

Therapeutic Evaluation of Unani Coded Drug UNIM-104 in Cases of Non-Alcoholic Fatty Liver Disease (NAFLD) – A Preliminary Clinical Trial

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Abstract

Fatty liver disease is caused by an accumulation of fat in the hepatocytes. Non Alcoholic Fatty Liver Disease (NAFLD) has been reported worldwide, estimated to be around 10–24% in various populations. There is no standard medical treatment specifically for “Non-alcoholic, non-Diabetic and non-obese Fatty liver Disease”, hence a preliminary clinical study has been conducted at RRIUM Chennai, to evaluate the safety and efficacy of the Unani coded drug UNIM-104 in the treatment of NAFLD. It was observed that there was reduction in the sign and symptoms at the end of trial with statistical improvement ($p < 0.05$) in Hounz field (HF) Units value on CT scan of liver.

Keywords: Non-Alcoholic Fatty Liver Disease (NAFLD), Fatty liver, *Tashhamul kabid*, Unani Medicine, UNIM 104 coded drug.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common clinic-pathological condition characterized by significant lipid deposition in the hepatocytes of the liver parenchyma. The pathological picture bears a striking resemblance to that of alcohol-induced liver injury, but it occurs in individuals who deny a significant history of alcohol ingestion. It comprises of a wide spectrum of liver damage, ranging from simple macrovesicular steatosis to steatohepatitis, advanced fibrosis, and cirrhosis (Angulo, 2002; Angulo *et al.*, 2003). Subsets of NAFLD which progress to cirrhosis are being increasingly recognized as a major cause of liver-related morbidity and mortality with the potential to progress to liver failure (David, 2005). The term non-alcoholic steatohepatitis, (NASH) and several other terms have been used to refer to this entity, including pseudo alcoholic liver disease, alcohol-like hepatitis, diabetic hepatitis, non-alcoholic Laennec’s disease, and steatonecrosis (Ludwig *et al.*, 1980). However, seeing that the disease represents a spectrum of pathology, the umbrella term “NAFLD,” was first introduced in 1986, became the preferred one (Sheth *et al.*, 1997). The spectrum ranges from simple benign fatty liver (hepatic steatosis) to NASH, characterized by fatty change with lobular inflammation, hepatocellular injury, and Mallory hyaline, progressive fibrosis, and cirrhosis, and has been defined both histologically and clinically (Tominaga *et al.*, 1995).

NAFLD has been reported worldwide but geographic variations in prevalence are evident. Although the worldwide prevalence has not yet been determined, it has been quoted as 10–24% in various populations (Angulo, 2002; Angulo *et al.*, 2003) and it is estimated to be the most common liver disease in the western world, and

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its prevalence is likely to increase (Tominaga *et al.*, 1995). It affects all racial and ethnic groups and has no age or sex predilection.

According to Unani system of medicine, the *Kabid* (liver) is the largest glandular organ in the body, It breakdown the nutrient materials, participate in the growth and development of human body and repair the wear and tear of the body (*Badal-e-Ma-Yatahallal*). According to Ibn-e-Sina, *Kabid* (liver) is considered the seat or centre of *Quwa-Al-Tabi'yah* (Natural Faculty) (Ibn-e-Sina 1906). It is responsible for the absorption, digestion, retention, metabolism and assimilation of food and excretion of *Fudhlat* (waste products) (Abusahal Masihi 810-895 A.D). In Unani classical text, *Su-e-Mizaj-e-Kabid* (alteration in normal temperament of liver) particularly due to *kasrate buroodat* (excessive coldness) somewhat resembles to NAFLD, in which liver is loaded with *Fudhlat* (waste products) and toxins which ultimately help in deposition of *Raddi Shaham* (abnormal excessive fats) (Ibn-e-Rushed, 1126-1198).

Till now there is no standard medical treatment for fatty liver diseases although several possible treatments are under investigation including Vitamin E and C, Ursodiol and other medications.⁹ In contrast Unani literature is replete with drugs administered for fatty liver like conditions which has the potential to detoxify the liver. However, considering necessity of novel medical intervention, the Central Council for Research in Unani Medicine, Ministry of Ayush, Govt. of India, had initiated a preliminary clinical study to test the safety and efficacy of the Unani coded drug UNIM-104 in the treatment of non-alcoholic, non-obese and non-diabetic fatty liver disease.

