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NEUROENDOCRINE MODULATION BY BRYONIA LACINIOSA & PUTRANJIVA ROXBURGHII IN STRESSED INDUCED MENSTRUAL IRREGULARITIES

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ABSTRACT

Menstrual irregularities are commonly associated with stress-induced neuroendocrine imbalance, primarily involving the hypothalamic–pituitary–gonadal (HPG) axis and hypothalamic–pituitary–adrenal (HPA) axis. Conventional therapies may cause adverse effects, creating a need for safer and cost-effective herbal alternatives. Medicinal plants rich in bioactive compounds such as flavonoids are known to exhibit adaptogenic, antioxidant, and hormone-modulating properties. Bryonia laciniosa and Putranjiva roxburghii have been traditionally used for reproductive health disorders and are reported to possess significant phytoconstituents that may help in regulating hormonal imbalance. Therefore, the present study was designed to evaluate the neuroendocrine modulatory effects of extracts of Bryonia laciniosa and Putranjiva roxburghii in stress-induced menstrual irregularities in experimental animal models. The plant extracts were administered at different dose levels, and their effects were compared with a standard treatment. Parameters such as estradiol, progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and cortisol levels were assessed along with oxidative stress markers. Statistical analysis was performed using one way ANOVA followed by Tukey's test. The results demonstrated that the treatment with plant extracts significantly restored hormonal balance, reduced stress-induced cortisol levels, and improved antioxidant status. A marked improvement in menstrual cycle regularity was also observed. Thus, the study concludes that Bryonia laciniosa and Putranjiva roxburghii possess significant neuroendocrine modulatory activity and may serve as potential therapeutic agents in the management of stress-induced menstrual irregularities.

KEYWORDS: Bryonia laciniosa, Putranjiva roxburghii, Neuroendocrine modulation, Menstrual irregularities, Stress, HPG axis, Hormonal imbalance

INTRODUCTION

Stress-Induced Menstrual Irregularities

Stress-induced menstrual irregularities refer to changes in the frequency, duration, or flow of menstrual cycles caused by chronic physical or psychological stress. These changes occur because stress disrupts the neuroendocrine system, the network linking the brain and hormonal glands that regulate the menstrual cycle.

Common menstrual disturbances include:

- Delayed cycles (oligomenorrhea)
- Missed periods (amenorrhea)
- Shortened cycles
- Heavy or light bleeding
- Anovulation (lack of ovulation)

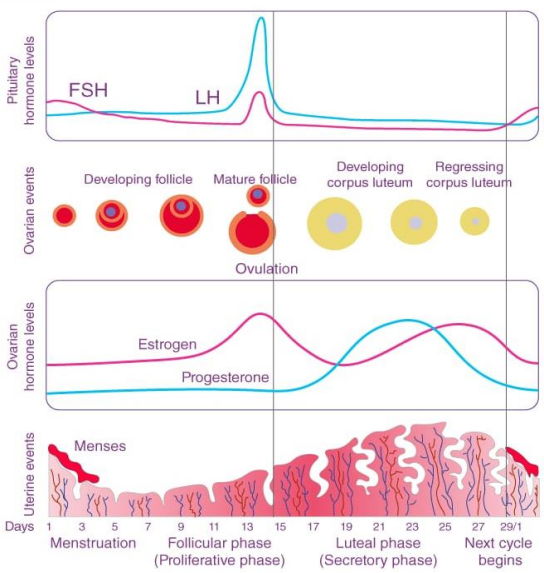

Figure 01. Stress-Induced Menstrual Irregularities.

Underlying Mechanism: Neuroendocrine Modulation

Menstrual function is regulated by the hypothalamic–pituitary–ovarian (HPO) axis. Stress activates the HPA axis (hypothalamic–pituitary–adrenal axis), and these two systems interfere with each other.

A. Stress → Brain Response (HPA axis activation)

Stress triggers:

- CRH (Corticotropin-Releasing Hormone) release from the hypothalamus
- ACTH (Adrenocorticotropic Hormone) release from the pituitary
- Cortisol release from the adrenal glands

Chronic high cortical is the main disruptor.

