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Clinical Impact of Medicinal Herbs in the Treatment of Osteosarcoma

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Abstract

Osteosarcoma is a type of bone cancer that initiates in the cells that establish bones. This mainly occurs in the long bones that make up the arms and legs. In present days, osteosarcoma is treated with many advanced drugs which have diverse side effects when compared to medicinal herbs and its phytoconstituents. This review mainly deals with different medicinal plants and its phytoconstituents used in the treatment of bone cancer. The review study showed that phytoconstituents of the herbs inhibited the growth of osteosarcoma cell by targeting proliferation and apoptosis. Thus, the findings might be useful for the development of new treatment strategies and their role in antitumor, effectiveness in osteosarcoma need to be explored further.

Keywords: Osteosarcoma, Medicinal Herbs, Phytoconstituents, Proliferation, Apoptosis

Introduction

Osteosarcoma (OS) is a type of cancer that starts in the bone. Osteosarcoma is also known as osteogenic sarcoma. It mostly occurs in children and young adults, but also can develop at any age group. Osteosarcoma 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. Most common sites where OS start are: femur, tibia, humerus, skull, jaw and pelvis [1]. OS can be classified based on the grade as high, intermediate and

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low. These grades mainly tell about the growth and spread of cancer to the other parts of the body. The type of bone tumors can be either malignant or benign [2]. Treatment includes chemotherapy, surgery and post-operative chemotherapy. Present mode of treatments are based on the drugs, which are expensive, causes cytotoxicity and may also modify the cell signaling pathway function [3]. Plants are considered as the valuable sources of bioactive compounds with antioxidant, antibacterial, antitumor and antimicrobial activities. These natural drugs are safe, cost effective and treatment can control the cancer development and progression. Natural products have been used for thousands of years in the management of several diseases including different types of cancer [4].

Herbs used in Osteosarcoma treatment

Medicinal herbs and their derivative phytoconstituents are being increasingly recognized as useful complementary treatments for different types of cancer [5]. India is the second largest manufacturer of medicinal plants. Some plant products had been marketed as anticancer drugs, based on the traditional uses and scientific reports. According to World Health Organization, about three-quarters of the world's population, currently uses herbs and other forms of traditional medicines to treat diseases [6].

Interestingly, Madhuri et al, and her research team reported that *Saussurea lappa* (Kuth root) are used in various traditional system of medicine for its anti-ulcer, anti-convulsant, anti-cancer, hepatoprotective, anti-arthritic and anti-viral activities. They reported the phytoconstituents isolated from this plant, such as costunolide, isodihydrocostunolide and cynaropicrin were proven to be bioactive and potential source for developing new molecules. Thus, these results proved that there are significant activities for new drug discovery [7]. Jin X et al, confirmed that costunolide limited the transcriptional activity of STAT3 and the phospho-STAT3 (Try-705) expression level. Costunolide suppressed downstream STAT3 target gene expression and subdued the growth and metastasis of osteosarcoma in vitro and in vivo. Thus, the study suggested that costunolide may serve as a possible intercession in osteosarcoma therapy [8].

Recently, Lin H et al., studied about *Physalis alkekengi* (winter cherry) often recognized as Chinese lantern, has a phytocompound Physakengose G (PG) which has an anticarcinogenic property. Their results showed that PG can inhibit the cell proliferation and induce apoptosis in human osteosarcoma cells. PG treatment blocked EGFR phophorylation and suppressed epidermal growth factor (EGF)-induced activation of downstream signaling molecules such as AKT and mTOR. PG treatment also resulted in lysosome dysfunction by altering lysosome acidification and LAMP1 levels, which led to autophagosome accumulation and autophagic flux inhibition. Hence, the findings revealed that PG has the potential role in the treatment of osetosarcoma [9].

However, Jurikova et al and team reported that *Vaccinium oxycoccos* (European cranberry)

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has a rich polyphenolic compounds such as anthocyanins, flavonols, ursolic acid which have antibacterial, antifungal and anticancer activities [10]. Chia-Cieh Wu et al, found that treatment with Ursolicacid (UA) suppressed the viability of human osteosarcoma MG-63 cells and induced cell cycle arrest at sub-G_1 and G2/M phases. UA induced apoptosis was significantly abolished in MG-63 cells that had been pretreated with inhibitors of caspase 3, 8 and 9 and ERK1/2. Protein analysis of mitogen-activated protein kinase (MAPK) showed an increase in activated ERK1/2 and p38 MAPK in UA treated MG-63 cells. Thus, the study provided evidence by demonstrating that UA can mediate caspase-dependent and ERK1/2 MAPK-associated apoptosis in osteosarcoma MG-63 cells [11]. Figure 1 represents the herbs used in the treatment of osteosarcoma.

Furthermore, *Epimedium koreanum* (Barrenwort) has a flavonoid compound Icariside which has many functions such as strengthened cardiovascular function, endocrine control, immunomodulatory function and anti-cancer activities. Zhang C et al, evaluated the effect of icariside on aberrant energy homeostasis. The reduction of glycolysis and mRNA translation in U2OS (osteosarcoma), S180 (fibrosarcoma) and SW1535 (chondrosarcoma) cells were observed. These cells interrupted the anomalous energy homeostasis of the sarcoma cells by blocking the mTORC1-4E-BP1 axis. Thus, the data provided a novel mechanism of Icariside, inhibited cell proliferation in sarcoma cells [12].

