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Aphrodisiac effects of *Panax* ginseng extract standardized with ginsenoside Rg3 in male rats

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Keywords

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Abstract

In traditional medicine, *Panax ginseng* has been used to treat various behavioral effects. However, a little is known about the effect of ginsenoside Rg3, the most ingredients in panax ginseng, on male copulatory and sexual behavior. The aim of the current study was to investigate the effect of *panax ginseng* extract standardized with ginsenoside Rg3 (PGRg3) on general mating behaviour, libido, potency and the adverse effects in normal male Sprague-Dawley rats. Four tests were carried out to evaluate different sexual parameters. Male rats were divided into different groups in each test and treated with different doses of PGRg3 (50, 250 and 500 mg/kg b.w.) and Sildenafil citrate (5 mg/kg b.w). Female rats with oestrus phase were used to analyze the mating behavior.The results indicated that PGRg3 significantly increased mounting frequency, intromission frequency, ejaculatory latency in the first and second series, erection, quick flips, long flips and aggregate of penile reflexes. Whereas, it significantly decreases mounting latency, intromission latency and post ejaculatory intervals in dose dependent manner. Moreover, PGRg3 was found to be devoid of any conspicuous gastric ulceration and any other adverse effects. PGRg3 extract at the higher dose (500 mg/kg b.w.) was comparable to the standards drug Sildenafil citrate with regards to all the tested parameters. It could be concluded that PGRg3 extract produced a significant and sustained increase in the sexual activity of normal male rats without any conspicuous gastric ulceration and adverse effects. The most important conclusion is that the resultant aphrodisiac effectively of PGRg3 extract lends support to the claims for its traditional usage in sexual disorders.

1. Introduction

Sexual dysfunction and/or erectile dysfunction (ED) are major challenges for an individual's subjective well-being. It is a common problem with increase in prevalence and etiological factors, including degenerative diseases, increase in injuries and stress associated with industrialized lifestyles [1]. Clinically, ED is defined as the persistent inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance [2] and it is a medical problem affecting young as well as old men. The incidence of ED increases with age, reaching 20-40% in men 60-69 yr of age and 50-100% in men in their 70s and 80s, depending on the differing definitions of ED in various studies [3]. Beyond the aging process, other cardiovascular (CV) risk factors such as hypertension, diabetes, smoking, obesity, and dyslipidemia have been shown to be significantly associated with ED [4][5].

Although a number of treatments became available in the last two decades, problems with costs, efficacy, safety and ease to administer were experienced [6]. These treatments ranged from herbal remedies used by native healers, mostly in the Eastern countries, to the more sophisticated designer drugs, which are based on a better understanding of the physiological mechanism of erection [2]. Dietary supplement use has experienced tremendous growth in the past years [7]. Supplements are becoming more important and more commonly used by consumers in their personal healthcare regimens [8] [9]. Numerous products are currently promoted for enhancing erectile function and sexual performance in men and are marketed with the implied assumption that they are safe and natural. Yet reports of adulteration for products in this category abound. Adulterants found in dietary supplements include, but aren't limited to, active pharmaceutical ingredients such as the PDE-5 inhibitors sildenafil (Viagra®), vardenafil (Levitra®), tadalafil (Cialis®) and, in an attempt to avoid detection, the unapproved analogues of these drugs [10][11][12][13][14][[15][16].

In recent years, several studies report the benefits of functional food and herbal ingredients such as *Panax ginseng* C.A. Meyer in the treatment of ED [17] [18]. For 2,000 years *Panax ginseng* has had a rich medicinal history [19]. Practitioners of Chinese medicine use it as a tonic and restorative to promote health and longevity [20]. It has been prescribed to improve stamina, concentration, stress resistance, and work efficiency

in the healthy as well as to improve well-being in patients with degenerative conditions associated with old age and chronic disease [21]. The tonic and adaptogenic activity of *Panax ginseng* is thought to enhance physical performance, which includes sexual stamina. The aim of the present study was to investigate the aphrodisiac effect of *Phoenix Ginseng* extract standardized with ginsenoside Rg3 in detail compared with the standard drug Sildenafil citrate (Viagra), using multiple parameters along with its probable gastric ulceration and adverse effects in sexually normal male Sprague-Dawley rats.

