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Phytotherapy and the Gonadal Axis: A Case of Amenorrhea and Hypertension Responsive to Herbal Remedies

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Abstract:
Phytotherapy is gaining increased interest as a complementary approach in the management of reproductive endocrine disorders, particularly those involving hypothalamic-pituitary-gonadal axis dysfunction. Medicinal plants rich in bioactive compounds—such as phytoestrogens, flavonoids, and polyphenols—have been traditionally used to alleviate menstrual disorders, support fertility, and manage menopausal symptoms.
This is the case of a 30-year-old female patient with a history of secondary amenorrhea and grade 3 hypertension. Evaluation of her amenorrhea revealed an isolated hypogonadotropic hypogonadism, with a Rathke's cleft cyst identified on hypothalamic-pituitary MRI. The patient reported resumption of her menstrual cycle following the intake of a mixture of medicinal plants, including anise, sandalwood, garden cress, and Nigella sativa. The evaluation of secondary causes of her hypertension was negative for pheochromocytoma, cushing's syndrome, and renovascular hypertension. The assessment of the renin–aldosterone system yielded borderline results, warranting further investigations to clarify the diagnosis.
This case underscores a potential interaction between phytotherapy and the hypothalamic–pituitary–gonadal axis, suggesting possible phytoestrogenic, antihypertensive, and bone-modulating effects of certain medicinal plants. These hypotheses warrant further investigation.

Introduction:
Alternative therapies, including phytotherapy, are gaining increasing attention for their potential to support the restoration of gonadal axis function, particularly in conditions such as hypogonadotropic hypogonadism and secondary amenorrhea. In this context, various medicinal plants are being explored for their endocrine-modulating properties, notably through their content in phytoestrogens, flavonoids, and other bioactive compounds. These substances may influence the hypothalamic–pituitary–gonadal axis by mimicking estrogenic activity, stimulating gonadotropin release, or modulating neurotransmitter pathways involved in reproductive hormone regulation.
Some plants traditionally used in women's health—such as Nigella sativa (1), anise (2), garden cress, have shown promising effects on menstrual regularity, hormonal profiles, or ovulatory function in preliminary

studies. However, the mechanisms remain poorly understood and likely multifactorial, involving central, peripheral, and metabolic pathways.

Case Report:

We report the case of a 30-year-old female patient, with grade 1 obesity, secondary amenorrhea since 2019, and grade 3 hypertension diagnosed four years ago, well controlled with amlodipine 5 mg/day. Her hypertension was first identified during hospitalization in 2021 for a COVID-19 infection, during which she reported frontal headaches, paroxysmal sweating, and palpitations consistent with Menard's triad.

The evaluation of her amenorrhea revealed Tanner stage 5 secondary sexual characteristics, moist vulva, reduced breast volume, hot flashes, dyspareunia, and decreased libido. Hormonal workup showed isolated hypogonadotropic hypogonadism (Table 1), with prolactin levels within the normal range and no dysfunction of other endocrine axes. Hypothalamic-pituitary MRI revealed a Rathke's cleft cyst, initially measuring 2 mm, which increased to 5 mm on follow-up imaging (Image1). The patient reluctantly disclosed having taken a 10-day course of a plant-based mixture containing anise, sandalwood, garden cress, and *Nigella sativa*, every month since 2021 although no dosages were specified. She reported experiencing two menstrual cycles following this herbal intake. However, the patient started using these plants in 2021 and has been taking them intermittently up to the present day. While the temporal correlation is suggestive, causality cannot be established. Bone densitometry revealed neither osteopenia nor osteoporosis.

Regarding her hypertension, urinary metanephrines were within normal limits, renal artery Doppler ultrasound showed no abnormalities, and the 1 mg overnight dexamethasone suppression test was normal. Evaluation of the renin-aldosterone system showed an aldosterone level of 572 pmol/L and a plasma renin activity of 10.8 mIU/L, with an aldosterone-to-renin ratio of 52.87 which falls within a borderline range. Ambulatory blood pressure monitoring (ABPM) indicated well-controlled hypertension. A saline infusion test is planned to further investigate the diagnosis. A phytovigilance report has been filed.

The patient is undergoing regular follow-up for the Rathke's cleft cyst identified on pituitary MRI. While often asymptomatic, its proximity to the pituitary may contribute to hypogonadotropic hypogonadism, although a direct causal link remains uncertain.

