*ejpmr, 2020,7(3), 304-313*

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

# RANDOMIZED DOUBLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL TO ASSESS THE SAFETY AND EFFICACY OF NRL/LP/201901 CAPSULES AS ADJUVANT THERAPY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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**Article Received on 24/12/2019** **Article Revised on 14/01/2020** **Article Accepted on 04/02/2020**

## ABSTRACT

**Background:** Diabetes is swiftly gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. Herbal supplements target the different pathological events from different mechanistic approaches, to manage glucose homeostasis and to improve the quality of life of the patient. **Aim:** The aim of the study was to evaluate the efficacy and safety of NRL/LP/201901 capsules in type 2 diabetic patients. **Materials and Methods:** A randomized double blind, placebo controlled, comparative, interventional, multi-centric, prospective clinical Study was conducted. Subjects were advised to take a dose of 1 capsule orally after evening/night meal with water for 90 days. Following parameters were assessed during study- Fasting Plasma Glucose (FPG), 2-hr Post-Meal Glucose (PMG), Haemoglobin A1c (HbA1c), Fasting Insulin (FI) and 2-hr Post-Meal Insulin (PMI), b-cell functions by [HOMA]-b, insulin resistance (IR) by HOMA-IR, anthropometric measurements from baseline to end of visit. **Results:** 100 subjects completed the study. It was evident that NRL/LP/201901 capsules significantly reduced fasting and post meal glucose levels along with HbA1c, there was significant reduction in insulin resistance evident by HOMA IR score. The quality of life in patients was improved in NRL/LP/201901 capsule treated group. It also improved lipid profile and anthropometric parameters which may be helpful in preventing CVS complications in diabetes mellitus. C - reactive protein (CRP) levels were significantly reduced after treatment of test drug. **Conclusion:** Thus "NRL/LP/201901" capsule is safe and effective medicine as an adjuvant for the treatment of Diabetes type 2.

**KEYWORDS:** Diabetes mellitus type2, HbA1c, Fasting insulin, herbal, CRP.

## INTRODUCTION

Diabetes is swiftly gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. According to Wild et al. the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease. India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country. Many influences affect the prevalence of disease throughout a country, and identification of those factors is necessary to facilitate change when facing health challenges.

The etiology of diabetes in India is multifactorial and includes genetic factors coupled with environmental influences such as obesity associated with rising living standards, steady urban migration, and lifestyle changes.[1]

The consequence of uncontrolled diabetes results in hyperglycemia or elevated blood sugar which after certain time leads to severe damage to numerous body organs, particularly the nerves and blood vessels. The published data reveals the prevalence of diabetes in 2014, 8.5% of adults aged 18 years and older while, in 2016, 1.6 million deaths were reported due to diabetes. The International Diabetes Federation in 2017 estimated

that 425 million people worldwide aged 18–99 years have diabetes mellitus with this number projected to increase to 693 million by 2045.[2]

The extensive study reported for diabetes revealed that diabetes is classified into five clusters based on its etiology and clinical management, amongst which three of them were found to be severe and two being mild. Cluster 1: severe autoimmune diabetes, characterized by insulin deficiency and the presence of autoantibodies. Cluster 2: severe insulin-deficient diabetes, which is characterized by adult age, insulin insufficiency, and deprived metabolic regulation. Cluster 3: severe insulin-resistant diabetes, which is characterized by severe insulin resistance and a considerably greater risk of kidney disease. Cluster 4: mild obesity-related diabetes, mostly diagnosed in 18–23% of obese subjects. Cluster 5: mild age-related diabetes, about 39–47% of elderly subjects is identified to have this type of diabetes.

Factors such as aging, obesity, physical inactivity, population growth and urbanization can gradually leads to steady increase in the number of patients with diabetes. In year 2000, prevalence of diabetes worldwide among adults is estimated to be approximately 171 million, whereas the number has been increased to 422 million (approximately 1 in every 11 people) in 2014. The prevalence of diabetes in the world is expected to be doubled to approximately 366 million in year 2030 due to demographic changes and most importantly, adaptation of sedentary life style by the people in the urban areas of the world.[3-5]

If this disease left untreated it can lead to acute fatal complications including diabetic ketoacidosis and coma due to exceptional increase in blood glucose. Additional dreadful consequences of diabetes include vascular complications due to damage of the vessels for high glucose level, may result in macrovascular and microvascular disorders. Consequences of microvascular complications are retinopathy, neuropathy, etc., whereas, macrovascular complications lead to cardiovascular complications. Other complications for chronic diabetic conditions include dementia, sexual dysfunction, depression and lower-limb amputations.[6-8]

Different categories of antidiabetic medications are there in the market for the remedial action, which includes insulin analogues, sulphonylureas, biguanides, dipeptidyl peptidase-4 inhibitors, thiazolidiones, α-glucosidase inhibitors, etc, where the mechanism of counteracting this increased glucose level is different for different categories.

