Food Processing & Nutritional Science

Research Article | Vol 2 Iss 2

Efficacy and Safety of a Standardized Extract of *Emblica officinalis* in the Management of Non-Alcoholic Fatty Liver Disease (NAFLD)" - An Open Label Clinical Study

Muhammed Majeed[1,2], Kalyanam Nagabhushanam[2], Lakshmi Mundkur[1], Shaheen Majeed[2,3,4] and Sujay Gowda[1*]

[1]*Sami-Sabinsa Group Limited, Department of Research & Development, Peenya Industrial Area, Bangalore, India*

[2]*Sabinsa Corporation, East Windsor, NJ, USA*

[3]*Sabinsa Corporation, Payson, UT, USA*

Correspondence should be addressed to Sujay Gowda, ClinWorld - Department of Clinical Research, # 19/1, 19/2, I Main, II Phase, Peenya Industrial Area, Bangalore 560 058, Karnataka, India

Received: August 30, 2021; Accepted: September 24, 2021; Published: October 1, 2021

ABSTRACT

OBJECTIVE

Non-alcoholic fatty liver disease (NAFLD), the most common chronic liver disease, is closely associated with metabolic syndrome and refers to the accumulation of hepatic steatosis not due to excess alcohol consumption. Various studies have exemplified the crucial role of oxidative stress in the pathogenesis of NAFLD. The present study evaluated the efficacy and safety of a novel extract from the fruits of *Emblica officinalis* (Amla Fruit Extract, AFE) containing 10% β-glucogallin along with hydrolyzable tannins as an antioxidant and hepato-protecting agent, in NAFLD patients.

METHODS

An open-label clinical study was conducted on 24 patients diagnosed with NAFLD, based on medical history and laboratory investigations for 90 days with 500 mg of AFE supplementation per day. The patients were evaluated clinically for the improvement of ALT, AST, reduction in oxidative stress levels and a quality of life (QOL) assessment at specific intervals for the duration of the study.

RESULTS

The mean change in antioxidant enzymes (Catalase, Glutathione Peroxidase, Superoxide Dismutase) from screening to final visit were statistically significant ($p \leq 0.05$). The mean serum ALT and AST levels were also significantly decreased with $p \leq 0.02$& $p \leq 0.04$, respectively. The QOL improved and no adverse events were reported during the entire study duration.

Citation: Muhammed Majeed, Efficacy and Safety of a Standardized Extract of Emblica officinalis in the Management of Non-Alcoholic Fatty Liver Disease (NAFLD)" - An Open Label Clinical Study. Food Proc Nutr Sci 2(2): 55-64.

CONCLUSIONS

The results demonstrated that supplementation with AFE could improve the liver functioning and blood antioxidant profile in patients with NAFLD, along with improvement in the quality of life.

KEYWORDS

Emblica officinalis; Amla; Nonalcoholic fatty liver disease; Antioxidants; Hepato-protection

INTRODUCTION

The accumulation of excess fat in the liver, in the absence of a significant quantity of alcohol consumption and other liver diseases, is defined as Nonalcoholic fatty liver disease (NAFLD), also known as the hepatic consequence of obesity and metabolic syndrome [1,2]. It encompasses a simple lipid accumulation in the liver to a more progressive stage of steatosis and fibrosis, which can lead to severe liver damage and hepatocellular carcinoma. In the last decade, it has become one of the most common "emerging" liver diseases worldwide, due to the increased prevalence of obesity and type 2 diabetes mellitus and sedentary lifestyle [1,3,4]. Epidemiological data shows the global prevalence of NAFLD at 24%-30% and increasing with each passing year [5]. As it currently stands, NAFLD has been projected to become the second most common reason to be listed for a liver transplant, with an increased mortality rate compared to the general population [6].

Its direct cost burden includes medical and diagnostic expenses, whereas the burden of the indirect costs is related to reduced health-related quality of life (HRQOL). NAFLD, with no proven treatment, poses the main challenge to the health care system in successfully managing this condition [7]. NAFLD has been considered as one of the leading causes of cryptogenic cirrhosis and chronic liver disease. The individuals with obesity, insulin resistance and diabetes mellitus, hyperlipidemia, and hypertension cardiovascular disease have a high risk to develop NAFLD [8].

