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Research Article

From orchard to bedside: Prospective, real-world study exploring the utility of Indian gooseberry (amlaki) in end stage hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, despite significant advances in its treatment. In Bangladesh, as in many other countries, most patients present at an advanced stage when curative options are no longer feasible. Therefore, it is essential to explore locally available, homegrown solutions to address this growing health challenge. A total of sixty patients with end-stage HCC were enrolled in this study and randomly assigned into 2 groups, each comprising 30 patients. Both groups received best supportive care. In addition, patients in Group A were received 1000 mg of *Phyllanthus emblica* extract in powder formulation in capsules. The study included drug collection, preparation, extraction, protein isolation, molecular docking, data analysis, and ultimately a clinical trial. The baseline characteristics of patients in both groups were comparable. The findings demonstrated a survival benefit and improvement in quality of life among patients treated with *Phyllanthus emblica* compared to the control group; however, these results were not statistically significant. Overall, the study established the safety and suggested limited efficacy of *Phyllanthus emblica* in patients with end-stage HCC. These findings may well pave the way for future research on repurposing and repositioning traditional medicines into modern medical practice.

Introduction

Hepatocellular carcinoma (HCC) is the 6th most common diagnosed cancer and the 3rd leading cause of cancer deaths globally (Ganjalikhaniet al., 2020). Annually, there are morethan 800,000 new cases of HCC resulting in 700,000 deaths per year globally (Ganjalikhani et al., 2020). Further adding to our worries, the incidence of HCC is on the rise across the globe, which has been attributed to

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increasing prevalence of chronic viral hepatitis B (HBV) and C (HCV), alcohol, and metabolic dysfunction associated fatty liver diseases and cirrhosis (Cho et al., 2023). Despite recent advances in therapeutics, overall survival in HCC remains dismal, with a 5-year survival rate of less than 15% (Yousef et al., 2020).

In Bangladesh, the picture is even gloomier as most of our HCC patients are diagnosed with end-stage disease. The reasons are multi-factorial, including a lack of effective surveillance for HCC and liver cirrhosis. We are hardly left with any option whatsoever, as at diagnosis, most HCC patients in Bangladesh are beyond indications for surgery, ablation, chemotherapy, chemoembolization, or a combination of these therapeutic approaches. The challenge is therefore to find homegrown remedies that offer some benefit to our end-stage HCC patients, who constitute the bulk of our HCC burden in this resource-constrained country.

With an array of shortcomings, right from a lack in funding to research infrastructure, research attitude, and appropriate human resources, finding the correct answer to this ever-imposing challenge is not any easy task for us. We simply cannot embark on the drug discovery and development race, as it is still not our dish of rice. Our focus is therefore on what is doable for us. We hypothesized that our traditional medical practice can be a game-changer. Despite having a rich heritage of traditional medical practice, the harsh reality is that most of our traditional medical literature is lost, with few exceptions.

Phyllanthus emblica is an important medicinal plant in Ayurveda and Unani medicine and is a key constituent of many herbal formulations. In the Indian subcontinent, it is known as *Amalaki* in Bengali and Sanskrit and Amla in Hindi (Fig.1). *Phyllanthus emblica* has been extensively studied for its phytoconstituents, biological activities, and therapeutic potential, and has been shown to possess anti-diabetic, anti-inflammatory, antioxidant, hepato-protective, radio-modulatory, and immune-modulatory properties (Yadav et al., 2017).

Fig. 1. *Phyllanthus emblica* (amlaki).

Phyllanthus emblica is rich in polyphenols and hydrolysable tannin-derived compounds, which prevent mutagenesis and lipid peroxidation induced by carcinogens. The therapeutic potential of different components of *Phyllanthus emblica* has been extensively studied. Most of its active constituents, namely tannins, chebulagic acid, ellagic acid, etc., have pro-apoptotic and anti-proliferative activity against cancer cells. Its phytoconstituents act synergistically to make *Phyllanthus emblica* a strong free-radical scavenger, which protects DNA damage from reactive oxygen species (Ngamkitidechakul et al., 2010). *Phyllanthus emblica* extracts inhibit the proliferation of various cancer cell lines, including A549, HepG2, HeLa, MDA-MB-231. (Ahmad et al., 2021).

