ORIGINAL ARTICLE

Role of Biobran (Arabinoxylan Rice Bran) on Patients with Advanced Stage Hepatocellular Carcinoma

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Abstract

Background and objectives: Carcinoma of liver – renowned, has taken third position in world ranking, comparing to other causes for cancer-related death, however, curative treatment of hepatocellular carcinoma (HCC) is largely absent and even proper management of HCC patients is extremely difficult. The situation becomes more complex when HCC patients are attended by physicians in their terminal state. Arabinoxylan rice bran (biobran) is an inherent product and hemicellulose which is denatured, as well as gained by hemicellulose including a number of hydrolyzing enzymes of carbohydrate from Shiitake mushrooms. It enhances activities of different immune cells and may exert some effects in cancer patients.

Materials and methods: In this observation study, the implication of biobran was assessed in a small group of 52 HCC patients. One halves of the patient received biobran and the other halves received best supportive care (BSC).

Results: Baseline parameters in two groups were mostly comparable. During observation after 30, 60, and 90 days, a total of six, one, and one patient were alive in biobran group, respectively. The survival of cancer patients of the BSC group was comparable at these time points (6, 1, and 0, respectively) with no statistical significance. After 30 days of treatment, those who were survived in biobran group, the mean CP score was 11.00 ± 1.55 and 10.50 ± 0.84 at pretreatment and posttreatment, respectively, ($p = 0.20$).

Conclusion: Biobran may be of some benefit for terminal HCC, however, more studies are warranted to optimize dose and duration of therapy.

Keywords: Biobran, Carcinoma of liver, Food supplement, Terminal stage.

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Introduction

Hepatocellular carcinoma (HCC) has taken fifth position among all cancers and being recognized as the third ranked common of all cancer-related deaths globally.[1] Being the fifth most common cancer in men and the eighth commonest in women, it is cleared that, malignancy of liver has proven its life-threatening impact.[2] The incidence of HCC in Bangladesh is the 8th among all cancers. Hepatocellular carcinoma ranks the third among all cancer-related deaths in Bangladesh.[3–5] However, in Bangladesh, most patients are diagnosed with advanced HCC due to the lack of the effective surveillance and monitoring system for HCC. The principal objective of the study is by using arabinoxylan rice bran (biobran), identifying the surviving time and enriching the living standard in terminal stage carcinoma of liver patients by using arabinoxylan rice bran (biobran).

The segment of rice which is found after taking away the husk and edible endosperm is called rice bran. Polysaccharides which have cell walls, having the rice seed endosperm. Carrying different kinds of bioactive components with chemo-preventive activity, rice bran includes γ-oryzanol, caffeic acid, ferulic acid, coumaric acid, tricin, phytic acid; the vitamin E isoforms α-tocopherol, γ-tocopherol, and various tocotrienols; phytosterols, for example, β-sitosterol, capesterol, stigmasterol, and carotenoids like α-carotene, β-carotene, lycopene, and lutein; micronutrients such as calcium, magnesium, and nine B vitamins; and essential amino acids such as histidine, tryptophan, arginine, and cysteine. The process of beneficial alteration of giving rise to rice bran with bacterial or fungal agents can enhance the biocompatibility by improving the efficacy of the antioxidant activities. The hemicellulose improves the extract with a huge number of carbohydrate-hydrolyzing enzymes accelerate the production of bio-brain from the shiitake mushroom.[6,7]

The only three footsteps of generating process of MGN-3/biobran are: (1) polysaccharides, removal whereas the source is from

