Mehamudgara Vati Attenuates Neuropathic Pain in High-Fat Diet and Streptozotocin-Induced Diabetic Rats

Shubham Varule*[1], Abhijeet Kulkarni[1],
[1]Department of School of Pharmaceutical Science, Sandip University, Nashik, Maharashtra 422213, India.
*** Corresponding Author:** Mr. Shubham Varule*[1],
Email: shubhsai7834@gmail.com

Abstract: Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia due to impaired insulin secretion or action. Diabetic neuropathy, a common complication, leads to pain, sensory loss, and motor deficits, and is often managed with synthetic drugs such as antidepressants and anticonvulsants, which are limited by adverse effects. Herbal and herbo-mineral formulations like Mehamudgara Vati (MMV) have shown antidiabetic and antioxidant properties, but their efficacy in neuropathic pain remains unclear. This study evaluated MMV in high-fat diet (HFD) and streptozotocin (STZ)-induced diabetic neuropathy in albino rats. Rats were fed HFD for eight weeks followed by STZ injection (35 mg/kg). Treatment groups included diabetic control (0.25% Na-CMC), MMV (100 mg/kg), amitriptyline (AMT, 10 mg/kg), and MMV (50 mg/kg) plus AMT (5 mg/kg) for six weeks. Behavioral assessments—including thermal hyperalgesia, cold allodynia, mechanical hyperalgesia, grip strength, walking function, locomotor activity, motor coordination, and oral glucose tolerance—showed significant improvement with MMV, especially in combination with AMT. Biochemical analyses revealed reductions in blood glucose, lipids, and malondialdehyde, with increased insulin and antioxidant (SOD, GSH, CAT) levels, and normalization of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). These findings suggest that MMV effectively alleviates diabetic neuropathy and exerts a synergistic effect with AMT, presenting a safe and promising alternative or adjunct to conventional therapies.

Keywords: Diabetic Neuropathy, Mehamudgara Vati, Amitriptyline, High-fat diet, Streptozotocin
How to cite this article: Varule S, Kulkarni A. Mehamudgara Vati Attenuates Neuropathic Pain in High-Fat Diet and Streptozotocin-Induced Diabetic Rats. Int J Drug Deliv Technol. 2026;16(6): 872-883. DOI: 10.25258/ijddt.16.6.127

1.0 Introduction:

Diabetes is increasingly recognized as a major public health concern in India, currently affecting over 62 million people. The country consistently ranks among those with the highest diabetes prevalence worldwide and is projected to witness the most significant rise in cases by 2030, with estimates approaching 80 million individuals (Chauhan et al, 2025; Kaveeshwar & Cornwall, 2014). Diabetes mellitus is a complex and multifactorial metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin secretion, defective insulin action, or a combination of both (Goyal et al, 2026). Sustained high blood glucose levels induce a cascade of metabolic disruptions, leading to progressive damage in multiple organs, including the eyes, kidneys, nerves, heart, and vasculature, which may ultimately result in organ dysfunction or failure (Wu et al, 2022; American Diabetes Association et al., 2009). Among the spectrum of chronic diabetic complications, diabetic neuropathy is the most common, affecting over half of all patients. It profoundly impacts quality of life, manifesting as sensory deficits, chronic pain, and motor impairments, thereby representing a significant clinical challenge in diabetes management (Rosenberger et al, 2020; Yang et al, 2025).

Diabetic neuropathy (DN) is a debilitating complication of diabetes, clinically manifested by tingling, numbness, burning sensations, and a progressive loss of perception to pain, temperature, and pressure. These sensory deficits increase the susceptibility to foot ulcers, delayed wound healing, motor weakness, infections, and in severe cases, limb amputation (Zhu et al, 2024). DN encompasses dysfunction of sensory, motor, and autonomic nerves, primarily driven by persistent hyperglycemia. Chronic elevation of blood glucose contributes to insulin resistance, dyslipidemia, oxidative stress, and excessive production of reactive oxygen species (ROS), which collectively trigger inflammation and neuronal injury (Xiaofeng & Tang, 2026). The recruitment and activation of macrophages within peripheral nerves further amplify cytokine-mediated inflammatory responses, exacerbating nerve damage. Additional pathophysiological mechanisms implicated in DN include the accumulation of advanced glycation end products (AGEs), dysregulation of the hexosamine and protein kinase C signaling pathways, and neurovascular dysfunction, all of which compromise nerve repair processes and promote the gradual progression of neuropathic injury (Nashtahosseini et al, 2025; Baum et al, 2021; Yang et al, 2025).

Management of diabetic neuropathy often relies on pharmacological agents that encompass multiple drug classes, including antioxidants like α-lipoic acid, antidepressants such as duloxetine, amitriptyline, and venlafaxine, anticonvulsants like

pregabalin and gabapentin, anti-arrhythmic drugs including lidocaine and mexiletine, polyphenolic compounds such as curcumin and resveratrol, and opioids like tramadol and tapentadol (Kaur et al, 2011; Cohen et al, 2015). While these therapies can provide symptomatic relief, their long-term use is frequently limited by adverse effects. Antidepressants and anticonvulsants often cause sedation, dizziness, weight gain, and gastrointestinal disturbances, whereas anti-arrhythmic agents may induce cardiac or central nervous system toxicity (Farach et al, 2012; Goldenberg, 2010). Opioids carry risks of constipation, sedation, dependence, and abuse potential, and even relatively safe compounds like antioxidants or polyphenols may lead to mild gastrointestinal upset or interact with other medications. These challenges highlight the difficulty of achieving sustained neuropathic pain control and emphasize the need for safer, effective, and well-tolerated alternatives (Paul et al, 2021; Khansari et al, 2013).

Ayurvedic and plant-derived formulations are generally cost-effective and possess a wide array of pharmacological activities, including anti-inflammatory, antioxidant, neuroprotective, and metabolic regulatory effects (Fürst et al, 2014). Such herbal products are often considered safer alternatives to conventional synthetic drugs, as they typically exhibit lower toxicity profiles and are associated with a reduced risk of adverse reactions. Moreover, many of these preparations contain multiple bioactive constituents that may act synergistically to target various pathological pathways simultaneously, offering a holistic approach to disease management (Zhang et al, 2015; Karimi et al, 2015).

Mehamudgara Vati is a classical herbo-mineral Ayurvedic formulation traditionally used to manage a broad spectrum of health conditions. It is recognized for its multifaceted therapeutic properties, including metabolic regulation, antioxidant, anti-inflammatory, and rejuvenating effects, which together contribute to its role in promoting overall health and managing chronic disorders (Tanna et al, 2011). Limited scientific studies and clinical investigations have demonstrated its antidiabetic potential, showing efficacy in controlling blood glucose levels and supporting metabolic function (Tanna et al, 2011). Nevertheless, its capacity to alleviate neuropathic pain has not been extensively studied, and the therapeutic outcome of combining Mehamudgara Vati with Amitriptyline in diabetic neuropathy remains unexplored. Accordingly, the present study was designed to assess the effects of Mehamudgara Vati on neuropathic pain, both alone and in combination with Amitriptyline.

