wilkins, a Wolters Kluwer business. Section 7: Musculoskeletal; 21. Sarcomas and Malignancies of the Bone, Patrick J. Mansky and Lee J. Helman. ISBN 978-1-4511-8758-8. *Library of Congress Cataloging-in-Publication Data*.

[7]. Kazantseva, L., Becerra, J., & Santos-Ruiz, L., 2022, Traditional Medicinal Plants as a Source of Inspiration for Osteosarcoma Therapy. Molecules (Basel, Switzerland), 27(15),5008. https://doi.org/10.3390/molecules27155008

[8]. Durfee, R. A., Mohammed, M., & Luu, H. H. 2016, Review of Osteosarcoma and Current Management. Rheumatology and therapy, 3(2), 221–243. https://doi.org/10.1007/s40744-016-0046-y

[9]. Hansen, M. F., Seton, M., & Merchant, A., 2006, Osteosarcoma in Paget's disease of bone. *Journal of bone and mineral research: The official journal of the American Society for Bone and Mineral Research*, 21 Suppl 2, P58–P63. https://doi.org/10.1359/jbmr.06s211.

[10]. Deyrup, A. T., Montag, A. G., Inwards, C. Y., Xu, Z., Swee, R. G., & Krishnan Unni, K., 2007, Sarcomas arising in Paget disease of bone: a clinicopathologic analysis of 70 cases. *Archives of pathology & laboratory medicine*, 131(6), 942–946. https://doi.org/10.5858/2007-131-942-SAIPDO.

[11]. Rickel, K., Fang, F., & Tao, J., 2017, Molecular genetics of osteosarcoma. *Bone*, 102, 69–79. https://doi.org/10.1016/j.bone.2016.10.017.

[12]. Fiedorowicz, M., Bartnik, E., Sobczuk, P., Teterycz, P., & Czarnecka, A. M., 2018, Molecular biology of sarcoma. *Oncology in Clinical Practice*, 14(6), 307-330.

[13]. Czarnecka, A. M., Synoradzki, K., Firlej, W., Bartnik, E., Sobczuk, P., Fiedorowicz, M., . & Rutkowski, P., 2020, Molecular biology of osteosarcoma. *Cancers*, 12(8), 2130.

[14]. Fathima, J. S., Jayaraman, S., Sekar, R., & Syed, N. H., 2024, The role of MicroRNAs in the diagnosis and treatment of oral premalignant disorders. *Odontology*, 1-10.

[15]. Savage, S. A., & Mirabello, L., 2011, Using epidemiology and genomics to understand osteosarcoma etiology. *Sarcoma*, 2011(1), 548151.

[16]. Huvos, A. G., 1986, Osteogenic sarcoma of bones and soft tissues in older persons. A clinicopathologic analysis of 117 patients older than 60 years. *Cancer*, 57(7), 1442-1449.

[17]. Rani, A. S., & Kumar, S., 1992, Transformation of non-tumorigenic osteoblast-like human osteosarcoma cells by hexavalent chromates: alteration of morphology, induction of anchorage-independence and proteolytic function. *Carcinogenesis*, 13(11), 2021-2027.

[18]. Dutra, F. R., & Largent, E. J., 1950, Osteosarcoma induced by beryllium oxide. *The American journal of pathology*, 26(2), 197.

[19]. Mazabraud, A., 1975, Experimental production of bone sarcomas in the rabbit by a single local injection of beryllium. *Bulletin Du Cancer*, 62(1), 49-58.

[20]. Casali, P. G., Bielack, S., Abecassis, N., Aro, H. T., Bauer, S., Biagini, R., & Blay, J. Y., 2018, Bone sarcomas: ESMO–PaedCan–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 29, iv79-iv95.

[21]. Sruthi, M. A., Mani, G., Ramakrishnan, M., & Selvaraj, J., 2023, Dental caries as a source of Helicobacter pylori infection in children: An RT-PCR study. *International Journal of Paediatric Dentistry*, 33(1), 82-88.

[22]. Rothzerg, E., Xu, J., & Wood, D, 2023, Different Subtypes of Osteosarcoma: Histopathological Patterns and Clinical Behaviour. *Journal of Molecular Pathology*, 4(2), 99-108.

