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Endocrine toxicity induced by plant growth regulators

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Abstract

Plant growth regulators (PGRs), are widely used to enhance agricultural productivity and have emerged as potential endocrine-disrupting chemicals (EDCs) with significant implications for animal and human health. Though they modulate plant growth through hormone like activity in numerous ways. This review explores the mechanisms and pathways through which PGRs induce toxicity in endocrine organs. PGRs can impair hormone biosynthesis, receptor signalling and metabolic enzyme function. It would lead to reproductive toxicity, developmental anomalies, neurological effects and systemic organ damage. Molecular and histopathological findings demonstrate PGR induced apoptosis, oxidative stress, DNA damage, and alterations in steroidogenesis and gene expression. These disruptions underline the need for toxicological evaluations and safer agricultural practices to minimize environmental and health risks associated with PGR exposure.

Keywords: Plant growth regulators, endocrine toxicity, giberellins, cytokinins, forchlorfenuron, ethephon

Introduction

Plant growth regulators (PGRs) are one among the most widely used pesticides, due to its relatively low toxicity compared to other options. These were discovered by Charles Darwin during his studies in plants way back in 20th century (Singh *et al*., 2021) [22]. An endogenous PGR are synthesized within a part of plant and transported to another part, where it induces physiological responses even in very low concentrations after binding with specific receptors at its site of action. Hence, they are also known by the name phytohormones. Plant produces hormones naturally in various sites like roots, leaves etc. and can regulate its growth and metabolism (Flasiński and Hąc-Wydro, 2014) [11]. They can be naturally occurring or synthetic, and their application has significantly impacted agricultural productivity by enhancing crop yields and providing substantial economic benefits (Rademacher, 2015) [20].

Classification of Plant Growth Regulators

Plant growth regulators, based on its origin are classified into natural and synthetic types and also into growth promoters and inhibitors based on its mechanism of action. Auxins, Gibberellins (GAs) and Cytokinins (CKs) are grouped under plant growth promoters while Abscisic acid (ABA) and Ethylene (C2 H4) are grouped into plant growth inhibitors. Brassinoide (BRs), Salicylates (SA), Jasmonates (JA) and derivatives and polyamies (PAs) are some other PGRs which were discovered recently (Mishra *et al*., 2024) [14].