However, long term treatment and side effect of the available hypoglycemic medications leading towards huge demand for efficacious agents working in diversified ways to avoid diabetic complications reducing side effects in the management of diabetic condition.[9-10]

The use of plants is one of the ancient traditions, being imposed to current society in the urge to evaluate the mechanism of their underlying pharmacological action and their associated benefits and adverse effects. Use of herbal medicines is still continued in modern society for the prevention, wellbeing and treatment of diabetes.

It has been observed that activity provided by herbs in multiple mechanisms will effectively control disease progression and improve quality of life of patients. To obtain multimodal activities in control of diabetes, certain purposeful mixtures of herb have been comprehensively evaluated for their effective uses in patients with diabetes. Such polyherbals are usually targeting the different pathological events throughout instigation and development of diabetes from different mechanistic approaches, to abolish the symptoms to improve the quality of life of the patient.

Many herbs have shown to have antidiabetic activity by regulating insulin secretion, insulin sensitivity to the cells, glucose abruption, etc. in order to improve the glycemic control of the patients. Addition to the glycemic control, some of the herbs depicted effectiveness in the control of cardiovascular complications by reducing TG, cholesterol levels, and BMI.

The general goal of management of diabetes and diabetes risk factors through adjuvant therapy with polyherbal formulation is to avoid acute decompensation, prevent or delay the appearance of late disease complications, decrease mortality, and maintain a good quality of life.

However, the aim of the study is to assess and analyze the herbal formulation in type 2 diabetes to validate the safety and efficacy of the herbal formulations.

## ETHICS

The study was registered with clinical study registry of India. Subjects were recruited prospectively in the study only after registration of clinical study on CTRI website. The CTRI registration number for the trial was CTRI/2019/05/019027 [Registered on: 09/05/2019].

## MATERIAL AND METHODS

### Product description

NRL/LP/201901 capsules, a polyherbal product manufactured by Netsurf Research Lab Pvt. Ltd. constitutes of various herbal extracts as mentioned in Table 1, hypothetized to be beneficial in the management of diabetes and related conditions.

**Table 1: Description of test product.**

| Sr. No. | Name of the Ingredient | Scientific Name | Type of Ingredient |
|---|---|---|---|
| 1. | Mamejao | *Enicostema litorale* | Dry Extract |
| 2. | Methi | *Trigonella foenum-graecum* | Dry Extract |
| 3. | Jamun | *Syzygium cumini* | Dry Extract |
| 4. | Karela | *Momordica charantia* | Dry Extract |
| 5. | Amla | *Emblica officinalis* | Dry Extract |
| 6. | Vijaysar | *Pterocarpus marsupium* | Dry Extract |
| 7. | Kutki | *Picrorrhiza kurroa* | Dry Extract |
| 8. | Shunthi | *Zingiber officinale* | Dry Extract |
| 9. | Neem | *Azadiracta indica* | Dry Extract |
| 10. | Gorakhchinch | *Garcinia combojia* | Dry Extract |
| 11. | Chiraita | *Swertia chirata* | Dry Extract |
| 12. | Gudmar | *Gymnema sylvestre* | Dry Extract |
| 13. | Chromium Picolinate | - | – |

**Study Design**

A Randomized, Double Blind, Placebo Controlled, Comparative, Interventional, Multi-centric, Prospective, Clinical Study was conducted.

**Recruitment Plan**

A sum total of 100 subjects (50 in each group) at the end of the study, additional subjects were recruited to complete the required number (100) of completed subjects for analysis. Subjects providing written informed consent and who are ready to provide regular follow ups till the completion of the study and meeting the inclusion and exclusion criteria were recruited in the study.

**Subject Inclusion Criteria**

Subjects having ages between 30-60 (both inclusive) both sex and receiving Oral Hypoglycemic Agents as on-going treatment for Type 2 Diabetes Mellitus were included in the study. Subjects with Hemoglobin A1c (HbA1c) >6.5% and <10% (both inclusive) and having Fasting Plasma Glucose (FPG) >130 mg/dL and < 250 mg/dL (both inclusive) were enrolled for the study.

**Subject Exclusion Criteria**

Subjects having Type 1 diabetes or undertaking Insulin treatment or having concurrent serious hepatic dysfunction (defined as AST and/or ALT >3 times of the upper normal limit) or renal dysfunction (defined as S. creatinine >1.4 mg/dl), uncontrolled pulmonary dysfunction (asthmatic and COPD patients) or other concurrent severe disease were not included in the study. Subjects who were pregnant or lactating or smoking or consuming alcoholics and/or drug abusers were also excluded. Subjects having evidence of malignancy or suffering from major systemic illness necessitating long term drug treatment (Rheumatoid arthritis, Psycho-Neuro- Endocrinal disorders, etc.) or renal dysfunction as evidenced by raised serum creatinine from renal function test were not included in the study. Subject with past history of serious arrhythmia or atrioventricular block meeting any of the below criteria were excluded from the study- uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg) and unwillingness to undergo therapy.

