Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

# Effect of SophorOx® on Oxidative Stress and Body Composition in Individuals with High BMI: A Randomized Controlled Trial

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**Purpose:** The study aimed to investigate the efficacy and safety of SophorOx® (LN-OS-22) on oxidative stress and body composition in adults with excessive body weight and obesity.

**Participants and Methods:** The 56-days randomized, double-blind, placebo-controlled, parallel-group, multi-centric clinical trial had individuals aged 30–60 years with body mass index (BMI) ≥25 to ≤34.9 kg/m$^2$. 68 participants were randomly allocated to LN-OS-22 or placebo groups. The primary outcome was improvement in the oxidative stress. Secondary outcomes were changes in plasma lipopolysaccharide (LPS) and serum malondialdehyde (MDA) levels, weight and waist circumference, inflammatory markers, and quality of life.

**Results:** At day 56, a statistically significant change in the 8-Isoprostane levels between LN-OS-22 vs placebo was observed ($p = 0.0222$). As compared to placebo, at the end of study, statistically significant reductions were demonstrated in body weight, waist circumference and BMI in the LN-OS-22 group ($p < 0.0001$). Also, a statistically significant change when compared to placebo for the energy/stamina domain ($p = 0.0300$) of the Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT) questionnaire was depicted in LN-OS-22 group.

**Conclusion:** The study demonstrates that LN-OS-22 was effective in reducing the oxidative stress, anthropometrics and improving the quality of life in individuals with overweight and obesity.

**Keywords:** obesity, oxidative stress, inflammation, weight loss, body composition

## Introduction

In a healthy individual, the balance between pro-oxidant generation such as Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) and antioxidant defense is autonomic in nature. Exposure to toxic xenobiotics coupled with the sedentary lifestyle, results in an imbalance between the pro-oxidants and antioxidants, leading to oxidative stress. Pro-oxidant antioxidant balance in the cell is shifted towards the pro-oxidants if the production of oxygen species is increased greatly or when levels of antioxidants are diminished. This state is called oxidative stress.[1] This oxidative stress is known to be one of the primary mechanism through which these lifestyle changes adversely affect individual health leading to a disruption of redox signaling and control and/or molecular damage.[2–5] As demonstrated by several studies, overproduction of ROS can lead to damage of cellular molecules gradually resulting into white adipose tissue accumulation and release of several pro-inflammatory cytokines.[6,7] Oxidative stress is known to trigger the deposition of white adipose tissue by increasing preadipocyte proliferation, adipocyte differentiation, and the size of mature adipocytes.[8] Other contributing factors of oxidative stress are low antioxidant defense,[9] chronic inflammation,[10] and postprandial ROS generation.[11] Therefore, obesity served as an ideal condition to investigate the antioxidant activity of LN-OS-22 extract.

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Several dietary practices have been shown to alleviate oxidative stress thereby minimizing the health associated hazards.[12] *Sophora japonica L (Styphnolobium japonicum)* has a rich history of use in traditional Chinese medicine. A wide range of biological activities of *Sophora japonica L* in vitro and in vivo have been reported such as anti-inflammatory, antibacterial, antiviral, anti-osteoporotic, antioxidant, radical scavenging, anti-hyperglycemic, anti-obesity, antitumor, and hemostatic effects.[13,14] *Sophora Japonica L* is one of the richest sources of rutin and quercetin flavonoids. Both of these flavonoids have been studied extensively for exploiting their use in improving human health.[15–20] Layn Natural Ingredients adopted *Sophora japonica L* under the "Adopt-an-Herb" initiative of the American Botanical Council and derived LN-OS-22. It was extracted from the flower bud of the plant, underwent ethanol/water extraction, and has been standardized to contain ≥90% flavonoids, primarily, quercetin, a rutin and other minor flavonoids. This extract has been tested in vitro in LPS-stimulated RAW 264.7 macrophages for its anti-inflammatory and antioxidant activity. The extract showed significant inhibition of pathways of inflammation and oxidative stress.[21] The biological activities were then confirmed by an in vivo study. Oral administration of this extract in exercised animals resulted in a significant decrease in oxidative stress and inflammatory biomarkers associated with the high-intensity exercise in a rodent model (Sprague-Dawley rat model).[22] The validation in humans of these in vitro and in vivo antioxidant activities was studied in the current randomized clinical trial.

A meta-analysis[23] of 50 clinical studies showed that individuals with overweight and obesity have a comparatively increased levels of 8-isoprostane, a reliable and stable biomarker of oxidative stress,[24] than healthy population. A reduction in the body weight is known to decrease oxidation markers in the body and thereby reduce obesity-related pathological risk factors.[8] Obesity is also known to be associated with chronic low-grade information.[25] A significant impact on the health-related quality of life is also seen in individuals with overweight and obesity.[26] Thus, the primary objective of the study was to assess the effect of the investigational product (IP), LN-OS-22 on oxidative stress. Body composition (BMI, body weight and waist circumference) were included as secondary objectives as clinical indicators of reduction in oxidative stress and inflammation. Furthermore, lipid peroxidation, metabolic endotoxemia as well as quality of life were also included as secondary objectives. The safety of 2-month administration of the Investigational Product (IP), LN-OS-22, was evaluated by monitoring the vitals as well as liver and kidney function biomarkers [serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), and creatinine] throughout the study.