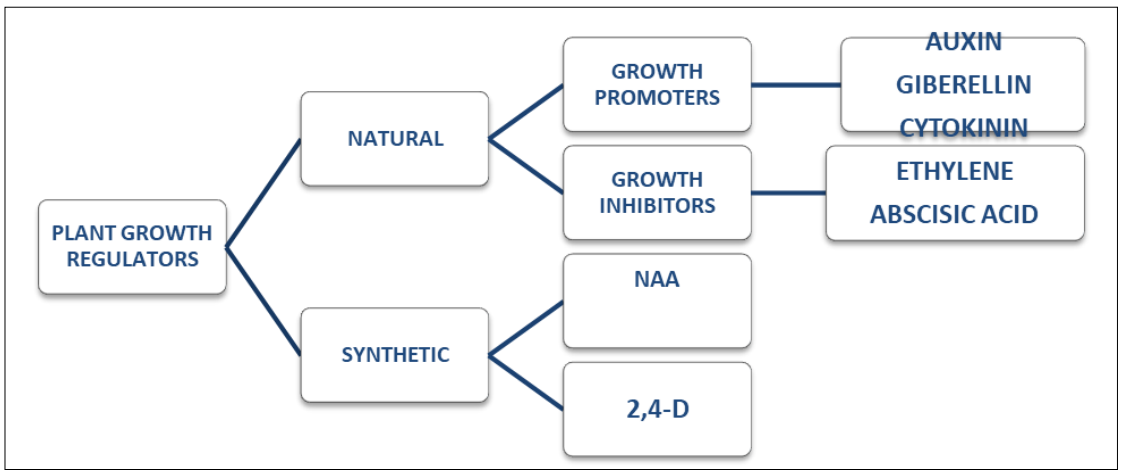


Fig 1: Classification of Plant Growth Regulators

Auxins

Auxins, are one of the plant hormones that have an important role in regulating growth and development. In plants auxins aid the process of cell elongation, formation and development of roots. Indole-3 acetic acid (IAA) is the well-known one among the natural auxins and are least stable. Apart from natural auxins there are many synthetic auxins that have been developed for agricultural and horticultural purposes due its stability and half-life (Saini *et al.,* 2013) [21]. Synthetic auxins are created to mimic the effects of natural auxins. 2,4-Dichlorophenoxyacetic Acid (2,4-D) and 1-Naphthaleneacetic Acid (NAA) are the main synthetic auxins which are commonly used in agricultural practice. (Small and Degenhardt, 2018) [2].

Gibberellins

Giberellins are naturally occurring plant hormone and are grouped under tetracyclic diterpenoid class. They play a crucial role in regulating various physiological processes throughout the life cycle of plants, such as seed germination, leaf expansion, pollen development and maturation, as well as the formation and growth of fruits, flowers, and seeds (Ogawa *et al*., 2003) [18]. Gibberellic acid was first discovered from a fungus called 'Gibberella' and later found in many plant parts that show active growth (Iqbal and Ashraf, 2013) [12]. They are used profusely in production of fruits and vegetables with better size, shape and also for parthenocarpy of grapes, berries and tomatoes. Gibberellins can also delay the ripening of fruits that improves its shelf life and marketability (Juska, 1958) [4]. Compounds like paclobutrazol, and ancymidol are synthetic chemicals that inhibit the synthesis of gibberellins (Nagar *et al.,* 2021) [15].

Cytokinins

Cytokinins play a vital role in regulating various physiological processes in plants, including cytokinesis (cell division), cell enlargement, dormancy breaking, flowering, fruiting, and delaying senescence. These properties are utilized for propagation of plants in nurseries, termination of dormancy of seeds and prolongation of the lifespan of plant tissues (Osugi and Sakakibara, 2015) [19]. Synthetic cytokinins compounds such as Thidiazuron (TDZ) and Forchlorfenuron (FCF) are widely used in modern agricultural practices to precisely regulate plant growth and development (Nisler, 2018) [16].

Ethylene

Ethylene plays a crucial role in regulating plant growth, fruit ripening, and senescence. Its primary application in agriculture is to accelerate ripening of fruit. Several synthetic compounds have been developed to imitate the effects of ethylene for controlled manipulation of plant growth and crop production. Ethephon (2-chloroethylphosphonic acid) is a widely used synthetic organophosphorus insecticide as plant growth promoter as it releases ethylene compound. After absorption, they are metabolised by plants and releases toxic metabolites, including ethylene oxide, which is converted into ethanediol and further to hydroxyethyl-glutathione and mercapturic acid (O'Brie and Benkova, 2013) [17].

Abscisic Acid

Abscisic acid (ABA) is an important plant hormone that regulates wide range of physiological and developmental processes in plants and is inhibitory in nature. As it controls the growth, germination and induces dormancy of seeds and aids to overcome environmental stresses like drought or salinity. The synthetic analogues of ABA are engineered to mimic the effects having greater stability and targeted action for agricultural practices (Rademacher, 2015) [20].

Other Plant Growth Regulators

Salicyclic Acid (SA)

Salicylic acid (SA), a phenolic compound structurally similar to aspirin (acetylsalicylic acid) and plays a crucial role in enhancing plant responses against various abiotic stresses and pathogenic attacks. Salicylic acid offers multiple benefits in agriculture, including its positive effects on fruit ripening, maintaining fruit firmness, boosting antioxidant activity, and improving disease resistance (Lauri *et al.,* 2016) [10].

Jasmonic Acid (JA)

Jasmonic acid (JA) and its volatile derivative, methyl jasmonate are lipid derived compounds that act as important signalling molecules in plants. The exogenous application of jasmonic acid suppresses plant growth but enhances several physiological processes such as senescence, fruit ripening, and activation of antioxidant defences. Moreover, JA is well-known for inducing the expression of genes responsible for the production of plant defence proteins, particularly under conditions of biotic stress (Lauri *et al.,* 2016) [10].

