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Review Article

HERBAL REMEDY FOR OSTEOSARCOMA - CHALLENGING EVOLUTION

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ABSTRACT

Bone cancer is the extremely rare type, which accounts for about 0.2% of all cancer. They metastasize the cancer cells to the bone parts which have an especially crucial mechanism of action while treating. It is treated with the advanced drugs, have effluent side effects when compared to the medicinal plants and phytoconstituents. The review effectively deals that the mechanism of action of different medicinal plants include *Phyllanthus urinaria, Aralia elata, Punica granatum, Anemone altaica,* and *Potentilla chinensis* and the phytoconstituents include corosolic acid, shikonin, thymoquinone, aloperine, and withaferin A. This review provides the detailed information about the importance of medicinal herbs in the treatment of bone cancer, besides the mechanism of action of several phytoconstituents in different cell lines used. In future, it is more useful for evaluating the treatment of bone cancer with phytoconstituents.

Keywords: Osteosarcoma, Phytoconstituents, Medicinal plants.

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INTRODUCTION

Osteosarcoma (OS) is a pleomorphic malignant tumor of bone in which the proliferating spindle cells produce osteoid or immature bone [1]. It is a deadly form of musculoskeletal cancer that most commonly causes patients to die due to pulmonary metastatic disease [2]. It arises in bone during the periods of rapid growth, and it primarily affects adolescents and young adults. While incidence is low, it predominately affects the adolescents and young adults, and if untreated it becomes fatal. OS arises most commonly in the metaphyseal region of long bones, within the medullary cavity and penetrates the cortex of the bone to involve the surrounding soft tissues [3]. The most common sites are: Femur (42% and 75% of which are in the distal femur), tibia (19% and 80% of which are in the proximal tibia), humerus (10% and 90% of which are in the proximal humerus) skull, and jaw (8%), and pelvis (8%). A number of variants of OS exist, including conventional types (osteoblastic, chondroblastic, and fibroblastic), telangiectatic, multifocal, parosteal, and periosteal [2]. Roughly 20% of patients present with clinically detectable metastatic disease. Interestingly, several human genetic disorders and familial cancer syndromes, such as Li-Fraumeni syndrome are linked to an increased risk of OS [4].

Treatment generally includes pre-operative chemotherapy, surgical resection, and post-operative chemotherapy [5]. The importance of adjuvant chemotherapy for treatment of OS is well established [1]. Despite modern treatment protocols that combine chemotherapy, surgical operation, and sometimes radiotherapy, the 5-year survival rate for sufferers recognized with OS remains at 60–70% [3]. The mainstay of therapy is surgical removal of the malignant lesion. Most often, limb-sparing (limb keeping) technique can be used to treat sufferers with this disease and thus, preserves its function. Chemotherapy is also required to deal with micrometastatic disease, which is present but frequently no longer detectable in most sufferers (~80%) on the time of analysis [2]. Agents who have shown activity against OS include doxorubicin, cisplatin, and high-dose methotrexate with leucovorin rescue (HDMTX). All sufferers received identical cumulative doses of cisplatin, doxorubicin, and HDMTX, and underwent definitive surgical resection of the primary tumor [1]. Hence, there is a real need to optimize present treatment techniques and to increase novel methods for treating OS [3]. Present modes of treatment are based on synthetic drugs/chemotherapy has limited potential, because they may be toxic and expensive and also modify the functioning of the cell signaling pathways. The available anticancer drug is often unsatisfactory due to the problem, which causes cytotoxicity to the normal cells along with cancer cells. Plants are considered as the valuable sources of bioactive compounds with antioxidant activity, which produce certain substances that have effects on living animal cells [6]. Natural drugs which are safe, low cost and powerful are needed to control the cancer development and progression. Natural products have been used for thousands of years in the management of several diseases including various types of cancer. It is also known that herbal constituents may also play a key role in cancer treatment through antitumor activity or by suppressing bioactivation of carcinogen. There are numerous medicinal plants/products which are beneficial for health and also have antitumor, antimicrobial, antibacterial, and antioxidant nature [7].