Materials and Methods

The study was a single blind, prospective clinical trial approved by the Institutional Ethical Committee of the Institute. Altogether 35 cases from GOPD of RRIUM, Chennai were enrolled in the study during the period 2010-2012 after getting voluntary informed consent from the participants. However, 5 patients were lost to follow up due to personal reasons. Subjects of either gender in the age group of 40-60 years, non-alcoholic, non-diabetic & non-obese, with or without sign & symptoms like fatigue, loss of appetite, malaise, dull ache in upper right abdomen, nausea, hepatomegaly and BMI ≤ 29.9 were included in the study. Diagnosis and grading of fatty liver was done on the basis of Ultra sonogram and CT Scan of upper abdomen. Subjects with pregnancy or lactation, those unwilling to give consent to abide by the protocol, systemic illness (cardiac, gastric, hepatic, renal, neurological disorders etc) were excluded from the study.

Clinical assessment and laboratory investigations were carried out at baseline and at 30 days interval and CT scan of upper abdomen for measuring liver Hounz

field (HF) unit at base line and end of the study to monitor the prognosis. The Unani coded drug UNIM-104 was given in form of 'Majoon' in a dosage of 5 gm twice a day with water before food for a period of 90 days. Patients were advised strictly to refrain from consumption of alcohol, high carbohydrate and high fat content diet.

Following investigations were carried out using standard laboratory techniques.

Blood: Hemogram with ESR, Fasting Blood Sugar, S. Bilirubin, SGOT, SGPT, S. Alkaline Phosphatase, S. Urea, S. Creatinine, S. Cholesterol, S. Triglycerides, HDL, LDL.

Urine: Routine and Microscopical examination.

Statistical analysis of the data was carried out using Student t test (paired). p value < 0.05 was considered to be significant.

Results and Discussion

NAFLD is an increasingly important chronic liver disease with a wide spectrum of histopathology, ranging from bland steatosis to cirrhosis. It is often asymptomatic and discovered incidentally on routine laboratory screening. In the absence of established therapies, treatment is generally directed at optimizing body weight and controlling risk factors.

In the present study it was observed that the prevalence is more in low socio economical class in age group between 40-45 years which might be due to patients attending RRIUM, Chennai from lower strata of society. It was also observed that 53.33% patients were of Balghami (phlegmatic temperament) and 36.66% were of Damavi Mizaj (sanguine temperament) suggesting that those with colder temperament and robust built are more susceptible to fatty liver thereby substantiating the claim made by Unani physicians (Ibn-e-Sina -19.6), Ibn-e-Rushad, 1980). Majority of the patients were overweight (BMI \geq 25), demonstrating that obesity is a predisposing risk factor for the development of NAFLD (Table-1).

Though majority of the trial participants were asymptomatic which corroborate various study findings, however dull ache in right hypochondrium was present in 69% of the cases Improvement in most of the sign and symptoms like nausea, anorexia and reduction in dull ache in right hypochondrium was recorded at the end of trial (Table 2) indicating the *Mushtahi*, *Muhallil*, *Musakhkhin*, and *Muqawwi kabilid* properties of polyherbal coded research formulation (UNIM 104).

No any appreciable improvement was observed in liver function tests and lipid profile as these parameters were within normal range during the course of trial. (Table 3 & 4) There might be no biochemical evidence of liver disease as stated

Table 1: Demographic data

S.No.	Demographic data	Unit	Mean ± SD	P value
1	Age	Mean ± SD	44.16 ± 7.29	
2	Gender	Male Female	16 (53.33%) 14 (46.67%)	
3	Duration of disease (months)	Mean ± SD	9.66 ± 10.57	
4	BMI (Kg/m ²)	Base line After treatment	28.05 ± 10.17 27.1 ± 1.68	> 0.028
5.	Body weight (kg)	Base line After treatment	73.8 ± 10.17 71.26 ± 10.11	> 0.42
6.	Mizaj	Damavi (sanguine) Balghami (phlegmatic) Saudavi (melancholic) Safravi (choleric)	11 (36.66%) 16 (53.33%) 2 (6.66%) 1 (3.33%)	

Table 2: Improvement in Sign & Symptom in NAFLD cases treated with UNIM-104

Status	No. of Cases	Fatigue	Malaise	Nausea	Loss of Appetite	Hepato-megaly	Dull ache in RUQ
Baseline	30 (100%)	12 (40%)	9 (30%)	6 (20%)	10 (33.3%)	7 (23.3%)	21 (70%)
After Treatment	30 (100%)	2 (6.6%)	Nil (0%)	Nil (0%)	Nil (0%)	Nil (0%)	6 (20%)

Table 3: Biochemical parameters in NAFLD cases treated with UNIM-104

S.No.	Parameters	Base Line	After 90 days	P-Value
1	AST (U/Lt)	20.72 ± 2.58	19.93 ± 2.29	>0.21
2	ALT (U/Lt)	24.41± 2.88	24.62 ± 3.29	> 0.79
3	Alkaline phosphatise (K.A Units)	6.27 ± 1.06	7.08 ± 1.53	> 0.20
4	Urea (mg/dl)	19.75 ± 5	21.85 ± 4.73	> 0.10
5	Creatinine (mg/dl)	0.76 ± 0.07	0.78 ± 0.05	> 0.20

by Kumar *et al.* (2005). Laboratory values may be normal in up to 80% of persons with fatty liver according to Tierney *et al.* (2010).