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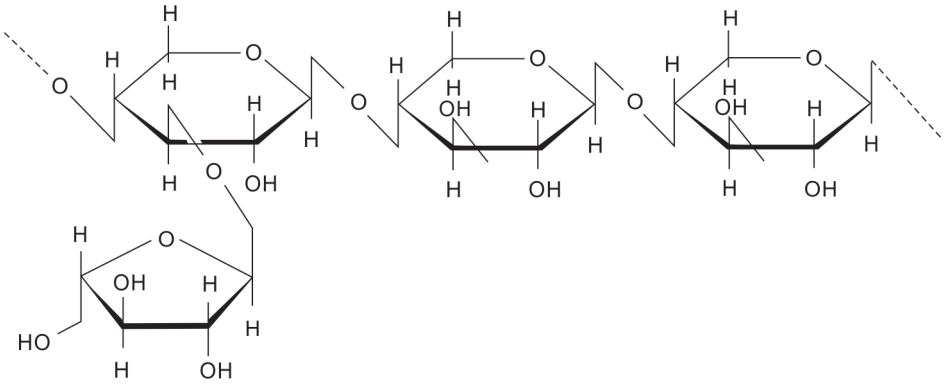
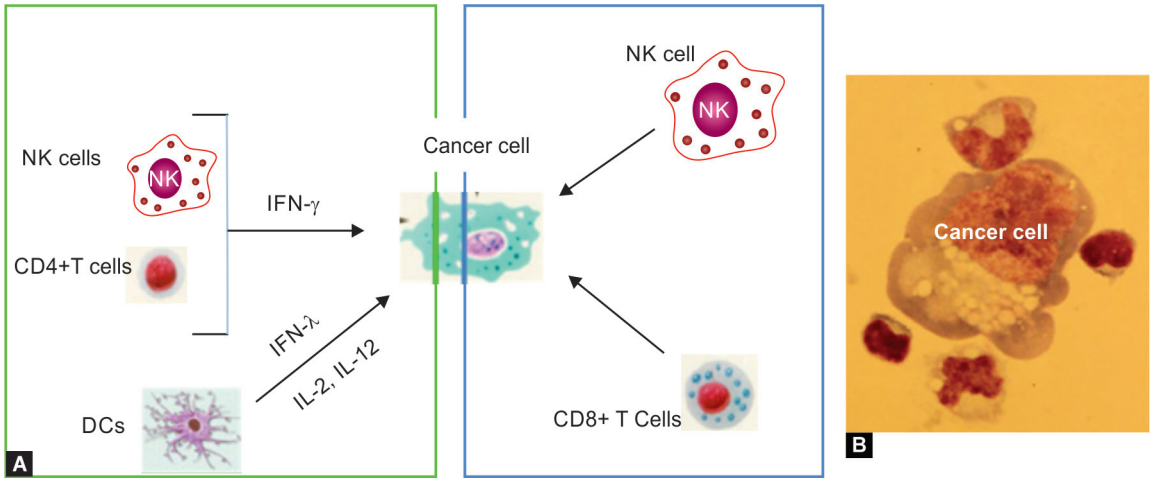


Fig. 1: Chemical structure of biobran



Figs 2A and B: Biobran increases the mode of action of varieties of immune cells to attack cancer cells. (A) Schematic of MGN-3 enhancement of cytotoxic reactivity of immune cells with anticancer effect and of production of different cytokines; (B) MGN-3 increases the binding of different immune cells to cancer cells. Notice the blebbing of this cancer cell membrane and the presence of vacuoles (Giemsa stain)

rice bran; (2) production from origin of multiple shiitake-derived carbohydrate-hydrolyzing enzymes used to alter the extracted polysaccharides; and (3) half of the reaction of hydrolysis in rice bran hemicellulose polysaccharides by the carbohydrate-hydrolyzing enzymes obtained from shiitake mushrooms. Last but not the lease, altering the elements with high heat and pressure and final outcome is, achieving a powder form.[6]

It was previously found that, through their capability in increasing apoptosis, the effect in non-carcinogenic of the rice bran-derived bioactive elements is arbitrated, reduce cell proliferation, and significantly change the enhancement of cell cycle in cancerous cells (Figs 1 and 2).[7]

The best supportive treatment measures in the mean of cancer patients are known as best support care (BSC). The European Organization for Research and Treatment of Cancer (EORTC) defines BSC as, "supportive treatment interventions in case of patients having carcinoma encompass the multi-professional approach to the individual all-encompassing physical, psychosocial, cultural needs and spiritual and should have the existence at all times of the illness for patients of all ages and regardless of the current treatment intention of the interventions directed against the illness." Approaching for the enhancing of the standard of life of patients through the management of pain as well as other physical, psychosocial, and spiritual problems.

Materials and Methods

A study which was observational in type, was run by the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka from September 2019 to December 2020. A sample size of 52 terminal stage of HCC patients was included [26 patients for biobran with BSC (biobran group) and 26 patients for BSC only)] clinical and biochemical parameters were evaluated at the level of standard, day-30, day-60, and day-90. Primary end point was durability at 3 months or death. Secondary end point was the improvement of quality of life assessed by the Eastern Cooperative Oncology Group (ECOG) performance status and improvement of liver function assessed by Child-Turcotte-Pugh (CTP) score.

