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Effect of Black Pepper on Biochemical and FibroScan Parameters in Patients with Grade 2 Non-alcoholic Fatty Liver Disease: A Randomized Controlled Trial

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is increasingly common and has limited approved pharmacologic treatments. Preclinical evidence suggests piperine (black pepper) may improve hepatic steatosis and metabolic parameters. To estimate the efficacy of crushed black pepper (piperine) supplementation on biochemical tests and FibroScan parameters in Grade 2 NAFLD patients. A randomized, double-blind, placebo-controlled trial was performed with 370 patients who were sonographically diagnosed with Grade 2 NAFLD. Participants were randomized 1:1 to receive crushed black pepper (20 mg daily; n = 185) or an identical placebo (n = 185) for 12 weeks. Primary outcomes were changes in liver enzymes (ALT, AST), lipid profile, glycemic indices (FBG, HOMA-IR), and FibroScan measurements (controlled attenuation parameter [CAP] and liver stiffness measurement [LSM]). Biochemical tests and FibroScan were done at baseline and after 12 weeks. Between-group comparisons used unpaired t-tests; within-group changes used paired t-tests. Significance was determined at $p<0.05$. 370 participants completed the trial. Compared with placebo, the piperine group showed statistically significant improvements after 12 weeks in liver enzymes (ALT, AST, GGT, ALP), lipid profile (↓TC, ↓LDL-C, ↓TG; ↑HDL-C), glycemic indices (↓FBG, ↓HOMA-IR), and FibroScan measures (↓CAP, ↓LSM) (all $p<0.05$). No serious adverse events were recorded. Daily supplementation with 20 mg crushed black pepper for 12 weeks improved biochemical markers and FibroScan measures in patients with Grade 2 NAFLD. Larger, longer trials are required to confirm prolonged effectiveness and safety.

Keywords: CAP, Fibro Scan, Liver Stiffness, NAFLD, Piperine.

Introduction

Non-alcoholic fatty liver disease (NAFLD) characterizes an excessive fat buildup in the liver of persons who have no or little alcohol intake. Presently, it is the most widespread chronic liver disease internationally, with estimates reaching 25% of the adult global population (1). It is particularly concerning in Asian populations, including India, where the prevalence has risen significantly in recent decades, paralleling the increase in obesity and metabolic syndrome (2, 3). Further, it is associated with components of metabolic syndrome (4). The pathogenesis of NAFLD is complex and multifactorial, involving interactions among genetic, environmental, and metabolic factors that contribute to hepatic inflammation, steatosis, and fibrosis (5). In addition, as the number of cases of NAFLD has increased significantly and its progression may insidiously occur to very severe illnesses, namely "nonalcoholic steatohepatitis (NASH)," "cirrhosis," and "hepatocellular carcinoma," treatment options for NAFLD are still limited (6). Existing management strategies for NAFLD are mainly focused on lifestyle modifications, namely weight loss through exercise and diet control (7). Several pharmacological interventions targeting different steps of NAFLD pathogenesis are still under investigation; however, the Food and Drug Administration (FDA) has stated that no drug exists to treat NAFLD (8). Natural compounds have gained greater attention, as they may offer hepatoprotective and metabolic benefits that help fill the gap in available therapeutic options. Among those compounds, "Black pepper (*Piper nigrum*)" and its major bioactive "Piperine" are known for their potential anti-obesity, anti-inflammatory and

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health-promoting properties. Previous investigations have demonstrated that Piperine can attenuate liver steatosis, increase insulin sensitivity, and modulate lipid metabolism in animal models of metabolic dysfunction and obesity. Further, Piperine has been shown to affect several mechanistic pathways linked to NAFLD pathogenesis, such as activation of the "PPARγ antagonism", "AMP-activated protein kinase (AMPK)," and "LXRα modulation" (8-10). Moreover, Piperine has been found to modify gut microbiota, improve glucose uptake in skeletal muscle via ROS-triggered stimulation of the signaling pathway of "CAMKK/AMPK", and ameliorate lipid metabolism by upregulating "ATP binding cassette sub-family G member 8 (ABCG8)" and "scavenger receptor class B type 1 (SR-B1)" transporters (11-13). Recent evidence indicates that Piperine can regulate circadian genetic factor "BMAL1" and "CLOCK" in lipid metabolism (14).

