

Chapter

Histopathological Impact of Exogenous Chemicals on the Pituitary Gland and Neuroprotective Role of Natural Plant Extracts (NPEs)

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Abstract

This chapter provides a comprehensive review of the histopathological impacts of exogenous chemicals on the pituitary gland and explores the ameliorative potential of Natural Plant Extracts (NPEs) as the neuroprotective agents. The pituitary gland functions as a critical link between the nervous and endocrine systems and anatomically comprises two major parts: the adenohypophysis and the neurohypophysis. The adenohypophysis is a highly vascular region composed of epithelial cells or follicles separated by sinusoids and supported by reticular tissue. Its specialized cells, acidophils and basophils, secrete key hormones essential for maintaining endocrine homeostasis. The pituitary gland is also a principal target of various exogenous chemicals, including insecticides, xenobiotics, environmental pollutants, flame retardants, pesticides, pyrethroids, and aerosols. Bioaccumulation of these agents leads to structural and functional impairments, lipid peroxidation, and oxidative stress, thereby disrupting hormone synthesis and secretion. Recent studies have investigated the neuroprotective efficacy of diverse NPEs in mitigating these toxic effects. These extracts enhance neuronal function by modulating molecular pathways, scavenging free radicals, and activating antioxidant enzymes that reduce neuronal stress. For example, *Nigella sativa* extract demonstrates significant rehabilitative effects against histopathological damage in the pituitary and hypothalamus, while *Vitex agnus-castus* extract improves the pituitary-gonadal axis. Overall, NPEs play a pivotal role in enhancing antioxidant defenses and supporting pituitary recovery. Pituitary rehabilitation remains a complex and underexplored area in histopathology due to limited available data. This review emphasizes the therapeutic potential of NPEs as the promising agents for restoring pituitary integrity following exposure to exogenous toxicants.

Keywords: adenohypophysis, hypothalamus, neuroglial cells, chromophobes, oxidative stress

1. Introduction

Exogenous chemicals exert detrimental effects on the hypothalamic-pituitary axis, disrupting endocrine homeostasis and normal hormonal regulation. Endocrine-disrupting chemicals (EDCs) are exogenous substances that adversely affect the health of the entire organism by interfering with hormone synthesis, secretion, transport, and receptor binding [1–3]. These compounds encompass a wide range of synthetic and natural agents capable of blocking or mimicking hormonal activity. Due to their extensive use across pharmaceutical, agricultural, industrial, and domestic sectors, humans are exposed to EDCs through multiple routes, including ingestion, inhalation, and dermal absorption [4, 5]. Many of these chemicals are lipophilic and persist within adipose tissue for prolonged periods, leading to bioaccumulation and long-term toxicity [6, 7].

The pituitary gland, a pivotal endocrine organ regulating multiple physiological processes, is a primary target of both acute and chronic exposure to EDCs. These substances can interfere with the synthesis and release of pituitary hormones either directly or through hypothalamic modulation. Although the precise mechanisms of action remain incompletely understood, evidence suggests that EDCs can disturb hormonal signaling and disrupt homeostasis throughout an individual's lifespan. Furthermore, they may induce epigenetic alterations such as DNA methylation, leading to changes in gene expression associated with endocrine dysfunction [8]. Epidemiological and experimental studies have established associations between specific EDCs and pituitary pathologies. For instance, exposure to dioxins has been correlated with an increased frequency of pituitary adenomas [9], particularly in populations with high exposure levels, where excessive growth hormone (GH) secretion contributes to tumorigenesis [10]. Benzene exposure has been shown to stimulate pituitary cell proliferation by activating the aryl hydrocarbon receptor (AHR) and its interacting protein (AIP), both of which play crucial roles in pituitary adenoma development [11–13]. Similarly, compounds such as benzene, nonylphenol, and phthalates can enhance GH secretion by influencing the hypothalamic-pituitary-somatotropic axis [14, 15].

Estrogenic agents also modulate pituitary hormone secretion. Estrogens are known to stimulate the release of prolactin (PRL) and GH [16, 17], while exogenous estrogenic chemicals such as dichlorodiphenyltrichloroethane (DDT), bisphenol A (BPA), and chlordane exert similar effects both *in vivo* and *in vitro* [18]. In addition to organic compounds, certain metal ions, termed *metalloestrogens*, display estrogen-like endocrine activity that interferes with PRL secretion [19]. Metals such as chromium and lead significantly alter PRL levels in humans [20], while molybdenum, mercury, and cadmium have also been implicated in pituitary hormone dysregulation [21, 22]. Collectively, these findings underscore the vulnerability of the hypothalamic-pituitary axis to exogenous chemical exposure. Understanding these mechanisms is essential for developing targeted therapeutic interventions and mitigating the endocrine toxicity associated with the environmental and industrial pollutants.

2. Overview of the endocrine system and exogenous chemical exposure

The endocrine system is a highly interconnected network of glands and organs responsible for the synthesis, storage, and secretion of hormones that regulate

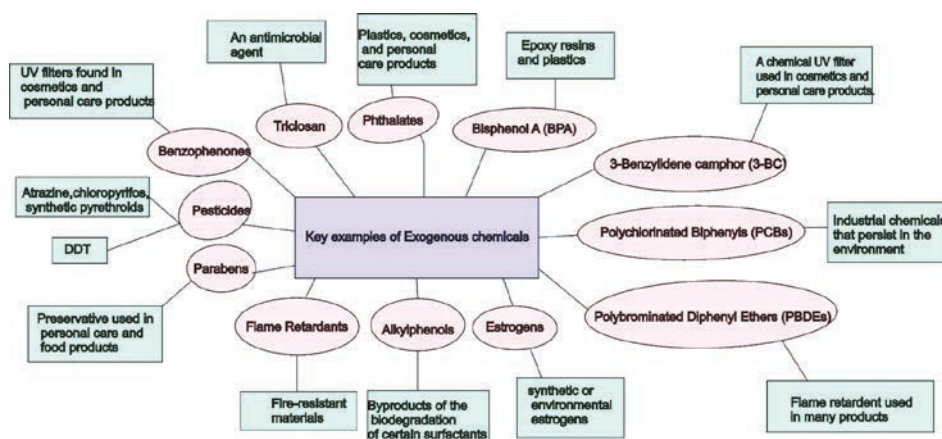


Figure 1.
 Potential sites of endocrine disruption by exogenous chemicals.

growth, metabolism, reproduction, and overall physiological balance. Under normal environmental conditions, this system maintains homeostasis and ensures optimal body function. However, the accumulation of exogenous chemicals from diverse sources including industrial, agricultural, pharmaceutical, and domestic activities—has been shown to disrupt the normal endocrine regulatory mechanisms (**Figure 1**). Exposure to these chemicals occurs primarily through ingestion, inhalation, or dermal absorption (**Figure 2**). Many of these compounds are lipophilic and tend to persist within body tissues, particularly adipose tissue, for extended periods, resulting in bioaccumulation and prolonged biological effects. Exogenous chemicals act through multiple mechanisms: They may mimic natural hormones, block receptor sites, or alter hormone synthesis and degradation. Additionally, they can enhance or suppress hormonal secretion and modify receptor sensitivity, ultimately disrupting physiological homeostasis (**Figure 3**) [23].

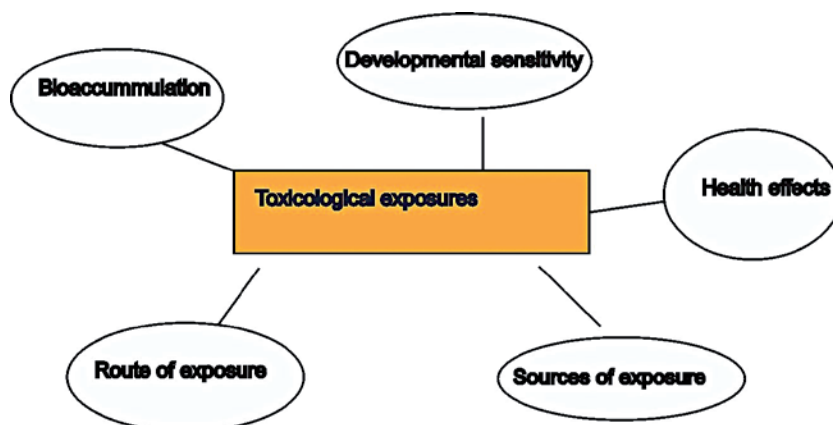


Figure 2.
 Pathways of endocrine-disrupting chemicals (EDCs) affecting hormone synthesis and release.

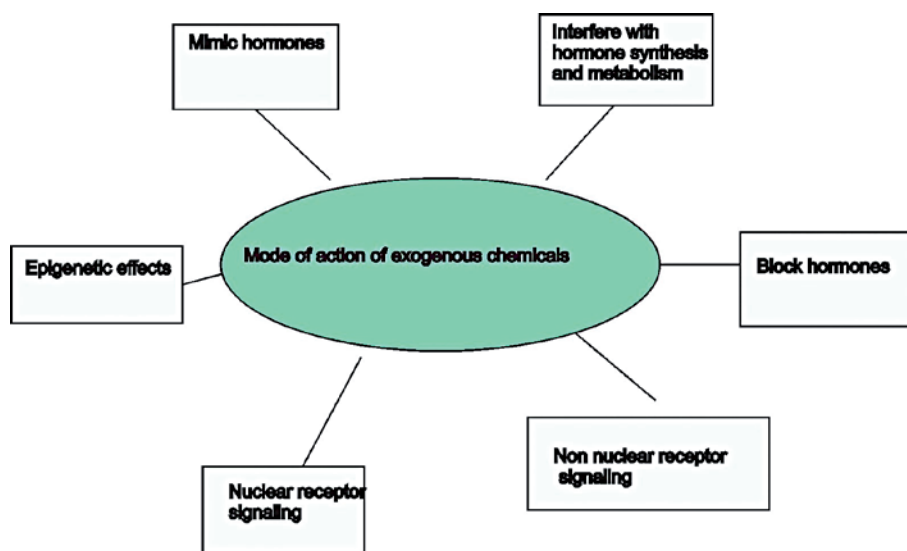


Figure 3.
Schematic representation of mode of action of exogenous chemicals in animals.