2. Materials and Methods

2.1. Plant material

The standardized *Panax ginseng* extract EFLA400 (Batch No. 303298) of *Panax ginseng* C. A. Mayer was prepared according to the published procedure (Korean patent 0425022, PCT/KR2003/000003) and was supplied from Lotte Group R & D Centre (Seoul, Korea).

2.2. Chemicals

Sildenafil citrate (Viagra) was purchased from Pfizer Inc. (Cairo, Egypt), ethinyl oestradiol, progesterone and xylocane ointment (5%) were purchased Sigma Chemical Co. (St. Louis, USA).

2.3. Animals

Twelve weeks old male (350-400 g) and female Sprague-Dawley rats (225-275 g) were purchased from Animal House Colony, NRC, Giza, Egypt. Animals were housed singly in separate standard cages and were maintained under standard laboratory conditions (temperature 24-28°C, relative humidity 60-70%, 12 h light-dark cycle) with free access to standard lab diet (Protein: 16.04%; Fat: 3.63%; Fiber: 4.1%, and metabolic energy: 0.012 MJ) and water *ad libitum* throughout the study except during the experiment. The study design was approved by the ethical committee for animal care and use of the National Research Center, Dokki, Cairo, Egypt.

2.4. Drug and PGRg3 preparation

PGRg3, Sildenafil citrate and ethinyl oestradiol were suspended in distilled water using Tween 80 (1%) and were administrated orally. Progesterone was dissolved in olive oil for subcutaneous injection. All the drug solutions were prepared just before the administration.

2.5. Mating behavior test

The test was carried out according to the methods described by Dewsbury and Davis [22] and Szechtman et al. [23] as modified by Amin et al. [24. Fifty healthy and sexually experienced male Sprague-Dawley rats that were showing brisk sexual activity were selected for the study. Animals were divided into 5 groups (10 rats/group) and kept singly in separate cages during the experiment. Group (1); received 10 ml/kg distilled water and represented the control group. Groups (2-4); received oral daily doses of PGRg3 (100, 250 and 500 mg/kg b.w, respectively) for 7 days at 18:00 h. Group (5); served as standard and was given orally suspension of sildenafil citrate (5 mg/kg b.w), 1 h prior to the commencement of the experiment. Since the male animals should not be tested in unfamiliar circumstances, the animals were bring to the laboratory and exposed to dim light (in 1 w fluorescent tube in a laboratory of 14' × 14') at the stipulated time of testing daily for 6 days before the experiment. The female animals were artificially brought into oestrus (heat) by orally administration of ethinyl oestradiol suspension (100 µg/animal) 48 h prior to the pairing plus progesterone injected subcutaneously (1 mg/animal) 6 h before the experiment [23]. The receptivity of the female animals was confirmed before the test by exposing them to male animals, other than the control, test and standard animals. The most receptive females were selected for the study. The experiment was carried out on the 7^{th} day after commencement of the treatment of the male animals at 20:00 h in the same laboratory and under the light of same intensity. One receptive female was introduced into each cages of one male. The observation for mating behaviour was immediately commence and continue for first 2 mating series.

The test was terminated if the male failed to evince sexual interest. If the female did not show receptivity she was replaced by another artificially warmed female. The occurrence of events and phases of mating were recorded on audio-cassette as soon as they appeared. Their disappearance was also recorded. Later, the frequencies and phases was determined from cassette transcriptions: number of mounts before ejaculation or mounting frequency (MF), number of intromission before ejaculation or intromission frequency (IF), time from the introduction of female into the cage of the male up to the first mount or mounting latency (ML), time from the introduction of the female up to the first intromission by the male or intromission latency (IL), time from the first intromission of a series up to the ejaculation or ejaculatory latency (EL), and time from the first ejaculation up to the next intromission by the same male or post ejaculatory interval (PEI). However, in the second mating series only the EL was recorded.

