**A novel protodioscin-enriched fenugreek seed extract (*Trigonella foenum-graecum*, family Fabaceae) improves free testosterone level and sperm profile in healthy volunteers**

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**Background**

A novel, patent-pending 20% protodioscin-enriched extract has been developed in our laboratories from fenugreek seeds (Furosap®). We assessed the efficacy of Furosap® in 50 male volunteers (age: 35-65 years) on free and total increased testosterone levels, sperm profile, mental alertness, cardiovascular health, mood, libido and quality of life.

**Methods**

Furosap® (500 mg/day/subject) was administered to these 50 male volunteers over a period of 12 weeks in an one-arm, open-labelled study, to determine the efficacy on free and total testosterone levels, sperm profile and sperm morphology, libido and erectile dysfunction, mood and mental alertness and broad spectrum safety parameters. Institution Review Board approval was obtained for this study and the study was registered at clinicaltrials.gov (NCT02702882).

**Results**

A statistically significant increase in free testosterone levels were observed in these volunteers following supplementation of Furosap®. Sperm morphology, sperm counts, mental alertness, mood, cardiovascular health and libido performance were significantly improved. Extensive blood chemistry analyses revealed broad spectrum safety. No significant changes were observed in serum lipid function, cholesterol, triglyceride, HDL and LDL levels and hemogram.

**Conclusions**

Results confirmed that this protodioscin-enriched extract from fenugreek seeds (Furosap) is safe and efficacious in boosting serum free testosterone levels, healthy sperm profile, mental alertness, cardiovascular health and overall performance in male volunteers.

**Keywords:** Standardized fenugreeks seed extract; Protodioscin; Testosterone booster; Sperm profile; Mood alleviation; Safety

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**Introduction**

Fenugreek plant and seeds are rich in soluble fibers, and extensively used in Ayurvedic, Chinese and Unani medicines for anti-inflammatory, anti-diabetic, antiseptic, aphrodisiac, women’s health and diverse health benefits for centuries (1-9). Fenugreek leaves, twigs, roots, sprouts, microgreens and the yellow- to amber-colored cuboid-shaped seeds are extensively used in versatile culinary purposes, spices, salads, soups, brewed into a tea, baked into a bread, and pickles in the Asian countries. (1-3, 7-15). The fenugreek seeds are often roasted to optimize bitterness and flavor (3,6,9). Literature reveals that fenugreek contains approximately 28% mucilage, 5% stronger-smelling, bitter fixed oil, rich in phosphates, lecithin and nucleoalbumin, considerable amounts readily absorbable iron in an organic form, as well as trigonelline, trimethylamine, choline, biotin, inositol, vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B5, vitamin B6, vitamin B9, vitamin B12, and vitamin D, diosgenin, diosgenin-D-glucoside, neurin, betaine, vitexin, vitexin-7-glucoside, yamogenin, vicenin, saponaretin and isoorientin (4-8,12).

Fenugreek and its seeds have exhibited versatile health benefits including antioxidant, anti-inflammatory benefits, anti-diabetic, hypercholesterolemia, polycystic ovary syndrome, gastric ulcer and hyperthyroidism, and exercise (4-12). The dose-dependent efficacy of fenugreek seed extract (0, 150 or 300 mg/kg body weight) was investigated over a period of 4 weeks in male mice on endurance capacity in a swimming model (13). The fenugreek seed (300 mg/kg body weight) significantly attenuated swimming endurance, which is reported by the authors that the utilization of fatty acids was significantly increased as an energy source. Arshadi et al. (2015) also assessed the efficacy of fenugreek seed (0, 0.8 or 1.6 g/kg body weight) extract in combination with swimming exercise compared to glibenclamide in type 2 diabetic male rats (14,15). Arshadi et al. concluded that fenugreek seed consumption, along with swimming exercise, induced a therapeutic efficacy on the improvement of ant-diabetic profiles including plasma insulin, HOMA-IR, plasma leptin and adiponectin (14,15).

In a placebo-controlled, double blind study in 49 resistance-trained male volunteers, Poole et al. (2010) assessed the effect of fenugreek supplementation (500 mg/day) on strength, body composition, muscle endurance, power output and hormonal profiles over a period of 8 weeks, and demonstrated that fenugreek can significantly increase upper- and lower-body strength, reduce body fat and improve overall body composition (16).