While black pepper supplementation has been shown to improve liver function and metabolic parameters in mice, the specific effects of this intervention on hepatic function and metabolic parameters in patients with established NAFLD remain unknown. However, few studies examined the impact of black pepper or Piperine on NAFLD patients. A previous study reported that a curcuminoid-piperine combination has shown benefits in NAFLD, improving antioxidant and anti-inflammatory status in cases with metabolic syndrome (15). Previous randomized controlled trials compared the impact of curcuminoids and piperine with placebo on biochemical variables and disease severity in NAFLD patients. Those trials concluded that a curcuminoid-piperine combination has valuable impacts on biochemical outcomes and disease severity in those patients (16-17).

A recent double-blind study compared the piperine and placebo treatments over 12 weeks in persons with NAFLD (grade 2 and 3) and early cirrhosis. It concluded that Piperine reduced alanine aminotransferase (ALT), and aspartate aminotransferase (AST), and enhanced lipid and glucose metabolism in those patients. Given the lack of approved clinical management for NAFLD and the promising effects of Piperine observed in that study, further research is warranted (18). To augment the current literature, this study aimed to examine the effect of Black Pepper on biochemical and FibroScan parameters in patients with NAFLD (grade 2).

Methodology

Study Design and Participants

This study embraced a randomized, single-blinded, placebo-controlled trial design to evaluate the effect of piperine supplementation on biochemical and FibroScan parameters in NAFLD patients. It was conducted at Yathart Hospital, Greater Noida. It was approved by the institutional ethics committee, in accordance with the Declaration of Helsinki. Ethical approval was granted by Sharda University in Greater Noida (reference number: SU/RES/SAHS/N and D/2021212365/710).

The inclusion criteria encompass patients aged 18-65 years who were confirmed with Grade 2 NAFLD by a Physician based on sonographic findings, both male and female patients, patients with body mass index (BMI) of 25 to 35 kg/m^2, and Patients who were willing to participate.

The exclusion criteria include patients having alcohol misuse, patients with a history of viral hepatitis, secondary sources of fatty liver disease, or other chronic liver ailments to eliminate confounding variables, those with significant cardiovascular or renal illnesses, those on drugs that influence liver function, those who are pregnant or lactating mothers, and those reporting allergies to black pepper.

Moreover, the sample size was computed to be 330 using the Australian Bureau of Statistics software, with a confidence level of 95%, a standard error of 0.02752, and a relative standard error of 5.50. Finally, a sample size of 370 was confirmed, given a projected 10% dropout rate. Three hundred seventy patients diagnosed with Grade 2 NAFLD according to medical and radiological criteria were selected using the selection criteria. Using simple random sampling, the selected patients were allocated to two groups, i.e., the "piperine supplementation" group (n=185) and the "placebo" group (n=185). Additionally, all participants were informed about the study's objectives, potential risks, and benefits. They were informed that their participation was voluntary. They gave written informed consent before the study commenced.

Treatment Interventions

In the piperine group, participants had a daily dose of 20 mg of crushed black pepper powder (95%

purity). Likewise, previous studies have used a single daily dose of 20 mg piperine for ten days in healthy subjects (19, 20). Another previous study stated that 5-20mg doses of piperine are commonly administered in clinical trials (21). In the placebo group, those had a similar substance with inactive ingredients. A recent study also used placebo capsules containing an ineffective ingredient, which were indistinguishable from piperine capsules (22). Both treatments were given orally for 12 weeks. During the study, participants were advised to maintain a consistent, healthy diet and to engage in routine exercise, such as walking for 30 minutes per day, 5 days a week, to lessen peripheral effects on biochemical and FibroScan variables. Participants were checked weekly to confirm their compliance with a healthy diet and exercise. Additionally, no dropouts and adverse events were reported by study participants.