**Study Objectives**

The primary objective of the study was to evaluate efficacy of NRL/LP/201901 in comparison to placebo in patients suffering from Type 2 Diabetes mellitus by assessing their change in Fasting Plasma Glucose (FPG), 2-hr Post-Meal Glucose (PMG), Haemoglobin A1c (HbA1c), Fasting Insulin (FI) and 2-hr Post-Meal Insulin (PMI).

The secondary objective of the study was to evaluate efficacy of NRL/LP/201901 in comparison to placebo in patients suffering from Type 2 Diabetes mellitus by assessing changes of the β-cell functions (homeostasis model assessment [HOMA]-b, insulin resistance (IR) by HOMA-IR, change in anthropometric measurements, change in levels of inflammatory marker like C-peptide and subjective assessment in each follow up such as week 0, 4, 8 and 12, regarding improvement of the clinical symptoms and quality of life associated with type 2 Diabetes Mellitus. Assessment of the tolerability, safety of NRL/LP/201901 in patients with Type 2 Diabetes Mellitus with respect to renal, liver and lipid function test and adverse event profiling for was performed.

**Dosage and Treatment Duration**

As per computer generated randomization list, subjects were randomized to either drug group or placebo group in 1:1 ratio. Subjects were advised to take given medication in a dose of 1 capsule orally after evening/night meal with water for 90 days.

**Study Visits/ Follow Ups**

Screening Visit (Up to Day- 7), Baseline Visit (Day 0), Visit 1 (Day 30), Visit 2 (Day 60), Visit 3 (Day 90). Subjects were allowed to come for follow up either 5 days prior or after the scheduled follow up visit, provided subject should continue the given treatment. A screening window of up to 7 days was kept, in case if there is delay in availability of tests reports or in case few tests need to be repeated.

**Study Procedures**

Written informed consent was obtained from the interested subjects prior to screening for possible inclusion in the study at OPD departments of both the study centres i.e. Lokmnmaya Medical Research Centre, Chinchwad, Pune; and Dr. D. Y. Patil College of Ayurveda & Research Centre, Pimpri, Pune. During Informed consent process, they were given enough time to read ICD (Informed Consent Document) which was printed in the languages best understood by them. Subjects were given freedom to ask the questions and all questions were answered by the Investigator or by other study staff. He/she agreed to participate in the study, a written informed consent for the same were obtained from him/her.

Pre diagnosed patient with Type 2 Diabetes mellitus went physical and systemic examinations. Subject's medical and surgical history was taken. Subject's current medications if any were noted in the CRF. Subjects were evaluated for current symptoms and quality of life questionnaire. If subject was not presenting any of the parameters listed in exclusion criteria, then was called next day morning on empty stomach for laboratory investigations. Diagnosis of Type 2 Diabetes mellitus was confirmed using laboratory parameters like fasting and post meal plasma glucose levels.

Subject's biochemical investigations were performed. UPT for the fertile females were carried out. The fertile females presenting negative results on UPT were only selected for the study. Subject's ECG (to rule out arrhythmia and recent ischemia) were performed. Only subjects with clinically non-significant or normal ECG readings were enrolled in the study. Subjects were advised to continue with current medication for Type 2 diabetes mellitus. Subjects were advised to refrain from any Nutraceuticals, Ayurvedic, homeopathic, Siddha, Unani etc. Subject was screened for anthropometric measurements.

On baseline visit, as per computer generated randomization list, subjects were randomized either to drug group or placebo group in 1:1 ratio. Subjects went for general and systemic examinations.

Subjects were advised not to consume alcohol, caffeine, and nicotine during the study period. As per computer generated randomization list, subject received either NRL/LP/201901 or placebo. All the subjects were closely monitored for any Adverse Events. If subject had AE/SAE, the details of the incidence were documented in the source document and CRF. SAE, if any, reported to the IEC in a SAE reporting form. Rescue medication and concomitant medication used, if any, were recorded in the CRF. On every follow up visit, as per computer generated randomization list, subject received either NRL/LP/201901 or placebo. On every follow up visit, blood samples of subjects for BSL-F and post meal were collected. Anthropometric measurements and quality of life data were recorded.

The containers provided to the subject on the previous visit were collected and remaining drug were counted to check missed dosage. Subjects who continuously missed dosing for >3 consecutive days or total missed dose >6 days during the study period were treated as drop outs. Subjects were called to follow up on day 30, 60 and 90.

On day 90, subject's global evaluation for overall improvement and Investigator's global evaluation for overall improvement were done. Subject's biochemical investigations and UPT were performed. Subject's data like anthropometric measurements, symptom grades, vitals were recorded. The container provided to the subject on the previous visit was collected and remaining drug was counted to check missed dosage. Subjects who continuously misses dosing for >3 consecutive days or total missed dose >6 days during the study period were treated as drop outs.

