RESEARCH PAPER

Protective Effect of Nardostachys Jatamansi against Dyslipidemia and Hepatorenal Injury in High-Fat Diet-Induced Rats

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ABSTRACT

Background: Nardostachys jatamansi (Valerianaceae), often referred an Indian spikenard, has been historically employed in the management metabolic and hepatobiliary diseases and is reported to possess antioxidant properties.

Objective: To investigate the antioxidant, hepatoprotective, and lipid-lowering effects of the ethanolic extract of Nardostachys jatamansi in a high-fat-diet (HFD)-induced dyslipidemia model in Wistar albino rats.

Methods: Thirty-six Wistar albino rats were selected and divided into 6 groups (n=6 per group): normal control (I), HFD control (II), Rosuvastatin (RS 100 mg/kg) (III), Nardostachys jatamansi extract 100, 200, and 300 mg/kg , designated as IV, V, and VI, respectively.

Results: Treatment with Nardostachys jatamansi (NJ) attenuated HFD-induced dyslipidemia, reduced hepatic injury markers (AST, ALT, ALP), lowered lipid peroxidation, and improved adiponectin levels compared with HFD control. Antioxidant defences were enhanced, as reflected by upregulated glutathione peroxidase (GPx), reduced glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) , which was supported by histological evidence of reduced hepatic steatosis and cell injury.

Conclusion: Nardostachys jatamansi extract demonstrates hepatoprotective, antioxidant, and metabolic regulatory effects in HFD-fed rats, suggesting its potential as a phytotherapeutic candidate for metabolic disturbances associated with oxidative stress.

Keywords: *Nardostachys jatamansi, high-fat diet, dyslipidemia, hepatoprotection, antioxidant enzymes, oxidative stress*
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INTRODUCTION

Prolonged intake of a high-fat diet promotes dyslipidemia, characterized by abnormal levels of circulating lipids such as cholesterol, triglycerides, and fatty acids, which contribute to metabolic disorders and cardiovascular disease[1]. Obesity is a major global contributor to this condition. Although conventional lipid-lowering drugs are effective, prolonged use may cause hepatic, renal, or gastrointestinal toxicity, leading to increasing interest in herbal alternatives with fewer side effects [2]. Oxidative stress, arising due to a disruption between reactive oxygen species (ROS) generation and the body's antioxidant defense, is the major contributing factor in the development of dyslipidemia and related disorders [3].

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Elevated levels of ROS, particularly reactive free radical species like hydroxyl radical (•OH) and superoxide anion (O_2^-), including non-radical activated oxygen species, can damage cellular membranes, lipids, DNA, and proteins, leading to lipid peroxidation and contributing to hepatic dysfunction and aging-related pathologies [4]. To counteract ROS, the body relies on endogenous antioxidant system such as glutathione (GSH), along with antioxidant enzymes like glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT), while dietary antioxidants, including tocopherols, tocotrienols (Vitamin E), lipoic acid, ascorbic acid (Vitamin C), and glutathione, provide additional protection. Plant-derived phytochemicals exhibit potent antioxidant activity and are increasingly explored as therapeutic agents due to their favourable safety profile compared with synthetic drugs [5]. Nardostachys jatamansi, a Himalayan medicinal herb rich in bioactive phytochemicals, including sesquiterpenoids, alkaloids, fatty acids, and esters, has been observed to exert antimicrobial, antihyperlipidemic, antioxidant, anti-anxiety, hepatoprotective, along with cardioprotective effects [6]. Although its potential against dyslipidemia remains underexplored, this study investigates the efficacy of NJ rhizome in mitigating dyslipidemia.

MATERIALS AND METHODS:

Animals:

Male Wistar albino rats weighing about 200 to 250 g were kept in cages of polypropylene, under maintained conditions (22 ± 2 °C) with a 12 h light and dark cycle. Animals were provided with commercial pellet chow and free access to water. All experiments were carried out following the guidelines of the institutional and university and the regulations of the Committee for Control and Supervision of Experiments on Animals (CPCSEA), with IAEC approval No.01/IAEC/2023

Experimental protocol:

Thirty-six Wistar Albino Rats (n = 6 per group) were assigned to six groups:

Group I – normal control.

Group II –high-fat-diet (HFD) control

Groups III–Rosuvastatin 10mg per kg of body weight, along with HFD

Groups IV-NJ 100mg per kg of body weight, along with HFD

Groups V-NJ 200mg per kg of body weight, along with HFD

Group VI-NJ 300mg per kg of body weight, along with HFD

Group III-VI received the respective treatments once daily by oral gavage for 5-9 weeks concurrently with HFD, along with drugs.