2.0 Materials and Methods:

2.1 Chemicals and reagents:

Amitriptyline, thiobarbituric acid, and hydrogen peroxide were procured from Sigma-Aldrich Chemicals Pvt. Ltd., India. Streptozotocin, sodium citrate, trichloroacetic acid, 5,5-dithiobis-(2-nitrobenzoic acid) (DTNB), nitro blue tetrazolium chloride (NBT), β-nicotinamide adenine dinucleotide phosphate (NADPH), citric acid, D-glucose, and sodium carboxymethyl cellulose were obtained from Sisco Research Laboratories Pvt. Ltd., Mumbai. Glucose monitoring equipment along with test strips (Contour Plus, India) were acquired from local suppliers in Pune. All other chemicals and reagents used were of analytical grade. Mehamudgara Vati (Shree Baidyanath Ayurved Bhawan Pvt. Ltd., India) was purchased from a local pharmacy.

2.2 Experimental animals:

Male Sprague Dawley rats (180–200 g) bred in-house were maintained in polypropylene cages under controlled environmental conditions, including a temperature of 22±1°C, relative humidity of 60–70%, and a 12 h light–dark cycle, in a registered animal facility. All experimental procedures were conducted in compliance with the guidelines of the Committee for the Control and Supervision of Experiments on Animals (CCSEA), Government of India. The study protocol (IIRT/IAEC/35/2024/028) received prior approval from the Institutional Animal Ethics Committee before initiation of the experiment.

2.3 Diabetes induction in rats:

Streptozotocin (STZ) was accurately weighed, and individual aliquots were prepared and kept on ice. Just before administration, STZ was freshly dissolved in ice-cold 100 mM sodium citrate buffer (pH 4.5) and passed through a 0.2 µm membrane filter. The buffer was added to each aliquot immediately prior to dosing, and all procedures were carried out under low-light conditions to prevent degradation of STZ (Motyl & McCabe, 2009).

Type 2 diabetes mellitus was induced using a modified high-fat diet (HFD) and STZ protocol. Animals assigned to the diabetic group were fed an HFD, while the normal control group received standard laboratory chow. The HFD was formulated by mixing powdered standard chow (25%) with sugar (25%), corn starch (10%), refined wheat flour (maida; 10%), cholesterol (0.20%), and dalda (29.8%). This diet was administered daily for 8 weeks. After prolonged HFD feeding, a single intraperitoneal injection of STZ (35 mg/kg) was given. Blood glucose levels were measured 48 hours post-STZ administration to confirm the induction of diabetes (Jain et al, 2014; Rahigude et al, 2012; Zhang et al, 2008).

2.4 Treatment schedule and experimental protocol:

A total of thirty animals were used in the study. Six rats were assigned to the normal control group, while the remaining animals were induced with diabetes. The normal control group received distilled water and was maintained under non-diabetic conditions. After three days of streptozotocin administration, diabetic animals were randomly divided into different experimental groups. The diabetic control group was administered the vehicle (0.25% sodium carboxymethyl cellulose). The standard treatment group received AMT at a dose of 10 mg/kg, whereas another group was treated with Mehamudgara Vati (MMV) at 100 mg/kg. Additionally, a combination group was administered MMV (50 mg/kg) along with a lower dose of AMT (5 mg/kg). Body weight and fasting blood glucose levels were recorded on a weekly basis throughout the experimental period.

2.5 Oral glucose tolerance test (OGTT):

Oral glucose tolerance was evaluated using the OGTT method. The assessment was performed after 8 weeks of high-fat diet feeding and prior to streptozotocin administration in overnight-fasted animals (12 h). Glucose was orally administered at a dose of 2 g/kg body weight, and blood samples were obtained from the tail vein at 0, 30, 60, and 120 min to measure glucose levels. Animals showing elevated glucose levels and impaired clearance were considered glucose intolerant. The OGTT was repeated at the end of the treatment period to determine the effect of drug interventions on glucose tolerance (Tang et al, 2018).

2.6 Development of diabetic neuropathy:

The development of diabetic neuropathy was comprehensively assessed in all experimental groups using multiple behavioral and functional tests. These included the tail immersion test to evaluate thermal hyperalgesia, the cold plate test for cold allodynia, the pinprick test to assess mechanical hyperalgesia, as well as grip strength and walking tests to measure neuromuscular function. Locomotor activity was quantified using an actophotometer, and motor coordination was evaluated with the rotarod test.

2.7 Behavioural Assessment:

2.7.1 Thermal hyperplasia:

Thermal nociceptive sensitivity was assessed following the method of Ramabadran et al. (1989) with slight modifications. The distal 5 cm of the tail was immersed in a water bath maintained at 50 ± 1 °C, and the latency to tail withdrawal (tail-flick response) was recorded as an index of nociception. Three consecutive readings were taken for each animal at 5-minute intervals, and the average was used for analysis. A maximum cut-off time of 15 s was applied to prevent tissue injury.

2.7.2 Cold allodynia:

The method of Kim & Kim (2013) and Lim et al, (2022) was followed to evaluate cold-induced nociceptive sensitivity using the cold plate assay. Each animal was placed in a transparent Perspex chamber on the cold plate of a hot/cold plate analgesia meter (IITC Life Science, Woodland Hills, CA, USA) and allowed a 5-min acclimatization period. The plate temperature was maintained at 4 ± 1 °C, and the latency to paw withdrawal was recorded as the nociceptive response. A maximum cut-off time of 20 s was applied to prevent tissue injury.

2.7.3 Grip Strength test:

Grip strength was evaluated using a modified wire hang test, based on the method described by Feng Q et al. (2014). Each rat was allowed to grasp a steel wire (2 mm in diameter, 35 mm in length), and the time taken for the animal to release the wire was recorded. The wire was positioned 50 cm above a flat surface to ensure safety and standardize the assessment.

2.7.4 Walking function test:

Walking ability was assessed using a horizontal rod traversal test based on established protocols. A cylindrical rod (6 cm diameter, 1 m length) was mounted horizontally at a height of 40 cm above the table. Rats were placed at one end and allowed up to 60 s to cross the full length. The time taken to traverse the rod was recorded, with animals that failed to complete the task or fell assigned a maximum score of 60 s. Each animal underwent three trials, and the average time was used for statistical evaluation (Anjaneyulu & Chopra, 2004).

2.7.5 Mechanical hyperalgesia (pinprick test):

Saraswat et al, 2020; Kanaan et al, 1999 described the assessment of mechanical nociception using the pinprick test. In this method, the plantar surface of the hind paw was gently stimulated with a bent gauge needle held perpendicular (90°) to the paw, ensuring the skin was not pierced. The latency to paw withdrawal was recorded as the nociceptive response, with a maximum cut-off time of 20 s applied to prevent tissue injury.

2.7.6 Locomotor activity:

The methods of Anjaneyulu & Chopra (2004) and Saraswat et al (2020) were followed to evaluate locomotor activity using an actophotometer equipped with a photocell-based digital counter. Each animal was placed individually in the apparatus for a 5-minute observation period, and locomotor behavior was quantified by recording the number of light-beam interruptions.

