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Polyherbal formulation managing E-Selectin: A novel strategy for the management of diabetic complications

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Microvascular damage in type-2 diabetes mellitus (T2DM) leads to a range of systemic illnesses, with neuropathy, nephropathy, and cardiovascular diseases being the most prevalent, representing significant global health concerns. Microvascular problems are made worse by aberrant e-selectin triggering in diabetes. Recent research suggest that polyherbal formulations (PHF) may target E-selectin and alleviate diabetes-related issues. The effect of a polyherbal aqueous extract formulation on the regulation of anti-inflammatory-mediated E-selectin was investigated in individuals with T2DM and diabetic comorbidities. A PHF made from seven potential antidiabetic herbs, individuals with diabetes, and individuals with diabetic complications like neuropathy and nephropathy (150) were subjected to the study. Baseline and end-of-study intervention (12 weeks) findings were analyzed using a statistical tool, the paired t-test. Diabetic, inflammatory, antioxidant, nephropathy, neuropathy profiles and diastolic blood pressure, additionally, E-selectin in the study group were statistically improved compared to baseline values. In individuals subjected to polyherbal formulation, the decline in E-selectin levels was especially noticeable. T2DM patients may benefit from phytochemicals in polyherbal therapy. Reducing E-selectin levels, it prevents infiltration of inflammatory cells. Additionally, this reduces diabetic complications and oxidative damage caused by inflammation. These findings provide insight into the impact of polyherbal therapy on inflammation. The results also imply that E-selectin may be a novel target for the management of problems associated with diabetes.

Keywords: CRP, E-selectin, Ferritin, IL-6, Nephropathy, Neuropathy, NLR ratio, Polyherbal formulation

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Noncommunicable diseases, especially diabetes mellitus and preventable metabolic disorders, affect a sizable portion of the global population. According to a 2021 International Diabetes Federation report, 537 million people worldwide, aged between 20 and 79, have diabetes. In 2021, the financial burden of illness was 966 billion dollars worldwide. It might gradually rise to 1054 billion by 2045[1].

T2DM, the inflammation-induced endocrine disease manifested by insulin resistance, was common in Western nations before the 19th century; now the rate of new cases is increasing in Asian nations, with India at the forefront. Recent research reports highlighted that economic expansion and urbanization were the primary causes of this increase, which resulted in sedentary lifestyles and poor eating habits that ultimately made insulin resistance worse[2].

The inflammatory process in diabetes affected the intimal layer of the circulatory system and changed endothelial functions. Recent research has shown that endothelial dysfunctions are the cause of diabetic complications. Increased expression of E-selectin

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protein on the endothelium lining's surface and recurrent inflammatory cell infiltration are signs of vascular injury[3].

If we concentrate on E-selectin level, disease complications are decreased, the healing process is enlightened, the inflammatory response is decreased, and the overall quality of life in diabetes is improved. Studies show that management of E-selectin level in diabetic nephropathy improves the quality of life and delays in deterioration of the kidney[4]. Studies with diabetic macular edema show increased serum soluble E-selectin associated with inflammation and abnormal vascular permeability, additionally to proliferative diabetic retinopathy. This emphasizes the necessity for therapeutic strategies designed to reduce serum E-selectin[5]. Anti-inflammatory medications are examples of conventional pharmacotherapy that modify the E-selectin levels. Statins, as anti-inflammatory pharmacotherapy, may protect the vascular system in diabetics by lowering E-selectin levels, but they may also have detrimental effects on the gastrointestinal, skeletal, and nervous systems[6]. In addition to allopathic treatments, researchers have looked into non-pharmacotherapy to modulate E-selectin and reduce the risk of complications from diabetes. People with noncommunicable diseases may have reduced expression of E-selectin levels and reduced vascular complications by maintaining an appropriate BMI, physical endurance, and consuming a food rich in antioxidants and anti-inflammatory molecules[7].

Since researches have shown that some herbal extracts can down regulate E-selectin expression, improve endothelial health, and decrease the incidence of vascular disorders, scientists have gained attention for polyherbal formulations in recent years as an additional strategy for treating diabetic complications[8]. Studies reveal that herbal extracts from plants such as *Phyllanthus emblica, Senna auriculata, Nigella sativa, Trigonella foenum-graecum, Tinospora cordifolia, Glycyrrhiza glabra,* and *Gymnema sylvestre* can directly or indirectly suppress E-selectin expression[9]. Furthermore, participants with mild to moderate hypercholesterolemia who used the polyherbal formulation known as the Dantonic Pill had a significant reduction in E-selectin levels after 12 weeks of treatment[10]. Ancient literature goes into considerable length about the concept of polyherbal combinations. Research has shown that polyherbal mixes generally exhibit more potent and effective therapeutic potential than single herbs. Thus, the primary objective of the current study was to develop a polyherbal mixture of plants with antidiabetic properties. The study also aims to evaluate the therapeutic efficacy of the formulation in reducing the expression of E-selectin.