Preparation of the Extract:

The roots of Nardostachys jatamansi were cleaned, air-dried, powdered, and defatted with petroleum ether using a Soxhlet extraction, followed by extraction with absolute ethanol until the solvent in the siphon became colourless. The concentrated extract was dried, stored in a desiccator, and orally administered to groups IV-VI at 100, 200, and 300 mg/kg, respectively, during the experiment [7].

Induction of Dyslipidemia:

The normal control Group (I) received a standard feed, whereas the other Groups (II-IV)were given a high-fat diet (HFD) ad libitum for 9 weeks. During weeks 5–9, Groups III–VI were treated with rosuvastatin (10 mg/kg/day) and NJ ethanolic extract (100, 200, and 300 mg/kg/day, respectively), administered orally by gavage concurrently with HFD feeding [8].

Sample Procurement:

At the conclusion of week 9, animals were subjected to overnight fasting and subsequently anesthetized using diethyl ether. Blood samples were obtained via the retro-orbital plexus, and serum was isolated through centrifugation at 2500 rpm for 10 minutes for biochemical analysis. Following euthanasia, the adipose tissue, liver, and kidneys were carefully removed, washed in chilled saline, weighed, and preserved in 10% formalin for histopathological examination [9].

Biochemical Parameters:

Based on the lipid profile results, the atherogenic index was calculated as total serum cholesterol/total serum HDL-C[10]. Liver tissue homogenates were centrifuged at 2000 rpm, and the supernatant was analysed for lipid peroxidation and antioxidant enzymes, including GPX [11], GSH [12], and CAT [13]. Serum biochemical markers (SGOT, SGPT, and ALP) were measured using standard analytical procedures.

Phytochemical Screening of NJ by GC-MS Analysis:

Metabolite profiling of the ethanolic extract of N. jatamansi was done using an Agilent 8890 gas chromatograph along with a 7000 GC/TQ mass spectrometer. Compound separation was carried out on a 30 m × 250 µm × 0.25 µm capillary column, with helium employed as the carrier gas and nitrogen as the collision gas. Samples were diluted in methanol before injection. The oven temperature was initially set to 50 °C (held for 1 min), then increased to 120°C at a rate of 5 °C/min (1 min hold), then increased to 210 °C at 10 °C/min (held for 1 min), and finally ramped for 280 °C at 10 °C/min with a 5-min hold, giving a total run time of 38 min. The mass spectrometer operated under electron ionization mode, scanning within a mass range of 30–900 m/z. Data collection and analysis were conducted using Mass Hunter software.

2. Histopathological Analysis:

Histopathological outcomes included microscopic examination of the Liver, kidney, and adipose tissues. Specimens underwent fixation in 10% neutral-buffered formalin, followed by paraffin processing, sectioning to 5 µm thickness, H&E staining, and examination using a light

microscope[14]. Histological findings were recorded in accordance with predefined assessment criteria.

3. Statistical Analysis:
Data are expressed as mean ± standard deviation (SD). Statistical significance was set at $p<0.05$. All statistical analyses were performed using one-way ANOVA with Dunnett's post hoc multiple comparison test in SPSS software, version 26.0.Graphs by Graph Pad Prism 10.

Results:

Phytochemical Screening:

GC–MS profiling of the ethanolic extract of Nardostachys jatamansi demonstrated a chemically diverse composition. More than 100 volatile and semi-volatile phytoconstituents were tentatively identified through comparison of retention times and mass spectra with the NIST database. The chromatogram indicated that the extract was primarily enriched with sesquiterpenes, oxygenated sesquiterpenes, and monoterpenes. Among the detected compounds, spirojatamol, nerolidol, patchouli alcohol, eucalyptol (1,8-cineole), α-terpineol, β-bisabolene, humulene, α-cadinol, and thymol showed relatively higher peak areas and were therefore classified as the major constituents (Table 1)

Table 1: Major phytoconstituents identified in the ethanolic extract of Nardostachys jatamansi by GC–MS

RT (min)	Compound name	Molecular formula	Match factor	Relative peak area (%)	Reported biological activity*
20.85	Spirojatamol	$C_{15}H_{26}O$	87.6	High	Antioxidant, neuroprotective
20.51	Nerolidol	$C_{15}H_{26}O$	88.8	Very high	Antioxidant, lipid-lowering
22.84	Patchouli alcohol	$C_{15}H_{26}O$	89.0	Very high	Anti-inflammatory, antioxidant
8.55	Eucalyptol (1,8-cineole)	$C_{10}H_{18}O$	96.5	Moderate	Antioxidant, hypolipidemic
13.01	α-Terpineol	$C_{10}H_{18}O$	91.4	Moderate	Antioxidant
20.47	β-Bisabolene	$C_{15}H_{24}$	81.3	High	Antioxidant
19.53	Humulene	$C_{15}H_{24}$	75.4	High	Anti-inflammatory
22.31	α-Cadinol	$C_{15}H_{26}O$	80.2	Moderate	Antioxidant
17.62	Thymol	$C_{10}H_{14}O$	75.2	Moderate	Strong antioxidant

Serum Biochemistries:

Effect of N.J on Atherogenic Index:
The atherogenic index, derived from serum total cholesterol and HDL-C levels, was elevated in HFD-fed rats verses normal control group. Treatment groups of NJ (IV, V, VI) and rosuvastatin (10 mg/kg) reduced the atherogenic index, restoring values toward near-normal levels (Table 2).