**Study Assessment**

***Assessment of efficacy***

To evaluate efficacy of NRL/LP/201901 in comparison to placebo in patients suffering from Type 2 Diabetes mellitus by following parameters were assessed change from baseline in Fasting Plasma Glucose (FPG), 2-hr Post-Meal Glucose (PMG), Haemoglobin A1c (HbA1c), Fasting Insulin (FI) and 2-hr Post-Meal Insulin (PMI) upto Week 12. Changes of the β-cell functions (homeostasis model assessment [HOMA]-b, insulin resistance (IR) by HOMA-IR, change in anthropometric measurements from baseline to end of visit, change in levels of inflammatory marker like C-peptide were checked. The subjective assessment in each follow up i.e. week 0, 4, 8 and 12, regarding improvement of the clinical symptoms and quality of life associated with type 2 Diabetes Mellitus was performed. The tolerability and safety of NRL/LP/201901 in patients with Type 2 Diabetes Mellitus was determined. The changes from Baseline in biochemical profile like renal, liver and lipid profile and urine parameters to Week 12 were determined. Assessment of Physician's and Subject's Clinical Global evaluation for overall efficacy was noted.

***Assessment of Safety***

Safety was assessed by clinical review of all safety parameters, including the following:

a. Adverse event reporting, as applicable
b. Vital signs (Pulse, Respiratory rate, Temperature, BP).
c. Assessment of Overall Safety and Tolerability of the product by the physician and subject on global assessment scale by the investigator and by subject. The criterion for the global assessment of overall safety is as follows:

**1 = Excellent Overall safety** (No adverse event/s reported)

**2 = Good Overall safety** (Mild adverse events (s) reported which subside with or without medication)
**3 = Fair Overall safety** (Moderate to severe adverse event(s) reported which subside with or without medication and do not necessitate stoppage of study treatment)
**4 = Poor Overall safety** (Severe or serious adverse event(s) which necessitate stoppage of study)

## STATISTICS

Sample size calculation was derived taking considerations of primary and secondary outcomes by a qualified statistician. The software used for calculation of sample size was SPSS version 10.0.

Based on the assumption of changes in primary outcomes from placebo at 80% power and 5% level of significance total 100 completer subjects were required in the study. Primary Efficacy end points and secondary end points were analyzed using per protocol analysis using ANOVA, Student 't' test and Chi-square tests whatever applicable as per nature of data.

### Adherence to Compliance

Patients without any major protocol violation were included in the per protocol population, including those patients who have treatment compliance, who did not take any prohibited medications during the study period and whose CRF were complete as required as per compliance.

## RESULTS

### Demographic details

In the present study, 103 subjects were screened. Out of 103 subjects, 3 lost to follow up in the study. 100 subjects were considered evaluable cases at the end of the study 50 in test and 50 in placebo treated group.

Out of 100 completed subjects, the mean age of male subjects were 46.72± 10.41 years and the mean age of female subjects was 48.34 ± 9.98 years. The Table 2 shows the details.

**Table 2: Demographic details.**

| Age/ Sex | Male (64) | Female (36) |
|---|---|---|
| Mean Age (yrs.) | 46.72 | 48.34 |
| SD | 10.41 | 9.98 |

### Efficacy Assessments

(For representation of results, subjects receiving NRL/LP/201901were considered as test group and subjects receiving placebo were considered as placebo group).

**1. Comparison of changes in mean Fasting Plasma Glucose (FPG) between the groups**

At baseline, mean FPG was 190.21mg/dl among Test group which was comparable to 184.42mg/dl among Placebo group and the difference was not significant. After 30 days of treatment, mean FBG showed a significant decrease by 14.76% among Test group and 0.04% among Placebo group from baseline. After 60 days of treatment, mean FPG showed a significant decrease by 22.45% among Test group and 1.08% increase among Placebo group from baseline. At the end of 90 days of treatment, mean FPG showed a significant decrease by 33.82% among Test group and 3% increase among Placebo group from baseline. When compared, treatment with NRL/LP/201901 significantly reduced elevated FBG than Placebo group. Data as shown in Table 3.

**Table 3: Changes in mean Fasting Plasma Glucose (FPG) between the groups.**

| Duration (Days) | Mean FPG (mg/ dl) (mean ± SD) | |
|---|---|---|
| | Drug (N = 50) | Placebo (N = 50) |
| Baseline | 190.21 ±41.34 | 184.42 ±38.33 |
| 30 | 162.13 ± 34.13 * | 184.34 ± 35.37 |
| 60 | 147.5 ± 28.53 * | 186.42 ± 34.71 |
| 90 | 125.87 ± 14.11 * | 191.71 ± 31.86 |

*NS = Not Significant *Significant p<0.01 By ANOVA followed by Dunnet (Between Groups)*

**2. Comparison of changes in mean Post meal Plasma Glucose (PMG) between the groups**

At baseline, mean PMG was 265.05mg/dl among Test group which was comparable to 268.5mg/dl among Placebo group and the difference was not significant. After 30 days of treatment, mean PMG showed a significant decrease by 13% among Test group and 1.59% among Placebo group from baseline. After 60 days of treatment, mean PMG showed a significant decrease by 22.60% among Test group and 0.43% increase among Placebo group from baseline. At the end of 90 days of treatment, mean PMG showed a significant decrease by 35.31% among Test group and 5% decrease among Placebo group from baseline. If compared, treatment with NRL/LP/201901 significantly reduced elevated PMG than Placebo group. Data as shown in Table 4.