Insulin resistance, lipid metabolism dysfunction, oxidative stress, inflammation, apoptosis, and fibrosis are the pathological events associated with the development of NAFLD, which ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) [8].

Herbal medicine supplement combined with other therapeutic approaches might provide feasible therapeutic strategies for patients with NAFLD [9].

A healthy lifestyle focusing on reducing body weight and increasing insulin sensitivity, including diet control and exercise regimens, forms the primary therapeutic approach. Although these are effective strategies in controlled clinical trials, they have limited impact at the population level, mainly due to poor patient compliance. Medicinal plants potentially constitute such active agents, and in recent years several studies have focused on natural products for the treatment of NAFLD due to their wide availability, low side effects, and proven therapeutic mechanisms and benefits [10,11].

Emblica officinalis Gaertn belongs to the Phyllanthaceae family, commonly called as Indian gooseberry, amla, and amalaki in Sanskrit. The plant is widely distributed in most tropical and subtropical countries [12]. *E. officinalis* is reported to have antioxidant, gastroprotective, anti-diabetic, hypolipidemic, hepatoprotective and antimicrobial activities [13,14]. It is a rich source of gallic acid and many known medicinally phytochemicals such as tannins, lignans, flavonoids, alkaloids, vitamin C, mucic acid, and ellagic acid [15].

Amla fruits have long been considered to be a rich in ascorbic acid. But the recent findings suggest the presence of trace amounts of Ascorbic acid in the fruits and attribute

the antioxidant effects to gallic acid esters such as β-Glucogallin [16,17].

Previous studies have revealed that *E. officinalis* exhibits inhibitory effects on hepatic steatosis and liver fibrosis in vitro, as well as gallic acid improves high fat diet (HFD)-induced dyslipidaemia, hepatosteatosis, and oxidative stress in vivo [18].

Saberry® is a proprietary patented extract of fresh *E. Officinalis* fruits, standardized for 10% β-glucogallin along with hydrolyzable tannins as biomarkers, reported to exhibit antioxidant and hepatoprotective activities [19]. Even though *E. Officinalis* fruit has been used for several health benefits, its properties may vary depending upon the methods of extraction. So, in this study, we aimed to evaluate the efficacy and safety of AFE containing 10% β-glucogallin along with hydrolyzable tannins (Saberry®) for the management of NAFLD by monitoring the serum liver enzymes, antioxidant status and lipid profile in patients with NAFLD.

MATERIALS AND METHODS

Study Design and Objectives

The study was an open clinical study initiated at Life Care Hospital, Bangalore, Karnataka, India, as per the ethical guidelines of the Declaration of Helsinki. The study was approved by the Institutional Ethics Committee and was registered prospectively with Clinical Trials Registry– India (CTRI) on 9/04/2016 with CTRI registration number CTRI/2016/04/006847. The objective of this study was to assess the hepatoprotective efficacy of AFE in patients suffering from Nonalcoholic Fatty Liver Disease, with improvement in liver function parameters, antioxidant enzymes, and lipid profile as primary endpoint and safety profile as the secondary endpoint

Inclusion and Exclusion Criteria: A total of 24 patients of either sex, 20 years to 60 years of age with BMI range from 25 kg/m^2 to 34 kg/m^2 able to give informed consent, diagnosed with NAFLD, refractive to statin treatment, CAGE Questionnaire score of 0 to 1, with diabetes and hyperlipidemia as co-morbid conditions were included in the study. Patients with hepatitis for more than 3 months, liver fibrosis, liver cirrhosis and other liver diseases, with history or evidence of other severe clinical conditions or disorders, pregnant and lactating women were excluded.

Diagnosis of NAFLD

Ultrasonography and its correlation with abnormal liver enzyme levels in serum were carried out for the diagnosis of NAFLD in new patients and confirmation in those already diagnosed with NAFLD. The CAGE questionnaire was adopted to rule out the alcohol-induced fatty liver. Based upon the confirmation of the diagnosis for NAFLD, patients were enrolled in the study.

Study Procedures

Twenty-four eligible patients with NAFLD were included in the study. All the patients were instructed regarding the study procedure, monthly follow up visits and the clinical investigations protocols. They were instructed to take AFE 500 mg capsule once a day for a period of 90 days.