The follow-up procedure was strictly maintained for all of the patients for at least 3 months or up to death. Adverse events were closely monitored. The death of admitted patients was recorded physically and those who died outside were recorded over the telephone.

Serum alanine aminotransferase (ALT), aspartate amino-transferase (AST), total bilirubin, prothrombin time (INR), serum albumin, serum creatinine, serum electrolyte, complete blood count (CBC), alpha-fetoprotein (AFP), and hepatitis B surface antigen (HBsAg) were checked for all patients. Also, antigens with hepatitis B (HBeAg), anti-HBe, and anti-HBc were measured,

Table 1: Baseline criteria of the study population

Characteristics	*Biobran (n = 26)*	*BSC (n = 26)*	*Total (n = 52)*	*p-value*
Age (years), Median (range)	52 (30–75)	50 (27–90)	51 (27–90)	[a]0.70[ns]
Sex				
Male	22 (85%)	24 (92%)	46 (88%)	[b]0.38[ns]
Female	4 (15%)	2 (8%)	6 (12%)	
Presentation				
Abdominal pain	19 (73%)	20 (77%)	39 (75%)	[b]0.75[ns]
Jaundice	14 (54%)	17 (65%)	31 (60%)	[b]0.48[ns]
Hb (gm/dL) (mean ± SD)	11.02 ± 1.57	11.36 ± 1.62	11.19 ± 1.59	[a]0.47[ns]
Platelet ($\times 10^3/mm^3$) (mean ± SD)	209 ± 115	198 ± 72	204 ± 96	[a]0.69[ns]
ALT (U/L) (mean ± SD)	95.72 ± 66.77	136.25 ± 107.85	115.57 ± 90.66	[a]0.12[ns]
S. bilirubin (mean ± SD)	6.51 ± 6.20	7.65 ± 5.10	7.07 ± 5.66	[a]0.49[ns]
S. albumin (mean ± SD)	2.36 ± 0.44	2.43 ± 0.49	2.39 ± 0.46	[a]0.63[ns]
INR (mean ± SD)	1.32 ± 0.30	1.53 ± 0.64	1.42 ± 0.50	[a]0.15[ns]
CP score (mean ± SD)	10.68 ± 0.99	10.54 ± 0.93	10.61 ± 0.95	[a]0.62[ns]
AFP (ng/mL)				
<200	6 (23%)	5 (19%)	11 (21%)	[b]0.12[ns]
≥200	20 (77%)	21 (81%)	41 (79%)	

BSC, best supportive care; ns, not significant; [a]*p* value reached from unpaired *t*-test; [b]*p* value reached from Chi-square test

if required. Using real-time PCR and anti HCV was checked and if positive, HCV RNA estimation was done. HBV DNA estimation was done for abdominal ultrasound, and CT scan/MRI and upper GI endoscopy were also accomplished as and when necessary. Fine needle aspiration for cytology was done where CT scan/MRI finding was inconclusive.

The information was gathered by the statistical package SPSS (version 20.0 IBM Corp: Armonk NY, USA). Variables in quantitative type distributing were published as mean ± standard deviation (SD) and those not normally distributed were expressed as median values (range). The Chi-square (χ^2) test and Fisher's exact test were used for comparing qualitative variables and the student's *t*-test and paired *t*-test for comparing quantitative continuous variables when appropriate. Survival was evaluated with the Kaplan–Meier method. The *p*-values < 0.05 was top of the notch.

Overall fitness of a patient was often assessed by a performance status scale named ECOG. The ultimate feedback for the performance status of patients is found worse in almost all malignancies.