Materials and Methods

Subjects

Participants aged 20 to 60 from KIMS&RF in West Godavari, Andhra Pradesh, were selected for the study based on American Diabetes Association criteria[11], indicating Type 2 Diabetes Mellitus (T2DM) through a fasting blood sugar level over 126 mg/dL, a 2-h post-load plasma glucose level exceeding 200 mg/dL, or a hemoglobin A1c level surpassing 6.5%. The study recruited participants with diabetic complications, focusing on those with diabetic nephropathy and neuropathy. Patients with diabetic neuropathy had a Neuropathy Disability Score (NDS) of 6 or higher, indicating painful distal symmetrical and sensory polyneuropathy for at least three months[12]. Those with diabetic nephropathy met criteria of a urinary albumin/creatinine ratio (UACR) ≥30 mg/g in at least 2 measurements over 3-6 months, and an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² sustained for more than 3 months[13].

Study design

T2DM patients at KIMS&RF took part in this comparative study between January and December of 2023. After their eligibility was evaluated, the control and diabetes were found to be qualified for the study. As per the study flowchart (Fig. 1), the participants were divided into the following groups: healthy adult volunteers in the control group (CON), type-2 diabetic subjects without complications in the disease group (DIAB), subjects with diabetic neuropathy in the study group (DIAB-NU), and subjects with diabetic nephropathy in the study group (DIAB-NP). All diabetic patients were receiving metformin-only treatment. After being segregated into the different groups, all participants were subjected to supplementation of an aqueous extract of a polyherbal formulation twice a day for 12 weeks. Serum-soluble E-selectin, CRP, ferritin, IL-6 nitro-tyrosine, glutathione, fasting blood glucose, and HbA1c levels were examined in all group members before and after intervention.

Ethics

According to the guidelines of the Indian Council of Medical Research, the Institutional Regulatory Authority's Ethical Committee authorized the procedure with register number (Ref No. IEC/PR/2022:114).

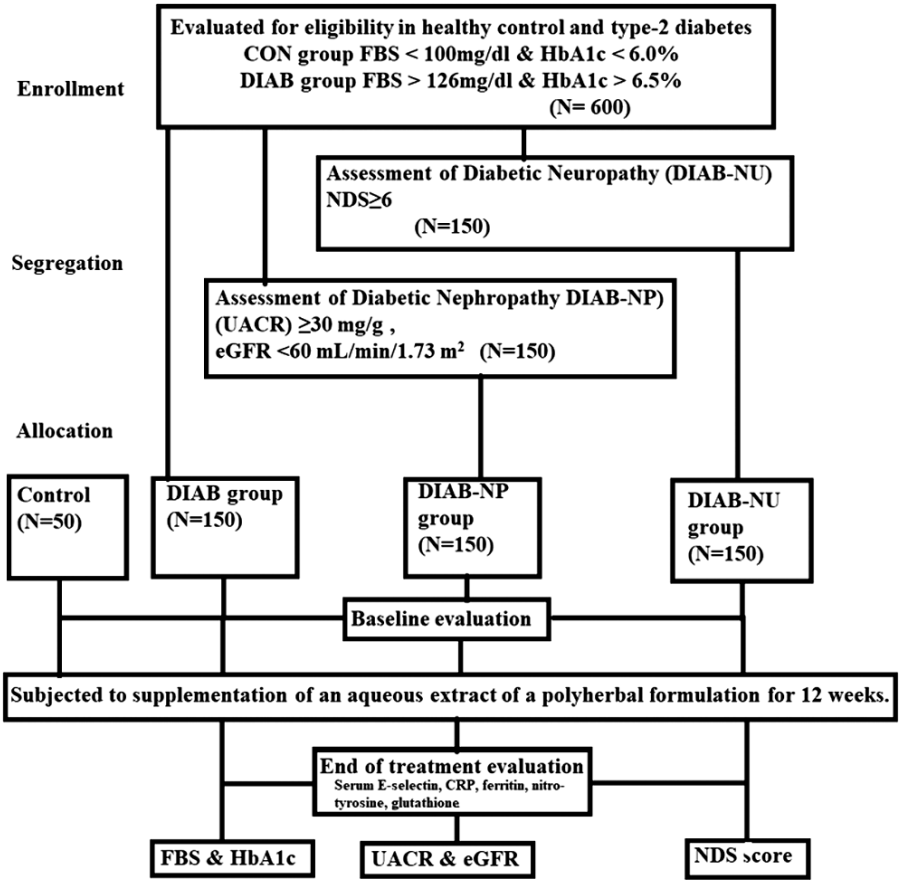

Fig. 1 — Study flow diagram

After receiving information, the aim of the study was explained in the local language to each patient in the intervention group, and a signature was obtained in a written informed consent form.