The enrolled patients were subjected to analysis of serum levels of alanine transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), triglycerides and cholesterol, and biomarkers, including Malondialdehyde, Reduced Glutathione and Antioxidant enzymes- (Catalase, Glutathione Peroxidase, Superoxide Dismutase) and Quality of life assessment at baseline visit and at the end of the study. Patients were evaluated for adverse events or concomitant medications every 30 days for a 90 days period.

Blood Sampling and Biochemical Parameters Evaluation

Fasted blood samples were collected, serum separated by centrifugation from the participants at baseline and after 90

days of AFE supplementation. All samples were stored at -20°C until analyzed. Serum was analyzed for ALT by IFCC with PNP, AST, and alkaline phosphatase ALP by IFCC without the PLP method. Total and direct bilirubin by Diazo methodology, Low-density lipoprotein cholesterol (LDL-C) by Direct–Homogenous cholesterol oxidation and peroxidation methodology, Triglycerides (TG) by ELISA in COBAS e501, ECLIA instrument, and antioxidant enzymes were measured by ELISA (Thermo Fisher Scientific, Headquarters: Waltham, Massachusetts, United States) using, ready kits as per manufacturer's instructions using, ready kits as per manufacturer's instructions. All the analyses were carried out as per manufacturers' manual user guidelines.

Quality of Life-related Assessments

The QOL assessment was taken at baseline and final visit using quality of life questionnaires.

Safety assessment was made based on the occurrence of adverse events and changes in vital parameters during the study duration. A telephonic follow up was made after 15 days of completion of the final visit to know the well-being of the patient.

Statistical Analyses

The statistical analysis was carried out by the SPSS statistics version17.0. Values are presented as means ± standard deviation (means ± SD). Comparison in mean value change from screening and baseline visit to the final visit of the study was carried by using paired t-test and Wilcoxon signed-rank test. A change in the P-value of <0.05 was considered statistically significant for all analyses.

RESULTS

Baseline Characteristics

A total of twenty-four patients were enrolled in the study, out of which 22 patients completed the study successfully. Two patients were lost to follow-up, citing a personal reason for not visiting the site (Figure 1). The mean age was 47.54 ± 9.99 yrs. ranging from 25 years to 60 years. The demographic characteristics of the study population on the baseline visit are summarized in Table 1.

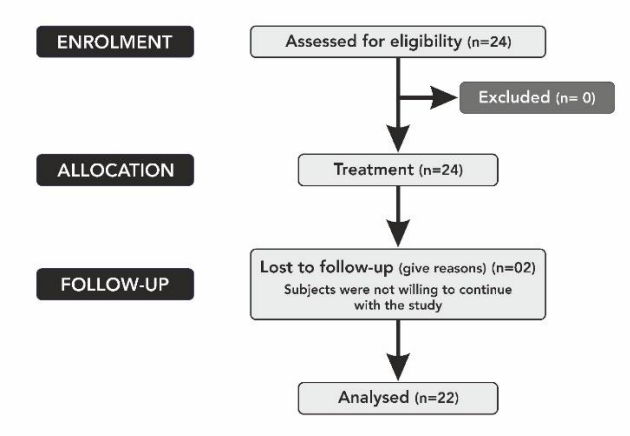

Figure 1: Consort diagram.

Demographics	Parameters	Baseline visit
Age (years)	N	24
	Mean	47.54
	SD	9.99
	Median	49.50
	(Min, Max)	(25,60)
Weight(kg)	N	22
	Mean	72.26
	SD	14.14
	Median	69.10
	(Min, Max)	(53.20,105)
Height(cm)	N	22
	Mean	157.94
	SD	7.26
	Median	158
	(Min, Max)	(143,174.9)
Gender	Male	7(29.2%)
	Female	15(70.80%)

Table 1: Demographic characteristics of study populations at baseline visit. **Note:** N= Total number of patients in the group, SD= Standard Deviation, (Min, Max) = (Minimum, Maximum).

