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**The anti-tumor potential of some naturally active substances
isolated from Chinese medicinal herbs in Osteosarcoma**

**Jing-nan Shen, Jun-qiang Yin, Zhi-qiang Zhao, Xian-biao Xie, Jin Wang,
Chang-ye Zou, Qing-lian Tang, Gang Huang**

**Authors' Affiliations: Department of Musculoskeletal Oncology, First Affiliated Hospital, Sun
Yat-Sen University, Guangzhou 510080, China**

Communication address: 58# zhongshan 2 road, Guangzhou 510080, P.R. China

Phone: +8618802006688

Abstract:

Background: Numerous osteosarcoma patients either are not sensitive to chemotherapy or develop drug resistance to current chemotherapy regimens. Some natural substances isolated from Chinese medicinal herbs have antitumor properties without obvious side effects. Therefore, developing more potentially useful therapeutic agents from natural origins could be beneficial in osteosarcoma.

Purposes: To investigate the in vitro and in vivo anti-osteosarcoma effects of some natural substances isolated from Chinese medicinal herbs and the molecular mechanism of action.

Materials and Methods: Dihydromyricetin (DHM) is derived from *Ampelopsis grossedentata*; Cinobufagin is a major component of cinobufacini (huachansu); Oridonin is a naturally active substance isolated from *Rabdosia rubescens*; Grifolin is from the edible bodies of the mushroom *Albatrellus confluens*; Quercetin is the most abundant molecule in the extensive class of polyphenolic flavonoids; Bufalin is major component of "Chan Su" obtained from the skin and parotid venom glands of toads; Flow cytometry were used to determine compound effects on cell cycle distribution and apoptosis; MTT assay and Clonogenic assay were performed to detect the proliferation; Real time PCR was used to analyze mRNA expression; The proteome profiler array (R&D system, USA), Two-dimensional gel electrophoresis (2DE) and immunoblots were performed to study phosphorylation signature of whole cell proteins and total protein steady state levels; Animal study was used to observe the antitumor potential in vivo.

Results: DHM caused DNA damage, induced apoptosis and decreased sphereformation capability in osteosarcoma cells. Mechanistic analysis showed that the anti-tumor potential is correlated with P38 MAPK and AMPK α / GSK-3 β /Sox2 signaling pathway; Cinobufagin induced apoptosis in cultured osteosarcoma cells involving in the GSK-3 β /NF- κ B pathway; Oridonin induced osteosarcoma cells apoptosis through decreasing the phosphorylation of AKT and ERK, and increasing the phosphorylation P38 MAPK and JNK; Grifolin induces apoptosis via inhibition of PI3K/AKT signaling pathway in human osteosarcoma cells; Quercetin induces apoptosis in the methotrexate-resistant osteosarcoma cell line U2OS/MTX300 via mitochondrial dysfunction and dephosphorylation of Akt; Bufalin exerted potent anti-osteosarcoma effects in vitro and in vivo, even in MTX resistant osteosarcoma cells by down-regulation of Heat shock protein 27.

Conclusions: These results demonstrated that some naturally active substances isolated from Chinese medicinal herbs may be promising agents for the treatment of osteosarcoma.