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RESEARCH ARTICLE

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Efficacy and Safety of Phyllanthus Niruri in Non-alcoholic Steatohepatitis Treatment: Pilot Study from Malaysia

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Abstract

Background: As *Phyllanthus niruri* has been shown to have anti-inflammatory, antioxidant and hepatoprotective properties, the current study was designed to examine its efficacy and safety in non-alcoholic steatohepatitis (NASH) treatment. **Methods:** Fifty-two patients with biopsy-proven possible or definite NASH from eight hospitals across Malaysia were randomized (1:1) to receive two capsules of *Phyllanthus niruri* (Hepar-P®; n=25) or matched placebo (n=27) three times daily for 48 weeks. The primary endpoint of efficacy was the changes in aspartate transaminase (AST) and alanine transaminase (ALT) levels, while the other biochemical, anthropometric and histological changes were used as the secondary endpoints. Safety of treatment was confirmed through adverse events (AEs) reporting, physical examination and regular monitoring of blood parameters. **Results:** After 48 weeks of treatment, the changes in the AST (p=0.39) and ALT (p>0.95) levels did not significantly differ between the *Phyllanthus* and placebo groups. There were also no significant differences in the changes of body mass index, HbA1C and lipid profile between the two groups. Furthermore, six patients in the *Phyllanthus* group consented to repeat biopsy at week 48, and no histological changes of clinical significance were observed. Mild or moderate AEs occurred throughout the study period in 76.9% of the patients, but were not significantly different between the two groups (p=0.42). **Conclusion:** Although *Phyllanthus niruri* was generally well tolerated with no significant safety concerns, the current study was unable to demonstrate its clinical benefits in NASH treatment.

Key words: Hepatocellular carcinoma, liver cirrhosis, Malaysia, non-alcoholic fatty liver disease, *Phyllanthus*.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming a major health problem worldwide, primarily due to the increase in the prevalence of obesity and metabolic syndrome.[1,2] Its progressive form, non-alcoholic steatohepatitis (NASH), has also been linked to numerous liver-related complications, such as cirrhosis and hepatocellular carcinoma.[3,4] The commonly used treatment strategies for NASH include lifestyle modification, improving insulin sensitivity, lowering lipid levels and the use of antioxidants. Nevertheless, it is noteworthy that, to date, no specific therapy has been approved for NASH.[5-8]

Phyllanthus niruri, a herb extensively used in traditional Malay, Chinese and Ayurvedic medicine, is a potential therapeutic agent for a wide range of liver diseases, as laboratory studies have confirmed its antiviral, anti-inflammatory, antioxidant and hepatoprotective properties.[9-13] However, it has never been tested in patients, particularly those with NASH. Hence, this pilot study was designed to confirm the efficacy and safety of a commercially available product, HEPAR-P® (Nova Laboratories), which was standardized to contain 250 mg of *Phyllanthus niruri* extract EPN 797 (4% of corilagin and 18% of phyllanthus flavonoids) per capsule.

MATERIALS AND METHODS

This randomized, double-blind, parallel-group, placebo-controlled trial took place in eight public tertiary hospitals in Malaysia. Eligible participants had to be aged 18 years or above, and had to have biopsy-proven possible (NAFLD activity score ≥3) or definite (NAFLD activity score ≥5) steatohepatitis.[14] Patients were excluded if they: 1) had a history of cirrhosis, hepatitis C and other liver diseases; 2) were pregnant or of childbearing potential; 3) consumed alcohol of more than 30 g (men) or 20 g (women) for at least three consecutive months over the past five years, and 4) had any serious medical conditions, which would preclude completion of the study.

