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Review Article

Hepatocellular Carcinomas Risk Factors, Diagnosis, Prevention and Frontier to Probiotic Treatment

Shaukat Ali[1],*, Sadia Batool[2], Fatima Javed Butt[2], Sundas Nasreen[1], Hafiz Muhammad Tahir[1]

[1]*Department of Zoology, Government College University, Lahore, Pakistan*
[2]*Department of Zoology, University of Azad Jammu and Kashmir, Muzaffarabad, Pakistan*

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Abstract | In the arena of latest technologies, researchers are looking for a unique treatment strategy for diagnosis and treatment of cancer; it is a second chief cause of deaths in the world. Advances in chemotherapeutic agents, various radiological techniques and bio-nanoparticles treatments (i.e., green synthesized metallic nanoparticles) attracted many researchers to conclude a novel cancer treatment strategy. Unluckily every strategy had some working limitations as a result of which cancer remained a catastrophe for humanity. The present review article devised the modern cancer treatment paradigm which proposed directions towards probiotics or biotics-cancer treatment strategy. The probiotics are present in the human gut region and acting as a health promoter; as they have antioxidative, immunomodulatory, antipathogenic and anti-cancerous properties. Review based on the futuristic and modern aspects of cancer treatment, we believe that probiotics based cancer treatment would be supportive to overcome the chemotherapeutic and radiological drawback sand provides an appropriate cancer treatment strategy. Anticipating various challenges, we expect that probiotics may become a potential cancer bio-theranostic in the field of medical sciences shortly. Appropriate monitoring and treatment are strongly recommended to prevent hepatocellular carcinoma complications.

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Introduction

Cancer: A life threat

The state of cancer is designated by uncontrolled cell division with successive invasions of healthy cells and tissues of the body. Mutations in genes trigger a series of events at the molecular level, leading to tumor formation and renal cell carcinoma (Hollstein *et al*., 2017; Aghamir *et al*., 2019). Cancer is a chief source of mortalities and morbidities throughout the world (Ferlay *et al*., 2019). American Cancer Society declared, the cancer global threat will rise to 21.7 million fresh cases by the year 2030 (Society). Both benign and malignant tumor is different from each other based on special features. As benign tumor does not invade all over the body while the malignant tumor invaded to various body regions (Bali *et al*., 2010; Liu *et al*., 2015; Israel *et al*., 2016). In underdeveloped regions, the cancer incidence rate is exponential rises in the coming years due to non-affordability and non-availability of the inexpensive treatment for cancer reduction (Baskar and Itahana, 2017; Bray *et al*., 2012).

Current efforts in the field of research have made noteworthy advancement in underscoring mechanisms and major risk factors of various cancers, these may be internal and external factors. Internal factors include gene mutations (Aghamir *et al*., 2019), irregular secretions of body hormones (Del Pup *et al*., 2019) and adverse immunological conditions that cause chronological

Corresponding author: Shaukat Ali
shaukatali134@yahoo.com

conditions that lead toward carcinogenesis (Chang *et al.*, 2019). External factors include exposure to different chemicals, heavy metals, radiations, fried meat, alcohol, toxic mushrooms, aflatoxins, tobacco smoke, passive smoking and viral infections (Anand *et al.*, 2008; Coughlin *et al.*, 2015; Yang *et al.*, 2019). Pancreatic cancer (PC) is caused by the exposure of chemicals and heavy metals (Antwi *et al.*, 2019). The exposure to various pesticides, chlorinated hydrocarbons, asbestos, and benzene also increase PC risk (Fritschi *et al.*, 2015; Antwi *et al.*, 2015; Antwi *et al.*, 2019).

The most important cause of death through cancer is its poor diagnosis. The most commonly used diagnostic techniques are X-rays, ultrasound scanning (US) and MRI (D'Onofrio *et al.*, 2019; Mannaerts *et al.*, 2019; Gureyev *et al.*, 2019). The probability of detection for ultrasound scanning is 65%-80% and has precision greater than 90% (Bolondi *et al.*, 2001; Bruix *et al.*, 2005; Bruix *et al.*, 2006). MRI is used to make the description and detection of hepatic malignant injuries better (França *et al.*, 2004). It has more accuracy as compared to the US or CT scan in the detection of HCC and analyzing the actual size of the tumor (Snowberger *et al.*, 2007).