Outcome Parameters

At baseline, the participants' demographic data were recorded. Before and after the treatment intervention, standardized procedures were used to take anthropometric measurements. Besides, an overnight fast (12-14 hours) was performed, after which blood samples were collected for biochemical assessments using enzymatic colorimetric methods in a qualified lab setting. The laboratory data measured in this study include i) liver enzymes like ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, and bilirubin, ii) lipid profile such as triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC), and iii) glycemic measures, namely, homeostasis model assessment of insulin resistance (HOMA-IR) and fasting blood glucose (FBG). Additionally, FibroScan® via transient elastography was performed to evaluate liver steatosis and fibrosis using the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), respectively. The M probe was utilized to measure the CAP and LSM values. The XL probe was applied to obese cases when the previous probe type was unsuccessful. Ten successful assessments were performed on each participant to explain the CAP and LSM. The CAP value was reliable if ten valid acquisitions were retrieved. The LSM value is consistent if the degree of success is more than 60% and its median or interquartile range is less than 30% (23, 24).

Statistical Analysis

The data analysis was done through "SPSS version 29.0 (IBM Corp., Armonk, NY, USA)." Data normality was assessed using the Shapiro-Wilk test. Continuous data were described using mean and standard deviation. Categorical variables were stated using frequencies and percentages. Variations in outcome measures within each group after the treatment intervention were analyzed using a paired t-test. In contrast, variations in outcome measures between groups at baseline and after the intervention (12 weeks) were evaluated using a chi-square test or an unpaired t-test, depending on the type of variables. The significance level was set at 5%.

Results

Among 370 patients with grade 2 NAFLD, 216 (58.4%) were males, and 154 (41.6%) were females. At baseline, the chi-square test showed that the piperine and placebo groups had no significant variations in demographic and anthropometric variables, including age, sex, body height, weight, waist-to-hip ratio, and BMI ($p>0.05$) , as shown in Table 1.

Table 1: Chi-Square Test Revealing Variations among Demographic and Anthropometric Variables at Baseline

Characteristics		Piperine Group (n=185)	Placebo Group (n=185)	p-value
Demographics				
Age (years)		42.8 ± 9.3	43.5 ± 8.9	0.754^{NS}
Sex	Male	111 (60.0)	105 (56.7)	0.795 ^{NS}
	Female	74 (40.0)	80 (43.3)	
Anthropometric Measurements				
Body Weight (kg)		82.5 ± 12.8	83.1 ± 13.2	0.856 ^{NS}
Height		167.2 ± 8.9	166.8 ± 9.1	0.724 ^{NS}
BMI (kg/m^2)		29.7 ± 3.8	30.1 ± 4.0	0.698 ^{NS}
Waist-Hip Ratio		0.93 ± 0.07	0.94 ± 0.08	0.602 ^{NS}

NS-Non- significant at 0.05 level ($p>0.05$)

Table 2: Paired 't' Test Comparing the Mean Values of the Biochemical and Fibroscan Parameters between Baseline and after Intervention in the Piperine Group (n=185)

