Non-Alcoholic Fatty Liver Disease (NAFLD) and the Clinical Evaluation of Luk Maghsool (*Coccus lacca* Kerr.), Sandroos (*Callitris rhomboidea* R.Br. ex Rich.), Ispaghol (*Plantago ovata* Forssk.) and Afsantin (*Artemisia absinthium* Linn.) in its Management- A Pilot Study

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Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) is increasing in proportion to rise in obesity. Now it has become the most common cause of chronic liver disease after hepatitis B, hepatitis C and alcohol. It can be classified into simple fatty liver disease (or Non Alcoholic Fatty Liver, NAFL) and Non Alcoholic Steatohepatitis (NASH). The former has a benign prognosis but latter is associated with fibrosis and progression to cirrhosis. In early stage, fat accumulates within hepatocytes whereas at the same time the process of lipids removal by oxidation or export can't keep pace with its biosynthesis.

The symptoms of both the settings are identical. They occur at any age and in children usually after 10 years. The most common symptoms are fatigue and discomfort in abdomen while patients who are obese with BMI > 25 about 1/3 have metabolic syndromes. Hepatomegaly may be present, although the signs of chronic liver disease are uncommon. Although its incidence is about 3% of population but it has come to our clinical observation that apart from obese patients, normal patients also have fatty liver on USG.

Keeping above facts in mind the present pilot study was conducted on the outdoor patients who attended the Moalejat and Modern Medicine OPD of Ajmal Khan Tibbiya College Hospital, Aligarh Muslim University, Aligarh. As there is no drug, so far, unequivocally proved to be effective in the prevention or regression of fatty liver, therefore, we opted the non pharmacopoeial preparation of Unani drugs to see its effect on established cases of NAFLD and only one type i.e NAFL was studied. There was no significant USG improvement by our drug formulation, yet clinical improvement was seen and was found to be significant to a great extent.

Key Words: Fatty Liver, Luk Maghsool *(Coccus lacca* Kerr.*),* Sandroos *(Callitris rhomboidea* R.Br. ex Rich. & A.Rich.*),* Ispaghol *(Plantago ovata* Forssk.*)* and Afsanteen *(Artemisia absinthium* Linn.*),* Non Alcoholic Fatty Liver Disease (NAFLD).

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is a disease of affluent societies and its prevalence is increasing in proportion to the rise in obesity. It has become the most common cause of chronic liver disease after hepatitis B, C and alcohol (Boon *et al.*, 2006). It was first described in the 1950s when fatty liver was characterised in a group of obese patients. In 1980, Ludwig at the

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Mayo clinic described to obese, diabetes, non alcoholic patients who had similar finding on liver biopsy to the patients with alcoholic liver disease, and the term non alcoholic steatohepatitis (NASH) was introduced. The prevalence of NAFLD in the United States and Europe ranges from 14-20% whereas that of NASH is around 3% of the general population, with fibrosis being seen in > 40% of significantly obese patients. The spectrum of NAFLD includes simple hepatic steatosis, which overtime can progress to NASH with the subsequent development of fibrosis and chirosis (Fausi *et al*., 2008).

NAFLD is usually asymptomatic although fatigue and discomfort in right upper quadrant may be reported (Schmotz *et al.,* 2008). Clinically most patients are symptomatic with abnormal liver function test (LFT) particularly elevation of transaminases. Usually the condition presents with abdominal discomfort, flatulence, dyspepsia and complication of cirrhosis like gastrointestinal bleeding. In many cases there is accidental discovery of fatty liver when the patients are subjected to utrasonography (USG) for some other reasons. Imaging technique like utrasonography, CT and MRI scanning are reliable for detecting moderate to severe fatty changes in the liver. However the liver biopsy remains the “Gold standard” for diagnosing NAFLD especially to exclude alcoholic liver disease. Its management basically depends on weight loss and pharmacotherapy. The aim of treatment is to slow down the progression of NAFLD and to prevent liver related illness and death (Panda *et al.,* 1991).