Polyherbal formulation & extraction

The polyherbal formulation was prepared from the leaf of *Tinospora cordifolia*, root of *Glycyrrhiza glabra*, pulp of *Phyllanthus emblica*, flower of *Senna auriculata*, seeds of *Nigella sativa*, seeds of *Trigonella foenum-graecum*, and leaf of *Gymnemasylvestre* purchased from Annai Aravindh Herbals and authenticated in the department of medicinal plants, at Dr Y.S.R. Horticulture University, Venkataramannagudem, West Godavari District, Andhra Pradesh, India. Plants were recognised and turned into a herbarium voucher (Voucher Number: 67/2022). A pilot study was conducted using different herbal ratios, including (1:1:1:1:0.5:1:1), (1:1:1:1:1:1:1), (1:1:1:1:2:1:1), and (1:1:1:1:3:1:1). During the study, potential antidiabetic activity was observed specifically with the ratio of (1:1:1:1:2:1:1). *Nigella sativa* was identified as a potential source of phytoconstituents of thymoquinone, an efficacious molecule that modulates E-selectin level. As a result, the optimal dosage for the polyherbal formulation was determined. The polyherbal formulation was prepared in the ratio of 1:1:1:1:2:1:1, and fine powder was prepared and stored in an airtight container. An aqueous extract was made from 20 g of polyherbal formulation in 300 mL of drinking water. The extract was reduce to 100 mL by boiling it for 10 min.

Statistical analysis

Descriptive statistics were obtained using the statistical program GraphPad Prism.8.0.2. Mean ± standard deviation (SD) for continuous variables and frequency with percentages for categorical variables were used to summarize the study's findings and demographic characteristics. A paired t-test for normally distributed data and a Mann-Whitney U test for non-normally distributed data were used to

evaluate statistical significance between baseline and treatment end. The ANOVA test was used to examine changes in important outcome measures over the course of the trial, which lasted up to 12 weeks, including the neuropathy parameters, nephropathy parameters, inflammatory parameters, and oxidative stress parameters.

Results

About 150 people with diabetic neuropathy (NDS 6 or higher, NSS 5 or higher, VAS 4 or higher), 150 with diabetic nephropathy (UACR at least 30 mg/g, eGFR below 60 mL/min/1.73 m²), and 50 healthy volunteers without diabetes were brought together. The goal was to see how well a polyherbal formulation could help manage diabetic complications. Their clinical and demographic details is listed in (Table 1), lined up with the study flowchart in (Fig. 1). Oral admiration of PHF indicated no adverse effect by liver and kidney function tests.

Attenuate effect of PHF on polyneuropathic complications in type-2 diabetic patients

The present study shows that neuropathic scores have a high impact in DIAB-NU group compared to the control group. But when the DIAB-NU group took the polyherbal formulation, their DPN scores dropped a lot from where they started ($p<0.001$; Table 2).

Poly-herbal formulation attenuates nephropathic complications in type-2 diabetic patients

UCAR and eGFR levels looked a lot different between the DIAB-NP and control groups, which points to more severe quality of life issues from diabetic complications. But here's the thing: when the DIAB-NP group got the polyherbal treatment, their UCAR dropped, and eGFR increased significantly by the end of the treatment compared to where they started ($p<0.001$; Fig. 2).

Effect of poly-herbal formulation therapy on inflammatory markers in diabetic complications

Significant average differences in inflammatory markers in serum CRP, IL-6, ferritin, and the NLR ratio of inflammation were found in all intervention groups compared with the control group. Treatment with the polyherbal formulation resulted in a statistically significant decrease before and after treatment ($p<0.001$; Table 3).