**Table 4: Changes in mean Post meal Plasma Glucose (PMG) between the groups.**

| Duration (Days) | Mean PMG (mg/ dl) (mean ± SD) | |
|---|---|---|
| | Drug (N = 50) | Placebo (N = 50) |
| Baseline | 265.05 ±58.06 | 268.5 ±61.84 |
| 30 | 230.74 ± 62.94* | 264.22 ± 56.44 |
| 60 | 205.16 ± 44.82* | 269.68 ± 49.02 |
| 90 | 171.45 ± 28.21* | 253.53 ± 45.38 |

*NS = Not Significant *Significant < 0.01By ANOVA followed by Dunnet (Between Groups)*

**3. Comparison of changes in mean % HbA1c between the groups**

At baseline, mean % HbA1c was 8.18% among Test group which was comparable to 8.68% among Placebo group and the difference was not significant. At the end of 90 days of treatment, mean % HbA1c showed a significant decrease by 25.18% among Test group and 7.6% decrease among Placebo group from baseline. If compared, treatment with NRL/LP/201901 significantly reduced elevated % HbA1c than Placebo group. Data as shown in Table 5.

**Table 5: Changes in mean % HbA1c between the groups.**

| Duration (Days) | Mean % HbA1c (mean ± SD) | |
|---|---|---|
| | Drug (N = 50) | Placebo (N = 50) |
| Baseline | 8.18± 1.10 | 8.68 ± 10.35 |
| 90 | 6.12 ±0.67 | 8.02 ± 1.10 |

*NS = Not Significant *Significant < 0.01 By ANOVA followed by Dunnet (Between Groups)*

**4. Comparison of changes in mean Fasting Insulin between the groups**

At baseline, Mean Fasting Insulin was 25.65mIU/L among Test group which was comparable to 25.69 mIU/L among Placebo group and the difference was not significant. At the end of 90 days of treatment, Mean Fasting Insulin showed a significant decrease by 43.86% among Test group and 3.73% increase among Placebo group from baseline. If compared, treatment with NRL/LP/201901 significantly reduced Mean Fasting Insulin than Placebo group. Data as shown in Table 6.

**Table 6: Changes in Mean Fasting Insulin between the groups.**

| Duration (Days) | Mean Fasting Insulin (mIU/L) (mean ± SD) | |
|---|---|---|
| | Drug (N = 50) | Placebo (N = 50) |
| Baseline | 25.65 ± 9.85 | 25.69 ± 9.70 |
| 90 | 14.4 ± 3.25* | 26.65 ± 9.25 |

*NS = Not Significant *Significant < 0.01 By ANOVA followed by Dunnet (Between Groups)*

**5. Comparison of changes in mean Post meal Insulin between the groups**

At baseline, Mean Post meal Insulin was 74.07 mIU/L among Test group which was comparable to 73.89 mIU/L among Placebo group and the difference was not significant. At the end of 90 days of treatment, Mean Post meal Insulin showed a significant decrease by 32.30% among Test group and 0.81% increase among Placebo group from baseline. If compared, treatment with NRL/LP/201901 significantly reduced Mean Post meal Insulin than Placebo group. Data as shown in Table 7.

**Table 7: Changes in Mean Post meal Insulin between the groups.**

| Duration (Days) | Mean Post meal Insulin (mIU/L) (mean ± SD) | |
|---|---|---|
| | Drug (N = 50) | Placebo (N = 50) |
| Baseline | 74.07± 9.92 | 73.89 ± 10.08 |
| 90 | 50.15 ± 8.12* | 74.49 ± 74.49 |

*NS = Not Significant *Significant < 0.01 By ANOVA followed by Dunnet (Between Groups)*

**6. Comparison of changes in mean C Reactive Protein levels (CRP) between the groups**

At baseline, Mean CRP was 3.92mg/L among Test group which was comparable to 3.39 mg/L among Placebo group and the difference was not significant. At the end of 90 days of treatment, Mean CRP showed a significant decrease by 36.73% among Test group and 7% decrease among Placebo group from baseline. If compared, treatment with NRL/LP/201901 significantly reduced Mean CRP than Placebo group. Data as shown in Table 8.