Parameters		Measurement time	Piperine Group(n=185)	Mean Difference	t-value (p-value)	95% CI for Difference
Biochemical	ALT (IU/L)	Baseline	78.6 ± 12.3	15.400	17.372*	(13.662, 17.138)
		After intervention	63.2 ± 11.8			
	AST (IU/L)	Baseline	59.4 ± 12.7	15.300	18.190*	(13.651, 16.949)
		After intervention	44.1 ± 9.5			
	GGT (IU/L)	Baseline	65.3 ± 17.2	13.600	11.572*	(11.297, 15.903)
		After intervention	51.7 ± 14.4			
	Albumin (g/dL)	Baseline	3.72 ± 0.4	-0.230	6.827*	(-0.296, -0.164)
		After intervention	3.95 ± 0.5			
	Bilirubin (mg/dL)	Baseline	0.60 ± 0.3	-0.360	13.581*	(-0.412, -0.308)
		After intervention	0.96 ± 0.4			
	ALP (IU/L)	Baseline	293.1 ± 9.5	39.900	56.218*	(38.509, 41.291)
		After intervention	253.2 ± 9.8			
	TC (mg/dL)	Baseline	221.5 ± 32.6	23.200	10.273*	(18.774, 27.626)
		After intervention	198.3 ± 28.4			
	LDL-C (mg/dL)	Baseline	143.8 ± 26.9	19.300	10.473*	(15.688, 22.912)
		After intervention	124.5 ± 22.7			
	HDL-C (mg/dL)	Baseline	41.3 ± 7.2	-5.500	10.604*	(-6.517, -4.483)
		After intervention	46.8 ± 6.9			
	TG (mg/dL)	Baseline	175.2 ± 45.8	32.600	10.403*	(26.458, 38.742)
		After intervention	142.6 ± 38.5			
	FBG (mg/dL)	Baseline	105.3 ± 12.6	8.600	9.910*	(6.899, 10.301)
		After intervention	96.7 ± 10.8			
	HOMA-IR	Baseline	4.08 ± 1.42	1.190	12.686*	(1.006, 1.374)
		After intervention	2.89 ± 1.05			
FibroScan	CAP (dB/m)	Baseline	302.9±25.9	15.300	8.293*	(11.684, 18.916)
		After intervention	287.6±24.2			
	LSM (kPa)	Baseline	9.1±1.8	0.700	5.572*	(0.454, 0.946)
		After intervention	8.4±1.6			

* Significant at 0.05 level (p<0.05)

Using the paired t-test, the piperine group demonstrated significant effects on biochemical parameters, including liver enzymes, lipid profile, and glycemic measures, at the end of treatment. It showed a significant decrease in liver enzymes, namely ALT, AST, GGT, and ALP, and an improvement in albumin and bilirubin levels (p<0.05). Additionally, it showed a significant reduction in lipid profile, including TG, TC, and LDL-C, with an improvement in HDL-C (p<0.05). Regarding glycemic measures, there was a significant decrease in FBG and HOMA-IR in the piperine group (p<0.05). Likewise, the piperine group exhibited a substantial effect on FibroScan parameters, with a reduction in CAP and LSM (p<0.05), as described in Table 2. Conversely, the placebo group presented no significant effect on any of the biochemical and FibroScan parameters measured between baseline and after intervention (after 12 weeks) (p>0.05), as shown in Table 3.

Table 3: Paired 't' test Comparing the Mean Values Observed at Baseline and after Intervention in the Placebo Group (n=185)

Parameters		Measurement time	Placebo Group (n=185)	Mean Difference	t-value (p-value)	95% CI for Difference
Biochemical	ALT (IU/L)	Baseline	75.4 ± 13.7	2.800	2.625^{NS}	(0.709, 4.891)
		After intervention	72.6 ± 15.2			
	AST (IU/L)	Baseline	56.8 ± 12.1	1.900	1.437^{NS}	(0.064, 3.736)
		After intervention	54.9 ± 13.3			
	GGT (IU/L)	Baseline	62.7 ± 18.5	2.400	1.807^{NS}	(-0.203, 5.003)
		After intervention	60.3 ± 17.6			
	Albumin (g/dL)	Baseline	3.9 ± 0.8	0.160	1.800^{NS}	(0.014, 0.334)
		After intervention	3.7 ± 0.9			
		Baseline	0.55 ± 0.8	-0.170	1.920^{NS}	(-0.344, 0.004)