# Materials and Methods

## Study Approval and Registration

This study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) recommendation on Good Clinical Practice (GCP)-E6 (R2), 2016, and National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017, India. The ethical approval for conduct of the study at three sites was provided by the independent ethics committee - Harmony Ethical Research Committee, Mumbai, India (Reg. No. ECR/1411/Inst/MH/2020). The eligible participants were enrolled in the study only after providing written consent for participation. The study was registered with the NIH ClinicalTrials.gov (Identifier: NCT05404217) and Clinical Trials Registry, India (Registration Number: CTRI/2022/06/043394). Vedic Lifesciences, Mumbai, India, monitored and audited the study to ensure the study protocol and ICH-GCP compliance. The study report conformed to the Consolidated Standard Reporting of Trials (CONSORT) guidelines.

## Study Design

The current study is a randomized, double-blind, placebo-controlled, parallel-group multi-centric study intended for evaluating the effect of 56-days administration of LN-OS-22 on oxidative stress and body composition in individuals with overweight and obesity. The study was conducted at three clinical sites in Mumbai, Maharashtra, India, under the supervision of qualified physicians from June 2022 to March 2023.

## Participants

The present study was conducted among adults aged ≥30 to ≤60 years with a BMI range of ≥25 to ≤34.9 kg/m$^2$. Individuals with at least three of the following five metabolic risk factors were included in the study: 1) waist circumference: male: ≥102 cm;

female ≥88 cm, 2) triglycerides >150 mg/dL, 3) systolic blood pressure ≥130 mm H and/or diastolic blood pressure ≥85 mm Hg, 4) fasting blood glucose ≥100 mg/dL, 5) high-density lipoproteins: male: <40 mg/dL; female: <50 mg/dL. Also, individuals who were physically inactive for 1/3rd of their wake time as per the Longitudinal Aging Study Amsterdam (LASA) sedentary behavior questionnaire were included. Individuals meeting the following criteria were excluded from the study: known cases of lactose intolerance, thyroid function test (TSH) level < 0.4 to > 4.2 mIU/L, known cases of type I diabetes mellitus and presence of uncontrolled type II diabetes mellitus [indicated by glycosylated hemoglobin (HbA1c) ≥ 6.5]. The other eligibility criteria are described in Table S1 (Supplementary Material).

The prospective participants fulfilling inclusion and exclusion criteria were randomized in the ratio of 1:1 for LN-OS-22 or placebo by the statistician who was not directly involved in the study. Based on the computer generated randomization chart, the participant identification numbers were generated which were printed on the product labels using a stratified block randomization method with a block of four. The randomization chart was generated by an independent statistician using StatsDirect software (Ver. 3.1.17). The participant, research staff, and Investigator were blinded to the study product allocation.

## Intervention

The investigational product (IP), LN-OS-22, is a polyphenolic supplementation comprising of rutin, quercetin, and other minor flavonoids. Previous studies have shown that quercetin up to a dose of 2000 mg and Rutin in a dose of 500 mg when administered for 6–8 weeks is safe in humans.[27–30] Thus, in the present study, 500 mg capsule of LN-OS-22 was administered to participants in one of the arms. The detailed percentage composition of the study products is given in Table 1. The placebo capsule contained 500 mg of Maltodextrin. All the participants were instructed to take two capsules a day orally with a glass of milk after breakfast daily. At each follow-up visit, the compliance to the intervention was ensured by counting the remaining number of capsules in the bottles. Any concomitant medication taken was recorded in the source document and Electronic-Case Record Form (e-CRF). The participants having at least 90% compliance during the intervention period were considered "completed intervention".

To preserve the blinding, the study products and the placebo capsules were matched for size, shape, color, and texture and packed in identical packaging. Layn Natural Ingredients, USA supplied the products for the study. The products were manufactured in compliance with good manufacturing practices and applicable regulations.

## Study Procedures

During the screening visit, the study procedures were thoroughly explained to the research participants in a language well understood by them, following which he/ she duly signed and dated informed consent. The participants were screened for the eligibility criteria, and those who qualified were instructed to report on day 0 for randomization and baseline assessments. The follow-up assessments were conducted on days 28 and 56, as depicted in (Figure 1). Demographic and baseline characteristics such as anthropometric parameters (height, weight and BMI), vital signs (pulse rate and blood pressure), clinical examination

**Table 1** Investigational Product Composition

| Study Product | Active Ingredients | Percentage | Total Composition |
|---|---|---|---|
| **LN-OS-22** | Quercetin | 51.7% | 94.81% |
| | Rutin | 40.75% | |
| | Kaempferol | 0.88% | |
| | Isorhamnetin | 1.33% | |
| | Genistin | 0.14% | |
| | Genistein | 0.005% | |
| **Placebo** | Maltodextrin | 100% | 100% |