As far as Unani concept is concerned the disease by this name is not found in any of the classical text books and literature. However, most of the Unani scholars have described certain diseases like Sua-e-Mizaj kabid which roughly matches with non alcoholic fatty liver disease. The first description of Sua-e-Mizaj kabid barid has been found in Hippocrates’s treaties, thereafter Galen, Akbar Arzani, Mohammad Sharif Khan, Mohammad Azam Khan and Ghulam Jilani have also discussed this disease in the light of their predecessors. In Western medicine also no specific treatment of this disease has been evolved so far. However the attainment of ideal body weight, physical exercise and use of lipid lowering agents like statins is being advocated.

The present study has been carried out firstly because to the best of our knowledge no such clinical trial has been done so far in the field of Unani Medicine and secondly to evaluate the efficacy of our drug formulation which includes *Luk Maghsool* (*Coccus lacca* Kerr.), Sandroos (*Callitris rhomboidea* R.Br. ex Rich.), Ispaghol (*Plantago ovata* Forssk.) *and* Afsanteen (*Artemisia absinthium* Linn.).

Material and Method

A pilot study was carried out on the patients attending the outdoor of Moalejat and Modern Medicine (OPD) of Ajmal Khan Tibbiya College Hospital, Aligarh Muslim University, Aligarh, with any of the following symptoms like anorexia, fatigue, malaise, upper abdominal discomfort, nausea, vomiting and obesity as presenting features. Those suffering from Thyroid Disorder, Chronic Renal Failure, Diabetes Mellitus, Ishaemic Heart Disease, Nephrotic Syndrome, consuming oral contraceptives, alcoholics and primary gout were excluded from the study. Similarly those suffering from cirrhosis of liver or who had taken any type of lipid lowering agents of any system of medicine for at least one year before the clinical trial were also excluded. The results at the end of study were compared to the findings of first day i.e. on the day of commencement of therapy. Therefore, each patient acted as his own control.

The trial was carried out after approval of departmental ethics committee and informed written consent from the patients between from February 2007 to September 2009. Each case was studied on following manner that is history taking, physical examination, biochemical tests and USG abdomen. The liver biopsy was not done because of the lack of the facility of stand by operation theatre. Apart from personal interrogation and dietary habits including food cooking medium, detail of presenting complaints like anorexia, fatigue, malaise, nausea and vomiting were recorded with specific note of the abdominal discomfort in the right hypochondrium. Relevant past illness and history regarding similar attack of symptoms was also noted. The weight of the patients and BMI was also recorded. In systemic examination all the systems were examined in detail with special emphasis on gastrointestinal system like tenderness, organomegaly, ascites, lump, hernial orifices and per rectal examination.

The drugs afsanteen, luk maghsool and sandroos were taken in the ratio of 8:2:2 by weight in gram and grinded to fine powder and the patients were advised to take 6 grams with plain water preferably on empty stomach in the morning and evening. Simultaneously saboos-e-ispaghol, telephone marked was also administered orally 5 grams at bed time for four months.

The routine investigations like haemogram, urine examination, stool examination and X- Ray Chest (PA View) were carried out. The special biochemical tests included Serum Bilirubin, AST, ALT, Alkaline Phosphotase, HBsAg, Serum cholesterol and Triglycerides. All the patients were subjected to USG abdomen before starting the treatment and at the termination of the trial. As and when require opinion of radiologist was also sought.

As there is no single criterion to diagnose non alcoholic fatty liver disease therefore the following criteria laid down by Davidson's Text book of Medicine was adopted. However the presence of atleast four or more parameters along with the bright liver on Utrasonography was taken as diagnostic.

1. Nausea or Vomiting or both
2. Abdominal discomfort
3. Right upper quadrant (RUQ) discomfort
4. Raised ALT and AST (Greater than twice the upper limit of normal)
5. Raised Alkaline Phosphatase
6. Hypertryglyceridaemia
7. BMI (More than 25)
8. Truncal obesity
9. Bright liver on Utrasonography of Abdomen

The patients were initially followed up for every fifteen days for two successive occasions then at monthly interval for four months. The initial 15 days visit was to know any side effect of drugs. The clinical examination and necessary biochemical investigations were carried out at monthly interval where as USG abdomen as already mentioned was done before and at the termination of therapy i.e. four months. All the results were statistically evaluated using paired't' test.

