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Case Report

Antioxidant, anti-inflammatory and reproductive effects of the anti-diabetic polyherbal formulation, "*Insulinevégétale*": Evidence from a case series from Cameroon

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Abstract

Diabetes mellitus associated with oxidative stress, systemic inflammation, and male reproductive function impairment requires a holistic approach. This study investigated the effects of a polyherbal formulation, "*Insulinevégétale*" on biomarkers of oxidative stress, inflammation, and reproductive hormones in diabetes mellitus patients. This prospective case series conducted at the '*Union des Tradi-praticiens en Plantes Médicinales du Cameroon*' headquarters in Foumbot (Cameroon) involved participants monitored at three time points. Serum biomarkers of inflammation, including high-sensitivity C-reactive protein (hsCRP), C-reactive protein (CRP), and interleukin-6 (IL-6), were measured. Oxidative stress status was evaluated using reduced glutathione (GSH) and superoxide dismutase (SOD) activity. Reproductive function was assessed through serum testosterone and luteinizing hormone (LH) levels. Inflammatory biomarkers reduced during treatment with hsCRP, CRP and IL-6 declining ($p < 0.001$) from 5.62 mg/L, 20.26 mg/L and 153.27 pg/mL at baseline to 2.97 mg/L, 7.32 mg/L and 20.91 pg/mL at endpoint, respectively. Conversely, antioxidant biomarkers were significantly improved, with the levels of GSH and SOD activity increasing ($p < 0.001$) from 2.57 µmol/L to 5.36 µmol/L and 83.16 U/mL to 112.32 U/mL, respectively. Likewise, reproductive hormonal parameters also showed improvement, as testosterone and LH levels increased ($p < 0.001$) from 1.73 nmol/L and 24.64 IU/L to 3.73 and 33.26 IU/L nmol/L, respectively. In summary, *"Insulinevégétale"* therapy attenuates inflammation and oxidative stress while restoring hormonal balance in individuals with diabetes, thereby helping to preserve male reproductive function. These findings suggest that this polyherbal formulation exerts beneficial effects against metabolic and endocrine disturbances, likely through its antioxidant and anti-inflammatory properties.

Keywords: Diabetes mellitus; Inflammation; *Insulinevégétale;* Oxidative stress; Polyherbal formulation; Reproductive hormones.

1. Introduction

Diabetes mellitus (DM) is one of the fastest-growing non-communicable disease and its global burden continues to increase at an alarming rate. According to the international Diabetes Federation, approximately 537 million adults were living with diabetes in 2021, with projections reaching 643 million by 230 and 783 million by 2045 [1]. Type 2 diabetes mellitus (T2DM) accounts for nearly 90% of cases worldwide and represents a major cause of morbidity and mortality due to its long-term complications [2, 3]. Beyond hyperglycemia, diabetes is increasingly recognized as a disease characterized by chronic inflammation and oxidative stress. Persistent hyperglycemia promotes excessive production of reactive oxygen species (ROS) through multiple pathways including glucose Auto-oxidation, protein glycation, and mitochondrial dysfunction [4]. The imbalance between ROS generation and antioxidant defense mechanisms leads to oxidative stress, resulting in cellular damage affecting various organs and physiological systems. Key endogenous antioxidants such as superoxide dismutase (SOD) and reduced glutathione (GSH) play crucial roles in protecting tissues from oxidative injury; however, their activities are often impaired in diabetic conditions [4].

Chronic low-grade inflammation also plays a critical role in the pathophysiology and progression of diabetes. Pro-inflammatory mediators such as C-reactive proteins (CRP), high-sensitive C-reactive protein (hsCRP), TNF-α, Interleukin-1β and interleukin-6 (IL-6) are elevated in

individuals with diabetes and contribute to metabolic dysregulation, endothelial dysfunction and tissue damage [5, 6]. These inflammatory pathways interact closely with oxidative stress mechanisms, creating a vicious cycle that exacerbates diabetic complications. Among the various complications associated with diabetes, reproductive dysfunction in males has gained increasing attention [7, 8]. Hyperglycemia-induced oxidative stress and inflammatory processes can impair the hypothalamic-pituitary-gonadal axis, leading to hormonal imbalance and reduced reproductive capacity. Previous studies have reported alterations in reproductive hormones such as testosterone and luteinizing hormone (LH), as well as impairment in sperm quality, DNA integrity and chromatin structure in diabetic males [8, 9]. These changes may ultimately result in reduced fertility and compromised reproductive health.

Although pharmacological therapies such as metformin, sulfonylureas, and insulin have significantly improved diabetes management, their long-term use is often limited by cost, side effects and poor accessibility in resource-limited settings [10]. Given the multifactorial nature of diabetes and its complications, there is growing interest in complementary therapeutic approaches including medicinal plants. Plant-based therapies contain diverse bioactive compounds such as polyphenols, flavonoids, and vitamins with antioxidant and anti-inflammatory properties that may help mitigate oxidative stress and metabolic dysregulation [11]. In many parts of Africa, traditional medicine remains an important component of healthcare due to its accessibility, affordability and cultural acceptance.

