



ORIGINAL RESEARCH PAPER

Urology

The herbal composition Green Love® improves erectile function in patients with erectile dysfunction -a pilot study to evaluate effectiveness and safety

KEY WORDS: Herbal composition, plant products, erectile dysfunction, Green Love®

Ralf Herwig	Dept. of Reconstructive Urology, Andrology and Mens's Health, Vienna Urology Foundation, Vienna, Austria
Joachim Greilberger	Institute for Physiological Chemistry, Medical University Graz, Graz, Austria
Michaela Greilberger	Institute of Scientific Laboratory, Schwarzl-Medical Center, Graz-Lassnitzhoehe, Austria

ABSTRACT	AIM: To examine the treatment efficacy of herbal composition (HC) Green Love in men with erectile dysfunction (ED).
	METHODS: A total of 25 patients presenting mild or mild to moderate ED were enrolled in a prospective study in which the efficacies of HC was compared to the status of ED before the use. The patients received 30 ml of HC. IIEF-5-score
	RESULTS: The five-item version of the International Index of Erectile Function (IIEF-5) score after the treatment was significantly higher in the HC group compared with that before the treatment (from 15.0 +/- 4.8 to 21.8 +/- 2.7, P < 0.0001). In the HC group, patients reported improved erection, significant in the global efficacy question (P < 0.0001). Scores on questions 2 (rigidity), 3 (penetration), 4 and 5 (maintenance), were significantly higher for HC than those in controls when those questions were answered after 2 days of each treatment (P < 0.0001). When the score in the HC group was compared to prior to treatment, there was a significant improvement in total score (IIEF-5 score) especially in questions 3 and 5 for the HC-treated group (P < 0.0001).
	CONCLUSION: Our data show that HC can be an effective alternative to more invasive approaches for treating mild to moderate male ED.

Introduction:

Erectile dysfunction (ED) and premature ejaculation (PE) are the two most prevalent male sexual dysfunctions(1). Erectile dysfunction may affect 30% to 50% of men aged 40 to 70 years, with age, smoking, and obesity being the main risk factors, although 20% of cases have psychological causes(2). ED also shares common risk factors with cardiovascular disease. Diagnosis is based on medical and sexual history, including validated questionnaires. Physical examination and laboratory testing must be tailored to the patient's complaints and risk factors. The standard urological treatment is based on phosphodiesterase type 5 inhibitors (PDE5-Is), including sildenafil, tadalafil, and vardenafil. Treatment options for patients who do not respond to PDE5-Is or for whom PDE5-Is are contraindicated include intracavernous injections, intraurethral alprostadil, vacuum constriction devices, or implantation of a penile prosthesis(1).

The use of plant or plant-based products to stimulate sexual desire and to enhance performance and enjoyment is almost as old as the human race itself. A number of herbal drugs have been validated for their effect on sexual behavior and fertility and can therefore serve as the identification of new chemical leads useful in sexual and erectile dysfunction(3).

Furthermore, Panax ginseng (Ginseng), Rhodiola rosea (Hong Jing Tian) and Schisandra chinensis (Wu Wei Zi) are well-known herbs in traditional Chinese medicine (TCM)(4). For P. ginseng, it has been shown to have an anti-inflammatory activity, affects pulmonary function and erectile dysfunction, improves cognition in patients with Alzheimer's disease and promotes sexual arousal(4). The administration of Korean red ginseng (KRG) has shown to have superior effects compared to the placebo or trazodone(5). Recently, de Andrade et al. demonstrated in a controlled randomized placebo-controlled trial that KRG can be an effective alternative to the invasive approaches for treating male ED(6).

We investigated a newly developed and registered herbal composition named Green Love® containing KRG with standard measurement tools for erectile dysfunction in a prospective controlled intra-individual comparison pilot study to evaluate the possible usefulness as a promotor of erectile function.