Informed consent was obtained from each participant. Randomization was conducted in a double-blind manner by using a computer-generated, center-specific randomization code list, whereby all eligible participants were randomly assigned (1:1) by an independent gastroenterologist to receive either two capsules of HEPAR-P® or matched placebo three times daily for 48 weeks. All participants received advices for lifestyle modification, and their compliance with treatment was assessed by pill counting during each visit. They were followed up at the second week, fourth week, monthly for the next five months, and thereafter every two months until completion of the treatment. The treatment efficacy was assessed mainly through the changes in aspartate transaminase (AST) and alanine transaminase (ALT) levels, while biochemical, anthropometric, and histological (for those who consented to repeat biopsy) changes were used as the secondary endpoints. Moreover, the safety of treatment was confirmed through adverse events (AEs) reporting, physical examination and regular monitoring of blood parameters.

Data Analysis and Sample Size: All categorical variables were summarized in frequencies and percentages, while numerical variables were expressed as means and standard deviations (SDs) for normally distributed data, or as medians and interquartile ranges (IQRs) for non-normally distributed data. Baseline characteristics of the participants in the two groups were compared using Pearson's chi-square, Fisher's exact, independent *t*, and Mann-Whitney tests, as appropriate. Intention-to-treat analysis was performed for both the interim (week 24) and end-of-treatment (week 48) assessments, with missing data imputed using the last-observation-carried-forward approach.[15] The overall changes, as well as the differences in the changes of AST level, ALT level, and other biochemical and anthropometric parameters between the two groups, were detected using repeated measures multifactorial ANCOVA. All the means presented were adjusted for the baseline characteristics. Furthermore, AEs occurring in the two groups were compared using Pearson's chi-square and Fisher's exact tests. All p-values were two tailed, and the significant level was set at 0.05.

The current study was powered to detect a mean difference (SD) of 10 (12) IU/L in AST levels between the two groups based on the finding of a clinical trial which enrolled similar patients.[16] To account for a 10% dropout rate, the required sample size was 25 per group for a power of 80% and an alpha of 0.05.[17] The study protocol was reviewed and approved by the Medical Research and Ethics Committee, the Ministry of Health Malaysia.

RESULTS

Of 59 patients screened for eligibility from January 2013 to January 2015, 52 (88.1%) were enrolled and assigned to receive *Phyllanthus niruri* capsule (n=25) or placebo (n=27). Two participants from the placebo group withdrew from the trial, but were included in the intention-to-treat population.

The participants were mostly male (65.4%) and Malay (67.3%), with a mean age of 44.3 years. The baseline characteristics of the *Phyllanthus* and placebo groups were not significantly different, except for body mass index (BMI), waist circumference, steatosis grade, and the use of

Table 1: Baseline characteristics of participants.