3. Hypothalamus-pituitary axis

Anatomically, the hypothalamus and pituitary gland are located in close proximity at the basal region of the brain, extending from the pituitary stalk (infundibulum) to the sella turcica. The hypothalamus communicates with the pituitary gland through a network of signaling molecules and neurohormones that travel *via* the hypophyseal portal system. These stimulatory and inhibitory hormones regulate the synthesis and release of pituitary hormones, which, in turn, control the activity of peripheral endocrine organs [24].

The hypothalamic-pituitary (HP) axis plays an essential role in maintaining endocrine balance and coordinating the body's physiological processes. The hypothalamus integrates neural and endocrine functions through specialized neuroglial cells that process sensory, emotional, and autonomic inputs to maintain homeostasis [25]. The hypothalamic nuclei perform neurosecretory functions by synthesizing and releasing hormones that modulate pituitary activity and, consequently, influence vital processes such as growth, metabolism, reproduction, lactation, and stress response [26, 27]. Two principal pathways characterize the functional organization of the HP axis: the hypothalamic-neurohypophyseal axis and the hypothalamic-adenohypophyseal axis. Together, these form the broader hypothalamic-pituitary-target organ (HPT) axis, encompassing regulatory interactions among the hypothalamus, pituitary gland, and peripheral endocrine glands. The anterior pituitary (adenohypophysis) contains five primary cell types—corticotropes, thyrotropes, somatotrophs, lactotrophs, and gonadotrophs; each responsible for secreting specific trophic hormones that act on their corresponding target glands (**Figure 4**).

The hypothalamus regulates the anterior pituitary through releasing hormones such as corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH), which are secreted by the periventricular and paraventricular nuclei. CRH stimulates the release of adrenocorticotrophic hormone (ACTH), while TRH induces thyroid-stimulating hormone (TSH) secretion. TSH, in turn, regulates

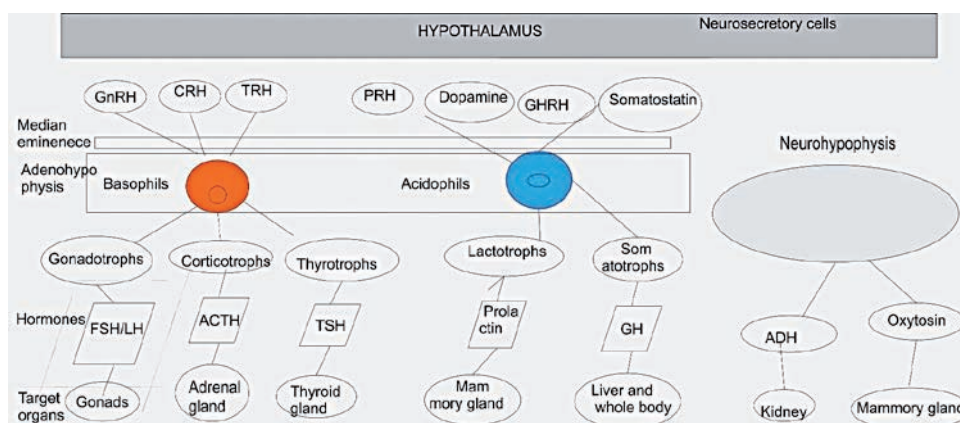


Figure 4.
 Functional overview of the hypothalamic-pituitary-target organ axis depicting hormone pathways and feedback mechanisms governing endocrine control.

the thyroid gland, controlling the synthesis and release of thyroxine (T4), triiodothyronine (T3), and other thyroid hormones essential for metabolic regulation (**Figure 5**) [28].

ACTH acts on the adrenal cortex to modulate glucose metabolism, water balance, and the synthesis of steroid hormones such as cortisol, androgens, and aldosterone through a negative feedback mechanism [29]. The arcuate nucleus of the hypothalamus secretes gonadotropin-releasing hormone (GnRH) and growth hormone-releasing hormone (GHRH), which stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from gonadotrophs and growth hormone (GH) from somatotrophs [25, 30]. Gonadotropins regulate gonadal function, gametogenesis, and the production of sex steroids in both males and females (**Figure 6**) [31].

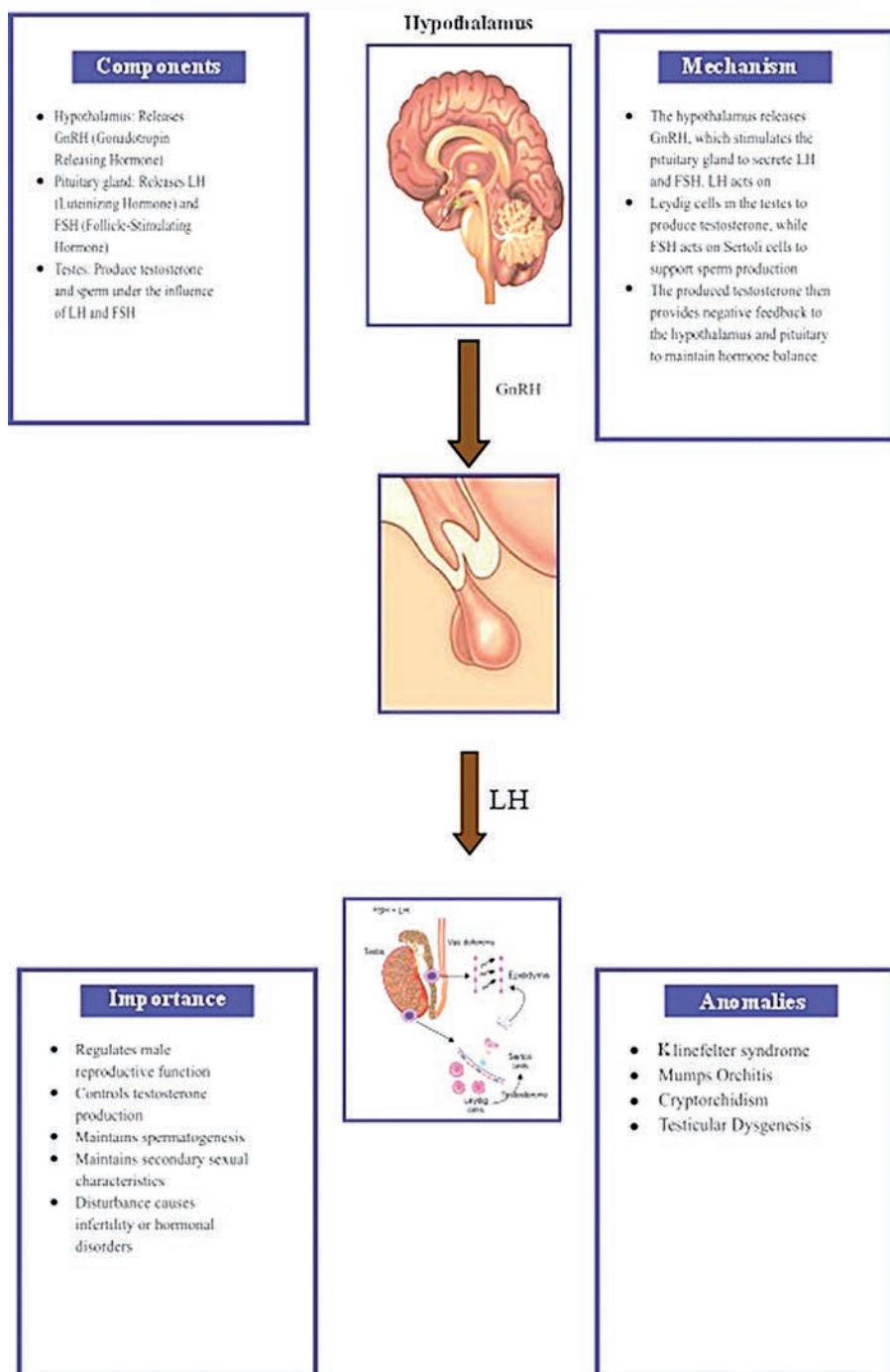
In addition, the posterior pituitary (neurohypophysis) serves as a reservoir for hormones synthesized by the hypothalamic magnocellular neurons located in the paraventricular nucleus (PVN) and supraoptic nucleus (SON). Through axonal projections, these neurons transport and secrete oxytocin and antidiuretic hormone (ADH or vasopressin) into the neurohypophysis for release into systemic circulation [32]. These hormones are critical for reproductive functions, lactation, and water electrolyte balance. Collectively, the hypothalamus-pituitary axis forms the central regulatory hub of the endocrine system, ensuring precise hormonal coordination and maintaining physiological homeostasis through feedback mechanisms between the brain and peripheral organs [33–35].