It has been demonstrated that *Phyllanthus emblica* reduces serum transaminases (ALT and AST), TNF-α, serum triglyceride (TG), IL-1β, and hepatic triglyceride (HTG) and increases the viability of hepatocytes following ethanol-induced liver injury in rats (Pramyothin et al., 2006). *Phyllanthus emblica* also exerts hepato-protective effects against anti-tubercular drugs as well as in carbon-tetrachloride (CCl4) and thioacetamide-induced hepatic fibrosis in rat models (Ahmad et al., 2021; Jose and Kuttan, 2000). In this article, we describe our recent, prospective, real-world experience with *Phyllanthus emblica* in patients with end-stage HCC.

Materials and Methods

Preparation and dose of the study drug

In this study, we used capsules containing a powder formulation of *Phyllanthus emblica* extract. The study determined the drug collection, preparation, extraction, protein preparation, molecular docking analysis and chemical content of *Phyllanthus emblica* extract capsules using high-performance liquid chromatography (HPLC) at the Institute of Technology Transfer and Innovation (ITTI), Bangladesh Council of Scientific and Industrial Research (BCSIR). ITTI also ensured that the powder formulation was pharmaceutical-grade and in compliance with the pharmacopoeia. Pharmaceutical-grade capsules were then manufactured by Beacon Pharmaceuticals PLC. Each capsule contained 500 mg *Phyllanthus emblica* extract.

Collection, extraction, and storage of the study drug

Phyllanthus emblica was collected from different super-shops in Dhaka city. The fruits were cleaned with running tap water, then immersed in a fruit and vegetable washing solution for 30 minutes. Washing was repeated in deionized water. The fruits were then chopped into small pieces and oven-dried at 60°C for 24 hours. After 24 hours, the dried fruits were ground into a powder and stored at room temperature in a dark place.

About 40 g of dried powder was added to 200 mL of analytical-grade methanol and incubated for 5 days at room temperature in the dark. After 5 days, the dissolved methanolic powder was filtered by Whatman Filter Paper No 1. Residues were collected in another jar, evaporated under reduced pressure, and dried using a rotary evaporator at 70°C for 3 days. The dried extracts were labeled and stored in sterile screw-capped bottles at 4°C in a refrigerator for further use.

Chromatographic investigation

Flavonoids were quantitatively analyzed using a reverse-phase HPLC system with a UV system. A C18 column (25 cm x 4.6 mm, 5 µm) was used to separate the compounds. Column temperature and flow rate were maintained at 35 °C and 1 mL/min, respectively. The injection volume was 10 µL, and detection was at 350 nm. The mobile phase was composed of 0.5% acetic acid in water and acetonitrile. Kaempferol concentration was 268.5485 mg/g in *Phyllanthus emblica* (Fig. 2).

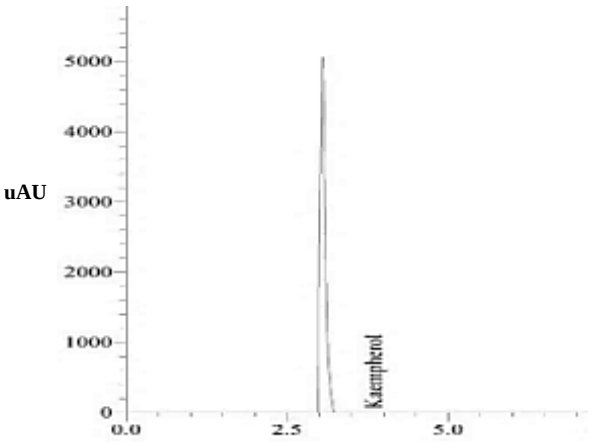

Fig. 2. HPLC Chromatogram of Kaempferol.