2.6. Libido test

This test was carried out by the method described by Amin et al. [24]. Another fifty sexually experienced male rats were divided into 5 groups (10 rata/group) and were kept singly in separate cages during the experiment. Group (1); represented the control group and received oral dose of distilled water (10 ml/kg b.w). Groups (2-4); received oral doses of PGRg3 suspension (100, 250 and 500 mg/kg b.w, respectively) once a day in the evening (18:00 h) for 7 days. Group (5); was served as standard and given oral dose of sildenafil citrate (5 mg/kg b.w) 1 h prior to the commencement of the experiment. The female rats were made receptive by hormonal treatment and all the animals were accustom to the testing condition as previously mentioned in the mating behavior test. The animals were observed for the mounting frequency (MF) on the evening of day seven at 20:00 h. The penis was exposed by retracting the sheath and 5% xylocaine ointment was applied 30, 15 and 5 min before starting observations. Each male animal was placed individually with the receptive female in the same cage. The number of mountings was noted and the animals were observed for intromission and ejaculation.

2.7. Potency test

The potency test was carried out according to the methods described previously [24]. Another fifty male rats were divided into 5 groups (10 rats/group) and were kept singly in separate cages during the experiment. Group (1); the control group, received oral dose of distilled water (10 ml/kg b.w). Groups (2-4); received daily oral dose of PGRg3 (100, 250 and 500 mg/kg b.w respectively) for 7 days. Group (5); received oral dose of sildenafil citrate (5 mg/kg b.w.) 1 h before the commencement of the experiment. On the 8^{th} day, the test for penile reflexes was carried out by placing the animal on its back in a glass cylinder partial restraint. The preputial sheath was push behind the glans by means of thumb and index finger and held in this manner for a period of 15 min. Such stimulation elicits a cluster of genital reflexes. The following components were recorded: Erections (E), Quick Flips (QF) and Long Flips (LF).

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2.8. Ulcerogenecity test

Another Forty male animals (350-400 g) were divided into 4 groups 10 rats/group) including the control group (received 10 ml/kg b.w of distilled water), the groups treated daily for 7 days with oral doses of PGRg3 (100, 250 and 500 mg/kg b.w. respectively). At the 8th day, all the animals were killed and the stomach was incised along the greater curvature and washed carefully with physiological saline and examined for any gastric lesions immediately using a magnifying glass. The number of erosions per stomach were assessed for severity by two observers, who were followed the same evaluation criteria, according to the score of Cioli et al. [25]: (0) absence of lesion, vasodilation or up to 3 pin point ulcers; (1) more than 3 pin point ulcers, (2) from 1 to 5 small ulcers (< 2 mm); (3) more than 5 small ulcers (< 2 mm) and (4) 1 or more giant ulcers.

2.9. Adverse effects

All treated rats were observed at least once daily for any overt sign of toxicity (salivation, rhinorrhoea, lachrymation, ptosis, writhing, convulsions and tremors), stress (erection of fur and exophalmia) and changes in behaviour (such as spontaneous movement in the cage, climbing, cleaning of face). In addition, food and water intake were noted.

2.10. Statistical analysis

All data were statistically analyzed using the General Linear Models Procedure of the Statistical Analysis System [26]. The significance of the differences among treatment groups was determined by Waller-Duncan k-ratio [27] . All statements of significance were based on probability of $P \leq 0.01$.

3. Results

3.1. Mating behavior test

The current results (Table 1) indicated that PGRg3 at the three tested doses increased significantly the mounting frequency (MF), intermission frequency (IF), ejaculatory latency in the first series (EL1) and ejaculatory latency in the second series (EL2) in a dose dependent manner compared with the control animals. Whereas; the extract at the same doses decreased significantly the mounting latency, intromission latency and post ejaculatory interval. The same data clearly indicated that administration of the standard drug Sildenafil citrate at 5 mg/kg b.w resulted in a significant increase in MF, IF, EL1 and EL2 accompanied by a significant decrease in ML, IL and PEI. It is of interest to mention that there is no significant difference between PGRg3 at the higher dose (500 mg/kg b.w.) and the standard drug regarding all the tested parameters although animals treated with PGRg3 at the higher dose showed an increase in the number of mount before ejaculation (MF) and the time from the first ejaculation up to the next intromission than the standard drug. On the other hand, EL2 recorded the same values in the animals received PGRg3 at 500 mg/kg b.w. and those in the standard drug group. However, the other parameters showed insignificant decrease compared to the standard drug.