Effect of poly-herbal formulation on nitrosative stress

The findings demonstrated that, in comparison to healthy human subjects, individuals with diabetes mellitus, diabetic neuropathy, and diabetic neuropathy had considerably higher serum 3-nitrotyrosine (3-NT) levels ($p<0.001$). Since an increase in protein 3-nitrotyrosine is a sign of nitrosative stress, it is thought to be the most accurate biomarker of

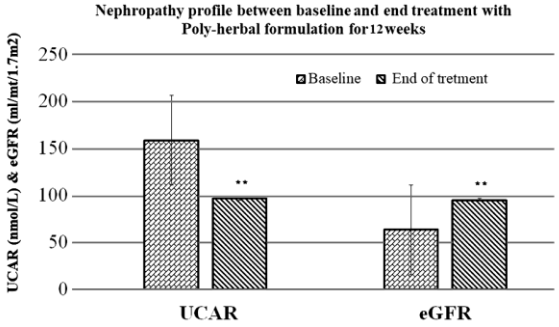

Fig. 2 — A comparison of nephropathy profile between baseline and end treatment of diabetic patients in the study groups

The bar diagram displays the statistical mean with +/- standard deviation of different groups. The statistical hypothesis of the investigation was defined as $p<0.01$* or $p<0.001$**

Table 1 — Effect of PHF on liver and Kidney function with demographic variables of the study group

Total patient	CON		DIAB		DIANB-NU		DIAB-NP	
	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment
Age	38.5±9.56		44.5±8.55		45.72±8.5		45.54±8.22	
Male	60%		70%		57%		52%	
Female	40%		30%		43%		48%	
Hypertension (%)	---		56%	43%*	50%	41%*	63%	44%*
FBS (mg/dL)	91.66±10.3	82±9.3	252.97±32.2	122±28**.	248.5±35.36	139.5±26.5**	273±67.46	133±31.5**
HbA1c(%)	5.40±0.25	05.3±0.2	8.86±0.73	6.5±0.7**	9.3±0.7	6.7±0.8**	9.5±0.7	6.9±0.6**
ALT (IU/L)	25.97±5.22	28.5±8.5	31.87±6.96	27.7±4.96	39.26±6.68	27.6±7.8	30.03±6.6	23.3±5.6
AST (IU/L)	23.10±4.00	24.5±6.00	26.76±4.97	21.6±5.5	31.97±4.28	22.4±3.33	34.5±5.8	22.5±3.5
ALP (IU/L)	136.76±26.61	121.5±22.55	148.47±29.7	106.44±31.4	119.57±23.73	103.51±18.11	132.11±25.5	101.23±22.5**
Creatinine (mg/dL)	0.9±0.2	0.82±0.18	1.54±0.3	1.02±0.17	1.39±0.30	1.01±0.20	2.5±0.18	1.85±0.22**
Urea (mg/dL)	22.5±3.57	20±3.7	32.05±4.2	24.5±3.5	37.3±5.5	21.93±7.5	54.55±6.5	29.5±5.5**

In this table we represented demographic variation and diabetic markers and drug toxicity profile evaluation in different study groups with displayed mean and standard deviation. Statistical investigation to define the study hypothesis by T-test with p-value. ($p<0.01$* or $p<0.001$**)

oxidative damage of functional proteins. Additionally, the role of 3-nitrotyrosine in diabetics receiving polyherbal formulations has been established. According to our unique data, patients with diabetic neuropathy and diabetic nephropathy treated with a polyherbal formulation had considerably lower levels of 3-nitrotyrosine than patients without diabetes ($p<0.001$; Fig. 3).

Poly-herbal formulation potential use in treating diabetes patients' glutathione deficiency

Research findings have shown that diabetic patients and those with diabetic complications such as diabetic neuropathy and diabetic nephropathy have notably lower levels of serum glutathione compared to healthy individuals ($p<0.001$). A decrease in glutathione is considered a hallmark of oxidative stress and a deficiency in antioxidants, making it a highly reliable biomarker of non-enzymatic antioxidants. Furthermore, the role of glutathione in diabetic patients who receive a polyherbal formulation has been established. Unique data indicates that diabetic patients with neuropathy and nephropathy who were treated with a polyherbal formulation exhibited significantly higher levels of glutathione compared to non-diabetic patients ($p<0.001$; Fig. 4).

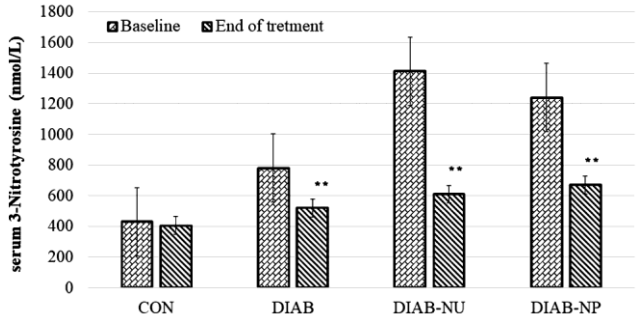

Fig. 3 — Baseline and end-of-treatment subjective on serum 3-Nitrotyrosinein different diabetic groups treated with Polyherbal formulation's for 12 weeks

The bar diagram displays the statistical mean with +/- standard deviation of different groups. The statistical hypothesis of the investigation was defined as $p<0.01$* or $p<0.001$**