In addition, *Reseda luteola* (Dyer's weed) has a phytocompound luteolin (LUT). LUT is a flavone which has anti-carcinogenic property. Baoliang Zhang et al, demonstrated that LUT induced autophagy in U2OS cells which acted as an enhancers to sensitize doxorubicin (DOX) - mediated autophagy signaling. The combined treatment of LUT and DOX greatly decreased the growth of U2OS, showed synergistic cytotoxicity. Hence, these results showed that LUT along with DOX can be used in the treatment of osteosarcoma (13). Yonghong Wang et al, studied LUT blocked the spread of osteosarcoma cells and triggered dose-dependent apoptosis by down-regulation of the expression of BCL-2, Caspase-3 and Survivin protein levels and upregulation of the BAX protein level expression. Therefore, luteolin could be used as a natural herbal treatment for osteosarcoma management [14].

Recently, Chang Chang et al, reported that the rhizome of *Anemone altaica* aqueous extract (AAE), suppressed the viability of HOS and U2OS cells in a concentration-dependent manner. The results showed that AAE significantly increased the amount of cell shrinkage (Sub-G1 fragements) in HOS and U2OS cells. However, 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 [ATP] ribose) polymerase-1 (PARP-1) was significantly increased. Thus, AAE has the ability as a useful therapeutic drug for treating human osteosarcoma [15].

Ko-Hsiu Lu et al, studied about *Phyllanthus urinaria* (Gripeweed) which are rich in bioactive compounds such as tannins, phenylpropanoids, terpenoids and phenolic compounds.

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These bioactive compounds widely have anti-inflammatory, anti-viral, anti-bacterial, anti-hepatotoxic and anti-cancer properties. They investigated the effect of *P.urinaria* extract (PUE) on cell viability, invasion and migration in the human osteosarcoma Saos-2 cell line. Their study demonstrated that PUE at different concentrations inhibited the migration/invasion capacities of Saos-2 without cytotoxic effects. Analysis confirmed that PUE inhibited phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 and AKT the inhibitory effects of PUE on urokinase-type plasminogen activator (u-PA) expression in Saos-2 cells. Thus, the study confirmed that PUE can produce anti-metastatic activity in Saos-2 cells [16].

Wu B et al, studied about *Agaricus blazei* (Mushroom) which is used to treat many disease like hepatitis, atherosclerosis, hyperlipidemia, diabetes and cancers. In this study, they have isolated Agaricusblazei polysaccharide (ABP-Ia) from the fruiting bodies of *Agaricus blazei*. ABP-Ia is a heteropolysaccharide fraction consisting of mannose and glucose with trace amount of rhamnose. The effect of ABP-Ia in three different concentrations on the cell growth and apoptosis was evaluated in osteosarcoma cell lines HOS and a normal human osteoblast cell line NHOst. ABP-Ia showed significant inhibitory effect against the growth of HOS cells, and a mild cytotoxicity to the HOS cells mediated by ABP-Ia was also observed. The results showed that ABP-Ia substantially induced apoptosis in a dose-dependent HOS cells. Thus we can conclude that ABP-Ia had an inhibitory effect on the growth of HOS cells through induction of apoptosis, with a minor toxicity to normal human osteoblast cell [17].

Furthermore, Song-Lin Shi et al, postulated that ginsenoside Rg1, cinnamic acid and tanshinone IIA were effective anticancer and antioxidant phytoconstituents of traditional Chinese herbal medicine of *Panax ginseng* (Ginseng), *Radix scrophulariae* (Xuanshen) and *Salvia mitiorrhiza* (Danshen), respectively. Ginsenoside Rg1, cinnamic acid, and tanshinone IIA treatment of osteosarcoma MG-63 cells decreased nucleophosmin expression in nuclear matrix and induced nucleophosmin translocation from nucleolus to nucleoplasm and cytoplasm, a process of dedifferentiating transformed cells. Ginsenoside Rg1, tanshinone IIA and cinnamic acid also regulated the oncogenes c-fos, c-cmyc and tumor suppressor genes, p53, Rb. Hence, the phytoconstituents could serve as protective and therapeutic agents against osteosarcoma treatment [18]. Thus, these herbs may be used as tremendous importance in the treatment of osteosarcoma.

Conclusion and future development

From centuries various plants have been used as medicines and therapeutics in human. Over the last few decades researchers are showing great interest and efforts in clinical studies and trials on their effects, usage, and the development of future medicines of herbs and their phytoconstituents as anti-cancer and chemoprevention agents. Anticancer drugs used in chemotherapy are often associated with severe side effects. Hence, developing a potential alternative with herbal compounds with less adverse effects has gained tremendous importance. Medicinal plants and its

phytoconstituents need to be progressed into the human clinical trial stage to further validate their effectiveness as alternate chemotherapeutic agents in the management of osteosarcoma. Clinical trials are still limited and need to be actively pursued. Many traditional remedies herb formulations, systematic and standardized research protocols need to be studied. At present, it is necessary for scientists and clinicians to actively consider how to create improve, do clinical survey and trial studies to discover and develop new phytomedicines for the cure of osteosarcoma and many other diseases.

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Author contributions:

Dhanraj Ganapathy: Researching data for article

Durairaj Sekar: review/ editing of manuscript before submission

Auxzilia Preethi: Conclusion and perspective writing

Rajesh Kumar S: Figure

Conflict of interest:

The authors declare that they have no conflict of interest.

Glossary:

Cancer: Cancer is a disease in which abnormal and uncontrollable growth of the cells that spread in different body tissues.

Osteosarcoma: Osteosarcoma is a type of bone cancer that begins in the cells that form bones.

Phytoconstituents: Phytoconstituents are chemical compounds that occur naturally in plants.

Anti-tumor: they inhibit or prevent the formation or growth of tumors.