2.7.7 Rota-rod performance:

Motor coordination and balance were assessed using a rota-rod apparatus featuring a rotating drum with a diameter of 75 mm. The rotation speed was set so that normal control rats could remain on the rod for over 5 minutes. Animals underwent three pre-test training sessions with at least 3 hours between sessions. During the evaluation, the time until the

animal fell from the rotating rod was recorded at rotational speeds of 15 and 25 rpm for each subject (Vera et al, 2013; Dhavale et al, 2025).

2.7.8 Biochemical estimations:

Serum lipid levels were measured using standard commercially available diagnostic kits. Oxidative stress markers, including malondialdehyde (MDA) as an indicator of lipid peroxidation, superoxide dismutase (SOD), reduced glutathione (GSH), and catalase (CAT), were analyzed in serum using a biochemistry analyzer (ChemXpress, Operon Biotech & Healthcare, India). Furthermore, serum concentrations of insulin, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were quantified using ELISA kits (GENLISA, Krishgen Biosystems, USA) with measurements taken on a UV/Vis microplate spectrophotometer (Thermo Scientific Multiskan SkyHigh, USA).

2.7.9 Statistical analysis:

Data are presented as mean ± standard deviation (SD) for each experimental group. Statistical analyses were performed using GraphPad Prism software. Differences between groups were assessed using either One-way or Two-way ANOVA, followed by Tukey's or Bonferroni's multiple comparison tests, respectively. Significance levels were indicated as *$p<0.05$, **$p<0.01$, ***$p<0.001$ versus diabetic control group, #$p<0.05$ versus normal control group, and Ψ denotes significant differences compared to the MMV-treated group.

3.0 Results and Discussion:

Diabetic neuropathy represents a major and progressively disabling complication of diabetes mellitus, marked by chronic pain, sensory impairment, motor deficits, oxidative stress, and neuroinflammatory changes. Sustained hyperglycemia initiates a series of interconnected metabolic and molecular disturbances, including impaired insulin signaling, altered lipid metabolism, overproduction of reactive oxygen species (ROS), and activation of pro-inflammatory pathways, which collectively contribute to neuronal injury and functional deterioration (Pittenger & Vinik, 2003; Hussain, 2025; Bhatti et al, 2022). These processes not only damage peripheral nerves but also disrupt normal pain perception and neuromuscular coordination. Considering the multifactorial nature of its pathogenesis, targeting multiple pathways simultaneously is essential for effective management of diabetic neuropathy (Bodman et al, 20226). In this context, the present study was designed to systematically evaluate the neuroprotective and antinociceptive potential of Mehamudgara Vati (MMV), both alone and in combination with AMT, using a high-fat diet (HFD) and streptozotocin (STZ)-induced experimental model of type 2 diabetic neuropathy, which closely replicates the metabolic and neurological alterations observed in clinical conditions.

The findings of the present study indicate that animals subjected to a high-fat diet (HFD) followed by low-dose STZ administration developed sustained hyperglycemia, impaired glucose tolerance, reduced insulin levels, and progressive alterations in body weight, confirming the successful establishment of a type 2 diabetic condition. These metabolic disturbances were associated with clear manifestations of neuropathic pain, including thermal hyperalgesia, cold allodynia, and mechanical hyperalgesia, along with reduced locomotor activity and impaired motor coordination. Such observations are in agreement with previous studies indicating that chronic hyperglycemia and insulin resistance are key contributors to diabetic neuropathy, primarily through mechanisms involving increased oxidative stress, mitochondrial dysfunction, and activation of inflammatory pathways (Zhang et al, 2008; Brito et al, 2025).

In the present study, diabetic control rats exhibited a distinct alteration in body weight pattern compared with normal control animals, showing a significant increase from week 4 through week 14 ($p<0.05$). Administration of MMV (100 mg/kg) effectively moderated this abnormal trend, indicating its role in regulating diabetes-associated weight changes. From weeks 9 to 10, MMV-treated animals showed significant improvement ($p<0.05$–0.01), while from weeks 11 to 14, a highly significant normalization of body weight was observed ($p<0.001$), with effects comparable to or greater than AMT. These changes may be attributed to improved metabolic regulation, including better insulin sensitivity and lipid metabolism. Treatment with AMT (10 mg/kg) also showed beneficial effects; however, the combination of MMV with low-dose AMT demonstrated enhanced efficacy, suggesting a synergistic interaction (Figure-1). Overall, MMV appears to play a key role in restoring energy balance and counteracting diabetes-associated body weight alterations (Dilworth et al, 2021).

OGTT assessment prior to STZ administration revealed that diabetic control rats exhibited significantly elevated fasting and post-glucose blood glucose levels at all time points compared with normal control animals ($p<0.05$), indicating impaired glucose tolerance. Administration of MMV (100 mg/kg) improved glucose tolerance, particularly at later time points ($p<0.05$–0.001), indicating its ability to enhance glucose utilization and insulin responsiveness. Treatment with AMT (10 mg/kg) also significantly reduced blood glucose levels at 60, 90, and 120 min ($p<0.05$–0.01), confirming its standard antihyperglycemic effect. Notably, the combination of MMV (50 mg/kg) with AMT (5 mg/kg) produced a more pronounced reduction in blood glucose levels across multiple time points ($p<0.05$–0.001), suggesting a synergistic improvement in glycemic control (Figure-2A). Following drug treatment, diabetic control rats

continued to exhibit significantly elevated glucose levels at all time points ($p<0.05$), indicating persistent glucose intolerance. MMV (100 mg/kg) demonstrated significant improvement, particularly during the early phases of glucose challenge ($p<0.001$), whereas AMT (10 mg/kg) showed a broader reduction across most time points ($p<0.001$; $p<0.05$ at 120 min) (Figure-2B). Overall, the enhanced effect observed with combination therapy highlights the contributory role of MMV in improving glucose homeostasis. Importantly, the combination therapy produced the most pronounced effect, significantly reducing blood glucose levels at all time intervals ($p<0.001$), with values approaching those of the normal control group, indicating improved glycemic control. These findings are consistent with the known pharmacological profile of Mehamudgara Vati, a classical Ayurvedic herbo-mineral formulation containing Lauha bhasma along with bioactive constituents such as Guggulu, Triphala, Shunthi, and Pippali (Tanna et al, 2011). The formulation exhibits antihyperglycemic, hypolipidemic, antioxidant, and immunomodulatory properties (Murudkar et al, 2022), which may collectively enhance glucose regulation and insulin sensitivity. The improved outcomes observed with combination therapy further highlight its potential as an adjunct treatment. Moreover, its multifaceted actions, including metabolic regulation and neuroprotection, may contribute to the management of early diabetic complications and support its therapeutic relevance in diabetic neuropathy.

