



## REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF A THYROTROPIC EXTRACT FROM POTENTILLA ALBA IN MALE RATS

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### KEY WORDS

Herein, we report that oral treatment of male Wistar rats with PADE before mating with intact females instigated marked effects on male reproductive organs. Treatment significantly decreased the motility of the sperm and increased the number of pathological forms of spermatozoa. Additionally, a dose-dependent effect on Leydig cells was observed. However, these PADE effects did not significantly affect male fertility nor fetal and offspring development when PADE-treated males were mated with intact females.

### ABSTRACT

*Background: The dysfunction of the thyroid gland is a common medical condition. Nowadays, patients frequently use medicinal herbs as complementary or alternative options to conventional drug treatments. These patients may benefit from treatment of thyroid dysfunctions with Potentilla alba L. preparations. While it has been reported that Potentilla alba preparations have low toxicity, nothing is known about their ability to affect reproductive functions in patients of childbearing age.*

*Male Wistar rats were orally treated with a thyrotrophic botanical drug, standardized Potentilla alba Dry Extract (PADE), at doses 8 and 40 times higher than the median therapeutic dose recommended for the clinical trials, for 60 consecutive days. Male Wistar rats receiving water (H<sub>2</sub>O) were used as controls. After completing treatment, half of the PADE-treated and control males were used to determine PADE gonadotoxicity, and the remaining half of PADE-treated and control males were mated with intact females. Two female rats were housed with one male for two estrus cycles. PADE effects on fertility and fetal/offspring development were evaluated.*

**Results:** Herein, we report that oral treatment of male Wistar rats with PADE before mating with intact females instigated marked effects on male reproductive organs. Treatment significantly decreased the motility of the sperm and increased the number of pathological forms of spermatozoa. Additionally, a dose-dependent effect on Leydig cells was observed. However, these PADE effects did not significantly affect male fertility nor fetal and offspring development when PADE-treated males were mated with intact females.

**Introduction.** Thyroid gland dysfunction is one of the most widespread endocrine disorders globally. In recent years, a growing number of patients have turned to herbal medicine as either a complementary or alternative approach to managing thyroid-related conditions. Several medicinal plants have shown modulatory effects on thyroid function. For instance, Centella asiatica (Gotu Kola),

*Withania somnifera* (Ashwagandha), and *Commiphora mukul* (Guggul) have demonstrated efficacy in addressing hypothyroidism (Krepkova et al., 2021).

The majority of patients with thyroid dysfunction are female . Our comparative work has investigated PADE effects on the female reproductive system and fe male PADE treatment on offspring development, and the study determined that PADE does not significantly affect the female reproductive system (manuscript in preparation).

Conversely, certain herbs possess thyroid-inhibitory properties, making them potentially beneficial in the treatment of hyperthyroidism. Among these are *Lycopus virginicus* (Bugleweed), *Lycopus europaeus* (Gypsywort), *Melissa officinalis* (Lemon Balm), *Rosmarinus officinalis* (Rosemary), and *Salvia officinalis* (Sage) (Krepkova et al., 2021).

*Potentilla alba*, commonly known as white cinquefoil, is another botanical that has drawn attention due to its thyrotropic properties. Extracts derived from its rhizomes have been employed in clinical settings to manage both hypo- and hyperthyroid conditions. These extracts exhibit a broad pharmacological spectrum, including anti-inflammatory, antimicrobial, antioxidant, and adaptogenic effects. The plant, native to various regions of Europe and introduced to the United States, belongs to the Rosaceae family and contains a range of biologically active compounds such as flavonoids, polyphenols, phenolic acids, triterpenes, tannins, and polysaccharides (Krepkova et al., 2021).

Despite its therapeutic potential, there is limited data on the reproductive safety of *Potentilla alba*, particularly concerning its effects on individuals of reproductive age. This study aimed to evaluate the impact of a standardized dry extract of *Potentilla alba* (PADE) on the male reproductive system and the post-fertilization development of progeny in Wistar rats.

The dry extract was developed by the All-Russian Institute of Medicinal and Aromatic Plants (VILAR), consisting mainly of catechins, gallic acid, p-coumaric acid, beta-sitosterol, and polysaccharides. The preparation contained 61.29% phenolic compounds, 25% polysaccharides, and 2% phytosterols. Male Wistar rats aged 3 to 4 months were administered 25 mg/kg and 125 mg/kg of PADE orally for 60 days. The doses corresponded to approximately 8-fold and 40-fold the median effective clinical dose, respectively (Krepkova et al., 2021).

