Journal of Ethnopharmacology and Toxicology

Review Article

Pesticides as an ovarian toxicant: a short review

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Volume: 1, Issue: 1, Pages: 6-12
DOI: https://doi.org/10.37446/jet/ra/1.1.2023.6-12
Received: 12 July 2023 / Accepted: 15 November 2023 / Published: 31 December 2023

Pesticides are extensively used in controlling agricultural pests. Pesticides-exposure of a variety of populations manifest an array of adverse effects and a large wide of studies have shown that pesticides are extremely toxic to female reproductive systems. It has been reported that these pollutants induce oxidative stress, apoptosis, endocrine disorders, and epigenetic alterations which are directly implicated in the declining fertility of females in non-target species. The literature and information present in this review highlighted the toxic effect of pesticides on the female reproductive system along with their possible mechanisms in ovarian tissue.

Keywords: *pesticides, female, oxidative stress, apoptosis, endocrine, epigenetic*

Introduction

Worldwide, pesticides are used in agriculture production, industries, and veterinary medicine in order to increase crop yields and provide economic benefits thereby controlling, repelling, destroying, preventing, or resisting a wide range of insect pests including Coleoptera, Hemiptera, Hymenoptera, Thysanoptera, Orthoptera and Diptera (Ggendiran et al. 2018; Kara & Oztaz, 2020, Iwuozor et al., 2023). During the last decades, the consumption of pesticides has been increased. In 2017, over 74 million tons of pesticides were used worldwide (Kara & Oztaz, 2020). Although pesticides have been shown to possess powerful insecticidal properties and a long spectrum of toxicity against many types of pests, yet they have a toxic effect against non-target species like humans (Mossa et al., 2013; Gajendiran et al., 2018; Arif et al., 2021). Due to their extensive use, pesticides leak into the environmental landscape, the water supplies, and the food chain and as a result, a large wide population has been significantly exposed to their deleterious effects. Thus, in addition to residues in food, pesticides are also readily absorbed through environmental exposures from neighboring agriculture areas and indoor use of a biocide, these pollutants are rapidly absorbed after oral and inhalation exposure however they are not easily absorbed through dermal exposure (ATSDR, 2003; Anderson et al., 2022; Munoz-Quezada et al., 2020). Indeed, it has been reported that pesticides like pyrethroids, pyrethrin, Organochloride, organic phosphorus, and carbamate have been considered endocrine disruptors that could affect the function of many nuclear hormone receptors (Mrettova et al., 2017). Also, pesticides are acutely neurotoxic in non-target organisms including humans showing neurochemical disruption and neurobehavior alteration (Anderson et al., 2022). Furthermore, it has been reported that pesticide exposure is positively associated with the augmentation of DNA damage leading to mutagenicity and carcinogenicity (Muranli et al., 2013). Alteration of antioxidant enzyme activities, free radical generation, and oxidative stress has also been reported (Sadowsk et al., 2010). Recently, the reproductive toxicity of pesticides has received much attention. As is shown in many recent studies, the reproductive system remains inherently susceptible to pesticide toxicity (Zhong et al., 2021; Song et al., 2022). In females, pesticides could disturb female ovarian functions thereby inhibiting of estradiol and progesterone production, a decrease of fertility, ovarian cycle failure, alteration of germ cell quality, oxidative stress, and DNA damage. Also, pesticides have an important impact on fetal development leading to birth defects and developmental retardation (Ravula et al., 2021; Arif et al., 2021; Jallouli et al., 2022). The present review aims to give an overview of the different ways of pesticide toxicity that leads to female reproductive system disruption.