Observations, Results and Discussion

Keeping in view the limitation of space the results are being depicted in tabular form.

Table 1: Distribution of Patients According to Age and Sex

Total No. of Patients - 25

Age Group	Male		Female	
	No. of Patients	Percentage	No. of Patients	Percentage
25-35	1	4	1	4
35-45	1	4	3	12
45-55	3	12	3	16
55-65	3	12	3	12
>65	2	8	4	16
Total	10	40	15	60

As depicted from the above table the maximum incidence of non alcoholic fatty liver was found to be present in both sexes between the age group of 45-55 years and above 65 years of age. These findings confirm with the standard description.

Table 2: Distribution of Patients According to their Occupation

Total No. of Patients - 25

Occupation	Number of Patients	Percentage
Student	0	0
Service	6	24
Labour	0	0
Business	12	48
House Wife	7	28
Total	25	100

It was observed that 24% cases were from service class, 48% were from business class and 28% were housewives but no patient was found from students as well as from labour class. These data clearly depict that physical exertion and low fat diet has protective effect for NAFLD as seen in the student and labour class. As the prosperity increase and physical exertion decrease there is a marked rise in the incidence of NAFLD and this seems to be the reason of fatty liver in remaining group.

Table 3: Distribution of Patients According to Dietary Habits

Total No. of Patients - 25

Dietary Habit	No. of Patients	Percentage
Vegetarian	5	20
Non-Vegetarian	10	80
Total	15	100

It was observed that the maximum number of cases were non-vegetarian i.e. 80%. This marked difference is beyond doubt that non vegetarian diets contain saturated fat which is more likely to give rise to NAFLD.

Table 4: Distribution of Patients According to Temperament

Total No. of Patients - 25

Temperament	Male	%	Female	%
Sanguinous (Damwi)	0	0	0	0
Bilious (Safravi)	2	8	0	0
Phlegmatic (Bhalghami)	8	32	12	48
Melancholic (Saudavi)	0	0	3	12
Total	10	40	15	60

The maximum number of cases belonged to phlegmatic temperament while no patient was found in sanguinous temperament. As our study shows that maximum patients were of phlegmatic temperament (balghami mizaj) who were also obese with BMI > 25 which is itself a very strong risk factor for the development of NAFLD.

Table 5: Prevalence of Symptoms

Total No. of Patients - 25

Symptom	Number of Patients	Percentage
Malaise	20	80
Weakness	10	40
Nausea	25	100
Vomiting	13	52
Anorexia	20	80
Insomnia	20	80
Jaundice	5	2
RUQ discomfort	25	100
Hepatomegaly	15	60
Tender liver	15	60
Obesity	17	68
Mean BMI (>27)	22	88
Non obese	8	32

From the above observations, it is evident that the symptoms which disturbed the patient maximum were malaise, nausea and upper abdominal discomfort followed by pain which was seen in almost all patients. Our findings are in tune with the classical presentation of this disease (Boon *et al.*, 2006; Fausi *et al.*, 2008; Schmotz *et al.,* 2008).

Table 6: Effect of Drugs on Symptoms

Total No. of Patients - 25

Symptom	Follow up (in days)					
	0 Day	15th Day	30th Day	60th Day	90th Day	120th Day
	Total No. of Patients	Improved %	Improved %	Improved %	Improved %	Improved %
Malaise	20	0	0	0	60	80
Weakness	10	0	0	0	50	80
Nausea	25	0	4	12	20	28
Vomiting	13	0	15.38	15.38	23	38.4
Anorexia	20	0	15	20	45	65
Insomnia	7	0	0	14.28	28.57	71.4
Jaundice (O/E)	5	0	0	0	0	40
RUQ Discomfort	25	0	0	0	4	8
Hepatomegaly	15	0	0	0	0	13.33
Tender Liver	15	0	0	0	6.7	20
Obesity	17	0	0	0	0	0
Mean BMI (>27)	25	0	0	0	0	4
Non Obese	8	0	0	0	0	0

The effects of drug with respect to time have been shown in the table. The maximum improvement 80% was observed in malaise and weakness followed by improvement in anorexia 65% of cases and improvement in tender hepatomegaly in 13.33% of the cases. Whereas there was decrease in nausea and right upper quadrant discomfort by 28% and 8% respectively. There was no loss of weight in either obese or non obese patients; hence no significant improvement was seen in BMI. As far as the improvement in malaise and nausea is concerned the effect may be due to the improvement in liver function which may be the general tonic effect of afsantin on liver and stomach and antipyretic effect imparting the general well being (Khan, ynm; Karim, 1185; Nadkarni, 1982).