Characteristics	Overall (n=52)	Phyllanthus (n=25)	Placebo (n=27)	p-value
Age, years, mean (SD)	44.3 (11.4)	45.7 (12.4)	43.1 (10.5)	0.43*
Gender, n (%)				**0.70†**
Male	34 (65.4)	17 (68.0)	17 (63.0)	
Female	18 (34.6)	8 (32.0)	10 (37.0)	
Ethnicity, n (%)				**0.12‡**
Malay	35 (67.3)	20 (80.0)	15 (55.6)	
Chinese	5 (9.6)	2 (8.0)	3 (11.1)	
Indian	5 (9.6)	0 (0.0)	5 (18.5)	
Others	7 (13.5)	3 (12.0)	4 (14.8)	
Diabetes, n (%)	22 (42.3)	9 (36.0)	13 (48.1)	0.38†
Hypertension, n (%)	27 (59.1)	12 (48.0)	15 (55.6)	0.59†
Dyslipidemia, n (%)	22 (42.3)	10 (40.0)	12 (44.4)	0.75†
Ischemic heart diseases, n (%)	3 (5.8)	0 (0.0)	3 (11.1)	0.24‡
Drugs, n (%)				
Gliclazide	10 (19.2)	4 (16.0)	6 (22.2)	0.57†
Metformin	24 (46.2)	11 (44.4)	13 (48.1)	0.76†
Insulin	2 (3.8)	1 (4.0)	1 (3.7)	>0.95‡
Statin	18 (34.6)	5 (20.0)	13 (48.1)	0.03†
Perindopril	11 (21.2)	4 (16.0)	7 (25.9)	0.38†
Amlodipine	17 (32.7)	6 (24.0)	11 (40.7)	0.20†
Angiotensin receptor blocker	8 (15.4)	5 (20.0)	3 (11.1)	0.46‡
Aspirin	9 (17.3)	4 (16.0)	5 (18.5)	>0.95‡
AST, IU/L, median (IQR)	42.5 (32.0)	42.0 (22.5)	43.0 (38.0)	
ALT, IU/L, mean (SD)	82.3 (39.6)	77.1 (30.9)	87.1 (46.3)	0.36*
FBS, mmol/L, median (IQR)	5.8 (2.7)	5.8 (2.6)	6.0 (3.3)	0.43§
HbA1C, %, median (IQR)	6.1 (1.4)	6.2 (1.4)	5.9 (1.9)	0.99§
Total cholesterol, mmol/L, mean (SD)	5.5 (1.3)	5.3 (1.8)	5.3 (1.4)	0.14*
Triglycerides, mmol/L, median (IQR)	1.7 (1.1)	1.7 (1.2)	1.6 (1.1)	0.99d
HDL, mmol/L, mean (SD)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	0.41*
LDL, mmol/L, mean (SD)	3.4 (1.1)	3.1 (1.1)	3.6 (1.1)	0.11*
BMI, kg/m2, mean (SD)	29.8 (5.3)	28.0 (4.9)	31.4 (5.3)	0.02*
Waist circumference, cm, mean (SD)	98.1 (12.4)	94.8 (11.4)	101.1 (12.8)	0.07*
NAFLD activity score				**0.54†**
3-4 – possible NASH	21 (40.4)	9 (36.0)	12 (44.4)	
5-8 – definite NASH	31 (59.6)	16 (64.0)	15 (55.6)	
Steatosis grade				**0.02‡**
1 - 5-33%	8 (15.4)	4 (16.0)	4 (14.8)	
2 - 34-66%	22 (42.3)	6 (24.0)	16 (59.3)	
3 - 66%	22 (42.3)	15 (60.0)	7 (25.9)	
Lobular inflammation				**0.27‡**
1 - <2	27 (51.9)	16 (64.0)	11 (40.7)	
2 - 2-4	22 (42.3)	8 (32.0)	14 (51.9)	
3 - >4	3 (5.8)	1 (4.0)	2 (7.4)	
Ballooning				**0.23‡**
0 - none	5 (9.6)	3 (12.0)	2 (7.4)	

1 - few	38 (73.1)	20 (80.0)	18 (66.7)	
2 - many	9 (17.3)	2 (8.0)	7 (25.9)	
Fibrosis stage				**0.20‡**
0 - none	22 (42.3)	12 (48.0)	10 (37.0)	
1a	12 (23.1)	6 (24.0)	6 (22.2)	
1b	1 (1.9)	1 (4.0)	0 (0.0)	
1c	1 (1.9)	0 (0.0)	1 (3.7)	
2	2 (3.8)	2 (8.0)	0 (0.0)	
3 – bridging	14 (26.9)	4 (16.0)	10 (37.0)	

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; FBS, fasting blood sugar; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SD, standard deviation.

* Independent t-test.

† Pearson's chi-square test.

‡ Fisher's exact test.

§ Mann-Whitney test.

statin (Table 1). There were also no significant differences in the changes of AST level, ALT level, and other biochemical and anthropometric parameters between the two groups (Table 2). Only six participants from the *Phyllanthus* group consented to repeat biopsy at week 48; nonetheless, none of them had achieved at least a 2-point increment in the NAFLD activity score. Furthermore, mild or moderate AEs were reported in 76.9% of the patients, but were not significantly different between the two groups (p=0.42). The most commonly reported AE in both the groups was upper respiratory tract infection (28.8%), followed by fever (19.2%) and coughing (15.4%). It is also noted that the placebo group had a higher incidence of dyspepsia (25.9% versus 0%; p=0.01). Aside from that, there were no severe or life-threatening AEs detected in both the groups (Table 3).