**Table 8: Changes in Mean CRP between the groups.**

| Duration (Days) | Mean CRP (mg/L) (mean ± SD) | |
|---|---|---|
| | Drug (N = 50) | Placebo (N = 50) |
| Baseline | 3.92±1.54 | 3.39 ± 2.10 |
| 90 | 2.48 ± 1.08* | 3.12± 2.43 |

*NS = Not Significant *Significant < 0.01 By ANOVA followed by Dunnet (Between Groups)*

**7. Comparison of changes in mean HOMA [b] score between the groups**

At baseline, mean HOMA [b] score was 0.0834 among Test group which was comparable to 0.0855 among Placebo group and the difference was not significant. At the end of 90 days of treatment, mean HOMA [b] score showed a non-significant decrease as 0.0765 among Test group and 0.0801 decreases among Placebo group from baseline. Data as shown in Table 9.

**Table 9: Changes in mean HOMA [b] score between the groups.**

| Duration (Days) | Mean HOMA [b] score (mean ± SD) | |
|---|---|---|
| | Drug (N = 50) | Placebo (N = 50) |
| Baseline | 0.0834 ±0.0563 | 0.0855 ± 0.0408 |
| 90 | 0.0765 ± 0.0236 NS | 0.0801 ± 0.0342 |

*NS = Not Significant *Significant < 0.01 By ANOVA followed by Dunnet (Between Groups)*

**8. Comparison of changes in mean HOMA-[IR] score between the groups**

At baseline, mean HOMA-[IR] score was 11.74 among Test group which was comparable to 11.73 among Placebo group and the difference was not significant. At the end of 90 days of treatment, mean HOMA-[IR] score showed a non-significant decrease by 67.80% among Test group and 6% increase among Placebo group from baseline. If compared, treatment with NRL/LP/201901 significantly reduced elevated Mean HOMA-[IR] score than Placebo group. Data as shown in Table 10.

**Table 10: Changes in mean HOMA- [IR] score between the groups.**

| Duration (Days) | Mean HOMA-[IR] score (mean ± SD) | |
|---|---|---|
| | Drug (N = 50) | Placebo (N = 50) |
| Baseline | 11.74 ± 4.40 | 11.73 ± 5.34 |
| 90 | 3.78 ± 1.11* | 12.03 ± 4.92 |

*NS = Not Significant *Significant < 0.01By ANOVA followed by Dunnet (Between Groups)*

**9. Comparison of changes in Assessment of improvement in Quality of Life based on QOLID Score between the groups**

At baseline, mean QOLID Score was 95.88 among Test group which was comparable to 96.57 among Placebo group and the difference was not significant. At day 60, mean QOLID Score was 128.71 i.e. 34.24% increased among Test group which was 83.08 i.e. 13% decreased among Placebo group. At the end of 90 days of treatment, mean QOLID Score showed a significant increase by 203.57% among Test group and 92.5% decrease among Placebo group from baseline. If compared, treatment with NRL/LP/201901 significantly increased Mean QOLID Score than Placebo group. Data as shown in Table 11.

**Table 11: Comparison of changes in Assessment of improvement in Quality of Life based on QOLID Score between the groups.**

| Duration (Days) | Mean QOLID score (mean ± SD) | |
|---|---|---|
| | Drug (N = 50) | Placebo (N = 50) |
| Baseline | 95.88 ± 5.65 | 96.57 ± 8.44 |
| 60 | 128.71± 9.41* | 83.08 ± 6.41* |
| 90 | 203.57 ± 12.69* | 92.5 ± 5.85 |

*NS = Not Significant *Significant < 0.01By ANOVA followed by Dunnet (Between Groups)*

**10. Comparison of changes in Assessment of anthropometric parameters between the groups**

There was significant reduction in body weight in kg in test treated group by average 4.38 kg in 90 days, whereas there was no reduction in body weight in placebo treated group. At day 90 there was significant reduction in waist circumference in test treated group by average 11.36 cm when compared to 3.04 cm increase in placebo counterpart at day 90. At day 90 there was significant reduction in hip circumference in test treated group by average 7.40 cm when compared to 3.66 cm increase inn placebo counterpart at day 90. At day 90 there was significant reduction in BMI in test treated group by average 1.90kg/$m^2$ when compared to 0.4kg/$m^2$ increase

in placebo counterpart at day 90. At day 90 there was significant reduction in body fat % as well as visceral fat % in test treated group when compared to placebo counterpart at day 90. At the end of 90 days of treatment, mean Resting Metabolism (kcal) showed a significant increase by 244.72 kcal among Test group when compared to placebo counterpart at day 90. If compared, treatment with NRL/LP/201901 significantly altered body weight, fat %, BMI and resting metabolic energy expenditure than Placebo group.

**11. Comparison in reduction in the dose of conventional treatment for diabetes mellitus**

There was significant reduction in doses of conventional treatment by NRL/LP/201901. In test group, adjuvant treatment with NRL/LP/201901 led to reduction of conventional antihyperglycemic agents in 40 subjects out of 50, of which 10 subjects completely stopped conventional medication after 60 days and were on test drug. In placebo group nobody shown reduction in conventional medicine till end of the study.