Effect of AFE on BMI and Lipid Profile

The mean BMI decreased significantly from 30.59 kg/m^2 at baseline to 28.66 kg/m^2 after the treatment [p ≤0.05, Table 2]. A reduction was observed in total cholesterol levels at the end of the study period in comparison to the baseline. Although other lipid parameters like LDL, VLDL, and triglycerides showed a decreasing trend, they were not statistically significant (Table 2).

Effect of AFE on liver enzymes

The mean serum ALT levels were 28.45 ± 11.00 and 23.68 ± 7.86 U/L before and after supplementation with AFE for 90 days, respectively (P = 0.02). While that of AST were 22 ± 19.00 and 20 ± 15.00 U/L, respectively (P = 0.04), suggesting a hepato-protective activity of AFE (Table 2). No significant difference was observed in total bilirubin, direct bilirubin, and ALP when compared to baseline.

Antioxidant Effect of AFE

A statistically significant difference of P <0.001 was observed in antioxidant enzymes at the end of the study when compared to baseline (Figure 2).

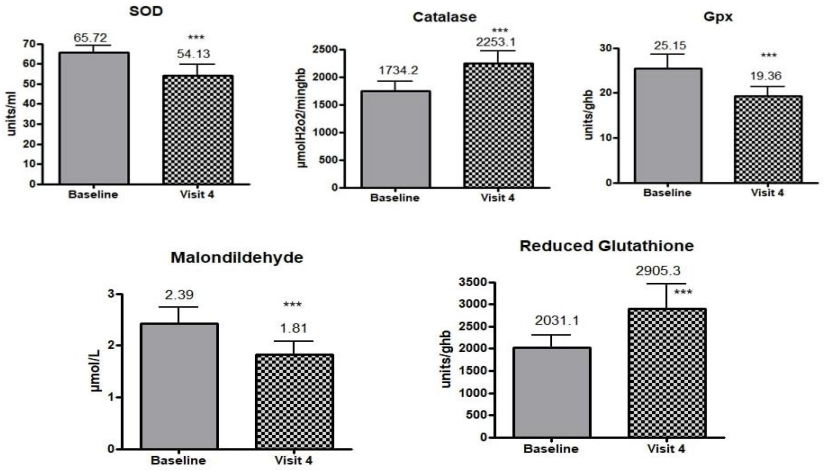

Figure 2: Anti-oxidant effects of AFE. Mean change in anti-oxidants from baseline to visit 4 using Wilcoxon signed rank test a) Superoxide Dismutase (SOD) b) Catalase (c) Glutathione peroxidase (d) Malondialdehyde (e) Reduced Glutathione. P value<0.001***.

Parameters	Before Treatment		After Treatment		*p*-value
	Mean	SD	Mean	SD	
Body Mass Index (kg/m^2)	30.59	7.98	28.66	5.22	0.05*
Total Bilirubin (mg/dl)	0.6	0.50	0.6	0.50	0.98
Direct Bilirubin (mg/dl)	0.2	0.10	0.2	0.20	0.29
Alkaline Phosphatase (U/L)	108	93	92	82	0.17
Alanine Aminotransferase (U/L)	28.45	11.00	23.68	7.86	0.02*
Aspartate Aminotransferase (U/L)	22	19	20	15	0.04*
Total Cholesterol mg/dL	192.8	41.5	177.5	41.5	0.06

Table 2: Effect of Saberry® on BMI liver enzymes and Lipid levels of NAFLD patients in comparison to the baseline visit. **Note:** SD: Standard Deviation: *p-value <0.05 using a paired t-test.

QOL Domains	Visit	Mean	SD	P value
Total Abdominal Symptoms (AS)	Baseline	15.09	2.09	0.001*
	Visit 4	12.64	2.13	
Total Fatigue (FA)	Baseline	25.91	2.31	0.001*
	Visit 4	21.27	3.07	
Total Systemic Symptoms (SS)	Baseline	26.55	2.26	0.001*
	Visit 4	22.77	2.84	
Total Activity (AC)	Baseline	15.40	1.91	0.001*
	Visit 4	23.77	2.84	
Total Emotional Function (EF)	Baseline	15.68	1.6	0.001*
	Visit 4	13.05	2.13	

Table 3: Competitive Quality of Life (QOL) analysis before and after AFE treatment. Note: QOL:quality of life, SD;standard deviation, Q:quartile,*P value <0.05.