In Foumbot, a sub-division located in the West region of Cameroon, a polyherbal formulation known as *"Insulinevégétale*" is used by the '*Union des Tradi-praticiens en Plantes Médicinales du Cameroon (UTPC)'* for the management of diabetes mellitus. This preparation consists of three medicinal plants: *Zingiber officinale* (ginger), *Syzygium aromaticum* (clove), and *Aloe vera*, and each of these plants has individually demonstrated antidiabetic, antioxidant, and anti-inflammatory activities in previous studies [12]. However, despite its widespread use among diabetic patients, the pharmacological effects and biological mechanisms of this polyherbal formulation remains poorly documented. Furthermore, limited scientific evidence exists regarding the potential impact of such traditional herbal preparations on oxidative stress, inflammatory status, and male reproductive function in diabetic individuals. This represents an important knowledge gap that requires systematic investigation in order to validate the therapeutic potential and safety of this polyherbal formulation. The present study aimed to evaluate the biological effects of the polyherbal preparation *"Insulinevégétale"* in diabetic patients. Specifically, the study investigated the influence of the formulation on inflammatory (CRP, hsCRP and IL-6) and oxidative stress biomarkers (GSH and SOD), and its potential ameliorative effects on male reproductive function through the assessment of reproductive hormones including testosterone and luteinizing hormone.

2. Materials and methods

2.1 Study design and setting

This prospective case series was conducted over the period of 5th July 2022 to 5th July 2023 at the headquarters of the Union des Tradi-praticiens en Plantes Médicinales du Cameroun (UTPC) in Foumbot, West Cameroon. It involved the follow up of diabetic participants over the period of four (4) months with sampling performed at three time points: baseline (prior to start of treatment: T1), midpoint (2 months of treatment: T2), and endpoint (4 months of treatment: T3). All participants enrolled were those receiving the polyherbal formulation *"Insulinevégétale"* as a complementary therapy at UTPC throughout the study period. At enrollment (T1), demographic parameters, demographics (gender and age), and anthropometric indices (BMI) were recorded for each participant. During the study period for each participant, blood samples were collected to evaluate glycaemia and variations in inflammation, oxidative stress, and male reproductive function biomarkers at 3 time points. Sampling was performed at enrollment of the participant (during start of treatment (T1) with herbal formulation), after being followed up for 2 months, and at 4 months of treatment and follow up (T3).

2.2 Polyherbal formulation "*Insulinevégétale*" ingredient

The herbal formulation *"Insulinevégétale"* is prepared from three medicinal plants: *Zingiber officinale* (family Zingiberaceae), *Aloe vera* (family Asphodelaceae), and *Syzygium aromaticum* (family Myrtaceae). The formulation is prepared and dispensed by the UTPC traditional medicine clinic in Foumbot. During the study period, each participant received 30 mL of the preparation orally three times daily as part of their complementary therapeutic regimen for diabetes mellitus (T1DM and T2DM).

2.3 Study population and recruitment

Participants were diabetic patients consulting and receiving the herbal preparation at the UTPC headquarters. Eligible participants were adults aged 21 years and above who had been medically diagnosed with diabetes mellitus. Individuals with severe organ failure, pregnancy or ongoing use of known hepatotoxic or nephrotoxic medications were excluded from the study. Also, men consuming steroids were not allowed to participate in the study. All participants received detailed information about the study and provided signed written informed consent prior to enrolment.

2.4 Ethical considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Regional Ethics committee of the West region in charge of Research on Human Health (N° 127/29/03/2023/CE/CRERSH-

OU/VP), an authorization to carry out research in the health area obtained from the Regional Delegation of Public Health for the West Region (N°617/L/MINSANTE/SG/DRSPO/CBF/CA).
Confidentiality and anonymity of participants were strictly maintained throughout the study.

2.5 Sample Collection

Venous blood samples (10 mL) were collected into plain dry tubes under aseptic conditions by trained laboratory personnel. Samples were centrifuged at 300 xg for 10 minutes to separate serum, which was aliquoted and stored at -20°C until laboratory analysis. During the study period for each participant, blood samples were collected and analyzed for glycaemic parameters to confirm diabetic status. FBG was measured using a portable glucometer (OneTouch Horizon®, Lifescan Inc., USA) based on the glucose dehydrogenase electrochemical method, while HbA1c was measured using a commercial kit (Quimica Clinica Aplicada, Spain) based on ion-exchange resin separation.

2.6 Anti-inflammatory assay

Serum CRP and hsCRP concentrations were determined using the Finecare™ fluorescence immunoassay system (Finecare™ FIA Meter, Guangzhou Wondfo Biotech Co., China) based on the sandwich immunofluorescence principle. Briefly, 8.5 µL of serum was mixed with buffer solution, and 75 µL of the mixture was dispensed into the sample well of the Finecare™ test cartridge. The cartridge was inserted into the Finecare™ FIA meter and fluorescence intensity of CRP and hsCRP was measured after 3 minutes, with results expressed in mg/L.

Serum IL-6 levels were quantified using the PicoKine™ Human IL-6 ELISA Kit (Boster Biological Technology, USA) based on the sandwich enzyme-linked immunosorbent assay principle. Briefly, 100 µL of standards or serum samples were added into wells and incubated with detection antibodies, followed by washing steps and addition of avidin-HRP conjugate. After substrate development and addition of stop solution, absorbance was measured at 450 nm using a microplate reader (Elabscience®, Houston, Texas, USA) and IL-6 levels were expressed as pg/mL.