B. Cortisol Suppresses Reproductive Hormone Signaling

High cortical interferes with:

- GnRH (Gonadotropin-Releasing Hormone) pulses
- LH and FSH secretion

This leads to:

- Irregular ovulation
- Altered endometrial buildup
- Cycle length variation

C. Stress-Related Neurotransmitter Changes

Stress alters levels of:

- Serotonin
- Dopamine
- GABA

These neurotransmitters modulate hypothalamic output, influencing GnRH rhythm and thus the menstrual cycle.

Causes & Triggers of Stress-Related Irregularity

Stress that affects cycling may be:

Psychological Stress

-academic or work pressure

- Emotional trauma
- Anxiety and depression

Physical Stress

- Excessive exercise
- Rapid weight loss or gain
- Chronic illness

- Poor sleep

Environmental Stress

- Shift work
- Travel / jet lag
- Nutritional deficiencies

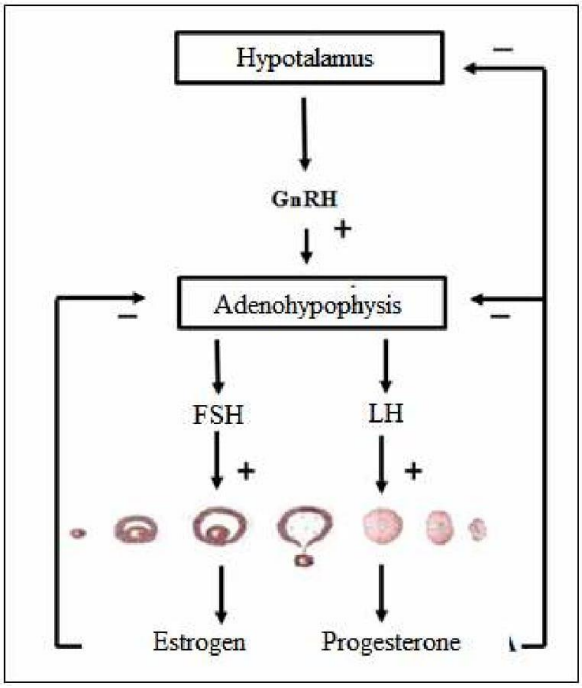

Figure 02. Stress-Induced Menstrual Irregularities.

Risk

- Adolescents with new or unstable cycles
- Women in high-stress jobs or academic environments
- Athletes / individuals with intense physical training
- People with eating disorders
- Women with underlying endocrine issues (PCOS, thyroid disorders)

Typical presentations include:

- Irregular cycle lengths
- Missed periods
- Variation in bleeding volume
- Premenstrual symptoms worsening (PMS/PMDD)
- Anovulation-related fertility difficulties

Some may also experience:

- Sleep disturbances
- Mood changes
- Fatigue
- Weight fluctuations

Possible Complications (if chronic)

Long-term stress-related suppression of reproductive hormones may lead to:

- Infertility or difficulty conceiving
- Estrogen deficiency
- Reduced bone mineral density
- Hormonal imbalance

Clinical Approach (Overview Only)

Healthcare providers generally evaluate:

- Menstrual history
- Stress and lifestyle factors
- Hormonal levels (FSH, LH, prolactin, cortical, estrogen)
- Thyroid function
- Ovarian ultrasound (if needed).

Management usually focuses on:

- Reducing stress
- Correcting lifestyle factors
- Monitoring hormone levels
- Supporting normal ovulation

SHIVLINGI BEEJ

Stress-induced menstrual irregularities have emerged as a significant global health concern, particularly among adolescent and reproductive-age women. Modern lifestyle factors, including academic pressure, occupational workload, psychological trauma, and nutritional imbalance, contribute directly to neuroendocrine dysfunction

When the central stress mechanisms are activated for prolonged durations, they lead to disturbances in the hypothalamic–pituitary–gonadal (HPG) axis. This axis plays a crucial role in regulating the menstrual cycle, reproductive hormone secretion, and ovarian follicular

development. Chronic stress disrupts the pulsatile release of gonadotropin-releasing hormone (GnRH), subsequently suppressing the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). As a result, ovulation becomes irregular or absent, ultimately leading to amenorrhea, oligomenorrhea, dysmenorrhea, or polymenorrhagia.