Brassinolides or Brassinosteroids (BRs)

Brassinolides or Brassinosteroids (BRs) are a class of steroidal compounds first identified in the pollen of oilseed rape. Later studies revealed that these compounds are widespread across various plant species and are found in all plant parts, particularly high concentrations in pollen and seeds. Brassinolides play a vital role in regulating cell cycle and promote cell division of plants. Although BRs have shown potential in improving crop yield and productivity, their practical application in agricultural practice remains relatively limited and not extensively documented (Lauri *et al.,* 2016) [10].

Characteristics of Endocrine Toxicity

Plant growth regulators (PGRs) possess endocrine-disrupting properties. Endocrine-disrupting chemicals (EDCs) are agents that interfere with the normal activity of the endocrine system by mimicking, blocking, or altering the action of endogenous hormones. Endocrine toxicity often presents as developmental and reproductive abnormalities (Wang and Hao, 2023) [25]. The endocrine system, comprising glands such as the hypothalamus, pituitary, thyroid, adrenal glands, ovaries, and testes, regulates essential physiological processes including growth, metabolism, reproduction, and homeostasis. Endocrine toxicity arises when chemicals disturb hormone synthesis, secretion, transport, metabolism, receptor binding, or clearance, leading to hormonal imbalances. Such disruptions can impair normal tissue function, inhibit growth, cause developmental anomalies, compromise reproductive capacity, and elevate the risk of hormone-dependent tumours (Wang *et al*., 2011) [24].

While PGRs are primarily utilized in agriculture to modulate plant growth and development, accumulating

evidence indicates that some PGRs may function as endocrine disruptors in animals and humans. These compounds can alter the synthesis and secretion of sex hormones, impair the structure and function of the reproductive system, and adversely affect the growth and development of progeny. Notably, certain PGRs have been identified as endocrine disruptors during both prenatal and postnatal stages. Chronic exposure to these substances has been associated with reproductive toxicity, developmental impairments, and an increased incidence of tumour formation (Garban and Ilia, 2024) [5]. Reproductive and developmental abnormalities are recognized as the primary adverse effects resulting from endocrine toxicity induced by plant growth regulators (Wang and Hao, 2023) [25].

