REVIEW ARTICLE

Anti-Microbial, Anti-Cancer and Immunomodulatory Properties of Proteinaceous Postbiotic Metabolite Produced by *Lactobacillus plantarum* I-UL4

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ABSTRACT

Bacteria and their metabolites are shown to be a potential therapeutic agent for cancer treatment. Much attention has been directed to Lactic acid bacteria (LAB) which exhibits several killing mechanisms via invasion and colonization of solid tumors. Discovery of the characteristics of postbiotic metabolites that exert the same probiotic effects has attracted immense attention towards anti-cancer effect. It is known that LAB improves health and composition of microbiota in the gut. Supplementation of LAB is proven to enhance the host immunity and modulation of the immune system to fight diseases including cancers. *Lactobacillus plantarum* I-UL4 is the LAB species isolated from Malaysian fermented food, *Tapai Ubi* which capable of producing bioactive metabolic products. In this review, the properties of UL4-PPM will be discussed including anti-microbial, anti-cancer and immunomodulatory effects. Overall, it would be beneficial to discover the potential effects of UL4-PPM to possibly serve as an alternative treatment for cancer.

Keywords: Cancer, Lactic acid bacteria, Metabolites, Immunity

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INTRODUCTION

Cancer is an emerging public health problem in developing countries and is the second most common disease leads to death in the United States. It is estimated that about 1,685,210 cases were expected in 2016 which is approximately over 4,600 new cancer cases were diagnoses each day worldwide (1). Colorectal cancer (CRC) is the third most commonly diagnosed cancer among both men and women in the United States. In Malaysia, colorectal cancer is the second most common cancer in both males and females in 2016. It is estimated that 2600 cases in men while 2000 cases in women were reported in Malaysia with 1300 and 1000 of mortality rate, respectively (2). Mortality due to colorectal cancer is increasing and has been reported as the fourth leading cause of cancer death worldwide (3). However, the reported incidence of colorectal cancer is higher in developed Asian countries such as Japan, South Korea, and Singapore compared to Malaysia and other developing Asian countries (4). Diet has been shown to reduce CRC incidence by approximately 80% as it has multiple effects which could alter the metabolome or metabolites composition of the host (5).

Despite the advancement in cancer discovery and therapy, cancer has remained a major burden of disease worldwide leading to high incidence of deaths. Furthermore, adverse side effects are generally associated with the currently available chemotherapeutic agents due to unspecific toxicity towards normal cells. Probiotics including LAB have been reported to promote health and can be a potential preventive and therapeutic agent (6). Probiotics are live microbial food supplements with the ability to beneficially affect the gut microbiota by attributing a variety of immunological and metabolic parameters. There are several well-defined mechanisms including alteration of normal microbial ecosystem composition, maintenance of the functions of gut lumen epithelial barrier, and modulation of mucosal and systemic immune responses of the host (7, 8). In addition, probiotics and their metabolite products, postbiotics, have been proposed as food supplements to promote health and intestinal composition, as well as therapeutic agents in inflammatory bowel disease (IBD) (9).

Recently, the potential of metabolite product synthesized from probiotics in exerting the probiotic effects outside living cells either using metabolite combinations (10) or in combination with other prebiotics has drawn a lot of attention (11). Metabolites have advantages in term of logistics as it is more stable as well as have a wider applications in food industries and as feed additives in livestock industries (12). Metabolites from dietary sources have been shown to affect the metabolism of the whole body by direct or indirect interaction with intestinal mucosa from the luminal side (13).

In this review article, the effects of proteinaceous postbiotic metabolite (PPM) produced by *Lactobacillus plantarum* I-UL4 namely afterward as UL4-PPM on anti-microbial, immunomodulatory and anti-carcinogenic properties will be discussed accordingly.

PROTEINACEOUS POSTBIOTIC METABOLITE FROM *Lactobacillus plantarum* I-UL4 (PPM-UL4)

LAB are abundantly present in fermented foods, vegetation, gastrointestinal (GI), oral cavity, and urogenital tract and are commonly associated with several health-promoting elements (8). The ability of LAB to serve as a food preservatives is due to the production of anti-microbial metabolites by targeting cell wall or membrane of the organisms such as organic acids and bacteriocins (14). Bacteriocins such as pyocin, colicin and microcin are one of the inhibitory metabolites produced by LAB consisting of amino acids that essentially play a role as to prevent the growth of competing microorganisms, and have been proven to also possess antineoplastic activity (15).

Lactobacillus plantarum I-UL4 is one of the LAB species isolated from Malaysian fermented food, Tapai Ubi (16) which has the ability to produce bioactive metabolic compounds termed as postbiotics. UL4-PPM is a postbiotics or metabolite produced by *Lactobacillus plantarum* I-UL4 which is believed to exert the probiotic effects without living cells (10, 17). To date, not much study has been done on the postbiotics, which are metabolite products from the probiotics in cancer-related study since it has been majorly described that LAB act as anti-cancer agent by modulating immune responses in *in vitro* and *in-vivo* studies (18-20).