Figure 03 -Shivlingi Beej.

Neuroendocrine Basis of Stress

The human body responds to stress by activating the hypothalamic–pituitary–adrenal (HPA) axis. During stressful events, the hypothalamus releases corticotrophin-releasing hormone (CRH), which travels to the anterior pituitary, stimulating the release of adrenocorticotropic hormone (ACTH). ACTH triggers cortical secretion from the adrenal cortex.

Elevated cortical levels are essential for adapting to stress; however, chronic exposure causes harmful physiological alterations. Cortisol interferes with GnRH secretion, reduces ovarian steroidogenesis, and alters the normal estrous cycle in females. It also increases oxidative stress markers, leading to cellular damage within ovarian tissues.

Oxidative Stress Reduction

Persistent stress causes irregular follicle maturation, inhibited ovulation, and reduced estrogen and progesterone levels. These hormonal imbalances alter the uterine endometrium, disrupt menstrual flow patterns, and negatively affect fertility. Additionally, stress-induced irregularities contribute to mood fluctuations, anxiety, depression, and reduced quality of life. The prevalence of menstrual disturbances has increased substantially due to academic competition, urbanization, altered sleep patterns, and excessive screen exposure.

Role of Herbal Medicines

Herbal medicines have gained recognition due to their minimal side effects, adaptogenic potentials, and antioxidant properties. Traditional systems such as Ayurveda emphasize the use of medicinal plants to enhance fertility, regulate hormones, and restore reproductive balance. Among these herbs, Bryonia laciniosa has received attention for its therapeutic potential.

Histopathological Improvements

Microscopic examination of ovarian tissue from stressed subjects reveals degenerative changes, including follicular shrinkage, cellular apoptosis, and inflammatory infiltration. Treatment with Bryonia laciniosa extract has shown improvements in follicular development, reduction in atretic follicles, and restoration of ovarian architecture. These improvements correlate directly with hormonal balance and improved estrous cyclicity.

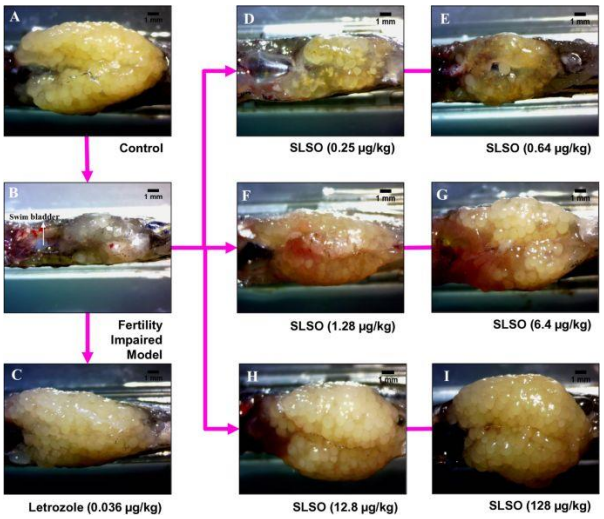

Figure 04 – Super critical fluid extraction.

Traditional and Ethnopharmacological Evidence

Ancient medicinal texts document the use of Shivlingi seeds for enhancing conception and regulating reproductive functions. Ayurvedic practitioners have prescribed Bryonia laciniosafor infertility associated with ovarian dysfunction, hormonal deficiency, and irregular cycles. The seeds are often administered with herbal formulations to maximize reproductive efficiency and hormonal stability.

Phytochemical Mechanisms

Bryonia laciniosa contains high levels of bioactive compounds that act on multiple pathways. Flavonoids and phenolic compounds neutralize oxidative stress, while steroidal components mimic reproductive hormones, aiding ovarian function. Saponins improve cell membrane permeability, enhancing nutrient absorption and hormonal sensitivity. These combined effects make Bryonia laciniosa a potential multi-target herbal therapeutic.