This study assessed the efficacy of a novel, patented fenugreek (*Trigonella foenum-graecum*) seed extract enriched in 20% protodioscin (Furosap®, US Patents# US 8,217,165 B2; US 8,754, 205 B2)(17,18) to boost free testosterone levels, sperm profile and morphology, sexual health, mood and mental alertness, and broad spectrum safety parameters in 50 male volunteers (Age: 35-65 years) over a period of 12 weeks.

**Materials and Methods**

***Trigonella foenum-graecum* Seed Extract**

A novel, patented fenugreek (*Trigonella foenum-graecum*) seed extract (color: off white to light yellow powder, characteristic odor) enriched in 20% protodioscin (Furosap®, Batch# FUP0814, US Patents# US 8,217,165 B2; US 8,754, 205 B2)(17,18). The powder is >95% soluble in water and moisture content is <5%, both residual solvent and residual pesticide comply with USP38 requirements, and the shelf-life is 2 years.

**Ethical Approval**

This study was registered at clinicaltrials.gov (NCT02702882), while the study design, recruitment and methods were performed in compliance and accordance with the ICH guidelines for Good Clinical Practices (GCP), including the archiving of essential documents, and per international ethical standards guaranteed by the Declaration of Helsinki and its subsequent amendments. Institutional Ethical Board for Medical Research and Institutional Ethics Committee (IEC) from the Ethical Board for Medical Research of Saroj Hospital & Maternity Center (Kanpur Road, Lucknow, Uttar Pradesh, India) approved this Clinical Study (Reference# EBMR/2014/07/28/01 dated July 28, 2014). The study was conducted in Saroj Hospital & Maternity Center (Kanpur Road, Lucknow, Uttar Pradesh, India). All subjects duly reviewed and signed the Consent Forms. The consent form was submitted with the protocol for review and approved by the IEC. Patient’s confidentiality was strictly maintained.

**Subject Recruitment and Compliance**

The subjects were systematically screened for the clinical study on the basis of the inclusion/ exclusion criteria as follows and fifty male subjects were enrolled (age: 43.08 + 7.35 years; body mass index (BMI): 25.46 + 4.13 kg/m2; body weight: 70.38 + 12.18 kg; systolic blood pressure 124 + 9.40 mm Hg; diastolic blood pressure 79.65 + 6.53 mm Hg; pulse 77.53 + 6.4 pulse/minute). Inclusion criteria: male subjects (age 35-65 years) diagnosed with symptomatic hypogonadism, understand the risks/benefits of the protocol and agrees to written as well as audio-visual informed consent; and Exclusion criteria: uncooperative subjects, receiving any other testosterone boosters for the last 2 months, suffering from coronary artery disease and allied complications, history of malignancy, coagulopathies (clotting and bleeding), psychiatric disorders or hypersensitivity to Furosap®, high alcohol intake (>2 drinks per day), abnormal hepatic or renal functions (ALT or AST > 2 times the upper limit of normal; creatinine> 125 μmol/L), impaired liver function >2.5 times the upper limit of normal, and any particular medical condition, where the investigator feels participation in this study could be detrimental to the subjects overall well-being. Enrolled subjects were given Furosap® (1 capsule of 500 mg each/day after breakfast) over a period of 12 consecutive weeks.

Furosap® was given to the subjects by the site staff and records were maintained in the IP accountability log. All data were maintained separately with the date/signature of the principal investigator & study coordinators. Any concomitant prescription medications taken during study participation were recorded on the case report forms (CRFs). All medications including prescription medications, over-the-counter medications (OTC) and non-prescription medications taken during the clinical study were meticulously recorded and routinely examined by the principal investigator & study coordinators.

**Methods**

The efficacy of Furosap® was assessed on 50 male volunteers and clinical evaluations were conducted at baseline, at the end of 4- and 8-weeks, and at the end of 12 weeks. BMI (kg/m2), free testosterone (pg/ml), total testosterone (ng/dl), dehydroepiandrosterone sufate (DHEA-S), fasting blood sugar (FBS), fasting lipid profile (total cholesterol, LDL, HDL, triglycerides, VLDL), liver function test (AST, ALT, ALP), semen examination (sperm count, sperm motility, sperm morphology and hemogram were extensively assessed at baseline and at the end of 12 weeks, respectively, while BMI, fasting lipid profile (total cholesterol, LDL, HDL, triglycerides, VLDL) and semen examination (sperm count, sperm motility, sperm morphology were assessed at the end of 4- and 8-weeks, respectively.