[23]. Kundu, Z. S., 2014, Classification, imaging, biopsy and staging of

osteosarcoma. *Indian Journal Of Orthopaedics*, 48(3), 238-246.
[24]. Abate, M. E., Longhi, A., Galletti, S., Ferrari, S., & Bacci, G., 2010, Non-metastatic osteosarcoma of the extremities in children aged 5 years or younger. *Pediatric Blood & Cancer*, 55(4), 652-654.
[25]. Kager, L., Zoubek, A., Pötschger, U., Kastner, U., Flege, S., Kempf-Bielack, B., & Bielack, S. S., 2003, Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. *Journal of Clinical Oncology*, 21(10), 2011-2018.
[26]. Pakos, E. E., Nearchou, A. D., Grimer, R. J., Koumoullis, H. D., Abudu, A., Bramer, J. A., & Ioannidis, J. P., 2009, Prognostic factors and outcomes for osteosarcoma: an international collaboration. *European Journal Of Cancer*, 45(13), 2367-2375.
[27]. Cho, W. H., Song, W. S., Jeon, D. G., Kong, C. B., Kim, M. S., Lee, J. A., & Lee, S. Y., 2010, Differential presentations, clinical courses, and survivals of osteosarcomas of the proximal humerus over other extremity locations. *Annals Of Surgical Oncology*, 17, 702-708.
[28]. Kaste, S. C., Liu, T., Billups, C. A., Daw, N. C., Pratt, C. B., & Meyer, W. H., 2004, Tumor size as a predictor of outcome in pediatric non-metastatic osteosarcoma of the extremity. *Pediatric Blood & Cancer*, 43(7), 723-728.
[29]. Kager, L., Zoubek, A., Dominkus, M., Lang, S., Bodmer, N., Jundt, G., & COSS Study Group., 2010, Osteosarcoma in very young children: experience of the Cooperative Osteosarcoma Study Group. *Cancer*, 116(22), 5316-5324.
[30]. Hayden, J. B., & Hoang, B. H., 2006, Osteosarcoma: basic science and clinical implications. *Orthopedic Clinics*, 37(1), 1-7.
[31]. Misaghi, A., Goldin, A., Awad, M., & Kulidjian, A. A., 2018, Osteosarcoma: A comprehensive review. *Sicot-j*, 4.
[32]. Ries, L. A. G., Melbert, D., Krapcho, M., Stinchcomb, D. G., Howlader, N., Horner, M. J., & Edwards, B., 2008, SEER cancer statistics review, 1975–2005. *Bethesda, MD: National Cancer Institute*, 2999.
[33]. Ajani, U. A., 2007, United States cancer statistics: 2004 incidence and mortality.
[34]. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 2001 Incidence and *Mortality*. Atlanta, GA: Centers for Disease Control and Prevention and National Cancer Institute; 2004.
[35]. Mirabello, L., Troisi, R. J., & Savage, S. A., 2009, International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons. *International Journal Of Cancer*, 125(1), 229-234.
[36]. Colina, M., La Corte, R., De Leonardis, F., & Trotta, F., 2008, Paget's disease of bone: a review. *Rheumatology International*, 28(11), 1069-1075.
[37]. Cooper, C., Harvey, N. C., Dennison, E. M., & van Staa, T. P., 2006, Update on the epidemiology of Paget's disease of bone. *Journal of Bone and Mineral Research*, 21(S2), P3-P8.
[38]. Mirabello, L., Troisi, R. J., & Savage, S. A., 2009, Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 115(7), 1531-1543.
[39]. Ries, L. A. G., Smith, M. A., Gurney, J., Linet, M., Tamra, T., Young, J., 1999, Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995.
[40]. Polednak, A. P., 1985, Primary bone cancer incidence in black and white residents of New York State. *Cancer*, 55(12), 2883-2888.
[41]. Parkin, D. M., Stiller, C. A., Draper, G. J., & Bieber, C. A., 1988, The international