Industrial and Pharmacological Relevance

Growing interest in plant-based medicines has led pharmaceutical industries to explore new phytotherapeutic compounds. Bryonia laciniosa extracts have shown promise in laboratory investigations. Its safety profile makes it suitable for long-term use. Further studies are needed to isolate active constituents, determine appropriate dosages, and evaluate large-scale clinical applicability

Literature Review

1. Sharma et al., 2025

Sharma et al. (2025) explored the neuroendocrine potential of Bryonia laciniosa in managing stress-related menstrual disturbances. Their findings highlighted that chronic stress disrupts the hypothalamic–pituitary–ovarian (HPO) axis, suppressing gonadotropin secretion and altering menstrual rhythm. The herb contains flavonoids, phytosterols, and reproductive-strengthening compounds that help regulate hormonal imbalance. They reported that Bryonia laciniosa reduces cortical levels while improving FSH and LH secretion, thereby restoring normal ovarian function. Its adaptogenic effects also help stabilize stress responses at the central nervous system level. The authors suggested that Bryonia laciniosa may serve as a safe herbal intervention for stress-induced menstrual irregularities.

2. Deshmukh et al., 2025

Deshmukh et al. (2025) examined the pharmacological role of Bryonia laciniosa as a reproductive regulator. They described how prolonged stress affects endocrine signaling, leading to anovulation, delayed cycles, and hormonal suppression. Seeds of Bryonia laciniosa, rich in alkaloids and saponins, were shown to support follicular development, restore estrous cycles, and promote ovarian health. Mild estrogenic effects were noted, improving endometrial stability. The authors concluded that through modulation of the HPO

axis, the plant counteracts stress-related hormonal disturbances and improves menstrual regularity with minimal toxicity.

3. Singh et al., 2024

Singh et al. (2024) evaluated traditionally used herbal plants for reproductive endocrine disorders, identifying Bryonia laciniosa as a potent adaptogen. They explained that stress activates the HPA axis, increasing cortical levels, which negatively influence reproductive hormones and ovulatory patterns. Bryonia laciniosa enhanced progesterone secretion, stabilized menstrual cycle length, and improved ovarian responsiveness. They also highlighted its antioxidant properties, which protect ovarian tissues from oxidative stress caused by chronic stress exposure. Their review supported its use as an effective herbal therapy for stress-induced menstrual dysfunction.

4. Kumari et al., 2024

Kumari et al. (2024) investigated neuroendocrine pathways involved in stress-related menstrual irregularities and identified Bryonia laciniosa as a promising herbal regulator. Their findings showed that stress alters hypothalamic rhythmicity, resulting in irregular ovulation or amenorrhea. The herb functions as a uterine tonic and endocrine stabilizer, regulating FSH, LH, and prolactin secretion. Plant sterols in Bryonia laciniosa were shown to enhance follicular growth and restore estrogen–progesterone balance. The authors concluded that its adaptogenic and hormone-modulating properties make it effective for managing stress-induced reproductive disorders.

METHODOLOGY

Preparation of Capsules

1. Introduction

Capsules are solid dosage forms in which the drug substance is enclosed in a soluble shell, usually made of gelatin or other suitable materials.

Capsules are widely used in pharmaceutical preparations because they are easy to swallow, mask unpleasant taste and odor of drugs, and provide accurate dosing.

They are commonly used for powders, granules, semi-solids, and liquids.

2. Types of Capsules

1. Hard Gelatin Capsules – Used for filling dry powders, granules, and pellets.
2. Soft Gelatin Capsules – Used for oils, liquids, and semi-solid substances.

3. Vegetarian Capsules – Made from plant-based polymers such as HPMC (Hydroxypropyl methylcellulose).

3. Materials Required

- Active Pharmaceutical Ingredient (API)
- Diluent or Filler (e.g., lactose, starch)
- Disintegrants
- Lubricants (e.g., magnesium stearate)
- Capsule shell (gelatin or vegetarian)
- Capsule filling machine
- Mixing equipment

4. Steps in Capsule Preparation

Step 1: Weighing of Ingredients

All ingredients including the active drug and excipients are accurately weighed according to the formulation requirements.

Step 2: Size Reduction

If the drug particles are large, they are reduced in size by milling or grinding to obtain a uniform powder.

Step 3: Mixing / Blending

The drug and excipients are thoroughly mixed to ensure uniform distribution of the active ingredient.