PLANTS IN THE TREATMENT OF OS

Chemotherapy is routinely used for cancer treatment. However, occasionally a number of undesired side effects and various kinds of toxicities may occur because of chemotherapeutic treatments [8]. Medicinal herbs and their derivative phytocompounds are being increasingly recognized as useful complementary treatments for different types of cancers [9]. Plant life has a long history of use in the treatment of cancer and played an important role as a source of effective anticancer agents [10]. 92 anticancer drugs commercially available before 1983 in the United States, approved worldwide between 1983 and 1994, approximately 62% can be related to natural origins [11]. India is the largest manufacturer of medicinal plants and is rightly called the "Botanical garden of the World." Considerable works had been finished on these plants, and some plant products had been marketed as anticancer drugs, based on the traditional uses and scientific reports. The World Health Organization, about three-quarters of the world's population, currently uses herbs and other forms of traditional medicines to treat diseases [12].

The rhizomes of *Anemone altaica*. Fisch. ex C. A. Mey aqueous extract (AAE), suppressed the viability of human OS (HOS) and U2OS cells in a concentration-structured manner. Flow cytometry analysis revealed that AAE significantly improved the amount of cell shrinkage (Sub-G1 fragments) in HOS and U2OS cells. Moreover, AAE increased cytosolic cytochrome c and Bax but decreased B cell lymphoma-2 (Bcl-2). The

amount of cleaved caspase-3 and poly- (adenosine diphosphate [ADP]-ribose) polymerase-1 (PARP-1) was significantly increased. AAE suppressed the growth of HOS and U2OS through the intrinsic apoptotic pathway. Thus, AAE has the great capacity as a useful therapeutic drug for HOS [13].

Aralia elata is a well-known traditional Chinese herbal medicine. MTT assays confirmed that a polysaccharide (acute eosinophilic pneumonia [AEP]-1) from the leaves of *A. elata* markedly inhibited the growth of U-2 OS cells in a dose- and time-structured fashion, suggesting a cytotoxic effect and also dose-dependently induced DNA fragmentation and induced apoptotic death in U2OS cells through the increased ratio of Bax/Bcl-2, depolarization of mitochondrial membrane ability and the release of cytochrome c from mitochondria into the cytoplasm. Moreover, AEP-1 treatment induces the activation of caspase-9 and caspase-3, as well as the cleavage of poly (ADP-ribose) polymerase (PAPR) in U-2 OS cells. Thus, those findings suggested that AEP-1 probably have an important potential as the most cancer preventive and therapeutic agent toward HOS [14].

Oldenlandia diffusa (OD) is a well-known traditional Chinese medicine, which is used to prevent and treat many disorders, particularly cancers. OD inhibited proliferation and triggered apoptosis inside the HOS MG-63 cell line in a time-dependent and dose-based manner. In addition, OD displayed inhibitory activity on MG-63 cell proliferation and invasion, and the study also showed that OD activity probably mediated with the aid of caspase activation. Consequently, the study suggested that OD might represent a novel, efficient candidate agent for OS treatment [15].

Phyllanthus urinaria is widely used as anti-inflammatory, antiviral, antibacterial, and anti-hepatotoxic medicines. The HOS Saos-2 cell line, and looked at the effect of *P. urinaria* extract (PUE) on several relevant proteases and signaling pathways. This study demonstrates that PUE, at various concentrations (from 0 to 100 mg/ml), awareness-dependently inhibited the migration/invasion capacities of Saos-2 without cytotoxic effects. Western blot analysis also confirmed that PUE inhibits phosphorylation of extracellular signal-regulated kinase (ERK)1/2 and AKT the inhibitory effects of PUE on u-PA expression in Saos-2 cells. The chromatin immunoprecipitation assay changed into reactive to the transcription protein SP-1, which became inhibited by means of PUE. It suppresses HOS Saos-2 cell invasion and migration by transcriptionally inhibiting u-PA through ERK and AKT signaling pathways. Therefore, PUE produces anti-metastatic activity in Saos-2 cells [16].