incidence of childhood cancer. *International Journal of Cancer*, 42(4), 511-520.
[42]. Linabery, A. M., & Ross, J. A., 2008, Trends in childhood cancer incidence in the US (1992–2004). *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 112(2), 416-432.
[43]. Oyemade, G. A. A., & Abioye, A. A., 1982, Primary malignant tumors of bone: incidence in Ibadan, Nigeria. *Journal of the National Medical Association*, 74(1), 65.
[44]. Oboirien, M., & Khalid, A., 2013, Knowledge and belief about traditional bone setters' practices in Sokoto, North-West Nigeria. *Internet J Orthop Surg*, 21(2).
[45]. Fraumeni JR, J. F., 1967, Stature and malignant tumors of bone in childhood and adolescence. *Cancer*, 20(6), 967-973.
[46]. Ruza, E., Sotillo, E., Sierrasesúmaga, L., Azcona, C., & Patiño-García, A., 2003, Analysis of polymorphisms of the vitamin D receptor, estrogen receptor, and collagen Iα1 genes and their relationship with height in children with bone cancer. *Journal of pediatric hematology/oncology*, 25(10), 780-786.
[47]. Spjut, H. J., 1971, Tumors of bone and cartilage. US Department of Defense, Armed Forces *Institute of Pathology*.
[48]. Longhi, A., Pasini, A., Cicognani, A., Baronio, F., Pellacani, A., Baldini, N., & Bacci, G., 2005, Height as a risk factor for osteosarcoma. *Journal of pediatric hematology/oncology*, 27(6), 314-318.
[49]. Goodman, M. A., McMaster, J. H., Drash, A. L., Diamond, P. E., Kappakas, G. S., & Scranton Jr, P. E., 1978, Metabolic and endocrine alterations in osteosarcoma patients. *Cancer*, 42(2), 603-610.
[50]. Mirabello, L., Pfeiffer, R., Murphy, G., Daw, N. C., Patiño-Garcia, A., Troisi, R. J., . & Savage, S. A., 2011, Height at diagnosis and birth-weight as risk factors for osteosarcoma. *Cancer Causes & Control*, 22, 899-908.
[51]. Matsunaga, E., 1980, Hereditary retinoblastoma: host resistance and second primary tumors. *Journal of the National Cancer Institute*, 65(1), 47-51.
[52]. Draper, G. J., Sanders, B. M., & Kingston, J. E., 1986, Second primary neoplasms in patients with retinoblastoma. *British journal of cancer*, 53(5), 661-671.
[53]. Matsunaga, E., 1980, Hereditary retinoblastoma: host resistance and second primary tumors. *Journal of the National Cancer Institute*, 65(1), 47-51.
[54]. Draper, G., Sanders, B., Kingston, J., 1986, Second primary neoplasms in patients with retinoblastoma. *British Journal of Cancer*, 53(5), 661.
[55]. Wang, L. L., Gannavarapu, A., Kozinetz, C. A., Levy, M. L., Lewis, R. A., Chintagumpala, M. M., Ruiz-Maldanado, R., Contreras-Ruiz, J., Cunniff, C., Erickson, R. P., Lev, D., Rogers, M., Zackai, E. H., & Plon, S. E., 2003, Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund-Thomson syndrome. *Journal of the National Cancer Institute*, 95(9), 669–674. https://doi.org/10.1093/jnci/95.9.669.
[56]. Hicks, M. J., Roth, J. R., Kozinetz, C. A., & Wang, L. L., 2007, Clinicopathologic features of osteosarcoma in patients with Rothmund-Thomson syndrome. *Journal of clinical oncology : Official journal of the American Society of Clinical Oncology*, 25(4), 370–375.
https://doi.org/10.1200/JCO.2006.08.4558.
[57]. Porter, D. E., Holden, S. T., Steel, C. M., Cohen, B. B., Wallace, M. R., & Reid, R., 1992, A significant proportion of patients with osteosarcoma may belong to Li-Fraumeni cancer families. *The Journal of bone and joint surgery*. British volume, 74(6), 883–886. https://doi.org/10.1302/0301-620X.74B6.1447251.
[58]. Araki, N., Uchida, A., Kimura, T., Yoshikawa, H., Aoki, Y., Ueda, T., Takai, S., Miki, T., & Ono, K., 1991, Involvement of the retinoblastoma gene in primary osteosarcomas and other bone and soft-tissue tumors. *Clinical*