In the behavioral tests, diabetic control rats showed a marked reduction in tail-flick latency compared with normal control animals, indicating significant thermal hyperalgesia ($p<0.05$) (Table-1). Administration of MMV (100 mg/kg) produced a notable improvement in nociceptive responses, as reflected by an increase in tail-flick latency ($p<0.05$), indicating attenuation of thermal hyperalgesia. Treatment with AMT (10 mg/kg) showed a more pronounced increase ($p<0.001$), while the combination of MMV (50 mg/kg) with AMT (5 mg/kg) resulted in a highly significant enhancement ($p<0.001$), suggesting a synergistic analgesic effect. In cold allodynia assessment, diabetic control rats exhibited a significant reduction in paw withdrawal latency ($p<0.05$), indicating increased cold sensitivity. MMV treatment significantly improved withdrawal time ($p<0.01$), whereas AMT produced a stronger effect ($p<0.001$). The combination therapy demonstrated the most marked improvement ($p<0.001$), indicating enhanced protection against cold-induced nociception. Diabetic rats also showed a significant decline in grip strength, reflecting neuromuscular impairment ($p<0.05$). Administration of MMV significantly improved grip strength ($p<0.01$), while AMT produced a more robust effect ($p<0.001$). Notably, the combination treatment resulted in a highly significant restoration of grip strength ($p<0.001$), indicating superior recovery of neuromuscular function. Similarly, in the walking function test, diabetic animals exhibited prolonged travelling time ($p<0.05$), indicative of impaired motor performance. MMV treatment significantly reduced travelling time ($p<0.05$), while AMT showed a greater improvement ($p<0.001$). The combination group displayed the most pronounced reduction ($p<0.001$), reflecting enhanced locomotor recovery. Mechanical hyperalgesia was also significantly elevated in diabetic rats ($p<0.05$). MMV treatment led to a significant reduction in response time ($p<0.05$), whereas AMT produced a more substantial decrease ($p<0.001$). Overall, the combination therapy consistently demonstrated superior efficacy across all behavioral parameters, highlighting a synergistic interaction in alleviating neuropathic pain and restoring motor function. The combination therapy produced the most significant reduction ($p<0.001$), indicating enhanced protective efficacy. The behavioral findings confirm the development of diabetic neuropathy, as indicated by thermal hyperalgesia, cold allodynia, mechanical hypersensitivity, reduced grip strength, and impaired motor coordination in diabetic control rats. These changes reflect dysfunction of small-diameter nociceptive fibers, primarily driven by chronic hyperglycemia-induced oxidative stress, neuroinflammation, and neuronal damage (Tian et al, 2024; Tsagareli et al, 2010). Administration of MMV produced significant improvements across all behavioral parameters, demonstrating its strong antinociceptive and neuroprotective potential, likely mediated through antioxidant and anti-inflammatory mechanisms. AMT also showed beneficial effects; however, the combination therapy resulted in the most pronounced recovery, indicating a synergistic interaction with enhanced therapeutic efficacy.

Furthermore, in the behavioral evaluations, diabetic control rats exhibited a significant ($p<0.05$) decline in locomotor activity along with reduced ($p<0.05$) falling latency in the rotarod test compared with normal control animals, indicating impaired spontaneous motor function and neuromuscular coordination (Table-1). Treatment of MMV (100 mg/kg) resulted in a significant improvement in locomotor activity and rotarod performance ($p<0.001$), indicating its strong potential to restore motor function and neuromuscular coordination. These beneficial effects may be attributed to its antioxidant and anti-inflammatory properties, which help mitigate oxidative damage, preserve neuronal integrity, and improve neuromuscular signaling. Treatment with AMT (10 mg/kg) also significantly enhanced locomotor counts and increased latency to fall ($p<0.001$), reflecting its established neuroprotective efficacy. Notably, the combination of MMV (50 mg/kg) with low-dose AMT (5 mg/kg)

produced the most pronounced restoration in both parameters ($p<0.001$), with values approaching those of normal control animals, suggesting a clear synergistic interaction. Beyond sensory deficits, diabetic neuropathy is frequently associated with impaired motor performance and reduced coordination (Muramatsu, 2020). In the present study, diabetic animals showed marked reductions in locomotor activity and rotarod performance, indicative of peripheral nerve damage and muscle weakness (Hossain et al, 2022). These deficits are largely driven by chronic hyperglycemia-induced oxidative stress, inflammation, and metabolic imbalance. The significant improvement observed with MMV highlights its role in preserving neuromuscular function, while the enhanced efficacy seen with combination therapy suggests complementary mechanisms, including improved metabolic regulation, suppression of inflammatory pathways, and protection of neuromuscular tissues.

Furthermore, diabetic control rats demonstrated a pronounced elevation in blood glucose levels accompanied by a significant ($p<0.05$) decline in serum insulin concentrations compared with normal control animals, confirming the establishment of hyperglycemia and impaired insulin secretion (Table-2). These alterations are characteristic of insulin resistance and β-cell dysfunction associated with type 2 diabetes (Harper et al, 2005). Administration of MMV (100 mg/kg) produced a significant reduction in blood glucose levels along with a marked improvement in insulin secretion ($p<0.001$), indicating its potent antihyperglycemic activity. These effects may be attributed to its ability to enhance insulin sensitivity, support pancreatic β-cell function, and regulate overall glucose metabolism. Treatment with AMT (10 mg/kg) also significantly lowered blood glucose levels and increased insulin concentrations ($p<0.001$), confirming its established efficacy in glycemic control. Notably, the combination of MMV (50 mg/kg) with low-dose AMT (5 mg/kg) yielded the most pronounced effects, with a highly significant reduction in blood glucose and a substantial elevation in insulin levels ($p<0.001$). This enhanced outcome suggests a synergistic interaction, potentially mediated through complementary mechanisms such as improved insulin signaling, attenuation of oxidative stress, and better metabolic regulation.

In biochemical evaluations, diabetic control rats displayed marked dyslipidemia in comparison to normal control animals, as evidenced by increased ($p<0.05$) levels of total cholesterol, triglycerides, LDL, and VLDL, along with a reduction in HDL levels, indicating a clear metabolic imbalance associated with diabetes (Table-2). Such lipid abnormalities are known to aggravate oxidative stress and inflammatory responses, contributing to neuronal damage and progression of diabetic neuropathy (Al-Ani et al, 2011; Vincent et al, 2009). Treatment of MMV (100 mg/kg) resulted in a significant correction of lipid abnormalities, as evidenced by reductions in total cholesterol, triglycerides, LDL, and VLDL levels along with an increase in HDL ($p<0.05–0.001$), indicating its role in regulating lipid metabolism and reducing lipotoxicity. These effects may be attributed to its antioxidant potential and its ability to modulate key enzymes involved in lipid homeostasis, thereby preserving neuronal membrane integrity and preventing lipid peroxidation (Dakal et al, 2025). AMT (10 mg/kg) also significantly improved lipid parameters by lowering atherogenic lipids and enhancing HDL levels ($p<0.01–0.001$), confirming its standard therapeutic efficacy. Notably, the combination of MMV (50 mg/kg) with low-dose AMT (5 mg/kg) produced the most pronounced effect, significantly normalizing all lipid parameters ($p<0.001$) and restoring them closer to normal levels. This enhanced outcome suggests a synergistic interaction, providing superior protection against metabolic disturbances and neuronal complications associated with diabetic neuropathy.