Improvement in anorexia may be due to the muhazzil (fat dissolvement effect of sandroos (Nadkarni, 1982; Husain, 1914; Hakim, 1924) as well as luk maghsool (Chopra, 1958) and hepatotonic effect of sandroos (Hakim, 1924), similar mechanism might be responsible for improvement in nausea and vomiting which may be due to additional carminative and appetizer

effect of afsantin (Rhazi, 1991; Lubhaya, 1982). As far as the regression in hepatomegaly and decrease in right upper quadrant discomfort is concerned the possible astringent, diuretics, antiseptic effect of afsantin and anti inflammatory effect of luk maghsool are likely to play a significant role (Khan, ynm; Karim, 1185; Israili, 1907).

It is also possible that the afsantin and luk maghsool might have lipolytic action in the hepatocytes due to its hot temperament. Over and above saboos-e-ispaghol might have acted as a barrier for absorption of fat from gastro intestinal tract. Therefore, it can be inferred that our drug combination which has several divergent properties which is the characteristic of a herbal drug might have acted as pivotal role in amelioration of signs and symptoms.

Table 7: Effect of Drugs on AST

Total No. of Patients - 25

Follow up (in days)				
0 Day	30th Day	60th Day	90th Day	120th Day
Mean + S.D. (U/L)	Mean + S.D. (U/L)	Mean + S.D. (U/L)	Mean + S.D. (U/L)	Mean + S.D. (U/L)
35.08 + 3.28	35.98 + 1.94	35.48 + 2.65	35.44 + 2.64	35.2 + 2.32
N = 25; t = 1.26				

The above table shows no significant change in AST level which implies that our drug combination has no hepatotoxic effect.

Table 8: Effect of Drugs on ALT

Total No. of Patients - 25

Follow up (in days)				
0 Day	30th Day	60th Day	90th Day	120th Day
Mean + S.D. (u/ml)	Mean + S.D. (u/ml)	Mean + S.D. (u/ml)	Mean + S.D. (u/ml)	Mean + S.D. (u/ml)
88.4 + 4.736	87.32 + 4.73	86.32 + 4.99	85.12 + 5.24	86.8 + 4.432
N = 25; t = 8.77 ; p<0.001				

Taking the face value there was no significant improvement. However paired test shows that these results are significant. The decreasing trend is indicating that either by altering the drug composition or by prolonging duration of treatment significant improvement may be expected.

Table 9: Effect of Drugs on Serum Alkaline Phosphatase

Total No. of Patients - 10

Follow up (in days)				
0 Day	30th Day	60th Day	90th Day	120th Day
Mean + S.D. (u/dl)	Mean + S.D. (u/dl)	Mean + S.D. (u/dl)	Mean + S.D. (u/dl)	Mean + S.D. (u/dl)
33.6 + 6.4	32.6 + 6.6	31.5+ 5.7	30.2 + 5.4	20.6 + 9.68
N = 10; t = 6.7 ; p<0.001				

Out of 25 patients 15 had normal serum alkaline phosphatase level. While in the remaining 10 patients the mean alkaline phosphatase was 33.6 $\pm$ 6.4 u/dl, which fell to 20.6 $\pm$ 9.68 u/dl, after 4 months of treatment and this fall was statistically highly significant.

The significant fall in patients with abnormal alkaline phosphatase may be attributed to the anti inflammatory effect of luk maghsool, which might have acted especially on the kupffer's cell reducing their inflammation and thereby facilitating the flow of bile. Other possible mechanisms involved may be due to the diuretic (mudir) and Naf-e-Zuafe Kabid (Hepatotonic) effect of Sandroos (Karim, 1185; Husain, 1914; Hakim, 1924; Chopra, 1958).