Impact of polyherbal formulations on E-selectin in patients with T2DM **and their complications**

Findings revealed that, in comparison to healthy human subjects, diabetic patients, diabetic complication condition like diabetic neuropathy & diabetic nephropathy patients had significantly higher serum E-selectin level ($p<0.001$). Since an increase in E-selectin is a defining feature of microvascular

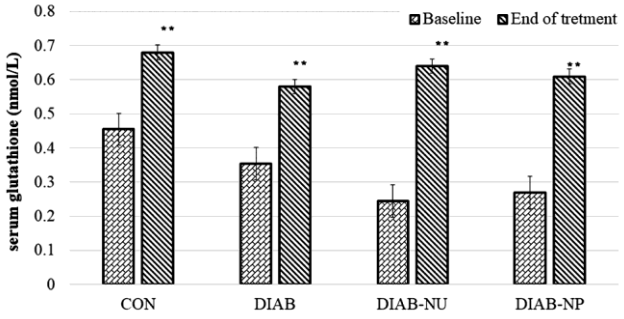

Fig. 4 — Baseline and end-of-treatment subjective on serum glutathione in different diabetic groups treated with polyherbal formulations for 12 weeks

The bar diagram displays the statistical mean with +/- standard deviation of study groups. The statistical hypothesis of the investigation was defined as $p<0.01$* or $p<0.001$**

Table 2 — A comparison of diabetic polyneuropathy scores between Baseline and end-of-treatment subjective of diabetic neuropathy patients treated with Poly-herbal formulation for 12 weeks

Variables	DIAB-NU(Baseline) (N=150)	DIAB-NU (end of treatment-Poly-herbal formulation (N=150)	P value
NDS	6.53±0.26	$4.54±0.23^{b}$**	<0.001
NSS	5.44±0.28	$3.53±0.28^{b}$**	<0.001
VAS	4.43±0.29	$2.64±0.24^{b}$**	<0.001

The table displays the mean with +/-standard deviation of 150 experimental subjects. The statistical hypothesis was justified by p value as $p<0.01$* or $p<0.001$**

Table 3 — Polyherbal formulation's effect on inflammatory markers in T2DM complications after 12 weeks of treatment

Total patient	CON(N=50)		DIAB (N=150)		DIANB-NU (N=150)		DIAB-NP (N=150)	
	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment
CRP (mg/dL)	0.39±0.05	0.22±0.04**	4.86±0.23	$2.5±0.32^{a}$**	5.3±0.33	$3.3±0.28^{b}$**	6.2±0.3	$3.1±0.4^{b}$**
Ferritin (ng/mL)	245±58	223±40**	387±40	$276±60^{a}$**	566±80	$360±85^{b}$**	590±90	$370±65^{b}$**
NLR ratio	1.7±0.5	1.3±0.55**	1.9±0.6	$1.45±0.6^{a}$**	3.75±0.6	$2.5±0.6^{b}$**	3.55±0.4	$2.7±0.6^{b}$**
IL-6 (pg/mL)	18.5±5.5	13.5±3.5**	37.2±8.5	$22.5±6.5^{a}$**	47.5±7.5	$28.7±6.0^{b}$**	55.7±6.6	$31.4±7.5^{b}$**

The average values for the 150 participants in the study, plus or minus the standard deviation, are displayed in the table. Results were considered statistically significant for this study if p was less than 0.01* or 0.001**. The bar graph illustrates the results of the ANOVA; in particular, it indicates which experimental groups deviate from the average of the control group (designated as "a") and which deviate from the average of the diabetes group (designated as "b")

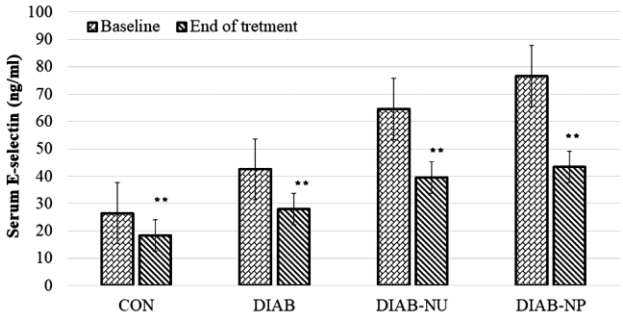

Fig. 5 — Baseline and end-of-treatment subjective on serum E-selectin in different diabetic groups treated with Polyherbal formulations for 12 weeks

The bar diagram displays the statistical mean with +/- standard deviation of study groups. The statistical hypothesis of the investigation was defined as $p<0.01$* or $p<0.001$**

complications, an increase in E-selectin is thought to be the most accurate biomarker of non-enzymatic antioxidant. The function of E-selectin in diabetic patients receiving Poly-herbal formulationhas also been identified. According to our unique data, patients with diabetic neuropathy and diabetic nephropathy treated with Poly-herbal formulation had significantly lower in E-selectin content than patients without diabetes ($p<0.001$; Fig. 5).