Induction of diabetes resulted in a pronounced oxidative stress state, as evidenced by a significant ($p<0.05$) increase in MDA levels along with a marked reduction in endogenous antioxidants such as reduced GSH, catalase, and SOD compared with normal control animals (Table-3). These alterations reflect enhanced lipid peroxidation and compromised antioxidant defense, which are critical contributors to neuronal damage in diabetic neuropathy (Figueroa-Romero et al, 2008; Andrea et al, 2004). Administration of MMV (100 mg/kg) significantly improved oxidative stress parameters, as evidenced by a reduction in MDA levels along with enhanced GSH, catalase, and SOD activities ($p<0.05–0.001$), indicating its potent antioxidant potential. These effects may be attributed to the presence of bioactive constituents with free radical scavenging and metal-chelating properties, thereby protecting neuronal integrity. Treatment with AMT (10 mg/kg) also significantly decreased MDA levels and restored antioxidant enzyme activities ($p<0.001$), confirming its established efficacy in attenuating oxidative stress. Notably, the combination of MMV (50 mg/kg) with low-dose AMT (5 mg/kg) produced the most pronounced antioxidant effect, significantly normalizing all measured parameters ($p<0.001$) and restoring them toward near-normal levels.

Neuroinflammation plays a pivotal role in the initiation and progression of diabetic neuropathy (Sandireddy et al, 2014; Fang et al, 2022). Elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β contribute to nociceptor sensitization, neuronal apoptosis, and impaired nerve regeneration (Zhang & AN, 2007; Skaper et

al, 2018). In the present study, Treatment of MMV resulted in a significant attenuation of inflammatory markers, as evidenced by decreased levels of TNF-α, IL-6, and IL-1β ($p<0.01$–0.001), indicating its notable anti-inflammatory potential. This effect may be attributed to its ability to modulate pro-inflammatory signaling pathways and protect against cytokine-mediated neuronal damage. Treatment with AMT (10 mg/kg) also significantly reduced the levels of these cytokines ($p<0.001$), confirming its established anti-inflammatory efficacy (Table-4). Importantly, the combination of MMV (50 mg/kg) with low-dose AMT (5 mg/kg) produced the most pronounced reduction in all measured cytokines ($p<0.001$), with values approaching those of normal control animals. This enhanced effect suggests a synergistic interaction, providing superior protection against inflammation-associated neuronal injury and strengthening its therapeutic relevance in diabetic neuropathy.

The findings of this study indicate that Mehamudgara Vati (MMV) provides multifaceted protection against diabetic neuropathy by improving glycemic control, correcting dyslipidemia, reducing oxidative stress, suppressing inflammation, and restoring sensory and motor functions. These effects are attributed to its complex herbo-mineral composition, including Lauha bhasma and bioactive herbs such as Guggulu, Triphala (Haritaki, Bibhitaki, Amalaki), Shunthi, Pippali, and others, which collectively exert antihyperglycemic, hypolipidemic, antioxidant, anti-inflammatory, and neuroprotective actions (Tanna et al., 2011). The constituents help regulate glucose and lipid metabolism, reduce oxidative damage, and prevent inflammatory neuronal injury, improving overall nerve function. Notably, combining MMV with AMT enhanced efficacy over individual treatments, suggesting a synergistic interaction. This synergy likely involves complementary mechanisms, including improved metabolic control, strengthened antioxidant defenses, and modulation of nociceptive and inflammatory pathways. Collectively, the cumulative and synergistic actions of MMV, especially with AMT, significantly attenuate neuropathic pain and functional deficits, highlighting its potential as an effective therapeutic strategy for diabetic neuropathy.

4.0 Conclusion:

The present investigation demonstrates that Mehamudgara Vati (MMV) showed potent antidiabetic and antineuropathic effects in high-fat diet and streptozotocin-induced diabetic neuropathy. It improved glycemic control, insulin levels, and lipid profiles while alleviating thermal hyperalgesia, cold allodynia, and mechanical hyperalgesia, along with enhancing motor coordination, grip strength, and locomotor activity. MMV also reduced oxidative stress, restored antioxidant defenses, and lowered pro-inflammatory cytokines, highlighting its antioxidant and anti-inflammatory actions. The combination of MMV with low-dose amitriptyline (AMT) showed superior efficacy, indicating a synergistic interaction and potential for dose reduction. These effects are likely mediated through the multifaceted herbo-mineral composition of MMV acting via complementary pathways. Overall, MMV, particularly with AMT, represents a promising adjunct therapy for diabetic neuropathy, supporting further mechanistic and clinical investigations.

5.0 Conflict of Interest:

The authors declare no conflict of interest

6.0 Financial Assistance:

This research work was not supported with financial assistance from any funding agencies.

7.0 Author Contribution:

S.V.- Conceptualization, methodology, investigation, and writing— original draft. A.K.- Conceptualization, data curation, formal analysis, validation, and writing—review and editing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

References:

- Al-Ani FS, Al-Nimer MS, Ali FS. Dyslipidemia as a contributory factor in etiopathogenesis of diabetic neuropathy. Indian J Endocrinol Metab. 2011 Apr;15(2):110-4. doi: 10.4103/2230-8210.81940.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009 Jan;32 Suppl 1(Suppl 1):S62-7. doi: 10.2337/dc09-S062.
- Andrea M. Vincent, James W. Russell, Phillip Low, Eva L. Feldman, Oxidative Stress in the Pathogenesis of Diabetic Neuropathy. Endocr Rev. 2004;25(4):612–628, https://doi.org/10.1210/er.2003-0019
- Anjaneyulu M, Chopra K. Quercetin attenuates thermal hyperalgesia and cold allodynia in STZ-induced diabetic rats. Indian J Exp Biol. 2004;42:766-769.
- Baum P, Toyka KV, Blüher M, Kosacka J, Nowicki M. Inflammatory Mechanisms in the Pathophysiology of Diabetic Peripheral Neuropathy (DN)-New Aspects. Int J Mol Sci. 2021 Oct 7;22(19):10835. doi: 10.3390/ijms221910835.
- Bhatti JS, Sehrawat A, Mishra J, Sidhu IS, Navik U, Khullar N, Kumar S, Bhatti GK, Reddy PH. Oxidative stress in the pathophysiology of type 2 diabetes and related complications: Current therapeutic

strategies and future perspectives. Free Radic Biol Med. 2022;184:114–134.

