



Probiotics supplementation in the management of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC, also known as primary liver cancer), is the fourth most frequent cancer and the third cause of deaths associated with cancer worldwide (1). HCC occurs in liver damaged tissue, due to chronic regenerative and inflammatory processes that contribute to the initiation and progression of the tumor (2). The main environmental factors associated with HCC are hepatotropic viral infection (hepatitis B and C, particularly), excessive consumption of alcohol, and exposure to aflatoxin through the diet. However, in the last 20 years, non-alcoholic fatty liver disease (NAFLD) has become a quickly emerging cause of end-stage liver disease worldwide. Typically, its hepatic injury starts with simple steatosis, which can progress to advanced stages such as non-alcoholic steatohepatitis (NASH), fibrosis and finally cirrhosis. Epidemiology studies report that about 3–15% of the obese patients with NASH progress to cirrhosis, and about 4–27% of NASH patients with cirrhosis present HCC (1).

Intestine and liver are strictly connected districts, as they are involved in nutrient absorption and metabolism. For this reason, is common to talk about the “gut-liver axis” (3,4), a connection that exposes directly the liver to gut-derived bacterial elements. In fact, portal blood flow transports to the liver products from gut, such as lipopolysaccharide (LPS), bacterial DNA and peptidoglycan (3). Actually, it has well established that human gastrointestinal tract, is an ecosystem also called microbiota, that contains up to 100 trillion of microbes of distinct taxonomy (2,000 different species) (4). Its composition varies in reason of multiple

factors such as the type of delivery, gender, host age, geographic location, ethnicity, and alimentary regimen. In healthy people, the prevalent bacterial phyla are *Firmicutes* (30–50%), *Bacteroidetes* (20–40%) and *Actinobacteria* (1–10%). The intestinal microbiota, which is around 1–2 kg of our body weight, is an essential component of healthy body and it is involved in many functions such as producing vitamins, degrading bile acids, modulating immunity and even treating diseases, such as cancer (3,4).

Maintaining an equilibrium within the microbiota components is essential as a barrier against external environment. A disequilibrium of microbiota components, termed intestinal dysbiosis, impairs gut homeostasis and leads to overgrowth of certain detrimental bacteria involved in the onset of a variety of diseases. Increasing evidences suggest that the gut-liver axis can be involved in HCC development. In particular, endotoxemia produced by an unbalanced gut microbiota, may contribute to hepatocarcinogenesis (5). Probiotics are defined by United Nations and WHO as “live microorganisms which when administered in adequate amounts confer a health benefit for the host” (6). Probiotics are commensal bacteria, as a functional food ingredient able to modulate the gut microbiota with benefits to the human health. Strains of *Lactobacillus* and *Bifidobacterium* species are commonly used as probiotics in fermented dairy products. Emerging evidences indicates that probiotics may also be used as a therapeutic approach for HCC (7,8).

Particularly, it has been reported that gut microbial

metabolites, as a lipoteichoic acids, elements of cell walls of gram-positive commensal bacteria, can induce the synthesis of prostaglandin E₂ (PGE₂) by hepatic stellate cells. PGE₂ contrasts the antitumor activity of CD8+ T cells, and therefore acts indirectly as facilitator for the onset and development of HCC (9). It is also well known that the microbial metabolism of ursodeoxycholic acid, is necessary for the expression of its protective effects against colonic inflammation, and induces apoptosis of HCC cell lines *in vitro* (10). The gut microbiota modulation, may be the bridge between ursodeoxycholic acid bioactivity and anticancer effects.

Recently, Wan and El-Nezami discuss the interplay between the intestinal microbes and HCC, and the potential role of probiotics supplementation in the treatment of patients with HCC. The review was published in the month of February 2018 on *HepatoBiliary Surgery and Nutrition* (11). The Authors support the role of intestinal bacteria in liver carcinogenesis, and highlight the concept that the manipulation of gut microbiota may represent a novel approach in the prevention and treatment of HCC.

Many pathogenetic mechanisms, including leaky gut, endotoxemia, toll like receptors, small intestinal bacterial overgrowth (SIBO) and immunomodulation, promote the development of HCC. The digestive apparatus contributes to the immune homeostasis by maintaining an intact barrier against LPS and gut microbes (12). In case of increased intestinal permeability, bacterial translocation and LPS accumulation, will lead to intestinal bacterial overgrowth with consequent SIBO. In patients with advanced liver diseases, detoxification, degradation, and clearance of LPS and other bacterial products are altered. In the gut microbiota profile of cirrhotic patients with HCC, the increased fecal counts of *Escherichia coli* have been reported, in line with pre-clinical studies that report excess levels of Gram-negative bacteria as a *Atopobium*, *Collinsella*, *Eggerthella*, and *Coriobacterium*, with increased blood serum levels of LPS (7,13). To the contrary, it has been reported that microbiota of HCC patients contains low levels of *Lactobacillus spp.*, *Bifidobacterium spp.*, and *Enterococcus spp.*, bacterial species that play a protective role against inflammatory diseases (13). In addition, two specific genera, *Oribacterium* and *Fusobacterium* are the most commonly isolated bacteria from tongue swab in these subjects, able to distinguish liver cancer patients from healthy subjects (14).

Probiotic mixtures demonstrated positive effect in *in vivo* studies on liver cancer. Antibiotic therapy has also been linked to decreased onset and progression of HCC

in several preclinical studies. However, in this research area human data are lacking. It is also important to highlight that rifaximin, an eubiotic compound capable to induce overgrowth of beneficial gut bacteria, such as *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus*, and to induce an anti-inflammatory action, has never been tested in preclinical models of HCC (7). Rifaximin may represent a promising therapeutic approach, due to its capacity to contrasts the reduction of beneficial bacterial species reported during the development of HCC.

In the last decades, knowledge on the gut-liver axis has improved. Literature confirms that intestinal bacteria have a deep relationship with the liver, and play a significant role in the pathogenesis of hepatic injury, fibrosis progression, cirrhosis, and its complications, including HCC (15). Moreover, the exact mechanisms of this connection are still unclear. Our knowledge about the clinical significance of the use of probiotics in liver diseases, begins to take shape. On the basis of the discussed evidences, and in agreement with the Authors it is possible to conclude that, probiotics supplementation may be a safe and low-cost strategies in this context. However, more extensive human clinical trials to better understand the impact of microbiota-host interactions, the gut microbiota influence on health and to investigate the possible use of selected bacterial strains as a therapeutic option in the clinical management of HCC, are needed.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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