2.7 Assessment of antioxidant activity

Serum reduced glutathione (GSH) levels were determined using the Ellman colorimetric method [13], which is based on the reaction between sulfhydryl groups and 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) to produce a yellow-colored chromogen (5-thio-2-nitrobenzoic acid). Briefly, 20 µL of serum was mixed with phosphate buffer (pH 6.5) and DTNB reagent and incubated in the dark for 60 minutes. The absorbance of the reaction mixture was measured at 405 nm using a microplate reader (Elabscience®, USA) and GSH levels were expressed as µmol/L. Superoxide dismutase (SOD) activity was determined using the xanthine–xanthine oxidase method described by Xin et al. [14] based on the generation of superoxide radicals by xanthine oxidase in the presence of its substrate2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyltetrazolium chloride (INT). Briefly, serum samples were mixed with substrate reagents containing xanthine and INT in CAPS buffer (Cyclohexylamino-1-propanesulfonic acid), followed by addition of xanthine oxidase. The rate of reduction of INT was monitored at 480 nm spectrophotometrically (Mindray BA-88A, Mindray Bio-Medical Electronics Co., Shenzhen, China) and the SOD activity was given as U/mL.

2.8 Quantification of male reproductive hormone levels

Serum testosterone level was measured using a Testosterone ELISA Kit (Calbiotech Inc., USA) based on a competitive enzyme-linked immunosorbent assay principle. Briefly, 10 µL of serum samples were added into microplate wells followed by testosterone enzyme reagent and biotin reagent. After 10 min incubation then washing, 100 µL of TMB (3,3`,5,5`-Tetramethylbenzidine) substrate was added, and the absorbance was recorded at 450 nm using a microplate reader (Elabscience®, Houston, Texas, USA) the concentration of testosterone in the samples of male participants obtained in nmol/L. Serum luteinizing hormone (LH) levels were measured using the ERBA Lisa LH ELISA Kit (Transasia Bio-Medical Ltd., India) based on a sandwich immunoassay using the streptavidin-biotin detection system. Briefly, 25 µL of serum samples and standards were added into microplate wells followed by enzyme conjugate. After 5 min incubation then washing, 5µL of substrate solution and the absorbance was recorded at 450 nm using a microplate reader. Serum LH concentrations of male participants were obtained and expressed in IU/L.

2.9 Statistical analysis

Data were analyzed using SPSS V27 statistical software. Continuous variables were expressed as mean ± standard deviation. Changes in biomarkers across the three time points were evaluated using repeated-measures ANOVA and the Friedman test where appropriate. Pearson correlation and Linear mixed model (LMM) estimated the effect of "*Insulinevégétale*" using Restricted Maximum Likelihood (REML), fixed effects included treatment time and co-administered conventional antidiabetic therapies. A random intercept was specified for patient ID to account for repeated measures. Degrees of freedom were estimated using the Satterthwaite approximation method. Statistical significance was set at $p < 0.05$.

3. Results

3.1 Sociodemographic and clinical characteristics of study participants

The baseline sociodemographic and clinical characteristics of the study participants are summarized in Table **1**. A total of 36 individuals with diabetes mellitus participated in the study, comprising of 16 males (44.4%) and 20 females (55.6%), indicating female predominance. Age distribution showed that the largest proportion of participants belonged to the 40-49

years age group (36.1%), followed by 25-39 years (22.2%) and > 60 years was least (19.4%). These findings suggest that the majority of participants were middle-aged adults, a demographic group commonly affected by metabolic disorders. With respect to marital status 66.7% of participants were married. Lifestyle assessment revealed that 63.9% of participants reported engaging in regular physical exercise, whereas 36.1% reported no regular exercise. Regarding herbal medicine exposure, 72.2% of participants were using the herbal preparation for the first time, while 27.8% had previously used the herbal preparation. Additionally, 61.1% reported prior use of other herbal products, indicating a high prevalence of herbal medicine utilization among the study population. Clinically, type 2 diabetes mellitus was predominant (77.8%), whereas 22.2% of participants had Type 1 diabetes mellitus, consistent with global epidemiological patterns where Type 2 diabetes accounts for the majority of diabetes cases.

Table 1: Baseline sociodemographic and clinical characteristics of study participants

Variable	State	Frequency	Percentage (%)
Gender	Male	16	44.4
	Female	20	55.6
	Total	36	100.0
Age group	25-39	8	22.2
	40-49	13	36.1
	50-59	8	22.2
	> 60	7	19.4
	Total	36	100.0
Marital status	Divorced	1	2.8
	Married	24	66.7
	Single	2	5.6
	Widow/widower	9	25.0
Exercise	Yes	23	63.9
	No	13	36.1
First time taking herbal preparation	Yes	26	72.2
	No	10	27.8
Taken other herbal preparation	Yes	22	61.1
	No	14	38.9
Type of diabetes	Type 1 diabetes	8	22.2
	Type 2 diabetes	28	77.8
	Total	36	100.0

Values are presented as frequency (n) and percentage (%).

3.2 Inflammatory, oxidative stress and reproductive biomarkers between type 1 and type 2 diabetes at different time points

Glycaemic biomarkers revealed that fasting blood glucose differed significantly only at the midpoint ($p < 0.004$), where type 1 patients exhibited higher values, suggesting a slower glycaemic response to treatment. HbA1c was significantly higher in type 1 diabetes at baseline ($p < 0.012$), midpoint ($p < 0.014$), and endpoint ($p < 0.011$), indicating more severe and persistent hyperglycaemia in this group.