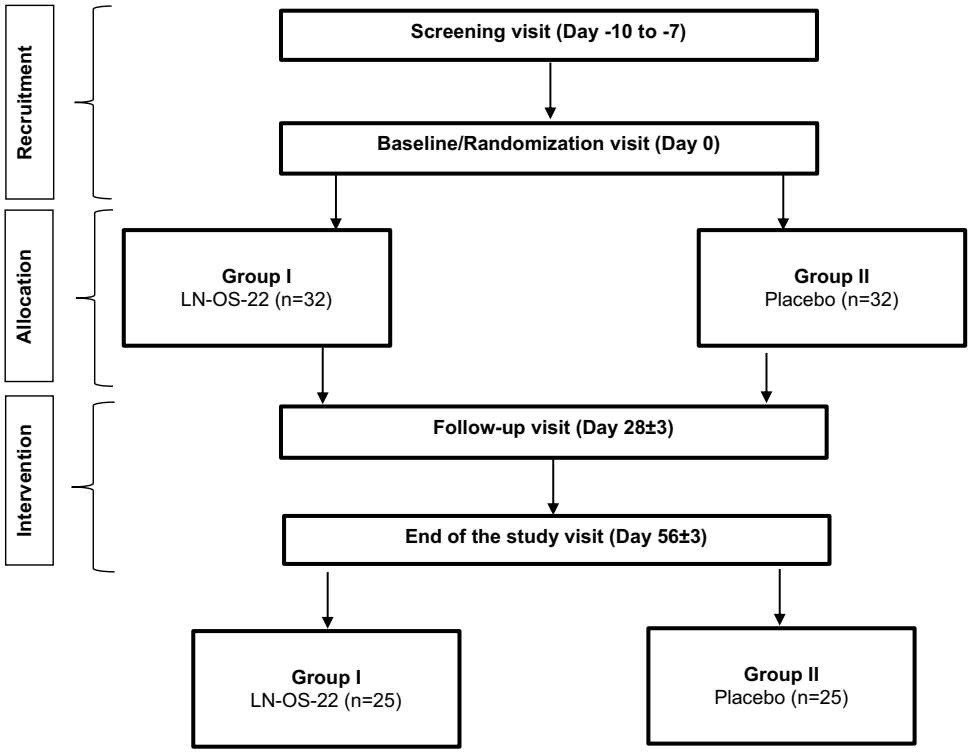


**Figure 1** Study flow chart.
**Abbreviation**: n; number of participants.

and medical history with prior and concomitant medication were recorded. Participants were asked to self-administer the LASA questionnaire. Participants were required to have a minimum of 90% Investigational Product (IP) compliance during the study. The detailed method of assessments is explained in the Supplementary Material.

## Study Outcomes

### Primary Outcome

The primary objective of the study was to assess the effect of 56 days of IP intake on the oxidative stress as compared to placebo. This was assessed by the change in serum levels of 8-isoprostane (8-iso-PGF2α) which is considered a reliable and pivotal biomarker of generalized as well as cellular oxidative stress.[31] The 8-iso-PGF2α levels were analyzed using sandwich ELISA technique.

### Secondary Outcomes

The secondary objective was to assess the effect of IP on body weight, waist circumference along with the inflammatory (CRP and IL-6) and lipid peroxidation biomarkers (MDA) along with the serum lipopolysaccharide (LPS) levels, a marker for the bacterial pollution. Lastly, effect of IP was assessed on the quality of life using Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT). The detailed study flow chart is shown in Figure 1. The participants were instructed to maintain their routine diet and physical activity levels throughout the study.

### Safety Outcomes

The safety of the IP was evaluated by measuring the liver and kidney function panel [serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), serum alkaline phosphatase (ALP) and serum creatinine]. Blood pressure, pulse rate along with adverse events were monitored throughout the study.

## Statistical Analysis

The sample size calculation was based on previous studies conducted to evaluate the efficacy of other products with similar objectives.[32–34] The null hypothesis was considered to be rejected in case LN-OS-22 was able to significantly reduce oxidative stress and body composition in a population with overweight and obesity as compared to the placebo. Data was checked for normality using Shapiro Wilk/Kolmogorov–Smirnov test. Mean change of serum levels of 8-isoprostane at 56 days from baseline was compared between the IP and placebo groups using ANCOVA. Mean change in the serum MDA, plasma LPS levels at 56 days from baseline were assessed on similar line of primary endpoints. Change in serum CRP, serum IL-6, weight and waist circumference, and IWQOL-Lite-CT from baseline to Day 28 and Day 56, in the IP and placebo groups was analyzed using multivariate ANCOVA. Data analyses were performed using R/R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/version4.0.5 and XLSTAT statistical and data analysis solution, New York, USA. https://www.xlstat.com./version2021.3.1.

## Quality Assurance

Vedic Lifesciences monitored and audited the study to ensure compliance with the study protocol and ICH-GCP E6 (R2) guidelines.

# Results

Out of 153 screened individuals, 68 met the predefined inclusion-exclusion criteria and were randomized into the study. Of these, 50 participants completed the study. The detailed participant disposition is presented in Figure 2.

## Demographic and Baseline Characteristics

Eligible individuals were randomized in a 1:1 ratio to receive either LN-OS-22 (n = 33) or placebo (n = 35). The enrolled participants had a mean age of 42 years and a mean BMI of 30.25 kg/m$^2$. The demographic and baseline characteristics of all the randomized participants are summarized in Table 2.

## Oxidative Stress

At the baseline, 8-Isoprostane levels matched between the groups ($p = 0.1016$). At day 28, the serum levels increased in both the LN-OS-22 and the placebo ($p = 0.7634$) groups. At day 56, the increase in the levels of the 8-isoprostane was significantly higher in the placebo group as compared to the IP ($p = 0.0222$) and this increase was significantly higher as compared to the baseline ($p = 0.0710$). Thus, at the end of the study, the LN-OS-22 helped restore the balance between anti- and pro-oxidative levels (Table 3).

## Body Composition

The LN-OS-22 study group demonstrated not only a statistically significant reduction in the body weight and BMI but also showed a clinically meaningful reduction in the waist circumference when compared with the placebo. Eight weeks' administration of the IP reduced the body weight by 2.07 (1.62) kgs as opposed to the placebo group which showed only a marginal reduction by 0.14 (1.53) kgs ($p < 0.0001$). The IP group, thus, also showed a statistically significant reduction in the BMI as compared to placebo ($p < 0.0001$). Similarly, waist circumference reduced by 2.58 (1.69) cm in the LN-OS-22 group as compared to the placebo which showed only a 0.31 (1.71) cm of reduction over 56 days of administration ($p < 0.0001$). This decrease in waist circumference resulted in the significant reduction in the waist-to-height ratio ($p = 0.0005$) (Table 4).