3.1 Hypothalamus-pituitary-gonadal (HPG) axis

The hypothalamus-pituitary-gonadal (HPG) axis plays a pivotal role in regulating reproductive physiology in both males and females. Disruption of this axis by exogenous chemicals can significantly impair fertility through hormonal imbalance and altered feedback regulation. Several studies have documented that exposure to organophosphates, diesel exhaust, cadmium, lead, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, and flame retardants adversely affects the HPG axis and reproductive function [36].

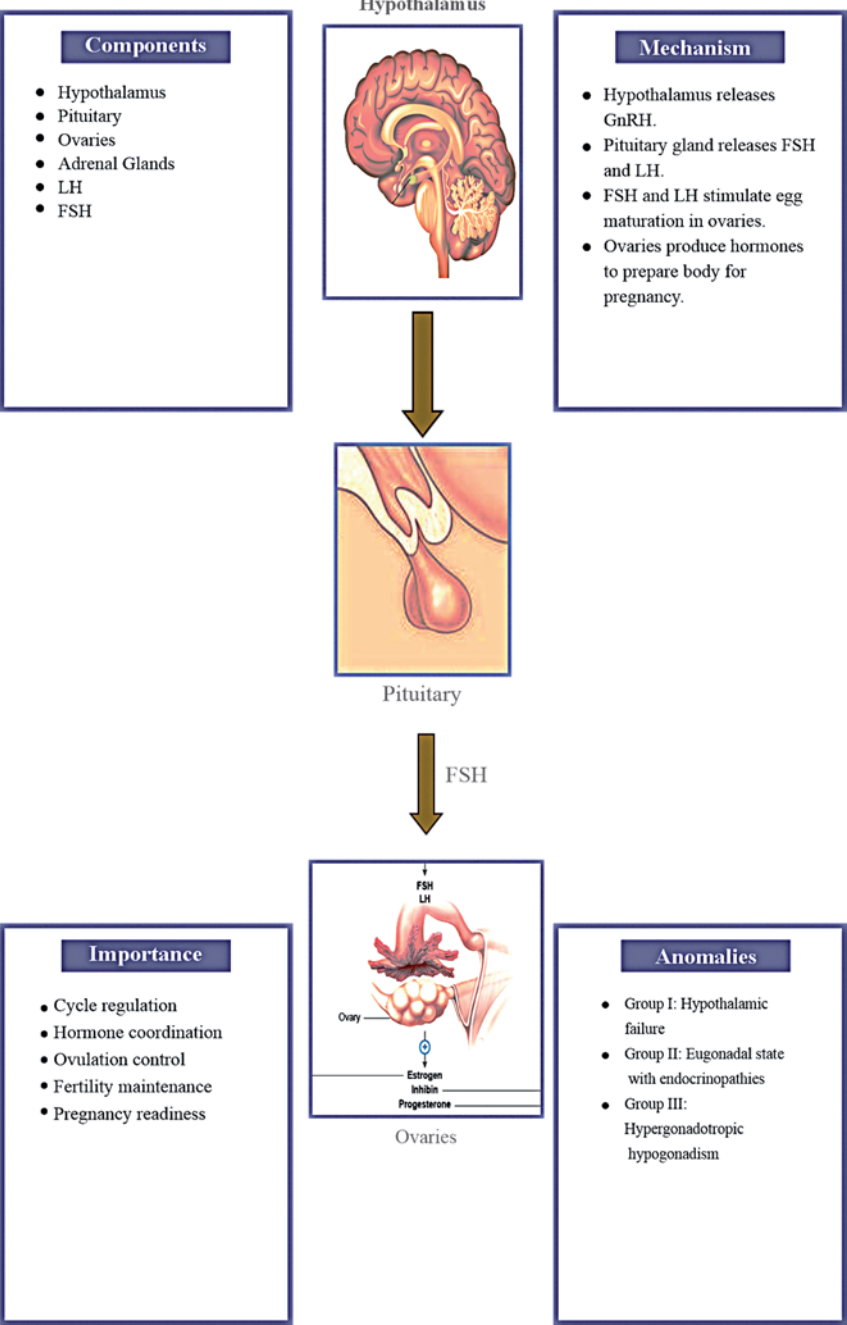
(a)

Hypothalamic-Pituitary Testicular Axis



(b)

Hypothalamus Pituitary Ovarian Axis



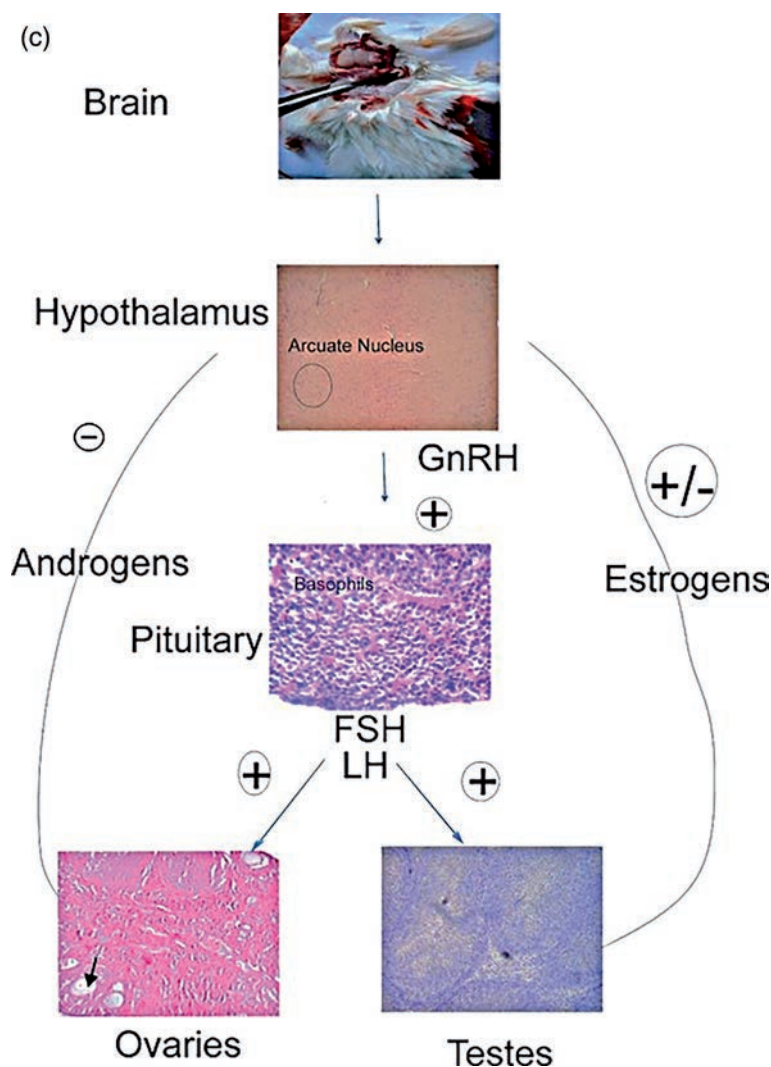


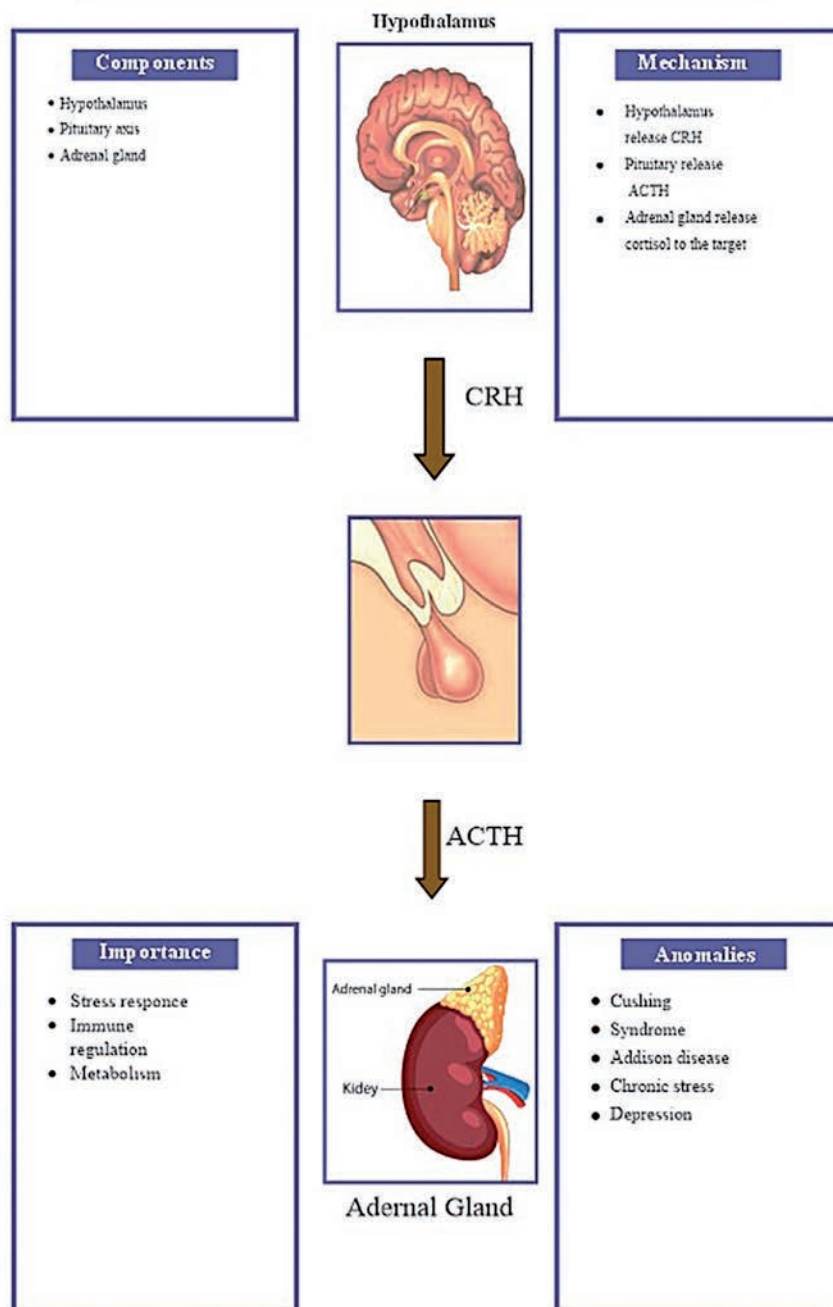
Figure 5.