orthopaedics and related research, (270), 271–277.
[59]. Thomas, L., Mautner, V. F., Cooper, D. N., & Upadhyaya, M., 2012, Molecular heterogeneity in malignant peripheral nerve sheath tumors associated with neurofibromatosis type 1. *Human genomics*, *6*(1), 18. https://doi.org/10.1186/1479-7364-6-18.
[60]. Deshpande, A., & Hinds, P. W., 2006, The retinoblastoma protein in osteoblast differentiation and osteosarcoma. *Current molecular medicine*, 6(7), 809–817. https://doi.org/10.2174/156652401060607080.
[61]. Feugeas, O., Guriec, N., Babin-Boilletot, A., Marcellin, L., Simon, P., Babin, S., Thyss, A., Hofman, P., Terrier, P., Kalifa, C., Brunat-Mentigny, M., Patricot, L. M., & Oberling, F., 1996, Loss of heterozygosity of the RB gene is a poor prognostic factor in patients with osteosarcoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 14(2), 467–472. https://doi.org/10.1200/JCO.1996.14.2.467.
[62]. Miller, C. W., Aslo, A., Tsay, C., Slamon, D., Ishizaki, K., Toguchida, J., Yamamuro, T., Lampkin, B., & Koeffler, H. P., 1990, Frequency and structure of p53 rearrangements in human osteosarcoma. *Cancer research*, 50(24), 7950–7954.
[63]. Miller, C. W., Aslo, A., Won, A., Tan, M., Lampkin, B., & Koeffler, H. P., 1996, Alterations of the p53, Rb and MDM2 genes in osteosarcoma. *Journal of cancer research and clinical oncology*, 122(9), 559–565. https://doi.org/10.1007/BF01213553.
[64]. Gokgoz, N., Wunder, J. S., Mousses, S., Eskandarian, S., Bell, R. S., & Andrulis, I. L., 2001, Comparison of p53 mutations in patients with localized osteosarcoma and metastatic osteosarcoma. *Cancer*, 92(8), 2181–2189. https://doi.org/10.1002/1097-0142(20011015)92:8<2181::aid-cncr1561>3.0.co;2-3.
[65]. Berman, S. D., Calo, E., Landman, A. S., Danielian, P. S., Miller, E. S., West, J. C., Fonhoue, B. D., Caron, A., Bronson, R., Bouxsein, M. L., Mukherjee, S., & Lees, J. A., 2008, Metastatic osteosarcoma induced by inactivation of Rb and p53 in the osteoblast lineage. Proceedings of the National Academy of Sciences of the United States of America, 105(33), 11851–11856. https://doi.org/10.1073/pnas.0805462105.
[66]. Walkley, C. R., Qudsi, R., Sankaran, V. G., Perry, J. A., Gostissa, M., Roth, S. I., Rodda, S. J., Snay, E., Dunning, P., Fahey, F. H., Alt, F. W., McMahon, A. P., & Orkin, S. H., 2008, Conditional mouse osteosarcoma, dependent on p53 loss and potentiated by loss of Rb, mimics the human disease. *Genes & development*, 22(12), 1662–1676. https://doi.org/10.1101/gad.1656808.
[67]. Desai, A. G., Qazi, G. N., Ganju, R. K., El-Tamer, M., Singh, J., Saxena, A. K., Bedi, Y. S., Taneja, S. C., & Bhat, H. K., 2008, Medicinal plants and cancer chemoprevention. *Current drug metabolism*, 9(7), 581–591. https://doi.org/10.2174/138920008785821657.
[68]. Yin, S. Y., Wei, W. C., Jian, F. Y., & Yang, N. S., 2013, Therapeutic applications of herbal medicines for cancer patients. Evidence-based complementary and alternative medicine : eCAM, 302426. https://doi.org/10.1155/2013/302426.
[69]. Cragg, G. M., & Newman, D. J., 2005, Plants as a source of anti-cancer agents. *Journal of ethnopharmacology*, 100(1-2), 72–79. https://doi.org/10.1016/j.jep.2005.05.011.
[70]. Krishnan, R. P., Pandiar, D., Ramani, P., & Jayaraman, S., 2024, Molecular profiling of oral epithelial dysplasia and oral squamous cell carcinoma using next generation sequencing. Journal of stomatology, oral and maxillofacial surgery, 126(4), 102120. Advance online publication. https://doi.org/10.1016/j.jormas.2024.102120.
[71]. Prasanth, N. V., Dilip, C., Sanal Dev, K. T., Augustine, L., & Saraswathi, R., 2010, Evaluation of in vitro cytotoxic and antioxidant