- Bodman MA, Dreyer MA, Varacallo MA. Diabetic Peripheral Neuropathy. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442009/
- Brito AKDS, Mendes AVDS, Timah Acha B, Santos Oliveira ASDS, Lopes Macedo J, Suzuki Cruzio A, Prianti MDG, et al. Experimental models of type 2 diabetes mellitus induced by combining hyperlipidemic diet (HFD) and streptozotocin administration in rats: An integrative review. Biomedicines. 2025;13(5):1158.
- Chauhan S, Khatib MN, Ballal S, Bansal P, Bhopte K, Gaidhane AM, Tomar BS, Ashraf A, Kumar MR, Chauhan AS, Shabil M, Jena D, Bushi G, Satapathy P, Jain L, Jaiswal V, Pant M. The rising burden of diabetes and state-wise variations in India: insights from the Global Burden of Disease Study 1990-2021 and projections to 2031. Front Endocrinol (Lausanne). 2025 May 12;16:1505143. doi: 10.3389/fendo.2025.1505143.
- Cohen K, Shinkazh N, Frank J, Israel I, Fellner C. Pharmacological treatment of diabetic peripheral neuropathy. P T. 2015 Jun;40(6):372-88. PMID: 26045647; PMCID: PMC4450668.
- Dakal TC, Xiao F, Bhusal CK, Sabapathy PC, Segal R, Chen J, Bai X. Lipids dysregulation in diseases: core concepts, targets and treatment strategies. Lipids Health Dis. 2025 Feb 21;24(1):61. doi: 10.1186/s12944-024-02425-1.
- Dhavale AS, Hariprasad MG, Ramaswamy R. Exploring neuroprotective activity of ethanolic rhizome extract of Alpinia calcarata in cisplatin-induced peripheral neuropathy in rats. J Appl Pharm Sci. 2025;15(01):266-275.
- Dilworth L, Facey A, Omoruyi F. Diabetes Mellitus and Its Metabolic Complications: The Role of Adipose Tissues. Int J Mol Sci. 2021 Jul 16;22(14):7644. doi: 10.3390/ijms22147644.
- Fang XX, Wang H, Song HL, Wang J, Zhang ZJ. Neuroinflammation Involved in Diabetes-Related Pain and Itch. Front Pharmacol. 2022 Jun 20;13:921612. doi: 10.3389/fphar.2022.921612.
- Farach FJ, Pruitt LD, Jun JJ, Jerud AB, Zoellner LA, Roy-Byrne PP. Pharmacological treatment of anxiety disorders: current treatments and future directions. J Anxiety Disord. 2012 Dec;26(8):833-43. doi: 10.1016/j.janxdis.2012.07.009.
- Feng Q, Ma Y, Mu S, Wu J, Chen S, Ouyang L, Lei W. Specific reactions of different striatal neuron types in morphology induced by quinolinic acid in rats. PLoS One. 2014 Mar 14;9(3):e91512. doi: 10.1371/journal.pone.0091512.
- Figueroa-Romero C, Sadidi M, Feldman EL. Mechanisms of disease: the oxidative stress theory of diabetic neuropathy. Rev Endocr Metab Disord. 2008 Dec;9(4):301-14. doi: 10.1007/s11154-008-9104-2.
- Fürst R, Zündorf I. Plant-derived anti-inflammatory compounds: hopes and disappointments regarding the translation of preclinical knowledge into clinical progress. Mediators Inflamm. 2014;2014:146832. doi: 10.1155/2014/146832.
- Goldenberg MM. Overview of drugs used for epilepsy and seizures: etiology, diagnosis, and treatment. P T. 2010 Jul;35(7):392-415.
- Goyal R, Singhal M, Jialal I. Type 2 Diabetes. [Updated 2023 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513253/
- Harper JM, Durkee SJ, Smith-Wheelock M, Miller RA. Hyperglycemia, impaired glucose tolerance and elevated glycated hemoglobin levels in a long-lived mouse stock. Exp Gerontol. 2005 Apr;40(4):303-14. doi: 10.1016/j.exger.2005.01.002.
- Hussain A. Chronic hyperglycemia and cardiovascular dysfunction: an in-depth exploration of metabolic and cellular pathways in type 2 diabetes mellitus. Cardiovasc Diabetol Endocrinol Rep. 2025 Dec 12;11(1):39. doi: 10.1186/s40842-025-00247-3.
- Jain D, Bansal MK, Dalvi R, Upganlawar A, Somani R. Protective effect of diosmin against diabetic neuropathy in experimental rats. J Integr Med. 2014; 12(1): 35-41. doi: 10.1016/S2095-4964(14)60001-7
- Kanaan SA, Saade NE, Haddad JJ, Abdelnoor AM, Atweh SF, Jabbur SJ, Safieh-Garabedian B. Endotoxin-induced local inflammation and hyperalgesia in rats and mice: a new model for inflammatory pain. Pain. 1996;66:373–379.
- Karimi A, Majlesi M, Rafieian-Kopaei M. Herbal versus synthetic drugs; beliefs and