Material and Methods:

Patients

Of 35 consecutive patients from our outpatient department with moderate/severe ED, evaluated with the standardized IIEF-5 score, 25 patients received the HC for use 30 to 40 minutes before sexual intercourse. The 10 remaining patients did not receive any treatment during observation time and served as control patients. Patients were asked to fill out the standardized IIEF-5 score prior to testing of HC. A complete work up was performed according to the guidelines of EAU for ED(1). Patients were then asked to drink 30 ml of the HC 30 minutes prior to planned intercourse. A reevaluation of IIEF-5 score was performed after two times of use of HC. Additional requested questions are listed in table 1.

Altogether, data from 24 patients using HC and 10 control patients were eligible, only one patient did not resend the IIEF-5 score after use of HC in time for evaluation.

Herbal Composition (Green Love)

The preparation of the HC Green Love (TIT GmbH, Vienna, Austria) is a registered (EU-Reg.-Nr: NUT_PL 2089/5) commercially available supplement tested negative for PDE5-inhibitors.

The herbal ingredients of HC are Panax quinquefolius, Radix ginseng, Rhizoma dioscoreae, Lyceum barbarum, Christianche Salsa, Rubus Chingii Hu, Fructus schisandrae, Poria Cocos and Euphoria longana.

The major ingredient Ginseng is the root of the perennial herbs of Panax quinquefolium and Panax ginseng which contain a series of tetracyclic triterpenoid saponins (ginsenosides) as active ingredients. It is considered a tonic or adaptogenic that enhances physical performance (including sexual), promotes vitality and increases resistance to stress and ageing. The adaptogenic properties of ginseng are believed to be due to its effects on hypothalamic-pituitary-adrenal axis, resulting in elevated plasma corticotropin and corticosteroids levels. When used appropriately, ginseng appears to be safe. Nevertheless, documented side effects include hypertension, diarrhoea, restlessness and mastalgia(7).

Questionnaire

The IIEF-5 consists of five items originating from the IIEF. Four of its five items were taken from the six-item erectile function domain

of the IIEF which is a validated measure as a diagnostic evaluation tool(8). The fifth item of the IIEF-5 concerns intercourse satisfaction.

Response options are based on rating scales from 0 to 5 or 1 to 5. The responses are summed resulting in a total IIEF-5 score ranging from 1 to 25, with lower values representing poorer sexual function. ED can be classified into five severity grades: absence of ED (IIEF-5 score 22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), and severe (1–7)(9, 10).

Questions 2 (rigidity), 3 (penetration), 4 and 5 (maintenance) represent different items and can therefore be analysed in subgroups.

Statistical methods

Statistical significance was defined as $p < 0.05$. For comparison of patient and reference group the unpaired t-test was used for numerical variables, and the Chi-squared test for categorical variables. Student's t-test was used to compare measure scores, controlling for demographics that differed significantly between patient and reference group.

Statistical analysis was performed using IBM® SPSS software 22.0, SPSS Inc., Chicago, IL, USA.

Results:

Patients work up:

No statistical difference could be determined according to age ($p > 0.05$) and onset of disease.

Additionally, no patient showed hormonal imbalance according to the normal range provided by the reference laboratory.

Intracorporal injection (ICI) testing with 20mg alprostadil revealed 20 patients with erection classified as E3, one classified as E2, and three classified as E4 according to the guidelines of EAU for ED(1). In the control group 8 revealed a classification as E3, one patient as E2 and one as E4.

Color Doppler Ultrasound and Ct cavernosography demonstrated a mixed arterial and venous insufficiency in 15 patients (62.5%), sole arterial insufficiency in 2 (8.33%) patients and a pure venous leak in 7 patients (29.17%) in the HC group, whereas the control group consisted of 6 patients with a mixed insufficiency, one with arterial insufficiency and 3 patients with a venous leak.

Again no statistical differences were found between the groups according to classification of erection and underlying cause ($p > 0.05$).

