MR-10®

Famenity

Men's Health

FDA NDIN

KFDA Certification

Achievement of
National Research Project

3 Independent Clinical Studies

Energize Men

* Non -GMO Botanical Extract, Water Soluble Powder.

White Paper: MR-10® for Men's Health

MR-10®: A Natural Botanical Ingredient Blend Clinically-Proven to Alleviate Symptoms of Andropause*

Introduction

MR-10® is a natural dietary ingredient blend composed of botanical bioactive compounds extracted from Korean dandelion and rooibos. In a series of published, peer-reviewed *in vitro*, *in vivo* and human clinical studies, researchers found that **MR-10® exerted significant improvements in alleviating various male andropause symptoms, up-regulating serum testosterone levels, and increasing sperm count and activity** [1,2]**.** In addition to proven efficacy, a suite of toxicology studies were conducted on MR-10® and found that it is a safe, nontoxic ingredient with no adverse effects reported.

Androgens are male sex hormones (such as testosterone) and as men age, it is common for androgen levels to progressively decline. Andropause is defined as a collection of symptoms experienced by some middle-aged or elderly men resulting from the gradual decline in testosterone levels over time. These symptoms can include fatigue, decrease in libido, loss of skeletal muscle mass, decrease in energy and physical capacity, depression, and decreased sperm motility [3-7]. A predominant proportion of aging and older men have reduced levels of serum testosterone, which is a major cause for andropause symptoms [8].

Safe, natural substances capable of reducing andropause symptoms in aging men are essential, due to the fact that an increasing proportion of men will become affected as the general life span is prolonged.

A team of Korean researchers with the support of the Korean Ministry of Health and Welfare screened a large number of natural substances in search of those that could promote health in aging men. **After extensive research, it was demonstrated that the herbal extract MR-10®, was safe and effective for alleviating symptoms related to andropause.**

Raw Materials

Korean dandelion (*Taraxacum platycarpum*) is a perennial herbaceous plant and member of the Asteraceae family. Korean dandelion has been used as a medicinal herbal remedy in ancient traditional Korean medicine for centuries. Rooibos (*Aspalathus linearis*) is a member of the Leguminosae family native to South Africa. Rooibos, meaning "red bush", is commonly consumed as a caffeine-free herbal tea.

Bulk Ingredient Characteristics and Applications

The bioactive components from the Korean dandelion plant and the fermented leaves of the rooibos plant are purified into a proprietary powdered extract. MR-10® is a free-flowing, gray-green powder and is shelf stable for up to 3 years when stored at room temperature. MR-10® is water-soluble and heat-stable and can be used as a formulation ingredient in various dietary supplement applications. **Serving forms include tablets, capsules, gel tabs, gummies, beverages, films and powdered mixes**. The recommended serving size is **400 mg/day**, as this was the dose tested in the human clinical trials that resulted in

significant improvement in andropause symptoms as well as a safe serving level established through toxicology testing.

REGULATORY SUMMARY

MR-10® Regulatory Status as a Dietary Ingredient in the United States

MR-10® is the first and only dietary ingredient complex of its kind to successfully file a **New Dietary Ingredient Notification with the US FDA (NDIN #1109).** In response, the FDA issued a "letter of acknowledgement without objection" in 2019. FDA reviewed the ingredient's identity, purity, limit on contaminant specifications, manufacturing process, historical consumption and a suite of toxicology data and had no objection to "a reasonable expectation of safety" established for MR-10® in order for it to be marketed and sold as a dietary ingredient in the United States.

MR-10® Regulatory Status as a Dietary Ingredient in Korea (Country of Origin)

MR-10® received certification from the **Ministry of Food & Drug Safety of Korea (MFDS)** as a Health Functional Food Ingredient with an authorized health claim (Recognition No: 2013-31 (2013.10.17) **Health claim: May help to maintain male health during andropause**). MFDS is the FDA-equivalent regulatory body in Korea and prior to granting the certification, the agency evaluated the safety and efficacy of the dietary ingredient. The agency states that only the party that's been granted the certification can make health claims regarding the efficacy and performance of the product.

MR-10® Regulatory Status as a Natural Health Product in Canada

MR-10® received certification from **Health Canada** as a Natural Health Product with an authorized health claim (NPN no. 80111522 (2021. 7), **Health claim: "Helps to reduce symptoms of age-related androgen decline.** Helps to improve quality of life in men suffering from age-related androgen decline."