facts. J Nephropharmacol. 2015 Jan 1;4(1):27-30.
- Kaur S, Pandhi P, Dutta P. Painful diabetic neuropathy: an update. Ann Neurosci. 2011 Oct;18(4):168-75. doi: 10.5214/ans.0972-7531.1118409.
- Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J. 2014 Jan 31;7(1):45-8. doi: 10.4066/AMJ.2013.1979.
- Khansari M, Sohrabi M, Zamani F. The Useage of Opioids and their Adverse Effects in Gastrointestinal Practice: A Review. Middle East J Dig Dis. 2013 Jan;5(1):5-16.
- Kim SO, Kim HJ. Berberine ameliorates cold and mechanical allodynia in a rat model of diabetic neuropathy. J Med Food. 2013 Jun;16(6):511-7. doi: 10.1089/jmf.2012.2648.
- Lim EY, Lee C, Kim YT. The Antinociceptive Potential of Camellia japonica Leaf Extract, (−)-Epicatechin, and Rutin against Chronic Constriction Injury-Induced Neuropathic Pain in Rats. Antioxidants 2022, 11, 410. https://doi.org/10.3390/antiox11020410
- Motyl K, McCabe LR. Streptozotocin, type I diabetes severity and bone. Biol Proced Online. 2009 Mar 6;11:296-315. doi: 10.1007/s12575-009-9000-5.
- Muramatsu K. Diabetes Mellitus-Related Dysfunction of the Motor System. Int J Mol Sci. 2020 Oct 11;21(20):7485. doi: 10.3390/ijms21207485.
- Murudkar PH, Tambe MS, Chandrasekar SB, Boddeda B and Pawar AT (2022), Common Ayurvedic, Chinese traditional and Unani antidiabetic formulations- a review. Front. Pharmacol. 13:991083.
- Nashtahosseini Z, Eslami M, Paraandavaji E, Haraj A, Dowlat BF, Hosseinzadeh E, Oksenych V, Naderian R. Cytokine Signaling in Diabetic Neuropathy: A Key Player in Peripheral Nerve Damage. Biomedicines. 2025 Feb 28;13(3):589. doi: 10.3390/biomedicines13030589.
- Paul AK, Smith CM, Rahmatullah M, Nissapatorn V, Wilairatana P, Spetea M, Gueven N, Dietis N. Opioid analgesia and opioid-induced adverse effects: a review. Pharmaceuticals (Basel). 2021;14(11):1091. doi: 10.3390/ph14111091.
- Pittenger G, Vinik A. Nerve growth factor and diabetic neuropathy. Exp Diabesity Res. 2003 Oct-Dec;4(4):271-85. doi: 10.1155/EDR.2003.271.
- Rahigude A, Bhutada P, Kaulaskar S, Aswar M, Otari K. Participation of antioxidant and cholinergic system in protective effect of naringenin against type-2 diabetes-induced memory dysfunction in rats. Neuroscience. 2012;13:226:62–72. doi: 10.1016/j.neuroscience.2012.09.026
- Ramabadran K, Bansinath M, Turndorf H, Puig MM. Tail immersion test for the evaluation of a nociceptive reaction in mice. Methodological considerations. J Pharmacol Methods. 1989 Mar;21(1):21-31. doi: 10.1016/0160-5402(89)90019-3.
- Rosenberger DC, Blechschmidt V, Timmerman H, Wolff A, Treede RD. Challenges of neuropathic pain: focus on diabetic neuropathy. J Neural Transm (Vienna). 2020 Apr;127(4):589-624. doi: 10.1007/s00702-020-02145-7.
- Sandireddy R, Yerra VG, Areti A, Komirishetty P, Kumar A. Neuroinflammation and oxidative stress in diabetic neuropathy: futuristic strategies based on these targets. Int J Endocrinol. 2014;2014:674987. doi: 10.1155/2014/674987.
- Saraswat N, Sachan N, Chandra P. Anti-diabetic, diabetic neuropathy protective action and mechanism of action involving oxidative pathway of chlorogenic acid isolated from Selinum vaginatum roots in rats. Heliyon. 2020;6(10):e05137.
- Skaper SD, Facci L, Zusso M and Giusti P (2018) An Inflammation-Centric View of Neurological Disease: Beyond the Neuron. Front Cell Neurosci. 12:72. doi: 10.3389/fncel.2018.00072
- Tang D, Liu L, Ajiakber D, Ye J, Xu J, Xin X. Anti-diabetic Effect of Punica granatum Flower Polyphenols Extract in Type 2 Diabetic Rats: Activation of Akt/GSK-3 and Inhibition of IRE1α-XBP1 Pathways. Front Endocrinol. 2018;9:586. doi: 10.3389/fendo.2018.00586
- Tanna I, Chandola HM, Joshi JR. Clinical efficacy of Mehamudgara vati in type 2 diabetes mellitus. Ayu. 2011 Jan;32(1):30-9. doi: 10.4103/0974-8520.85722. PMID: 22131755; PMCID: PMC3215414.
- Tanna I, Samarakoon SM, Chandola HM, Shukla VJ. Physico-chemical analysis of a Herbo-mineral compound Mehamudgara vati - A pilot study. Ayu. 2011 Oct;32(4):572-5. doi: 10.4103/0974-8520.96136.
- Tanna I, Chandola HM, Joshi JR. Clinical efficacy of Mehamudgara vati in type 2 diabetes mellitus. Ayu . 2011 Jan;32(1):30-9.

- Tian T, Li H, Zhang S, Yang M. Characterization of sensory and motor dysfunction and morphological alterations in late stages of type 2 diabetic mice. Front Endocrinol (Lausanne). 2024 Mar 11;15:1374689. doi: 10.3389/fendo.2024.1374689.
- Tsagareli MG, Tsiklauri N, Zanotto KL, Carstens MI, Klein AH, Sawyer CM, Gurtskaia G, Abzianidze E, Carstens E. Behavioral evidence of thermal hyperalgesia and mechanical allodynia induced by intradermal cinnamaldehyde in rats. Neurosci Lett. 2010 Apr 12;473(3):233-236. doi: 10.1016/j.neulet.2010.02.056.
- Vera G, Cabezos PA, Martín MI, Abalo R. Characterization of cannabinoid-induced relief of neuropathic pain in a rat model of cisplatin-induced neuropathy. Pharmacol Biochem Behav. 2013 Apr;105:205–12. doi: https://doi.org/10.1016/j.pbb.2013.02.008
- Vincent AM, Hinder LM, Pop-Busui R, Feldman EL. Hyperlipidemia: a new therapeutic target for diabetic neuropathy. J Peripher Nerv Syst. 2009 Dec;14(4):257-67. doi: 10.1111/j.1529-8027.2009.00237.x.
- Wu H, Norton V, Cui K, Zhu B, Bhattacharjee S, Lu YW, Wang B, Shan D, Wong S, Dong Y, Chan SL, Cowan D, Xu J, Bielenberg DR, Zhou C, Chen H. Diabetes and Its Cardiovascular Complications: Comprehensive Network and Systematic Analyses. Front Cardiovasc Med. 2022 Feb 17;9:841928. doi: 10.3389/fcvm.2022.841928.
- Xiaofeng, Dai, and Tang Mingze. 2026. "Diabetic Peripheral Neuropathy: Molecular Staging, Risk Factors, Therapeutics, and Emerging Trends," Med Research: 1–34. https://doi.org/10.1002/mdr2.70060.
- Yang Y, Zhao B, Wang Y, Lan H, Liu X, Hu Y, Cao P. Diabetic neuropathy: cutting-edge research and future directions. Signal Transduct Target Ther. 2025 Apr 25;10(1):132. doi: 10.1038/s41392-025-02175-1.
- Zhang J, Onakpoya IJ, Posadzki P, Eddouks M. The safety of herbal medicine: from prejudice to evidence. Evid Based Complement Alternat Med. 2015;2015:316706. doi: 10.1155/2015/316706.
- Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin. 2007 Spring;45(2):27-37. doi: 10.1097/AIA.0b013e318034194e.
- Zhang M, Lv XY, Li J, Xu ZG, Chen L. The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model. Exp Diabetes Res. 2008;2008:704045. doi: 10.1155/2008/704045. Epub 2009 Jan 4.
- Zhang M, Lv XY, Li J, Xu ZG, Chen L. The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model. Exp Diabetes Res. 2008;2008:704045. doi: 10.1155/2008/704045.
- Zhu J, Hu Z, Luo Y, Liu Y, Luo W, Du X, Luo Z, Hu J and Peng S (2024) Diabetic peripheral neuropathy: pathogenetic mechanisms and treatment. Front. Endocrinol. 14:1265372. doi: 10.3389/fendo.2023.1265372

TABLES:

Table 1: Effect of MMV on behavioral tests

Groups	Thermal Allodynia (Tail Flick Time-sec)	Cold Allodynia (Paw Withdrawal Time-sec)	Grip Strength Test (Grip Time-sec)	Walking Function Test-(Travelling Time-sec)	Mechanical Hyperalgesia-Pin Prick Test-(Response Time-sec)	Locomotor Activity (No. of counts)	Rota-rod Test (Falling Latency-sec)
NC	14.5±2.7	16.4±2.7	123.7±12.3	10.8±1.4	2.6±0.8	182.5±11.4	128.8±9.4
DC	2.6±1.4#	3.6±0.9#	39.2±16.4#	21.0±2.9#	8.3±1.3#	34.3±5.4#	27.5±9.5#
AMT-10	8.1±1.5***	9.8±1.1***	82.8±7.6***	12.8±1.9***	4.4±0.8***	137.7±19.9***	103.7±14.5***
MMV-100	6.5±1.9*	10.8±1.0**	73.8±11.3**	16.4±3.5*	6.7±0.8*	102.3±10.5***	76.8±9.6***

MMV-50+AMT-5	9.2±1.7***Ψ	14.6±2.3***Ψ	100.7±22.4***Ψ	11.8±1.0***Ψ	5.1±0.7***Ψ	128.0±8.4***Ψ	99.2±8.1***Ψ

Values in the results are expressed as mean± SD (n=6), #p<0.05 significantly different in comparison to NC. *p<0.05, **p<0.01, ***p<0.001 significantly different in comparison to DC. Ψ significantly different in comparison to MMV. (A one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison t-test).

