

## A Comparative Study of Fraxinus Excelsior Plus Vitamin-E with Vitamin-E Alone on Liver Function in Non-Alcoholic Fatty Liver Disease (NAFLD) Patients

Anil Kumar Jangir<sup>1</sup>, Rajendra Singh Tanwar<sup>2</sup>, Puneet Saxena<sup>3</sup>, Aradhana Sharma<sup>4\*</sup>, S.S. Dariya<sup>5</sup>

<sup>1</sup>Junior Resident, Upgraded Department of Medicine, S.M.S. Medical College & Hospital, Jaipur, Rajasthan, India

<sup>2</sup>Senior Professor, Upgraded Department of Medicine, S.M.S. Medical College & Hospital, Jaipur, Rajasthan, India

<sup>3</sup>Senior Professor and Unit Head, Upgraded Department of Medicine, S.M.S. Medical College & Hospital, Jaipur, Rajasthan, India

<sup>4</sup>Associate Professor, Upgraded Department of Medicine, S.M.S. Medical College & Hospital, Jaipur, Rajasthan, India

<sup>5</sup>Junior Specialist, Upgraded Department of Medicine, S.M.S. Medical College & Hospital, Jaipur, Rajasthan, India

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### Abstract

**Aims and Objectives:** To find the effect of fraxinus excelsior plus vitamin-E with vitamin-E alone on liver function in non-alcoholic fatty liver disease (NAFLD) patients. **Material and Methods:** This was a hospital based observational study. The study was conducted on 270 patients, diagnosed with NAFLD by Ultra sonography (USG) with baseline deranged LFT and lipid profile then were divided in two groups of patients. Each group consist of 135 patients, group 1 subjects received Vitamin E alone and group 2 subjects received Vitamin E plus Fraxinus Excelsior. LFT, lipid profile and steatohepatitis grade were investigated in four visits (day 1<sup>st</sup>, day 30<sup>th</sup> day, 60<sup>th</sup> and day90<sup>th</sup>). **Results:** In this study baseline LFT and lipid profile of the patients were deranged in both groups but statistically no significant difference in baseline LFT and lipid profile between both groups. During 2<sup>nd</sup> (day 30<sup>th</sup>), 3<sup>rd</sup> (day60<sup>th</sup>) and 4<sup>th</sup> (day90<sup>th</sup>) visits mean AST, ALT, ALP, TC, LDL were improved in both groups including steatohepatitis grade, but more improvement was occurred in group 2 who received combination of Vitamin E + Fraxinus excelsior. There was no statistically significant difference in the mean value of LFT and lipid profile between both group at 30<sup>th</sup> day but statistical significance found between both group at 60<sup>th</sup> day and at 90<sup>th</sup> day. Steatohepatitis grades were improved in both groups. At 30day, grade 2 was seen maximum in both groups i.e. 70 (51.9%) and 62 (45.9%) in group 1 and group 2 respectively followed by grade 3. At 60<sup>th</sup> day steatohepatitis grade was improved in both groups, grade 2 was seen maximum in both groups i.e. 58 (43%) and 52 (38.4%) in group 1 and group 2 respectively followed by one. And 90<sup>th</sup> day steatohepatitis grade was improved in both groups grade 2 was seen maximum in groups 1 i.e. 63 (46.7%) followed by grade 1 i.e. 40 (29.6%) and in group 2, grade 1 was seen maximum i.e.54 (40%) followed by no grade in 45(33.3%). **Conclusion:** In this study, it was observed that consumption of fraxinus excelsior and vitamin E is associated with statistically significant improvement in LFT, lipid profile and steatohepatitis grade as compared to consumption of vitamin E alone.

**Keywords:** Non-alcoholic Liver Disease, Steatohepatitis, Lipid Profile.

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### Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of excessive fat in the liver, as demonstrated by imaging or by histology, in the setting of no significant alcohol consumption and the absence of any secondary cause[1]. NAFLD is strongly associated with obesity and related metabolic disorders such as insulin resistance and dyslipidemia. NAFLD prevalence in Asian countries ranges from 12% - 24% and is associated with age, gender, locality and ethnicity[2]. In India, the prevalence is up to 32% in general population and higher incidence is reported in obese (57.5% - 74%) and diabetic (56.5%) populations[3].

In spite of high prevalence of NAFLD in Asian countries and globally, there is currently no definitive treatment for NAFLD. Besides lifestyle modifications, physical exercise and dietary control, there are no US Food and Drug Administration-approved medications for patients with NAFLD. It is acknowledged that vitamin E is the

major lipid-soluble chain-breaking antioxidant, found in human body. In addition to its anti-oxidative properties, molecules of the vitamin E family exert antiatherogenic and anti-inflammatory activities and are also found to be decreased in NASH patients compared to healthy controls, forming a theoretical basis for its use in the treatment of NASH[4,5].