**12. Changes in lipid profile**

At the end of 90 days of treatment, mean total cholesterol and triglycerides showed a significant reduction 26.32 and 27.41 mg/dl respectively among Test group when compared to placebo counterpart at day 90. When compared, treatment with NRL/LP/201901 significantly altered total cholesterol and triglycerides than placebo group.

## DISCUSSION

Diabetes mellitus is a metabolic disorder and its consequences disturbance in metabolic system, it needs multifunctional and synergistic properties of medicinal Herbs and Nutraceuticals for the management of DM. All ingredients used in the test product have been used since ancient periods by the physicians of traditional medicine and scientifically proven to be effective in the management of DM. Since it is a multiherb nutraceuticals product it has a manifold and comprehensive action on several facets of DM. It was observed that adjuvant therapy with NRL/LP/201901 was effective in reducing elevated levels of FPG from baseline till day 30, 60 and 90 days.

Fasting hyperglycemia is a spectacle that has been perceived in fundamentally all persons with DM and may be due to deregulation of the regular circadian hormonal configurations resulting in increased hepatic glucose production. Fasting hyperglycemia commonly can be accredited to insufficient or incorrect hepatic insulinization, the potential of NRL/LP/201901 in reducing FPG was evidence of better utilization of glucose to get transformed to energy and improvement in insulin resistance so the insulinization of hepatic tissue happens to reduce the hyperglycemia in fasting. This effect was clinically evident as patient reported less fatigue than baseline to Day 60.

It was also noted that adjuvant therapy with NRL/LP/201901 was effective in reducing elevated levels of PMG from baseline till Day 30 as well as Day 60. There can be a strong connection of probable alpha glycosidase inhibitory action of NRL/LP/201901 in type 2 DM which slow down the digestion of carbohydrates in the small intestine and consequently can help to decrease afterward meal blood sugar levels.

NRL/LP/201901 as an adjuvant therapy was significantly effective in reducing levels of % HbA1c from baseline to day 90 i.e. end of study. HbA1c is a long-term glycemic index and mostly depends on RBCs' life span which is varied person to person. However, a one-month period is usually enough for HbA1c changes reach its 50% maximum capacity and after three months, 90% of HbA1c changes are detectable. Therefore, conducting a trial for at least three months long would cover study subjects' difference in RBCs life span. The magnitude of reduction in HbA1c was lesser in case of patients with chronic i.e. suffering from diabetes mellitus from more than 5 years and reduction in HbA1c was greater in patients suffering from diabetes mellitus since less than 5 years. Lower HbA1c values have been associated with fewer and delayed microvascular and macrovascular complications. The goal of diabetes mellitus management should be to maintain the lowest possible HbA1c without severe or prolonged hypoglycemia or hyperglycemia. With the treatment of NRL/LP/201901 the significant reduction in HbA1c was achieved.

NRL/LP/201901 can provide protection in arresting progression of pathophysiology of diabetic complications by making good glycemic support over long period of time. The probable mechanism could be by reducing insulin resistance in type 2 diabetes mellitus. The HOMA model is the most widely used surrogate measure for assessing in insulin resistance and beta-cell function in clinical studies. Both high HOMA-IR and low HOMA-B were associated with increased prevalence of impaired glucose tolerance (IGT) and type 2 diabetes mellitus. Insulin resistance is characterized by decrease in insulin mediated glucose disposal in insulin sensitive tissue and increased hepatic glucose production whereas beta-cell dysfunction occurs when beta-cells are unable to compensate for the insulin resistance. Measurement of both of these parameters at diagnosis of T2DM can be a potential tool in evaluation, risk stratification and monitoring treatment of DM. There was significant reduction in [HOMA]-IR score in type 2 Diabetes mellitus suggestive of increasing insulin sensitivity and reducing insulin resistance through improved insulin receptor signaling cascade. Treatment with NRL/LP/201901 demonstrated decreased [HOMA]-IR score the probable action could be due to improved signaling of insulin receptor and glucose update.[11]

NRL/LP/201901 capsule was safe in subjects suffering from Diabetes type 2. NRL/LP/201901 capsule was

significantly effective in improving symptoms like polyuria, polydipsia, polyphagia and fatigue.

The treatment with NRL/LP/201901 compared to placebo was able to reduce the CRP levels which were elevated in diabetic subjects. C-reactive protein (CRP), a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease. It has also been reported that serum CRP levels are elevated in patients with impaired glucose tolerance (IGT) or diabetes. Reduction of CRP levels by treatment of NRL/LP/201901 compared to placebo can suggest of potential role of NRL/LP/201901 in reducing progression of cardiovascular diabetic complications.