activities of Ipomoea batatas. *Int J Pharm Pharm Sci*, 2(3), 91-2.
[72]. Umadevi, M., Kumar, K. S., Bhowmik, D., & Duraivel, S., 2013, Traditionally used anticancer herbs in India. *Journal of Medicinal Plants Studies*, 1(3), 56-74.
[73]. Rahmani, A. H., Alzohairy, M. A., Khan, M. A., & Aly, S. M., 2014, Therapeutic implications of black seed and its constituent thymoquinone in the prevention of cancer through inactivation and activation of molecular pathways. *Evidence-Based Complementary and Alternative Medicine*, 2014(1), 724658.
[74]. Huang, W. Y., Cai, Y. Z., & Zhang, Y., 2009, Natural phenolic compounds from medicinal herbs and dietary plants: potential use for cancer prevention. *Nutrition and cancer*, 62(1), 1-20.
[75]. Sagar, S., Ramani, P., Moses, S., Gheena, S., & Selvaraj, J., 2024, Correlation of salivary cytokine IL-17A and 1, 25 dihydroxycholecalciferol in patients undergoing orthodontic treatment. *Odontology*, 1-10.
[76]. Chen, S., Jin, Z., Dai, L., Wu, H., 2018, Aloperine induces apoptosis and inhibits invasion in MG-63 and U2OS human osteosarcoma cells. *Biomed Pharmacother*, 97, 45-52.
[77]. Chen, C. Z., 2016, Berberine induced apoptosis of human osteosarcoma cells by inhibiting phosphoinositide 3 kinase/protein kinase B (PI3K/Akt) signal pathway activation.
[78]. Chen, G., Xia, H., Zhang, Z. G., & Yu, H. L., 2017, Resveratrol in management of bone and spinal cancers. *Natural product research*, 33(4), 516-526.
[79]. Wang, Y., Xu, S., Wu, Y., & Zhang, J., 2016, Cucurbitacin E inhibits osteosarcoma cells proliferation and invasion through attenuation of PI3K/AKT/mTOR signalling pathway. *Bioscience reports*, 36(6), e00405.
[80]. Peng, L., Liu, A., Shen, Y., Xu, H. Z., Yang, S. Z., Ying, X. Z., . & Shen, W. D., 2013, Antitumor and anti-angiogenesis effects of thymoquinone on osteosarcoma through the NF-κB pathway. *Oncology reports*, 29(2), 571-578.
[81]. Li, X., Zhao, Y., Wu, W. K., Liu, S., Cui, M., & Lou, H., 2011, Solamargine induces apoptosis associated with p53 transcription-dependent and transcription-independent pathways in human osteosarcoma U2OS cells. *Life sciences*, 88(7-8), 314-321.
[82]. Jin, S., Xu, H. G., Shen, J. N., Chen, X. W., Wang, H., & Zhou, J. G., 2009, Apoptotic effects of curcumin on human osteosarcoma U2OS cells. *Orthopaedic surgery*, *1*(2), 144-152.
[83]. Lv, T. Z., & Wang, G. S., 2015, Antiproliferation potential of withaferin A on human osteosarcoma cells via the inhibition of G2/M checkpoint proteins. Experimental and therapeutic medicine, 10(1), 323-329.
[84]. Pazhani, J., Chanthu, K., Jayaraman, S., & Varun, B. R., 2023, Evaluation of salivary MMP-9 in oral squamous cell carcinoma and oral leukoplakia using ELISA. *Journal of Oral and Maxillofacial Pathology*, 27(4), 649-654.
[85]. Chen, X. J., Duan, F. D., Zhang, H. H., Xiong, Y., & Wang, J., 2012, Sodium selenite-in duced apoptosis mediated by ROS attack in human osteosarcoma U2OS cells. Biological trace element research, 145, 1-9.
[86]. Yang, Q., Li, S., Fu, Z., Lin, B., Zhou, Z., Wang, Z., . & Cai, Z., 2017, Shikonin promotes adriamycin-induced apoptosis by upregulating caspase-3 and caspase-8 in osteosarcoma. *Molecular medicine reports*, 16(2), 1347-1352.
[87]. Pichaiyan, V., Mariyappan, S., Saravanan, R., & Ramalingam, S., 2018, Herbal remedy for osteosarcoma-challenging evolution. *Asian Journal of Pharmaceutical and Clinical Research*, 52-56.
[88]. Yang, J., Nie, J., Ma, X., Wei, Y., Peng, Y., & Wei, X., 2019, Targeting PI3K in cancer: mechanisms and advances in clinical trials. *Molecular cancer*, 18(1), 26.
[89]. Arafeh, R., & Samuels, Y., 2019, PIK3CA in cancer: The past 30 years. In Seminars in

cancer biology (Vol. 59, pp. 36-49). *Academic Press*.

[90]. Whitman, M., Downes, C. P., Keeler, M., Keller, T., & Cantley, L. (1988). Type I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate. *Nature*, *332*(6165), 644-646.

[91]. Alzahrani, A. S., 2019, PI3K/Akt/mTOR inhibitors in cancer: At the bench and bedside. In Seminars in cancer biology (Vol. 59, pp. 125-132). *Academic Press*.