## Inflammatory & Lipid Peroxidation Markers

At baseline, the groups seemed statistically similar for inflammatory and lipid peroxidation markers ($p > 0.05$). After 8 weeks of study period, the LN-OS-22 group showed lower levels of the CRP as compared to the placebo, however, the levels of CRP increased in both the groups from baseline. Similarly, the IL-6 levels were also lower in the intervention

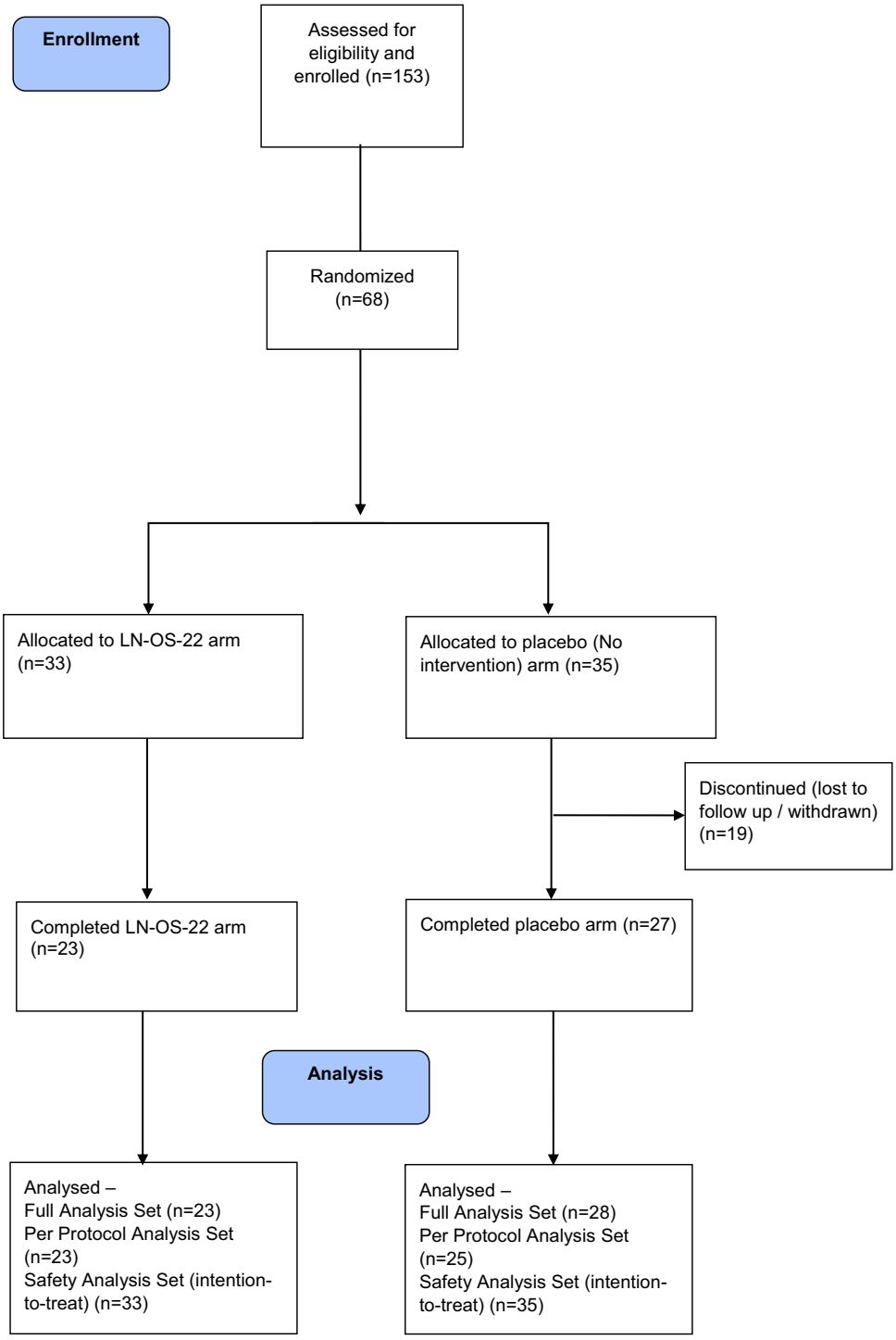


**Figure 2** Participant Disposition.
**Abbreviation**: n; number of participants,

group as compared to the placebo group however the results were not statistically significant (Table 5) By the end of the study, a reduction in the mean MDA levels was observed in both study groups. The LN-OS-22 showed a greater mean reduction of 5.52 (70.99) EU/mL of LPS levels in comparison to the placebo study group (Table 5).