Table 2: Effect of MMV on blood glucose, insulin and lipid levels

Groups	Biochemical Parameters						
	Glucose (mg/dL)	Insulin (uIU/ml)	Total Cholesterol (mg/dL)	TGs (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	VLDL (mg/dL)
NC	108.7±14.8	159.54±11.7	37.3±1.9	65.1±8.2	42.7±8.3	29.0±5.2	13.0±1.6
DC	271.6±17.6	65.20±5.1#	69.9±11.3#	170.5±16.9#	96.4±11.1#	13.4±2.1#	34.1±3.4#
AMT-10	149.0±17.2***	120.76±20.2***	43.1±4.7**	91.8±12.2***	52.0±7.7***	25.7±4.1***	18.4±2.4***
MMV-100	187.7±17.7***	110.4±7.7***	55.2±9.6*	118.7±10.7***	76.2±7.7**	19.4±2.0*	23.7±2.1***
MMV-50+AMT-5	138.5±7.6***Ψ	134.5±17.3***Ψ	39.1±6.3***Ψ	96.0±7.6***Ψ	58.4±8.6***Ψ	23.8±3.0***	19.2±1.5***Ψ

Values in the results are expressed as mean± SD (n=6), #p<0.05 significantly different in comparison to NC. *p<0.05, **p<0.01, ***p<0.001 significantly different in comparison to DC. Ψ significantly different in comparison to MMV. (A one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison t-test).

Table 3: Effect of MMV on antioxidant components

Groups	MDA (nM/mg of tissue)	GSH (uM/mg of protein)	Catalase (U/mg protein)	SOD (U/mg protein)
NC	67.7±7.4	21.5±1.2	18.6±0.0	84.8±8.7
DC	168.6±16.0#	11.1±1.0#	3.1±0.0#	27.9±2.5#
AMT-10	107.3±9.9***	18.1±2.5***	12.1±2.1***	48.8±2.6***
MMV-100	121.4±15.0***	14.3±1.5*	9.6±1.3***	43.8±8.6**
MMV-50+AMT-5	94.6±9.1***Ψ	17.7±2.1***Ψ	13.0±1.3***Ψ	70.2±4.9***Ψ

Values in the results are expressed as mean± SD (n=6), #p<0.05 significantly different in comparison to NC. *p<0.05, **p<0.01, ***p<0.001 significantly different in comparison to DC. Ψ significantly different in comparison to MMV. (A one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison t-test).

Table 4: Effect of MMV on pro-inflammatory cytokines

Groups	TNF-α (pg/mL)	IL-6 (pg/mL)	IL-1β (pg/mL)
NC	86.6±10.0	175.0±11.4	105.6±12.4
DC	415.9±61.5#	406.8±27.9#	393.6±5.1#
AMT-10	187.6±13.8***	245.3±29.1***	170.4±20.2***
MMV-100	289.8±61.8***	298.1±30.4***	317.2±7.7**
MMV-50+AMT-5	203.4±18.7***Ψ	238.5±40.8***Ψ	232.6±17.3***Ψ

Values in the results are expressed as mean± SD (n=6), #p<0.05 significantly different in comparison to NC. *p<0.05, **p<0.01, ***p<0.001 significantly different in comparison to DC. Ψ significantly different in comparison to MMV. (A one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison t-test).

FIGURES

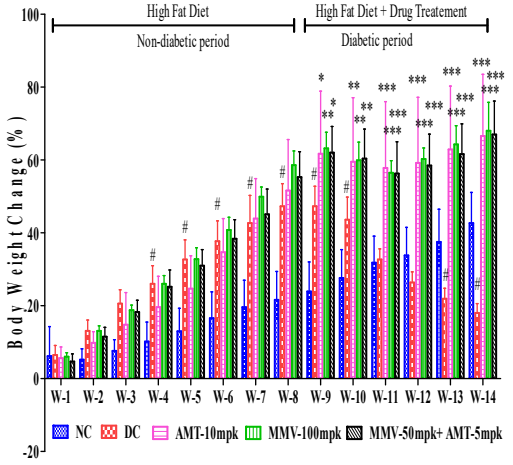


Figure-1: Effect of MMV on animal body weight change. Values in the results are expressed as mean± SD, (n=6); Data is analyzed by Two-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison t-test; #p<0.05 significantly different in comparison to NC. *p<0.05, **p<0.01, ***p<0.001, significantly different in comparison to DC.

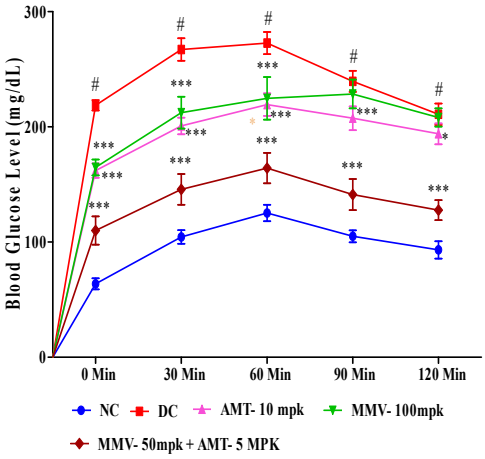
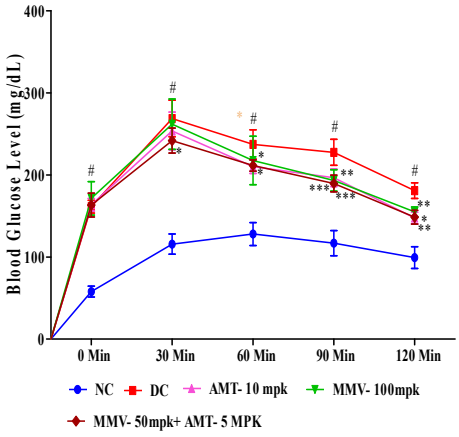


Figure 2- A) Oral Glucose Tolerance Test (Before STZ Injection) B) Oral Glucose Tolerance Test (After the completion of drug treatment). Values in the results are expressed as mean± SD, (n=6); Data is analyzed by Two-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison t-test; #p<0.05 significantly different in comparison to NC. *p<0.05, **p<0.01, ***p<0.001, significantly different in comparison to DC.

A)



B)