

## MASTER'S THESIS

### A Study on Anti-melanoma Effects and Mechanisms of Dioscin in Combination with Oxymatrine

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## ABSTRACT

Melanoma is one of the most lethal cancers. Its pathogenesis is not fully understood. High expression of *HID1* is positively correlated with survival time of melanoma patients, although the role of *HID1* in melanoma development has not been characterized. Traditional Chinese medicine doctors regard “dampness and toxin” as major causes of melanoma. Therefore, “dispelling dampness and resolving toxin” is the main strategy for treating melanoma. Dioscin, a natural steroid saponin, is an active component of Chinese medicinal herbs used to dispel dampness and resolve toxin. It has potent anti-melanoma effects. While, it was reported to induce hepatotoxicity, which restricts its clinical application. Another Chinese medicinal herb-derived compound oxymatrine, a quinolizidine alkaloid, is endowed with hepatoprotective action and has anti-melanoma effects. Therefore, the combination of dioscin and oxymatrine (Dio-plus-Oxy) is expected to be a safe and effective modality for melanoma treatment. In this study, we aimed to investigate the anti-melanoma effects and mechanisms of action of Dio-plus-Oxy.

In cell assays, Dio-plus-Oxy exerted synergistic effects in reducing melanoma cell viability. Moreover, the combination inhibited migration and induced apoptosis in melanoma cells. In normal skin cells, the combination exhibited less toxicity than in melanoma cells. In animal assays, intragastric administration of Dio-plus-Oxy suppressed melanoma growth without overt toxicity in mice. In addition, Dio-plus-Oxy decreased regulatory T cells, and increased dendritic cells (DCs) and cytotoxic T lymphocytes (CTLs, i.e., CD8<sup>+</sup> T cells) in mouse tumor tissues; and increased DCs in spleens of the melanoma-bearing mice. These findings suggest that remodeling tumor microenvironment is one of the anti-melanoma mechanisms of Dio-plus-Oxy. RNA sequencing analyses revealed that the expression of *HID1* gene in melanoma cells was

significantly upregulated by Dio-plus-Oxy. This result was confirmed by RT-qPCR. Silencing HID1 reduced Dio-plus-Oxy-induced melanoma cell apoptosis, indicating that HID1 upregulation is another mechanism underlying the anti-melanoma effects of Dio-plus-Oxy.

In summary, Dio-plus-Oxy has anti-melanoma effects in cell and mouse models. Reprogramming tumor microenvironment and upregulating HID1 expression contribute to the anti-melanoma activity of Dio-plus-Oxy. This study suggests that Dio-plus-Oxy has potential to be developed into a novel medication for treating melanoma.

**Keywords:** melanoma; dioscin; oxymatrine; HID1; tumor microenvironment