Table 4: Lipid profile in NAFLD cases treated with UNIM-104

S. No.	Parameters	Base Line	After 30 days	After 60 days	After 90 days	P value
1	Serum Cholesterol (mg/dl)	221.82 ± 45.83	211.93 ± 40.73	205.89 ± 37.80	211.41 ± 38.21	> 0.34
2	Serum Triglycerides (mg/dl)	136.79 ± 43.46	127.58 ± 37.42	125.20 ± 49.21	131.96 ± 43.72	> 0.47
3	HDL (mg/dl)	42.55 ± 1.86	-	-	42.17 ± 2.21	> 0.47
4	LDL (mg/dl)	152.17 ± 38.31	-	-	142.93 ± 32.74	> 0.31

Computed tomography is the most reliable imaging modality in the diagnosis of fatty liver because there is a close correlation between the CT attenuation value and the degree of fat deposition in the liver parenchyma. Non-contrast CT attenuation value of the normal liver are on average 8 Hounsfield units (HU) higher than that of the spleen (Lavine *et al.*, 2000). Normally the attenuation of the hepatic parenchyma is 50 to 75 HU in a non-contrast CT scan and declines by 1.6 HU for each milligram of triglyceride accumulated per gram of liver tissue (Subbarao *et al.*, 2003, Crowley *et al.*, 2007 & Goldman *et al.*, 2008). The study revealed significant improvement ($p < 0.01$) in terms of H.U. unit values which enhanced from 36.69 to 46.95 (Mean) indicating that test drug (UNIM 104) significantly decreased the accumulated fat from liver due to its *Muhallil* (Anti-inflammatory), *Musakhkhin* (calorifaecient) and Muqawwi kacid (liver tonic) properties. The *haar* temperament of UNIM 104 may be responsible in mobilization and redistribution of *Radi Shaham*, (morbid fat) which eventually decreases the deposition (*Fudhlat* or waste products like alcohol, fats, toxins) of liver (Table 5 & Figure 1).

Table 5: Improvement in C.T Scan H.F Unit values in NAFLD cases treated with UNIM-104

CT Scan finding	Base Line	After 90 days	P-Value
Liver Hounz field (HF) unit	36.69 ± 10.33	46.95 ± 9.58	<0.01**

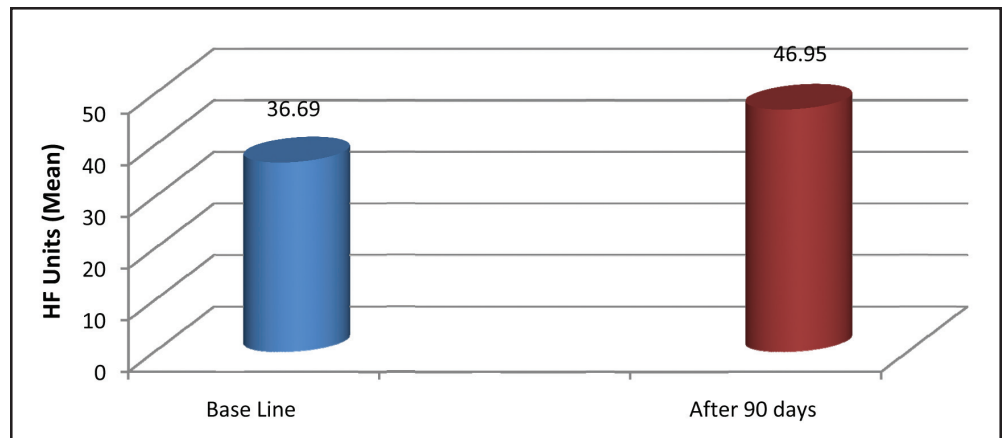


Figure 1: Improvement in C.T Scan H.F Unit values in NAFLD cases treated with UNIM-104

No adverse effects were observed during and after the trial with the test drug. The maintenance of laboratory investigations throughout the course of study attests that the test drug is safe for the patients (Table 3).

Conclusion

It may be concluded that coded Unani formulation UNIM-104 is safe and effective in the management of Non Alcoholic Fatty liver. It has encouraging potential for mobilization and redistribution of deposited *Raddi Shaham* (abnormal excessive fats) from the liver with no major adverse effects. However, large, long-term, controlled studies may throw more information about its efficacy.

Acknowledgment

The authors are thankful to the Director General and Dy. Director General, Central Council for Research in Unani Medicine, New Delhi, for their valuable suggestions, timely guidance and providing technical facilities in conducting the trial at RRIUM, Chennai.

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