Table 2:Effect of Nardostachys jatamansi on serum lipid profile and atherogenic index in high-fat diet–induced dyslipidemic rats (9th week). Compared with the normal control group, significant differences were observed. Data are expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparison test. $p < 0.05$ was considered statistically significant. * Indicates significant difference compared with the control group; # indicates significant difference compared with the HFD group

Group	TG (mg/dL)	HDL (mg/dL)	AIP
Control	172 ± 9.8	38 ± 2.45	0.66 ± 0.05
HFD	268 ± 3.0	22 ± 4.9	1.09 ± 0.10*
HFD + ROS (10 mg/kg)	143 ± 9.6	52 ± 2.9	0.44 ± 0.11#
HFD + *N. jatamansi* (100 mg/kg)	160 ± 9.7	44 ± 8.2	0.56 ± 0.07#
HFD + *N. jatamansi* (200 mg/kg)	130 ± 9.6	47 ± 1.9	0.44 ± 0.07#
HFD + *N. jatamansi* (300 mg/kg)	129 ± 1.8	51 ± 2.5	0.40 ± 0.03#

Effect of N.J on serum SGOT, SGPT, and ALP:
Serum AST (SGOT), ALT (SGPT), and ALP levels were significantly elevated in the HFD group compared with the normal control group, indicating hepatic dysfunction. Treatment with N. jatamansi (Groups IV–VI) significantly reduced AST, ALT, and ALP levels relative to the HFD group, suggesting a protective effect on liver function (Figure 1).