DISCUSSION

Although there have been numerous studies into the anti-inflammatory, antioxidant and hepatoprotective properties of *Phyllanthus niruri*,[9,18] the current study, to the best knowledge of the authors, is the first to investigate its value specifically in NASH treatment. Besides, different from the other preclinical studies which were primarily limited by the variations in methods,[9] this is the first randomized controlled trial designed to determine the effectiveness and safety of a commercially available product containing a standardized content of *Phyllanthus niruri* extract. The strength of the current study also lies in the 48-week follow-up period, which is consistent with the recommendation of the American Association for Study of Liver Diseases on

Table 2: AST level, ALT level, and other biochemical and anthropometric changes after 48 weeks of treatment.

Variables	Overall (n=52) Adjusted mean (SE)*	p-value	Phyllanthus (n=25) Adjusted mean (SE)*	Placebo (n=27)	p-value
AST, IU/L		**0.87**			**0.39**
Baseline	48.2 (9.7)		44.3 (10.1)	52.1 (9.7)	
Week 24	74.6 (17.6)		74.4 (18.4)	74.9 (17.6)	
Week 48	58.3 (19.5)		59.4 (20.4)	57.1 (19.5)	
ALT, IU/L		**0.45**			**>0.95**
Baseline	75.4 (15.1)		80.6 (16.0)	70.3 (15.0)	
Week 24	121.9 (31.1)		127.8 (32.9)	116.0 (30.8)	
Week 48	109.0 (30.7)		114.7 (32.5)	103.3 (30.4)	
FBS, mmol/L		**0.50**			**0.54**
Baseline	5.6 (1.4)		5.4 (1.4)	5.8 (1.4)	
Week 24	5.0 (2.9)		5.4 (3.1)	4.6 (3.0)	
Week 48	6.9 (1.6)		7.2 (1.7)	6.6 (1.6)	
HbA1c, %		**0.52**			**0.33**

Baseline	7.2 (0.9)		7.2 (0.9)	7.3 (0.9)	
Week 24	8.7 (0.9)		8.6 (0.9)	8.7 (0.9)	
Week 48	8.2 (0.9)		8.4 (1.0)	8.1 (0.9)	
Total cholesterol, mmol/L		**0.05**			**0.10**
Baseline	5.4 (0.2)		5.4 (0.2)	5.5 (0.2)	
Week 24	4.4 (0.6)		4.6 (0.6)	4.2 (0.6)	
Week 48	4.6 (0.8)		4.8 (0.8)	4.4 (0.8)	
Triglycerides, mmol/L		**0.49**			**0.33**
Baseline	2.3 (0.3)		2.4 (0.4)	2.2 (0.3)	
Week 24	2.8 (1.3)		3.3 (1.4)	2.3 (1.3)	
Week 48	2.5 (0.7)		2.9 (0.8)	2.1 (0.7)	
HDL, mmol/L		**0.80**			**0.65**
Baseline	1.1 (0.2)		1.1 (0.2)	1.1 (0.2)	
Week 24	0.9 (0.2)		0.9 (0.2)	0.9 (0.2)	
Week 48	1.1 (0.2)		1.1 (0.2)	1.0 (0.2)	
LDL, mmol/L		**0.10**			**0.80**
Baseline	3.4 (0.2)		3.5 (0.2)	3.4 (0.2)	
Week 24	2.1 (0.5)		2.2 (0.5)	1.9 (0.5)	
Week 48	2.5 (0.8)		2.5 (0.8)	2.4 (0.8)	
BMI, kg/m2		**0.94**			**0.91**
Baseline	28.0 (1.9)		27.7 (2.0)	28.3 (1.9)	
Week 24	28.9 (2.0)		28.6 (2.1)	29.2 (2.0)	
Week 48	27.4 (2.2)		27.1 (2.3)	27.6 (2.2)	
Waist circumference, cm		**0.79**			**0.18**
Baseline	101.0 (4.5)		101.1 (4.8)	100.9 (4.5)	
Week 24	100.3 (4.2)		101.9 (4.5)	98.7 (4.2)	
Week 48	97.1 (3.9)		97.6 (4.1)	96.7 (3.9)	

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error.