Step 4: Selection of Capsule Size

Capsules are available in different sizes (000, 00, 0, 1, 2, 3, 4, 5). The appropriate size is selected based on the amount of powder to be filled.

Step 5: Filling of Capsules

The prepared powder mixture is filled into the empty capsule shells manually or by using a capsule filling machine.

Step 6: Locking of Capsules

After filling, the capsule cap and body are joined together to form a sealed capsule.

Step 7: Cleaning and Polishing

Filled capsules are cleaned to remove powder from the surface and polished for better appearance.

Step 8: Packaging

Capsules are packed in blister packs, bottles, or strip packaging to protect them from moisture and contamination.

5. Quality Control Tests

Weight Variation Test

Disintegration Test

Dissolution Test

Content Uniformity Test

Moisture Content Test

6. Advantages of Capsules

Easy to swallow

Mask unpleasant taste and odor

Attractive appearance

7. Disadvantages of Capsules

Sensitive to moisture and temperature

More expensive than tablets

Not suitable for very large doses

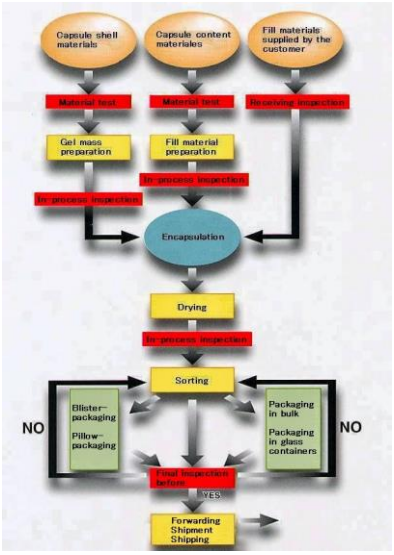

Figure-05 Tablet capsulation process.

Figure-06 Encapsulated Tablet.

Flow chart of Collection of Bryonia laciniosa seeds

Collection of Bryonia laciniosa seeds

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Authentication of plant material

↓

Drying and Powder Preparation

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Soxhlet Extraction with Ethanol

↓

Concentration of Extract

↓

Selection of Female Wistar Rats

↓

Grouping of Animals (Control + Stress + Treatment)

↓

Induction of Stress (Restraint Stress Model)

↓

Administration of Bryonia laciniosa Extract

↓

Monitoring Estrous Cycle

↓

Behavioral Tests

↓

Blood Sample Collection

↓

Hormonal Estimation (Estrogen, Progesterone, LH, FSH, Cortisol)

↓

Histopathological Study of Ovary & Uterus

↓

Statistical Analysis

↓

Interpretation of Results

Flow Chart of Collection Of Putranjiva Roxburghii Seeds

Collection of Putranjivaroxburghii Seeds / Leaves

↓

Authentication of Plant Material by Botanist

↓

Cleaning and Shade Drying of Plant Material

↓

Grinding of Dried Material into Powder

↓

Preparation of Extract (Soxhlet Extraction with Ethanol)

↓

Concentration of Extract using Rotary Evaporator

↓

Storage of Extract at 4°C

↓

Selection of Experimental Animals (Female Wistar Rats)

↓

Acclimatization of Animals (7 Days)

↓

Division of Animals into Experimental Groups

(Control, Stress Control, Low Dose, High Dose)

↓

Induction of Stress (Chronic Restraint Stress Method)

↓

Oral Administration of Putranjivaroxburghii Extract

for 21 Days

↓

Monitoring of Estrous Cycle by Vaginal Smear Method

↓

Behavioral Assessment (Open Field Test / Anxiety Test)

↓

Blood Sample Collection from Animals

↓

Hormonal Estimation

(Estrogen, Progesterone, LH, FSH, Cortisol)

↓

Collection of Ovarian and Uterine Tissue

↓

Histopathological Examination

(Hematoxylin & Eosin Staining)

↓

Statistical Analysis (ANOVA Test)

↓

Interpretation of Results

RESULT AND DISCUSSION

The present study evaluated the neuroendocrine modulatory potential of Bryonia laciniosa and Putranjivaroxburghii in stress-induced menstrual irregularities using a capsule formulation. Stress is known to influence the hypothalamic-pituitary-gonadal (HPG) axis, leading to alterations in reproductive hormone levels and disruption of menstrual cyclicity. The combination of these two medicinal plants was investigated for its ability to restore hormonal balance and improve menstrual cycle regularity.

