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UNRAVELING THE ROLE OF ANTIOXIDANTS IN MITIGATION OF CYPERMETHRIN INDUCED REPRODUCTIVE TOXICITY

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ABSTRACT: Despite widespread worries about Cypermethrin's toxicity, it is widely used in agriculture as insecticide and in veterinary medicine. There is currently no antidote for Cypermethrin poisoning, even though this synthetic Pyrethroid can have devastating effects on the body. Cypermethrin exposure not only affects magnesium and ATPase but also inhibits sodium channel activity. In addition to its neurotoxic effects, Cypermethrin induces the production of microsomal enzymes in the liver. It exhibits high hazardous properties, whether ingested orally or through skin contact, with animals generally showing higher tolerance levels compared to humans. Moreover, Cypermethrin is known to induce oxidative stress and reproductive toxicity, further adding to its potential risks.In this study, we dug through the literature and analyzed many studies for the better understanding of how antioxidants can help to reduce oxidative stress and repair the damaged reproductive system from Cypermethrin intoxication. This current research seeks to answer these questions by analyzing the effects of Cypermethrin on male and female rats and their subsequent recovery of reproductive function after exposure to various antioxidants such as vitamin E and C, the spice curcumin, Resveratrol,and the extract of the plant *TribulusTerrestre's*.

Keywords: *Reproductive toxicity, Antioxidants, Cypermethrin, Oxidative Stress.*

1. INTRODUCTION

One of the most popular classes of pesticides is synthetic pyrethroids. Because of their excellent efficiency against a wide range of insects, rapid biodegradation, minimal mammalian toxicity, and target orientated method of action, these insecticides have seen an upsurge in use in recent years at the expense of organochlorines, organophosphates, and carbamates. Cypermethrin is widely used type-II synthetic pyrethroid with use in agriculture, forestry, public and animal health. Recent investigations on laboratory animals have indicated that Cypermethrin has a deleterious effect on the neurological system (Singh et. al., 2012), hepatic and renal system (Sushma, 2010) and male reproductive system (Wang, 2010). Because human spermatogenesis may be sensitive to continuous exposure to chemicals at extremely low levels, reports of cypermethrin's reproductive toxicity are

very concerning. As a result, we set out to investigate whether Cypermethrin exposure in male Wistar rats causes any kind of reproductive damage.

There is a complex network of antioxidant enzymes and free radical scavengers in testicular tissue that protects spermatogenic and steroid genic processes from the effects of long-term xenobiotic exposure. Because of oxidative damage is thought to be the primary cause of diminished testicular function (Akbari, 2022).Antioxidant defense systems are crucial for excessive lipid peroxidation (LPO) and oxidative damage may result from continuous exposure to xenobiotic like Cypermethrin (El-Shenawy et. al., 2013).Endogenous antioxidants employ free radical scavenging, to reduce oxidative stress in the testes and promote healthy regulation of the spermatogenic cycle and steroid genic function (Nasiri et. al., 2014). Every day, more and more people are turning to plant-based remedies to help with their health problems. Phytochemicals are used to treat a wide variety of ailmentsdevoid of any unwanted side effects. Red wine contains a naturally occurring polyphenol component called resveratrol (3,5,4'-trihydroxy-trans-stilbene). Grape seed extract, grape juice, and grape skincontains high concentrations of resveratrol. Resveratrol's physiological effects include its potent antioxidant property, which is attributed to its ability to inhibit LPO (Lipid Peroxidation) and its action on platelets (Gulcin, 2010) and inflammation (Collodel, 2011).Resveratrol activates various cellular and molecular effectors, with the estrogen response systems being particularly noteworthy among them. Because of its ability to influence estrogen-response pathways, resveratrol may play an active role in boosting male reproduction (Bhat KPL, 2001).

Male fertility involves a series of physiological processes, depends on the combined effects of genetic, physiological, and environmental factors. Intact structural and functional integrity of the male reproductive system enables the effective fertility. Male reproductive system mainly comprises of testis, ductus deferens, epididymis, accessory glands and structurally external penis and scrotum and involved in the continuous production, maturation, storage, and the release of male gametes (spermatozoa) through ejaculation during the sexual act (Agarwal et. al, 2017).