**Table 2** Demographics and Baseline Characteristics of Randomized Participants

| Parameters | Categories | LN-OS-22 (N=33) | Placebo (N=35) | Total (N=68) | *p-value |
|---|---|---|---|---|---|
| **Age (Years)** | Mean | 42.85 (7.42) | 40.57 (5.91) | 41.68 (6.73) | 0.1652 (T) |
| | (Min, Max) | (31.00, 57.00) | (31.00, 52.00) | (31.00, 57.00) | |
| **Gender** | Male | 10 (30.30%) | 12 (34.29%) | 22 (32.35%) | 0.7257 (C) |
| | Female | 23 (69.70%) | 23 (65.71%) | 46 (67.65%) | |
| **Height (cm)** | Mean | 158.34 (7.96) | 157.83 (8.98) | 158.08 (8.44) | 0.8065 (T) |
| | (Min, Max) | (143.06, 179.31) | (140.85, 175.00) | (140.85, 179.31) | |
| **Weight (kg)** | Mean | 75.66 (8.89) | 76.07 (10.47) | 75.87 (9.66) | 0.8644 (T) |
| | (Min, Max) | (57.80, 98.00) | (60.00, 102.30) | (57.80, 102.30) | |
| **BMI (kg/m$^2$)** | Mean | 30.14 (2.84) | 30.36 (2.64) | 30.25 (2.72) | 0.7390 (T) |
| | (Min, Max) | (25.68, 34.51) | (25.48, 34.82) | (25.48, 34.82) | |

**Notes**: *p values were calculated using two sample *t*-test (T) for continuous variables and Chi Square (C) test for categorical variables. Percentages were calculated using respective column header count as denominator.
**Abbreviations**: SD; standard deviation, N; number of participants.

**Table 3** Summary of 8-Isoprostane Levels of the mITT Population

| Parameters | Visit | LN-OS-22 (N=23) | | Placebo (N=28) | | p value$ |
|---|---|---|---|---|---|---|
| | | Mean (SD) | 95% CI | Mean (SD) | 95% CI | |
| **8-Isoprostane (pg/mL)** | **Day 0** | 102.41 (60) | (76.46, 128.35) | 175.26 (218.87) | (90.39, 260.13) | 0.1016 (T) |
| | **Day 56** | 109.03 (73.72) | (77.16, 140.91) | 216.33 (205.7) | (136.56, 296.09) | 0.0147 (T) |
| | **Change from baseline at day 56** | 6.63 (85.19) | (−30.21, 43.47) | 41.07 (115.64) | (−3.77, 85.91) | |
| | **p value#** | 0.0222 (A) | | | | |
| | **p value*** | 0.7126 (T) | | 0.0710 (T) | | |

**Notes**: $p-value was calculated using two sample *t*-test (T). *p-values were calculated using paired *t*-test (T). #p-values were calculated using ANCOVA with treatment as factor and baseline value, age and BMI as covariate vs placebo.
**Abbreviations**: CI; confidence interval, N; number of participants, mITT; modified intention to treat, SD; standard deviation.

**Table 4** Summary of Anthropometric Measurements of the mITT Population

| Parameters | Visit | LN-OS-22 (N=23) | | Placebo (N=28) | | p value$ |
|---|---|---|---|---|---|---|
| | | Mean (SD) | 95% CI | Mean (SD) | 95% CI | |
| **Body Weight (kgs)** | **Day 0** | 77.25 (7.24) | (74.12, 80.38) | 75.99 (10.74) | (71.82, 80.15) | 0.6317 (T) |
| | **Day 56** | 75.18 (7.1) | (72.11, 78.25) | 76.12 (10.58) | (72.02, 80.23) | 0.7169 (T) |
| | **Change from baseline at day 56** | −2.07 (1.62) | (−2.77, −1.37) | 0.14 (1.53) | (−0.45, 0.73) | |
| | **p value#** | <0.0001 (A) | | | | |
| | **p value*** | <0.0001 (T) | | 0.6339 (T) | | |

(*Continued*)

**Table 4** (Continued).

| Parameters | Visit | LN-OS-22 (N=23) | | Placebo (N=28) | | p value[$] |
|---|---|---|---|---|---|---|
| | | Mean (SD) | 95% CI | Mean (SD) | 95% CI | |
| **Waist circumference (cm)** | **Day 0** | 103.16 (7.3) | (100.00, 106.32) | 102.53 (7.94) | (99.45, 105.61) | 0.7706 (T) |
| | **Day 56** | 100.58 (6.85) | (97.62, 103.54) | 102.22 (7.55) | (99.29, 105.15) | 0.4264 (T) |
| | **Change from baseline at day 56** | −2.58 (1.69) | (−3.31, −1.85) | −0.31 (1.71) | (−0.98, 0.35) | |
| | **p value[#]** | <0.0001 (A) | | | | |
| | **p value*** | <0.0001 (T) | | 0.3457 (T) | | |
| **Waist to height ratio** | **Day 0** | 0.65 (0.06) | (0.62, 0.68) | 0.65 (0.04) | (0.63, 0.67) | 0.8763 (T) |
| | **Day 56** | 0.63 (0.06) | (0.61, 0.66) | 0.65 (0.04) | (0.63, 0.66) | 0.2995 (T) |
| | **Change from baseline at day 56** | −0.02 (0.01) | (−0.02, −0.01) | 0 (0.01) | (−0.01, 0.00) | |
| | **p value[#]** | 0.0005 (A) | | | | |
| | **p value*** | <0.0001 (T) | | 0.1018 (T) | | |
| **BMI (kg/m$^2$)** | **Day 0** | 30.45 (2.71) | (29.28, 31.62) | 30.44 (2.69) | (29.39, 31.48) | 0.9888 (T) |
| | **Day 56** | 29.65 (2.88) | (28.40, 30.89) | 30.5 (2.62) | (29.48, 31.51) | 0.2759 (T) |
| | **Change from baseline at day 56** | −0.8 (0.61) | (−1.06, −0.54) | 0.06 (0.6) | (−0.17, 0.29) | |
| | **p value[#]** | <0.0001 (A) | | | | |
| | **p value*** | <0.0001 (T) | | 0.5984 (T) | | |

**Notes**: [$]p-value was calculated using two sample *t*-test (T). *p-values were calculated using paired *t*-test (T). [#]p-values were calculated using ANCOVA with treatment as factor and baseline value, age and BMI as covariate vs placebo.