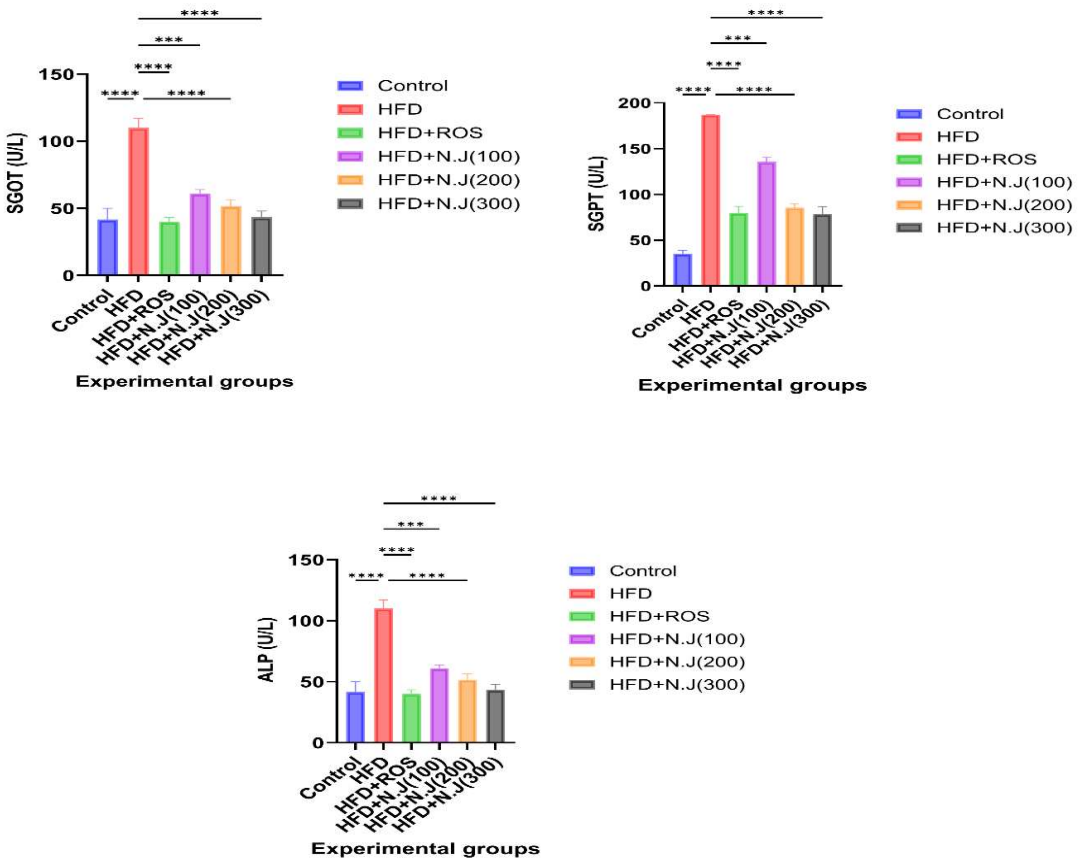

Figure 1: NJ effect on serum SGOT, SGPT, and ALP levels in high-fat diet–induced dyslipidemic rats, indicating hepatocellular damage. (A) SGOT, (B) SGPT, (C)ALP levels of control, HFD, HFD + ROS drug, and HFD + *N. jatamansi*–treated groups (LD, MD, HD). Values are expressed as Mean ± SEM (n = 6).One-way ANOVA followed by Dunnett's multiple comparison test. Significant changes are calculated as *P < 0.05,**P < 0.01, ***P < 0.001, and ****P<0.0001 vs HFD group. Values with P < 0.05 were considered statistically significant.

Tissue biochemistries:

Effect of N.J on Antioxidant Parameters:

Hepatic GPx, GSH, SOD, and CAT levels showed a significant decline in the HFD group compared with controls, indicating oxidative stress. N. jatamansi treatment (Groups IV–VI) restored these antioxidant enzymes to normal levels (Figure 2).

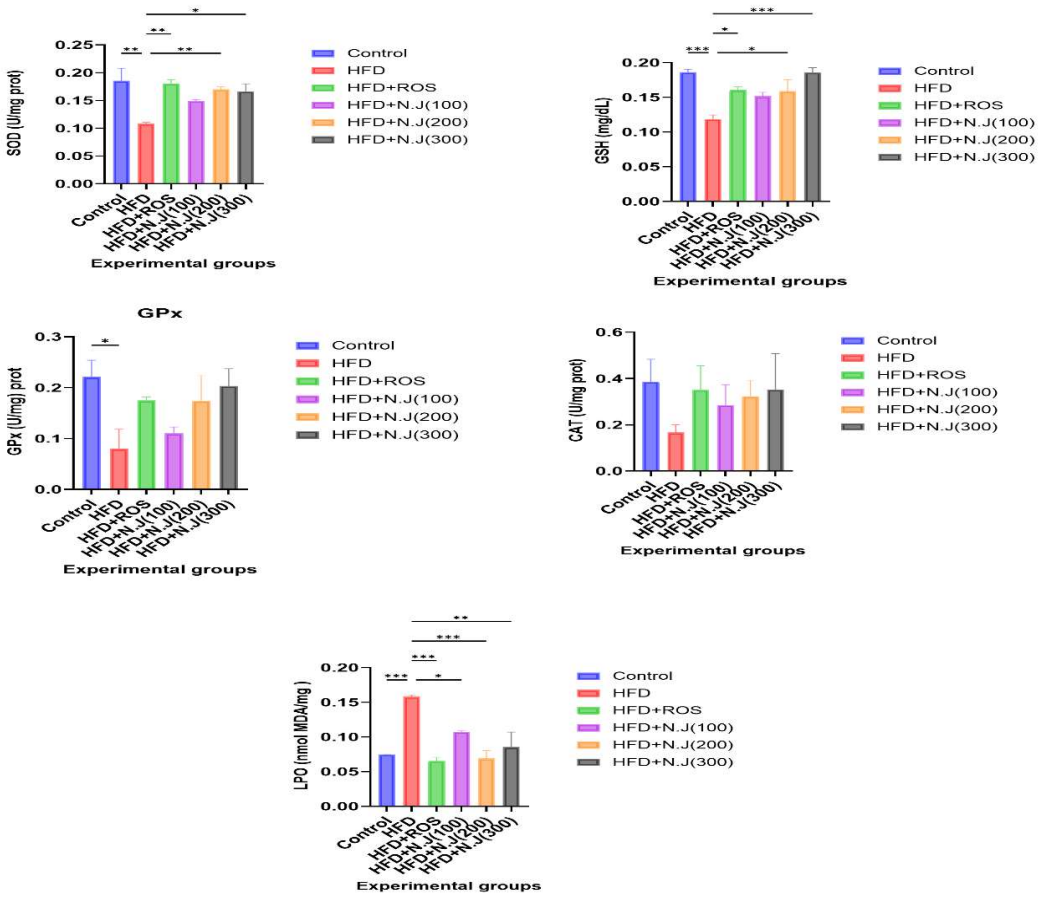

Figure 2:Figure X: Effect of Nardostachys jatamansi on hepatic lipid peroxidation and antioxidant defense system in high-fat diet–fed rats. (A) SOD , (B) GSH, (C) GPx, (D) CAT, and (E) LPO levels in control, HFD, HFD + ROS drug, and HFD +NJ–treated groups (LD, MD, HD), respectively. Data are presented as mean ± SEM (n = 6). Statistical analysis was carried out using one-way ANOVA followed by Dunnett's post hoc test for multiple comparisons. Levels of significance were denoted as *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001 when compared with the HFD group. A value of P < 0.05 was considered statistically significant.