IIEF-5 questionnaire results and additional scoring:

No significant difference was found during a time period of 3 months in the control group.

The levels of serum testosterone, prolactin and cholesterol after the treatment were not statistically significantly different between the HC and the control group ($P > 0.05$).

The mean IIEF-5 score before use of HC was 15.0 (+/- 4.86; Min : 4; Max : 23; Median : 15.0). After the use of HC a significant increase in IIEF-5 score with a mean score of 21.8 (Std. dev. : 2.73; Min : 15; Max : 25; Median : 23) was determined ($p > 0.0001$, Figure 1). After the use 68% reached a score that states „no erectile dysfunction“, further 24% reported about „mild ED“. A significant shift in ED classification towards „mild ED“ and „no ED“ could be observed ($p < 0.0001$, Figure 2).

Scores on questions 2 (rigidity), 3 (penetration), 4 and 5 (maintenance), were significantly higher after the intake of HC than those before use of HC or in controls when those questions were answered 2 days after treatment ($P < 0.0001$). Especially in sub analysis of Question 3 (penetration, Figure 3) and 5 (maintenance, Figure 4) significant difference could be recorded

between before HC (mean Q3 : 2.89 +/- 1.23; mean Q5 : 3.22 +/- 0.88) and after (mean Q3 : 4.5 +/- 0.62; mean Q5 : 4.44 +/- 0.61) use of HC ($p < 0.0001$).

In the HC group, patients reported about subjectively significantly improved erections in the global efficacy question ($P < 0.0001$).

On a subjective ranking from 0 (very bad) to 5 (very good) for the taste, the HC reached a mean score of 4.42.

Asking the additional question if HC has contributed to better sexual intercourse 91.67% ($n=22$) affirmed a positive effect on erectile function and 8.33% ($n=2$) stated a slight betterment. None of the patient abnegated a positive effect on sexual ability.

Asking for the likelihood to reuse the product again, on a scale from 0 (never again) to 10 (forever) the score reached a mean score of 9.29 (Min : 4; Max : 10).

Side effects:

Only one patient (4%) reported about fugitive headache as a possible side effect of the HC (Figure 5). This sensation disappeared within one hour after onset and did not avert sufficient sexual intercourse. None of the above mentioned known possible side effects was noted.

Duration of action:

Included into the survey was the duration of the effectivity of the HC. Of all patients included 21 persons answered the question. Altogether 52% of the questioned described a positive effect of more than 6 to 12 hours. Counting the responds for lasting of effect remarked, 85% of the respondent described a positive effect of 6 hours and more. Further results are demonstrated in Table 1 and Figure 6.

Case report:

A 57 year old patient included in this study had a previous history of prostate cancer. He underwent nerve sparing radical retropubic prostatectomy in 2014 and had additional radiotherapy a year later. His continence was perfect after therapy, but postoperatively he suffered from severe erectile dysfunction. His IIEF-5 score prior to HC testing was 13 with the use of PDE5-inhibitors. Additionally, he suffered from side effects of which the most prominent reported is a strong headache that detained him from having sexual intercourse. After using HC the patient reached an IIEF-5 score of 23 (no evidence for erectile dysfunction) without noticing any side effects.

Discussion:

Erectile dysfunction is a common sexual problem affecting many men irrespective of cultures, beliefs and nationalities. While medical therapy for ED has been revolutionized by the advent of oral phosphodiesterase type 5 inhibitors and intracavernosal injection of vasoactive agents, recent technological advances such as stem cell therapy, low intensity shock wave and newer generation of penile prosthesis implant offer hope to men who do not respond to conventional medical therapy.

In contrast, traditional and complementary medicine (TCM) focuses on the restoration and better overall bodily regulation with the use of various herbal and animal products as well as exercises to invigorate qi (energy) in vital organs. Western medicine involves an analysis of ED symptom and underlying causes that contribute to ED, while TCM emphasizes the concept of holism and harmonization of body organs to achieve natural sexual life(11).