**Abbreviations**: BMI, body mass index, CI; confidence interval, mITT; modified intention to treat, N; number of participants SD; standard deviation.

**Table 5** Summary of Inflammatory and Lipid Peroxidation Biomarkers of the mITT Population

| Parameters | Visit | LN-OS-22 (N=23) | | Placebo (N=28) | | p value[$] |
|---|---|---|---|---|---|---|
| | | Mean (SD) | 95% CI | Mean (SD) | 95% CI | |
| **CRP (mg/L)** | **Day 0** | 5.63 (6.17) | (2.96, 8.30) | 5.75 (5.39) | (3.65, 7.84) | 0.9433 (T) |
| | **Day 56** | 6.3 (9.18) | (2.33, 10.27) | 7.45 (7.03) | (4.72, 10.17) | 0.6157 (T) |
| | **Change from baseline at day 56** | 0.67 (9.92) | (−3.62, 4.96) | 1.7 (6.17) | (−0.69, 4.10) | |
| | **p value[#]** | 0.8116 (A) | | | | |
| | **p value*** | 0.7481 (T) | | 0.1557 (T) | | |
| **IL-6 (pg/mL)** | **Day 0** | 7.03 (9.49) | (2.93, 11.14) | 77.45 (374.07) | (−67.60, 222.50) | 0.3282 (T) |
| | **Day 56** | 7.5 (5.74) | (5.02, 9.98) | 13.03 (18.16) | (5.99, 20.07) | 0.1374 (T) |
| | **Change from baseline at day 56** | 0.46 (11.89) | (−4.68, 5.60) | −64.42 (376.76) | (−210.51, 81.67) | |
| | **p value[#]** | 0.1786 (A) | | | | |
| | **p value*** | 0.8535 (T) | | 0.3736 (T) | | |

(*Continued*)

**Table 5** (Continued).

| Parameters | Visit | LN-OS-22 (N=23) | | Placebo (N=28) | | p value[$] |
|---|---|---|---|---|---|---|
| | | Mean (SD) | 95% CI | Mean (SD) | 95% CI | |
| MDA (nmol/mL) | Day 0 | 0.68 (0.36) | (0.52, 0.83) | 0.66 (0.39) | (0.51, 0.81) | 0.9013 (T) |
| | Day 56 | 0.5 (0.37) | (0.34, 0.67) | 0.38 (0.4) | (0.22, 0.53) | 0.2545 (T) |
| | Change from baseline at day 56 | −0.17 (0.64) | (−0.45, 0.10) | −0.29 (0.47) | (−0.47, −0.10) | |
| | p value[#] | 0.3871 (A) | | | | |
| | p value* | 0.2102 (T) | | 0.0036 (T) | | |
| LPS (EU/mL) | Day 0 | 72.61 (47.79) | (51.94, 93.27) | 78.21 (55.45) | (56.71, 99.71) | 0.7041 (T) |
| | Day 56 | 67.09 (87.45) | (29.27, 104.90) | 74.75 (61.22) | (51.01, 98.49) | 0.7150 (T) |
| | Change from baseline at day 56 | −5.52 (70.99) | (−36.22, 25.18) | −3.46 (52.62) | (−23.87, 16.94) | |
| | p value[#] | 0.9093 (A) | | | | |
| | p value* | 0.7127 (T) | | 0.7303 (T) | | |

**Notes**: [$]p-value was calculated using two sample *t*-test (T). *p-values were calculated using paired *t*-test (T). [#]p-values were calculated using ANCOVA with treatment as factor and baseline value, age and BMI as covariate vs placebo.
**Abbreviations**: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; LPS, lipopolysaccharide; MDA, malondialdehyde; mITT, modified intention to treat; N, number of participants; SD, standard deviation.

## Quality of Life

On days 28 and 56, the change in the quality of life in the IP group was statistically significant as indicated by p = 0.0029 and p = 0.0004, respectively, when compared to baseline. After 56 days of intervention, LN-OS-22 group demonstrated a statistically significant change when compared to placebo for the energy/stamina domain (p = 0.0300) of the IWQOL-Lite-CT questionnaire. Also, at day 56, when compared to baseline, statistically significant results were demonstrated in the IP group in the physical impact (p = 0.0047), emotions (p = 0.0003), self-confidence/self-esteem (p = 0.0236) domains (Table 6).