-	29/09/20	25/12/20	29/12/20	09/03/22	14/03/22	29/08/23	01/11/23	22/11/23
Œstradiol	38.4 pg/mL (18–147)	15 pg/mL	23 pg/mL	98 pg/mL (21–251)	111 pg/mL (21–251)	<24 pg/mL (21–251)	<24 pg/mL (21–251)	<24 pg/mL (21–251)
FSH	3.88 uIU/mL (2.9–12)	0.95 mIU/mL (3.03–8.08)	-	2.21 mIU/mL (3.03–8.08)	1 mIU/mL (3.03–8.08)	5.24 mIU/mL (3.03–8.08)	1 mIU/mL (3.03–8.08)	3.64 mIU/mL (3.03–8.08)
LH	7.50 uIU/m	0.18 mIU/m	-	-	1.37 mIU/mL	0.41 mIU/mL	0.69 mIU/mL	-

	L (22–105)	L (2.3–6.6)			(2.39–6.60)	(3.03–8.08)	(3.03–8.08)	
Prolactin	-	2.7 ng/ml	-	9.84 ng/ml	9.80 ng/ml	8.35 ng/ml	18 ng/ml	2.9 ng/ml
Herbal intake right before testing	No	No	No	Yes (anise, sandalwood, garden cress, Nigella sativa, 10 days)	Yes (anise, sandalwood, garden cress, Nigella sativa, 10 days)	Yes (anise, sandalwood, garden cress, Nigella sativa, 10 days)	Yes (anise, sandalwood, garden cress, Nigella sativa, 10 days)	Yes (anise, sandalwood, garden cress, Nigella sativa, 10 days)
Sample taken on day 3 of cycle	No	No	No	No	No	No	No	Yes

Table 1: Assessment of hormonal levels in our patient

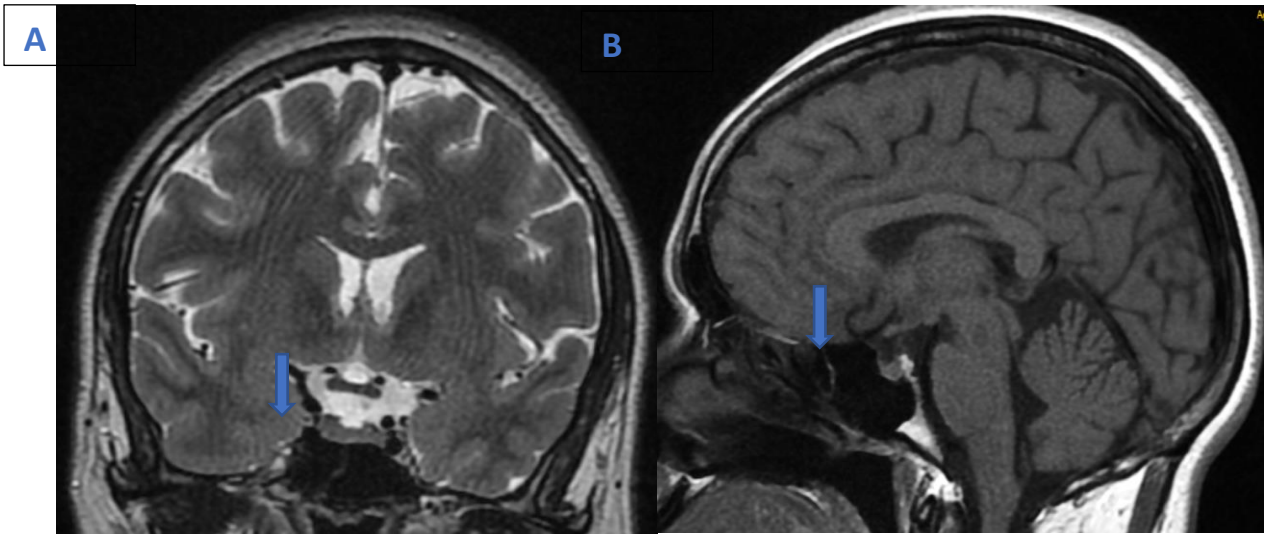

Image 1: MRI of the pituitary gland showing a Rathke's cleft cyst (blue arrow), A: T2-weighted coronal section, B: T1-weighted sagittal section

Discussion:

Pimpinella anisum (anise) and Nigella sativa have long been valued for their estrogenic properties, with historical use dating back to antiquity, when Pliny the Elder described their aphrodisiac and galactagogue effects. The estrogenic activity of anethole, anise's main compound, was demonstrated by Zondek and Bergmann in 1938 (3), and has been further confirmed by other recent studies (4). Anise has also been traditionally used for its analgesic, carminative, antiseptic, and diuretic properties (4), and is known for its antimicrobial, antioxidant, muscle-relaxant, and gastroprotective effects. In gynecology, it is used to alleviate premenstrual syndrome and dysmenorrhea, stimulate lactation and libido, and has shown benefits for glycemic control and anticonvulsant activity (4). Clinical studies have supported its role in reducing

climacteric symptoms (5) and in treating primary dysmenorrhea when combined with celery, saffron, and anise (6). A recent clinical trial (7) showed that *Nigella sativa* supplementation in postmenopausal women increased estradiol levels and improved vaginal health, suggesting potential estrogenic effects without significant change in FSH levels. However, in our patient, no increase in estradiol levels was observed.

Anethole, the main phytoestrogen in anise, acts as a hormonal receptor modulator, which explains its traditional use as an estrogenic agent. One study (8) demonstrated its strong estrogenic activity in a human placental model. However, Tabanca et al. (9) found no significant correlation between anethole content and estrogenic activity, suggesting the involvement of other constituents. Among the different plant parts, the oils extracted from the fruits showed the most potent estrogenic activity, followed by the aerial parts and roots, although still less potent than 17β-estradiol (9).

From a cardiovascular standpoint, aqueous extract of P. anisum has shown hypotensive effects by reducing systolic blood pressure in both normotensive and hypertensive rats, possibly via calcium channel blockade in cardiac and vascular smooth muscle cells. A study published in 2019 confirmed this mechanism while ruling out other actions such as diuresis or angiotensin receptor blockade (10).

Beyond its hormonal effects, Pimpinella anisum has shown potential in promoting bone health and exerting anticancer activity. An aqueous extract was found to stimulate osteoblast differentiation and mineralization without inducing proliferation in uterine cells, suggesting a selective estrogen receptor modulator (SERM-like) effect (11). This extract, rich in flavonoids and phytoestrogens, also demonstrated antioxidant, antitumor, and bone-protective properties (12).

Nigella sativa has shown diuretic, antihypertensive, and estrogenic properties. In hypertensive rats, it increased diuresis and reduced blood pressure (13). These effects are likely mediated by diuretic and possibly central mechanisms (14). Its estrogenic activity, evidenced by increased estrogen levels and vaginal epithelial cornification, is attributed to its content in flavonoids, sterols, and polyunsaturated fatty acids (15).

Lepidium sativum (Garden cress) seeds contain bioactive compounds such as flavonoids (apigenin, quercetin, kaempferol), phenolic acids, and glucosinolates, which have been associated with mild phytoestrogenic activity. Preclinical studies, particularly in ovariectomized rats, have shown that Lepidium sativum extracts may increase uterine weight and serum estradiol levels, suggesting estrogenic effects. These findings support the plant's traditional use as an emmenagogue. However, clinical data in humans are currently insufficient to confirm these effects or determine their relevance at commonly consumed doses. (16)

Currently, available data do not report phytoestrogenic effects associated with the use of sandalwood.

In our patient, the herbal mixture—which she has been taking intermittently since 2021—may have aided menstrual resumption while maintaining controlled blood pressure on 5 mg of amlodipine, without bone complications related to hypogonadism. However, gonadotropic levels remain low (Table 1), consistent with hypogonadotropic hypogonadism. Limitations include lack of precise dosing and post-treatment hormonal data. The temporal link does not establish causality, and controlled studies on this plant combination are lacking.

Conclusion:

While phytotherapy—including *Pimpinella anisum* and *Nigella sativa*—may exert estrogenic and antihypertensive effects through various mechanisms, current evidence remains insufficient to establish causality. In our setting, the use of medicinal plants is common, but precise dosage and standardization

are often lacking. This observation calls for rigorous clinical studies to elucidate the mechanisms by which certain herbal compounds may modulate endocrine function, and to assess their safety and efficacy in hormonal disorders.