A: Structural components, regulatory mechanisms, and clinical anomalies of the hypothalamic-pituitary-gonadal axis in male. B: Overview of the components, mechanisms, functional significance, and disorders of the hypothalamic-pituitary-gonadal (ovarian) axis. C: The schematic diagram of histological and anatomical depiction of hypothalamus pituitary gonadal axis.

The hypothalamic arcuate nucleus secretes gonadotropin-releasing hormone (GnRH), which acts on the adenohypophysis to stimulate the synthesis and secretion of gonadotropins-luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones enter the systemic circulation and target the gonads, where they regulate spermatogenesis in males and oogenesis in females [37, 38]. In response, the gonads produce sex steroids such as estrogen, testosterone, and inhibin, which exert negative feedback on both the hypothalamus and pituitary gland to modulate GnRH and gonadotropin release. This feedback loop maintains hormonal balance and reproductive homeostasis. However, exposure to endocrine-disrupting chemicals can interfere with these signaling pathways, leading to impaired gametogenesis and reduced fertility (**Figure 5A-C**) [39, 40].

(a)

Hypothalamus Pituitary Adrenal Axis



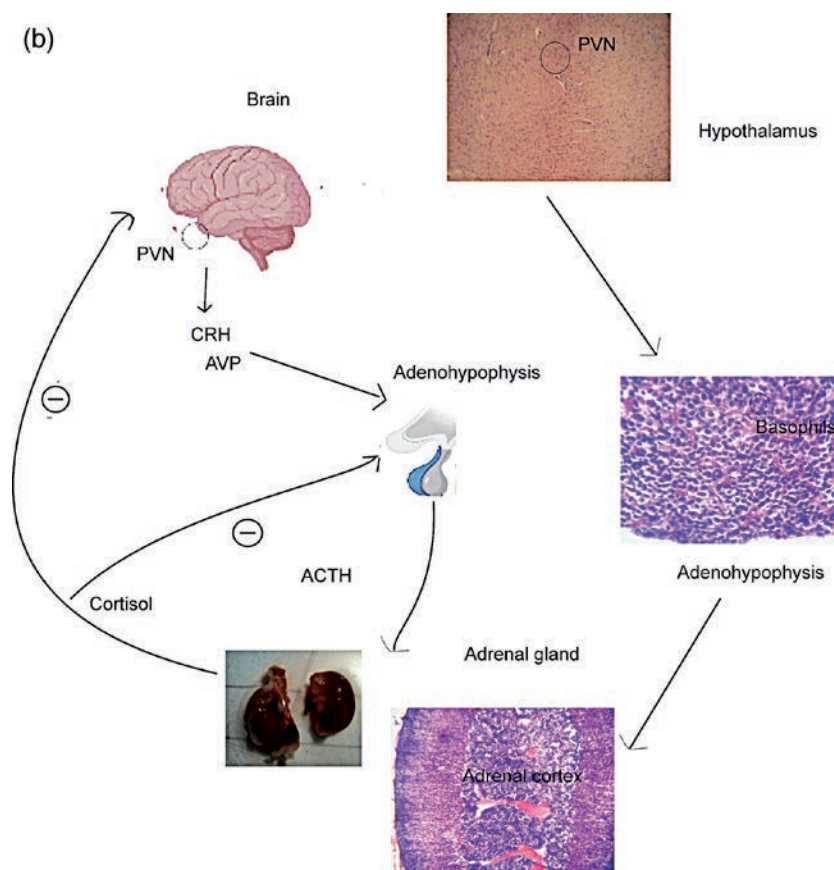


Figure 6.

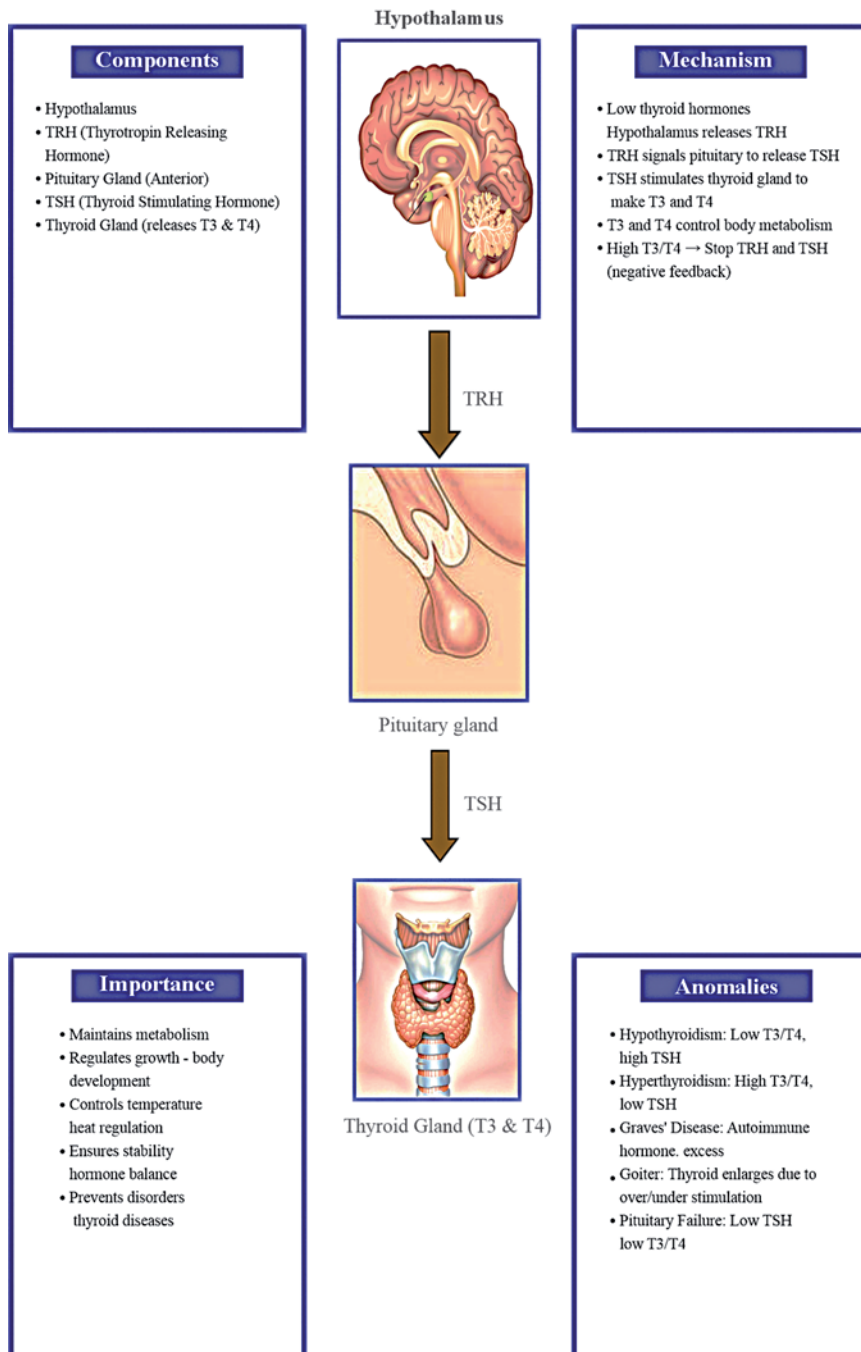
A: Overview of the components, regulatory mechanisms, functional significance, and disorders of the hypothalamic-pituitary-adrenal axis. B: Schematic representation of the hypothalamus-pituitary-adrenal (HPA) axis illustrating the regulatory interactions among the hypothalamus, pituitary gland, and adrenal cortex, and the feedback mechanisms controlling glucocorticoid secretion in response to stress and chemical exposure.

3.2 Hypothalamus-pituitary-adrenal (HPA) axis

The hypothalamus-pituitary-adrenal (HPA) axis is a fundamental component of the neuroendocrine system that regulates stress response, immune function, metabolism, and cardiovascular homeostasis. The hypothalamic paraventricular nucleus (PVN) secretes corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) in response to stress or exposure to exogenous chemicals. These neurohormones act synergistically on the adenohypophysis stimulating the secretion of adrenocorticotrophic hormone (ACTH) into the bloodstream. ACTH subsequently triggers the adrenal cortex to release glucocorticoids, primarily cortisol, which regulates numerous physiological processes [41, 42]. To prevent overstimulation of the HPA axis, glucocorticoids exert negative feedback control on both the hypothalamus and the pituitary glands, thereby maintaining hormonal equilibrium (**Figure 6A and B**). The adrenal glands play a vital role in adapting to stress, modulating immune responses, and maintaining metabolic and cardiovascular stability. Despite their physiological significance, the adrenal glands have often been overlooked in toxicological evaluations.