Effect of NJ on Oxidative stress marker Lipid peroxidase:

Hepatic lipid peroxidation was significantly increased in the HFD group compared to the normal control group. NJ-treated Groups (IV–VI) showed a significant reduction in lipid peroxidation levels (Figure 2).

Effect of NJ on hepatic, renal, and adipose tissue histology:

Histopathological examination of liver tissues from the normal control group (I) reported normal architecture of lobular and hepatic cords. Whereas, the HFD group (II) showed marked pathological changes, including hepatocellular lipid accumulation, ballooning degeneration, sinusoidal widening, central vein congestion, and periportal inflammation. Treatment with rosuvastatin (Group III) and NJ (Groups IV–VI) progressively restored hepatic architecture, with Group VI showing near-complete normalization (Figure 3). Renal sections from the normal control group showed normal glomeruli with intact proximal and distal convoluted tubules and Bowman's space. The HFD group demonstrated severe renal damage, including reduced glomerular mass, enlarged Bowman's space, tubular degeneration, glomerulosclerosis, segmental necrosis, mononuclear inflammatory infiltration, and basement membrane thickening. Groups III–VI showed marked improvement in renal architecture, with restoration of glomerular structure and normalization of most tubules, although mild residual damage persisted (Figure 4). Adipose tissue from the HFD group showed pronounced adipocyte hypertrophy with heterogeneous cell size, thickened septa, and focal inflammation. NJ treatment significantly reduced adipocyte size and restored near-normal morphology, with Group VI showing almost complete normalization (Figure 5).

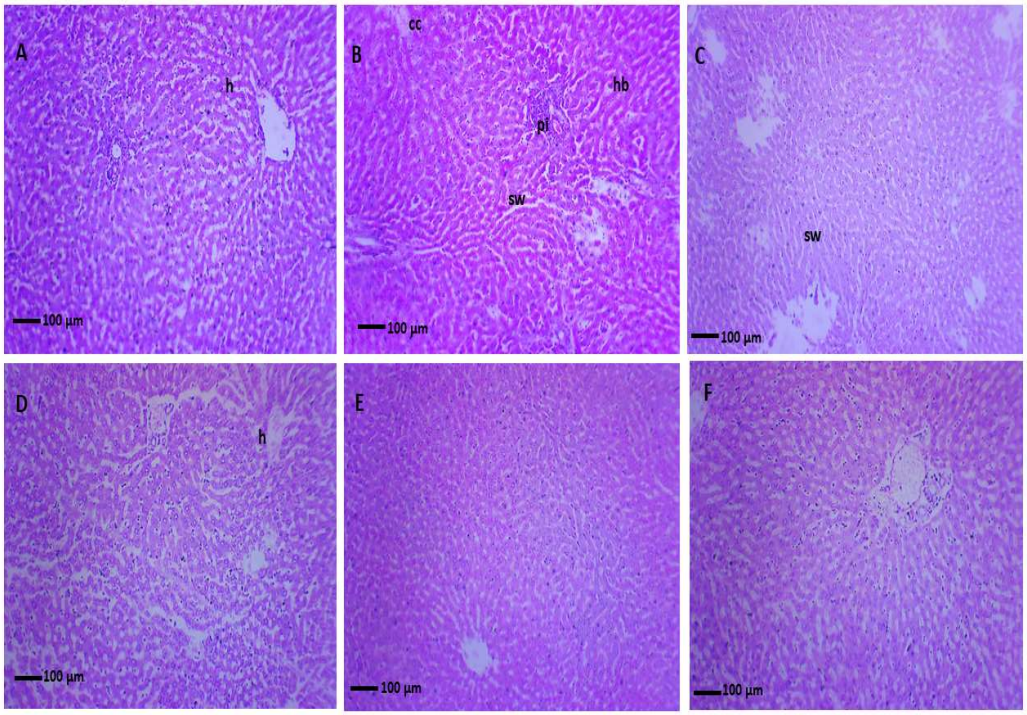

Figure 4. Effect of ethanol extract of *Nardostachys jatamansi* (N.J.) on liver histopathology in high-fat diet (HFD)–induced dyslipidemic rats. (A) Normal control; (B) HFD control; (C) HFD + rosuvastatin; (D–F) HFD + *N. jatamansi* (100, 200, and 300 mg/kg). H&E-stained liver sections show intact hepatic architecture in controls, while HFD causes hepatocyte ballooning (hb), central vein congestion (cc), periportal inflammation (pi), and sinusoidal widening (sw). Rosuvastatin and *N. jatamansi* treatments show progressive restoration of hepatic architecture, with near-normal histology in higher doses. Scale bar = 100 µm.