Pomegranate peels (*Punica granatum* L.), one of the most valuable by-products of the food industry, have attracted lot attention due to its wide range of bioactivities. Polysaccharide from pomegranate peels (PPP) was found to induce the arrest of G2/M segment, induce apoptosis, and inhibit the growth of U-2 OS (OS) cells in a dose-based way. Western blotting analysis showed that PPP precipitated the mitochondrial apoptotic pathway, as indicated through a growth in Bax/Bcl-2 ratios, a loss of mitochondrial membrane potential, release of cytochrome c, activation of caspase-9 and caspase-3, and cleavage of PARP in U-2 OS cells. Hence, the study suggested that PPP might be a strong chemotherapeutic agent against OS [17].

The ethanol extracts of *Potentilla chinensis* triggered early and late apoptosis within the most cancer cells. Flow cytometric analysis revealed that the extract triggered G0/G1-cell cycle arrest, which also showed significant dose-dependent and caused a significant and concentration-dependent reduction in cell migration. Hence, the extract exhibited a selective cytotoxic effect against MG-63 OS cells, in order that it serves as a novel therapeutic agent toward OS [18].

Rheum palmatum L. (Dahuang) is a wild rebus, erect, glabrous, and perennial aromatic herb. The crude extract of *R. palmatum* L. (CERP) substantially brought about cytotoxic effects in U-2 OS HOS cancer cells through S phase arrest and induce nuclear DNA damage and condensation were seemed to activate cysteine proteases of the caspase family; such as caspase-3, -8, and -9, and the induction of apoptosis to be correlated with the caspase-dependent pathway. CERP increased the levels the ranges of Bax, Bak, Bad, cyclin B, Fas, PARP, GRP78, GADD153, apoptosis-inducing factor (AIF), Endo G, Calpain-2, p21, and p27, but decreased the levels of Bcl-2, Bcl-X, X-linked inhibitor of apoptosis (XIAP), AKT, cell division cycle 25 homolog A, cyclin-dependent kinase 2 (CDK2), cyclin A, and cyclin E of U-2 OS cells. It was also observed that CERP promoted the expression of AIF, Endo G, GADD153, and cytochrome c. Those results indicate that CERP has anticancer activity on OS cells [19,20].

Sarcandra glabra (Thunb.) Nakai is a plant belonging to the own family of Chloranthaceae which exhibits anti-cancer activities. An ethyl acetate (EA) extract of *S. glabra* suppresses the proliferation of human leukemic -60 cells by means of upregulating the pro-apoptotic Bax/Bcl-2 ratio associated with cell cycle arrest. Hence, these results suggest that SGP-2 has anticancer potential in the treatment of HOS [21].

Selaginella tamariscina is a traditional medicinal plant for treatment of some advanced cancers within the orient. It possesses anti-inflammatory, antibacterial, antihypertensive, and anti-hyperglycemic activities. Zymographic and western blot analyses revealed that *S. tamariscina* inhibited the matrix metalloproteinase (MMP)-2 and MMP-9 enzyme activity, as well as protein expression. Western blot analysis also showed that it possesses an antimetastatic activity in OS cells by way of downregulating MMP-2 and MMP-9 secretions and growing tissue inhibitor of metallopeptidases (TIMP)-1 and TIMP-2 expressions through p38 and AKT-structured pathways and may be a powerful candidate to expand a preventive agent for OS metastasis [22].

Viscum album L. extracts are widespread in complementary most cancers medicine in Europe and used in several cancer types. *V. album* L. includes a large number of chemically special substances: Lectins, triterpenic acids, viscotoxins, phenolic acids, flavonoids, oligo- and polysaccharides. A whole mistletoe extract Viscum TT re-created by combining an aqueous extract (viscum) and a triterpene (TT) extract was tested for its anticancer ability in OS. The whole mistletoe extract Viscum TT led to strong inhibition of proliferation and synergistic apoptosis induction in OS cells. In the investigations of the mechanism of action, inhibitors of apoptosis which includes XIAP, BIRC5, and CLSPN showed a clear downregulation after Viscum TT treatment. In addition, coremedy with doxorubicin, etoposide, and ifosfamide further enhanced apoptosis induction, also synergistically. Hence, Viscum TT may represent a promising adjuvant therapy in pediatric OS [23].