	Bilirubin (mg/dL)	After intervention	0.72 ± 0.9			
	ALP (IU/L)	Baseline	285.1 ± 11.6	2.300	1.834 NS	(-0.165, 4.765)
		After intervention	282.8 ± 12.5			
	TC (mg/dL)	Baseline	220.4 ± 31.5	3.500	1.494 NS	(-1.090, 8.090)
		After intervention	216.9 ± 32.2			
	LDL-C (mg/dL)	Baseline	142.1 ± 26.1	2.600	1.331 NS	(-1.228, 6.428)
		After intervention	139.5 ± 27.0			
	HDL-C (mg/dL)	Baseline	43.3 ± 6.5	0.900	1.854 NS	(-0.051, 1.851)
		After intervention	42.4 ± 6.7			
	TG (mg/dL)	Baseline	171.7 ± 43.2	3.400	1.054 NS	(-2.921, 9.721)
		After intervention	168.3 ± 44.5			
	FBG (mg/dL)	Baseline	103.1 ± 12.3	1.300	1.483 NS	(-0.418, 3.018)
		After intervention	101.8 ± 11.5			
	HOMA-IR	Baseline	3.96 ± 1.31	0.090	0.934 NS	(-0.099, 0.279)
		After intervention	3.87 ± 1.31			
	CAP (dB/m)	Baseline	299.9±26.8	2.500	1.276 NS	(-1.341, 6.341)
		After intervention	297.4±26.5			
FibroScan	LSM (kPa)	Baseline	8.2±2.2	-0.400	1.788 NS	(-0.840, 0.040)
		After intervention	8.6±2.1			

NS-non-significant at 0.05 level (p > 0.05)

Table 4: Unpaired 't' Test Comparing Biochemical and Fibroscan Variables between Piperine and Placebo Groups at Baseline and after Intervention

Parameters		Baseline			After intervention		
		Mean Difference	t-value (p-value)	95% CI for Difference	Mean Difference	t-value (p-value)	95% CI for Difference
Biochemical	ALT (IU/L)	3.20	1.364 NS	(0.54, 5.86)	-9.40	6.644*	(-12.18, -6.62)
	AST (IU/L)	2.60	1.016 NS	(0.06, 5.14)	-10.80	8.988*	(-13.16, -8.44)
	GGT (IU/L)	2.60	1.400 NS	(-1.05, 6.25)	-8.60	5.144*	(-11.89, -5.31)
	Albumin (g/dL)	-0.18	1.737 NS	(-0.31, -0.05)	0.25	3.303*	(0.10, 0.40)
	Bilirubin (mg/dL)	0.05	0.796 NS	(-0.07, 0.17)	0.24	3.314*	(0.10, 0.38)
	ALP (IU/L)	8.00	2.957 NS	(5.83, 10.17)	-29.60	25.347*	(-31.90, -27.30)
	TC (mg/dL)	1.10	0.330 NS	(-5.45, 7.65)	-18.60	5.892*	(-24.81, -12.39)
	LDL-C (mg/dL)	1.70	0.617 NS	(-3.72, 7.12)	-15.00	5.784*	(-20.10, -9.90)
	HDL-C (mg/dL)	-2.00	2.004 NS	(-3.40, -0.60)	4.40	6.223*	(3.01, 5.79)
	TG (mg/dL)	3.50	0.756 NS	(-5.60, 12.60)	-25.70	5.941*	(-34.21, -17.19)
	FBG (mg/dL)	2.20	1.699 NS	(-0.35, 4.75)	-5.10	4.397*	(-7.38, -2.82)
	HOMA-IR	0.12	0.845 NS	(-0.16, 0.40)	-0.98	-7.940*	(-1.22, -0.74)
FibroScan	CAP (dB/m)	3.00	1.095 NS	(-2.39, 8.39)	-9.80	-3.714*	(-14.99, -4.61)
	LSM (kPa)	0.90	2.306 NS	(0.49, 1.31)	-0.20	-3.530*	(-0.58, 0.18)

NS-non-significant at 0.05 level (p > 0.05); * Significant at 0.05 level (p < 0.05)