Effect of AFE on Symptomatic Parameters

A marked improvement in terms of relief of symptoms and quality of life was observed in the final visit compared to the screening visit (Table 3).

Safety of AFE Supplementation

No statistically significant changes were observed with respect to vitals (Figure 3), hematological parameters (Table 4) and clinical findings from screening to the end of the treatment.

In some of the hematological parameters, little minor variations were noted, and the investigator opined them as clinically not significant. Also, no adverse and serious adverse events were reported during the study.

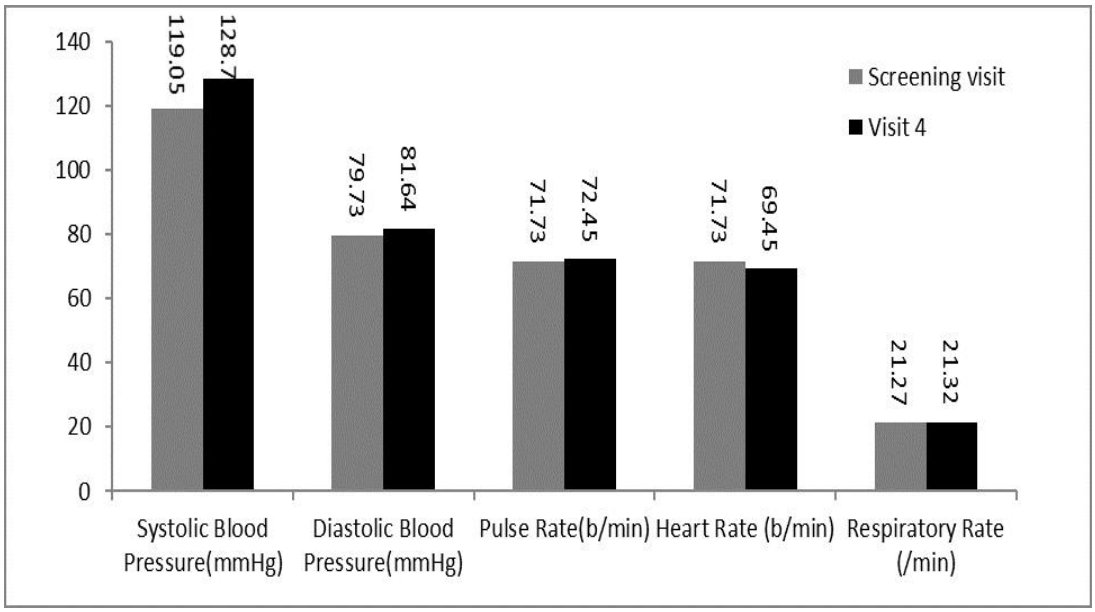

Figure 3: Mean change in the vitals from screening to visit [4].

Parameters	Screening visit	Final visit
Haemoglobin (g/dl)	13.32	13.40
Haematocrit (%)	38.83	38.98
RBC (mil/cumm)	4.89	4.86
Platelet count (cumm)	286409.09	287454.55
Leukocyte count(cumm)	8750	9200
Neutrophils (%)	59.73	56.95
Lymphocytes (%)	33.86	34.64
Monocytes (%)	3	3
Eosinophil (%)	3	4
Basophils (%)	0.00	0.00
MCV (fl)	81.9	83.5
MCH	27.10	28.42
MCHC (%)	33.75	34.52
MPV (fl)	10.28	10.22

Table 4: Haematology parameters. MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, MPV: Mean Platelet Volume.

DISCUSSION

NAFLD is a disease with genetic, environmental, metabolic, and stress-related components with increasing prevalence with changes in lifestyle. Natural products have shown the potential to reduce the severity of NAFLD [20,21]. The present study demonstrates that supplementation of AFE significantly reduces the level of AST and ALT in serum, ameliorates the antioxidant enzymes and improves the quality of life in NAFLD patients. These results support the earlier observation that AFE could reduce the hepatotoxicity induced by carbon tetrachloride (CCl4) in rats by elevating the antioxidant enzyme levels MDA (a marker of lipid peroxidation) GSH, SOD, Catalase and GPx and reducing the AST and ALT levels in female Wistar rats [19].