(a)

Hypothalamic Thyroid Pituitary Axis



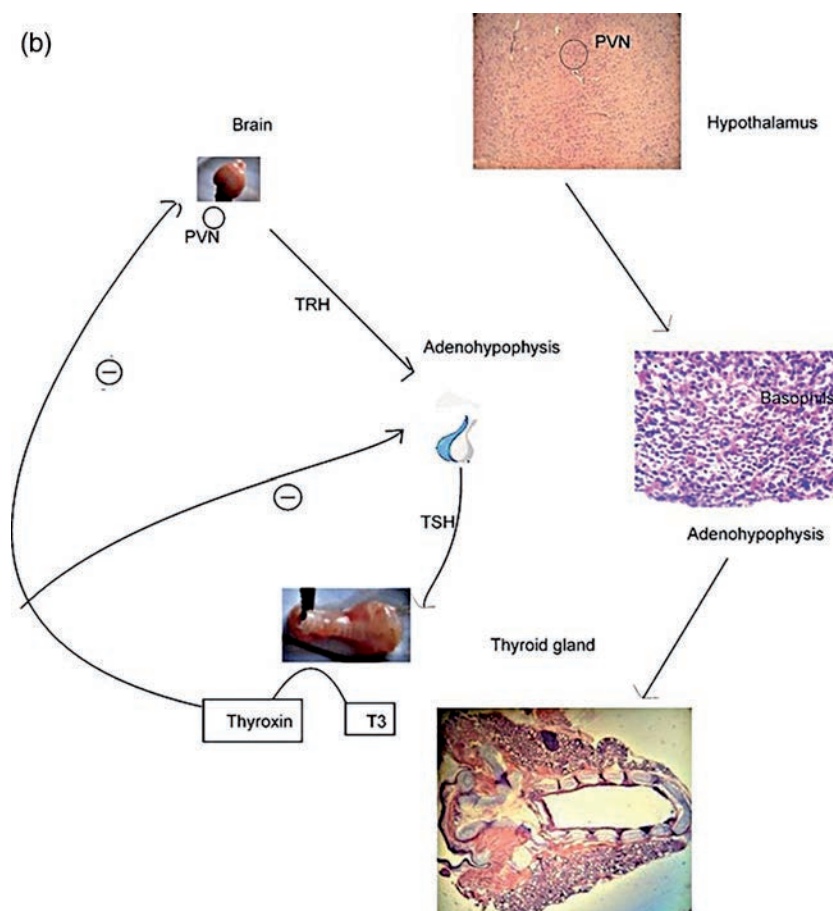


Figure 7.

A: Schematic representation of the components, mechanisms, and anomalies of the hypothalamic-pituitary-thyroid axis. B: Schematic representation of the hypothalamus-pituitary-thyroid (HPT) axis, illustrating the regulatory interactions among the hypothalamus, pituitary gland, and thyroid gland, including feedback control of thyroxine (T₄) and triiodothyronine (T₃) secretion.

Recent studies have identified approximately 60 compounds that induce adrenocortical toxicity in both animal models and humans, acting as endocrine-disrupting chemicals (EDCs). These xenobiotics adversely affect adrenal gland morphology, weight, and steroidogenic pathways. Furthermore, they disrupt glucocorticoid and mineralocorticoid receptor functions and alter catecholamine secretion. Histopathological investigations of bifenthrin-exposed mice have revealed notable changes, including hypertrophy of chromaffin cells in the adrenal medulla with cytoplasmic granule depletion, indicative of impaired catecholamine secretion [43]. Additionally, hyperplasia in the zona fasciculata of the adrenal cortex suggests enhanced glucocorticoid synthesis and release, reflecting adaptive or toxic responses to chemical stressors.

3.3 Hypothalamus-pituitary-thyroid (HPT) axis

The hypothalamus-pituitary-thyroid (HPT) axis is one of the principal neuroendocrine regulatory systems that maintain metabolic and physiological homeostasis in

mammals. The hypothalamic paraventricular nucleus (PVN) synthesizes and secretes thyrotropin-releasing hormone (TRH), which acts on the anterior pituitary (adenohypophysis) to stimulate the secretion of thyroid-stimulating hormone (TSH) into the bloodstream [36]. TSH then targets the thyroid follicles, promoting the synthesis and release of the thyroid hormones thyroxine (T4) and triiodothyronine (T3).

These hormones regulate a wide range of biological functions, including energy metabolism, thermoregulation, growth, and development. To maintain endocrine equilibrium, thyroid hormones exert a classic negative feedback effect on both the hypothalamus and the pituitary gland, thereby inhibiting excessive TRH and TSH secretion and preventing overactivation of the HPT axis (**Figure 7A and B**). Dysregulation of the HPT axis caused by exogenous chemicals or endocrine-disrupting compounds (EDCs) may lead to metabolic abnormalities, altered growth patterns, and developmental or reproductive impairments. Understanding the mechanisms of such disruptions is critical for assessing potential risks associated with environmental toxicants and for maintaining endocrine health [37, 44].

4. Methodology

4.1 Experimental design

Healthy adult mice were randomly assigned to three experimental groups, each comprising an equal number of animals. The Control Group was maintained under standard laboratory conditions and provided with food and water *ad libitum*. The Toxicant-Treated Group received a selected exogenous chemical for a defined exposure period to evaluate its deleterious effects on the hypothalamic-pituitary axis. Toxicant + Natural Plant Extract (NPE) Group was initially exposed to the same toxicant conditions as the second group, followed by the oral administration of the selected natural plant extract during the recovery phase to assess its ameliorative efficacy.

4.2 Histological examination

At the end of the exposure and recovery periods, animals were anesthetized, and the brains including the hypothalamus and pituitary gland were carefully dissected. The tissues were fixed in 10% neutral-buffered formalin, dehydrated, cleared, and embedded in paraffin wax. Serial sections of 5 μm thickness were prepared and stained with Hematoxylin and Eosin (H&E) for routine light microscopic examination. The histoarchitecture of the hypothalamus and adenohypophysis was evaluated for evidence of structural alterations, neuronal degeneration, cytoplasmic vacuolation, and recovery-associated changes.

4.3 Micrometric analysis

Quantitative histo-morphometric analysis was performed using a compound micrometer calibrated with a stage micrometer. For each animal, the mean cross-sectional area of neuronal cell bodies and the number of neurons per defined area (2500 μm^2) were recorded. Data were expressed as mean $\pm$ standard error of the mean (SEM). Statistical comparisons among groups were performed using one-way analysis of variance (ANOVA), followed by appropriate post hoc tests, with significance considered at $p \leq 0.05$ [39, 45].

4.4 Electron microscopy

Selected tissue samples were post-fixed in 1% osmium tetroxide, dehydrated through a graded ethanol series, and embedded in epoxy resin. Ultrathin sections (60–90 nm) were prepared using an ultramicrotome, stained with uranyl acetate and lead citrate, and examined under a transmission electron microscope (TEM). Ultrastructural changes in pituitary cells (acidophils, basophils, and chromophobes) and hypothalamic neurons were documented, including evaluation of organelle integrity, nuclear morphology, and cytoplasmic inclusions.

4.5 Ethical considerations

All experimental procedures involving animals were performed in compliance with institutional ethical standards and the guidelines of the Institutional Animal Ethics Committee (Approval No. Code: SU/ZoL/2666). Measures were taken to minimize animal suffering, and all protocols adhered to internationally accepted principles for laboratory animal care and welfare.

5. Hypothalamus histology with light microscope

5.1 Control group

Histological examination of the hypothalamus in the control group revealed a normal cytoarchitectural organization. The hypothalamic region consisted of well-defined neurosecretory nuclei containing numerous neuronal cell bodies. Neuroglial cells were observed interspersed among the hypothalamic secretory nuclei and nerve tracts, maintaining typical morphological features and structural integrity (**Figure 8A**).

5.2 Chemical-induced changes

In the exogenous chemical-treated group, prominent histopathological alterations were observed. The neurosecretory tracts appeared dispersed, with focal degeneration of neuroglial cells and neuronal shrinkage. Marked vacuolation within neuronal cytoplasm and degeneration of hypothalamic tracts were evident, accompanied by mild edema and water retention. The neuronal content of hypothalamic nuclei was depleted, and localized lesions were noted, occasionally associated with infiltration of macrophages. Several neurosecretory cells exhibited elongated or distorted nuclei, indicating cytotoxic stress (**Figure 8B**).

5.3 NPE-induced recovery

In the natural plant extract (NPE)-treated group, substantial recovery in hypothalamic morphology was evident compared to the toxicant-exposed animals. Degenerative signs in the neurosecretory tracts and neuroglial cells were markedly reduced, and the overall architecture of the hypothalamus approached normalcy. Regenerative changes were apparent, characterized by proliferating neuroglial cells and partial restoration of the neuronal content within the hypothalamic nuclei.