PHYTOCONSTITUENTS IN THE TREATMENT OF OS

Natural products are commonly safe, effective, and less expensive substitutes of anticancer chemotherapeutics [7]. Natural therapies, such as the use of plant-derived products in most cancer treatment, can also reduce adverse side effects [8]. Several reports describe that the anticancer activity of medicinal plants is due to the presence of antioxidants in them. In fact, the medicinal plants are easily available, cheaper, and possess no toxicity as compared to the modern (allopathic) drugs. Secondary metabolites such as polyphenols, terpenes, and alkaloids have been suggested to possess antimutagenic and anticancer properties in many research [12]. Plant-derived compounds had been an important source of several clinically useful anticancer agents. Natural phenolic compounds play an important role in cancer prevention and treatment. Various bioactivities of phenolic compounds are responsible for their chemopreventive properties (e.g., antioxidant, anticarcinogenic, or antimutagenic, and anti-inflammatory effects) [24].

Aloperine (ALO) is a novel alkaloid drug extracted from *S. alopecuroides* and exerts anti-inflammatory, anti-allergenic, antitumor, and antiviral effects. DAPI assays and flow cytometry showed that ALO induced apoptosis of OS cells. Moreover, the outcomes of western blotting and quantitative real-time polymerase chain reaction indicated that ALO upregulated protein and mRNA of Bax and cleaved caspase-3, while downregulated Bcl-2. Besides, ALO inhibited the invasion of MG-63 and

U2OS cells through suppression of PI3K/AKT signaling pathway on OS cells [25].

Astragaloside IV (3-O-beta-D-xylopyranosyl-6-O-beta-D-glucopyranosyl-cycloastragenol), a potent ingredient extracted from Astragalus membranaceus Bunge. It suppressed cell proliferation and enhanced chemosensitivity in OS cell lines and xenograft. Caspase-dependent Fas/FasL signaling turned into worried in cisplatin brought on apoptosis, which becomes greater by Astragaloside IV. It indicated that Astragaloside IV might be a promising therapeutic agent for OS treatment [26].

Berberine (BBR), an isoquinoline alkaloid component aspect in several Chinese herbs including Huang lian, that have antimicrobial, anti-inflammatory, anti-diabetic, and anti-angiogenesis, and cholesterol reducing effects. The proliferation effect of U20S changed into examined by MTT assay and the percentage of apoptotic cells was determined by flow cytometric analysis. This treatment caused dose-structured inhibiting proliferation and inducing apoptosis of U20S cell through inhibiting the PI3K/AKT signaling pathway activation results in upregulating the expression of Bax, and PARP and downregulating the expression of Bcl-2 and caspase3. Thus, the study supports that BBR might be a good alternative therapy for treatment of OS within the clinical practice [27].

Columbamine (COL), an active component of the herb *Coptis chinensis*, inhibited the proliferation and neovascularization of metastatic OS U2OS cells. It's effectively suppressed U2OS cell proliferation *in vitro* with an inhibitory concentration 50 of 21.31±0.38 μM, with low cytotoxicity. Mechanistic studies revealed that COL induces cell cycle arrest at the G2/M transition that is related to attenuating CDK6 gene expression and diminishing STAT3 phosphorylation and did not promote U2OS cell apoptosis at any of the dosages tested. In addition, COL inhibited U2OS cell-mediated neovascularization, which was observed by the downregulation of MMP 2 expression and reduction of cell migration, adhesion, and invasion. Hence, the study showed that COL exerts anti-proliferative and anti-vasculogenic effects on metastatic HOS U2OS cells with low toxicity and used as a potential anti-OS and anticancer drug [28].

