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Abstract

Euphorbia helioscopia L. exhibits promising therapeutic effects on hemangioendothelioma and melanoma through angiogenesis inhibition

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Background: Euphorbia helioscopia L (EHL), a widely used medicinal plant in traditional Chinese medicine, has shown promising effects on certain cancers. However, previous studies on EHL did not elucidate the underlying molecular mechanisms. Herein, for the first time, we present the strong therapeutic potential of EHL extracts on malignant hemangioendothelioma, a rare type of vascular tumor.

Purpose: To investigate the potential anti-tumor mechanism of extracts of EHL on hemangioendothelioma and melanoma.

Methods: The dried stems and leaves of EHL were extracted with Ethyl Acetate and n-Butyl alcohol, yielding two crude extracts Ethyl Acetate fraction (EA) and n-Butyl alcohol fraction (Bu). EA and Bu were prepared to assess the potential mechanism by assays for cell proliferation, cell cycle, apoptosis, colony formation, tube formation, cellular metabolic activity, reactive oxygen species (ROS), N-Acetylcysteine (NAC) antagonism, RNA expression and western blot. To further confirm the anti-tumor effect of EHL in vivo, we established hemangioendothelioma and melanoma tumor-bearing mouse model using nude mice and administered with EA and Bu, tracked alterations in tumor volume and survival rate. Furthermore, tissue samples were obtained for histological, protein, and genetic investigations.

Results: We demonstrate that the injection of EA and Bu, significantly inhibits tumor growth and prolongs the lifespan of tumor-bearing mice. Bu treatment exhibited a remarkable 33 % healing effect on the primary hemangioendothelioma tumor, bringing the survival rate to a level comparable to that of healthy mice. Mechanically, both EA and Bu impair respiratory chain complexes, leading to mitochondrial dysfunction and accumulation of reactive oxygen species (ROS), resulting in DNA damage, cell apoptosis, and finally blocked angiogenesis. While EA demonstrates robust inhibitory effects on cancer cell growth and a broader impact on metabolism in vitro, the in vivo effect of Bu surpasses that of EA in terms of strength. EA and Bu also exhibit potent anti-tumor effects on a primary melanoma model by inhibiting angiogenesis. Importantly, when compared to other compounds used in the treatment of hemangioendothelioma, EA and Bu demonstrate more profound anti-tumor effects.

Conclusion: For the first time, our findings reveal that EHL extracts, especially the high polarity compounds, exhibit potent anti-tumor effects by targeting cellular metabolism, specifically through the inhibition of mitochondria-related metabolic activities. This leads to the accumulation of ROS and effectively suppresses abnormal angiogenesis.

Keywords: Angiogenesis; Electron transport chain complex; Euphorbia helioscopia extracts; Hemangioendothelioma; Mitochondrial function; ROS.

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