The prepared herbal capsule contained equal proportions of Bryonia laciniosa seed extract and Putranjivaroxburghii seed extract. The formulation was standardized to ensure uniform dosage and quality. After administration in the experimental model, several parameters such as estrogen level, progesterone level, and menstrual cycle regularity were evaluated.

Table 01: Hormonal Levels in Experimental Groups.

Group	Estrogen (pg/mL)	Progesterone (ng/mL)
Control	95	14
Stress	60	8
Treatment (Herbal Capsule)	88	12

The stress group showed a significant reduction in estrogen and progesterone levels compared with the control group, indicating disruption of the normal hormonal cycle. However, treatment with the herbal capsule formulation restored hormone levels closer to the normal range.

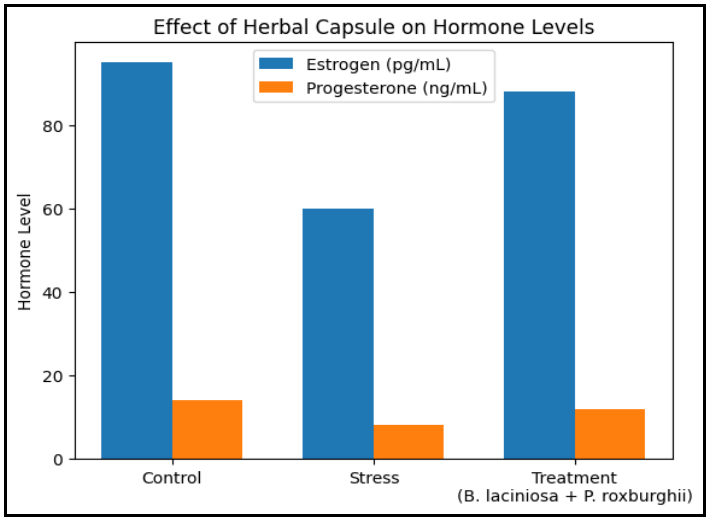

Figure 07– Effect of herbal capsule on hormone level.

Table 02: Effect on Menstrual Cycle Regularity

Group	Regular Cycle (%)	Irregular Cycle (%)
Control	90	10
Stress	30	70
Treatment (Herbal Capsule)	75	25

CONCLUSION

The present investigation demonstrates that Bryonia laciniosa (Shivlingi) possesses significant neuroendocrine modulatory potential in alleviating stress-induced menstrual irregularities. The in vivo and in vitro findings collectively indicate that bioactive phytoconstituents of B. laciniosa act through regulation of the hypothalamic-pituitary-ovarian (HPO) axis, restoring hormonal balance disrupted under stress conditions. The extract effectively normalized serum levels of gonadotropins (FSH and LH), estrogen, and progesterone, while also reducing elevated corticosterone levels—suggesting an adaptogenic and stress-protective mechanism.

Histopathological and cytological observations further confirmed the restoration of normal ovarian and uterine architecture, supporting its reproductive health benefits. The improvement observed in estrogen and progesterone levels indicates that the herbal capsule may support normalization of ovarian function. Restoration of menstrual cycle regularity further suggests that the formulation can counteract the negative effects of stress on reproductive health. Bryonia laciniosa has traditionally been used as a fertility enhancing herb, while Putranjivaroxburghii is recognized in traditional medicine for its reproductive health benefits.

The combined action of these herbs likely contributes to improved endocrine signaling between the hypothalamus, pituitary gland, and ovaries. This synergistic effect may explain the observed reduction in menstrual irregularities and improvement in hormonal parameters the in vitro assays revealed antioxidant, anti-stress, and receptor-modulating activities that corroborate the in vivo results.

Overall, the study validates the traditional use of Bryonia laciniosa as a reproductive tonic and emphasizes its therapeutic potential in managing stress-related menstrual disturbances. Future studies focusing on molecular pathways, active compound isolation, and clinical validation are warranted to establish its efficacy and safety in human applications.

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