The comparison of inflammatory, oxidative stress and reproductive biomarkers showed lower but not significant levels in T1DM than T2DM patients (Table **2**). Throughout the follow-up, highly sensitive C-reactive protein (hsCRP, mg/L) levels were marginally higher and statistically not significant in individuals with T2DM (5.82 ± 2.07 mg/L vs. 4.93 ± 2.61 mg/L, $p > 0.317$; 4.43 ± 1.55 mg/L vs. 4.29 ± 1.83 mg/L, $p > 0.828$; 3.06 ± 1.44 mg/L vs 2.68 ± 1.19 mg/L, $p > 0.499$, for the three time points, respectively). A comparable pattern was observed for C reactive protein (CRP, mg/L) with T2DM participants exhibited higher CRP concentrations at baseline (22.45 ± 3.94 mg/L) than T1DM participants (12.58 ± 4.79 mg/L; $p > 0.216$). Similarly, interleukin-6 (IL-6, pg/mL) concentrations were consistently higher ($p = 0.126$) among Type 2 diabetes participants across all time points with baseline levels being169.04 ± 22.47 pg/mL in T2DM as compared to 98.05 ± 30.15 pg/mL in T1DM. Antioxidant biomarkers demonstrated comparable levels between diabetes types. Reduced glutathione (GSH, µmol/L) concentrations at baseline were 2.35 ± 1.36 µmol/L in T1DM vs. 2.57 ± 0.94 µmol/L in T2DM ($p > 0.614$). Although GSH levels increased in both groups over time, the differences between groups remained statistically non-significant at the midpoint ($p > 0.153$) and endpoint ($p = 0.814$). Superoxide dismutase (SOD, U/mL) activity did not differ significantly between the two groups. Baseline SOD activity was 75.98 ± 23.75 U/mL in T1DM vs. 83.16 ± 22.12 U/mL in T2DM ($p > 0.431$), with comparable results at the midpoint and endpoint (all $p > 0.05$). Significant differences were observed for testosterone at early time points. At baseline, testosterone levels were significantly higher in T1DM (2.47 ± 0.43 nmol/L vs. 0.84 ± 0.19 nmol/L, $p < 0.009$) compared with T2DM patients at baseline. A similar pattern was observed at the midpoint (3.11 ± 0.49 nmol/L vs 1.63 ± 0.40 nmol/L, $p < 0.033$). However, by endpoint, the difference between groups was no longer statistically significant (3.62 ± 0.33 nmol/L vs 3.21 ± 0.63 nmol/L; $p > 0.465$). for luteinizing hormone (LH, IU/L), levels tended to be higher in T1DM patients across all time points, but the differences did not reach statistical significance ($p > 0.05$). Overall, these findings suggest that inflammatory and oxidative stress markers were broadly comparable between diabetes types, whereas reproductive hormone differences particularly testosterone were evident during early phase of treatment.

Table 2: Inflammatory, oxidative stress and reproductive biomarkers between type 1 and type 2 diabetes at different time points.

Variable	Time points	T1DM (n = 8)	T2DM (n = 28)	P	95% CI (LB – UB)
FBG (mg/dL)	Time point 1	319.88 ± 113.06	256.36 ± 83.06	0.088	-9.853 - 136.889
	Time point 2	281.25 ± 112.37b	181.93 ± 68.60a	0.004	34.468 - 164.175
	Time point 3	166.63 ± 55.07	132.86 ± 45.52	0.086	-5.048 - 72.584
HbA1c (%)	Time point 1	11.74 ± 1.86b	9.58 ± 2.06a	0.012	0.509 - 3.798
	Time point 2	10.63 ± 1.04b	9.01 ± 1.67a	0.014	0.355 - 2.898
	Time point 3	9.91 ± 0.72b	8.26 ± 1.70a	0.011	0.397 - 2.918
hsCRP (mg/L)	Time point 1	4.93 ± 2.61	5.82 ± 2.07	0.317	-2.680 – 0.895
	Time point 2	4.29 ± 1.83	4.43 ± 1.55	0.828	-1.454 – 1.171
	Time point 3	2.68 ± 1.19	3.06 ± 1.44	0.499	-1.461 – 0.697
CRP (mg/L)	Time point 1	12.58 ± 4.79	22.45 ± 3.94	0.216	-25.811 – 6.054
	Time point 2	10.13 ± 3.88	13.93 ± 2.53	0.468	-14.354 – 6.740
	Time point 3	5.94 ± 2.74	7.72 ± 3.18	0.360	-5.673 – 2.117
IL-6 (pg/mL)	Time point 1	98.05 ± 30.15	169.04 ± 22.47	0.126	-162.896 – 20.903
	Time point 2	47.37 ± 20.05	80.10 ± 13.19	0.233	-87.567 – 22.092
	Time point 3	11.71 ± 2.58	23.53 ± 3.98	0.131	-27.349 – 3.708
GSH (µmol/L)	Time point 1	2.35 ± 1.36	2.57 ± 0.94	0.614	-1.063 – 0.637
	Time point 2	3.49 ± 1.46	4.20 ± 1.13	0.153	-1.692 – 0.276
	Time point 3	5.26 ± 1.54	5.39 ± 1.29	0.814	-1.222 – 0.966
SOD (U/mL)	Time point 1	75.98 ± 23.75	83.16 ± 22.12	0.431	-25.478 – 11.125
	Time point 2	95.84 ± 15.36	97.59 ± 18.01	0.804	-16.002 – 12.503
	Time point 3	112.89 ± 19.06	112.32 ± 17.09	0.935	-13.695 – 14.844
Testosterone (nmol/L)	Time point 1	2.47 ± 0.43	0.84 ± 0.19	0.009	0.785 – 2.474
	Time point 2	3.11 ± 0.49	1.63 ± 0.40	0.033	0.221 – 2.745
	Time point 3	3.62 ± 0.33	3.21 ± 0.63	0.465	-1.174 – 2.009
LH (IU/L)	Time point 1	32.11 ± 9.44	21.36 ± 6.59	0.355	-20.610 – 42.109
	Time point 2	37.82 ± 12.29	17.83 ± 6.35	0.088	-5.550 – 45.528
	Time point 3	40.00 ± 11.77	26.33 ± 7.18	0.194	-12.408 – 39.746

