**Bitter Melon’s Sweet Promise: Role in Oral Cancer Therapy**

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Head and neck cancer (HNC) is the sixth most prevalent cancer in the world, and oral squamous cell carcinoma (OSCC)/oral cancer is the most common subtype with 5‐year survival rate around 50%. Oral cancer is often associated with tobacco use, excessive alcohol consumption, betel quid chewing and human papillomavirus (HPV) infection. However, HPV infection is predicted to decline in the future due to successful vaccination campaigns and better prognosis. In other tumor sites, precision medicine has leveraged our understanding of tumors’ biology to create highly effective therapies. However, breakthroughs have been elusive due to significant limitations in our understanding of oral cancer’s unique biology. Current clinical outcomes are insufficiently robust, despite the development of various therapies, and new effective approaches are an unmet need. Programmed cell death receptor monoclonal antibodies nivolumab and pembrolizumab were approved in 2016 to treat the advanced and therapy resistance cases with limited success due to resistance and adverse side effects. Natural products have anti-cancer properties, particularly in the regulation of glycolysis and lipid metabolism, and the activation of cell death. Active ingredients derived from natural products are drawing attention as an alternative approach for anti-cancer therapy. Thus, there is a critical clinical need to better understand the disease process, and to identify novel targets to improve therapeutic strategies for successfully managing this disease. The goal of this study was to define how bitter melon or momordicine-I exerts its anticancer activity and underlying mechanism. I will briefly cover the introduction of bitter melon, its effect on oral cancer cells and immune system. I will talk about the active component momordicine-I (M-I) of bitter melon and discuss the effect of momordicine-I (M-I) on metabolic pathways in oral cancer cells and mouse models. I will also discuss the effect of M-I in microenvironment in OSCC tumor bearing mice.

Our study is the first to demonstrate the multifaceted effects of bitter melon and M-I in reprogramming glucose and lipid metabolism, inducing autophagy, disrupting mitochondrial function in oral cancer cells, and reducing tumor volume, which highlights its potential as a therapeutic agent targeting metabolic vulnerabilities in cancer. The metabolic changes in M-I treated OSCC cells could affect the tumor microenvironment, influencing interactions with stromal cells and the immune system. The lipidomic alterations induced by M-I treatment in OSCC cells, coupled with the observed mitochondrial dysfunction, underscore the potential of M-I as a multifaceted therapeutic agent. Our studies provide new insights into the heterogeneous immune cell populations, their functional phenotypes within the tumor microenvironment (TME), and how M-I affects this immune landscape, conferring antitumor effects to OSCC in syngeneic mouse models. This study has also some limitations. Metabolic rewiring unquestionably affects cancer cell proliferation, and the translation of metabolic reprogramming into clinical care will be beneficial, however, dependency on metabolic pathways is not universal for all cancer types. M-I treatment causes a distinct transcriptomic signature in the TME, which involves immunomodulation that disrupts tumor-promoting M2 TAMs and B-cell populations, thus restoring effective immunosurveillance over tumor cells. However, other signaling pathways in tumor and stromal cells may also be involved for regression of tumors following M-I treatment and needs further investigation. Together our findings open new avenues for the development of targeted therapies for oral cancer.

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**Related Publications**

1. Rajamoorthi A, Shrivastava S, Steele R, Nerurkar P, Gonzalez JG, Crawford S, Varvares M, Ray RB. Bitter melon reduces head and neck squamous cell carcinoma growth by targeting c-Met signaling. PLoS One. 2013 Oct 17;8(10):e78006. doi: 10.1371/journal.pone.0078006. PMID: 24147107; PMCID: PMC3798549.
2. Bhattacharya S, Muhammad N, Steele R, Kornbluth J, Ray RB. Bitter Melon Enhances Natural Killer-Mediated Toxicity against Head and Neck Cancer Cells. Cancer Prev Res (Phila). 2017 Jun;10(6):337-344. doi: 10.1158/1940-6207.CAPR-17-0046. Epub 2017 May 2. PMID: 28465362; PMCID: PMC5499682.
3. Sur S, Ray RB. Bitter Melon (Momordica Charantia), a Nutraceutical Approach for Cancer Prevention and Therapy. Cancers (Basel). 2020 Jul 27;12(8):2064. doi: 10.3390/cancers12082064. PMID: 32726914; PMCID: PMC7464160.
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5. Sur S, Bhartiya P, Steele R, Brennan M, DiPaolo RJ, Ray RB. Momordicine-I Suppresses Head and Neck Cancer Growth by Reprogrammimg Immunosuppressive Effect of the Tumor-Infiltrating Macrophages and B Lymphocytes. Mol Cancer Ther. 2024 May 2;23(5):672-682. doi: 10.1158/1535-7163.MCT-23-0718. PMID: 38315993; PMCID: PMC11065610.