The leaves & bark of fraxinus excelsior contain-calcium malate, tannin, some free malic acid< mannitol, dextrose inositol, gum, quercitrin & aromatic volatile oil. Fraxinus excelsior L extract was found to activate peroxisome proliferator activated receptor alpha and thereby helps in improving the lipid profile. Evidence suggests that extracts of F. excelsior promote insulin sensitivity and increase adiponectin-leptin ratio thereby reducing fat mass and body. Weight. F. excelsior has also exhibited beneficial effects in improving dyslipidemia [4]. Vitamin E being an antioxidant target on Hit-2 stage in non-alcoholic steatohepatitis (NASH). There is need for drug which works on steatosis (Hit-1 stage). Fraxinus excelsior works on Hit-1 stage, so, we can use fraxinus excelsior & vitamin E combination for NAFLD patients. There are few studies in India on Fraxinus excelsior plus Vitamin E combination especially in Rajasthan, there is no study available on Fraxinus excelsior plus Vitamin E combination in NAFLD patients.

\*Correspondence

Aradhana Sharma

Associate Professor, Upgraded Department of Medicine, S.M.S. Medical College & Hospital, Jaipur, Rajasthan, India.

E-mail: [aradhanas1@gmail.com](mailto:aradhanas1@gmail.com)

**Materials and Methods**

After taking written and informed consent from the participants and approval from Institutional Ethical Committee, 270 patients were selected for the study. This was the hospital based observational study and was conducted in Department of General medicine, SMS medical college and attached group of hospitals, Jaipur, Rajasthan. 270 patients diagnosed with NAFLD by Ultra sonography (USG) with

baseline deranged LFT and lipid profile were divided in two groups of patients. 270 eligible cases were randomly allocated into two study groups. Each group consist of 135 patients (n=135/group):

**Group 1:** Subjects received Vitamin E alone

**Group 2:** Subjects received Vitamin E plus F. Excelsior

**Flowchart**

Visit 1	Day 1	Total 270 NAFLD patients satisfying the inclusion / exclusion criteria were enrolled. NAFLD - patients were randomly divided into 2 groups & received either the fraxinus excelsior plus Vit E or vitamin E alone BID for 12 weeks.
Visit 2	Day 30	Physical examination, drug dispensing, clinical parameters was observed.
Visit 3	Day 60	Physical examination, drug dispensing, clinical parameters was observed.
Visit 4	Day 90	Physical examination, Biochemical, clinical parameters was observed.

**Statistical Analysis**

Independent t-test and ANOVA test were used to compare the continuous variable and chi- square test was used for categorical variables. Nonparametric Mann Whitney test and Kruskal Wallis test were used in case of data did not follow a normal distribution. Data are presented as mean (standard deviation) or number or proportions. A p-value <0.05 was considered as statistically significant.

**Results**

The study was conducted amongst 270 adult patients diagnosed NAFLD. Thus, 270 study participants were included for the analysis which was equal to the estimated sample size and randomized in two group.

In this study baseline mean age, weight, height, BMI, and HbA1c difference were not statistically significant in group 1 and group 2 respectively (p-value 0.317,0.965,0.750, and 0.613). (Table 1)

The baseline LFT and lipid profile of the patients were deranged in both groups but no statistically significant difference in baseline LFT and lipid profile between both groups. (Table 2)

In this study, maximum patients in both group during baseline visit had grade 2 steatosis i.e. 62(45.9%) and 65 (48.1%) in group 1 and 2 respectively followed by grade 3. (Table 3)

This study revealed that during 2<sup>nd</sup> visit at 30<sup>th</sup> day, mean AST, ALT, ALP, TC, LDL were im- proved in both group but more improvement was occurred in group 2 who received combination of Vit E + Frexinus excelsior. There was no statistically significant difference in the mean value of LFT and lipid profile between both group at 30<sup>th</sup> day. (Table 4)

The steatohepatitis grade was improved in both groups. Grade 2 was seen maximum in both groups i.e. 70 (51.9%) and 62 (45.9%) in

group 1 and group 2 respectively followed by grade 3. Grade 0 or no steatosis was seen in 4 patients in group 2. And this steatosis grade difference was noted statistically significant (p value 0,012) between both group during the 2<sup>nd</sup> visit at 30<sup>th</sup> day. (Table 5)

The study revealed that during 3<sup>rd</sup> visit at 60<sup>th</sup> day, mean AST, ALT, ALP, TC, LDL were im- proved in both group but more improvement was occurred in group 2 who received combination of Vitamin E + Frexinus excelsior. There was a statistically significant difference in the mean value of LFT and lipid profile between both group at 60<sup>th</sup> day. (Table 6)

In our study, steatohepatitis grade was improved in both groups. Grade 2 was seen maximum in both groups i.e. 58 (43%) and 52 (38.4%) in group 1 and group 2 respectively followed by grade.