Oxidative toxicity

The female reproductive system has a crucial role in maintaining the production and the genesis of germ cells/ova, fertilization, and implantation. Thus, disturbance of the female reproductive system could lead to infertility disorders (Bhardwag et al., 2021). Overproduction of reactive species of oxygen (ROS) and nitrogen induces homeostasis disruption and overwhelms the antioxidant defense efficiency of the organism. It has been reported that pesticides could exert their harmful effect in the female reproductive system via the generation of oxidative stress (Sharma et al., 2015; Arab et al., 2018; Terayama et al., 2022). Indeed, oxidative stress generation, as a result of free radical increase, is responsible for reproductive dysfunction, thus, it is of great interest to understand the impact of pesticide-induced oxidative stress generation and its association with female reproductive function. Pesticides are known to impair the balance between oxidative and antioxidant defense leading to an extensive generation of free radicals and thus oxidative stress has occurred (Bhardwaj et al. 2020). It has been reported that allethrin, synthetic pyrethroids, induced oxidative stress in rat ovaries showing a marked increase in MDA levels associated with a decline in SOD, CAT, and GSH activities (Jallouli et al., 2022). Also, oxidative stress is assigned a causal role in female ovarian function troubles thereby affecting oocyte quality, oogenesis, and folliculogenesis which leads to oocyte aging and fertility declining (Prasad et al., 2016). The imbalance between antioxidant and ROS production is responsible for many female reproductive diseases namely endometriosis and polycystic ovary syndrome (Agrawal et al., 2012). Malathion, belonging to the group of organophosphorus pesticides, was documented to induce lipid peroxidation and oxidative stress in rat ovaries which inhibited the proliferation of granulosa cells, influenced oocyte development, the high level of ROS in follicular fluid influenced oocyte quality, and lead to estrous cycle alterations (Wang et al., 2018; Yong et al., 2021). A study conducted by Sharma et al. 2018, reported that exposure to Triazophos, which is a non-systemic broad-spectrum organophosphate was associated with antioxidant system impairment by increasing lipid peroxidation and altering antioxidant enzyme activities in the ovary of female Wistar rats. Organochlorine pesticides (OCPs) are widely used insecticides in agriculture and the chemical industries and they are considered persistent organic pollutants (De Rosa et al., 2022). It has been documented that organochlorines like hexachlorocyclohexane, DDE, and Dieldrin are responsible for oxidative stress and ROS production and subsequently cause Intra Uterine Growth Retardation and epithelial ovarian cancer (Bhardwaj et el. 2020). Since, ROS could contribute to tumor development exclusively by activating signaling pathways including NF-KB and upregulation of its downstream targets such as IL-1B, IL-6, and IL-8 (Shah et al., 2020).

Autophagy and Apoptotic toxicity

Autophagy is a physiological, intracellular mechanism for the protection and recycling of cellular organelles: damaged organelles, a pathogen introduced into the cell, misfolded proteins... are thus collected and transported to the lysosomes to be degraded. Part of the cytoplasm is thus recycled by its own lysosomes. This mechanism is also a source of energy and amino acids in stressful conditions for the cell, such as hypoxia, lack of nutrients (fasting), or exposure to drug treatments (Mizushima, 2007). Apoptosis (or programmed cell death) is a natural process by which cells activate their self-destruct to maintain cellular homeostasis. It is one of the regular pathways of programmed cell death that is physiologically and genetically controlled. This phenomenon is necessary for the development and survival of multicellular organisms (Voss & Strasser, 2020). The main biochemical and morphological features that identified this process are plasma membrane blebbing, cell shrinkage, chromatin condensation, and DNA fragmentation (Fakai et al., 2019). In ovaries, germ cell death through apoptosis in a highly organized manner constitutes a fundamental physiological process of oogenesis to maintain the female potential fertility.

However, pesticide-mediated impairment of this programmed cell death process leading to compromised female fertility has been documented by numerous published studies. Indeed, a growing amount of evidence has demonstrated that oxidative stress could induce apoptosis, autophagy, or both through different pathways: Jallouli et al., 2022 reported that allethrin treatment induced apoptosis and autophagy in rat ovary showing that ROS substantially activates autophagy in follicular granulosa through inactivation of the PI3K/AKT/mTOR signaling pathway, however, in the case of the excessive ROS generation, apoptosis could arise as a consequence of the failure of autophagy to maintain cell repair. Also, endosulfan exposure could induce oxidative stress which augments granulosa cell apoptosis and follicular atresia (Sharma et al., 2011). In the same case, malathion-induced oxidative stress could lead to apoptosis and autophagy in ovaries and granular cells showing that malathion increased the pro-apoptotic cleaved caspase-3 levels in ovaries (Yong et al., 2021). Captan, a non-systematic fungicide, was found to affect ovarian homeostasis and oocyte development thereby inducing autophagy and early apoptosis as indicated by Tunel staining which indicated a substantial increase in the number of follicles with apoptotic granulosa cells, the enhanced level of γH2AX, LC3, and Annexian-V and increased expression of the related gene as (He et al., 2022). Histomorphological studies of Wistar rat ovary exposed to triazophos showed a dramatic increase in the number of apoptotic cells in ovarian granulosa cells (Sharma et al., 2014).