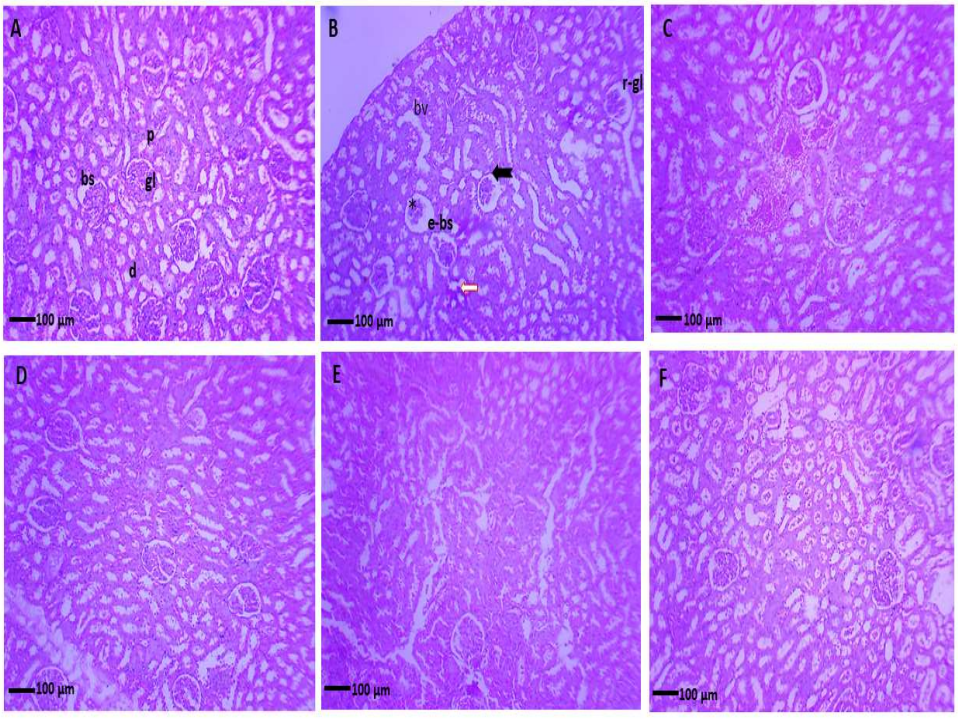

Figure: 5 Effect of ethanol extract of *Nardostachys jatamansi* (N.J.) on kidney histopathology in high-fat diet (HFD)–induced dyslipidemic rats. (A) Normal control; (B) HFD control; (C) HFD + rosuvastatin; (D–F) HFD + *N. jatamansi* (100, 200, and 300 mg/kg). H&E-stained kidney sections of controls showed normal renal architecture with intact glomeruli (gl), Bowman's space (bs), and proximal (p) and distal tubules (d). The HFD group exhibited severe renal damage, including glomerular atrophy (*), enlarged Bowman's space (e-bs), tubular degeneration (⇦ glomerulosclerosis, necrosis, inflammatory cell infiltration, and basement membrane thickening (⬅). Treatment groups showed marked improvement with near-normal glomeruli and tubules, with only mild residual changes. Scale bar = 100 µm.