Recently, the group of Xiong et al. demonstrated her analysis showing that some Chinese herb formulae or combined with classical urological therapy to have significant effects on cure rate, total clinical effective rates, IIEF-5 scores, erectile quality scores, erection angles of penis and recovery times of erection compared with the controls.(12)

In fact, herbal remedies from several parts of the world have been

traditionally known for long, and were recently reconsidered and are now being studied to demonstrate their eventual potential in the treatment of ED. Among the various examples reported in the literature and reviewed, plants and extracts containing polyphenols—especially a class of compounds called kaussiananones—appear to be particularly effective and promising against ED(13).

Furthermore, traditional herbs have become known world-wide as an 'instant' treatment(14). The modern view of the management of erectile dysfunction subscribes to a single etiology, i.e. the mechanism of erection. A large number of pharmacological agents are orally consumed and vasoactive agents inserted intraurethrally or injected intrapenially to regain good erection. Modern phytochemicals have developed from traditional herbs. Phytochemicals focus their mechanism of healing action to the root cause, i.e. the inability to control the proper function of the whole body system. Hence phytochemicals manage erectile dysfunction in the frame of sexual dysfunction as a whole entity(14).

The investigated HC Green Love contains a composition of *Panax quinquefolius*, *Radix ginseng*, *Rhizoma dioscoreae*, *Lyceum barbarum*, *Christanthe Salsa*, *Rubus Chingii Hu*, *Fructus schisandrae*, *Poria Cocos* and *Euphoria longana*. All of these ingredients are described to play a role in sexual function(4, 6, 15–25).

In our prospective controlled intra-individual comparison pilot study we could demonstrate a significant difference ($p < 0.0001$) in IIEF-5 score before and after use of HC with more than 5 points difference between the distinct points of evaluation. These findings are comparable to prior reports about the benefit of herbal medications in case of erectile dysfunction(6).

Side effects during use of herbal extracts are always controversially discussed in the literature. Eight trials reported mild adverse drug reactions, mostly involving gastrointestinal symptoms(12).

Despite a fugitive headache in one patient, possibly connected to the intake of HC, no major side effects could be detected in this pilot investigation. These data also are in consistency with previously published data from a systematic review of about 1415 relevant studies including 30 controlled randomized trials(26). Therefore, we consider this special formulation to be safe in use with a low likelihood to develop minor side effects.

Literatur about the duration of action is lacking. This might be due to the fact, that many different formulations and combinations of different herbs are available and non of them is really comparable to each other. It is assumed that there is a dose- and duration dependency. In a rat model administration of Ginseng berry extract increased intracavernosal pressure (ICP) in a rat in vivo model in both a dose- and duration-dependent manner. Intracellular NO production in human microvascular endothelial cells could be induced by Ginseng berry extract and inhibited by N(G)-monomethyl-L-arginine. The authors state, that in conclusion, Ginseng berry extract had a greater relaxation effect on rabbit corpus cavernosum smooth muscle than did KRG extract, and increased ICP in a rat model in both a dose- and a duration-dependent manner. This relaxing effect might be mediated by NO production(27). In our observation 85% of the participants reported about a duration of positive effects on erection for 6 hours and more 52% remarked an enhanced effect between 6 and 12 hours, 19% of the probands had an effect of more than 12 hours.