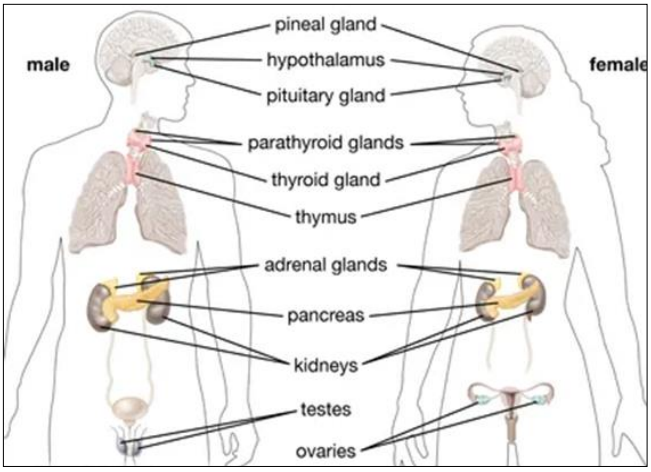


Fig 2

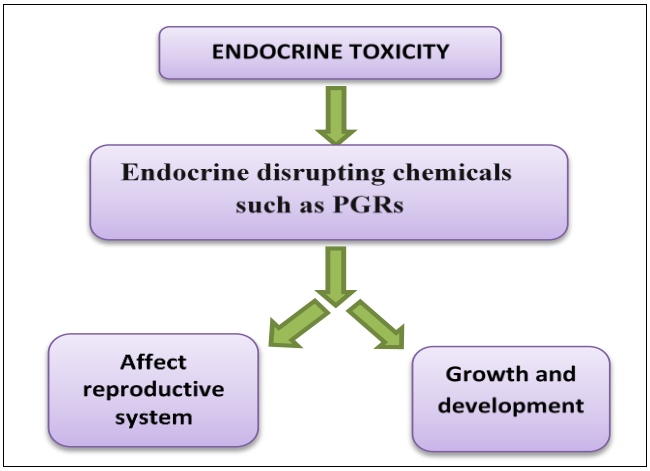
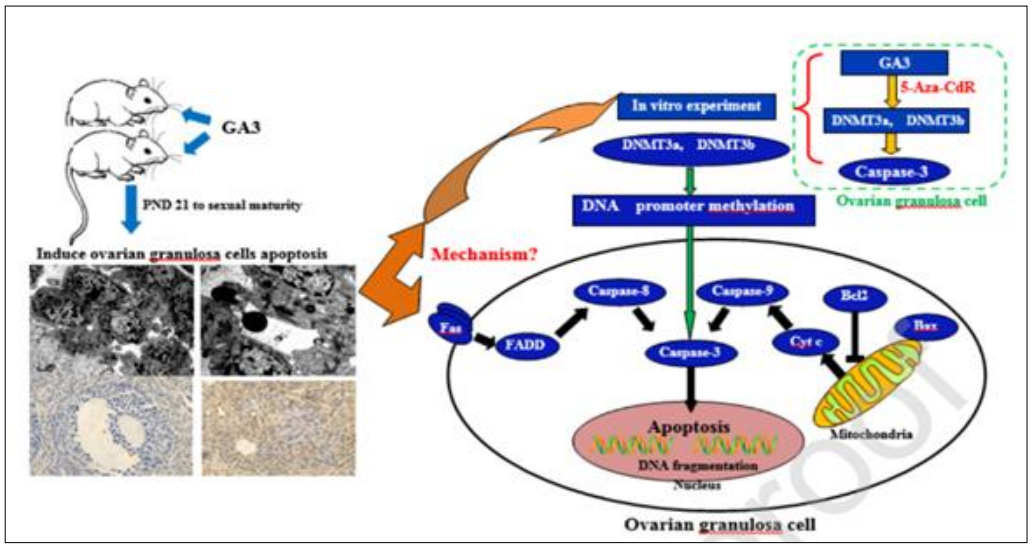


Fig 3

Endocrine Toxicity Induced by Plant Growth Regulators



The exposure to gibberellic acid (GA_3) impairs ovarian follicular development by inducing apoptosis in granulosa cells, primarily through activation of the Fas-mediated death ligand/receptor apoptotic signalling pathway. Additionally, GA_3 exposure altered DNA methylation patterns, potentially contributing to the upregulation of the caspase-3 gene and enhancing apoptotic activity. Gibberellic acid (GA_3) possesses a molecular structure like steroid hormones and can cause disruption of ovarian steroidogenesis. Upregulation of caspase-3, -8, and -9 indicates that GA_3 promotes apoptosis via caspase-dependent pathways (Guo *et al.*, (2020) [6]. In males, GA_3 administration has been associated with reduced sperm quality, motility, concentration, viability, and increased sperm abnormalities due to suppression of testosterone and luteinizing hormone levels through downregulation of 3β-hydroxysteroid dehydrogenase and P450scc gene expression (Soliman *et al.*, 2021) [23]. Histopathological evaluations revealed non-stage-specific spermatogenic disturbances, including germ cell vacuolation, disorganization, and exfoliation, associated with elevated malondialdehyde (MDA) levels and lipid peroxidation, leading to impaired spermatogenesis and Leydig cell degeneration (Hassan *et al.*, 2013) [8].

Chronic administration of forchlorfenuron (FCF) resulted in uterine fluid accumulation, ovarian atrophy, reduced corpus luteum formation, increased follicular atresia, and interstitial hyperplasia in rats. *In vitro*, FCF treatment also significantly decreased granulosa cell (GC) numbers and reduced H295R adrenal cell viability (Bu *et al.*, 2019) [1]. FCF exhibited a concentration-dependent antiproliferative effect on both GCs and H295R cells, accompanied by downregulation of critical steroidogenic genes, including Steroidogenic Acute Regulatory Protein (StAR), 3β-Hydroxysteroid Dehydrogenase (3β-HSD), 17β-HSD, CYP17A1, and CYP19A1. This suppression led to decreased synthesis of progesterone (P_4) and estradiol (E_2) due to impaired

cholesterol metabolism and conversion to steroid hormones, ultimately inhibiting follicular development (Wei *et al*., 2019) [26].