β-glucogallin pertains to the class of hydrolyzable tannins is also referred to as 1-O-galloyl-β-D-glucose is a purified standardized extract of *E. officinalis* fruit. Since the first revelation of β-glucogallin and its beneficial aspects in amla fruit by Majeed et al., (2009), multiple studies have demonstrated the positive therapeutic effects of AFE on human health [22]. In a murine study, β-glucogallin effectively inhibited aldose reductase in macrophages and ophthalmic tissue reduced sorbitol levels in macrophages and also reduced the number of inflammatory cells that infiltrate to oculas in experimental mice induced with uveitis [23].In an ex vivo design of cataract disease, β-glucogallin demonstrated potent activity in the inhibition of aldolase reductase, which is implicated in the pathogenesis of cataract [24]. In a recent study AFE containing 10% β-glucogallin was reported to have an inhibitory activity towards α-amylase, α-glucosidase and Dipeptidyl peptidase 4 (DPP-4) in vitro suggesting, that it may be useful for the management of type 2 diabetes [25].

AFE containing 10% β-glucogallin has been reported to have an excellent antioxidant activity earlier [26,27]. It was shown to reduce reactive oxygen species generated by exposure to UV rays in fibroblast cells in vitro [27]. The liver represents one of the major organs attacked by ROS [28], which can initiate fibrosis and cause liver damage. Oxidative stress in the liver is induced by exogenous parameters such as drugs, toxins, food additives, as well as endogenous factors, including obesity and insulin resistance [29]. Oxidative stress is known to disrupt proteins and lipids, induce apoptosis of hepatocytes, induce the expression of profibrotic and inflammatory mediators from kupffer cells and activate hepatic stellate cells to initiate fibrosis [28]. Patients with NAFLD demonstrated increased levels of MDA, GPx, SOD and decreased catalase and GSH [30,31]. Our results corroborated with these clinical data as the SOD and Gpx levels were found to decrease, while GSH and catalase levels increased from baseline with AFE supplementation. The increase in SOD and Gpx in NAFLD patients is thought to be an adaptive response to oxidative stress [30]. Impaired antioxidant defense mechanisms are implicated to be a major factor in the pathogenesis of NAFLD/NASH [32]. We observed a reduction in oxidative stress as seen by an increase in GSH, catalase, decrease in MDA, GPx and SOD and non-invasive biomarkers in the serum of patients treated with AFE, suggesting that the primary mechanism of action of AFE could be mediated by its potent antioxidant activity, restoring the antioxidant defense mechanism in the liver. We also observed improvement in liver enzymes compared to screening with improvement in BMI, total fatigue and total activity, suggesting a significant improvement in the quality of life compared to baseline visit.

In a recent study, a link between ROS and over nutrition and high-fat diet, metabolic syndrome, hypertension and T2DMwas observed in an animal model [33]. ROS levels are also increased in abdominal obesity, a major factor in metabolic syndrome [34]. Several studies have also demonstrated that increased oxidative stress is associated with the pathogenesis of insulin resistance and adipokine regulation [35].

Thus, a reduction in oxidative stress is likely to benefit in reducing metabolic syndrome, which in turn will be beneficial in reducing the severity of NAFLD.

Supplementation with AFE in patients with NAFLD was safe and well-tolerated with good compliance. There were no serious adverse events reported during the study. This lends strong support that AFE was safe for human use for better liver functioning and also in managing antioxidant enzymes.

Few limitations of the study include, an open label design and the number of participants. Since AFE was a novel preparation of its kind, the primary aim was to evaluate the efficacy of in patients with diagnosed NAFLD. We have included patients who had taken first line therapy for NAFLD and also those patients whose therapy expectation was not met. In future large a scale study with a double-blind placebo-controlled design will be planned, to further understand the efficacy of AFE in different stages of NAFLD.

In conclusion, in terms of biochemical and antioxidant enzymes improvement, AFE supplementation was effective in the management of NAFLD.