Cancer is treated through chemotherapy therapy, radiation, immunotherapy, surgery, vaccination against cancer, photodynamic therapy and stem cell transformation is mainly used, often accompanied by severe side effects. These effects include limited bioavailability, toxicity, non-specificity and restriction in metastasis (Patra *et al.*, 2014; Lim *et al.*, 2011; Mukherjee *et al.*, 2016). Modern research developed effective treatment possibilities that are potent against various cancers with little or without damage to healthy cells and tissues. This recent option of treatment is provided by nanobiotechnology which plays a vital role in cancer treatment. Nanobiotechnology research present that AgNPs have a potential source against cancer diagnostic, its therapeutic, imaging and drug delivery agents (Ovais *et al.*, 2017).

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is considered as a 5th frequent type of all malignancy and 2nd common reason for tumors which leads to death globally (Petrick *et al.*, 2019; Hsu *et al.*, 2010). Hepatocellular carcinoma represents 85% to 90% of primary malignant tumors (Stefaniuk, 2010). It is etiologically as well as histologically different from other types of primary liver cancer (Yu *et al.*, 2008). Approximately I million people die due to viral hepatitis and hepatocellular carcinoma (Asrani *et al.*, 2019) and 700,000 people die of liver cancer every year globally (Ferlay *et al.*, 2015).

Causes of hepatocellular carcinoma

Hepatocellular Carcinoma is a frequent form of cancer in which an epithelial tumor appeared by the transformation of hepatocytes (El–Serag and Rudolph, 2007). Cirrhosis Patients have the maximum opportunity of developing liver cancer (Forner *et al.*, 2012; Asrani *et al.*, 2019). About 90-95% of people who have developed HCC are cirrhotic however HCC can also arise in non-cirrhotic people. Cirrhosis can develop because of HCV/HBV infectivity. Prolonged HBV infectivity is the most frequent reason for the development of HCC throughout the world whereas in Europe, the most common reason for HCC is HCV infection. If someone is suffering from HCV or HBV infection then developing the risk of HCC would be 3-5% each year (Calle *et al.*, 2003; Chuang *et al.*, 2009; Bruix and Llovet, 2009; Asrani *et al.*, 2019).

The Risk of HCC will further increase by the co-infection of HCV or HBV. Some other causes include metabolic syndrome, primary biliary cirrhosis alcoholism, diabetes, smoking and genetic hemochromatosis. Hepatocellular carcinoma may also be linked with elevated aflatoxins i.e., several mycotoxins formed by the fungus *Aspergillus flavus* and *Aspergillus parasiticus* in foodstuff. In Asia and Africa (sub-Saharan) this cancer is caused because of contaminated foodstuffs (specifically by the fungus), like grains and peanuts (Calle *et al.*, 2003; Chuang *et al.*, 2009; Bruix and Llovet, 2009; Asrani *et al.*, 2019).

Various microorganisms are considered as class 1 carcinogens, such as Epstein–Barr virus, HBV, HCV and *Helicobacter pylori,* were declared to develop various cancers including gastric cancer, leukemia, hepatocellular carcinoma and lymphoma (Oh and Weiderpass, 2014). In the presence of different types of pathogenic microorganisms, host environmental conditions such as diet (O'Keefe, 2016), inflammation (Morgan *et al.*, 2012; Gevers *et al.*, 2014; Mottawea *et al.*, 2016), cigarette smoke and antibiotics (Biedermann *et al.*, 2013; Raymond *et al.*, 2016), alters the gut microbiota composition and metabolic activity in host, which may lead to neoplastic changes (Figure 1).