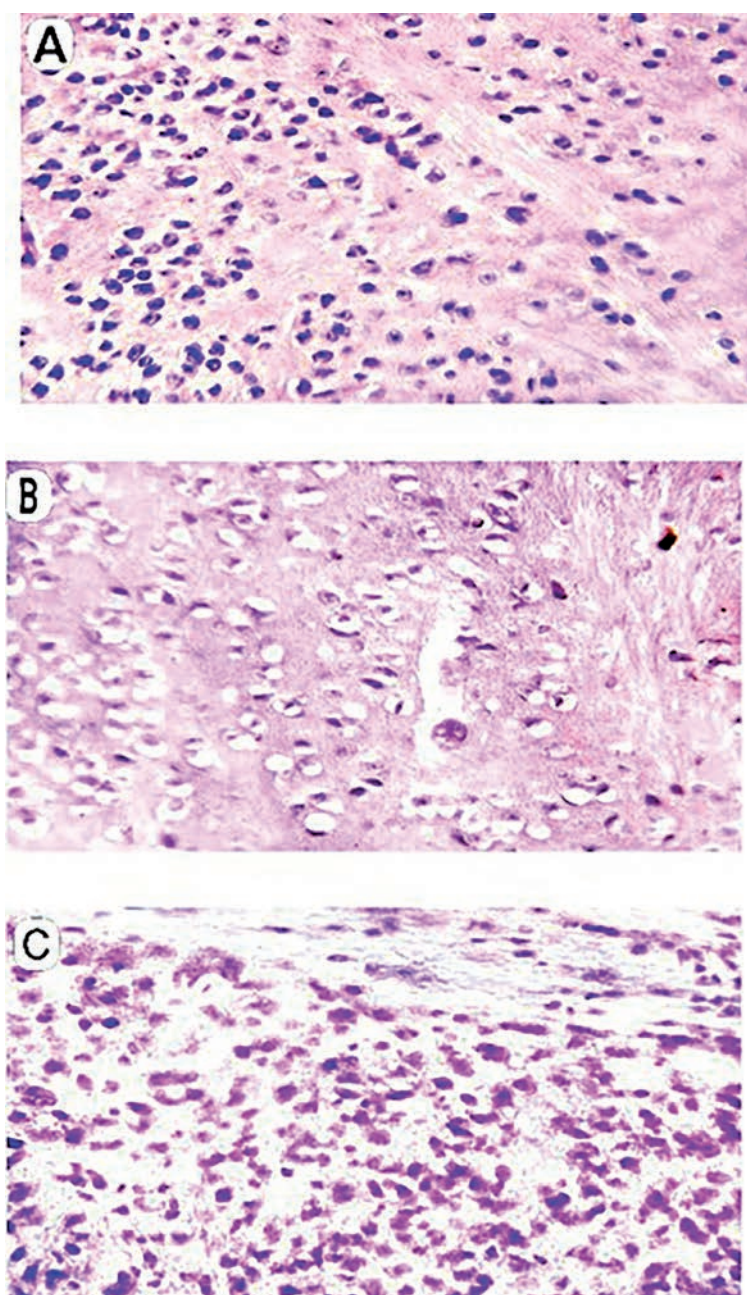


Figure 8.
 Light micrographs of hypothalamic tissue under different treatment conditions: (A) control group showing normal neuronal and neuroglial morphology; (B) exogenous chemical-treated group exhibiting vacuolation, degeneration of neuroglial cells, and disrupted hypothalamic tracts; (C) natural plant extract (NPE)-treated group displaying regenerative features and restoration of hypothalamic architecture (H&E stain, $\times 400$). a: Normal tracts of hypothalamus, b: hypothalamus nuclei, c: damaged tract of hypothalamic, d: hypothalamic tract degeneration with water retention, e: hypothalamic nuclei with depleted neuronal content, f: regeneration of hypothalamic tract, g: rehabilitation of neuronal contents in hypothalamic nuclei, h: hypothalamic nuclei showing regenerative activity.

Micrometric parameters	Control group	Toxicant-treated group	Toxicant+NPE-treated group
Cross-sectional area of cell body (μm^2) ^{***}	65.17 $\pm$ 1.19 ^c	17.50 $\pm$ 0.53 ^a	43.50 $\pm$ 0.88 ^b
Number of neurons per unit area (2500 μm^2) ^{***}	6.56 $\pm$ 0.34 ^c	3.30 $\pm$ 0.18 ^a	4.22 $\pm$ 0.23 ^{ab}

^{*} $p \leq 0.05$; ^{**} $p \leq 0.001$; ^{***} $p \leq 0.0001$. Any two groups not sharing a common lower-case superscript differ significantly ($p \leq 0.05$) with each other.
^{a,b,c} This notation reflects the post-hoc pairwise comparisons conducted after ANOVA to identify statistically distinct groupings.

Table 1.

Micrometric measurements of hypothalamic neurons in control, toxicant-exposed, and natural plant extract-treated groups, including cell size and neuronal density.

The hypothalamic tracts displayed improved continuity and reduced vacuolation, reflecting the ameliorative potential of NPEs against chemical-induced neurotoxicity (Figure 8C).

5.4 Micrometric variations in the hypothalamus

Quantitative micrometric evaluation supported the histological findings. Statistical analysis (one-way ANOVA) revealed a significant decrease ($p \leq 0.05$) in the mean neuronal diameter and neuronal count per unit area in both the toxicant-treated and toxicant + NPE groups compared with the control group. However, the toxicant + NPE group exhibited a significant improvement in neuronal size relative to the toxicant-only group, indicating partial recovery. In contrast, no statistically significant difference was observed in neuronal density between the toxicant-treated and toxicant + NPE-treated groups, suggesting that neuronal regeneration was limited primarily to cytoplasmic restoration rather than complete repopulation (Table 1).

6. Histological landmarks of the adenohypophysis (anterior pituitary)

6.1 Control histology

Light microscopic analysis of the adenohypophysis in the control group revealed that the pituitary cells, primarily pituicytes, were organized into nests and cords separated by fibrovascular sinusoids. The histological sections demonstrated typical cellular morphology, including well-positioned nuclei and cytoplasm with eosinophilic characteristics, indicative of active protein synthesis and storage. Two main cell types were distinguishable:

1. *Chromophobes*: These were relatively small cells, representing approximately 50% of the adenohypophyseal population, characterized by weakly stained cytoplasm.
2. *Chromophils*: Larger cells with strongly stained cytoplasm, further classified into acidophils and basophils based on staining properties. Acidophils were smaller with irregular, faint nuclei, whereas basophils exhibited prominent nuclei and cytoplasmic granules (Figure 9A).

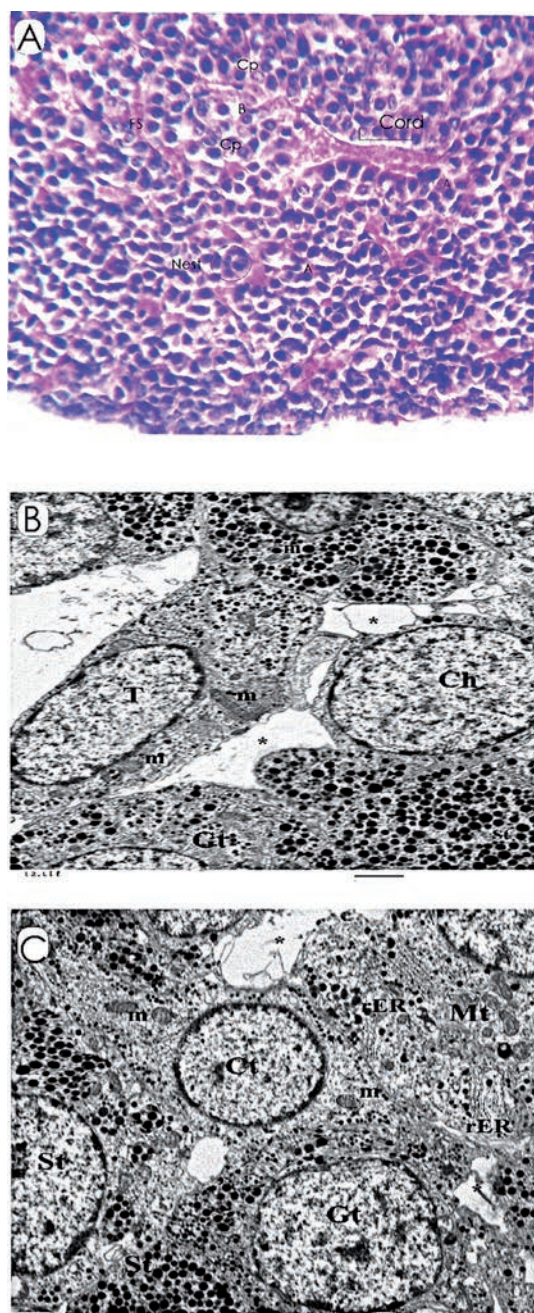


Figure 9.
 A. Light micrograph of control adenohypophysis showing nests and cords of pituicytes, chromophils, and chromophobes (H&E stain, ×400); B. electron micrograph depicting somatotrophs, gonadotrophs, and thyrotrophs with characteristic secretory granules and mitochondria (TEM, ×12,000); C. electron micrograph illustrating corticotropes and lactotrophs with peripheral secretory granules and associated capillary network (TEM, ×12,000) with the chromophobe cell (Ch), somatotrophs (St), gonadotroph cell (Gt) a thyrotrope (Th).

Electron microscopy provided detailed ultrastructural insights. Chromophobes were small, scattered cells lacking distinctive granules. Chromophils contained electron-dense secretory granules with characteristic size, shape, and density, facilitating precise identification of different cell types (**Figure 10A**).