Similarly, administration of 2,4-dichlorophenoxyacetic acid (2,4-D) in Wistar rats significantly reduced sperm count, motility, and serum testosterone levels, while increasing sperm abnormalities. 2,4-D directly impaired Leydig cell function, disrupting androgen biosynthesis and increasing testicular cholesterol accumulation. The decline in testosterone levels impaired the hypothalamic-pituitary-gonadal axis feedback, resulting in elevated serum FSH and LH levels. Reduced inhibin production by Sertoli cells further contributed to altered gonadotropin secretion, collectively impairing spermatogenesis and reproductive development (Marouani *et al*., 2017) [13].

Harada *et al.* (2016) [7] demonstrated that 2,4-dichlorophenoxyacetic acid (2,4-D), a weak peroxisome proliferator in hepatocytes, impairs testicular function through peroxisome proliferator-activated receptor α (PPARα), which is also expressed in Leydig cells. In wild-type mice, 2,4-D treatment significantly reduced testicular testosterone levels, causing degeneration of spermatocytes and Sertoli cells. This reduction was associated with decreased cholesterol synthesis in Leydig cells due to downregulation of 3-hydroxy-3-methylglutaryl-CoA synthase 1 and reductase, enzymes critical for de novo cholesterogenesis.

In a study by Celik *et al.* (2007) [3], male Sprague-Dawley albino rats were exposed to the plant growth regulators (PGRs) 2,3,5-triiodobenzoic acid (TIBA), naphthaleneacetic acid (NAA), and 2,4-dichlorophenoxyacetic acid (2,4-D). Treatment resulted in significant inhibition of antioxidant defense enzymes, including glutathione peroxidase (GPx), reduced glutathione (GSH), glutathione reductase (GR), glutathione-S-transferase (GST), and catalase (CAT). Alterations in immune-related enzymes, adenosine deaminase (ADA) and myeloperoxidase (MPO), were also observed. Additionally, lipid peroxidation, indicated by elevated malondialdehyde (MDA) levels. Although antioxidant mechanisms were activated in response to oxidative stress, they were insufficient to prevent lipid peroxidation in rat tissues.

Huang *et al.* (2022) [9] investigated the reproductive toxicity of ethephon in female C57 mice. Ethephon exposure disrupted the pituitary–ovarian axis, altering serum levels of progesterone (P), oestradiol (E2), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). A significant reduction in ovarian apoptosis was observed, allowing aberrant follicular survival and promoting ovarian tumorigenesis. Overall, the study highlights ethephon's potential to induce reproductive dysfunction through hormonal imbalance and disrupted ovarian cell regulation.

Wang *et al*. (2011) [24] evaluated the acute toxicity and teratogenic effects of five common plant growth regulators (PGRs)—Atonik, Cytokinin, Ethephon, Gibberellic acid, and Paclobutrazol on *Daphnia magna*. Microscopic examination revealed that all five PGRs induced developmental abnormalities, including malformations of the second antenna, rostrum, malpighian tubes, sensory bristles, and tail spine, often leading to functional impairment or mortality. Paclobutrazol and Cytokinin exhibited particularly strong teratogenic effects compared to other PGRs. The study clearly demonstrated that PGRs can induce both acute toxicity and teratogenicity in *Daphnia magna* neonates and embryos.

Conclusion

Plant growth regulators (PGRs), while beneficial in enhancing agricultural productivity, pose significant toxicological risks due to their endocrine-disrupting potential. Chronic exposure to certain PGRs can interfere with hormone synthesis, receptor signalling, and metabolic pathways, affecting multiple endocrine organs including the reproductive glands, thyroid, adrenal glands, and kidneys. These disruptions can lead to reproductive dysfunction, developmental anomalies, neuroendocrine impairments, and organ-specific toxicities such as cardiotoxicity, nephrotoxicity, and hepatotoxicity. The ability of PGRs to induce apoptosis, oxidative stress, and epigenetic modifications further underscores their potential to cause long term health effects. Therefore, regulatory oversight, risk assessment, and safer agricultural practices are crucial to mitigate the health hazards associated with PGR exposure.

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