Prevalence of hepatocellular carcinoma

Hepatocellular carcinoma is more frequent in men than in women. It is the 2nd main reason of death (due to cancer) in men throughout the world, especially in those countries which are not well developed while the sixth main reason of cancer death in those countries which are developed as shown by Figure 2 (Petrick *et al.*, 2019). About 782,500 new cases of HCC had been seen throughout the world during 2012 and from the 745,500 victims died, out of which China single has half of the aggregate cases of HCC and deaths due to it. Western Africa, East and South-East Asia have high incidence rates of liver cancer while Central, Eastern and Northern Europe and South-Central Asia have fewer incidence rates of HCC. Hepatocellular carcinoma is the most dominant primary

liver cancer throughout the world *i.e.*, almost 70% to 90% (London and McGlynn, 2006). Owing to the increased rate of liver fluke infectivity, Cholangiocarcinoma (which starts mainly from the bile duct epithelial lining) is more prevalent in some parts of Asia and Thailand but it is uncommon in most regions of the world (Shen *et al.*, 2010).

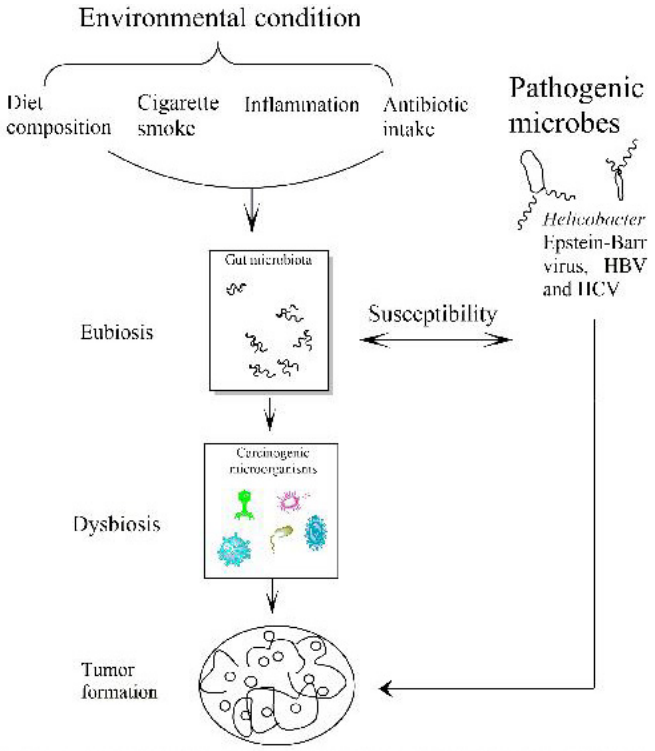

Figure 1: Environmental factors play a role in the promotion of dysbiosis and pathogen-derived susceptibility to tumor formation. These factors such as diet components, inflammation, and antibiotics involved in the disruption of the healthy microbiota, which associated with dysbiosis.

The prevalence of HCC is increasing in Western Europe, Northern America and some parts of Oceania where the risk of cancer was low in the past (Howlader *et al.*, 2014) and increasing prevalence in expressed in Figure 1. In the United States, the increasing prevalence of HCC reflects the increasing possibility of diabetes mellitus and obesity, an increase in severe infection of HCV due to mistreatment, which was more familiar in the late 19th century (Mittal and El-Serag, 2013; Altekruse *et al.*, 2009). Conversely, in areas like Japan and China where the risk of HCC was high in the past, the prevalence of HCC is decreasing. This decreasing prevalence is mostly because of decreasing the risk of HCV and HBV infection in Japan and China respectively due to better sanitation and cleanliness (Center and Jemal, 2011). According to a report in Taiwan, Universal HBV vaccination program for children that was started in 1984, has decreased the risk and occurrence of HCC up to 80% (Chiang *et al.*, 2013). Though, in many countries of Asia vaccination programs of HBV are not much involved in reducing the incidence rates of liver cancer rates because this program is implemented recently (Torre *et al.*, 2015).