Coptisine, an active component of the herb *Coptidis rhizoma*, markedly inhibited aggressive OS cell proliferation. Coptisine induced cell cycle arrest at the G0/G1 phase through downregulation of CDK4 and cyclin D1 expression and effectively suppressed tumor growth. Coptisine appreciably impeded OS cell migration, invasion, and capillary-such as network formation by decreasing the expression of VE-cadherin, integrin-3, and diminishing STAT3 phosphorylation. Thus, these data suggest that coptisine exerts a strong anti- OS effect with very low toxicity and is an ability anti-OS drug candidate [29].

Corosolic acid (CRA), a pentacyclic TT isolated from medicinal herbs, consisting of *Schisandra chinensis*, *Lagerstroemia speciosa*, *Orthosi phonstamineus,* and *Eriobotrya japonica.* It suppresses the growth of various types of tumors, the inhibitory effect of CRA in OS MG-63 cells was investigated, and the results revealed that it significantly inhibited the viability of MG-63 cells in a dose- and time-established way. It was observed that the apoptosis of MG-63 cells induced by CRA was closely related to activation of caspase-3 and caspase-9, loss of mitochondrial membrane ability. Therefore, those results indicated that CRA should induce apoptosis of OS cells through activating the mitochondrial pathway [30].

Cucurbitacin E (CuE), an amazing member of triterpenoid family isolated from plants, has been confirmed as an antitumor agent using inhibiting proliferation, migration, and metastasis in diverse cancer. The present study aimed to test whether CuE could inhibit increase and invasion of OS cells and monitoring its underlying molecular mechanism. After various concentrations of CuE treatment, the anti-proliferative effect of CuE became assessed using the cell counting Kit-8 assay. Cell cycle distribution was analyzed by propidium iodide staining. CuE inhibited cell growth and invasion, induced a cell cycle arrest and triggered apoptosis and modulated the expression of cell growth, cell cycle, and cell apoptosis regulators. CuE inhibited the PI3K/AKT/mTOR pathway and epithelial-mesenchymal transition, which suppressed the invasion and metastasis of OS. Our study demonstrated that CuE could inhibit OS tumor growth and invasion through inhibiting the PI3K/AKT/mTOR signaling pathway. Our findings suggest that CuE can be considered to be a promising anticancer agent for OS [31].

Curcumin, an active factor derived from the rhizome of the plant, *Curcuma longa*, has antioxidant, anti-inflammatory, and anticancer properties. Curcumin confirmed the growth of inhibitory effects on U2OS cells in a dose- and time-structured way, inducing significant G1 arrest and apoptosis in U2OS cells. This curcumin-induced apoptosis in U2OS cells was accompanied by upregulation of Bax, Bak, and p-Bad and downregulation of Bcl-2, however, no effect on the levels of Bcl-XL or Bad proteins were noted. Moreover, curcumin treatment resulted in a significant reduction of mitochondrial membrane ability and increase in the concentrations of mitochondrial cytochrome C and caspase-3 [32].

5,7dihydroxy3',4',6trimethoxy flavone, normally known as eupatilin, is extracted from *Artemisia asiatica* Nakai and consists of pharmacologically active ingredients and has been established to exert anticancer, antioxidative, and anti-inflammatory effects. The experimental results revealed that eupatilin inhibited U2-OS cell growth in a concentration-based manner and induced G2/M phase cell cycle arrest and apoptosis. Western blot analysis indicated that it was able to cause the mitochondrial apoptotic pathway, by the enhanced Bax/Bcl-2 ratio, decrease in mitochondrial membrane capability, the release of cytochrome *c*, caspase-3 and -9 activation and PAPR cleavage detected in the U2-OS cells. Hence, eupatilin may, therefore, represent a novel anticancer drug for use in the treatment of OS [33].