Anti-oxidant assay

Radical scavenging action of *Phyllanthus emblica* against the stable 2, 2-diphenyl-2-picrylhydrazyl (DPPH) radical was measured spectrophotometrically. In order to measure the DPPH scavenging activity of *Phyllanthus emblica*, a DPPH solution was prepared by adding DPPH (12.5 mg) to 50 mL of methanol. Absorbance of this stock solution was measured at 517 nm. The DPPH solution was diluted with methanol to an absorbance of 0.98 and stored in an amber-colored bottle ready for use. An aliquot of 200 µL of *Phyllanthus emblica* at different concentrations (120, 140, 160, 180, and 200 µg/mL prepared in methanol) was added to 1 mL of DPPH solution. The reaction mixture was incubated at 37 °C in the dark for 20–30 min. Absorbance decrease was determined at 517 nm. Ascorbic acid was used as a standard. The reaction was performed in triplicate. Scavenging activity was calculated by using the following equation, where Q represents DPPH scavenging activity.

$$Q(\%) = \frac{\text{Absorbance of control} - \text{Absorbance of sample}}{\text{Absorbance of control}} \times 100$$

Protein preparation, molecular docking, analysis, and visualization

The 3D crystal structure of ornithine amino-transferase, OAT (PDB ID: 6OIA) was obtained from the Protein Data Bank (PDB) in PDB format. Heteroatoms and water molecules were deleted from the protein chain using the Discovery Studio (Version 4.1) software package and subsequently reinserted for energy minimization, using the conjugate gradient technique to remove bad contacts between protein atoms, in Swiss-PDB Viewer (Version 4.1.0). Finally, the optimized structures were subjected to molecular docking against the active phytocompounds (chebulagic acid, quercetin, ellagic acid, kaempferol, chebulic acid, gallic acid, and ascorbic acid) retrieved from the PubChem database. Docking was done using the PyRx (Version 0.8) software package. Flexible docking was performed with a center grid box size of 30.4498, 24.1222, and 34.2317 Å along the x, y, and z directions, respectively, where the entire protein was covered by the grid box. Moreover, Discovery Studio (Version 4.1) was used for nonbonded interaction calculation and to analyze and visualize docking results (Table 1 and Fig. 3).

Table 1. Docking score of different phytochemicals of *Phyllanthus emblica* with standard drug.

Compound name	Binding affinity (kcal/mol)
Chebulagic acid	-9.5
Quercetin	-8
Ellagic acid	-8
Kaempferol	7.8
Chebulic acid	-6.9
Gallic acid	-6
Ascorbic Acid	-5.8
Cabozantinib(Std)	-8.6

Patient selection

Ethical approval of this observational study was obtained from the Institutional Review Board of Bangladesh Medical University (BMU) (approval no. 4460). The study commenced on July 15, 2023, and was completed on August 14, 2024. Patients with HCC (BCLC-D), irrespective of etiology, with ECOG performance status >2 or CTP score C, age >18 years, and both genders attending the Department of Hepatology, BMU for treatment were included in the study. Patients diagnosed with another cancer in addition to HCC and

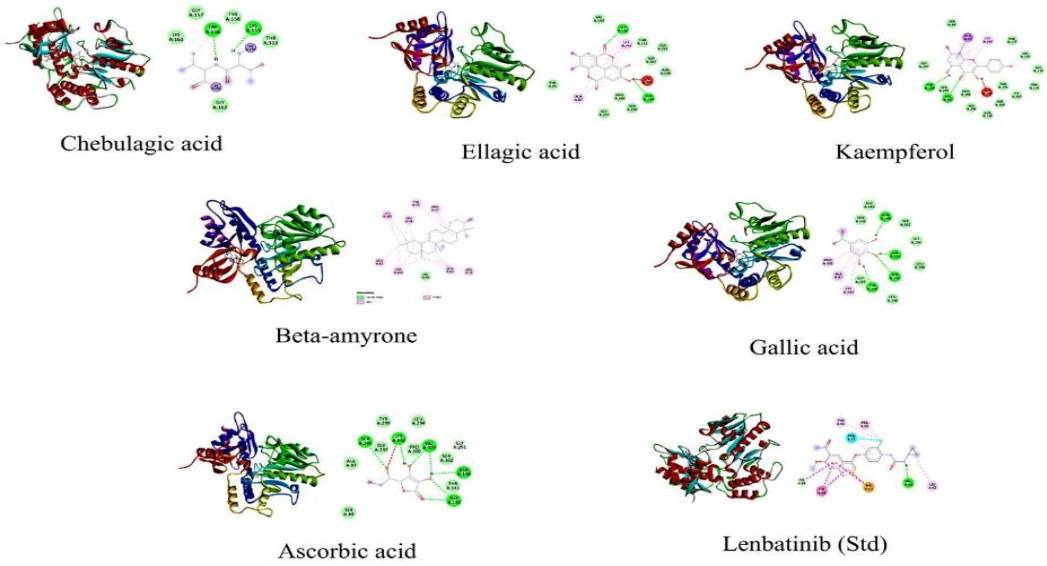

Fig. 3. Docking of different phytochemicals of *Phyllanthus emblica* with standard drug.

patients with co-morbid conditions like severe congestive cardiac failure (CCF), ischemic heart diseases (IHD), recent myocardial infarction (MI), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) etc. were excluded.