- *Somatotrophs (acidophilic cells)*: Predominant in the adenohypophysis, these cells are spherical with dispersed chromatin and prominent nucleoli. Secretory granules were abundant, round, and uniformly electron-dense, occupying the cytoplasm. The rough endoplasmic reticulum (RER) and mitochondria were less prominent in standard sections (**Figure 9B**).
- *Gonadotrophs*: Spherical cells containing smaller, electron-dense, round secretory granules compared to somatotrophs, with variability in granule size.
- *Thyrotrophs*: Triangular cells with elongated morphology, eccentric nuclei, and longitudinal mitochondria. Secretory granules were small, circular, and centrally located. These cells were closely associated with a dense network of capillaries (**Figure 9B**).
- *Corticotrophs*: Intermediate-sized, elongated cells with centrally located large nuclei and compact spherical mitochondria. Granules were tiny, homogenous, and positioned at the cell periphery (**Figure 9C**).
- *Lactotrophs*: Cells exhibited dispersed, extended RER cisternae throughout the cytoplasm and mitochondria, with peripheral accumulation of secretory granules. Lactotrophs were closely associated with a perforated capillary network (**Figure 9C**).

These observations confirm the heterogeneity of the adenohypophyseal cell population and the distinct ultrastructural characteristics associated with their respective secretory functions, forming the basis for subsequent comparisons with chemically exposed and NPE-treated groups.

6.2 Chemical-induced histopathological changes in the adenohypophysis

Light microscopic observations of the adenohypophysis in the chemically exposed group (H&E staining) revealed prominent histopathological alterations characterized by severe disruption of the normal cellular organization. The typical nests and cords of chromophilic cells exhibited critical degenerative changes, with the loss of eosinophilic staining characteristics and the appearance of cellular debris and vacuolation within sinusoidal spaces. Marked histopathological variations were evident, including empty intercellular spaces, cellular hypertrophy, and secondary atrophy, ultimately leading to tissue disintegration and focal destruction of the normally organized adenohypophyseal architecture.

The nuclei of chromophobic cells appeared oval rather than the characteristic spherical form, and the sinusoids exhibited reduced staining intensity. Toxicant exposure induced pronounced architectural distortion, resulting in poorly defined cell boundaries and loss of normal cytoplasmic staining. Many cells were faintly stained, resembling chromophobes, while others appeared shrunken with large cytoplasmic vacuoles (**Figure 10A**).

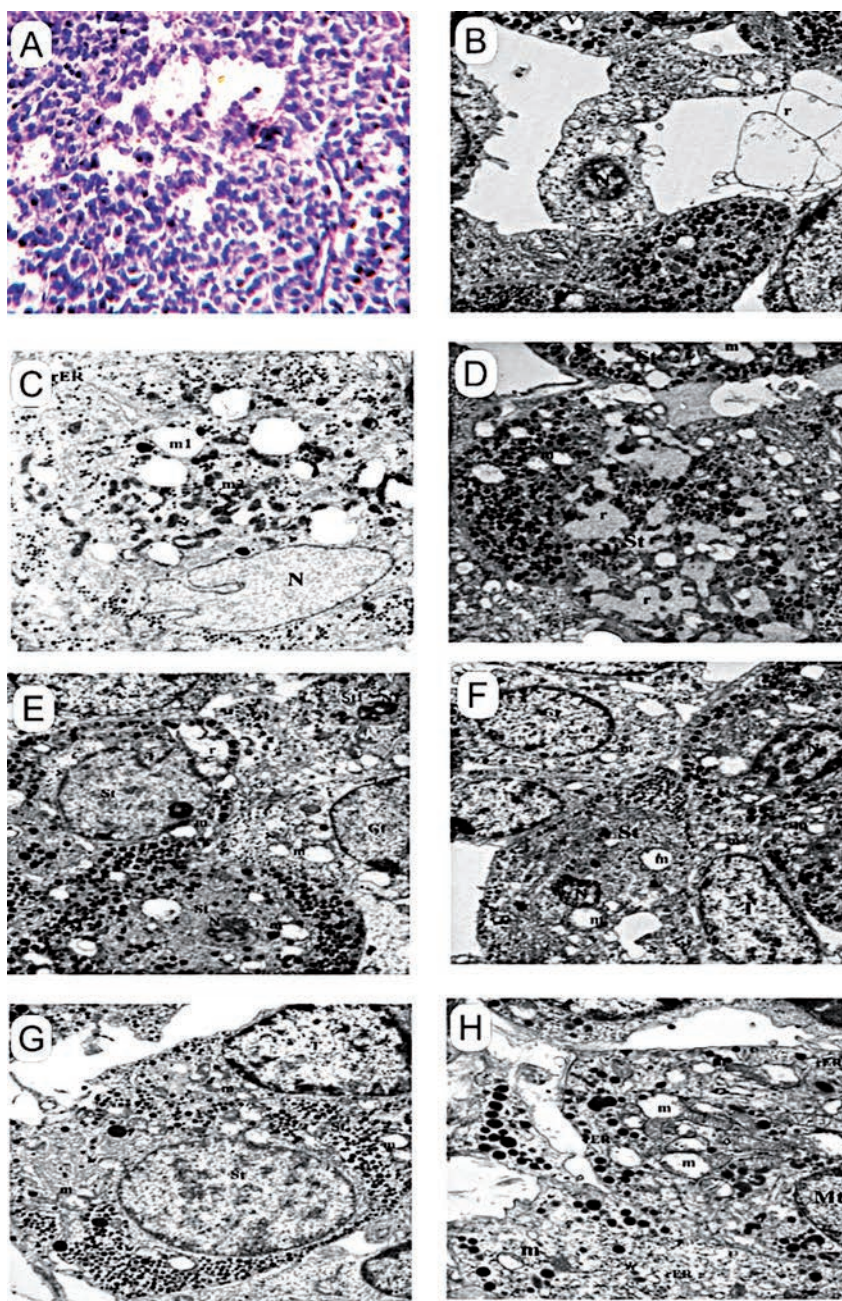


Figure 10.

A. Light micrograph of adenohypophysis showing vacuolations, disrupted nests, and cellular debris after chemical exposure (H&E stain, $\times 400$); B–C. Electron micrographs showing swollen mitochondria, dilated rough endoplasmic reticulum, and irregular nuclei (N) in chromophobes (TEM, $\times 12,000$); cavities in mitochondria (m1), concentrated mitochondria (m2), and dilated rough endoplasmic reticulum (RER); D–E. Somatotrophs exhibiting peripheral nuclei and vacuolated mitochondria; gonadotrophs with degenerative granules and swollen organelles (TEM, $\times 12,000$): somatotrophs (St). E. Somatotrophs (St). A gonadotroph (Gt); F–H. Thyrotrophs and lactotrophs showing loss of cristae, cytoplasmic vacuolation, and condensed nuclear chromatin (TEM, $\times 12,000$): Gonadotroph (Gt) a thyrotrophin (T); G. Triangular thyrotrope (T). Somatotrophs (St); H. Lactotroph.

6.3 Ultrastructural alterations (electron microscopy)

Transmission electron microscopy (TEM) further corroborated these findings, revealing marked ultrastructural degeneration. Chromophobes exhibited nonspecific granules and could not be clearly differentiated from other cell types. Mitochondria displayed swelling and loss of cristae, with some appearing condensed, while others were expanded with disrupted membranes. The rough endoplasmic reticulum (RER) appeared dilated, and nuclei were asymmetrical and irregularly contoured (**Figure 10B–C**).

Despite extensive cellular damage, certain secretory cells remained partially identifiable due to the presence of residual granules and characteristic mitochondria:

- *Somatotrophs*: Nuclei were displaced toward the cell periphery, and the cytoplasm showed depletion of secretory granules. Mitochondria appeared swollen and vacuolated, reflecting severe metabolic stress (**Figure 10D–E**).
- *Gonadotrophs*: Displayed enlarged mitochondria devoid of internal cristae, along with degeneration of large secretory granules, leaving behind scattered smaller granules (**Figure 10E–F**).
- *Thyrotrophs*: Retained their overall nuclear morphology similar to the control group; however, their cytoplasmic mitochondria showed loss of cristae, vacuolations, and granule depletion. Some thyrotrophs preserved their triangular structure, containing small uniform secretory granules and swollen mitochondria, while exhibiting condensed nuclear chromatin (**Figure 10G**).
- *Lactotrophs*: Exhibited the most prominent toxic manifestations, with severely hypertrophic mitochondria, complete loss of internal cristae, expanded RER cisternae, and irregularly sized granules distributed throughout the cytoplasm (**Figure 10H**).

These findings collectively indicate that chemical exposure induces profound degenerative and necrotic changes in the adenohypophysis, impairing both its structural integrity and secretory function.

6.4 NPE-induced recovery

Histological analysis of the adenohypophysis in the Natural Plant Extract (NPE)-treated group using H&E staining revealed marked protective and restorative effects following chemical-induced damage. The characteristic cords of chromophilic cells showed notable reorganization, with the reappearance of eosinophilic staining and partial restoration of the sinusoidal architecture. Previously empty intercellular spaces were reduced as a result of cellular regeneration and reformation of glandular tissue integrity.

The shrunken and distorted cells regained their normal morphology, and the spherical nuclear architecture was re-established, indicating active recovery. Signs of cellular swelling and intracellular edema were diminished, while secondary atrophic changes were reversed. Quantitative observations indicated a significant increase in the number of cells per unit area compared to the toxicant-exposed group, confirming enhanced tissue regeneration (**Table 2**).