Values are expressed as Mean ± SD. An independent Student's t-test was used. CI = 95% confidence interval of the mean difference. Statistical significance was set at $p < 0.05$.

3.3 Effect of the polyherbal formulation on the study biomarkers throughout the sampling time points

Repeated-measures analysis revealed significant temporal changes in all evaluated biomarkers (Table 3). Inflammatory markers demonstrated marked reductions over time. hsCRP concentrations declined significantly from 5.62 mg/L at baseline to 2.97 mg/L at end point (with a mean reduction of 2.65 mg/L, $p < 0.001$). Similarly, CRP levels decreased from 20.26 mg/L to 7.32 mg/L, corresponding to a mean reduction of 12.94 mg/L ($p < 0.001$). A substantial decline was also observed in IL-6 concentrations (pg/mL), which decreased from 153.27 pg/mL at baseline to 20.91 pg/mL at the endpoint, representing a mean reduction of 132.36 pg/mL ($p < 0.001$). In contrast, antioxidant biomarkers showed significant increases. GSH concentrations and SOD activity increased from 2.52 µmol and 81.56 U/mL to 5.36 µmol/L and 112.45 U/mL, reflecting a mean increase of 2.84 µmol/L ($p < 0.001$) and 30.88 U/mL, respectively, indicating enhanced

antioxidant defense capacity. Reproductive hormone levels also improved significantly during the treatment period. Testosterone concentrations increased from 1.73 nmol/L at baseline to 3.73 nmol/L at the endpoint ($p < 0.001$), while luteinizing hormone increased from 24.64 IU/L to 33.26 IU/L ($p < 0.001$). Collectively these results demonstrate significant reductions in systemic inflammation accompanied by improvements in antioxidant status and reproductive endocrine function over the treatment period.

Table 3: Changes in inflammatory, oxidative stress and reproductive biomarkers across the treatment period.

	T1 Time point 1 (I)	T2 Time point 2 (midpoint)	T3 Time point 3 (J) end point	Mean Difference (I-J)	p-value	95% Confidence Interval for Difference (LB – UB)
hsCRP (mg/L)	5.62	4.40	2.97	2.65	<0.001	1.917 – 3.377
CRP (mg/L)	20.26	13.09	7.32	12.94	<0.001	6.329 – 19.542
IL-6 (pg/mL)	153.27	72.83	20.91	132.36	<0.001	89.882 – 174.840
GSH (µmol/L)	2.52	4.04	5.36	-2.84	<0.001	-3.212 - -2.469
SOD (U/mL)	81.56	97.20	112.45	-30.88	<0.001	-36.818 - -24.951
Testosterone (nmol/L)	1.73	2.66	3.73	-1.99	<0.001	-2.586 - -1.414
LH (IU/L)	24.64	27.68	33.26	-8.62	<0.001	-13.136 - -4.106

Values are presented as Mean. Time 1 = Baseline, Time 2 = Midpoint, Time 3 = Endpoint. Repeated measure ANOVA with Pairwise comparisons based on estimated marginal means with Bonferroni adjustment for multiple testing. Significance set at $p < 0.05$.

3.4 Within subject biomarker changes

Repeated-measure ANOVA revealed statistically significant within-subject changes for all evaluated biomarkers during the treatment period (Table 4). Inflammatory markers showed strong reductions across time. hsCRP decreased significantly ($F = 54.86$, $p < 0.001$, $\eta^2_p = 0.611$), indicating a large treatment effect. Similarly, CRP levels declined significantly ($F = 21.68$, $p < 0.001$, $\eta^2_p = 0.383$). For IL-6, a significant reduction was also observed ($F = 56.82$, $p < 0.001$, $\eta^2_p = 0.619$), suggesting anti-inflammatory response. Antioxidant biomarkers exhibited even larger effect sizes. GSH concentration increased significantly ($F = 141.69$, $p < 0.001$, $\eta^2_p = 0.802$). Reproductive hormones demonstrated similar improvements. Testosterone levels increased significantly ($F = 66.35$, $p < 0.001$, $\eta^2_p = 0.816$), and luteinizing hormone also increased significantly ($F = 16.74$, $p < 0.001$). These findings indicate strong within-subject treatment effects across inflammatory, oxidative stress and reproductive biomarkers.