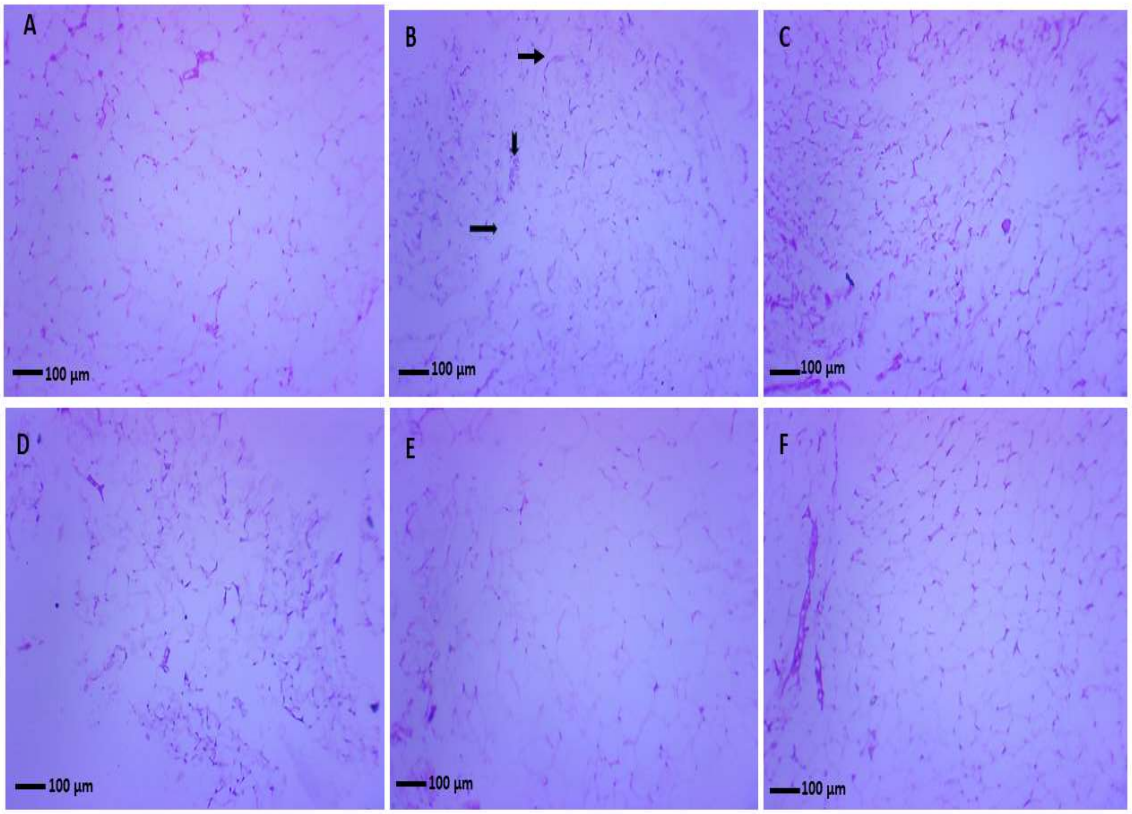

Figure 6: Effect of ethanol extract of *Nardostachys jatamansi* (N.J.) on adipose tissue histopathology in HFD-induced dyslipidemic rats.(A) Normal control; (B) HFD control; (C) HFD + rosuvastatin; (D–F) HFD + *N. jatamansi* (100, 200, and 300 mg/kg) H&E-stained adipose tissues. Adipose tissue of control showed normal architecture. The HFD group exhibited marked adipocyte hypertrophy (➡) , heterogeneous cell size with thickened septa (➡) and focal inflammation (⬇) . *N. jatamansi* treatment reduced adipocyte size and restored near-normal morphology, with Group VI showing substantial improvement toward normal architecture

DISCUSSION:

The current study aimed to assess the antioxidant and anti-dyslipidemic potential of NJ in a rat model of HFD–induced dyslipidemia. Dysregulated lipid metabolism accompanied by elevated oxidative stress is a central pathogenic mechanism of metabolic syndrome, contributing to inflammation and organ damage [15,16]. Even though conventional hypolipidemic drugs are effective in lowering lipid values, their prolonged usage is associated with various ill-effects [17], and they lack intrinsic antioxidant activity [18]. In contrast, NJ has been reported to suppress plasma triglyceride synthesis [19] and inhibit hydroxyl free radical generation [20], suggesting dual benefits in managing lipid abnormalities and oxidative stress. The pharmacological efficacy of NJ can be attributed to its diverse bioactive constituents. Kim KW et al documented a study in which desoxo-narchinol A, as the major phytoconstituent of NJ, exhibited potent anti-inflammatory effects by suppressing LPS-induced , prostaglandin E2,nitric oxide, IL-1β, TNF-α and IL-6, with downregulating iNOS and COX-2 in both in vitro and in vivo models [21]. Similar studies by Bae et al, Shin et al reported that Nardostachin inhibits iNOS, TNF-α, COX-2, and other mediators for inflammation by NF-κB inhibition, modulation of p38 and JNK MAPK pathways, and interference with TLR4/MyD88-dependent signalling [22,23,24,25]. These mechanisms provide a strong molecular basis for the observed antioxidant and anti-dyslipidemic effects of NJ in the present study.

Phytochemical Screening:

The enrichment of sesquiterpenes and oxygenated terpenoids in the ethanolic extract of NJ provides a plausible chemical explanation for the antioxidant and antidyslipidemic effects observed in the present study. Several of the predominant constituents, including spirojatamol [26],nerolidol[27] , patchouli alcohol[28] , eucalyptol[29] , and α-terpineol[30] , have been widely reported to exhibit antioxidant, anti-inflammatory, and lipid-regulatory activities. Notably, characteristic non-volatile marker compounds such as nardostachins and jatamansoic acid were not detected in the GC–MS analysis. This is likely due to their non-volatile and thermolabile nature, which restricts their detection by GC–MS without derivatization. As GC–MS primarily identifies volatile and semi-volatile compounds, the present findings represent the terpenoid-rich fraction of NJ.