Discussion

The World Health Organization, the ACCORD study, and the diabetes trial demonstrate that blood glucose monitoring can lessen clinical consequences[14]. However, complete resolution may not be achieved, indicating the need for other treatment approaches. Diabetes mellitus is linked to mild inflammation, weakening antioxidant defenses, and increased risk of complications due to E-selectin protein[15]. Increased blood sugar causes inflammatory responses that damage cells and prolong the illness cycle. The main objective of modern pharmaceutical treatments is to manage blood glucose, although reducing inflammation and oxidative stress is as important. As a novel approach to lessen the clinical effects of diabetes, current research focuses on controlling E-selectin.

When several herbs work together to produce a therapeutic effect greater than the sum of their individual effects, this is known as a polyherbal composition. This synergistic activity may lower dosages and side effects in addition to improving efficacy. The synergistic effect of a medicine is enhanced by the ideas of pharmacokinetics and pharmacodynamics. When one herb improves another's absorption, distribution, metabolism, or excretion, this is known as pharmacokinetic synergism. On the other hand, elements that target distinct pathways but have comparable effects are included in pharmacodynamic synergism.

Polyherbal therapy is superior to a single drugSrivastava *et al*[16]. The idea of polyherbalism is emphasized in the Sharangdhar Samhita, an ancient Ayurvedic literature from 1300 AD. In 2011, Salehi *et al.*[17] found that using herbal treatments to treat diabetes and its complications was both safe and beneficial.In an experiment conducted by Perumal *et al.*[18], the antidiabetic properties of mono-herbal and polyherbal combinations of ethanolic isolation of *Taraxacum officinale* and *Momordica charantia* were found to be time-tested. In comparison to the mono-herbal form, the results demonstrate a super combination with improved antidiabetic activities, high inhibitory potentials toward DPP-4, α-amylase, and α-glucosidase, antioxidant capacity, and optimal efficacy in decreasing blood glucose. Due to the negative side effects of the commercial medications now on the market, a polyherbal combination rich in bioactive substances can be further processed into a complex phytotherapeutic cure with synergistic action for type 2 diabetes. One such polyherbal formulation's anti-diabetic qualities were assessed in a 2022 study by Bhaskarrao *et al.*[19] where the extracts of the stems of *Tinospora cordifolia*, leaves of *Ocimum sanctum*, and *Azadirachta indica* were used. When comparing polyherbal formulations to single-herbal formulations, the study's findings highlighted notable anti-diabetic, anti-inflammatory, and antihyperlipidemic benefits in diabetic rats, making them more effective. This further demonstrates that a key factor in a formulation's effectiveness is the synergistic mechanism of different secondary metabolites present in plant mixes[20].

In this study, we picked a mix of herbs: *Tinospora cordifolia* leaves, *Glycyrrhiza glabra* roots, *Phyllanthus emblica* pulp, *Senna auriculata* flowers, *Nigella sativa* seeds, *Trigonella foenum-graecum* seeds, and *Gymnema sylvestre* leaves. Each of these plants already has known antidiabetic effects. When orally administered as a combined formulation, the mixture of phyto-ingredients demonstrated a clinically meaningful reduction in diabetic parameters. The combined preparation consistently outperformed the

individual components, suggesting an additive or synergistic action with potential relevance for the management of diabetes and its associated complications. Asper authors' knowledge, this is the first study to investigate vascular damage parameters, such as E-selectin combined with oxidative stress, antioxidant, and glycemic parameters in different complications of diabetic groups with a single PHF formulation intervention.

The observed changes in these parameters suggest that PHF may offer adjunctive benefit in the clinical management of diabetic complications. An examination of the hypoglycemic activity of the polyherbal formulation in individuals with diabetes, diabetic neuropathy, and diabetic nephropathy revealed significant improvement ($p<0.001$; Table 1). Consistent with a study by Kurian *et al*.[21] in 2014, it was observed that short-term supplementation of the polyherbal formulation G-400 can mitigate hyperglycemia and hyperlipidemia in patients with T2DM. Additionally, supplementation with 10 g of *Tinospora cordifolia* leaf powder was found to improve glucose tolerance in patients with T2DM[22]. The observed anti-hyperglycemic effect of PHF can be attributed to various mechanisms, including the decrease of gluconeogenesis in hepatocytes and inhibitory effects on glycosidase by the alkaloids of *T. cordifolia* and *S. auriculata*[22]. Furthermore, the flavonoids of *Glycyrrhiza glabra* and *Phyllanthus emblica* were found to enhance insulin sensitivity through the Akt cascade[23] while thymoquinone from *Nigella sativa* improved beta-cell functions[24]. Moreover, ferulic acid and coumaric acid from *T.foenum-graecum*, along with Rutin, Quercetin, Lupeol, and Kaempferol from *Gymnema sylvestre*, were observed to enhance insulin sensitivity, beta-cell function, and decrease intestinal glucose absorption[25]. In conclusion, the polyherbal formulation demonstrates potential in effectively managing diabetes through multiple mechanisms to improve glycemic control.