Micrometric parameters	Control group	Toxicant-treated group	Toxicant+NPE-treated group
Number of acidophils per unit area (2500 μm^2) ^{***}	12.73 $\pm$ 0.51 ^c	4.6 $\pm$ 0.36 ^a	7.33 $\pm$ 0.88 ^b
Number of basophils per unit area (2500 μm^2) ^{***}	6.40 $\pm$ 0.34 ^a	9.8 $\pm$ 0.37 ^c	8.86 $\pm$ 0.68 ^b
Number of chromophobes per unit area (2500 μm^2) ^{***}	1.46 $\pm$ 0.13 ^b	0.00 $\pm$ 0.00 ^a	0.00 $\pm$ 0.00 ^a
Total number of pituicytes per unit area (2500 μm^2) ^{***}	20.6 $\pm$ 0.73 ^b	14.4 $\pm$ 0.51 ^a	16.2 $\pm$ 0.61 ^a

^a $p \leq 0.05$; ^b $p \leq 0.001$; ^c $p \leq 0.0001$. Any two groups not sharing a common lower-case superscript differ significantly ($p \leq 0.05$) with each other.
^{a,b,c} This notation reflects the post-hoc pairwise comparisons conducted after ANOVA to identify statistically distinct groupings.

Table 2.
 Micrometric analysis of cell size and numerical variations of adenohypophyseal cell types across control, toxicant-exposed, and NPE-treated groups.

The NPE-treated sections also displayed evidence of heightened mitotic activity, suggesting rapid cellular turnover and repair. All phases of mitosis were observed, reflecting active proliferative recovery processes within the adenohypophysis. Rehabilitating nuclei undergoing karyokinesis were evident, along with scattered vacuolations and residual cellular debris, signifying ongoing tissue restoration. Additionally, the presence of typical macrophages was noted, indicating the phagocytic clearance of necrotic material and support for tissue remodeling (**Figure 11**).

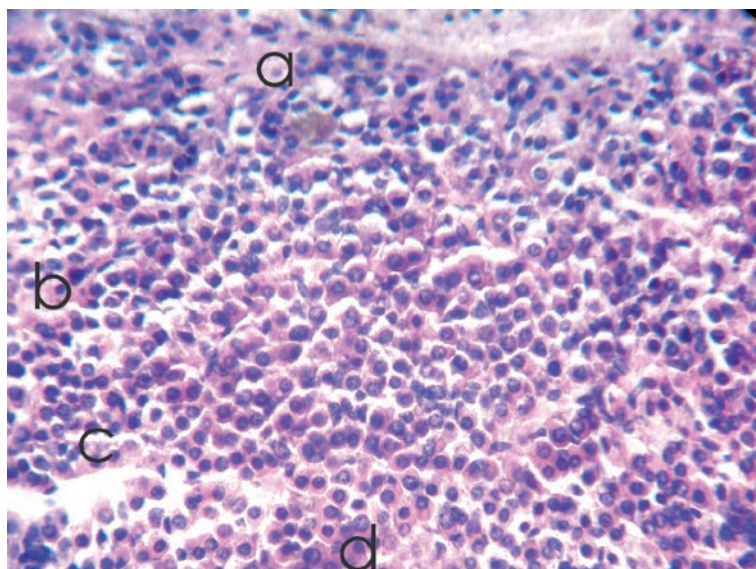


Figure 11.
 Light micrograph of adenohypophysis in the NPE-treated group showing reappearance of eosinophilic chromophilic cells, restored sinusoidal spaces, mitotic activity, and macrophage infiltration indicating recovery (H&E stain, $\times 400$): a: regenerative activity, b: macrophage, c: vacuolations due to cell damage, d: karyokinesis.

6.5 Micrometric variations of the adenohypophysis

Micrometric analysis further substantiated the histological observations. Statistical evaluation of the mean number of acidophils per unit area ($2500\ \mu\text{m}^2$) of the adenohypophysis revealed a significant decline ($p \leq 0.05$) in both the toxicant-exposed and toxicant + NPE-treated groups when compared with the control group. In contrast, the mean number of basophilic cells per unit area showed a significant increase ($p \geq 0.05$) in the toxicant and toxicant + NPE groups relative to the control, although no significant difference was observed between the toxicant and toxicant + NPE groups.

Similarly, the mean number of chromophobes per unit area ($2500\ \mu\text{m}^2$) demonstrated a significant reduction ($p \leq 0.05$) in the toxicant and toxicant + NPE-treated animals compared with the control. Furthermore, one-way ANOVA analysis of the total number of pituicytes per unit area ($2500\ \mu\text{m}^2$) revealed a significant decrease ($p \leq 0.05$) in the toxicant and toxicant + NPE groups as compared to the control group, confirming the quantitative impact of toxicant exposure and the partial restorative effect of NPE administration (Table 2).

7. Neuroprotective effects of natural plant extracts (NPE) on the pituitary gland

The pituitary gland, often referred to as the *master gland*, plays a central role in regulating endocrine functions and maintaining neuroendocrine balance. It is highly sensitive to environmental toxicants, including endocrine-disrupting chemicals (EDCs), oxidative agents, and heavy metals, which can impair the hypothalamic-pituitary connectivity and disrupt hormonal synthesis and secretion. Exposure to such toxicants induces biochemical and histopathological alterations, compromising the release of essential hormones such as prolactin, growth hormone (GH), and adrenocorticotrophic hormone (ACTH). Accumulating evidence suggests that medicinal plants possess bioactive constituents capable of mitigating these adverse effects by protecting neuronal and secretory components of the pituitary gland [46–49]. These plant-derived compounds exhibit neuroprotective, antioxidant, anti-inflammatory, and adaptogenic properties that enhance endocrine resilience and cellular repair mechanisms.

7.1 Mechanisms of neuroprotection by natural plant extracts

Phytochemicals such as flavonoids, phenolic acids, alkaloids, and terpenoids play pivotal roles in neutralizing reactive oxygen and nitrogen species, thereby reducing oxidative stress and lipid peroxidation. Extracts of *Curcuma longa* (curcumin), *Camellia sinensis* (green tea polyphenols), and *Withania somnifera* (withanolides) have been shown to restore redox balance in endocrine tissues, preserve mitochondrial function, and limit apoptotic cell loss under toxic stress [50–56]. Several botanicals also modulate hypothalamic-pituitary-adrenal (HPA) axis activity. *Panax ginseng* and *Rhodiola rosea* exhibit adaptogenic and neuromodulatory actions that prevent excessive activation of corticotropin-releasing hormone (CRH) and ACTH pathways. By attenuating chronic stress-induced hyperstimulation, these agents help maintain hormonal homeostasis and protect against pituitary hypertrophy and degeneration [57, 58].

7.2 Neuroendocrine and cytoprotective actions

Plants containing phytoestrogens, such as *Glycine max* and *Pueraria mirifica*, exert mild estrogenic and anti-estrogenic effects that stabilize hormonal equilibrium in the presence of synthetic endocrine disruptors. These phyto-compounds competitively bind to estrogen receptors in pituitary tissues, blocking toxic xenoestrogen interactions and thus minimizing endocrine disruption. Additionally, resveratrol and quercetin inhibit cytochrome P450-mediated bioactivation of toxicants, reducing pituitary cytotoxicity [59–61].

Certain NPEs also enhance cellular repair and neurotrophic support. *Ginkgo biloba* extracts, rich in ginkgolides, increase cerebral perfusion and upregulate neurotrophic factor expression, thereby improving hypothalamic signaling and supporting pituitary function. Similarly, *Bacopa monnieri* enhances synaptic plasticity and neurotransmitter modulation, improving pituitary responsiveness to hypothalamic inputs [62, 63].

7.3 Histological and functional restoration

Histopathological studies demonstrate that NPE treatment following chemical exposure can reverse architectural disorganization and restore cellular morphology of the pituitary gland. Extracts of *Nigella sativa* and *Moringa oleifera* have shown prominent cytoprotective and regenerative effects, reducing cytoplasmic vacuolation, normalizing chromophil distribution, and restoring eosinophilic characteristics in pituitary tissues. These improvements coincide with the enhanced activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), along with reduced malondialdehyde (MDA) levels, indicating lower oxidative damage [64–66]. Compounds such as curcumin, and polyphenols are also known to upregulate cellular defense pathways, improving mitochondrial energy metabolism and reinforcing the antioxidant–anti-apoptotic balance required for pituitary recovery.

7.4 Integrative mechanistic insight

Despite substantial evidence of NPE efficacy, the precise molecular mechanisms underlying pituitary neuroprotection remain incompletely understood. Future research should explore key signaling cascades, particularly those involving Nrf2, NF- κ B, and MAPK pathways, which regulate antioxidant enzyme expression and cellular stress responses within pituitary tissues. Furthermore, standardization of plant extracts, along with controlled experimental validation, is necessary to determine optimal doses, bioavailability, and long-term safety [67–70].

7.5 Summary and implications

Collectively, available data support the hypothesis that plant-derived neuroprotective agents provide an effective natural therapeutic strategy for maintaining pituitary health against chemical and oxidative insults. Through their combined antioxidant, anti-inflammatory, neurotrophic, and endocrine-modulating properties, these compounds help restore cellular homeostasis and hormonal balance. This integrative perspective reinforces the therapeutic potential of medicinal plants in mitigating pituitary dysfunctions and associated neuroendocrine disorders. The convergence of

oxidative stress theory, HPA axis regulation, and NPEst response underlines a shared mechanistic framework through which bioactive phytochemicals safeguard pituitary structure and function [46, 57].

8. Conclusion

Natural plant extracts represent a promising therapeutic approach for preserving the structural and functional integrity of the pituitary gland against oxidative, environmental, and chemical insults. These botanicals exert the cytoprotective effects through their potent antioxidant, anti-inflammatory, and hormone-modulating mechanisms. By restoring neurophysiological stability and endocrine balance, medicinal plants demonstrate significant potential as complementary interventions for the prevention and management of pituitary dysfunctions.

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Conflict of interest

The authors declare that they have no conflict of interest.

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