* Repeated measures multifactorial ANCOVA, adjusted with all variables presented in Table 1.

Table 3: AEs reported over the 48-week treatment period.

Events	Overall (n=52)	Phyllanthus (n=25)	Placebo (n=27)	p-value
Any AEs, n (%)	40 (76.9)	18 (72.0)	22 (81.5)	0.42*
Severe or life-threatening AEs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Mild or moderate AEs, n (%)				
Upper respiratory infection	15 (28.8)	6 (24.0)	9 (33.3)	0.46*
Fever	10 (19.2)	6 (24.0)	4 (14.8)	0.40*
Coughing	8 (15.4)	5 (20.0)	3 (11.1)	0.46†
Rash/ pruritis	8 (15.4)	2 (8.0)	6 (22.2)	0.25†
Dyspepsia	7 (13.5)	0 (0.0)	7 (25.9)	0.01†
Abdominal pain	5 (9.6)	3 (12.0)	2 (7.4)	0.66†
Diarrhea	5 (9.6)	3 (12.0)	2 (7.4)	0.66†
Myalgia	5 (9.6)	4 (16.0)	1 (3.7)	0.18†
Nausea/ vomiting	4 (7.7)	3 (12.0)	1 (3.7)	0.34*

AE, adverse event.* Pearson's chi-square test. † Fisher's exact test.

the duration for NASH trials.[19]

Similar with a previous trial of *Phyllanthus urinaria*,[20] the current study was not able to demonstrate significant changes in the AST and ALT levels of the *Phyllanthus* group after 48 weeks of treatment. Furthermore, no histological changes of clinical significance, defined as an increment of at least two points in NAFLD activity score,[19] were observed in all the six participants from the *Phyllanthus* group who consented to repeat biopsy at the end of the treatment period. Overall, the finding implies that this widely available herb is unlikely to have substantial effects in NASH treatment. However, despite the negative finding for efficacy, the AEs reported throughout the 48-week study period did not differ between the *Phyllanthus* and control groups. Additionally, there were no severe or life-threatening AEs detected, indicating that the product tested in the current study is generally well tolerated and safe for long-term consumption.

Moreover, in spite of the treatment received by the patients, it is worth noting that there was no considerable improvement in their BMI, HbA1C and lipid profile after 48 weeks. A similar trend was also observed in the trial of *Phyllanthus urinaria*,[20] suggesting that lifestyle management of NASH patients is insufficient in general. Remarkably, a wide range of lifestyle interventions, either by diet or exercise, have been consistently reported to have a positive impact on reducing liver fat, necroinflammation and blood sugar.[5] In an attempt to delay or reverse the effects of NASH, an effort to promote the awareness about the importance of lifestyle changes is therefore warranted, given that the treatment options for NASH is as yet limited.[7,8]

The major limitation of the current study is the relatively small sample size, which may have contributed to the differences in the baseline characteristics between the two groups;[21] nevertheless, the means presented for all the endpoints in the study were adjusted for the confounding influence of these variables. Besides, notwithstanding the fact that resolution of steatohepatitis and improvement in NAFLD activity score are the primary endpoints recommended for NASH trials, biopsy was not repeated for most of the participants after the treatment was discontinued. However, as the first attempt to confirm the biologic effect and safety of *Phyllanthus niruri* in NASH treatment, the current pilot study evaluated the changes in AST and ALT levels of the participants, both of which are also acceptable efficacy endpoints.[19]

CONCLUSION

Despite the promising preclinical data, the current study was not able to demonstrate the clinical benefits of a commercially available product containing *Phyllanthus niruri* extract in NASH treatment. Nonetheless, the product was confirmed to be safe for long-term consumption.

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ABBREVIATION USED

NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; AST: aspartate transaminase; ALT: alanine transaminase.

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CONFLICT OF INTEREST

No conflicts of interest.

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