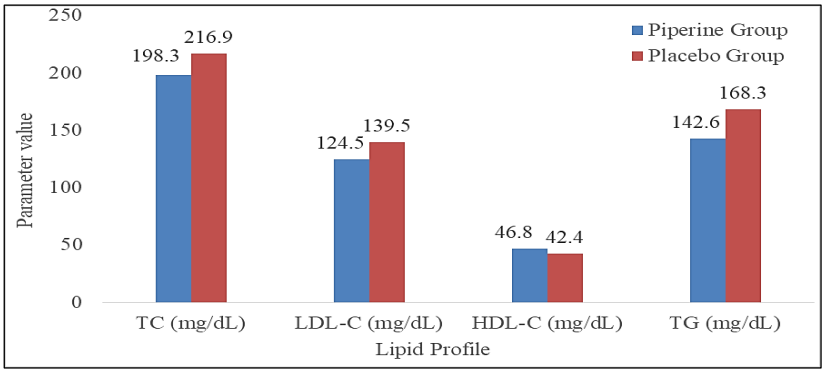

Figure 1: Comparison of Lipid Profile Parameters between Piperine and Placebo groups after Intervention (12 weeks)

At baseline, no significant changes were observed in the mean values of all biochemical and FibroScan parameters between the piperine and placebo groups ($p>0.05$). Nevertheless, after intervention (12 weeks), significant differences emerged in the mean scores of all biochemical parameters, including liver enzymes, glycemic measures, and lipid profile, between the Piperine and placebo groups ($p < 0.05$). Figure 1 describes the lipid profile parameters between the Piperine and placebo groups after 12 weeks. Similarly, there were significant differences in the mean values of FibroScan parameters, such as CAP and LSM, between the piperine and placebo groups ($p < 0.05$). While reviewing the mean scores, the piperine group, which received black pepper powder, showed better results than the placebo group, treated with a similar substance with inactive ingredients, in controlling biochemical and FibroScan parameters in grade 2 NAFLD patients, as described in Table 4.

Discussion

This study examined the effects of 12 weeks of Black Pepper supplementation on biochemical parameters, including liver enzymes, lipid profile, and glycemic measures, as well as FibroScan parameters, including CAP and LSM, in patients with grade 2 NAFLD. The outcomes showed that daily intake of 20mg of crushed black pepper had a significant effect on all biochemical and FibroScan parameters, such as CAP and LSM, compared with placebo, and it appeared to be a safe and promising adjunctive treatment.

Moreover, the Piperine group showed a significant decrease in liver enzymes, such as serum ALP, ALT, GGT, and AST, and an increase in albumin and bilirubin levels compared with the placebo group. This suggests a possible hepatoprotective effect of piperine, by reducing hepatic inflammation and steatosis. Furthermore, this observation might be due to Piperine's significant impact on decreasing liver enzymes and on ameliorating lipid and glucose metabolism (18). A recent study reported that Piperine can reduce hepatic inflammation (a substantial reduction in ALT) by modulating inflammatory pathways and cytokine production (22). Another recent study stated that Piperine attenuates inflammation by inhibiting NF-κB signaling pathways and reducing the production of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, in both in vitro and in vivo NAFLD models (25). Furthermore, previous studies stated that Piperine can attenuate hepatic steatosis and normalize transaminase levels in high-fat diet-induced liver injury models (26, 27). In alignment with this outcome, a recent study found that Piperine significantly reduced ALT, AST, GGT, and ALP, and increased albumin and bilirubin levels in NAFLD cases with early cirrhosis. However, it showed a significant difference between piperine and placebo treatment only for ALT and AST levels (18). Consistent with the preclinical studies in which Piperine attenuates in animals with high-fat diet (HFD) triggered hepatic steatosis (12, 24). An earlier study also reported that Piperine supplementation reversed liver steatosis and normalized transaminase levels in rats fed an HFD, due to enhanced fatty acid oxidation and reduced lipogenesis in the liver (24).