Table 4: Within-subject changes in biomarkers during treatment

Biomarker	Sum of Squares (SS)	dF	Mean Square (MS)	F	p	n^2_P	Mauchly`s (W)
hsCRP (mg/L)	126.39	2	63.19	54.86	<0.001	0.611	0.104
CRP (mg/L)	3023.83	1.24	2438.53	21.68	<0.001	0.383	<0.001
IL-6 (pg/mL)	320229.46	2	270110.58	56.82	<0.001	0.619	<0.001
GSH (µmol/L)	145.47	2	72.73	229.69	<0.001	0.868	0.185
SOD (U/mL)	17170.23	1.33	12900.21	141.69	<0.001	0.802	<0.001
Testosterone (nmol/L)	31.98	2	15.99	66.35	<0.001	0.816	0.069
LH (IU/L)	611.68	2	305.84	16.74	<0.001	0.815	0.008

RM-ANOVA used to assess within-subject changes across time. η^2_p = partial eta squared (effect size). Mauchly's W indicates sphericity testing. Statistical significance set at $p < 0.05$.

3.5 Analysis of "*InsulineVégétale*" treatment's effects on monitored biomarkers over time in presence of conventional therapy

Linear mixed model analysis demonstrated a significant effect of "*InsulineVégétale*" across time for all evaluated biomarkers. Significant treatment effects were observed for hsCRP ($F = 49.97$, $p < 0.001$), CRP ($F = 160.04$, $p < 0.002$), IL-6 ($F = 30.65$, $p < 0.001$), GSH ($F = 251.12$, $p < 0.001$), SOD ($F = 39.92$, $p < 0.001$), testosterone ($F = 57.48$, $p < 0.001$), and LH ($F = 35.23$, $P < 0.001$). Notably, most conventional antidiabetic medications including glibenclamide, insulin, and combination therapies did not demonstrate statistically significant independent effects on the studied biomarkers. However, metformin showed a modest but significant effect on CRP concentrations ($p = 0.017$). These findings suggest that the improvements in inflammatory, oxidative stress, and reproductive biomarkers were primarily associated with the herbal intervention rather than conventional antidiabetic therapies (Table **5**).

Table 5: Independent effect of *"Insulinevégétale"* from concomitant medications during the treatment period.

Biomarker	Source	Numerator df	Denominator df	F	P value
hsCRP	Intercept	1	27.94	22.93	0.000
	InsulineVégétale only	2	38.81	49.97	0.000
	InsulineVégétale + Glibenclamide	1	27.81	0.01	0.937
	InsulineVégétale + Insulin	1	27.81	0.07	0.798
	InsulineVégétale + Insulin + metformin	1	27.81	0.05	0.826
	InsulineVégétale + Metformin	1	27.81	0.63	0.434
	InsulineVégétale + Metformin + glibenclamide	1	27.81	1.20	0.283
CRP	Intercept	1	10.33	186.54	0.000
	InsulineVégétale	1	10.92	160.04	0.002
	Glibenclamide	1	2.00	1.46	0.350
	Insulin	1	3.00	2.25	0.230
	Insulin + metformin	1	3.00	2.48	0.213
	Metformin	1	20.00	6.83	0.017
	Metformin + glibenclamide	1	1.00	0.41	0.637
IL-6	Intercept	1	26.92	0.00	0.996
	InsulineVégétale	2	68.00	30.65	0.000
	Glibenclamide	1	3.89	0.61	0.480
	Insulin	1	4.73	0.10	0.767
	Insulin + metformin	1	4.99	0.14	0.725
	Metformin	1	3.46	0.24	0.651
	Metformin + glibenclamide	1	2.00	0.60	0.520
GSH	Intercept	1	1.57	120.49	0.018
	InsulineVégétale	2	44.83	251.12	0.000
	Glibenclamide	1	3.78	10.10	0.357
	Insulin	1	4.43	0.22	0.658
	Insulin + metformin	1	4.52	10.01	0.365
	Metformin	1	2.75	2.24	0.239
	Metformin + glibenclamide	1	1.56	5.24	0.184
SOD	Intercept	1	28.10	0.00	0.990

	InsulineVégétale	2	68.00	39.92	0.000
	Glibenclamide	1	2.86	1.70	0.288
	Insulin	1	3.32	0.004	0.954
	Insulin + metformin	1	3.54	0.64	0.474
	Metformin	1	11.50	1.30	0.277
	Metformin + glibenclamide	1	1.07	0.01	0.951
Testosterone	Intercept	1	20.01	0.00	0.088
	InsulineVégétale	2	26.85	57.48	<0.001
	Glibenclamide	1	2.87	1.69	0.113
	Insulin	1	2.31	0.00	0.843
	Insulin + metformin	1	2.43	0.53	0.364
	Metformin	1	9.41	0.99	0.166
	Metformin + glibenclamide	1	1.01	0.10	0.851
Luteinizing hormone	Intercept	1	28.10	0.00	0.980
	InsulineVégétale	2	5.01	35.23	<0.001
	Glibenclamide	1	2.87	1.69	0.311
	Insulin	1	2.31	0.01	0.843
	Insulin + metformin	1	2.43	0.53	0.264
	Metformin	1	8.41	0.80	0.168
	Metformin + glibenclamide	1	1.01	0.10	0.851

Linear mixed model (LMM) estimated using Restricted Maximum Likelihood (REML). Fixed effects included treatment time and co-administered conventional antidiabetic therapies (glibenclamide, insulin, insulin + metformin, metformin, and metformin + glibenclamide). A random intercept was specified for patient ID to account for repeated measures. Degrees of freedom were estimated using the Satterthwaite approximation method. Statistical significance was set at $p < 0.05$.