Results

Guideline of the Study Patients

The characteristics according to the control group of the respondents are described in Table 1. The average age of the population of the patients was 52 years in the biobran group and 50 years in the BSC group. There was male predominance (85% in biobran group and 92% in BSC group). Pain in abdomen was the most common presentation and found in 73% patients of biobran group and 77% of BSC group expressed pain in abdomen. The average hemoglobin level was 11.02 ± 1.57 (gm/dL) in biobran group and 11.36 ± 1.62 (gm/dL) in BSC group. The mean platelet count was found 209 ± 115 × $10^3/mm^3$ in biobran group and 198 ± 72 × $10^3/mm^3$ in BSC group. The mean ALT was found 95.72 ± 66.77 U/L in biobran group and 136.25 ± 107.85 U/L in BSC group. The average serum bilirubin was found 6.51 ± 6.20 mg/dL in biobran group and 7.65 ± 5.10 mg/dL in BSC group. The mean serum

Table 2: Distribution of the study patients by etiology

	Biobran (n = 26)		*BSC (n = 26)*		*Total (N = 52)*	
Etiology	*N*	*%*	*N*	*%*	*n*	*%*
CHB	22	85	20	77	42	81
CHC	3	11	1	4	4	8
Others	1	4	5	19	6	11

BSC, best supportive care

Table 3: Comparison of Child–Pugh score between two groups after 30 days

Survived patients after 30 days (n = 12)	*Child–Pugh score (Mean ± SD)*		
	Pretreatment	*After 30 days*	*p-value*
Biobran group (*n* = 6)	11.00 ± 1.55	10.50 ± 0.84	0.20 [ns]
BSC group (*n* = 6)	10.50 ± 1.05	11.00 ± 1.27	0.29[ns]

BSC, best supportive care; ns, non-significant

Table 4: Distribution of the baseline ECOG performance status of study patients

ECOG performance status	*Biobran (n = 26)*	*BSC (n = 26)*	*Total (n = 52)*	*p-value*
PS ≤ 2	0 (0%)	4 (15%)	4 (8%)	0.11[ns]
PS 3	17 (65%)	15 (58%)	32 (61%)	
PS 4	9 (35%)	7 (27%)	16 (31%)	

BSC, best supportive care; ns, non-significant. *p* value reached from Chi-square test

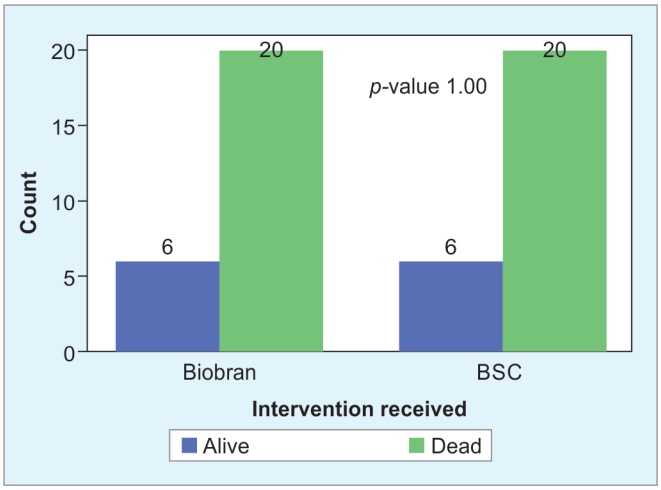


Fig. 3: Bar diagram showing outcome of patient after 30 days

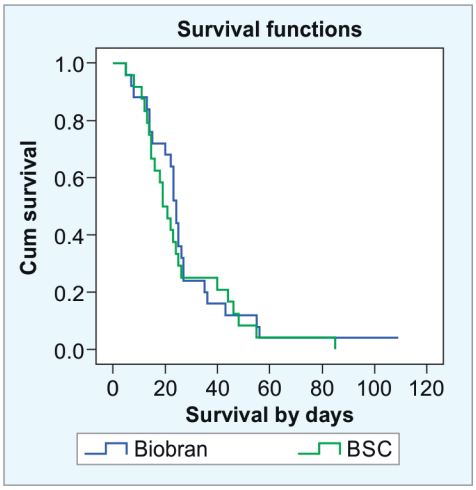


Fig. 4: Kaplan Meier curve for survival

Table 5: Usage of biobran resulted in improvement of ECOG performance status after 30 days

Surviving patients after 30 days (n = 12)	*PS improvement after 30 days*			
	Yes	*No*	*Total*	*p-value*
Biobran group (*n* = 6)	4 (67%)	2 (33%)	6 (100%)	0.014[s]
BSC group (*n* = 6)	0 (0%)	6 (100%)	6 (100%)	