The clinical study's objective was to ascertain how well a polyherbal mixture of seven plants can lessen diabetic neuropathy symptoms. Diabetic neuropathy patients scored higher on tests such as the VAS, NDS, and NSS and had a lower quality of life, according to studies. The illness is linked to low antioxidant levels, glucose auto oxidation, increased ROS, and abnormal insulin signaling pathways, which result in mitochondrial dysfunction and neuroinflammation.

A polyherbal formulation has been demonstrated to enhance several parameters associated with symptoms of diabetic neuropathy in affected persons, according to a recent study. Diabetic polyneuropathy (DPN) metrics, including NDS, NSS, and VAS ratings, showed a substantial improvement throughout the course of the trial, according to researchers (Fig. 2 and Table 2; $p<0.001$). In a 2022 study by Golsorkhi *et al.*[26] it was discovered that children and adolescents with neuropsychiatric disorders experienced positive effects from consuming polyherbal formulations as supplements for anxiety and depression. Researchers believe that phytochemicals such as quercetin, rutin, catechin, diosmin, kaempferol, and naringin, along with tannins and saponins, offer potential benefits for diabetic neuropathy (DN) due to their anti-inflammatory, antioxidant, and neuroprotective properties, as well as their ability to promote nerve repair and growth. The study also demonstrated that the rich flavonoid fractions in polyherbal formulations play a possible role in attenuating diabetic neuropathy (DN)[27]. Specific herbs used in polyherbal formulations contain significant quantities of flavonoids, tannins, and saponins. For example, *Tinospora cordifolia* contains 79.46 mg QE/g of flavonoids, *Glycyrrhiza glabra* contains 8.5 mg%, *Phyllanthus emblica* contains 5.816 mg QE/g, *Senna auriculata* contains 285 mg QE/g, *Nigella sativa* contains 2-4 mg/g, and *Tinospora cordifolia* contains 4.23 QE/g of dry weight. After three months of treatment with the polyherbal formulation, there was a substantial decrease in blood pressure and urine protein (UCAR) and an increase in glomerular filtration rate (GFR) compared to the healthy control group (Fig. 3 and Table 1; $p<0.001$). Furthermore, at the end of the three-month treatment period, the hypertension levels of the diabetic group dropped by 13%, those of the diabetic neuropathy group by 9%, and those of the diabetic nephropathy group by 19% from the baseline, indicating a specific antihypertensive impact of the polyherbal formulation.

Supplementation of *Tinospora cordifolia* has been shown to effectively suppress sympathetic nervous system over activation, significantly lowering mean systolic blood pressure and heart rate in physically stressed individuals, per Salve BA *et al*. (2015)[28]. Additionally, a three-month therapy period demonstrated an increase in estimated glomerular filtration rate and a decrease in urinary protein

creatinine ratio, highlighting the nephron-protective effects of the polyherbal formulation, which is crucial for managing diabetic nephropathy.

As per a 2017 study by Xu *et al.*[29], ginsenoside saponin administration significantly increased GFR in 91 patients suffering from renal impairment, and related symptoms were also improved. An oral supplement containing 22.1 mg of curcumin (from 500 mg turmeric) reduced proteinuria as well as serum inflammatory markers TGF-β and IL-8 in hypertensive T2DM patients with overt nephropathy when administered for eight weeks[30]. The observed reduction in proteinuria could be due to higher concentrations of nephroprotective substances such as flavonoids, terpenoids, phenolic acids, carotenoids, and sterols.These beneficial compounds are present in several plants used in polyherbal formulations, including *Tinospora cordifolia, G. glabra, P. emblica, S. auriculata, N. sativa, T. foenum-graecum,* and *G. sylvestre*.