3.2. Test for libido

The test for libido showed that administration of PGRg3 increased the mounting frequency (MF) at the three tested doses (Table 2). The extract at 100 and 250 mg/kg b.w. significantly increased MF compared to the control group although there was a significant difference between these groups and the group received the extract at the higher dose (500 mg/kg b.w.) and those received the standard drug sildenafil. On the other hand, there was no significant difference in MF between the higher dose group (500 mg/kg b.w.) and the group received sildenafil. The number of intromission before ejaculation or intromission frequency (IF) and ejaculation were found to be absent in the entire treatment group including the standard drug group (Table 2).

3.3. Test for potency

The current results for potency test (Table 3) indicated that the three tested doses of PGRg3 and the standard drug significantly increased erection (E), quick flips (QF), long flips as well as the aggregate of these penile reflexes (TPR) compared to the control group. Although there was a significant difference in all the test for potency parameters between the groups treated with PGRg3 at 50 and 100 mg/kg b.w. and the sildenafil group, the group received the higher dose of PGRg3 (500 mg/kg b.w) was comparable to the sildenafil group in all the tested parameters.

3.4. Test for ulcerogenecity

The current study revealed that treatment with PGRg3 for 7 days at the three tested doses did not result in any ulceration in gastric mucosa of male Sprague-Dawley rats (Fig. 1). Moreover, there were neither treatment related defects nor overt clinical signs of toxicity (salivation, rhinorrhoea, lachrymation, ptosis, writhing, convulsions and tremors), stress (erection of fur and exophalmia) and changes in behaviour (such as spontaneous movement in the cage, climbing, cleaning of face) and appearance evident. The food and water intake of all groups of rats treated with the three tested doses of PGRg3 and the standard drug remained similar to those of the control group.

Table 1: Effect of PGRg3 mating behavior in male rats

Parameter	control	PGRg3 (100 mg)	PGRg3 (250 mg)	PGRg3 (500 mg)	Sildenafil citrate*
Mounting Frequency (MF)	12.5 ± 0.43^{a}	15.3 ± 0.5^{b}	18.3 ± 0.76^{c}	37.7 ± 1.23^{d}	37.5 ± 1.4^{d}
Intromission Frequency (IF)	11.3 ± 1.05^{a}	14.3 ± 0.7^{b}	18.3 ± 1.1^{c}	26.5 ± 0.7^{d}	26.8 ± 0.6^{d}
Mounting Latency (ML, sec)	22.3 ± 0.8^{a}	18.8 ± 0.6^{b}	15.5 ± 0.8^{c}	10.5 ± 0.4^{c}	10.17 ± 0.48^{c}
Intromission Latency (IL, sec)	46.17 ± 1.8^{a}	42.3 ± 2.14^{b}	39 ±1.65^{c}	34.8 ± 1.01^{d}	37.33 ± 1.45^{e}
Ejaculatory Latency in first series (EL 1, sec)	68 ± 1.67^{a}	74.16 ± 2.18^{b}	84 ± 2.62^{c}	117 ± 3.37^{d}	119 ± 3.25^{d}
Ejaculatory Latency in second series (EL 2 , sec)	90 ± 2.65^{a}	110.8 ± 3.86^{b}	134.3 ± 2.25^{c}	148.5 ± 2.4^{d}	148.5 ± 2.2^{d}
Post Ejaculatory Interval (PEI, sec)	519.7 ± 16.4^{a}	444.5 ± 10.6^{b}	405.7 ± 11.1^{c}	299.7 ± 3.6^{d}	295.5 ± 7.02^{d}

**Sildenafil citrate was used at 5 mg/kg b.w*

Within each raw, means superscript with different letters are significantly different (P≤ 0.01).

