

Immunomodulatory Effects of *Momordica charantia* Extract in the Prevention of Oral Cancer

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Abstract

In recent times, bitter melon extract (BME) has gained significant attention for its anticancer efficacy against various malignancies. In this issue, Sur and colleagues show that BME prevents the development of 4-nitronitroquinoline 1-oxide-induced oral dysplasia and squamous cell carcinoma (SCC) in an immunocompetent mouse model. Importantly, gene ontology and pathway analyses revealed

an elevated expression of s100a9, IL23a, IL1 β , and PDCD1/PD1 of immune system during oral cancer development, which was significantly suppressed by BME. Overall, this study demonstrates the potential clinical benefits of BME in preventing and delaying the progression of oral dysplasia to SCC. *Cancer Prev Res*; 11(4); 185–6. ©2018 AACR. See related article by Sur et al., p. 191

Worldwide, head and neck cancer, which includes all oral, laryngeal, and pharyngeal sites, is the sixth most common cancer, accounting for about 643,000 new cases annually (1). The 5-year survival rate in oral cancer patients varies from 81% for those with localized disease to 42% for those with regional disease and 17% if distant metastases are present (2). Oral squamous cell carcinoma (OSCC) is the most common histologic type, and it accounts for more than 90% of oral cancers (1, 2). Early diagnosis for oral cancer has not improved over time, and up to 77% of oral cancer cases are diagnosed at late stages. Approximately one third of treated patients (including surgery, radiotherapy, and chemotherapy) will experience local or regional recurrence and/or distant metastasis. The main risk factors for oral cancer are exposure to tobacco smoke, smokeless tobacco, alcohol excess, and human papilloma virus (1). Avoidance of risk factors has only been partially successful largely due to the addictive power of tobacco smoking and alcohol consumption (3).

A number of chemopreventive agents, both naturally occurring and synthetic, were studied using 4-nitroquinoline-1-oxide (4-NQO)-induced oral cancers in rodent models (2, 4). Multiple agents, including isotretinoin, celecoxib, and erlotinib, were used in randomized che-

moprevention clinical trials; however, no effective and tolerable agent was identified for the prevention of OSCC (4). Bitter melon (*Momordica charantia*) extract (BME) has recently come into focus for its potential anticancer efficacy. It has been traditionally used as a folk medicine/ayurvedic medicine since ancient times for the treatment of type II diabetes and the associated metabolic aberrations. Ray and colleagues first demonstrated its antiproliferative effect on breast cancer cells (5). Subsequently, her group and other investigators showed that BME has chemopreventive effect in different preclinical cancer models like head and neck, breast, prostate, pancreas, skin, stomach, and colon without any side effects (5–7). In this issue of *Cancer Prevention Research*, Sur and colleagues of the same group discussed the novel immunomodulatory role of BME in the prevention of carcinogen-induced oral cancer (8).

In this study, the authors used 4-NQO to induce invasive OSCC, especially in the tongue, in immunocompetent mice. Carcinomas of the tongue are the most common OSCC (25%–80%; ref. 9). 4-NQO is a synthetic, water-soluble carcinogen, which exhibits a very strong mutational preference (A-G nucleotide substitution) for the oral cavity, and tumor progression at a particular site will depend on additional factors, such as inflammatory and immunologic responses, resulting in histologic and molecular alterations similar to human oral carcinogenesis (2, 9). The authors observed that administration of BME with the 4-NQO in drinking water prevented OSCC development with no remarkable pathologic and histologic sign in the mice.

Bhattacharya and colleagues recently showed the *in vivo* immunomodulatory role of BME in HNSCC in a syngeneic mouse model (10). From RNA-seq analysis,

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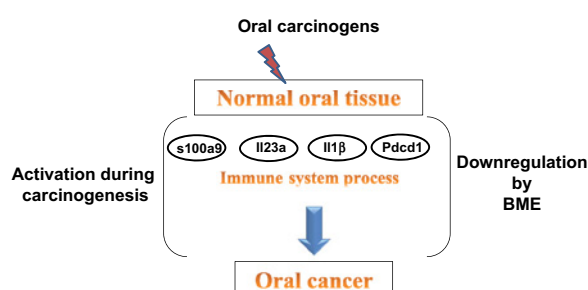


Figure 1.

Diagrammatic representation showing activation of immune system molecules during 4-NQO-induced oral carcinogenesis and modulation by BME during prevention of the carcinogenesis.

the authors identified modulation in the immune system process in 4-NQO-induced OSCC and in the prevention of OSCC by BME. Immunosuppression and deregulation of inflammatory mediators, such as cytokine/chemokines, which are present in the tumor microenvironment, are one of the hallmarks of inflammation-mediated tumorigenesis. Preclinical and clinical evidence has revealed that early transformed cells express antigens that allow the immune system to recognize them and initiate an immune response. To overcome the antineoplastic effects of the immune system, tumor cells may transmit immunosuppressive signals mediated by inflammatory cytokines, immune checkpoint molecules to the tumor microenvironment, which enable cancer progression (11). Their study showed significant upregulation of proinflammatory genes *s100a9*, *IL23a*, *IL1b* as well as immune checkpoint gene *PDCD1/PD1*, during carcinogen-induced OSCC (Fig. 1). Upregulation of these immune system-associated markers was reported

in human HNSCC (11). Pharmaceutical targeting of *s100a9* and *PD1* showed a promising effect in phase I–III clinical trials against different cancers (4). Their observations clearly demonstrated remarkable downregulation of these genes following BME treatment. Thus, these observations indicated the potential role of BME in the prevention of carcinogen-induced oral cancer. In addition, elevated expression of *MMP9*, one of the known OSCC oncogenes associated with ossification, invasion, and metastasis (2), showed significant reduction following the BME treatment. Their study also showed modulation in lipid metabolism pathways by BME treatment. Cancer cells frequently show alteration in cellular metabolism, and different *in vitro* and *in vivo* studies reported potential beneficial effects of bitter melon against lipid and glucose metabolic dysfunction (6). Thus, their observation indicates the modulation of multiple cellular events at a time during BME-mediated oral cancer prevention.

In conclusion, the authors proposed the potential anticancer efficacy of BME in prevention of oral cancer by modulating different biological processes, including those of the immune system. Thus, this study may have importance not only for the treatment of oral cancer but also for the treatment of other cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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