CONCLUSION

The clinical study clearly shows that supplementation with AFE improved the liver functioning antioxidant profile in the blood, with a concomitant reduction in the weight and improvement in the quality of life in the NAFLD patients. There were no abnormalities noticed in the laboratory, physical and vital parameters and AFE showed a major impact in improving the lifestyle of the patients. Therefore, it may be concluded Saberry®- the amla fruit extract with 10% β glucogallin is an effective and safe hepatoprotective supplement for managing NAFLD.

ACKNOWLEDGMENT

This trial was sponsored and supported by Sami-Sabinsa Group Limited, Bangalore, India. We thank the clinical trial principal investigator and team members of Life Care Hospital, Bangalore for conducting this clinical trial.

CONFLICT OF INTEREST

All the authors are employees of Sami-Sabinsa Group or Sabinsa Corporation. Saberry® is manufactured and marketed by Sami-Sabinsa group of companies.

REFERENCES

1. Sayiner M, Koenig A, Henry L, et al. (2016) Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in the United States and the rest of the world. Clinics in Liver Disease 20 (2): 205-214.
2. Angulo P (2002) Nonalcoholic fatty liver disease. New England Journal of Medicine 346(16): 1221-1231.
3. Bedogni G, Miglioli L, Masutti F, et al. (2005) Prevalence of and risk factors for nonalcoholic fatty liver disease: The Dionysos nutrition and liver study. Hepatology (Baltimore, Md) 42(1): 44-52.
4. Masarone M, Federico A, Abenavoli L, et al. (2014) Non alcoholic fatty liver: Epidemiology and natural history. Reviews on recent clinical trials 9(3): 126-33.
5. Carr RM, Oranu A, Khungar V (2016) Nonalcoholic fatty liver disease: Pathophysiology and management. Gastroenterology Clinics of North America 45(4): 639-652.
6. Pais R, Barritt ASt, Calmus Y, et al. (2016) NAFLD and liver transplantation: Current burden and expected challenges. Journal of Hepatology 65(6): 1245-1257.
7. Tolman KG, Dalpiaz AS (2007) Treatment of non-alcoholic fatty liver disease. Therapeutics and Clinical Risk Management 3(6): 1153-1163.

8. Paschos P, Paletas K (2009) Non alcoholic fatty liver disease and metabolic syndrome. Hippokratia 13(1): 9-19.
9. Xu Y, Guo W, Zhang C, et al. (2020) Herbal medicine in the treatment of non-alcoholic fatty liver diseases-efficacy, action mechanism, and clinical application. Frontiers in Pharmacology 11: 601.
10. Yao H, Qiao YJ, Zhao YL, et al. (2016) Herbal medicines and nonalcoholic fatty liver disease. World Journal of Gastroenterology 22(30): 6890-6905.
11. Xiao J, Fai So K, et al. (2013) Recent advances in the herbal treatment of non-alcoholic Fatty liver disease. Journal of Traditional And Complementary Medicine 3(2): 88-94.
12. Patel S, Goyal RK (2012) *Emblica officinalis* Geart: A comprehensive review on phytochemistry, pharmacology and ethnomedicinal uses. Research Journal of Medicinal Plant 6: 6-16.
13. Krishnaveni M, Mirunalini S (2010) Therapeutic potential of *Phyllanthus emblica* (amla): The ayurvedic wonder. Journal of Basic and Clinical Physiology and Pharmacology 21(1): 93-105.
14. Yang B, Liu P (2014) Composition and biological activities of hydrolyzable tannins of fruits of *Phyllanthus emblica*. Journal of Agricultural and Food Chemistry 62(3): 529-541.
15. Wu L, Zhang Q, Liang W, et al. (2021) Phytochemical analysis using uplc-ms^n combined with network pharmacology approaches to explore the biomarkers for the quality control of the anticancer tannin fraction of *phyllanthus emblica] l.* habitat in Nepal. Evidence-Based Complementary and Alternative Medicine 2021: 6623791.
16. Majeed M, Bhat B, Jadhav A, et al. (2009) Ascorbic acid and tannins from *Emblica officinalis* Gaertn. Fruits - A Revisit. Journal of Agricultural and Food Chemistry 57(1): 220-225.
17. Olennikov D, Kashchenko N, Schwabl H, et al. (2015) New mucic acid gallates from *Phyllanthus emblica*. Chemistry of Natural Compounds 51: 666-670
18. Huang CZ, Tung YT, Hsia SM, et al. (2017) The hepatoprotective effect of *Phyllanthus emblica L.* fruit on high fat diet-induced non-alcoholic fatty liver disease (NAFLD) in SD rats. Food & function 8(2): 842-850.
19. Majeed M, Majeed S, Nagabhushanam K, et al. (2015) Amelioration of carbon tetrachloride induced hepatotoxicity by β-glucogallin, a gallic acid derivative of *Emblica Officinalis* Gaertn. (Euphorbiaceae). International Journal of Science Research 4: 696-701.
20. Feng WW, Kuang SY, Tu C, et al. (2018) Natural products berberine and curcumin exhibited better ameliorative effects on rats with non-alcohol fatty liver disease than lovastatin. Biomedicine & Pharmacotherapy- Biomedecine & pharmacotherapie 99: 325-333.
21. Banach M, Patti AM, Giglio RV, et al. (2018) The role of nutraceuticals in statin intolerant patients. Journal of the American College of Cardiology 72(1): 96-118.
22. Li L, Chang KC, Zhou Y, et al. (2014) Design of an amide N-glycoside derivative of beta-glucogallin: A stable, potent, and specific inhibitor of aldose reductase. Journal of Medicinal Chemistry 57(1): 71-77.
23. Chang KC, Laffin B, Ponder J, et al. (2013) Beta-glucogallin reduces the expression of lipopolysaccharide-induced inflammatory markers by inhibition of aldose reductase in murine macrophages and ocular tissues. Chemico BiologicL Interaction 202(1-3): 283-287.
24. Puppala M, Ponder J, Suryanarayana P, et al. (2012) The isolation and characterization of beta-glucogallin as a novel aldose reductase inhibitor from *Emblica officinalis*. PLoS One. 7(4): e31399.