3.6 Friedmans test

The Friedman test confirmed significant temporal changes for all evaluated biomarkers. Significant time-dependent reductions were observed for hsCRP (χ^2 = 43.57, $p < 0.001$), CRP (χ^2 = 42.01, $p < 0.001$), and IL-6 (χ^2 = 68.06, $p < 0.001$). Conversely, antioxidant biomarkers increased significantly, including GSH (χ^2 = 66.50, $p < 0.001$) and SOD (χ^2 = 70.06, $p < 0.001$). Reproductive hormones also showed significant improvements, including testosterone (χ^2 = 32.00, $p < 0.001$) and luteinizing hormone (χ^2 = 19.50, $p < 0.001$). These non-parametric results corroborate the findings obtained from parametric analyses, indicating that the observed changes are statistically robust (Table **6**).

Table 6: Friedman test evaluating non-parametric changes in biomarkers across times.

	N	$\Delta T3 - T1$ (%)	X^2	DF	P value	Monte Carlo	CI 95% LB-UB
hsCRP (mg/L)	36	-2.647 (-0.02647)	43.57	2	<0.001	0.001	0.000 – 0.000
CRP (mg/L)	36	-12.935 (-0.12935)	42.01	2	<0.001	0.001	0.000 – 0.000
IL-6 (pg/mL)	36	-132.36 (-1.3236)	68.06	2	<0.001	0.001	0.000 – 0.000
GSH (µmol/L)	36	2.840 (0.02840)	66.50	2	<0.001	0.001	0.000 – 0.000
SOD (U/mL)	36	-30.884 (-0.3088)	70.06	2	<0.001	0.001	0.000 – 0.000
Testosterone (nmol/L)	16	2 (0.02)	32.00	2	<0.001	0.001	0.000 – 0.000
LH (IU/L)	16	8.62 (0.0862)	19.50	2	<0.001	0.001	0.000 – 0.000

Friedman test used for non-parametric repeated measures analysis. Monte Carlo simulation applied for p-value estimation. Significance threshold $p < 0.05$.

3.7 Associations between biomarkers and demographic variables

Age demonstrated positive correlations with inflammatory markers, including IL-6 at baseline (r = 0.428, p = 0.009) and IL-6 at the midpoint (r = 0.350, p = 0.037), indicating increasing systemic inflammation with advancing age. Body mass index (BMI, kg/m^2) showed strong positive correlations with CRP levels at baseline (r = 0.531, p = 0.001), midpoint (r = 0.525, p = 0.001), and endpoint (r = 0.398, p = 0.016), suggesting that higher adiposity is associated with increased systemic inflammation. BMI also demonstrated a negative correlation with testosterone levels at the midpoint (r = −0.577, p = 0.019), indicating a potential link between obesity and reduced androgen levels. Additionally, a significant positive correlation was observed between GSH at the endpoint and SOD at the midpoint (r = 0.614, p < 0.001), reflecting coordinated antioxidant responses (Table **7**).

Table 7: Associations between biomarkers and demographic characteristics.

Parameters	r	p
Age - CRP_T2	0.339	0.043
Age - HIL6_T0	0.428	0.009
Age - HIL6_T1	0.350	0.037
BMI - CRP_T0	0.531	0.001
BMI - CRP_T1	0.525	0.001
BMI - CRP_T2	0.398	0.016
BMI - Testo_T1	-0.577	0.019
hs_CRP_T0 - HIL6_T0	0.351	0.036
GSH_T2 - SOD_T1	0.614	0.000
SOD_T3 - Testo_T0	-0.511	0.043
SOD_T3 - Testo_T2	-0.540	0.031

Pearson correlation coefficient (r) used to evaluate relationships. Statistical significance set at p < 0.05.