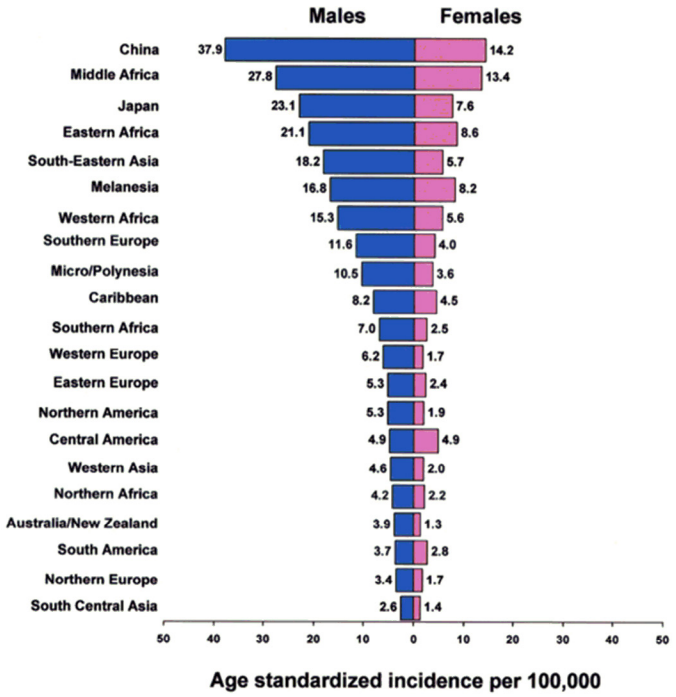

Figure 2: Prevalence of liver cancer.

Various serological markers are mostly tested in HCC including serum Alfa fetoprotein (Natsuyama *et al.*, 2019; Lersritwimanmaen and Nimanong, 2018; Sternby-Eilard *et al.*, 2018), Alanine Transaminase (ALT), Aspartate Transaminase AST, Lactate Dehydrogenase (Ramakrishnan *et al.*, 2007), 5-nucleotidase (Dar *et al.*, 2019; Shali *et al.*, 2019) and Gamma-glutamyl transferase (Wang *et al.*, 2019).

Preventions

The latest information related important factors for the prevention of HCC are completely explored. Amongst these, the vaccine of HBV designed for the prevention of infection by HBV is a glance of confidence in the field. It is proved that HCC development is strongly prevented by vaccination of HBV (Chang *et al.*, 1997).

Sorafenib

Sorafenib is the typical remedy for traditional HCC (Khan *et al.*, 2018). In 3rd phase, double-blind, randomized and placebo-controlled analysis of Sorafenib is an effective cure for liver cancer afterward local ablation or medical resection so 1,114 patients are enrolled they randomly take either placebo or Sorafenib for four years or awaiting tumor reappearance. The group of researchers currently declared that neither its primary and secondary endpoints, reappearance-free existence and nor survival were met (Bruix *et al.*, 2009).

Curcumin

Curcumin is a polyphenol, which is usually used as a spice in cooking in Indian. It received great media

attention after the beginning of experiments on a national level and the role of combining curcumin supplementation and chemotherapy in bowel cancer. *In vitro*, Curcumin can stimulate apoptosis in numerous tumor cell lines. It is shown from animal models that it can stop HCC in murine models and rat model (Afrin *et al.*, 2018).