Table 2: Effect of PGRg3 on Mounting Frequency (test for libido) in male rats

Groups	Mounting Frequency (MF)	Intromission Frequency (IF)	Ejaculation (EJ)
control	16.8 ± 1.5^{a}	Nil	Absent
PGRg3 (100 mg)	25.5 ± 1.4^{b}	Nil	Absent
PGRg3 (250 mg)	38.5 ± 1.1^{c}	Nil	Absent
PGRg3 (500 mg)	56 ± 3.2^{d}	Nil	Absent
Sildenafil citrate*	56.5 ± 2.6^{d}	Nil	Absent

**Sildenafil citrate was used at 5 mg/kg b.w*
Means superscript with different letters are significantly different (P≤ 0.01).

Table 3: Effect of PGRg3 on Penile reflexes (test for potency)

Groups	Erections (E)	Quick Flips (QF)	Long Flips (LF)	Total Penile Reflexes (TPR)
Control	7.17 ± 0.5^{a}	5.5 ± 0.43^{a}	2.3 ± 0.42^{a}	15.5 ± 0.43^{a}
PGRg3 (100 mg)	10.17 ± 0.5^{b}	7 ± 0.37^{b}	4.2 ± 0.5^{b}	16.8 ± 0.54^{a}
PGRg3 (250 mg)	15 ± 0.9^{c}	8.5 ± 0.67^{c}	8.8 ± 0.47^{c}	18.5 ± 0.43^{b}
PGRg3 (500 mg)	28.17 ± 1.14^{d}	10 ± 0.51^{d}	29.3 ± 1.12^{d}	29.3 ± 1.12^{c}
Sildenafil citrate*	29.5 ± 1.18^{d}	10 ± 0.58^{d}	31.16 ± 1.08^{d}	31.16 ± 1.08^{c}

**Sildenafil citrate was used at 5 mg/kg b.w*
Within each column, means superscript with different letters are significantly different (P≤ 0.01).

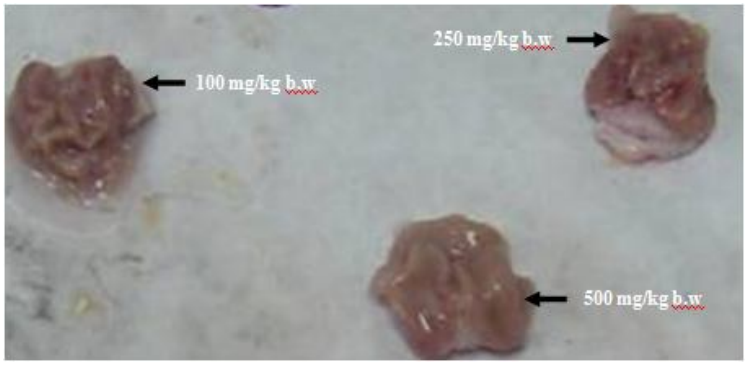

Fig. 1: Photograph of gastric mucosa of male Sprague-Dawley showing that no ulceration was found in any of PGRg3-treated rats at the three tested doses.