Very encouraging is the case report of a patient after nerve sparing radical retropubic prostatectomy, which demonstrates, that treatment with herbal ingredients might be a save and effective alternative treatment to regain erectile function after unsuccessful therapy with PDE5-inhibitors due to side effects, even if a placebo effect might play a significant role in this case. These facts are also found in recent reports from Zhao et al. These authors remarked, that unripe *R. coreanus* extract exerts a relaxing effect on penile

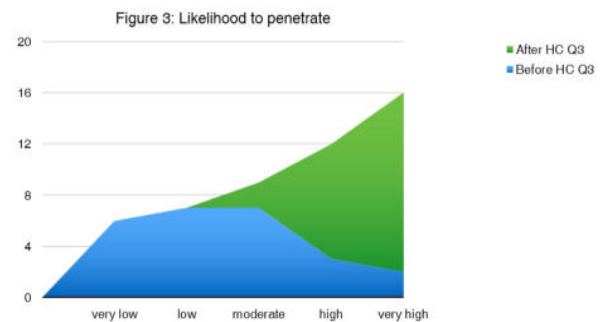
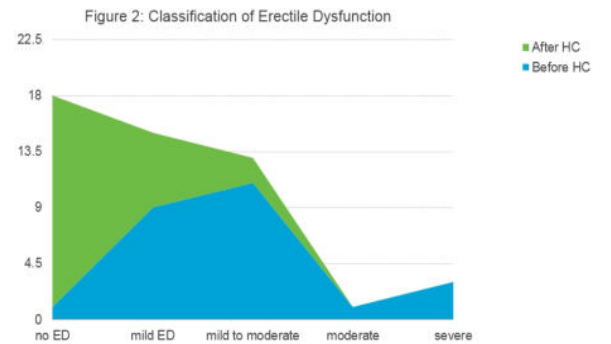
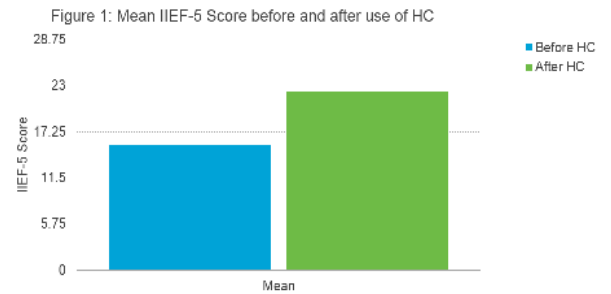
cavernous tissue in part by activating the NO-cGMP system and stated that it may improve erectile dysfunction (ED), which does not completely respond to sildenafil citrate(28).

Conclusion:

In summary, our preliminary data from this prospective controlled pilot study using the HC Green Love® demonstrate a significant improvement in erectile function over 6 hours and more with low amount of minor side effects. Of course, these data have to be confirmed in a larger double-blind randomized placebo controlled trial in a larger group of patients.

Additionally, further photochemical studies of many other herbal plants are needed to explain the inconsistent results found with other herbal plants, such as in diversities of Ginseng, *Eurycoma longifolia*, *Pimpinella prucen*, *Muara puama*, *Ginkgo biloba*, *Yohimbe* etc.

Figures and Tables:



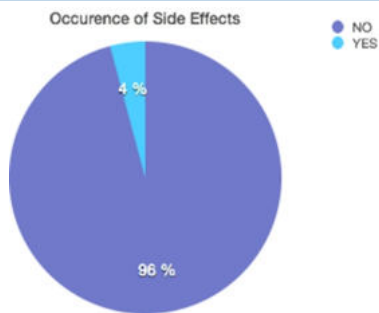


Figure 5: Occurrence of side effects.

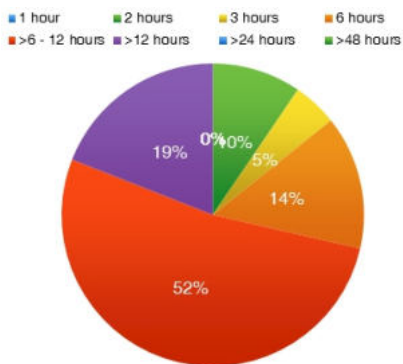


Figure 6: Percentage of votes for duration of action

Duration of action	Number
1 hour	0
2 hours	2
3 hours	1
6 hours	3
>6 - 12 hours	11
>12 hours	4
>24 hours	0
>48 hours	0

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