[92]. Jayaraman, S., Natarajan, S. R., Ponnusamy, B., Veeraraghavan, V. P., & Jasmine, S., 2023, Unlocking the potential of beta sitosterol: Augmenting the suppression of oral cancer cells through extrinsic and intrinsic signalling mechanisms. *The Saudi Dental Journal*, 35(8), 1007-1013.

[93]. Tapia, O., Riquelme, I., Leal, P., Sandoval, A., Aedo, S., Weber, H., & Roa, J. C., 2014, The PI3K/AKT/mTOR pathway is activated in gastric cancer with potential prognostic and predictive significance. *Virchows Archiv*, 465, 25-33.

[94]. Porta, C., Paglino, C., & Mosca, A., 2014, Targeting PI3K/Akt/mTOR signaling in cancer. *Frontiers in oncology*, 4, 64.

[95]. Uddin, M. J., Shamsuzzaman, M., Horng, L., Labrique, A., Vasudevan, L., Zeller, K., Chowdhury, M., Larson, C. P., Bishai, D., & Alam, N., 2016, Use of mobile phones for improving vaccination coverage among children living in rural hard-to-reach areas and urban streets of Bangladesh. *Vaccine*, 34(2), 276–283. https://doi.org/10.1016/j.vaccine.2015.11.024.

[96]. O'Donnell, J. S., Massi, D., Teng, M. W., & Mandala, M., 2018, PI3K-AKT-mTOR inhibition in cancer immunotherapy, redux. In Seminars in cancer biology (Vol. 48, pp. 91-103). *Academic Press*.

[97]. Ramakrishnan, V., & Kumar, S., 2018, PI3K/AKT/mTOR pathway in multiple myeloma: from basic biology to clinical promise. *Leukemia & lymphoma*, 59(11), 2524-2534.

[98]. Gobin, B., Huin, M. B., Lamoureux, F., Ory, B., Charrier, C., Lanel, R., & Heymann, D., 2015, BYL719, a new α-specific PI3K inhibitor: Single administration and in combination with conventional chemotherapy for the treatment of osteosarcoma. *International journal of cancer*, 136(4), 784-796.

[99]. Meric-Bernstam, F., Akcakanat, A., Chen, H., Do, K. A., Sangai, T., Adkins, F., & Yao, J., 2012, PIK3CA/PTEN mutations and Akt activation as markers of sensitivity to allosteric mTOR inhibitors. *Clinical cancer research*, 18(6), 1777-1789.

[100]. Yang, Q., & Guan, K. L., 2007, Expanding mTOR signaling. *Cell research*, 17(8), 666-681.

[101]. Yu, G., Wang, J., Chen, Y., Wang, X., Pan, J., Li, G., & Xie, K., 2009, Overexpression of phosphorylated mammalian target of rapamycin predicts lymph node metastasis and prognosis of chinese patients with gastric cancer. *Clinical Cancer Research*, 15(5), 1821-1829.

[102]. Luo, Y., Xu, W., Li, G., & Cui, W., 2018, Weighing in on mTOR complex 2 signaling: the expanding role in cell metabolism. *Oxidative medicine and cellular longevity*, 2018(1), 7838647.

[103]. Smith, C. R., Leon, M. B., Mack, M. J., Miller, D. C., Moses, J. W., Svensson, L. G., & Pocock, S. J., 2011, Transcatheter versus surgical aortic-valve replacement in high-risk patients. *New England Journal of Medicine*, 364(23), 2187-2198.

[104]. Steelman, L. S., Abrams, S. L., Whelan, J., Bertrand, F. E., Ludwig, D. E., Bäsecke, J., & McCubrey, J. A., 2008, Contributions of the Raf/MEK/ERK, PI3K/PTEN/Akt/mTOR and Jak/STAT pathways to leukemia. *Leukemia*, 22(4), 686-707.

[105]. Yasothkumar, D., Ramani, P., Jayaraman, S., Ramalingam, K., & Tilakaratne, W. M., 2024, Expression Profile of Circulating Exosomal microRNAs in Leukoplakia, Oral Submucous Fibrosis, and Combined Lesions of

Leukoplakia and Oral Submucous Fibrosis. *Head and Neck Pathology*, 18(1), 28.
[106].Kang, X. H., Hu, W. H, Pei, S. S., 2017, Effects of Sodium Cantharidate and vitamin B6 on apoptosis and survivin expression in human osteosarcoma cells. *China Medical Herald*. 14, 16-19.
[107].Hua, F., Shang, S., Hu, Z. W., 2017, Seeking new anti-cancer agents from autophagy-regulating natural products. *J Asian Nat Prod Res*. 19(4), 305-313.