Atherogenic Index:

Kalpana et al. reported that an increased atherogenic index, reflecting enhanced deposition of lipids, foam cells, and atherosclerotic plaques in various organs, is closely

associated with elevated oxidative stress in these tissues [31]. Similarly, Jain et al. demonstrated that high-fat diet (HFD) feeding significantly increases the atherogenic index while simultaneously reducing the HDL/LDL ratio [32], thereby promoting an atherogenic lipid profile. Rousset et al. further highlighted the pivotal role of lecithin–cholesterol acyltransferase (LCAT) in lipid homeostasis, showing that this enzyme converts free cholesterol into cholesteryl esters, thereby facilitating HDL maturation and enhancing reverse cholesterol transport [33]. In addition, Lund-Katz et al. demonstrated that the anti-atherogenic property of HDL is largely mediated by its capacity to eliminate accumulated cholesterol from peripheral tissues and transfer it to the liver for elimination[34,35]. A similar protective mechanism appears to operate in the present study, where NJ administration to HFD-fed rats significantly reduced the atherogenic index and elevated HDL levels. This improvement in lipoprotein balance suggests enhanced reverse cholesterol transport and reduced lipid accumulation in peripheral tissues, which together contribute to the observed anti-dyslipidemic and anti-atherogenic effects of the extract.

SGOT(ALT) ,SGPT(AST) and ALP:

Alanine aminotransferase , aspartate aminotransferase , and alkaline phosphatase are widely used biochemical markers of hepatic injury. Fraser et al. documented that the US (NHANES) National Health and Nutrition Examination Survey has recognized increased levels of ALT (>30 U/L) as a reliable indicator of non-alcoholic fatty liver disease (NAFLD) [36]. Recknagel et al. further reported that increased circulating levels of ALT, AST, and ALP reflect hepatocellular damage and enzyme leakage in to the bloodstream ,serving as a sensitive indicator of hepatic dysfunction [37]. In the present study, HFD-fed rats exhibited significantly elevated ALT, AST, and ALP levels, indicating hepatocellular injury and impaired liver function, which is consistent with previous reports demonstrating that chronic high-fat intake induces hepatic steatosis, inflammation, and necrosis. Treatment with Nardostachys jatamansi, particularly at higher doses, significantly reduced these enzyme levels toward normal, demonstrating a marked hepatoprotective effect[38].Treatment with N. jatamansi, particularly at higher doses, normalized these elevated enzymes, demonstrating its hepatoprotective activity. Deemes et al. reported that elevated ALP levels in HFD-induced models are commonly associated with hepatobiliary dysfunction and intrahepatic cholestasis. The normalization of ALP levels following N. jatamansi treatment in the present study further supports its ability to preserve hepatobiliary integrity and improve liver function [39] .

LPO:

Pellegrino and Liou et al. reported that oxidative stress is a hallmark of dyslipidemia, resulting from chronic disturbances in lipid metabolism [40,41,] leading to impaired antioxidant protection system defences and excessive production of ROS. Memisogullari et al. further demonstrated that oxygen-free radicals target cell membranes, polyunsaturated fatty acids resulting in elevated lipid peroxidation (LPO) and causing membrane dysfunction through altered enzyme and receptor activity and reduced fluidity [42,43]. In this study, N.jatamansi treatment lowered LPO levels, reflecting suppression of LPO reactions and decreased free radical production.

GPX, GSH, SOD, CAT:

Emami et al. and Kumar et al. demonstrated that HFD reduces the activities of glutathione peroxidase (GPx), reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT), contributing to hepatic injury, fatty liver, and atherosclerosis [44,45]. Similar observations were made in the present study, where HFD-fed rats showed marked reductions in these antioxidant enzymes. Subhashini et al. and Lyle et al. showed that N jatamansi normalized these enzymes in doxorubicin-induced and chronic fatigue stress models 46,47.Since Hyperglycemia and hyperlipidemia are widely recognized to induce excessive reactive oxygen species, which play a role in the development of metabolic disorders 48, the antioxidant enzyme activities like reduced glutathione, superoxide dismutase(SOD), and catalase (CAT) were measured in liver tissues in HFD group II. The current study found that N.J restored GPx, GSH, SOD, and CAT in HFD-fed rats, confirming its antioxidant potential.

Conclusion: Nardostachys jatamansi exhibited potent anti-dyslipidemic, antioxidant, and hepatoprotective effects in the high-fat diet–induced dyslipidemia model by improving lipid profile, reducing atherogenic index, and normalizing liver enzymes. The reduction in lipid peroxidation49 and restoration of antioxidant enzymes (GPx, GSH, SOD, and CAT) indicate that its protective action is largely mediated through attenuation of oxidative stress and hepatic injury. Bioactive constituents such as desoxo-narchinol A and nardostachin further support its anti-inflammatory and lipid-regulating mechanisms, highlighting its potential as a multi-targeted therapy for dyslipidemia and related metabolic complications.

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