25. Majeed M, Majeed S, Mundkur L, et al. (2019) Standardized *Emblica officinalis* fruit extract inhibited the activities of alpha-amylase, alpha-glucosidase, dipeptidyl peptidase-4 and displayed antioxidant potential. Journal of Science of Food and Agriculture 100(2): 509-516.
26. Majeed M, Bhat B, Sushmita TS (2010) Inhibition of UV induced adversaries by β-glucogallin from Amla (*Emblica officinalis* Gaertn.) fruits. Indian J of Natural Products and Resources 1(4): 462-465.
27. Majeed M, Bhat B, Anand ST, et al. (2011) Inhibition of UV-induced ROS and collagen damage by *Phyllanthus emblica* extract in normal human dermal fibroblasts. Journal of Cosmetic Science 62(1): 49-56.
28. Sanchez-Valle V, Chavez-Tapia NC, Uribe M, et al. (2012) Role of oxidative stress and molecular changes in liver fibrosis: a review. Current Medicinal Chemistry 19(28): 4850-4860.
29. Li S, Tan H-Y, Wang N, et al. (2015) The role of oxidative stress and antioxidants in liver diseases. International journal of Molecular Sciences 16(11):26087-26124.
30. Kumar A, Sharma A, Duseja A, et al. (2013) Patients with nonalcoholic fatty liver disease (NAFLD) have higher oxidative stress in comparison to chronic viral hepatitis. Journal of Clinical Experimental Hepatology 3(1): 12-18.
31. Ore A, Akinloye OA (2019) Oxidative stress and antioxidant biomarkers in clinical and experimental models of non-alcoholic fatty liver disease. Medicina (Kaunas) 55(2): 26.
32. Koruk M, Taysi S, Savas MC, et al. (2004) Oxidative stress and enzymatic antioxidant status in patients with nonalcoholic steatohepatitis. Annals of Clinical & Laboratory Science 34(1): 57-62.
33. Dobrian AD, Davies MJ, Schriver SD, et al. (2001) Oxidative stress in a rat model of obesity-induced hypertension. Hypertension (Dallas, Tex : 1979) 37(2 Pt 2): 554-560.
34. Vincent HK, Taylor AG (2006) Biomarkers and potential mechanisms of obesity-induced oxidant stress in humans. International Journal of Obesity 30(3): 400-418.
35. Houstis N, Rosen ED, Lander ES (2006) Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature 440(7086): 944-948.