Baseline clinical evaluation and several investigations were done to meet inclusion and exclusion criteria namely, complete blood count (CBC), serum bilirubin, serum albumin, serum alanine aminotransferase (ALT), prothrombin time, serum creatinine, random blood sugar (RBS), urine routine microscopic examination (RME), alpha feto-protein (AFP) from Departments of Clinical Pathology, Biochemistry, Hematology and Microbiology, HBsAg (ELISA), Anti HBc (total) (ELISA) and Anti-HCV (ELISA) from Department of Virology, Chest X-ray (P/A view), ultrasonogram of whole abdomen and triphasic computed tomography (CT) scan of hepato-biliary system (HBS) from Radiology and Imaging Department and endoscopy of upper gastrointestinal (UGIT) at the Hepatology Department of BMU. Fine needle aspiration (FNA) from hepatic space-occupying lesions was performed in patients where indicated.

After diagnosis of end-stage HCC, the potential benefits and risks of the use of *Phyllanthus emblica* extract in capsule form were explained to the patients. They were properly informed and explained about the study's purpose and procedures. After obtaining written informed consent, 60 patients with end-stage HCC were enrolled in the study. The sample size was determined using Morgan's table for sample size. The patients were randomized into 2 groups by block randomization. Half of them (Group A, 30 patients) were selected for *Phyllanthus emblica* therapy plus best supportive care (BSC), and the other half (Group B, 30 patients) were selected for BSC only. Group A received *Phyllanthus emblica* 1000 mg daily and were followed up at 1 and 3 months or up to death. Group B patients were also followed up in a similar manner. BSC, included maintenance of nutritional status and palliative care, including but not restricted to management of pain, weakness, anorexia, insomnia, respiratory distress, ascites, coagulopathy, encephalopathy, etc. The objective of the study was to compare survival and performance status between *Phyllanthus emblica* and BSC groups.

Monitoring and compliance

The study was conducted at the Department of Hepatology of BMU between 2023 and 2024. Close communication was maintained with all patients. Permanent and present addresses and landline/cell phone numbers of all patients were kept on record. To improve patient compliance, a telephone survey was done every 2 weeks. Attendants or relatives were requested to monitor patients'drug intake. Patients were asked to bring empty capsule strips during each visit. All patients were advised to contact the study team immediately in case of any adverse event. Each patient was followed up at 1 and 3 months from initiation of treatment. Patients were encouraged to consume healthy foods as much as possible, if needed in smaller quantities, and on multiple occasions, with special emphasis on animal protein.

Results

All data were presented as mean±standard deviation (SD) and analyzed using the statistical package SPSS (version 26.0, IBM Corp., Armonk NY, USA). Qualitative data were analyzed by the Chi-square test, and quantitative data were analyzed by the Student´s t-test. The Wilcoxon rank sum was used to compare laboratory parameters and measurements before and after treatment. A statistically significant result was considered when the p-value was less than 0.05.

Comparison of demographic characteristics between the *Phyllanthus emblica* group and the BSC groups revealed that age and sex distribution were similar between the two groups. The mean age of the *Phyllanthus emblica* group was 53.5±12.1 years,

compared to the BSC group's mean age of 49.9±12.87 years, which was not statistically significant (p=0.260). Regarding sex distribution, both groups were predominantly male, with 96.7% of the *Phyllanthus emblica* group and 93.3% of the BSC group being males. The difference in sex distribution between the groups was also not statistically significant (p=0.554) (Table 2).

Jaundice was universal in both groups, present in 100% of the *Phyllanthus emblica* group and 96.7% of the BSC group. Ascites was also prevalent, observed in 96.7% of the *Phyllanthus emblica* group and 100% of the BSC group. Similarly, hepatic encephalopathy was observed in 23.3% of *Phyllanthus emblica*groupcompared to 26.7% of BSC group (Table 2).