The outcomes showed a significant decrease in TG, TC, and LDL-C, and a substantial increase in HDL-C in the Piperine group compared with the placebo group. This outcome is supported by new research, which found that serum TC, LDL-C, and TG levels were significantly decreased after treatment in those who received Piperine compared with those who received a placebo. However, serum HDL-C levels failed to show significant variation between the treatment interventions (18). The potential mechanisms by which Piperine may have lipid-lowering effects include upregulation of ABCG8 and SR-B1 transporters, which aid cholesterol efflux and excretion, as well as antagonism of LXRα, a nuclear receptor involved in lipid metabolism (28, 29). In addition, research in animals fed an HFD confirmed that Piperine could decrease the liver mRNA expression of "sterol regulator element binding proteins-1c (SREBP-1c)" and "fatty acid synthase (FAS)" (28). A previous study demonstrated the beneficial role of Piperine in reducing glucose levels and dyslipidemia, as well as in downregulating the mRNA expression of Sfrp5, MEST, and PTRF/Cavin1 (8). Also, Piperine protects against obesity and regulates lipogenic and lipolytic genes, which are more active in visceral fat than in subcutaneous fat (30). A recent study found that Piperine can reduce the levels of hepatic lipogenesis via inducing the transporter protein of ATP-binding cassette sgm8 (Abcg8) and hepatic scavenger receptor b1 (Sr-b1) in the small

intestine of high-fat diet mice (12). Researchers have suggested that Piperine may have lipid-lowering effects, including upregulation of SR-B1 and ABCG8 transporters, which aid cholesterol efflux and excretion, as well as antagonism of LXRα, a nuclear receptor involved in lipid metabolism (10, 12).

FBG and HOMA-IR levels significantly declined in the piperine group compared with the placebo group after the treatment intervention, which agrees with the results of previous studies (18). Recent studies demonstrated that Piperine increased insulin sensitivity and positively modulated glucose metabolism in rodent models of obesity and insulin resistance (31, 32). In the current study, the observed significant effect of Piperine might be due to its promising action in insulin resistance and liver steatosis by weakening Srebp1c, CD36, Lxr-α, FAS, and Chrebp-α in the HFD mouse model (33). Also, in skeletal muscle, Piperine enhances glucose uptake via stimulation of the CAMKK/AMPK signaling pathway and reduces inflammation-induced insulin resistance (32, 33). A previous study reported that Piperine exerts its protective role against hyperglycemia by stimulating the CAMKK/AMPK signaling pathway (in a reactive oxygen species-dependent manner) and thereby increasing glucose uptake in rat skeletal muscle (13). Additionally, Piperine enhances insulin sensitivity by activating AMPK signaling pathways and improving Glucose transporter 4 (GLUT4) translocation in skeletal muscle (34). A recent study reported that piperine can increase pancreatic superoxide dismutase activity and decrease malondialdehyde (MDA) levels in streptozotocin-induced diabetic mice, thereby ameliorating oxidative stress in pancreatic β-cells and inhibiting apoptosis in these cells (35).

Additionally, the CAP and LSM values in the Piperine group were statistically lower than those in the placebo group ($p<0.05$) after 12 weeks. This observation might be based on previous studies on animals, which reported that Piperine exerts anti-fibrotic effects in the liver, skin, heart, pancreas, and submucosal tissues through various mechanisms (36-39). Piperine's action on insulin resistance and liver steatosis has been demonstrated in rats with HFD-induced obesity, via the weakening of PI3K-Akt and adiponectin-AMPK signaling (28). A recent study found that Piperine effectively reduced liver steatosis, inflammation, hepatocyte injury, and fibrosis in mice fed a methionine-choline-deficient (MCD) diet. Additionally, treatment with Piperine led to a decrease in pyroptosis markers—specifically Nucleotide-binding oligomerization domain, Leucine-rich Repeat and Pyrin domain containing 3 (NLRP3), Apoptosis-associated speck-like protein containing a CARD (ASC), caspase-1 p20, and Gasdermin D (GSDMD), and a decline in IL-1β and Lactate Dehydrogenase (LDH) release. The activation of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) was also suppressed by piperine treatment and the compound BAY11-7082 was observed to down regulate pyroptosis-related proteins. Overall, Piperine improved the progression of nonalcoholic steatohepatitis (NASH), and its therapeutic effects were linked to the inhibition of hepatocyte pyroptosis caused by NF-κB activation (25). In line with the current study's outcomes on CAP and LSM values, a recent study found that the combination of Piperine with other compounds, such as garcinol and curcuminoids, resulted in greater reductions in CAP and LSM than placebo in NASH patients (36).