Free testosterone was measured using a Dia Sources’ ELISA kit (catalog#CAN-FTE-260) purchased from Krishgen Biosystems, Mumbai, India, and total testosterone was assessed using an automated bidirectionally interfaced Chemiluminescent Immunoassay (CLIA) from Siemens Health Care Pvt Ltd, Mumbai, India. Dehydroepiandrosterone sulfate (DHEA-S) was assessed using the Cobas Electrochemiluminescence Immunoassay (ECLIA) (catalog# 03000087122) kit purchased from Roche Diagnostics India Pvt Ltd, Mumbai, India. Hemoglobin level was evaluated using a Sysmex fully automated bidirectional analyzer (SYSMEX XN-1000) purchased from Transasia Bio Medicals Ltd, Mumbai, India, and fasting blood glucose (FBS) levels were assessed using photometry technology (Agappe Diagnostics Ltd, Mumbai, India). Aspartate Aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT), blood urea nitrogen (BUN), cholesterol, triglycerides, high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), very low density lipoprotein (VLDL), total leukocytes count (TLC), neutrophils, lymphocytes, monocytes, eosinophils and basophils in Central Processing Lab (CPL, a division of Thyrocare, Mumbai, India) and Regional Processing Lab (RPL, a division of Thyrocare, Mumbai, India). Sperm count, sperm motility and abnormal sperm morphology were assessed in Nigam Pathology (Lucknow, India).

**Adverse Events**

Adverse event reporting was strictly enforced.

**Statistical Analysis**

Data is expressed as mean ± SD (standard deviation) or SEM (standard error mean). All parametric and non-parametric assessments were conducted. Wilcoxon signed-rank test, a nonparametric test equivalent to the dependent t-test, was used for assessing mental alertness, mood, reflex erection and overall performance.

**Results**

**Furosap®-induced effect on free testosterone and total testosterone**

Male volunteers were treated with FS over a period of 12 consecutive weeks. Free testosterone and total testosterone levels were assessed at baseline and at the end of 12 weeks of treatment (Figure 1). Furosap®-induced a significant increase in free testosterone level by approximately 1.47-fold (p value = 0.0004\*\*), while the total testosterone level was increased marginally by only 1.08-fold (p-value = 0.164ns).

**Effect of Furosap® on sperm count (millions/ml), sperm motility (%) and abnormal sperm morphology (%) at baseline, 4-, 8- and 12-weeks of treatment**

Sperm count (millions/ml), sperm motility (%) and abnormal sperm morphology (%) were evaluated at baseline, after 4 weeks, after 8 weeks and after 12 weeks following supplementation of FS. Sperm count and sperm motility were significantly increased at the end of 4-, 8- and 12-weeks of FS treatment, while abnormal sperm morphology (%) reduced at all these time point. Although, abnormal sperm morphology (%) was reduced at 4-weeks post-treatment, however, it was not significant. However, abnormal sperm morphology (%) was significantly reduced both at 8- and 12-weeks post-treatment, respectively (Table 1).

**Effect of Furosap® on dehydroepiandrosterone sulfate (DHEA-S), fasting blood sugar (FBS)**

**and total leukocyte count (TLC)**

DHEA-S, FBS and TLC levels were measured at baseline and at 12 weeks of treatment. No significant changes were observed. (Figure 2)

**Time-dependent effect of Furosap on mental alertness, mood alleviation, reflex erection and overall performance at baseline, week 4-, week 8- and week 12 of treatment**

Mental alertness, mood alleviation, reflex erection and overall performance were assessed at baseline, week 4, week 8 and week 12 of treatment (data not shown). Wilcoxon signed-rank test, a nonparametric test equivalent to the dependent t-test, were used to assess the statistical significance. Significant improvements were observed for all these parameters at all time points.

**Effect of Furosap® on serum chemistry parameters following supplementation of Furosap® over a period of 12 weeks**

No significant changes were observed in serum aspartate aminotransferase/glutamic oxaloacetic transaminase (AST/GOT), alanine aminotransferase/glutamic pyruvic transaminase (ALT/GPT), alkaline phosphatase (ALP) and blood urea nitrogen (BUN) following treatment with Furosap® over a period of 12 weeks.

**Time-dependent effect of Furosap® on cholesterol, triglycerides, serum HDL-C, LDL-C and VLDL-C**

No significant changes were observed in cholesterol, triglycerides, serum HDL-C, LDL-C and VLDL-C levels following supplementation of Furosap® over a period of 4-, 8- or 12-weeks of treatment

**Effects on neutrophils, lymphocytes, monocytes, eosinophils, basophils and hemoglobin levels following supplementation of Furosap®**

Furosap® didn’t induce any significant effects on neutrophils, lymphocytes, monocytes, eosinophils and basophils over a period of 4-, 8- or 12-weeks of treatment. A small decrease was observed in the hemoglobin level, however, the baseline and 12-weeks post-treatment hemoglobin levels lied within the normal range.