1.1.Cypermethrin Toxicity

Cypermethrin is manufactured pyrethroids that are broadly utilized as a pesticide for break, fissure, and spot treatment in horticulture, family, and creature farming. All eight chiral isomers are present in this compound (Valles SM, Koehler PG, 1997). (See Fig 1)

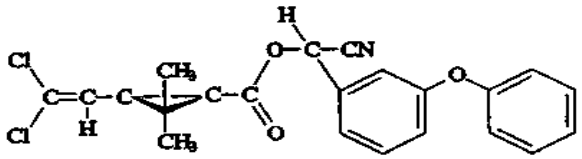

Figure 1: Structure of Cypermethrin (both alpha and beta carbons) (Baldwin, M.K., 1977a)

Molecular formula: C22H19Cl2NO3, Molecular weight: 416.3

Cypermethrin is a somewhat hazardous substance whether either orally or absorbed topically. The most observed reactions or symptoms that occur when the skin is exposed to a substance. These reactions include irritation, itching of the skin and eyes, numbness, a sensation of pins and needles, a burning feeling, loss of control over urine or bowel movements, clumsiness, muscle spasms, and in severe cases, even death. Inebriation with Cypermethrin and other manufactured pyrethroids principally influences the anxious and muscle frameworks. Acute oral dosages of 10-10g are potentially deadly in mammals (Olsen KR, 1994), while chronic oral doses of 100-1000mg/kg are hazardous.The dosage of 10-10g is incorrect. The LD50 (dose that kills 50% of the test population) of cypermethrin in rats is 250 mg/kg, which means that a 1 kg rat would need to ingest 250 mg of cypermethrin to be killed. For a human, the LD50 is estimated to be 500 mg/kg, so a 70 kg person would need to ingest 35,000 mg of cypermethrin to be killed. Inhaling lethal concentrations can result in respiratory paralysis and death. The misuse of chemicals intended for animals, crop protection, or vector control is a significant cause of poisoning in dogs and cats. The lack of specific instructions for pets on the packaging of such products contributes to this problem. Cypermethrin's intense neurotoxicity is interceded generally by expanded movement in the focal sensory system. Cypermethrin also causes neurotoxicity by altering the concentration of GABA. In addition, Cypermethrin's capacity to stimulate free radical production contributes to its neurotoxicity (Nasiri et. al., 2014).

A pesticide known as cypermethrin can be utilized for the management of a wide variety of pests. It is a neurotoxin since it comes from the pyrethroid family of insecticides, which is a class of chemicals that is commonly used. Cypermethrin may also have an influence on reproduction, and this is true for both males and females. Cypermethrin has the potential to interfere with the process of spermatogenesis, which is the production of sperm in males (Nasiri, et. al, 2018). This can result in a decrease in the number of sperm, as well as their motility and shape. Cypermethrin can block steroidogenesis, which is the process through which sex hormones are produced. This can lead to lower testosterone levels, which can have several impacts, including decreased libido, erectile dysfunction, and infertility. Infertility can also be caused by decreased testosterone levels. Cypermethrin has the potential to prevent ovulation and interfere with the development of embryos in female animals (Das, et. al., 2016). This can result in a decline in fertility as well as an increase in the risk of miscarriage. Cypermethrin can also have estrogenic effects, which can lead to abnormalities in the menstrual cycle and an increased risk of breast cancer. Cypermethrin can also cause an increase in the chance of developing prostate cancer.

In a variety of investigations that were conducted on animals, the toxicity of cypermethrin to reproductive systems was revealed. On the other hand, it is not quite clear to what extent these impacts take place in human beings.

CYP enzymes are a group of enzymes that are involved in the metabolism of a wide variety of compounds, including drugs, toxins, and hormones. CYP enzymes can also produce reactive oxygen species (ROS), which are unstable molecules that can damage cells. Oxidative stress is a condition that occurs when there is an imbalance between the production of ROS and the body's ability to detoxify them. Oxidative stress can damage cells and tissues, and it has been linked to a few diseases, including cancer, heart disease, and neurodegenerative disorders.

Piperine is a compound that is found in black pepper. It has been shown to have antioxidant and anti-inflammatory properties. In (Dash, et. al., 2014), peperino has been shown to protect cells from oxidative stress caused by CYP enzymes.