1. Grade 0 or no steatosis was seen in 8(5.9%) and 24(17.8%) patients in group 1 and 2 respectively. And this steatosis grade difference was noted statistically significant (p value 0.003) between both group during the 3<sup>rd</sup> visit at 60<sup>th</sup> day. (Table 7)

Current study revealed that during 4<sup>th</sup> visit at 90<sup>th</sup> day, mean AST, ALT, ALP, TC, LDL were improved in both group but more improvement was occurred in group 2 who received combination of Vit E + Frexinus excelsior. There was a statistically significant difference in the mean value of LFT and lipid profile between both group at 90<sup>th</sup> day. (Table 8)

In our study, steatohepatitis grade was improved in both groups. Grade 2 was seen maximum in groups 1 i.e. 63 (46.7%) followed by grade 1 i.e. 40 (29.6%) and in group 2, grade 1 was seen maximum i.e.54 (40%) followed by no grade in 45(33.3%). And this steatosis grade difference was noted statistically significant (p value 0.001) between both group during the 4<sup>th</sup> visit at 90<sup>th</sup> day.(Table 9)

**Table 1: Baseline parameters of both groups**

Parameter	Group	Mean	Std. deviation	Median	Minimum	Maximum	P-value
Age	Group-1	53.119	9.5433	52.0	31.0	80.0	0.317
	Group-2	52.015	8.5116	52.0	30.0	7.0	
Weight	Group-1	77.07	8.362	79.0	58	92	0.965
	Group-2	77.02	8.275	79.0	58	92	
Height	Group-1	170.6	6.18	170.0	161	179	0.750
	Group-2	170.39	6.413	170.0	158	179	
BMI	Group-1	26.591	3.626	25.911	18.513	35.056	0.887
	Group-2	26.653	3.618	25.911	18.937	35.600	
HbA1c	Group-1	6.962	1.5714	6.500	5.2	11.1	0.613
	Group-2	7.062	1.6722	6.500	5.2	11.1	

**Table 2: Comparison of baseline LFT and lipid profile between both groups**

Group	1			2			p-value
	Mean	SD	Median	Mean	SD	Median	
AST	329.8	246.08	230	354.6	260	321	0.498
ALT	339.20	251.1	238.0	362.35	264.38	238	0.547
ALP	172.978	78.5501	180.000	174.170	80.0849	178.000	0.902
TC	254.356	87.8545	230.000	259.030	90.0182	230.000	0.666
LDL	163.104	79.8594	140.000	162.756	80.1089	140.000	0.971

HDL	58.348	29.7593	60.000	58.585	31.1241	60.000	0.949
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**Table 3: Comparison of baseline steatohepatitis grade between both groups**

			Group	
			1	2
Grade	1	Count	20	12
		% within Group	14.8%	8.9%
	2	Count	62	65
		% within Group	45.9%	48.1%
	3	Count	53	58
		% within Group	39.3%	43.0%
Total		Count	135	135
		% within Group	100.0%	100.0%

**Table 4: Comparison of LFT and lipid profile at day 30 between both groups**

Group	1			2			p-value
	Mean	SD	Median	Mean	SD	Median	
AST	89.119	54.0754	80.000	85.185	47.3578	78.000	0.525
ALT	102.000	62.1332	98.000	94.570	51.9323	88.000	0.287
ALP	172.978	78.5501	180.000	166.289	74.7388	180.000	0.474
TC	254.356	87.8545	230.000	321.867	494.0766	220.000	0.119
LDL	163.104	79.8594	140.000	157.896	75.8583	129.000	0.583
HDL	58.348	29.7593	60.000	61.815	28.1261	60.000	0.326

**Table 5: Comparison of steatohepatitis grade at day 30 between both groups**

			Group		p-value
			1	2	
Grade	0	Count	0	4	0.012
		% within Group	0.0%	3.0%	
	1	Count	24	40	
		% within Group	17.8%	29.6%	
	2	Count	70	62	
		% within Group	51.9%	45.9%	
	3	Count	41	29	
		% within Group	30.4%	21.5%	
Total		Count	135	135	
		% within Group	100.0%	100.0%	

**Table 6: Comparison of LFT and lipid profile at day 60 between both groups**

Group	1			2			p-value
	Mean	SD	Median	Mean	SD	Median	
AST	80.911	41.5592	77.00	67.748	37.0449	60.000	0.006
ALT	93.570	52.8500	88.00	71.556	42.7210	68.000	0.001
ALP	153.007	67.0615	160.00	128.896	53.6921	120.00	0.001
TC	234.622	74.7070	200.00	204.244	82.1492	190.00	0.002
LDL	147.815	60.5125	130.00	122.593	38.4532	108.00	0.001
HDL	65.133	26.9825	60.000	72.333	26.0725	78.000	0.027