ANTIMICROBIAL PROPERTIES OF PPM-UL4

A few studies have shown that UL4-PPM encouraged the growth, reduced plasma cholesterol and enhanced the population of indigenous LAB in the intestine and faeces of rats (12). It is associated with a reduction of lowered faecal pH and faecal *Enterobacteriaceae* counts after supplementation with UL4- PPM (12, 16, 21). Modler et al. (22) suggested that reduction in intestinal pH may influenced the progression of large-bowel cancer by preventing the growth of putrefactive bacteria in the gut.

UL4-PPM could be a potential alternative for antibiotic growth promoters (AGPs) as a study conducted in broilers shown that UL4-PPM improved growth performance, LAB count and the concentration of fecal volatile fatty acid, while reducing in the number of *Enterobacteriaceae* (17). In fact, it could be beneficial as some pathogenic bacteria are resistant to numerous antimicrobial agents and potentially lethal when transmitted to humans (23). Anti-microbial properties of UL4-PPM are mainly due to its bactericidal and bacteriostatic effects that can kill pathogenic bacteria in gastrointestinal microflora (17). Report have also shown that increased in villi surface would increase nutrient absorption in small intestine (24).

IMMUNOMODULATORY AND ANTI-CARCINOGENIC ATTRIBUTES BY PPM-UL4

There are several established drugs for standard first line therapy for CRC such as irinotecan, oxaliplatin and cetuximab. Nevertheless, the drugs have various adverse side effects. Therefore, much attention has been focused on the development of natural product-based anticancer agents that have the advantages as they are believed to have lesser side effects. LAB was found to improve gastrointestinal microbial population (25), exert antimicrobial activities and anti-carcinogenic properties (26). For example, azurin is a well-characterized bacteriocin discovered to exhibit cytostatic and apoptotic effect against human colon cancer cells (27). In addition, colicins which are metabolites produced by *Escherichia coli* has been shown to induce cell death in tumor cells by targeting the proteins located on the outer surface of the cells through antibody recognition (28, 29). Thus, these bacteriocins are believed to specifically target tumor cells (30).

The anti-cancer activities of UL4-PPM towards a breast cancer cell line has been reported in 2015 (31). The similar properties have been proposed for LAB mediated activation of immune response and metabolic activity in colon cancer cells (32). Even though several studies have clearly demonstrated the chemopreventive effects of dietary supplements of LAB against the development of colon cancer (33-35), however the chemopreventive and inhibitory effects of postbiotics or metabolite products from probiotics on colon cancer is very limited. Recently, probiotic metabolites have been shown to affect various functions at the cellular and molecular level including the initiation and progression of colon cancer which they may lead and regulate various metabolic signaling pathways. Signaling pathway involve are crucially responsible for cell proliferation, invasion, apoptosis, inflammation, angiogenesis, and ultimately cancer metastasis (13, 35). A few evidences have demonstrated that metabolites from probiotic cultures could reduce cell proliferation of human colon cancer cells (36, 37). A study has shown that the colorectal cancer severity in azoxymethane-induced rats could be reduced substantially when treated with UL4-PPM in drinking water (38). In this study, treatment with UL4-PPM reduced the total number of aberrant crypt foci (ACF) and crypt multiplicity, the incidence of tumor, adenoma and adenocarcinoma, with decreased expression of Я-catenin, indicating the reduction in the severity of colon cancer in animal colon cancer model. Modulation of microbial environment and several composition of the gut contribute to a better health status and providing beneficial effects to the host. Probiotic was found to reduce an inflammation in patients with gastrointestinal diseases (39). It has been demonstrated that tumor development and cancer metastasis may commonly occur in immunocompromised people. Thus, stimulation of the immune system may enhance host defense towards tumor cells which is also believed to be one of the most important mechanisms to treat the disease. UL4-PPM also has the ability to enhance the level of several cytokines or interleukins which are IFN-γ, TNF-α, IL-12 and IL-5 in serum and immune organs (spleen and thymus) that are crucially involve in the inhibition of colon carcinogenesis (38). Immunomodulatory activities of probiotics by regulating the production of anti- or pro-inflammatory interleukins (IL) resulted in the prevention of excessive immune response in inflammatory bowel diseases (40). Therefore, it is postulated that UL4-PPM may exhibit antineoplastic activity due to its immunomodulatory properties in the host.

CONCLUSION

UL4-PPM, the metabolites produced by *L. plantarum* I-UL4, has shown to exert anti-microbial, immunomodulatory and anti-carcinogenic properties in *in vitro* and *in-vivo* studies. Promisingly, UL4-PPM can be developed as a potential agent in prevention and treatment of CRC.

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