Biochemical parameters between the two groups were also similar (Table 3). Imaging showed similar numbers of space-occupying lesions, portal vein thrombus, and extrahepatic metastases in both groups. The same goes for the aetiology of end-stage HCC, with HBV the leading cause in both groups (Table 4).

At 1 month follow-up, hepatic encephalopathy was

Table 2. Baseline demographic and clinical characteristics of the study subject

Variable	Study Subject		*p* value
	Phyllanthus emblica (n=30), n(%)	BSC (n=30), n (%)	
Age (year)[a]	53.5±12.1 (Range: 30-80)	49.9±12.87 (Range: 27-75)	0.260
Age distribution (yr.)			
< 40	6 (20.0)[b]	8 (26.7)	NS
> 40	24 (80.0)	22 (73.3)	
Gender			
Male	29 (96.7)	28 (93.3)	0.554
Female	1 (3.3)	2 (6.7)	
Physical examination			
Jaundice	30 (100)	29 (96.7)	0.313
Presence of ascites	29 (96.7)	30 (100)	0.313
Hepatic encephalopathy	7 (23.3)	8 (26.7)	0.766
Imaging findings			
Number of space occupying lesion (SOL)			
1	0 (0.0)	3 (10.0)	0.076
2-3	2 (6.7)	0 (0.0)	0.150
>3	28 (93.3)	27 (90.0)	0.640
Portal vein thrombosis	23 (76.7)	17 (56.7)	0.100
Extrahepatic metastasis	7 (23.3)	9 (30.0)	0.559

[a]Mean±SD; [b]Numbers in parentheses show percentage; CN, not significant; Unpaired t-test and Chi-square test were performed. A $p<0.05$ was considered as significant.

Table 3. Baseline biochemical characteristics and etiology of the study sujbect

Variable	*Phyllanthus emblica* (n=30)	BSC (n=30)	*p*-value
Haemoglobin (gm/dl)	11.5±2.1	10.7±1.7	0.119
Platelet (10^9/L)	208.0±78.2	230.0±119.9	0.401
ALT (U/L)	103.5±80.7	95.6±61.4	0.672
S. Bilirubin (mg/dl)	7.75±10.02	10.5±10.3	0.303
S. Albumin (g/dl)	3.24±4.50	2.65±0.63	0.479
INR	1.41±0.49	1.39±0.37	0.868
S. Creatinine (mg/dl)	0.92±0.31	1.09±0.40	0.075
Na (mmol/L)	129.5±5.3	130.9±5.3	0.308
K (mmol/L)	4.55±0.84	4.37±0.95	0.425
AFP (ng/ml)	17328.4±37116.8	8218.0±19229.2	0.237
≤200	8(26.7%)	13(43.3%)	
201-400	2(6.7%)	2(6.7%)	
>400	20(66.7%)	15(50.0%)	
Child-Turcotte-Pugh score(CTP)	10.1±0.8	10.17±1.46	0.913

[a]Mean±SD; [b]Numbers in parentheses show percentage; Unpaired t-test and Mann-Whitney testwere performed. A $p<0.05$ was considered as significant.

Table 4. Etiology of the study subject.

Variables	Study Subject		*p* value
	Phyllanthus emblica (n=30) n (%)	BCS (n=30) n(%)	
Hepatitis B virus (HBV)	18 (60.0)	17 (56.7)	
Hepatitis C virus (HCV)	4 (13.3)	4 (13.3)	
Non-alcoholic steatohepatitis(NASH)	3 (10.0)	3 (10.0)	0.3
Occult hepatitis B virus infection (OBI)	4 (13.3)	1 (13.3)	
Others	1 (13.3)	5 (16.7)	
Total	30 (100)	30 (100)	

Numbers in parentheses show percentages; Chi-square test was performed; A p-value <0.05 was considered as significant.

reported in 35.7% BSC group, but absent in *Phyllanthus emblica* group, with a statistically significant difference (p=0.014) (Table 5). CTP value was also significantly lower in the *Phyllanthusemblica* group (10.00 ± 0.96) compared to the BSC group (11.07±1.21) (p = 0.015) (Table 6).

Table 5. Physical examination of the study subjects at 1 month (n=29).