BSC, best supportive care; PS, ECOG performance status; s, significant. *p* value reached from Fisher's exact test

Table 6: Outcome of the patients after 60 days

	Biobran group (n = 26)		*BSC group (n = 26)*		
Outcome	*N*	*%*	*N*	*%*	*p-value*
Survived	1	4	1	4	0.98[ns]
Dead	25	96	25	96	

BSC, best supportive care; ns, non-significant. *p* value reached from Chi-square test

Table 7: Patients outcome after 90 days

	Biobran group (n = 26)		*BSC group (n = 26)*		
Outcome	*N*	*%*	*N*	*%*	*p-value*
Survived	1	4	0	0	0.32[ns]
Dead	25	96	26	100	

BSC, best supportive care; ns, non-significant. *p* value reached from Chi-square test

albumin was found 2.36 ± 0.44 gm/dL in biobran group and 2.43 ± 0.49 gm/dL in BSC group. The median INR was found 1.32 ± 0.30 in biobran group and 1.53 ± 0.64 in BSC group. Mean Child–Pugh score was found 10.68 ± 0.99 in biobran group and 10.54 ± 0.93 in BSC group. AFP level ≥ 200 ng/mL was found in 77% patients of biobran group and 81% of BSC group.

Maximum patients were infected with HBV in both groups (Table 2).

No significant difference was seen in Child–Pugh score in both groups due to supplement use (Table 3).

In Table 4, baseline ECOG performance status was evaluated.

As shown in Table 5, usage of biobran resulted in improvement of ECOG performance status after 30 days.

Outcome of the Enrolled Respondents

After 30 days of follow-up, 6 (23%) patients survived in both biobran group and BSC group (Fig. 3). After 60 days, one (4%) patient survived in each group, and after 90 days, one (4%) patient survived in the biobran group but no patient survived in the BSC group (Tables 6 and 7). These differences were not top of the notch ($p > 0.05$). The middle survival time for enrolled respondents, biobran group respondents, and BSC division respondents were 23 days (95% CI: 20–25), 24 days (95% CI: 22–25) and 19 days (95% CI: 14–23), respectively. The Kaplan–Meier curve for overall survival is presented in Figure 4, showed no significant survival difference between two groups at 30, 60, and 90 days.

Discussion

Regarding baseline ECOG performance status of the patients, the current study found that the majority of the terminal stage HCC patients presented with PS 3, 65% in the biobran group and 58% in the BSC group. However, no vital existence of ($p > 0.05$) variety is observed between the groups.

After 30 days of treatment, the majority of (67%) patients of the biobran group had shown improvement of performance status; but in the BSC group, there was no improvement in performance status among patients. This difference was statistically significant (<0.05). This observation is consistent with the observation of Takahara and Sano;[8,9] they found that the administration of biobran improves the quality of life in cancer bearing patients, including HCC patients.

In the present study, no significant improvement of Child–Pugh score was detected between the two groups after giving the treatment. In this study, it was observed that biobran administration had no survival benefit at 30, 60, and 90 days follow-up. Similarly, earlier study carried out by another study[10] which illustrated no change in survival time by using various BRMs in HCC patients. In terminal stage (BCLC-D) HCC patients, the middle durability time is 3 months guided by the European Association for the study of liver (2018). In this study, the middle durable time for all the respondents, biobran group patients, and BSC group patients were 23, 24, and 19 days, respectively, for lower median survival time.[8] They found in their study the median survival time was 1 month for terminal stage HCC patients. In the current study, it is observed that AFP

level ≥ 200 ng/mL was associated with worse survival (*p*-value 0.047). Similar observation had been made by a previous established study[8] where AFP ≥ 400 ng/mL was associated with worse survival. The present study didn't observe any adverse effects of biobran. Other studies also showed that none of the patients was developed any negative reaction produced by biobran.[8,11] The overall fitness of a patient was often assessed by the ECOG performance status scale. The patient's outcome with three or four performance status is worse near to close to all carcinomas.

Conclusion

It can be concluded that biobran may have some transient effect on improving quality of life in terminal stage HCC patients, which was observed by improvement of ECOG Performance Status. However, this was not sustained. The sample size is so small that further validation is essential. However, it does not seem that biobran improves survival or regresses HCC progression. The effect of ECOG performance improvement by biobran may be applied on a case-by-case basis.

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