Références:

1. Mahmoudian A, Ashouri A, Bilandi RR, Mohammadzadeh F, Dashti S, Bahri N. The possible short-term effect of *Nigella sativa* L in the management of adolescent polycystic ovarian syndrome: results of a randomized controlled trial. *J Ovarian Res*. 2024;17(1):144. doi:10.1186/s13048-024-01460-x.
2. Aćimović M, Dojčinović N. A review of pharmacological properties of anise (*Pimpinella anisum* L.). *Lek Sirov*. 2014;34(1):3–17. doi:10.5937/leksir1434003A.
3. Zondek B, Bergmann E. Phenol methyl ethers as oestrogenic agents. *Biochem J*. 1938;32:641–645.
4. Al-Snafi AE. Constituents and therapeutic activities of *Pimpinella anisum*: A review. *Int J Biol Pharm Sci Arch.* 2024;8(2):67–78.
5. Nahidi F, Kariman N, Simbar M, Mojab F. The study on the effects of *Pimpinella anisum* on relief and recurrence of menopausal hot flashes. *Iran J Pharm Res*. 2012;11:1079–1085.
6. Khoda Karami N, Moattar F, Ghahiri A. Comparison of effectiveness of an herbal drug (celery, saffron, anise) and mefenamic acid capsule on primary dysmenorrhea. *Ofogh Danesh*. 2008;14:11–19.
7. Sukatendel K, Hasibuan RH, Siregar MF, Faradina D, Edianto D, Lintang LS, Rusda M, Inriani V. Effect of Nigella sativa seed extract on estradiol, FSH levels, and vaginal maturity index in menopausal women: a randomized controlled trial. Narra J. 2025;5(1):1399.
8. Fouyet S, Olivier E, Leproux P, Dutot M, Rat P. Evaluation of placental toxicity of five essential oils and their potential endocrine-disrupting effects. *Curr Issues Mol Biol*. 2022;44:2794–2810.
9. Tabanca N, Khan SI, Bedir E, Annavarapu S, Willett K, Khan IA, et al. Estrogenic activity of isolated compounds and essential oils of *Pimpinella* species from Turkey, evaluated using a recombinant yeast screen. *Planta Med*. 2004;70(8):728–735. doi:10.1055/s-2004-827203.
10. Pontes VCB, Rodrigues DP, Caetano A, Gamberini MT. Preclinical investigation of the cardiovascular actions induced by aqueous extract of *Pimpinella anisum* L. seeds in rats. *J Ethnopharmacol*. 2019;237:74–80. doi:10.1016/j.jep.2019.03.050.
11. Kassi E, Papoutsi Z, Fokialakis N, Messari I, Mitakou S, Moutsatsou P. Greek plant extracts exhibit selective estrogen receptor modulator (SERM)-like properties. *J Agric Food Chem*. 2004;52(23):6956–6961. doi:10.1021/jf0400765.
12. Jabbar AAJ, Alamri ZZ, Abdulla MA, Salim Amur Al Sinawi Z, Alfaifi SM. Anise (*Pimpinella anisum* L.) attenuates azoxymethane-induced colorectal cancer by antioxidant, anti-inflammatory, and anti-apoptotic pathways in rats. *Environ Sci Pollut Res*. 2023. doi:10.1007/s11356-023-31349-z.
13. Niu Y, Zhou L, Meng L, Chen S, Ma C, Liu Z, Kang W. Recent Progress on Chemical Constituents and Pharmacological Effects of the Genus Nigella. *Evidence-Based Complementary and Alternative Medicine*. 2022;2022:article ID 1337573. doi:10.1155/2022/1337573.
14. Kavyani, Z., Musazadeh, V., Safaei, E., Mohammadi Asmaroud, M., Khashakichafi, F., Sedgh Ahrabi, S., & Dehghan, P. (2022). Antihypertensive effects of *Nigella sativa* supplementation: An updated systematic review and meta-analysis of randomized controlled trials. *Phytotherapy Research*, 36(6), 2281–2296.
15. Ibrahim RM, Hamdan NS, Mahmud R, Imam MU, Saini SM, Rashid SN, et al. A randomized controlled trial on hypolipidemic effects of *Nigella sativa* seed powder in menopausal women. *J Transl*

Med. 2014;12:82. doi:10.1186/1479-5876-12-82.

16. Azene M, Habte K, Tkuwab H. Nutritional, health benefits and toxicity of underutilized garden cress seeds and its functional food products: a review. *Food Prod Process Nutr*. 2022;4:33. doi:10.1186/s43014-022-00114-z.