**Table 6** Summary of IWQOL-Lite-CT of the mITT Population

| Parameters | Visit | LN-OS-22 (N=23) | | Placebo (N=28) | | p value[$] |
|---|---|---|---|---|---|---|
| | | Mean (SD) | 95% CI | Mean (SD) | 95% CI | |
| Physical Impact | Day 0 | 10.22 (4.84) | (8.12, 12.31) | 9.61 (4.57) | (7.84, 11.38) | 0.6460 (T) |
| | Day 56 | 7.00 (4.72) | (4.96, 9.04) | 7.64 (4.6) | (5.86, 9.43) | 0.6259 (T) |
| | Change from baseline at day 56 | −3.22 (4.91) | (−5.34, −1.10) | −1.96 (5.55) | (−4.12, 0.19) | |
| | p value[#] | 0.4721 (A) | | | | |
| | p value* | 0.0047 (T) | | 0.0718 (T) | | |
| Energy/Stamina | Day 0 | 2.43 (1.38) | (1.84, 3.03) | 1.96 (1.23) | (1.49, 2.44) | 0.2039 (T) |
| | Day 56 | 1.57 (1.38) | (0.97, 2.16) | 1.89 (1.29) | (1.39, 2.39) | 0.3847 (T) |
| | Change from baseline at day 56 | −0.87 (1.18) | (−1.38, −0.36) | −0.07 (1.33) | (−0.59, 0.44) | |
| | p value[#] | 0.0300 (A) | | | | |
| | p value* | 0.0019 (T) | | 0.7787 (T) | | |

(*Continued*)

**Table 6** (Continued).

| Parameters | Visit | LN-OS-22 (N=23) | | Placebo (N=28) | | p value[$] |
|---|---|---|---|---|---|---|
| | | Mean (SD) | 95% CI | Mean (SD) | 95% CI | |
| **Emotions** | **Day 0** | 12.26 (4.87) | (10.15, 14.37) | 11.32 (5.16) | (9.32, 13.32) | 0.5105 (T) |
| | **Day 56** | 8.39 (4.39) | (6.49, 10.29) | 9.46 (5.14) | (7.47, 11.46) | 0.4323 (T) |
| | **Change from baseline at day 56** | −3.87 (4.26) | (−5.71, −2.03) | −1.86 (5.68) | (−4.06, 0.35) | |
| | **p value[#]** | 0.1929 (A) | | | | |
| | **p value*** | 0.0003 (T) | | 0.0951 (T) | | |
| **Self-confidence/Self-esteem** | **Day 0** | 11.17 (6.1) | (8.53, 13.81) | 10.32 (5.62) | (8.14, 12.50) | 0.6065 (T) |
| | **Day 56** | 8.83 (4.5) | (6.88, 10.77) | 8.54 (5.41) | (6.44, 10.63) | 0.8380 (T) |
| | **Change from baseline at day 56** | −2.35 (4.63) | (−4.35, −0.35) | −1.79 (5.51) | (−3.92, 0.35) | |
| | **p value[#]** | 0.7382 (A) | | | | |
| | **p value*** | 0.0236 (T) | | 0.0980 (T) | | |
| **Sexual life** | **Day 0** | 1.65 (1.19) | (1.14, 2.17) | 1.36 (1.16) | (0.91, 1.81) | 0.3766 (T) |
| | **Day 56** | 1.3 (0.88) | (0.93, 1.68) | 1.39 (1.03) | (0.99, 1.79) | 0.7456 (T) |
| | **Change from baseline at day 56** | −0.35 (1.3) | (−0.91, 0.21) | 0.04 (1.4) | (−0.51, 0.58) | |
| | **p value[#]** | 0.4867 (A) | | | | |
| | **p value*** | 0.2130 (T) | | 0.8937 (T) | | |
| **Social life** | **Day 0** | 1.48 (1.24) | (0.94, 2.01) | 1.46 (1.17) | (1.01, 1.92) | 0.9672 (T) |
| | **Day 56** | 1.52 (1.08) | (1.05, 1.99) | 1.39 (1.23) | (0.92, 1.87) | 0.6957 (T) |
| | **Change from baseline at day 56** | 0.04 (0.93) | (−0.36, 0.44) | −0.07 (1.27) | (−0.57, 0.42) | |
| | **p value[#]** | 0.7373 (A) | | | | |
| | **p value*** | 0.8243 (T) | | 0.7691 (T) | | |
| **Productivity** | **Day 0** | 1.91 (1.44) | (1.29, 2.54) | 1.89 (1.4) | (1.35, 2.43) | 0.9599 (T) |
| | **Day 56** | 1.52 (1.34) | (0.94, 2.10) | 1.61 (1.4) | (1.07, 2.15) | 0.8260 (T) |
| | **Change from baseline at day 56** | −0.39 (1.27) | (−0.94, 0.16) | −0.29 (1.36) | (−0.81, 0.24) | |
| | **p value[#]** | 0.5402 (A) | | | | |
| | **p value*** | 0.1536 (T) | | 0.2750 (T) | | |
| **Total score** | **Day 0** | 41.13 (18.28) | (33.23, 49.03) | 37.93 (18.24) | (30.86, 45.00) | 0.5360 (T) |
| | **Day 56** | 30.13 (16.08) | (23.18, 37.08) | 31.93 (18.34) | (24.82, 39.04) | 0.7144 (T) |
| | **Change from baseline at day 56** | −11 (12.8) | (−16.54, −5.46) | −6 (19.16) | (−13.43, 1.43) | |
| | **p value[#]** | 0.3045 (A) | | | | |
| | **p value*** | 0.0004 (T) | | 0.1091 (T) | | |

**Notes**: [$]p-value was calculated using two sample *t*-test (T). *p-values were calculated using paired *t*-test (T). [#]p-values were calculated using ANCOVA with treatment as factor and baseline value, age and BMI as covariate vs placebo.

**Abbreviations**: CI, confidence interval; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite-Clinical Trials Version; N, number of participants; mITT, modified intention to treat; SD, standard deviation.

## Safety Outcomes

No significant change in safety parameters was observed during the study in the IP group compared to baseline and placebo. Only five adverse events were reported during the study in the IP group – 1) high SGPT and ALP levels, 2) dry cough, 3) high IL-6 levels, 4) high CRP levels, 5) high SGPT and SGOT levels. None of the adverse events were found related to the study products. No serious adverse event was reported during the study (Table S2) (Supplementary Material).