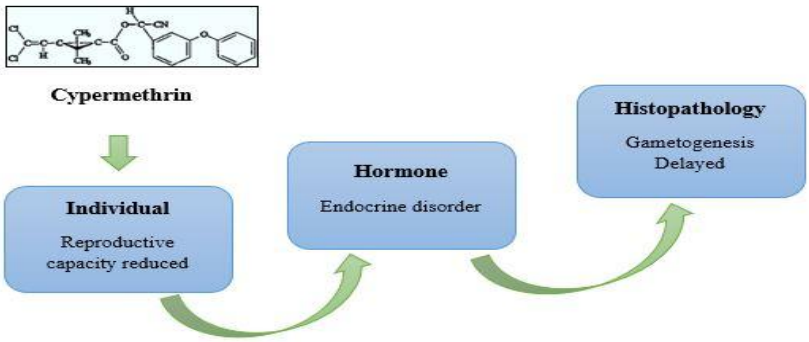

Figure 2: Reproductive toxicity induced by Cypermethrin.

In addition, CYP is a potent inducer of apoptosis that draws the attention towards its role in inducing testicular germ cells apoptosis. Few reports suggest its involvement in inducing apoptosis human neuroblastoma cells where CYP in combination with chlorpyrifos triggered cell death either by causing genomic DNA fragmentation (Raszewski et al., 2015) or by affecting Bcl-2, Bcl-xL and caspase-3 activation (Raszewski et al., 2015). CYP administration through intra peritonealor oral resulted in ROS generation (Giray et al., 2001). Altered pituitary-gonadal hormones, steroidogenic enzymes (Sharma et al., 2018) or modulating apoptotic and anti-apoptotic pathways may be the mechanism of CYP toxicity. All these studies suggest that CYP toxicity on functional and physiological aspect of reproductive system is a great matter of concern which further needs to be explored.

1.2.Mechanism of CYP

CYP arbitrate via complex mechanisms. It acts like endocrine disruptor, anti-androgen, xenoestrogen and depends upon target gene expression or cellular growth effects. It consists of an alpha-Ciano group attached to the benzylic carbon which enhances the insecticidal properties which

cause toxic signs of choreoathetosis with salivation (CS-syndrome) in the rat and bursts of spikes in the cerebral motor nerve of the cockroach.

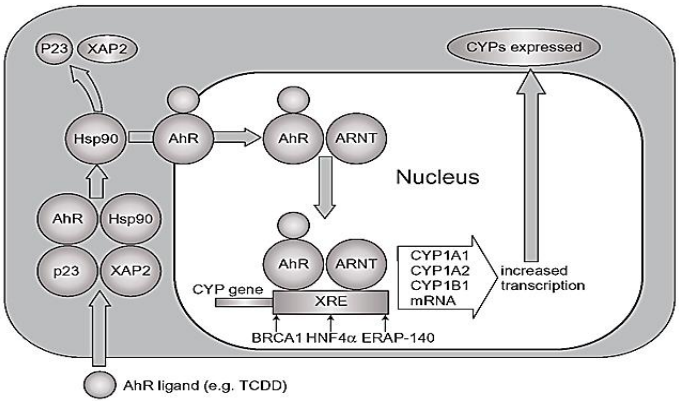

Figure 3: Mechanism of CYP

Figure 1 shows the diagram of the nuclear hormone signaling pathways. The arrows indicate the direction of the signaling pathways, while the dashed arrows indicate the direction of the feedback loops.

CYPs: Cytochrome P450 enzymes, AhR: Aryl hydrocarbon receptor

ARNT: Aryl hydrocarbon receptor nuclear translocator, XRE: Xenobiotic responsive element

Hsp90: Heat shock protein 90, BRCA1: Breast cancer 1, HNF4α: Hepatocyte nuclear factor 4α

ERAP-140: Estrogen-related receptor-associated protein 140,

TCDD: 2,3,7,8-Tetrachlorodibenzo-p-dioxin

Androgens mediate a wide range of developmental and physiological responses in the male rat and are vital for testicular, accessory sex gland development and function, pubertal sexual maturation in multiple organs, maintenance of spermatogenesis, maturation of sperm, male gonadotropin regulation through feedback loops and various male secondary characteristics such as bone mass, musculature, fat distribution and hair patterning. CYP interferes with androgen action and has a greater impact on male developmental programming, reproductive tract maturation and one of the major pathways through which it operates is AR mediated signaling. Primary androgenic hormones, testosterone and it metabolite DHT (5-α-dihydrotestosterone) mediate their biological effects predominantly through binding to the AR and is expressed in many end-organs including the hypothalamus, pituitary, liver, prostate and testis (Matsumoto et al., 2008). CYP can interfere with androgen-dependent mechanisms and affect male reproductive tract health, and these include androgen synthesis, metabolism and clearance, feedback regulation, AR expression in target organs and direct AR binding. CYP is known to be anti-androgen, inhibits synthesis of testosterone binding to AR and sex hormone binding globulin. CYP elicits anti androgenic activity by interfering with

interleukin-6 (IL-6) -induced ligand-independent AR signaling through signal transducer and activator of transcription 3 (Zhou et al., 2017).