The ingredients present in NRL/LP/201901 were known to produce beneficial effects in diabetes management. The activity of NRL/LP/201901 in reducing inflammatory CRP markers could be contributed to the antioxidant ingredients present in formulation.[12]

In the present study test drug produced profound effects in reducing body weight in overweight diabetic subjects. There was significant reduction in waist and hip circumference and BMI. There was significant fat and inch loss in three months with test drug treatment. The resting metabolic rate was enhanced significantly by treatment with NRL/LP/201901 capsule which indicates that there was improvement in metabolic rate and thus muscle energy expenditure homeostasis which help diabetic subjects to achieve sustained glycemic control.

The effect was profoundly visible in reduction of total cholesterol and triglyceride which are probable risk factors in cardiovascular complications.

It was evident from study that there was no significant change in liver, renal and blood parameters before and after treatment that indicates safety of the product.

As per global assessment for overall improvement assessed by investigator, 100% subjects of NRL/LP/201901 capsule group reported to have very much- much improvement as compared to Placebo group at the end of the study.

As per global assessment for overall improvement assessed by subjects, 100% subjects of NRL/LP/201901 capsule treated group reported to have very much- much improvement as compared to Placebo group at the end of the study. In both the groups, the drug compliance was good in 100% subjects at the end of the study.

To comment on the overall study design and the outcomes, it's very clear that NRL/LP/201901 hold promising position in management of diabetes and related complications as a result of well conceptualized product supported with highest quality raw material and manufacturing process.

This study result reveals that, 16% of cases had adverse event among Drug which was comparable to 20% in Placebo group and the difference was not statistically significant. The severity of events was mild to moderate in all the cases and which were resolved without any treatment or rescue for one to three days. In all cases association of events were unlikely or unrelated to drug. It indicated safety of test product in diabetic individuals for consumption in long term duration.

There was significant reduction in doses of conventional treatment by NRL/LP/201901 suggesting potential adjuvant role.

The NRL/LP/201901 capsules were designed and developed keeping in mind the requirement of body to rearrange metabolic changes to achieve normal glucose and lipid metabolism. One of the objectives of therapeutic goal the product is to reduce the propensity of diabetic patient to get the macro and microvascular diabetic complications. Assessment of Anthropometric changes were planned to get idea of the action of NRL/LP/201901 capsules over body fat composition which is the major risk factor in developing diabetes from pre diabetic state as well as proneness of diabetic individual towards macro and micro vascular complications.

Several previous cohort studies that compared different anthropometric measurements with regard to diabetes risk prediction suggest that anthropometric measurements that describe central fat distribution, in particular waist circumference may be superior to measurements of general adiposity.

Cardiovascular complications are the leading cause of morbidity and mortality among patients with type 2 diabetes, and cardiovascular disease (CVD) risk is 2 to 8-fold higher in the diabetic population than it is in non-diabetic individuals of a similar age, sex and ethnicity. Furthermore, macrovascular complications are the largest contributor to the direct and indirect costs of diabetes.

Microvascular diabetic complications are caused by injuries to the small blood vessels. These include retinopathy (retina lesions), nephropathy (kidney) and neuropathy (nervous system). The risk of getting microvascular complications is also proposed to be result of central obesity and inflammation, which can be very well indicated by anthropometric analysis of patients with DM.

There is obvious correlation of diabetes related complications and obesity. Thus a pharmacological intervention for diabetes not only aims at reducing hyperglycemia but to align deranged metabolic pattern and reduce the central obesity thus oxidative stress and inflammatory changes.

In the present study test drug produced profound effects in reducing body weight in overweight diabetic subjects. There was significant reduction in waist and hip circumference and BMI. There is significant fat and inch loss in three months with test drug treatment. The resting metabolic rate was enhanced significantly by treatment with NRL/LP/201901 capsule which indicates that there was improvement in metabolic rate and thus muscle energy expenditure homeostasis which help diabetic subjects to achieve sustained glycemic control.[13-14]

## CONCLUSION

NRL/LP/201901 capsule was safe in subjects suffering from Diabetes type 2. NRL/LP/201901 capsule was significantly effective in improving symptoms like polyuria, polydipsia, polyphagia and fatigue. It was evident that NRL/LP/201901 capsule significantly reduced fasting and post meal glucose levels along with HbA1c, there was significant reduction in insulin resistance evident by HOMA IR score. The quality of life in patients was elevated in NRL/LP/201901 capsule treated group.

NRL/LP/201901 capsule improved lipid profile and anthropometric parameters which indicates that it was beneficial in reducing lipid metabolism as well which may be helpful in preventing CVS complications in diabetes mellitus.

There was significant reduction in doses of conventional treatment by treatment of NRL/LP/201901 capsule it suggest effectiveness of NRL/LP/201901 capsule as an adjuvant to reduce the conventional antidiabetic doses.

Thus "NRL/LP/201901" capsule was found safe and effective medicine as an adjuvant for the treatment of Diabetes type 2.

## CONFLICTS OF INTEREST

No conflicts of interest.

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