Interferon-based therapy in HBV and HCV-related HCC

Interferon (IFN) contains anti-proliferative, immune-modulatory and antiviral properties. In the past before the development of advance anticancer and antiviral treatments, conventional IFN was widely verified for HCC remedy and prevention. In the adjuvant setting, conventional IFN therapy show variable results, meta-analyses verified that adjuvant IFN therapy enhances overall survival (Shen *et al.*, 2010; Breitenstein *et al.*, 2009; Singal *et al.*, 2010). Generally, the results of adjuvant IFN therapy were not favorable to prevent HBV related HCC(Chen *et al.*, 2012; Lo *et al.*, 2007; Sun *et al.*, 2016). Though, this treatment was beneficial for few subgroups. For instance, high expression of RIG-I and low expression of miR-26 show good effects on IFN therapy (Ji *et al.*, 2009; Hou *et al.*, 2014). If we compare HBV with HCV, it shows more response to conventional IFN therapy. The possibilities for the development of Hepatocellular carcinoma are reduced more effectively by Interferon in patients who are affected with prolonged infection of HCV as compared to those who are affected by prolonged HBV infection. According to random control experimentation accomplished in Japan, 49 patients having HCV-related HCC were treated with IFN-α after full ethanol ablation. The patients who were treated, 14 (29%) showed persistent antiviral responses. Comparing with the 25 patients who were not treated with adjuvant IFN-α, the rates of 1st reoccurrence of disease were the same, but the patients who were treated with adjuvant IFN-α, the rates of 2nd and 3rd reoccurrence of disease were decreased in them (Shiratori *et al.*, 2003). In an Italian, randomized control test for patients having HCV-related HCC, adjuvant IFN-α does not affect overall recurrence. Though, in the patients who were adherent to the treatment, adjuvant IFN-α decreased late reappearance in the pure HCV subgroup (Mazzaferro *et al.*, 2006).

Cancer treatment: nanotechnology, plants and cancer

Metal nanoparticles are considered as an efficient biomedical applicant due to their multifunctional theranostic abilities, as their antitumor, antimicrobial and drug carrier properties (Mukherjee *et al.*, 2014; Mukherjee *et al.*, 2013; Mukherjee *et al.*, 2016). Oral administration of AgNPs indicates their bright future, as they are potent cancer theranostics agents (Munger *et al.*, 2014). The phytochemical-based green synthesized biocompatible colloidal gold nanoparticles (AuNPs) have biomedical applications because of their numerous benefits (eco-friendly, safer, energy-efficient, simple, cost-effective and minor toxicity) over conventional chemical synthetic measures. Biogenic AuNPs exhibits a potential anti-cancer activity by generating oxidative stress and reactive oxygen species (Ovais *et al.*, 2017; Ali *et al.*, 2016).

Probiotics: beneficial microorganisms

Probiotics mean "for life". Probiotics are naturally occurring beneficial organisms that aid in digestion and inhibit pathogenic bacteria in the intestine. Due to the beneficial impact of microorganisms used as probiotics, during the last decade, progressive attention has been focused on biological and molecular characterization and improvement of such microbes (Dinan and Cryan, 2017; Ajmal and Ahmed, 2009). Probiotics are currently the subject of significant clinical research. Different probiotic strains play a significant role in ameliorating chronic intestinal inflammation, diarrhea, constipation, vaginitis, irritable bowel syndrome, atopic dermatitis, sepsis, food allergies, and liver disease. Probiotics modulate systemic and mucosal immune function, improve intestinal barrier function, alter gut micro-ecology and exert metabolic effects on the host (Dinan and Cryan, 2017; Wallace *et al.*, 2011).

Probiotics novelty towards HCC treatment

A bacterium (or any microbe) needs to be isolated, purified, characterized and proved to be beneficial to health when it is administered before it can be designated as a probiotic. Successful probiotics strains need to be able to survive passage through the upper gastrointestinal tract, multiply, colonize and function in the gut. They are mostly of human origin (Saarela *et al.*, 2000). Probiotics are valuable microorganisms, their survival based on discerning fermented food ingredients known as prebiotics and have potential against hepatocellular carcinoma (HCC) by producing anti-inflammatory metabolites.

Regulation of Th17 response

Probiotics including *Prevotella* and *Oscillibacter* secrete anti-inflammatory metabolites that are responsible to regulate T-cell differentiation, reduction of Th17 cell polarization and encouraged the differentiation of anti-inflammatory Treg/Tr1 cells in the GIT. Th17 reduction suppresses tumor development and decreases angiogenesis. Prohep is a novel probiotic mixture that plays a significant role in HCC treatment significantly in mice and modulation of gut microbiota (Li *et al.*, 2016; Murugaiyan and Saha, 2009). Probiotics play a significant role in various cancers as listed in Table 1.

Mechanisms of action of probiotics against hepatocellular carcinoma

Probiotics exert their anticancerous agents through many mechanisms including a direct impact on modulating gut microbiota, through immune modulation, improved intestinal barrier function, decreased bacterial

Table 1: Probiotics potential against cancer treatment.