HUMAN CLINICAL TRIALS

I. "Improvement of andropause symptoms by dandelion and rooibos extract complex MR-10® in aging male" [1]

For this 4-week, double blind, randomized, placebo-controlled trial, the researchers recruited thirty men over 40 years of age at Chung-Ang University Medical Center, Seoul, Korea. The test material was a botanical blend of Korean dandelion and rooibos extract, named "CRS-10" in the study. MR-10® is the registered trade name for the CRS-10 test material used in the study, produced by the same manufacturer and of the same botanical and phytochemical composition. Volunteers were distributed into one of three groups: group 1 (n = 10) was the placebo control, group 2 (n = 10) was treated with 200 mg/d of MR-10® and group 3 (n = 10) was treated with 400 mg/d of MR-10®. Clinical data was obtained through the Aging Males Symptoms (AMS) scale questionnaire before and after the 4-week regimen.

The AMS scale is one of the most commonly used scales worldwide to measure health-related quality of life (QOL) markers and symptoms arising in aging men. The questions are designed to assess the symptoms that are associated with androgen decline. Each question is to be answered on a scale from 1 to 5. The 17 questions are divided into 3 subscales—psychological, somatic, and sexual symptoms—and are summed up for the total score. The psychological subscale evaluates the following symptoms: depressive mood, feeling burned out, increased irritability, anxiety, and nervousness; the somatic subscale consists of increased joint complaints, increased sweating, need for more sleep, impaired well-being, increased sleep disturbances, muscular weakness, physical exhaustion, and decrease of beard growth; and the sexual subscale consists of impaired sexual potency, fewer morning erections, disturbed libido, and feelings that the subject has passed his "peak". A total score of ≥ 27 has been defined as suggestive of androgen deficiency [9].

Results. Higher AMS scores indicate a greater severity of negative symptoms, whereas lower scores indicate lower to no severity. **After 4 weeks of administration, the men treated with 400 mg/day of MR-10® had a significant reduction in their AMS scores. Compared to baseline, the**

AMS scores decreased by about 20% (P <0.05) in the 400 mg/kg group whereas there was no significant difference in the placebo group ((P>0.05), Fig. 1).

Therefore, the effective clinical dose in this study for the reduction of andropause symptoms was 400 mg/ day of MR-10®.

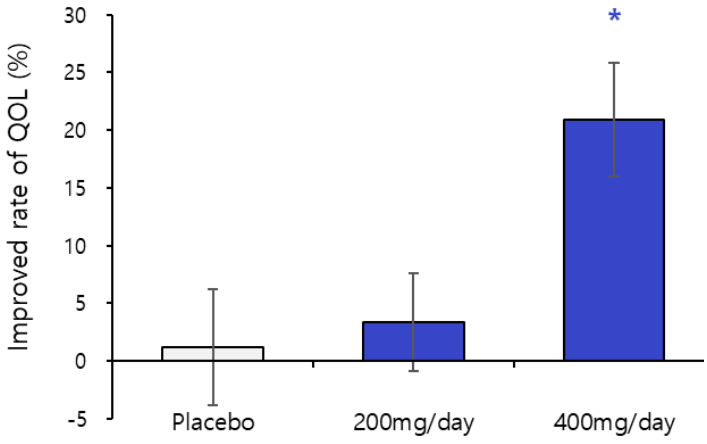

Figure 1. Percent Improvement from baseline in AMS scores. Significant differences are denoted by * (P < 0.05).

II. "MR-10® Enhances Men's Health by Improving Endogenous Male Sex Hormone Generation" [2]

Aging Males' Symptoms and ADAM Questionnaires

This was a 4-week, double blind, randomized, placebo controlled clinical trial. Demographic and clinical data were obtained through questionnaires and interviews with the participants, and the levels of serum hormones and enzymes were measured. Researchers blinded to all clinical information randomly distributed each participant to either the MR-10® (n=48) or placebo (control) group (n=48). Before taking either MR-10® or the placebo, each participant underwent a baseline assessment of height, weight, body mass index (BMI), and serum chemistry. Participants took a capsule containing either 200 mg MR-10® or the placebo twice a day (400 mg/day) for 4 weeks.

In order to assess andropause symptoms, the researchers used the Androgen Deficiency in Aging Males (ADAM) and Aging Males' Symptoms (AMS) clinical questionnaires at weeks 0 and 4.

The ADAM questionnaire is a 10-item screening tool for identifying androgen deficiency in aging men. If a participant responds affirmatively to decreased libido or strength of erection or gives a positive response to any 3 of the nonspecific questions including fatigability, decreased muscle strength, mood changes, and loss of height, he is considered as having symptoms suggestive of androgen deficiency [9].

Results. In the **MR-10® treatment group, the prevalence of andropause as assessed by the ADAM questionnaire dropped from about 80% to 42% after a month of MR-10®** supplementation at a dose of 400 mg/day, whereas in the placebo control group, there was no significant difference (Fig 2). In regards to AMS scores, the MR-10® group decreased from 37.2 before treatment to 30.9 after treatment (P< 0.05), whereas no change was observed in the placebo control group (P> 0.05, Fig. 3). The improvement rate in the MR-10® group was 20% (P< 0.05).

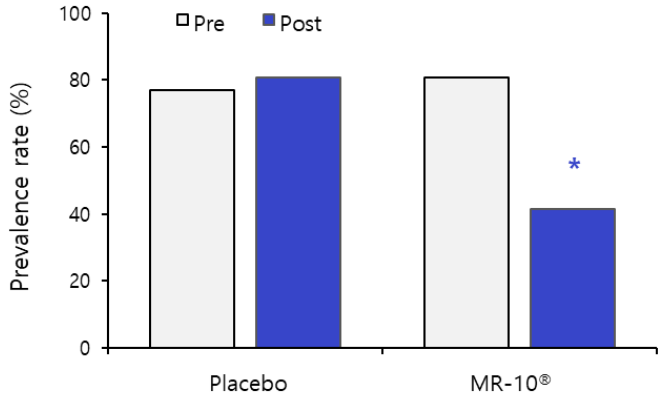

Figure 2. A comparison of the ADAM score between MR-10® and placebo groups. Significant differences are denoted by * (P < 0.05).

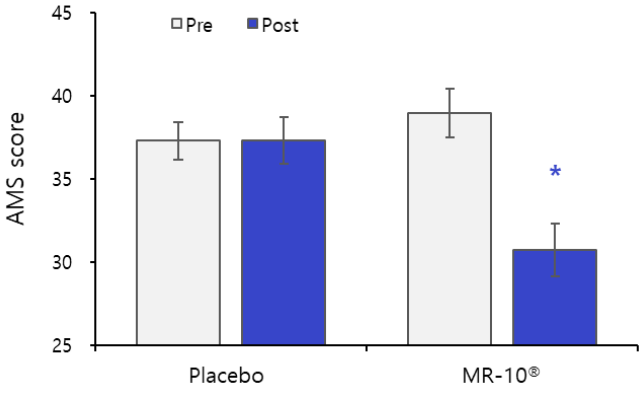

Figure 3. A comparison of the AMS score between MR-10® and placebo groups. Significant differences are denoted by * (P < 0.05).

Therefore, MR-10® improved the andropausal symptoms related to male vitality, emotional state, joint and muscle pain, sleep, and sexual function by about 20%.

International Prostate Symptoms Score (IPSS)

The International Prostate Symptom Score (IPSS) was developed to be an objective assessment of lower urinary tract symptoms and related discomfort that can occur in cases of poor prostate health. The scores are based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. Patients choose answers indicating increasing severity of the particular symptom. The urinary symptoms assessed relate to incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia (excessive urination at night).

The researchers in this study used the IPSS questionnaire at weeks 0 and 4.

Results. In the MR-10® treatment group, mean IPSS scores decreased from 11.5 before treatment to 8.79 after treatment ($P<0.05$), whereas no significant change was observed in the placebo control group ($P>0.05$). The improvement rate in the MR-10® group was 24% ($P<0.05$, Fig. 4) [10].

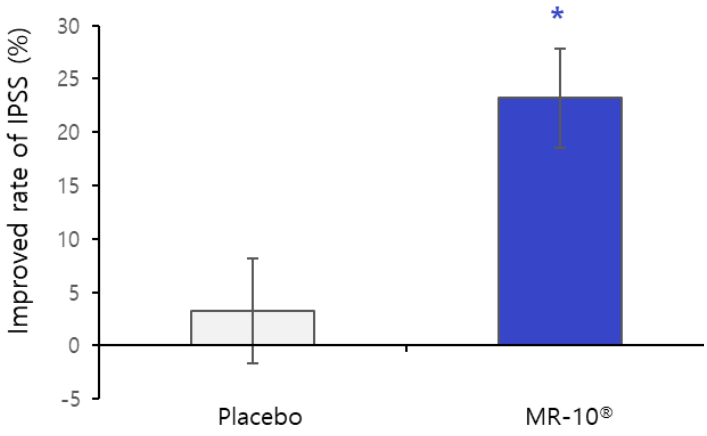

Figure 4. A comparison of the IPSS between MR-10® and placebo groups. Significant differences are denoted by * ($P < 0.05$).

Blood Tests and Sex Hormones

Fasting blood samples of the study participants were obtained to measure the levels of total testosterone (TT), free testosterone (FT) and dehydroepiandrosterone (DHEA), a sex hormone precursor. In addition, sex-hormone binding globulin (SHBG) levels were analyzed. SHBG tends to increase with age, and SHBG binds to free testosterone meaning that higher levels of SHBG may decrease the levels of circulating free testosterone in the body.

Results. The levels of TT, FT, and DHEA were 14.4% ($P< 0.05$), 22.4% ($P< 0.05$), and 32% ($P< 0.05$) higher than basal levels, respectively, after ingestion of MR-10® for 4 weeks, whereas there were no significant differences in the placebo control group (Fig. 5A–C).

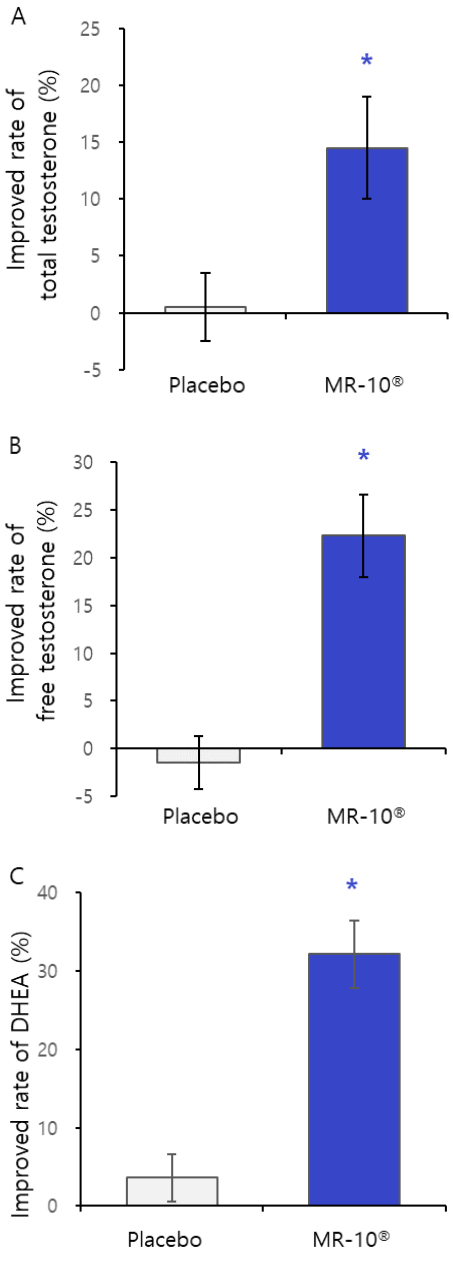

Figure 5. A-C. A comparison of serum testosterone, free testosterone, and DHEA levels between MR-10® and placebo groups. Significant differences are denoted by * ($P < 0.05$).

In addition, in the **MR-10® treatment group, SHBG levels were reduced in 68% of the men**, whereas the number of men in the placebo control group with reduced SHBG levels was not statistically significant. SHBG levels were an average of 6.2% (P<0.05) lower after MR-10® treatment than before treatment.

Thus, the results showed that MR-10® improved levels of serum testosterone precursors (DHEA), testosterone, free testosterone and SHBG.

Safety Assessment

As part of the safety assessment, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvate transaminase (GPT) were analyzed, as they are considered general markers for indicating potential liver injury. In addition, prostate-specific antigen (PSA) levels were analyzed. PSA levels tend to increase with age, and higher levels can also be a side effect of testosterone replacement therapy and an indicator for compromised prostate health.

Results. There was no significant change in the levels of GOT, GPT or PSA in either the MR-10® or placebo groups.

Preclinical Studies and Cell Proliferation Assay [1]

In this study, the researchers analyzed the effects of MR-10®, Korean dandelion and rooibos extract on serum testosterone levels, physical exertion capacity, and spermatogenesis (production of sperm) in aging male rats.

Ten aging male rats (18 weeks old) were orally administrated 40 mg/kg of MR-10® daily for 4 weeks as the experimental group and an additional 10 rats were administered 40 mg/kg of flour daily as the control group.

Measurement of serum testosterone levels

Blood samples were collected from the test animals and the amount of serum testosterone was measured by a standard coated-tube radioimmunoassay kit.

Results. MR-10® significantly up-regulated serum testosterone levels from approximately 3.52 ng/ml to 5.04 ng/ml. The **improvement rate was about 43%** compared to baseline, whereas no significant increase was detected in the control group (p<0.05, Fig.6).

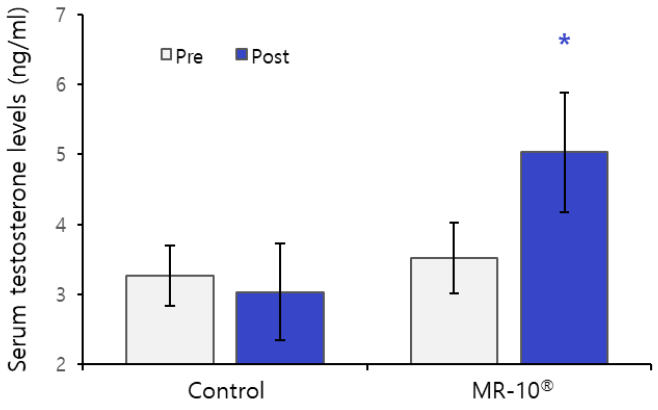

Figure 6. Increased serum testosterone level by MR-10®.Significant differences are denoted by * P < 0.05.

Rotarod and Swimming Retention Test

Testosterone enhances physical locomotion capacity [11]. To determine the effects MR-10® or placebo had on physical strength and locomotive ability, rats were evaluated via rotarod and swimming retention tests and the results were recorded throughout the course of the study period. The rats were trained in rotarod and swimming exercises for 3 times a day for 30 days.

Results. The latency time it took to fall off the rotarod increased from about 200 sec to 250 sec in the MR-10® group, representing a 25% improvement, whereas the controls showed no increase in latency time. Furthermore, the **MR-10®-treated rats demonstrated significantly increased swimming time compared to the control group** (p<0.05), while the control rats had no significant improvement.

Sperm count and activity

To investigate the effects MR-10® had on spermatogenesis (production of sperm), sperm count and activity were evaluated in the control and MR-10®-treated rats. A hemocytometer was used to determine the number of spermatozoa. Sperm activity was represented as a portion of active sperm 4 h after sperm acquisition and the mobile sperm were enumerated.

Results. The sperm count per gram of epididymis significantly increased from approximately 51.6 × 10^6 to

approximately 60.8 × 10^6 in the MR-10® treatment group, representing a 20% improvement rate (P< 0.05,), whereas no significant change in the sperm number was detected in the control rats. In regards to sperm activity, the **percentage of active sperm in the MR-10® treatment group markedly increased from 50% to 71%, representing an over 40% improvement** (P< 0.05, Fig.7), whereas no significant difference was detected in the control. The control group displayed no differences in both the number and activity of sperm.

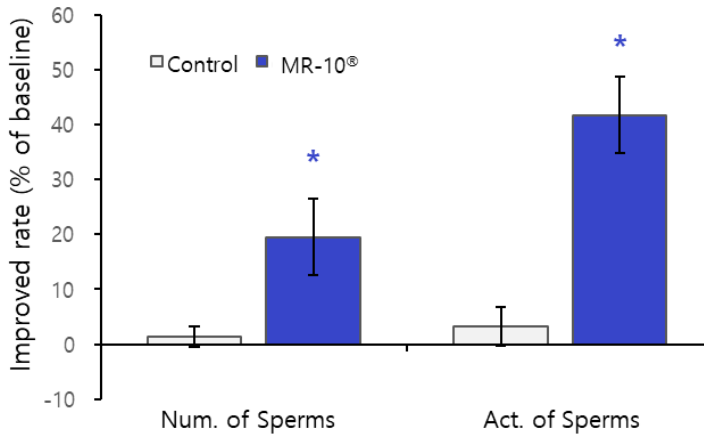

Figure 7. Sperm count and activity by MR-10® and control treatments presented as a percentage compared to baseline. Significant differences are denoted by * P < 0.05.

Cell viability assay

Leydig cells are located in the connective tissue surrounding the sperm-producing tubules in the male testes and are responsible for the production and secretion of testosterone in the body. TM3 cells are Leydig cell lines derived from mouse testes and were the cell line used in this cell viability assay.

This study analyzed the effects of extracts from dandelion (ED) or rooibos (ER) individually and the complex of ED and ER (MR-10®) on TM3 Leydig cells, and determined whether the extracts had a protective effect on the cells in conditions of low serum levels and oxidative stress.

In low serum (1%) medium, TM3 cells display a general decrease in proliferation rate as well as induction of apoptotic cell death. Thus, low serum medium in this study represented stressful conditions for TM3 cells.

In addition, hydrogen peroxide (H_2O_2) is an oxidizing agent which produces free radicals and leads to oxidative damage to proteins and membrane lipids. To determine whether the ED, ER, or MR-10® could protect TM3 cells from H_2O_2-induced damage, TM3 cells were pretreated with 10 µg/ml and 50 µg/ml of dandelion, rooibos or MR-10® extracts and incubated with H_2O_2. Cell viability in low serum and H_2O_2 conditions was analyzed with the Alamar Blue assay.

Results. In low serum conditions, treatment of MR-10® increased the survival rate of TM3 cells (Fig. 8A). Treatment of MR-10® also significantly increased cell viability of TM3 cells by up to 38% (p<0.05), while statistically significant increased cell viability was not detected from the treatment of either ED or ER extracts individually. **This suggests a synergistic effect of the combined extracts.** Moreover, the cells in MR-10®-treated media appeared healthy without apoptotic features, whereas some control cells displayed apoptotic morphological features, such as floating and loss of cellular shape (Fig. 8B).

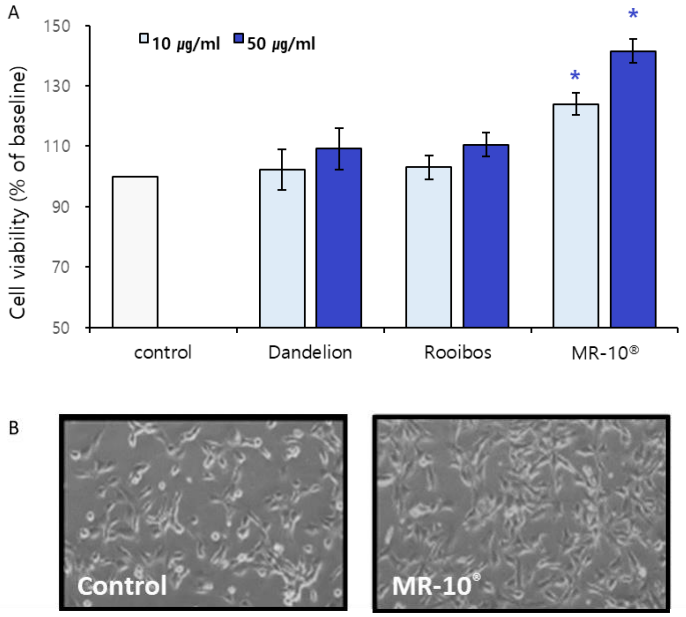

Figure 8. A-B. Protective effect of MR-10® against low serum-stress (A). The photographs represent the optical phase contrast microscopic morphology (B). The values are mean ± SE of four separate independent experiments. Significant differences are denoted by * P < 0.05.

MR-10® protected TM3 cells against H_2O_2 - induced cellular stress

As expected, 2 h incubation with H_2O_2 significantly decreased cell viability by 40% compared to the cells cultured without H_2O_2. However, cell viability increased to 138% and 148% with MR-10® treatment concentrations of 10 µg/ml and 50 µg/ml, respectively, indicating a dose-dependent protective effect (Fig. 9). ED and ER demonstrated cell viability increases as well; however MR-10® was much more effective in protecting TM3 cells than were ED or ER alone.

Through the results of this study, it was determined that MR-10® increased TM3 cell viability in stressed conditions (e.g., low serum medium) and effectively protected TM3 cells against physiological oxidative stress. **The results indicate that MR-10® may play a significant positive role in maintaining the health of TM3 cells, and thus may result in the sustained production of testosterone.**

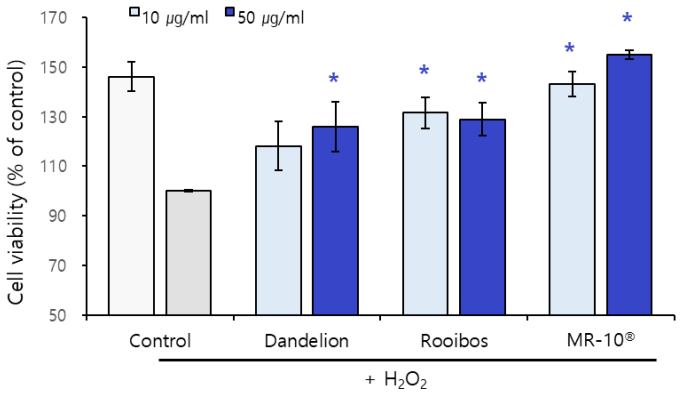

Figure 9. Cell viability of TM3 cells treated with H_2O_2 in presence of dandelion extract, rooibos extract or MR-10®. Significant differences are denoted by * $P < 0.05$.

Overall, MR-10® protected TM3 cells from low serum conditions and oxidative stress. In addition, MR-10® treatment resulted in higher levels of testosterone and activation of spermatogenesis in rats.

Conclusion

In conclusion, MR-10® effectively improved andropause symptoms and testosterone levels in aging men in two clinical studies and also enhanced physical performance and activation of spermatogenesis in an animal model. These positive effects may have occurred through protection and activation of Leydig cells, together with induced generation of endogenous testosterone.

The results of various *in vivo, in vitro* and human clinical trials indicate the potential for MR-10® to be a safe and efficacious natural substance for reducing and alleviating the symptoms of andropause in aging men.

References

1. Noh, YH, et al. "Improvement of andropause symptoms by dandelion and rooibos extract complex CRS-10 in aging male" *Nutritional Research Practice* 6.6 (2012): 505-512.

2. Noh, YH "MR-10 enhances men's health by improving endogenous male sex hormone generation" *Journal of Medicinal Food* 21.12 (2018): 1288-1294.

3.Travison, TG, et al. "Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation" *The Journal of Gerontology Series A* 66A.10 (2011): 1090-1099.

4. Tan, RS, et al. "Impact of obesity on hypogonadism in the andropause" *International Journal of Andrology* 25.4 (2002): 195-201.

5. Vermeulen, A, et al. "Ageing of the hypothalamo-pituitary-testicular axis in men"*Hormone Research in Paediatrics* 43 (1995): 25-8.

6. Vermeulen, A. "Environment, human reproduction, menopause,and andropause"*Environmental Health Perspectives Supplements*101 Suppl 2 (1993):91-100.

7. Bornman, MS, et al. "Serum testosterone levels in South Africanmen and the onset of androgen decline in ageing males"*South Africa Journal of Surgery* 45(2)(2007):62, 64.

8. Chen, RY, et al. "Self-referred older Asian males in a men's health clinic: the inter-relationships between androgens, metabolic parameters and quality of life measures" *The Aging Male* 13 (2010): 233-41.

9. Chueh, KS, et al. "The Comparison of the Aging Male Symptoms (AMS) Scale andAndrogen Deficiency in the Aging Male (ADAM) Questionnaire toDetect Androgen Deficiency in Middle-Aged Men" *Journal of Andrology* 33(5) (2012): 817-23.

10. Clinical Trial Report (2012, Chung-Ang University, College of Medicine), "Human trial of the herbal complex extract CRS-10 (MR-10) for treating andropause".

11. Sattler, F, et al. "Testosterone threshold levels and lean tissue mass targets needed to enhance skeletal muscle strength and function: the HORMA trial" *The Journal of Gerontology Series A* 66A.1 (2011): 122-129.

White Paper prepared by: US Botanical Safety Laboratory, 1463 Sand Hill Rd. Ste 305 Candler, NC 28715. Contact: support@usbsl.org

Famenity

E-mail: sales@famenity.com Website: www.famenity.com