Endocrine System disruption

Due to their harmful effects on reproductive hormone pathways as well as ovulation and implantation, pesticides could be identified as endocrine disruptors (Kara & Oztas 2020). Pesticide intoxication could lead to estrogen/progesterone balance disruption at all stages of hormonal regulation starting with germ cell maturation, fertilization, embryogenesis, and finally fetal development (Bretvelt et al., 2006). Pesticides that could alter hormonal function are commonly identified as Endocrine Disrupting Compounds (ECD) (Combarnous, 2017). ECD could interfere with the elimination, synthesis, transport, secretion, or action of natural hormonal in the organism which influence the maintenance of homeostasis, reproductive functions, and behaviour (Gore, 2016). The hormonal function could be impaired in many pathways due to pesticide toxicity, the interference of pesticides with the hormonal synthesis chain could affect the hormone production or in some other cases get different properties (Bretvelt et al., 2006). As documented in a large number of studies, pesticides could be responsible for enhanced estradiol levels (Taxvig et al., 2013; Gerunova et al., 2019). Imidazole, fenarimol, and prochloraz are characterized by the ability to inhibit estrogen biosynthesis through the inhibition of CY19 aromatase activity as well as the prevention of the conversation of androgens to estrogens (Caron-Beaudoin et al., 2018; Sharma et al., 2021). Also, fungicides such as iron, and sodium N-methyl dithiocarbone (SMD) possess the ability to inhibit the dopamine -beta-hydroxylase activity which reduces the conversation of dopamine to norepinephrine and leads to alteration in hypothalamic catecholamine activity involved in producing the proestrus surge in LH responsible for the progress of the final stage of oogenesis (Liu et al., 2022; Sliman et al., 2018). Another way of pesticide-hormonal disruption is the interference with the hormone receptor which is considered the main mechanism of pesticide disruption namely the androgen receptor or the estrogen receptor.

Hormone and receptor affinity is specific and characterized by a price fit. It has been reported that a large wide of environmental pollutants including pesticides could interrupt this process by complete or partial receptor binding (Jain et al., 2023). This mechanism of endocrine disruption leads to GnRH decrease, LH, and FSH production resulting in a lack of estradiol through altering of receptor affinity or agonistic and antagonistic effects (Sifaks et al., 2017). According to Mrettova et al., 2018, pesticides like deltamethrin, and cypermethrin could affect endometrial glands and inhibit the steroid hormone levels, particularly progesterone and estradiol, also, pyrethroid metabolites could likely bind to estrogen receptors. Organochlorine pesticides were characterized by estrogenic properties showing the change in hormone receptor number and affinity for specific molecules (Tiemann, 2008; Qi et al., 2022). Persistent pesticides such as DDT, chlordane fenvalerate, and toxaphene could alter the endocrine system function by activating alpha and beta estrogen receptors (Lemaire et al., 2006).

Epigenetic mechanism

Another way of pesticide toxicity that is documented by many recent studies is epigenetic modification. Epigenetics indicates all molecular pathways that could modulate a genotype expression into a specific phenotype (Dupont et al., 2009). The epigenetic process involves DNA methylation, non-coding RNA, histone modification, RNA methylation, and chromatin structure (Nilsson et al., 2012). A large wide of investigations have reported a link between pesticide toxicity and epigenetic alterations in ovaries. It has been reported that the pesticide methoxychlor (MTX) causes hypermethylation in multiple CpG sites in the ERβ promoter sequences (Zama & Uzumcu, 2009). In his study, Manikkam et al., 2014, showed that methoxychlor exposure of F0 generation gestation females promotes the epigenetic transgenerational inheritance of diseases across the female germline. Also, it has been reported that F0 gestating female rats transiently exposed to fungicides and pesticide mixture during embryonic gonadal developed transgenerational disease phenotypes in F1 and F3 including an increase in cysts, a decline in the ovarian primordial follicles pool size as well as a transgenerational effect on the transcriptome and epigenome in the F3 generation granular cells (Nilson et al., 2012). The herbicide glyphosate could, also, develop the epigenetic transgenerational inheritance of adult-onset disease, thus, ovarian disorders resulted in the appearance of ovary polycystic showing an augment in the number of large ovarian cysts and granulosa cells are almost negligible. Notably, contrary to F1, it was observed that glyphosate lineages F2 and F3 had higher levels of ovarian disease (Kubsad et al., 2019).

Conclusion

As detailed in this review, considering literature data reported that pesticides are considered potent that alter physiological functions in ovarian tissue. Pesticides have been shown to produce oxidative stress, apoptosis, endocrine, disorders, and epigenetic alterations which directly cause infertility and a decrease in the reproductive potential of females. A large amount of data was obtained based on mammal studies. However, further studies on other species are required to enlighten the harmful effect of pesticides on the reproductive system.

Author contributions

I. Khaled: conceptualize and write the first draft, I. Saidi: write the first draft.

Funding

No funding

Conflict of interest

The author declares no conflict of interest. The manuscript has not been submitted for publication in other journal.

Ethics approval

Not applicable

Availability of data and material

The datasets generated and/or analysed during the current study available from the corresponding author on reasonable request.

Competing Interests

The author declares no conflict of interest. The manuscript has not been submitted for publication in other journal.

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