# Discussion

Obesity has been purported as a global pandemic in recent times with a well-established relationship with oxidative imbalance. Studies have shown that individuals with higher BMI have increased productions of 8-isoprostane.[6,35–37] The levels of 8-isoprostane are known to increase in response to oxidative stress.[38] Hence, 8-Isoprostane, which is considered as the most stable biomarker of oxidative stress was assessed in the serum of the participants enrolled in the study.[39] In the present study, participants with increased body weight and at a risk of metabolic syndrome showed a trend of increasing oxidative stress over next eight weeks. Dietary polyphenols (or flavonoids) serve as effective scavengers for free radicals and ROS. They possess the capacity to neutralize ROS or inhibit cellular oxidative stress, thereby preventing damage to biomolecules such as lipids, proteins, and DNA. This phenomenon is commonly referred to as the antioxidant effects of dietary polyphenols.[40] The IP consistent with this known antioxidant effect of polyphenols, helped to cease the increase of 8-isoprostane, whereas in the placebo group the oxidative stress continued to increase till the end of the study. Oxidative imbalance arises due to a deficiency in the antioxidant defense system (ADS) resulting from impaired production or distribution of antioxidants (AO) or surplus of ROS.[41] These results of the present study are similar to the effect of Vitamin E, wherein 6-month supplementation led to the reduction in the 8-Isoprostane levels thus ceasing oxidative stress.[42] In another study conducted by Askari et al, eight weeks of quercetin supplementation proved to be efficacious in reducing oxidative stress.[32]

Obesity is known to disrupt the antioxidant tissue defenses and this disruption has been found to be related to a low intake of dietary phytochemicals and antioxidants that possess antioxidant capacity. An inverse correlation of oxidative stress with high BMI, waist circumference, waist-to-hip ratio and plasma oxidative stress was demonstrated in a study conducted by Vincent.[43] Polyphenols exhibit potential anti-obesity properties, with proposed mechanisms for weight management including the promotion of thermogenesis and increased energy expenditure,[44] inhibition of adipocyte differentiation and growth,[45] augmentation of lipolysis and induction of β-oxidation,[46] and reduction of appetite.[47] The anti-obesity effect of our present study is in line with the known effects of polyphenols like rutin and quercetin. After 56 days of intervention, a mean reduction in the BMI of 0.8 (0.61) $kg/m^2$ was seen in the LN-OS-22 study group as opposed to placebo where the mean BMI showed an increase by 0.06 (0.6) $kg/m^2$; and this result of the IP group was statistically significant when compared to placebo as well as baseline ($p<0.0001$). Also, at the end of the study, when compared with placebo, a statistically significant reduction was observed in the waist circumference ($p < 0.0001$), waist-to height ratio ($p = 0.0005$) as well as body weight ($p < 0.0001$) in the intervention group. Thus, the anthropometric endpoints of the present study proved to be positive in the LN-OS-22 study group.

Oxidative stress and the increased body weight can have a significant impact on the quality of life.[48] In the present study, a statistically significant change in the total scores of the IWQOL-Lite-CT was depicted after 56 days of intervention in the IP group ($p = 0.0004$). When compared to baseline, the IP group showed significant improvement in the physical impact, energy/stamina, emotions and self-confidence/self-esteem domains of the IWQOL-Lite-CT questionnaire. Thus, it can be concluded that the study group LN-OS-22 positively influenced the quality of life of individuals. No statistically significant results were demonstrated in the intervention group on inflammatory (CRP and IL-6), lipid peroxidation (MDA) as well as metabolic endotoxemia (LPS) biomarkers. This can be attributed to the small sample size of the study. Nevertheless, the investigational product LN-OS-22 proved to be efficacious in reducing the oxidative stress, body weight, BMI and waist circumference of individuals with overweight and obesity as well as improved the quality of life of individuals with overweight and obesity.

## Conclusion

The present randomized clinical trial concludes that the LN-OS-22 has antioxidant potential thereby helping to maintain healthy body composition. It also has shown promise of reducing the risk of metabolic dysfunction by maintaining healthy waist to height ratio. The study product LN-OS-22 was found to be well tolerated.

## Abbreviations

BMI, Body Mass Index; BP, Blood Pressure; CONSORT, Consolidated Standards Of Reporting Trials; CRP, C-Reactive Protein; EC, Ethics Committee; e-CRF, Electronic-Case Record Form; GMP, Good Manufacturing Practice; IP, Investigational Product; ICH-GCP, International Conference On Harmonization-Good Clinical Practice; IL, Interleukin; LASA, Longitudinal Aging Study Amsterdam (LASA); LPS, Lipopolysaccharide; MDA, Malondialdehyde; PR, Pulse rate; ROS, Reactive Oxygen Species; RNS, Reactive Nitrogen Species; ALP, Serum Alkaline Phosphatase; SGOT, Serum Glutamic-Oxaloacetic Transaminase; SGPT, Serum Glutamic-Pyruvic Transaminase; IWQOL-Lite-CT, Weight on Quality of Life-Lite-Clinical Trials Version.

## Data Sharing Statement

The data used in the study is available on reasonable request from the corresponding author with due permission from the sponsor.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Mr James Roza is an employee for Layn, outside the submitted work; and Layn Corp. will use this research to market this ingredient (SophorOx®) as a dietary supplement worldwide. The authors report no other conflicts of interest in this work.

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