Variables	Study Subject		*p* value
	Phyllanthus emblica (n=30) n (%)	BCS (n=30) n(%)	
Jaundice	14 (93.3)	13 (92.9)	0.960
Presence of ascites	14 (100)	14 (100)	1.00
Hepatic encephalopathy	0 (0.0)	5 (35.7)	0.014

Numbers in parentheses show percentages; Chi-square test was performed; A p-value <0.05 was considered as significant.

At the 3-months follow-up, the CTP value was slightly lower in the *Phyllanthus emblica* group (10.00±1.41) compared to BSC group (11.33±2.08), but the difference was not statistically significant (p=0.355) (Table 6).

Table 6. Etiology of the study subject.

CTP Value	Study Subject		*p* value
	Phyllanthus emblica (n=30), n (%)	BCS (n=30), n(%)	
Baseline	10.1 ± 0.8	10.2±1.5	0.913
1st follow up (1st month)	10.0±1.0 (n=15)	11.1±1.2 (n=14)	0.015
2nd follow up (3rd month)	10.0±1.4 (n=4)	11.3±2.1 (n=3)	0.355

[a]Mean±SD; Chi-square and Fisher Exact test were performed; A p-value <0.05 was considered as significant.

At the 3-month follow-up, 75.0% patients in the *Phyllanthus emblica* group and 33.3% of the BSC group were classified as Eastern Cooperative Oncology Group (ECOG) performance status (PS) 3, indicating a better performance status in the *Phyllanthus emblica* group, though the difference was not statistically significant (p=0.270) (Table 7).

Table 7. Distribution of the study patients by Eastern Cooperative Oncology Group.

ECOG	Study Subject		*p* value
	Phyllanthus emblica (n=30), n (%)	BCS (n=30), n(%)	
Baseline			
ECOG PS2	0 (0.0)	3 (10.0)	
ECOG PS3	21 (70.0)	17 (56.7)	0.176
ECOG PS4	9 (30.0)	10 (33.3)	
1st follow up (1st month)	(n=15)	(n=14)	
ECOG PS2	2 (13.3)	1 (7.1)	
ECOG PS3	10 (66.7)	7 (50.0)	0.453
ECOG PS4	3 (20.0)	6 (42.9)	
2nd follow up (3rd month)	(n=4)	(n=3)	
ECOG PS3	3 (75.0)	1 (33.3)	0.270
ECOG PS4	1 (25.0)	2 (66.7)	

[a]Mean±SD; Chi-square and Fisher Exact test were performed; A p-value <0.05 was considered as significant.

At 1-month follow-up, 50.0% of patients in the *Phyllanthus emblica* group and 53.3% of patients in the BSC group expired. Although more patients survived in *Phyllanthus emblica* group, it was not statistically significant. At 3-month follow-up, 73.3% in the *Phyllanthus emblica* group and 78.6% in the BSC group died, once again showing statistically non-significant survival benefit in the *Phyllanthus emblica* group (Fig. 4).

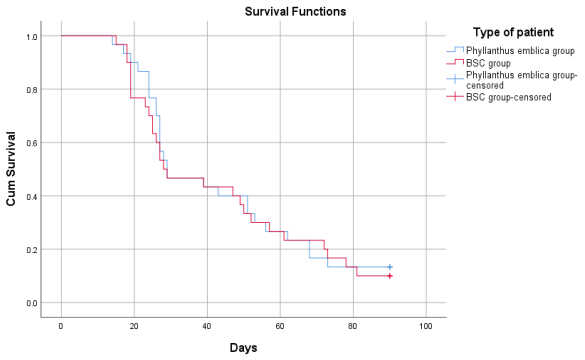

Fig. 4. Kaplan-Meier curve for survival of HCC patients.

Discussion

A review of the literature reveals that several nutrients and herbs have been used in HCC, mainly with preventive intent. Consuming fish rich in n-3 polyunsaturated fatty acids, or supplementing with n-3 polyunsaturated fatty acids, was protective against HCC development in patients with chronic HBV and HCV infection (Sawada et al., 2012). Similarly, studies suggest that fresh fruits and vegetables rich in polyphenols regulate multiple intracellular signaling pathways and reduce the risk of HCC development (Cazarolli et al., 2008; Kiruthiga et al., 2020). The protective role of coffee, which is rich in polyphenols and contains antioxidants and anti-mutagenic compounds, against HCC is also well established (Tao et al., 2008; Kennedyet al., 2017).