**Table 7: Comparison of steatohepatitis at day 60 between both groups**

			Group		p-value
			1	2	
Grade	0	Count	8	24	0.003
		% within Group	5.9%	17.8%	
	1	Count	40	45	
		% within Group	29.6%	33.3%	
	2	Count	58	52	
		% within Group	43.0%	38.5%	
	3	Count	29	14	
		% within Group	21.5%	10.4%	
Total		Count	135	135	
		% within Group	100.0%	100.0%	

**Table 8: Comparison of LFT and lipid profile at day 90 between both groups**

Group	1			2			p-value
	Mean	SD	Median	Mean	SD	Median	
AST	78.630	37.8480	77.000	50.867	31.3478	40.000	0.007
ALT	87.881	43.9364	87.000	72.756	42.0067	70.000	0.001
ALP	140.719	54.2545	152.00	122.33	51.28	110.00	0.011
TC	211.578	57.8315	189.00	191.10	62.62	178.00	0.005
LDL	134.719	50.0098	122.00	120.007	37.206	107.0	0.028

HDL	72.244	26.7527	78.000	79.622	28.8493	82.000	0.029
<b>Table 9: Comparison of steatohepatitis at day 90 between both groups</b>							
		<b>Group</b>				<b>p-value</b>	
		<b>1</b>		<b>2</b>			
Grade	0	Count	16	45	0.001		
		% within Group	11.9%	33.3%			
	1	Count	40	54			
		% within Group	29.6%	40.0%			
	2	Count	63	36			
		% within Group	46.7%	26.7%			
	3	Count	16	0			
		% within Group	11.9%	0.0%			
Total		Count	135	135			
		% within Group	100.0%	100.0%			

### Discussion

NAFLD is an important cause of morbidity and mortality worldwide due to cardiovascular and oncologic sequelae as well because it is rapidly becoming a leading cause of end stage liver disease and liver transplant. There is no definite treatment for NAFLD.

In our study mean age, weight, gender, height, BMI differences were not found statistically significant in baseline characteristics between both groups. Study by Prasad VGM et al[6] reported similar patient characteristics. Brill et al[7] also reported similar results while comparing the different methods of treatment for NAFLD. In our study, baseline LFT and lipid profile of the patients were deranged in both groups but no statistically significant difference in baseline LFT and lipid profile between both groups. This is supported by study conducted by Mansour-Ghanaei R et al[8].

In our study the baseline mean AST, ALT, ALP, TC and LDL was 329.8, 339.2, 172.98, 254.36 and 163.10 respectively. After 90 days treatment with Vitamin E these were 78.63, 87.88, 140.7, 211.57 and 134.7 respectively which showed a significant improvement in the LFT and lipid profile. Current study also revealed that steatosis of the patient who received Vitamin E had also been improved at the end of the 90<sup>th</sup> day and 16 patients out of 135 patients did not have any type of steatosis at the end of the study from the zero patients in the beginning and 40 patients were in grade 1 type of steatosis. Similar results were reported by, Lavine et al[9] who conducted a multi-center, double-blind, double-placebo, randomized clinical trial in pediatric patients. In this TONIC randomized controlled trial involved 173 children and adolescents with a mean age of 13 years that received metformin (500 mg twice daily), vitamin E (400 IU twice daily), or placebo twice daily for 96 weeks.

Similarly, Prasad VGM et al[6] reported that After 12 weeks of treatment with vitamin E and Fraxinus excelsior, 21% patients had no steatosis, 58.79% patients were in Grade 1 steatosis, 19.57% in grade II steatosis and only 0.63% patients in Grade III steatosis. The mean reductions in AST and ALT were significant at week 6 and week 12. Patil et al[4], in 2018 reported that combination of Vitamin E (400 IU) and F. excelsior (500 mg) were found to be more effective than vitamin E monotherapy in the treatment of NAFLD patients by improving the lipid profile and liver function. A meta-analysis of randomized controlled trials conducted by Sato K, et al[10] found vitamin E significantly improved liver function and histologic changes in patients with NAFLD/NASH.

### Conclusion

In this study, it was observed that consumption of fraxinus excelsior plus vitamin E is associated with statistically significant improvement in LFT, lipid profile and steatohepatitis grade, as compared to vitamin E alone. So current study revealed that Vitamin E and F. excelsior combination is more effective in the treatment of NAFLD in routine clinical practice. Its consumption is associated with improvement in liver steatosis and liver function parameters (AST

**Conflict of Interest: Nil**

**Source of support: Nil**

and ALT). Given the limited therapeutic options in NAFLD, this combination has the potential to bridge the therapeutic gap in management of NAFLD.

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