The polyphenolic fraction of green tea (green tea polyphenols [GTP]) has been shown to have antitumor effects on various malignant cell lines to inhibit growth and induce apoptosis in HOS SAOS-2 cells. Treatment of SAOS-2 cells with GTP (20–60 μg/ml) resulted in reduced cell proliferation and induction of apoptosis, which correlated with decreased nuclear DNA binding of nuclear factor kappa (NF-κB)/p65 and lowering of NF-κB/p65 and p50 levels in the cytoplasm and nucleus. This treatment of cells has reduced IκB-α phosphorylation but had no effect on its protein expression. Furthermore, this treatment resulted in the inhibition of IκK-α and IκK-β, the upstream kinases that phosphorylate IκB-α. The increase in apoptosis in SAOS-2 cells was accompanied by a decrease in the protein expression of Bcl-2 and a concomitant increase in the levels of Bax. This treatment of SAOS-2 cells also resulted in significant activation of caspases as evident by increased levels of cleaved caspase-3 and caspase-8 in these cells. Hence, these studies indicate that GTP is a candidate therapeutic for OS [34].

Plumbagin (5-hydroxy-2-methyl-1,4-naphtho quinone), a yellow pigment is natural occurring quinonoid constituent of *Plumbago zeylanica* L. (Plumbaginaceae). It exhibits various biological activities such as antiatherogenic, anticancer, anti-proliferative, cardiotonic, chemoprevention, hepatoprotective, and neuroprotective effects. It also exhibits pro-apoptotic and radio-sensitizing activities in distinct tumor cells. It has significantly induced growth inhibition against OS MG-63 cells, primarily by S-phase cell cycle arrest which is confirmed by the downregulation of cyclin A and CDK2 protein levels determined by western blot analysis. It was also found that plumbagin has brought out the DNA damage in MG-63 cells, subsequently initiating the arrest in S-phase, which is evident by the upregulation of phosphorylated p53 and histone. Thus, the study suggested that it to be a potential compound in treatment in opposition to the malignant HOS [35].

Polyphyllin I (PPI) is an ethanol extraction from *Paris polyphylla Smith var. yunnanensis.* PPI inhibited viability, proliferation, migration, and invasion of MG-63, Saos-2, and U-2 OS OS cells, and led to S-phase arrest

and apoptosis. Exposure of OS cells to PPI triggered inactivation of the intrinsic nuclear component κB (NF-κB) and activation of unfolded protein response/endoplasmic reticulum stress signaling cascade in OS cells, followed by downregulation of anti-apoptotic proteins, with up regulation of pro-apoptotic proteins. Thus, it can be used for OS treatment [36].

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a natural polyphenol compound, widely found in plants such as grape skin, raspberries, mulberries, cranberries, blueberries, and peanuts which have been widely reported as an anticancer molecule. It possesses antioxidative, anti-inflammatory, anti-aging, antiviral, and anticancer properties. It also exhibits multiple tumor-suppressing activities in bone cancer by affecting a series of critical events and has been found very effective in inhibiting proliferation in HOS cells by means attenuating the β-catenin signaling and also inducing apoptosis [37].

Sodium selenite (Na2SeO3, SSE) is an inorganic Se compound that is widely used in most cancers chemoprevention studies. SSE also inhibited cell viability through apoptosis, as evidenced by the formation of apoptotic bodies, generation of reactive oxygen species (ROS), and accumulation of cells at some point of the advanced phase of apoptosis. SSE-triggered apoptosis correlated with the activation of CASP 3, downregulation of Bcl-2, and upregulation of P53, and PTEN in U2OS cells. Thus, the studies state that SSE is a promising anticancer compound that would be used in future therapies for OS [38].

Solamargine (SM), a steroidal glycoalkaloid isolated from the Chinese herb *Solanum incanum*. It appreciably reduced cell viability and induced apoptosis in OS U2OS cell. Thus, increases the mRNA and protein expressions of p53 and Bax. The expression of Bcl-2 (an anti-apoptotic protein) was also reduced. Furthermore, SM triggered mitochondrial translocation of p53, loss of mitochondrial membrane capacity, cytochrome c release activation of caspase-9 and -3, and induced apoptosis. Therefore, the study suggested that SM is a powerful inducer of apoptosis through p53 activation and may use as a potential therapeutic agent for OS [39].