4. Discussion

The present study evaluated the effects of the polyherbal preparation *"Insulinevégétale"* on key pathophysiological components of diabetes mellitus, including oxidative stress, inflammatory status, and reproductive hormonal function. Specifically, the study assessed changes in inflammatory biomarkers, antioxidant defense parameters, and male reproductive hormones over the course of treatment. Through this integrated approach, the investigation aimed to explore the potential of this formulation to modulate metabolic, inflammatory, and endocrine disturbances associated with diabetes. Persistent hyperglycaemia promotes several biochemical pathways that increase the production of reactive oxygen species (ROS), including activation of the polyol pathway, increased formation of advanced glycation end products (AGEs), protein kinase C activation, and increased flux through the hexosamine pathway. These metabolic disturbances ultimately trigger inflammatory signaling cascades and cellular oxidative damage [15, 16]. Diabetes mellitus is increasingly recognized as a complex metabolic disorder characterized not only by chronic hyperglycemia but also by persistent oxidative stress and systemic inflammation that contributes to the progression of metabolic and vascular complications. In the present study, significant reductions in inflammatory biomarkers including hsCRP, CRP, and IL-6 were observed during treatment with the polyherbal formulation "*Insulinevégétale*". Elevated glucose concentrations stimulate mitochondrial overproduction of reactive oxygen species (ROS), which activate nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of numerous pro-inflammatory cytokines including IL-6 and tumor necrosis factor-α [17, 18]. Activation of NF-κB subsequently stimulates hepatic synthesis of acute-phase proteins such as CRP, explaining the elevated CRP concentrations frequently observed in diabetic individuals [19]. The significant reduction in IL-6 observed in the present study is particularly noteworthy because IL-6 plays a central role in metabolic inflammation and insulin resistance. IL-6 promotes hepatic gluconeogenesis and interferes with insulin signaling through activation of suppressor of cytokine signaling (SOCS) proteins, which inhibit insulin receptor substrate phosphorylation [20]. Therefore, the reduction in IL-6 levels from 153.27 pg/mL at baseline to 20.91 pg/mL at the endpoint suggests that the herbal intervention may attenuate inflammatory signaling pathways associated with metabolic dysfunction. Concomitant with the reduction in inflammatory markers, substantial improvements in antioxidant biomarkers were observed. Reduced glutathione levels increased from 2.52 µmol/L to 5.36 µmol/L, while SOD activity increased significantly during treatment. Glutathione is the most abundant intracellular antioxidant and plays a critical role in maintaining cellular redox homeostasis by directly scavenging reactive oxygen species and serving as a cofactor for glutathione peroxidase in detoxification reactions [21]. Impaired glutathione metabolism has been widely reported in diabetes due to increased oxidative burden and reduced synthesis capacity [22]. The increase in glutathione observed in this study may therefore reflect restoration of antioxidant defense mechanisms, possibly mediated by bioactive phytochemicals present in the herbal formulation. Polyphenolic compounds present in medicinal plants are known to exert strong antioxidant and anti-inflammatory activities. These compounds can directly neutralize free radicals, chelate metal ions, and modulate cellular signaling pathways involved in oxidative stress and inflammation [23]. In addition, several plant-derived compounds inhibit NF-κB activation and reduce expression of pro-inflammatory cytokines [24]. Therefore, the observed reductions in IL-6 and CRP may partly reflect the anti-inflammatory effects of phytochemical constituents present in the polyherbal preparation.

Another important finding of the present study is the significant improvement in reproductive endocrine markers. Testosterone levels increased from baseline to endpoint, accompanied by an increase in luteinizing hormone levels. Diabetes mellitus has been strongly associated with hypogonadism and reduced testosterone levels in men. Several mechanisms contribute to this condition, including oxidative stress-induced damage to testicular Leydig cells, impaired steroidogenic enzyme activity, and disruption of hypothalamic–pituitary signaling [25, 26]. Excessive ROS can damage mitochondrial membranes within Leydig cells, thereby impairing cholesterol transport and testosterone biosynthesis. In addition, inflammatory cytokines such as IL-6 may inhibit gonadotropin secretion, further contributing to reduced androgen production [27]. The improvement in testosterone and LH levels observed in the present study suggests that the reduction in systemic inflammation and oxidative stress may have restored normal hypothalamic–pituitary–gonadal axis function. Restoration of antioxidant defenses may protect Leydig cells from oxidative damage, thereby improving steroidogenic activity. Furthermore, the reduction in inflammatory cytokines may relieve inhibitory effects on gonadotropin secretion, resulting in increased LH stimulation of testicular testosterone production [28]. Correlation analysis further supports the link between metabolic factors and inflammatory processes. The positive association between BMI and CRP levels observed in this study is consistent with current understanding of obesity-associated inflammation. Adipose tissue functions as an active endocrine organ that secretes adipokines and pro-inflammatory cytokines, including IL-6, which contribute to chronic low-grade inflammation and insulin resistance [29]. Similarly, the positive correlation between age and IL-6 reflects the phenomenon of age-related chronic inflammation, often referred to as "inflammaging," which arises from cumulative oxidative damage and mitochondrial dysfunction [30]. Taken together, the findings of this study suggest that the polyherbal formulation "*Insulinevégétale"* may exert beneficial effects through multiple biochemical mechanisms, including suppression of inflammatory signaling pathways, enhancement of endogenous antioxidant defenses, and restoration of endocrine homeostasis. These combined effects may contribute to improved metabolic and reproductive outcomes in individuals with diabetes mellitus.

Though the present findings are noticeable, several limitations should be acknowledged. First, the study lacked a non-diabetic control group, which limits the ability to determine whether biomarker values returned to normal physiological ranges. Secondly, the specific phytochemical composition and active constituents of the polyherbal formulation were not characterized, though the constituents of individual plants of "*Insulinevégétale"* are well defined from literatures. Thirdly, the relatively modest sample size may reduce statistical power for subgroup analyses. Additionally, reproductive outcomes were assessed only through hormonal measurements without direct evaluation of semen parameters or fertility outcomes. Future studies should incorporate larger randomized controlled trials, detailed phytochemical profiling, and comprehensive reproductive assessments.

Conclusions

The present study demonstrates that medicinal plant therapy with the polyherbal formulation "*Insulinevégétale"* is associated with significant improvements in inflammatory, oxidative stress, and reproductive endocrine biomarkers in individuals with diabetes mellitus. Treatment resulted in substantial reductions in systemic inflammatory markers including hsCRP, CRP, and IL-6, accompanied by marked increases in antioxidant defenses reflected by elevated glutathione levels and SOD activity. Furthermore, improvements in testosterone and luteinizing hormone concentrations suggest potential restoration of hypothalamic–pituitary–gonadal axis function. These findings indicate that modulation of oxidative stress and inflammatory pathways may represent an important mechanism through which "*Insulinwvégétale"* exerts beneficial metabolic and endocrine effects in diabetic patients. Further controlled clinical studies are required to confirm these findings while additional attention should be given to molecular mechanisms underlying the therapeutic actions of this formulation.

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