4. Discussion

Ginseng, the root of *Panax ginseng* C.A. Meyer, is a traditional folk medicine that is reported to have many beneficial effects. In Asian countries, ginseng has been used by both patients and healthy individuals to restore and enhance vital energy [28]. Several studies and clinical trials have investigated the pharmaceutical effects, efficacies, and active components of ginseng [29]. In addition, studies have proposed that ginseng reduces physical, chemical, and biological stress, while increasing general vitality and immune function, including physical and mental capacity [30][31]. The chemical constituents of ginseng have been identified and approximately 40 active ingredients, including ginsenosides, polyacetylenes, sesquiterpenes, polysaccharides, and peptidoglycans, have been isolated [32]. Ginsenosides are well characterized and known to have a four-ring steroid-like structure with sugar moieties attached and exert their diverse effects in central and peripheral nervous systems [33]. Within the ginsenoside fraction of ginseng, particular attention was focused on ginsenoside Rg3, as it had been ascribed potent vasodilator properties in animal models and is thought to be a significant contributor to ginseng-mediated vasoactivity [34][35]. Jang et al. [36] evaluated the evidence regarding the effectiveness of red ginseng for treating ED and suggested a significant effect of red ginseng for the treatment of ED.
In the current study, we evaluated the effect of *panax ginseng* extract standardized with ginsenoside Rg3 (PGRg3) on general mating behaviour, libido, potency and the adverse effects in normal male Sprague-Dawley rats. The results indicated that PGRg3 possesses a significant sexual function enhancing activity as observed in sexual behaviour tests. PGRg3 significantly increased MF, IF, EL1 and EL2 accompanied with a significant reduction in ML and IL which indicated a sexual function improving effect and proved that PGRg3 is endowed with sexual function improving activity. This is in consonance with our earlier results which showed a sexual function improving effect of PGRg3 in male mice [37][38]. Although the established drug (Sildenafil citrate) exhibited, as expected, tremendous activity. The increase of MF and IF in PGRg3-treated rats (indicating the sexual motivation and efficiency of erection and penile orientation) and increasing of the libido might be the result of increase in the several hormones that are secreted from pituitary [39].
On the other hand, PGRg3 significantly increased the frequency of all the components of penile reflexes (E, QF and LF) in the tested animals as compared to control group but comparatively lesser than the standard drug. The aggregate of penile reflexes was also found to be increased in the animals treated with PGRg3 and sildenafil citrate however, there was no significant difference between the groups received the extract at the low dose (100 mg/kg b.w.) and those in the control group. Therefore, the current results revealed that PGRg3 produced a marked increase in potency at the doses as low as 250 mg/kg b.w. It was suggested that PGRg3-induced changes in neurotransmitter levels or their action at cellular levels [40] could change sexual behaviour [41]. Hence, the increased sexual function could be also due to the nervous stimulant action of PGRg3

[31][42]. On the other hand, several reports revealed that ginsenosides inhibit voltage-gated Ca^{2+} channels in the dorsal root ganglion nociceptive neurons and adrenal chromaffin cells [43] and also inhibit brain voltage-gated Na^{+} channels [43][44][45]. Moreover, the resultant aphrodisiac affectivity of PGRg3 extract might also be increasing the release of nitric oxide [46][47] although there is also a possible impact on the hypothalamus-pituitary-adrenal (HPA) axis with a corresponding impact on cortisteroid and prolactin levels.

In a previous work, we reported that PGRg3 administration increased testosterone secretion [38]. The increase in the levels of testosterone in adult males resulted in a moderate but significant increase in sexual desire and libido [48] which may be responsible for the enhanced sexual behaviour in the animals [49] and probably raise the level of luteinizing hormones (LH) [41][50][51]. The prolonged of ejaculatory latency in the PGRg3-treated rats indicating an increase of ejaculatory threshold [51]. Moreover, the steroidal saponins such as PGRg3 increase LH and FSH levels that in turn increase testosterone. These hormones are found at high concentrations in rat testis and seminal fluids [39]. Testosterone also enhances sexual desire, index of libido, motivation and sexual performance.

Different herbs are reported to produce an increase in gastric acid secretion by a cholinergic mechanism [52], thus, their use for sexual invigoration may cause gastric ulceration and other adverse effects. Therefore, ulcerogenic and other adverse effects of PGRg3 were also evaluated. The results of this evaluation were negative. This suggests that the short term use of PGRg3 for this purpose is apparently safe.

5. Conclusion

The results indicated that the traditional folk medicine, *panax ginseng* via its higher content of PGRg3 can produced a significant and sustained increase in the sexual activity of normal male rats, without any conspicuous gastric ulceration and adverse effects. Thus, the resultant aphrodisiac effectivity of the extract lends support to the claims for its traditional usage in sexual disorders. The mechanism by which PGRg3 may induce its action may be hormonal and/or nervous stimulant.

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