**Discussion**

A broad spectrum of studies have demonstrated that fenugreek (*Trigonella foenum-*graecum) has exhibited a significant number of health benefits. Fenugreek attenuated body weight gain, obesity and metabolic syndrome related complications, improved insulin sensitivity, anti-diabetic efficacy, muscle building, physical and sexual health, polycystic ovary syndrome, women reproductive disorders and several others (2,4,6-12). In ancient days, Ayurvedic, Unani and Chinese medicines have repeated demonstrated the multiple medicinal and therapeutic benefits of fenugreek leaves, twigs and seeds in a broad spectrum of human diseases and ailments including diabetes, obesity, women reproductive disorders, muscle building and wrestling (4-7,19-23). Fenugreek seeds have demonstrated to contain selected furostanolic saponins, protodioscin, B vitamins, vitamin D, 4-hydroxyisoleucine, diosgenin, diosgenin-D-glucoside and others. An in vitro study by Tomcik et al. (24) demonstrated that fenugreek seeds in combination with insulin significantly modulated creatine content via a mechanism which is independent of the activity of sodium- and chloride-dependent creatine transporter, SLC6A8 (24). In the recent past, another independent study by

Hamden et al. (25) demonstrated that following administration of fenugreek seeds to diabetic rats significantly decreased the sperm shape abnormality and improved the sperm count. Furthermore, potential protective efficacy of fenugreek seed extract was observed on reproductive systems, as demonstrated by histological studies on testis and epididymis (25). Aswar et al. (26) assessed the efficacy of fenugreek seed extract (10 mg/kg s.c. bi-weekly or 10 and 35 mg/kg body weight orally on immature castrated male Wistar rats. Some anabolic activity was observed in these animals without androgenic activity (26).

Multiple human studies were conducted in the recent past demonstrating the efficacy of fenugreek seeds in boosting both free- and total testosterone levels, sexual and physical health. Testosterone has also been demonstrated to attenuate lean body mass and stronger bones. A clinical investigation in 49 resistance-trained male subjects demonstrated that fenugreek seed extract (500 mg/day) had a significant impact on both upper- and lower-body strength and body composition in a double-blind placebo-controlled study (16). Three independent studies demonstrated the clinical efficacy fenugreek extract in boosting testosterone levels (27-29). The authors indicated that a positive effect was observed on the physiological aspects of libido, muscle strength and energy. The second study was conducted in 80 healthy menstruating women who reported low sexual drive (age: 20 to 49 years; dose: 600 mg/day), which demonstrated that fenugreek seed extract is beneficial for boosting sexual arousal and desire in women. The third randomized, double-blind, placebo-controlled study was conducted in 120 men (age: 43-70 years; daily dose of fenugreek extract: 600 mg) over a period of 12 weeks. Both free and total testosterone levels and sexual function increased significantly after 12 weeks of treatment (27-29).

This investigation exhibited that Furosap®, enriched in 20% protodioscin, is instrumental in significantly enhancing free testosterone level, sperm count, sperm motility, mental alertness, mood alleviation, reflex erection and overall performance in healthy male volunteers.

**Conclusion**

This clinical study demonstrates that Furosap®, a novel, 20% protodioscin-enriched extract from *Trigonella foenum-graecum* seeds, significantly increased free testosterone level by 1.47-fold (p value = 0.000\*\*) following treatment for a period of 12 weeks, while the total testosterone level was marginally increased by 1.08-fold. Statistically significant increases were observed in sperm count and sperm motility at 4-, 8- and 12-weeks of Furosap® treatment, while, a statistically significant decrease in abnormal sperm morphology was observed. Mental alertness, mood alleviation, reflex erection and overall performance were significantly alleviated at week-4, week-8 and week-12 of treatment. Cardiovascular health was significantly improved. Broad spectrum lipid profile and blood chemistry analyses data demonstrated the safety of Furosap®.

**Authors’ Contributions & Conflict of Interest**

All authors contributed to this study. AM is the principal investigator and NV is the co-principal investigator, organized, coordinated the study and analyzed the data. MB and HGP served as consultants and coordinated in writing the manuscript and coordinated with AM, NV and DB. DB is the chief scientific officer of Cepham, Inc., and AS is the president of Cepham Inc. AM, NV, MB, HGP and DB have no competing interests.

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