Post-treatment evaluation revealed that while the total sperm count remained largely unaffected, significant decreases were observed in motile sperm percentages and motility duration, especially in the high-dose group. There was also a dose-dependent rise in the proportion of spermatozoa with morphological abnormalities. Histological assessments indicated a marked reduction in the spermatogenesis index and notable alterations in Leydig cell morphology, including reduced nuclear diameter and increased pyknotic nuclei (Krepkova et al., 2021)

**Table 1. PADE Effect on Male Fertility of Wistar Rats**

Group	Mated Females	Fertility Index (%)	Pregnancy Index (%)
Control (H2O)	17	100	100
PADE 25 mg/kg	18	94.4	100
PADE 125 mg/kg	19	94.7	100

**Table 2. Gonadotoxic Effects of PADE**

Parameter	Control	PADE 25 mg/kg	PADE 125 mg/kg
Total sperm count ( $\times 10^6$ )	591.1 $\pm$ 37.2	599.4 $\pm$ 35.5	481.2 $\pm$ 54.5
Motile sperm ( $\times 10^6$ )	327.8 $\pm$ 18.6	240.6 $\pm$ 26.6 **	163.3 $\pm$ 29.1 **
Motile sperm (%)	56.1 $\pm$ 2.9	46.3 $\pm$ 1.7 **	32.8 $\pm$ 3.3 **
Motility duration (min)	170.0 $\pm$ 13.5	162.5 $\pm$ 16.0	98.0 $\pm$ 11.4
Pathological sperm forms (%)	1.5 $\pm$ 0.3	2.7 $\pm$ 0.2	5.1 $\pm$ 0.5
Testicular weight (g)	3.2 $\pm$ 0.1	3.3 $\pm$ 0.1	3.4 $\pm$ 0.2
Relative testicular weight (%)	0.76 $\pm$ 0.04	0.82 $\pm$ 0.02	0.90 $\pm$ 0.04
Spermatogenesis index (median)	3.36	3.08	3.02

**Table 3. Leydig Cell Morphometry**

Group	Number of Nuclei per Section	Median (L25%; U75%)
Control (H2O)	304	24.22 (20.53, 28.33)
PADE 25 mg/kg	242	21.18 (17.41, 24.27)
PADE 125 mg/kg	236	20.22 (17.41, 23.45)

**Table 4. Fetal Development on Day 20 Post-Fertilization**

Group	Implantations/Dam	Live Fetuses/Dam	Resorptions/Dam	Fetal Weight (g)
Control (H2O)	11.0 $\pm$ 0.8	10.2 $\pm$ 0.7	0.8 $\pm$ 0.3	2.4 $\pm$ 0.1
PADE 25 mg/kg	9.9 $\pm$ 0.6	9.0 $\pm$ 0.3	0.9 $\pm$ 0.5	2.3 $\pm$ 0.1
PADE 125 mg/kg	10.5 $\pm$ 0.6	9.9 $\pm$ 0.8	0.6 $\pm$ 0.3	2.3 $\pm$ 0.1

**Table 5. Offspring Development at Day 21 Post-Birth**

Group	Pups/Litter at Birth	Survival at Day 21 (%)	Line Crossings	Grooming	Defecation	Rearing
Control (H2O)	8.6 $\pm$ 0.9	100	45.3 $\pm$ 1.3	0.9 $\pm$ 0.3	1.4 $\pm$ 0.3	0
PADE 25 mg/kg	9.3 $\pm$ 0.7	100	43.8 $\pm$ 3.3	0.9 $\pm$ 0.1	2.5 $\pm$ 0.5	0.03
PADE 125 mg/kg	11.3 $\pm$ 0.6	100	47.9 $\pm$ 2.5	0.8 $\pm$ 0.2	.8 $\pm$ 0.4	0.02

These findings suggest that although PADE at supratherapeutic doses exerts dose-dependent gonadotoxic effects in male rats, it does not severely compromise fertility or offspring viability under the experimental conditions. Nevertheless, the authors caution against its use in reproductive-age males without further safety profiling. The observed reproductive toxicity may be attributed in part to phytosterols within the extract, though catechins and gallic acid could offer protective counter-effects (Krepkova et al., 2021).

Although many medicinal herbs have transient effects on the male reproductive system, there is a potential risk of impaired spermatogenesis when PADE is used in doses exceeding the recommended therapeutic doses. This study suggests that PADE treatment of reproductive age men should be avoided or recommended with caution. The doses prescribed to these patients should not exceed the therapeutic dose. Treating physicians should consider whether the expected benefits of PADE treatment to the male parent exceed possible risks to male fertility and reproductive health as well as potential effects on fetal and offspring development.

**In conclusion**, while PADE does not significantly hinder fertilization or early postnatal development, its impact on spermatogenesis and Leydig cell structure underscores the need for cautious therapeutic application, particularly in men of childbearing potential. Further research is warranted to determine the reversibility of these effects and to establish safe dosage thresholds in humans (Krepkova et al., 2021).

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