Shikonin (SK), an active constituent extracted from a Chinese medicinal herb, *Lithospermum erythrorhizon*, has been shown to exert antitumor effects. Western blot analysis revealed increased expression levels of Bax, caspase-3, caspase-8, and PARP in U2OS and MG63 cells with the treatment of SK and ADM. Flow cytometric analysis showed that the combined treatment of SK and ADM significantly precipitated apoptosis probably by inducing caspase-3 and caspase-8 dependent apoptosis in the OS cells and maybe ability enhancer in the treatment of drug-resistant primary OS [40].

Tanshinone IIA (Tan IIA) is an active ingredient extracted from the widely used Danshen root (*Salvia miltiorrhiza* Bunge), a traditional Chinese medicine. It inhibits proliferation and induces apoptosis in the HOS cell line MG-63 in a time-dependent and dose-based way. In addition, it displays inhibitory activity on OS cell migration and invasion. Mechanistic studies show that Tan IIA activity is mediated by caspase activation and it was also shown to reduce anti-apoptotic Bcl-2, MMP-2, and MMP-9 levels, whereas it increased proapoptotic Bax levels. These data suggest that Tan IIA may be a novel, efficient candidate agent for OS treatment [41].

Thymoquinone (TQ), the predominant bioactive constituent derived from the medicinal spice *Nigella sativa* (also known as black cumin), it caused a higher percentage of growth inhibition and apoptosis within the HOS cell line SaOS-2 compared to that of control in a dose-dependent manner. The EMSA assay and western blot evaluation found that the TQ significantly downregulated NF-κB DNA-binding activity, XIAP, surviving, and VEGF in SaOS-2 cells, and inhibits tumor angiogenesis and tumor growth through suppressing NF-κB and its regulated molecules on SaOS-2 cells [42].

Withaferin A (WA) is a well-known steroidal lactone of the medicinally important plant, *Withania somnifera.* They are reported to possess anticancer properties. Flow cytometric analysis revealed that WA induced cell cycle arrest at the G2/M phase, which was associated with the inhibition of cyclin B1, cyclin A, CDK2, and p-Cdc2 (Tyr15) expression, an increase in the levels of p-Chk1 (Ser345) and p-Chk2 (Thr68) and attenuation of the expression levels of G2/M checkpoint proteins. Hence, the results revealed that WA exhibited potent anti-proliferative effects on the HOS cell lines, MG-63, and U2OS [43].

Wogonin (5,7-dihydroxy-8-methoxyflavone) is a flavone constituent of *Scutellaria baicalensis* with various beneficial biological activities, and it has been shown to have tumor healing ability *in vitro* and *in vivo*. Flow cytometric assay indicated that it precipitated sub-G_1 phase (apoptosis) and increased caspase-3 activity in examined cells. It also brought about apoptosis in U-2 OS cells was also confirmed by DAPI staining. Furthermore, results from Western blotting indicated that it extended the levels of Bad, Bax, cytochrome *c*, cleaved caspase-9, cleaved caspase-3, AIF, Endo G, Fas/CD95, caspase-8, GADD153, GRP78, ATF-6α, calpain 1, calpain 2, and caspase-4 then leading to cell apoptosis. Thus, the study suggests that wogonin could be developed for the treatment of HOS in the future [44].

CONCLUSION

For the betterment, while treating cancer with the drugs, it is more effective when treated with the medicinal plants. Thus, the above review replenishes the usage of the medicinal herbs for especially the treatment of bone cancer, and it has the potential access to cancer treatment.

AUTHOR'S CONTRIBUTION

Sivakumar Ramalingam has provided the design, intellectual content, innovations, and protocol for the review article. VigneshPichaiyan has majorly performed the review. Sasikala Mariyappan and Renuka Saravanan have a minor role in performing the review, and sincerely authored the article.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

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