1.3.Metabolism of CYP

In mammals synthetic pyrethroids are generally metabolized through ester hydrolysis, oxidation, and conjugation. After absorption in the gastrointestinal tract, CYP is metabolized via cleavage of the ester bond to phenoxy benzoic acid (PBA) and cyclopropane carboxylic acid (CPA). The PBA moiety is excreted as conjugate differential in different animal species. PBA is further metabolized to a hydroxy derivative and conjugated as glucuronate, or sulphate and CPA moiety is mainly excreted as a glucuronate. Due to the lipophilic nature of CYP, the maximum tissue concentrations were recorded in body fat, kidneys, liver, skin, ovaries, and adrenals.

The elimination of CYP from fat is approximately 3 to 4 times slower than in other tissues (WHO, 1989).

Studies related to half-life of CYP have shown 8 weeks in soil, almost 100 days in water and it persists about three months in household treatment for pests. Human volunteer studies has shown that urinary metabolite profile by oral and dermal routes submit that CYP might be significantly metabolized in the skin before systemic circulation occurs and major urinary metabolites of CYP are a variety of conjugates of cis and trans 3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid (DCVA), 3-phenoxybenzoic acid (3PBA), and 3-(4'-hydroxyphenoxy) benzoic acid (4OH3PBA)

1.4 Pyrethroids Induced Toxicity

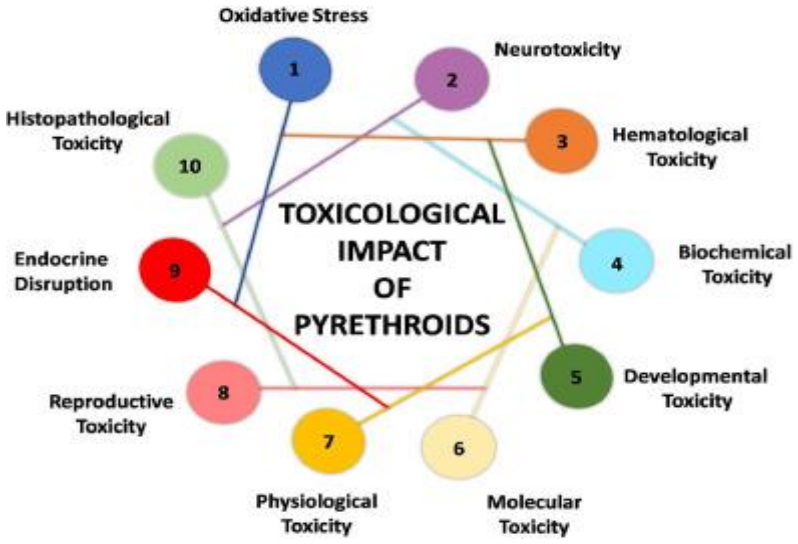

Figure 6: Toxicological impacts of Cypermethrin toxicity

For more than 40 years, pyrethroids are the pesticides used in agriculture and public health programs, constitute 25% of the insecticidal market worldwide (Shafer et al., 2005). Pyrethroids

derived from pyrethrin and isolated from Chrysanthemum plant Cineria folium (Casida, 1980) were extensively used due to non-persistence, decreased photostability and easy biodegradability over organophosphates, carbamates, and organochlorides. Synthetic pyrethroids were introduced into the market as allethrin in 1949. Pyrethroids can be recognized by the suffix-thing and most common pyrethroids include allethrin, deltamethrin, cyfluthrin, permethrin and cypermethrin, etc. These pesticides were used to control agricultural pest, veterinary, household, and horticultural practices. As per EPA, atleast18 different pesticides were registered for use on agricultural crops for human consumption (Elbert et al., 2008). Researchers have shown that via ingestion, inhalation and through dermal routes these pyrethroid pesticides were incorporated into humans (Saillenfait et al., 2015). