A green and black tea extract benefits urological health in men with lower urinary tract symptoms

Aaron Katz, Mitchell Efros, Jed Kaminetsky, Kelli Herrlinger, Diana Chirouzes, Michael Ceddia

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Abstract

Objectives: The objective of this study was to examine the effects of a green and black tea extract blend [AssuriTEA Men's Health (AMH)] in men with lower urinary tract symptoms (LUTS).

Methods: In this randomized, double-blind, placebo-controlled study, 46 men aged 30–70 with an American Urologic Association symptom score (AUAss) of at least 8 and up to 24 were randomized to 500 mg AMH, 1000 mg AMH, or placebo daily for 12 weeks. Measurements were taken at baseline (BL), week 6 and week 12 for AUAss, simple uroflowmetry, postvoid residual volume (PVR), C-reactive protein (CRP), Short-Form 36 Health Survey (SF-36), and International Index of Erectile Function (IIEF).

Results: A total of 40 subjects completed the study. AUAss decreased 34.5% from BL to week 12 in the 1000 mg AMH group ($p = 0.008$). At week 12, CRP increased in the 500 mg AMH ($p = 0.003$) and placebo ($p = 0.012$) groups from their BL levels but not in the 1000 mg group. Average urine flow (Qmean) increased in the 500 mg ($p = 0.033$) and 1000 mg AMH ($p = 0.002$) groups *versus* placebo. PVR decreased in the 1000 mg AMH group ($p = 0.034$) from BL at week 6. Treatment group effects were observed for the physical functioning and sexual desire domains of the SF-36 and IIEF ($p = 0.051$ and $p = 0.005$ respectively). AMH was well tolerated.

Conclusions: Oral administration of AMH improved LUTS and quality of life in as little as 6 weeks.

Keywords: green tea, black tea, lower urinary tract symptoms, Men's Health, clinical trial

Introduction

The prevalence of moderate to severe lower urinary tract symptoms (LUTS) affects up to 50–90% of men by the eighth decade of life [Wei *et al.* 2005; McVary, 2006]. LUTS may be classified into voiding and irritative symptoms. Voiding symptoms include obstructive symptoms such as hesitancy, weak stream, straining to pass urine, prolonged micturition and a feeling of incomplete emptying. Irritative symptoms include urgency, frequency and nocturia. LUTS are quantified on a scale of 0–35 using the validated American Urologic Association Symptom Index questionnaire [McVary *et al.* 2011]. Inflammation has been suggested as a contributing factor to bothersome LUTS and benign prostatic hyperplasia (BPH), with studies showing that inflammatory cells and proinflammatory cytokines may be involved in the proliferation of prostate tissue

[Kim *et al.* 2013]. Data from the Prostate Cancer Prevention Trial also demonstrated that elevated inflammatory biomarkers such as C-reactive protein (CRP) and interleukin 6 might increase the risk of BPH [Tab Schenk *et al.* 2010].

LUTS are either managed through watchful waiting, drug therapy, surgery, or complementary approaches for treatment that include the use of dietary supplements such as saw palmetto (*Serenoa repens*) and pygeum (*Pygeum africanum*); however, there have been contradictory results reported for these agents in the literature [Jones *et al.* 2010; Dvorkin and Song, 2002; Tacklind *et al.* 2009].

Camellia sinensis (tea), and in particular green and black teas, have been studied due to their potent antioxidant and anti-inflammatory effects. Green tea and black tea are produced based on different

Correspondence to:

Aaron Katz, MD
Winthrop University
Hospital, 1501 Franklin
Avenue, Garden City, NY
11530, USA
akatz@winthrop.org

Mitchell Efros, MD
Winthrop University
Hospital, Garden City,
NY, USA

Jed Kaminetsky, MD
New York University, New
York, NY, USA

Kelli Herrlinger, MSc
Diana Chirouzes, MSc
Michael Ceddia, PhD
Kemin Foods, L.C. Des
Moines, IA, USA

processing methods of *Camellia sinensis* leaves. Green tea is produced by exposure of the leaves to sunlight or hot air. Black tea has a similar process but following dehydration, leaves are allowed to ferment thereby releasing components that give black tea its distinctive flavor and color, but renders differences in bioactive components. Large epidemiologic studies report links between tea consumption and reduced incidence of diseases with pathologies associated with oxidative stress and/or chronic inflammation such as obesity, diabetes mellitus, cardiovascular disease, and urologic conditions such as BPH and prostate cancer [Bettuzzi *et al.* 2006; Hsu *et al.* 2010].

No clinical studies have examined the effect of green tea, black tea, or combined administration on LUTS; therefore, the aim of this clinical study was to assess a novel, patent-pending blend of green and black tea extracts in men with LUTS. Our hypothesis was that green and black tea may be beneficial in reducing LUTS in men.

Materials and methods

This was a prospectively designed, randomized, double-blind, placebo-controlled, multicenter, IRB approved (Quorum Institutional Review Board, Seattle, WA) human clinical trial performed in accordance with Good Clinical Practices. Between December 2011 and July 2012, eligible men between 30 and 70 years of age with moderate to severe LUTS at screening [American Urological Association symptom score (AUAss) ≥ 8 and ≤ 24] provided written informed consent to participate in the study. Men completed a medical history and were excluded if they were using any medical therapy for LUTS, including 5α reductase inhibitors or α blockers, taking any oral α agonist, tricyclic antidepressant, anticholinergic or cholinergic medication, had any past surgical procedure for BPH, had known renal or hepatic insufficiency or any current genitourinary cancer. Additional exclusion criteria included use of any dietary supplements for LUTS, use of any dietary supplement that might affect antioxidant status or any formulation similarly named 'antioxidant formula'. Finally, men who drank more than one cup of tea or more than two cups of coffee or energy drinks per day or had a history of smoking within the past 3 months were excluded from the study.

The study agent was a novel, patent-pending, proprietary blend of green and black tea extracts,

AssuriTEA Men's Health (AMH, Kemin Foods, L.C., Des Moines, IA, USA). AMH is a unique, water-extracted tea ingredient that has already been shown to have potent *in vitro* and *ex vivo* antioxidant activity (unpublished data). Patients who met eligibility criteria were randomized using a computer-generated list to one of three study arms for 12 weeks: 500 mg AMH per day, 1000 mg AMH per day or placebo, ingested in two divided doses with meals, for a total of four capsules daily for all groups. AMH was standardized to contain a minimum 40% total polyphenols, minimum 20% total catechins and theaflavins, 7–14% epigallocatechin-3-gallate, and a maximum of 12% caffeine. All capsules were opaque and indistinguishable, with both researchers and subjects blinded to treatment assignment. Evaluable subjects were defined as those completing the trial with a compliance of at least 80% as measured by pill count. Throughout the intervention, subjects were instructed to maintain baseline (BL) consumption of medications and supplements as reported in the medical history.

The primary outcome was the AUAss. Secondary measures included blood markers, objective urological tests, and scores on quantitative questionnaires. Blood measures included CRP (Esoterix, Cranford, NJ, USA), [Ferric Antioxidant Reducing Capacity (FRAP), Cayman Chemical, Ann Arbor, MI, USA] and cellular antioxidant protection (CAP-e, Natural Immune Systems Laboratories, Klamath Falls, OR, USA). At BL and week 12, subjects were asked to avoid food and drink except water for 8 h prior to the blood draw. For the final visit, subjects were asked to take their last dose of the study agent the day before the scheduled visit (~18 h prior to blood draw). Blood for the antioxidant measures was immediately processed and serum was stored at -80°C for batch processing. Urological measures included average urinary flow rate (Q_{mean}) and maximum urinary flow rate (Q_{max}) using simple uroflowmetry (Dantec, Urolyn, UK) and measurement of postvoid residual volume (PVR) using ultrasonography (Verathon, Bothell, WA, USA). Quantitative questionnaires included the Short-Form 36 (SF-36) and the International Erectile Function Index (IIEF). Measures were assessed at BL, week 6, and week 12 excluding serum antioxidant measurements which were evaluated at BL and week 12 only. Safety and tolerability of the product was assessed through evaluation of adverse events (AEs), clinical laboratory tests (hematology and hepatic function) and monitoring of vital signs.

AEs were classified according to the severity and relationship to the study product. Safety monitoring was continuously performed during the intervention and participants were interviewed and examined by a study physician at all three time points. AEs were graded using National Cancer Institute, Common Terminology Criteria for Adverse Events, Version 3.0.

Statistical analysis

Statistics are presented as mean $\pm$ standard error of the mean for normally distributed variables (e.g. age). Sample size was calculated based on mean improvements and standard deviations observed in AUA symptom score as reported by Barry and colleagues [Barry *et al.* 1992]. Using an α equivalent to 0.05 (two sided) and a power of 0.80, the estimated required sample size was 11 completers per group. Statistical analysis was performed on the evaluable subjects per protocol. Outcome scores were evaluated using repeated measures analysis of variance performed using SAS Version 9.1 (Cary, NC, USA). The main effects of treatment and time were evaluated along with the interaction between these factors. Contrasts of interest were constructed and individually evaluated. Although descriptive statistics were computed for the raw values of BL and post-treatment outcome raw scores, the least squares means were used to summarize findings for change scores that were evaluated by analysis of variance. All tests were two tailed and statistical significance was defined at p up to 0.05. Change scores from BL at the post-treatment time points (week 6 and week 12) were analyzed for the variables AUAss, CRP, Qmax, Qmean, PVR, IIEF, SF-36, and FRAP and CAP-e (at week 12 only).

Results

Subjects

Fifty-nine subjects were screened, 46 were enrolled and randomized, and 40 were evaluable (Figure 1). BL characteristics of the population are in Table 1. There were no differences in BL characteristics (Table 1). Table 1 also shows the AUAss breakdown of subjects within each group experiencing either moderate or severe LUTS at BL.

AUA symptom score

The mean value of the AUAss decreased 6.16 points (-34.5%) over 12 weeks in the 1000 mg

AMH group, with scores of 17.85 ± 1.04 , 13.00 ± 1.45 , and 11.69 ± 1.42 at BL, week 6 ($p = 0.035$ *versus* BL), and week 12 ($p = 0.008$ *versus* BL) respectively (Figure 2). Twelve of thirteen men in the 1000 mg AMH group demonstrated a decrease in AUAss within 6 weeks. Over 12 weeks, mean AUAss decreased 17.3% (-3.33 points) in the 500 mg AMH group and 18.1% (-3.34 points) in the placebo group. AUAss at BL, week 6, and week 12 in the 500 mg AMH group was 19.20 ± 1.00 , 19.27 ± 1.31 , and 15.87 ± 2.16 respectively. In the placebo group, AUAss was 18.42 ± 1.35 , 15.33 ± 1.85 , and 15.08 ± 2.36 at BL, week 6, and week 12, respectively. There were no significant differences in AUAss changes from BL for either the 500 mg AMH group or placebo groups.

Secondary measurements

The percent change of CRP significantly increased over 12 weeks within the placebo group ($p = 0.012$) and the 500 mg AMH group ($p = 0.003$), but was unchanged in the 1000 mg AMH group (Figure 3). In addition, a significant difference in the percent change of CRP from baseline to week 12 was identified for 1000 mg AMH *versus* placebo ($p = 0.048$).

Qmean as measured by uroflowmetry identified a significant main treatment effect ($p = 0.015$). Qmean in the 500 mg AMH group at week 12 significantly increased in comparison to placebo ($p = 0.033$). Qmean at BL, week 6, and week 12 in the 500 mg AMH and placebo groups was 6.19 ± 0.92 , 6.15 ± 1.10 , 6.44 ± 0.82 , and 7.28 ± 0.80 , 5.87 ± 0.63 , 5.22 ± 0.69 respectively. The 1000 mg AMH group (7.97 ± 1.27 [BL]) had an increased Qmean at week 6 (10.05 ± 1.98 , $p = 0.003$) and week 12 (8.40 ± 1.64 , $p = 0.025$) *versus* placebo (Table 2). PVR was significantly reduced with 1000 mg AMH at week 6 (41.55 ± 10.10 ml) *versus* BL (65.39 ± 13.22 ml, $p = 0.034$), corresponding to a decrease of 23.84 ml (Table 2). There were no significant changes identified for Qmax, CAP-e, or FRAP.

Evaluation of the IIEF subsections found overall treatment group effects in the sexual desire domain ($p = 0.005$) with improvements at week 6 ($p = 0.041$) and week 12 ($p = 0.015$) in the 1000 mg AMH group *versus* BL. Although no change was identified in the overall SF-36 score, there was a significant main treatment effect across three groups in the SF-36 physical functioning domain after 12 weeks ($p = 0.051$). The

Figure 1. CONSORT diagram demonstrating trial flow.

Table 1. Baseline characteristics.

Characteristic	Arm 1: 500 mg	Arm 2: 1000 mg	Arm 3: placebo	p value
N	15	13	12	n/a
Mean age (years)	56.77 [2.83]	55.94 [1.71]	57.68 [2.11]	0.925
BMI (kg/m ²)	30.04 [1.66]	27.79 [1.77]	30.59 [2.39]	0.523
AUAss	19.20 [1.01]	17.85 [1.04]	18.42 [1.35]	0.818
Moderate LUTS* [number (%)]	7 (46.7%)	8 (61.55%)	7 (58.3%)	n/a
Severe LUTS* [number (%)]	8 (53.3%)	5 (38.5%)	5 (41.7%)	n/a
CRP (mg/liter)	2.76 [0.67]	2.23 [0.36]	3.39 [1.61]	0.714

Mean [standard error of the mean] (unless otherwise specified).
 *Moderate LUTS defined as an AUAss of 8–19.
 *Severe LUTS defined as an AUAss of 20–24.
 AUAss, American Urological Association Symptom Index score; BMI, body mass index; CRP, C-reactive protein; LUTS, lower urinary tract symptoms.

Figure 2. Two-way repeated measures of change from baseline for each treatment group, $*p = 0.0349$ versus baseline, $**p = 0.0083$ versus baseline. 1000 mg treatment decreased American Urological Association (AUA) symptom score at week 6 and week 12 compared with baseline, while 500 mg and placebo had no significant effect on lowering AUA symptom score. Data are presented as mean $\pm$ standard error of the mean.

physical functioning subsection showed improvements for the change from BL to week 12 ($p = 0.008$) for the 1000 mg AMH group versus placebo.

Safety and tolerability

During the course of the study, six subjects were lost to follow up. No subjects experienced negative changes in laboratory or vital sign assessments. AEs within the 40 completers included one report of deep vein thrombosis (500 mg AMH) that was deemed to be unrelated to the study intervention by the medical oversight. AEs in which the subject discontinued the study agent included one case of fatigue (500 mg AMH), which was

deemed possibly related to the study product. The evaluation of vital signs for product safety and tolerance showed blood pressure changes, with all subjects maintaining normal nonhypotensive values throughout the study. From BL to week 6, diastolic blood pressure significantly decreased in the 500 mg AMH group in comparison to placebo (-3.2 versus -0.3 mmHg, $p = 0.020$), while in the 1000 mg AMH group it significantly decreased 4.2 mmHg from BL to week 6 in comparison to the change in the placebo ($p = 0.003$). Following administration of 1000 mg AMH, the change in systolic blood pressure from BL to week 6 was significant (-4.9 mmHg, $p = 0.035$), and the change from BL to week 12 showed a decreasing trend (-4.3 mmHg, $p = 0.079$).

Comment

Epidemiological studies have reported the potential benefit of green and black tea reducing the incidence of several conditions, such as cardiovascular disease, metabolic disorders, and cancer (including prostate cancer) [Bettuzzi *et al.* 2006; Hsu *et al.* 2010; Bogdanski *et al.* 2012]. The current study was the first known to analyze the effect of administration of a blended, water-extracted green and black tea extract on LUTS in men with moderate to severe symptoms. The 34.5% decrease over BL observed in AUAss following 12 weeks of supplementation with 1000 mg of AMH is similar to or better than pharmacological or certain nutraceutical agents. A study of 493 men consuming tamsulosin, an α blocker, demonstrated a 37.5% improvement over BL following a 45-day multicenter intervention [Flannery *et al.* 2006]. AUAss improvements with AMH exceeded similar length studies testing

Figure 3. Two-way repeated measures of percent change from baseline. 1000 mg AssuriTEA Men's Health (AMH) resulted in no change in C-reactive protein (CRP) levels at week 12 while the placebo and 500 mg AMH groups demonstrated significant increases. Data are presented as mean $\pm$ standard error of the mean.

$*p = 0.0116$ versus baseline, $**p = 0.0026$ versus baseline.

Table 2. Simple uroflowmetry measurements.

Characteristic	Arm 1: 500 mg	Arm 2: 1000 mg	Arm 3: placebo
<i>n</i>	15	13	12
Qmean (ml/s)			
BL	6.19 [0.92]	7.97 [1.27]	7.28 [0.80]
Week 6	6.15 [1.10]	10.05 [1.98]*	5.87 [0.63]
Week 12	6.44 [0.82]^	8.40 [1.64]**	5.22 [0.69]
Qmax (ml/s)			
BL	11.36 [1.64]	14.22 [2.26]	12.19 [1.24]
Week 6	10.67 [1.91]	17.17 [3.25]	10.16 [0.96]
Week 12	12.78 [2.12]	14.71 [2.90]	9.94 [0.91]
PVR (ml)			
BL	54.87 [13.06]	65.39 [13.22]	35.64 [12.13]
Week 6	57.31 [12.14]	41.55 [10.10]***	25.97 [7.11]
Week 12	47.07 [11.87]	50.61 [11.12]	34.43 [7.92]

^*p* = 0.033, **p* = 0.003, ***p* = 0.025, ****p* = 0.034.
BL, baseline; Qmax, maximum urinary flow rate; Qmean, average urinary flow rate; PVR, postvoid residual.

saw palmetto, a dietary supplement currently marketed for prostate health. Randomized, double-blind, placebo-controlled studies in men taking saw palmetto for 12 weeks reported varied responses from no improvement up to a 4.6 point improvement in AUAss or International Prostate Symptom Score [Willetts *et al.* 2003; Bent *et al.* 2006; Hong *et al.* 2009].

It has been reported that a reduction in AUAss of three points or more results in a clinically meaningful reduction of symptoms as perceived by the patient [Barry *et al.* 1992]. However, perceptible differences have been found to be dependent upon BL scores, with a two-point decrease meaningful for men with BL AUAss of 8–19 (moderate symptoms), while a six-point decrease was needed in men with a BL score of 20 or greater [Barry *et al.* 1992]. In the present study in the 1000 mg AMH group, 75% of subjects experiencing moderate LUTS at BL showed a clinically relevant improvement in AUAss within 6 weeks, while 80% of men with severe LUTS at BL demonstrated a clinically relevant improvement after 12 weeks. After 12 weeks of intervention, subtraction of the observed placebo effect (3.34-point decrease in AUAss from BL) from the effect seen in 1000 mg AMH (6.16-point decrease in AUAss from BL) yields a 2.82-point difference. Given that the initial AUAss for all participants in the current trial was 18.58 ± 0.64 , although the changes in the 1000 mg AMH group at week 12 was not statistically significant from that of the

placebo, this 2.82-point decrease over the placebo effect confirms a clinically relevant improvement with 1000 mg AMH *versus* placebo over 12 weeks.

The percentage of subjects who achieved a clinically significant (at least a two-point decrease for moderate LUTS at BL or at least a six-point decrease for severe LUTS at BL) improvement (69.2% at both week 6 and week 12) was constant for 1000 mg AMH from week 6 to week 12. Although AMH at 500 mg was not effective over 12 weeks at statistically reducing the AUAss, an additional 20% of subjects consuming 500 mg/day of AMH achieved a clinically significant improvement in AUAss from week 6 (33%) to week 12 (53%). This supports the notion that there may be a longer loading period at doses less than 1000 mg/day AMH in order to observe changes in parameters of urological health.

The subjective improvements in AUAss are supported by beneficial changes in the objective measurements PVR, Qmean, and CRP. PVR is monitored clinically in patients with BPH as a nonspecific measure of severity. Recent studies have shown that increased PVR at BL may be related to BPH clinical events, including increased IPSS or AUAss. In addition, residual urine remaining in the bladder can result in urinary retention, urinary urgency, upper urinary tract infection, and renal failure. The current study demonstrated a significant reduction in PVR in 1000 mg AMH, indicating not only improved

comfort for the patient in the short term but also potential long-term urological health benefits following consumption of 1000 mg AMH.

Literature suggests that inflammation may be a predictor of LUTS [Kim *et al.* 2013; Liao *et al.* 2011]. Worsening symptoms during watchful waiting may be expected to occur in the LUTS population; therefore, it is not uncommon to observe CRP increases in some populations during clinical trials of similar duration [Stull *et al.* 2010]. It is therefore possible that individuals who were randomly assigned to placebo may have experienced an increase in inflammation and therefore an increase in the associated CRP levels. This study suggests that daily oral administration of 1000 mg AMH may be acting to reduce LUTS through an anti-inflammatory mechanism of action.

AMH was determined to be safe and tolerable. AMH did not result in any AEs related to tea extract consumption, such as increases in liver enzymes or nausea [Sarma *et al.* 2008]. There were no reported AEs of retrograde ejaculation or headaches, the two most commonly reported AEs in many LUTS studies [McVary *et al.* 2011; Flannery *et al.* 2006]. Furthermore, the evaluation of vital signs for product safety and tolerance revealed small beneficial systolic and diastolic blood pressure changes. An important differentiating point about AMH administration was that there were no reported negative sexual side effects (as occurs with many current treatment options); AMH actually led to self-reported improvements in sexual desire and physical functioning.

Limitations of the current study include that the range of BL AUAss defined by the inclusion criteria might not allow investigation into the possible benefit of AMH in populations with mild or the most severe LUTS. In addition, the 12-week follow-up time point limits the ability to determine all potential long-term effects. Larger, prospectively designed, randomized studies with long-term follow-up periods are warranted to determine efficacy at lower doses, examine additional outcomes, and verify the effectiveness of green and black tea in reducing LUTS. Strengths of the study include the randomized, double-blind, placebo-controlled design, including multiple doses of the study agent. In addition, the study evaluated efficacy using both objective and subjective measurements and evaluated the potential mechanisms of action, specifically the anti-inflammatory and antioxidant capabilities of AMH.

Conclusion

The aim of this study was to assess the safety and efficacy of a novel green and black tea agent in the treatment of LUTS in men with known or suspected BPH. Treatment with 1000 mg AMH daily was effective in reducing AUAss in as little as 6 weeks, with a continued decrease resulting in an overall 6.16-point decrease following 12 weeks of supplementation. Moreover, the agent was well tolerated. Evaluation of additional objective and subjective LUTS measurements showed decreases in PVR, increases in average urinary flow rate, improvements in quality of life and sexual function, and moderated inflammation. AMH is an effective all-natural alternative for men seeking relief from LUTS.

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Kemin Foods L.C., Des Moines, IA, USA.

Conflict of interest statement

Kelli Herrlinger, Diana Chirouzes and Michael Ceddia are employed by Kemin Foods L.C.

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