Notably, the placebo group did not exhibit a significant effect on biochemical parameters, including liver enzymes, lipid profile, and glycemic measures. It also did not show any significant effect on FibroScan parameters, namely CAP and LSM. Furthermore, it failed to show any substantial changes in any biochemical or FibroScan parameters after treatment, compared with the piperine group. This observation might be due to the placebo effect from using an identical capsule containing inert substances. In contrast, a recent study found that the placebo group showed a significant decrease in AST, ALT, albumin, cholesterol, LDL, and TG; however, it failed to demonstrate a substantial effect on ALP, bilirubin, HDL, FBG, Hb1AC, HOMA, and GGT levels (18). Another recent research found that the placebo group experienced a substantial improvement in LSM values, with no significant decline in CAP values, following placebo treatment (36).

Though this study was conducted with a large sample, future studies can be carried out with a massive nationwide sample to enhance the generalizability of the outcomes. Also, it is limited to patients with a specific grade (Grade 2) of NAFLD, necessitating the inclusion of Grade 3

cases in future studies. More research can be carried out with NAFLD patients across all grades to compare the impact of Piperine on different fatty liver grades (disease severity from mild steatosis to advanced fibrosis) using laboratory and ultrasound analyses. Notably, further studies are essential to evaluate the safety and effectiveness of prolonged piperine intake, particularly in diverse populations with varying stages of metabolic and hepatic disorders.

Conclusion

Piperine supplementation showed a significant effect on biochemical parameters, namely, liver enzymes, lipid profile, and glycemic measures, compared to the placebo group in individuals with Grade 2 of NAFLD. It also effectively reduced FibroScan parameters, such as CAP and LSM values, indicating decreased liver steatosis and fibrosis and demonstrating that it is a safe therapeutic option for NAFLD. Although the placebo treatment showed minor changes in selected parameters, it failed to establish a substantial difference from the Piperine group, as the placebo group received a similar substance with inactive ingredients. The results concluded that Piperine is an auspicious adjuvant in the management of patients with NAFLD. However, future trials with follow-up are needed to explore long-term efficacy and safety, different doses, varied treatment durations, and mechanisms of action in human subjects with NAFLD. Besides, this study showed statistically significant outcomes, which would be clinically meaningful, as the patient's physical function and quality of life may be improved by controlling biochemical and FibroScan parameters through piperine treatment. Such improvement can be assessed using validated tools in future studies.

Abbreviations

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CAP: Controlled attenuation parameter, HOMA-IR: Homeostasis model assessment of insulin resistance, LSM: Liver stiffness measurement, NAFLD: Non-alcoholic fatty liver disease.

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Author Contributions

Beenish Zohra: conceptualization, drafted the manuscript, Suyash Saxena: data collection, clinical assessment, Mirza Kifayat: data collection, clinical assessment, Shruti Sharma: performed statistical analysis. All authors reviewed and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest

Declaration of Artificial Intelligence (AI) Assistance

Generative AI tools were not used to generate scientific content, data, or results.

Ethics Approval

The study was approved by the Institutional Ethics Committee of Sharda University, Greater Noida (Ref no.SU/RES/SAHS/N and D/2021212365/710). Written informed consent was obtained from all participants.

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