Probiotics strains	Cancer treatment	Significant role	Reference
Bacillus polyfermenticus	Colon cancer treatment	Antitumor effect against HT-29, DLD-1 and Caco-2 cells.	(Ma *et al.*, 2010)
Lactobacillus acidophilus	Role against HCC and human colon cancer.	It exerts the anti-tumorous activity in Encapsulated form.	(Urbanska *et al.*, 2009; Lee *et al.*, 2008)
L. casei and *L. rhamnosus*	Against colorectal cancer	Effect on human colorectal HCT-116 cells which decreased metastasis	(Escamilla *et al.*, 2012)
L. plantarum	colon cancer	Exhibit a promising antioxidant property to decrease carcinoma	(Hakansson *et al.*, 2012)
Prohep (probiotic mixture) including *Prevotella* and *Oscillibacter*	Potential against Hepatocellular carcinoma (HCC)	Reduction of Th17 cell polarization and encourage the anti-inflammatory Treg/Tr1 cells differentiation.	(Li *et al.*, 2016)
Propionibacterium spp	Colorectal cancer (CRC) prevention	By killing CRC cells	(Hakansson *et al.*, 2012; Lan *et al.*, 2007)
Propionibacterium freudenreichii	Works against gastric cancer	Proapoptotic potential against gastric cancer HGT-1 cells.	(Cousin *et al.*, 2012)

translocation, anti-inflammatory and anti-pathogenic activities, as well as reducing tumor formation and metastasis [reviewed in (Yu and Li, 2016)].

Binding/adsorption of carcinogens

Some previous studies explained that the probiotics (strains of lactic acid bacteria) can bind and immobilize the dietary toxic substances such as mycotoxins in the gut lumen to decrease the toxicity of these substances and thus resulting in the improvement of gut and liver health. These probiotics bacteria can reverse the toxic effects of mycotoxins on intestinal epithelia (El-Nezami *et al.*, 2002; El-Nezami *et al.*, 2002b). Aflatoxin B1 (AFB1)-induced decrease in the trans-epithelial electrical resistance (TEER) was abolished by probiotic bacteria indicating the ability of the bacterial strain to bind with AFB1. This leads to a decrease in AFB1 bioavailability (Gratz *et al.*, 2006). These reports confirm that probiotics decreased the bioavailability of carcinogen AFB1, and thus reduce HCC incidences.

Improvement of intestinal barrier function

An efficient gut barrier is significant to regulate the diffusion of bacterial components into the liver. By damaging the intestinal barrier function the intestinal permeability to gut-derived LPS is increased which results in HCC pathogenesis by provoking pro-inflammatory responses in the liver (Yu *et al.*, 2010). Probiotics change the microbiota composition to reduce the outgrowth of Gram-negative bacteria and thus enhancing the intestinal barrier that prevents the translocation of endotoxins. As a result, tumorigenic inflammation in the liver was minimized (Zhang *et al.*, 2012).

Modulation of short-chain fatty acids (SCFA) production

Some important probiotics including bifidobacteria and lactobacilli can change the composition of gut microbiota and thus the production of Short-chain fatty acids (LeBlanc *et al.*, 2017) that results in the reduction of risk of developing cancer, including HCC. It had studied that the anti-cancer effects of probiotics were due to the production of SCFA (Li *et al.*, 2016).

Conclusions and future perspective

In conclusion, liver cancer is a very fatal disease which is associated with various risk factors. The incidences of HCC are increasing globally. Probiotics may represent innovative, safe and low-cost strategies to prevent or treat HCC by changing the composition of gut microbiota. Probiotics show their anti-cancer effects by various mechanisms including regulation of Th17 response, Binding/adsorption of carcinogens, improvement of intestinal barrier function, Modulation of SCFA production. The extensive mechanistic investigations on gut microbiota and suitable selection of useful bacterial strains are required to establish probiotics as an alternative therapeutic method for cancer.

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