Tyrosine is converted to 3-nitrotyrosine (3-NT) when peroxynitrite becomes reactive. This is significant because 3-NT essentially identifies oxidative and nitrosative stress, which is present in a variety of illnesses, including inflammation, cardiac issues, neurological conditions, and more[31]. A high 3-NT indicates that reactive chemicals are pounding cells. This hint aids medical professionals in identifying problems early and monitoring the effectiveness of treatment. Conversely, there is glutathione, also known as GSH. It is used by cells to combat reactive oxygen species. A decrease in GSH is a warning sign that the cell's defenses are failing. Diabetes consequences, such as peripheral diabetic neuropathy, are characterized by both low GSH and high 3-NT.

According to the study, a polyherbal supplement significantly improved stress management in diabetics. Their glutathione levels increased, and their nitrogen levels decreased after three months. Another study from 2022 found that patients with type 2 diabetes who received *Phyllanthus emblica* extract had higher levels of glutathione and lower levels of reactive nitrogen species[32]. Then, in 2025, scientists discovered that curcuminoid supplementation increased plasma antioxidant levels and decreased oxidative stress[33]. Additionally, *Glycyrrhiza glabra* flavonoids reduced oxidative stress and alleviated problems in diabetes patients[34]. A 2024 case study revealed that the Siddha formulation Sirupeelai Kudineer improved kidney parameters in diabetic nephropathy patients, suggesting its potential for use with hypoglycemic drugs[35]. The findings propose an antioxidant-focused therapeutic approach for managing diabetic complications, contrasting with existing pharmaceutical treatments.

The CRP, ferritin, and IL-6 NLR data from the research demonstrated that taking a polyherbal supplement significantly improved diabetes and related conditions. The results of the study showed that taking a polyherbal formulation supplement significantly decreased inflammation in issues related to diabetes. Consistent with our findings, Chumpolphant *et al.*[36] reported a decrease in inflammatory markers TNF-α, IL-6, and VEGFA in diabetic ulcer patients after polyherbal formulation treatment. Unlike current pharmaceutical treatments, the results of our study suggest a novel therapeutic approach for diabetic complications that stresses antioxidant boosting as a critical component in treating microvascular difficulties. Ma[37] and colleagues showed back in 2022 that taking 500 mg of resveratrol a day lowers certain pro-inflammatory markers things like tumor necrosis factor-α, interleukin-1β, and interleukin-6in older adults with type 2 diabetes. Around the same time, Mobasseri and his team found that saffron supplements also dialed down inflammation in people with T2DM[38].

According to our research, E-selectin levels are much greater in diabetics than in healthy individuals ($p<0.001$). However, those E-selectin levels decreased after we administered a polyherbal combination. In 2020, Marino and his colleagues noted that anthocyanidins can influence the production of E-selectin, a protein closely associated with inflammation[39]. In 2020, Bujor's team discovered that, at least in tests, phytochemicals such as terpenoids, flavonoids, and alkaloids can actually shield blood vessels from harm[40]. This suggests that they have potential as multi-target medications. There are further ones. Quercetin has been linked to increased E-selectin in some inflammatory conditions. *Glycyrrhiza glabra, Phyllanthus emblica, Gymnema sylvestre,* and *Nigella sativa* are examples of polyherbal formulas high in flavonoids and polyphenols that seem to stop the inflammatory spike in E-selectin.

Limitations of the study

Since this study was conducted at a single location, other variables may have affected the findings. Researchers need to conduct larger, multicenter trials to truly support these conclusions. We can better

understand how these drugs regulate blood sugar and prevent small blood vessel problems in individuals with type 2 diabetes by delving deeper into their molecular mechanisms.

Conclusion

Our data clearly illustrated the link between vascular damage by-product E-selectin and antioxidant deficiency in the study population. When study subject oral consumption of PHF increases, non-enzymatic antioxidant GSH increases, and inflammatory markers like IL-6, NLR ratio, and CRP decrease. Oxidative stress-induced inflammation in the vascular system E-selectin is a promising new target for preventing diabetic complications due to inflammation. Our results shed light on how this polyherbal combination works at the molecular level, especially when it comes to inflammation. Honestly, this new eye opening for treating diabetes complications needs clinical trials. More testing can push diabetes care forward; tackle some tough problems, and even help cut healthcare costs.

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Author Contributions

The research concept was designed by MV, SL, and MN; the benchwork of the study was carried out by SC, AD, and MB. The architecture of the manuscript is framed by MV, MN, and SL. The data science burden is taken care of by SL, SC, and AD. Final approval of the document by every researcher who contributed and submitted to the journal.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

Ethics Approval

According to the guidelines of the Indian Council of Medical Research, the Institutional Regulatory Authority's Ethical Committee authorized the procedure with register number (Ref No. IEC/PR/2022:114).

Informed Consent

After explaining the purpose of the study, written informed consent was obtained from all participants.

Data Availability

The corresponding author will provide study data upon request.

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