However, our focus was more on treatment. Earlier, we worked with herbal medicines produced in the West for the management of end-stage HCC. We conducted two clinical trials with a combination of *Camellia sinensis* (green tea), *Cinnamomum verum* (cinnamone) and *Glycyrrhiza glabra* (glycyrrhizin),

among others, in 29 and 60 patients (Matsui et al., 2002; Morihara et al., 2012). In vitro studies have shown that this combination inhibits HCC cell line proliferation by inducing cell cycle arrest, inhibiting cancer cell proliferation, differentiation,angiogenesis, invasion and metastasis and by stimulating apoptosis (Al-Mahtab et al., 2015). Both studies revealed no significant short-time survival or quality of life benefits. Similarly, our third study with rice bran, which is known for its chemopreventive effect by increasing apoptosis, reducing cell cycle proliferation, and alteration of cancer cell cycle, (Henderson et al., 2012) also showed a non-significant survival benefit and improvement of quality of life in end-stage HCC (Ashrafujjaman et al., 2023). Similarly, other researchers have shown a beneficial role for nutrients in end-stage HCC (Matsui et al., 2002; Morihara et al., 2012).

Our present study revealed a non-statistically significant survival benefit among end-stage-HCC patients treated with locally developed *Phyllanthus emblica* capsules. Similarly, although patients in the *Phyllanthus emblica* group had better outcomes, the difference was not statistically significant. These findings are similar to those of our previous studies on food supplements in end-stage HCC (Matsui et al., 2002; Morihara et al., 2012;Ashrafujjaman et al., 2023). It is well known that end-stage HCC has a very poor outcome with a median survival of 3 to 4 months (Kumar and Panda, 2014).

Limitations

Our sample size was modest. However, having said so, it is also a reality that this type of study with terminally ill patients with end-stage HCC is challenging anywhere in the world, which is why studies involving such patients are not plentiful in the literature. We found that several other phytochemicals in *Phyllanthus emblica*, such as chebulagic acid and ellagic acid, were also effective according to our docking results, but we unfortunately couldn't extract them due to our limitations.

Conclusion

Although we couldn't demonstrate significant improvements in quality of life or survival in end-stage HCC patients treated with *Phyllanthus emblica*, our study is significant for several reasons. It established the safety and limited efficacy of *Phyllanthus emblica* in end-stage HCC. It is one of the early attempts to establish traditional medical knowledge with a modern scientific approach from Bangladesh, where review of traditional medical literature and identifying a prospective remedy, collection of ingredient, laboratory based research and finally human study - the 'bench to bed side' exercise was performed through collaboration between basic and medical scientists belonging to multiple centres with maximum utilization of available resources and with minimum costs involved. It is also an example of academia-industry collaboration. This study may well open a new era of research into repurposing and repositioning our traditional medicines for modern medical practice.

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Authors contribution

Md. Rezwanur Rahman: Conducted the study. Manas Saha: Assisted in the study.Mamun Al Mahtab, Md. Abdur Rahim, Sheikh Mohammad Noor E Alam and Dulal Chandra Das: Supervised the study.Rezaul Karim, Rakibul Hasan, Debabrata Karmakar: Performed molecular docking & stimulation and prepared amlaki powder for capsules.Gazi Nurun Nahar Sultana, Sitesh Chandra Bachar, Md. Zakir Sultan and Sheikh Mohammad Fazle Akbar: High Performance Liquid Chromatography. M Shahabuddin K. Choudhuri, Noureen Amin, Musarrat Mahtab: Helped in literature search. Mamun Al Mahtab, Chowdhury Faiz Hossain: Drafted the manuscript. Md. Rezwanur Rahman, Manas Saha, Rokshana Begum, Md. Enayet Ali Pramanik, Sheikh Zahir Raihan, and Ahmed Lutful

Moben: Reviewed the manuscript and did statistical analysis. Rabinarayan Acharya, Anagha Ranade: Revised the manuscript. Mamun Al Mahtab, Sakirul Khan, Rabinarayan Acharya, Sheikh Mohammad Fazle Akbar: Conceptualized the study.

Conflict of interest

The authors declare no conflict of interest.

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