Table 10: Effect of Drugs on Serum Bilirubin

Total No. of Patients - 8

Follow up (in days)				
0 Day	30th Day	60th Day	90th Day	120th Day
Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)
2.81 + 0.43	2.5 + 0.37	2.37+ 0.37	2.43 + 0.32	1.82 + 0.31
N = 8; t = 8.4 ; p<0.001				

Out of 25 patients 17 had normal serum bilirubin throughout the study. In remaining 8 mean serum bilirubin before treatment was marginally high and was 2.81 $\pm$ 0.43 mg/dl which reduce to 1.82 $\pm$ 0.31 mg/dl after the completion of the therapy.

The fall in the mean serum bilirubin in test group may be due to the diuretic (mudir) effect of afsantin and muhalil (anti inflammatory), muqqawi jigar (hepato protective) effect of luk maghsool. This effect may also be attributed to

nafe zuafe kabid (hepato tonic) of sandroos (Khan, YNM; Hakim, 1924; Israili, 1907).

Table 11: Effect of Drugs on Total Cholesterol

Total No. of Patients - 8

Follow up (in days)				
0 Day	30th Day	60th Day	90th Day	120th Day
Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)
279.25 + 9.43	279 + 9.43	278.75+ 9.25	277.7 + 10.81	276.62 + 10.46
N = 8; t = 2.9 ; p<0.05				

17 patients had normal total cholesterol level. Whereas in 8 remaining patients mean cholesterol level before onset of treatment was 279.25 $\pm$ 9.43 mg/dl showing a marginal fall to 276.62 $\pm$ 10.46 which have no clinical significance. The marginal fall although insignificant but may be due to the Qabiz (Astringent), Mugharri (Mucilaginous) and Mullayan (Laxative) effect of Ispaghol which causes hindrance in absorption of fat from gastro intestinal tract (Rhazi, 1991; Lubhaya, 1982). Muhazzil (Fat dissolvent) effect of Luk Maghsool, Muhazzil and Mujjafif-e-Ratubat-e-Badan (absorbent) effect of Sandroos might be the other factors for lowering the serum cholesterol (Karim, 1185; Hakim, 1924).

Table 12: Effect of Drugs on Tryglycerides

Total No. of Patients - 25

Follow up (in days)				
0 Day	30th Day	60th Day	90th Day	120th Day
Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)	Mean + S.D. (mg/dl)
124.9 + 24.44	124.8 + 24.32	124.8+ 24.32	123.4 + 24.4	123.2 + 25.47
N = 25; t = 2.6 ; p<0.05				

The mean serum fasting triglycerides level before treatment was 124.9 $\pm$ 24.44 mg/dl, and it fell only by 1.7 mg/dl after 4 months of treatment which has no significant value. These observations show that our drugs have no significant effects on serum fasting triglycerides reason of which remains to be explained by employing advance pharmacological studies.

Table 13: Effect of Drugs on Brightness of Liver

Total No. of Patients - 25

USG Impression	Follow up (in days)		
	Before Treatment	After Treatment	
	0 day	120th day	
	Total No. of Patients	No. of Patients	Improved Percentage
Brightnesss of Liver	25	23	08

All the patients were subjected to Ultrasonography of Hepatobiliary system before and at the termination of therapy. Brightness of liver on the gray scale was noted objectively in all the 25 patients showing brightness of liver before starting the treatment. It was observed only in two patients that there was significant decrease in the liver brightness. This effect may be explained due to hindrance to absorption of fat from gastro intestinal tract because of Sabos-e-Ispaghol. The hot temperament of the test drugs Afsantin, Luk Maghsool and Sandroos (Karim, 1185; Husain, 1914; Hakim, 1924; Chopra, 1958), which might have caused redistribution and dislocation of fat from hepatocytes.

Conclusion

This study shows the effect of Unani formulation has an encouraging potential in Non- Alcoholic Fatty Liver Disease management with no major adverse effects and tolerated this therapy well. Further long term studies to determine the relapse rate and the effect of Unani formulation on deranged liver function along with increased dose and/or addition/deletion of drug ingredients need to be done.

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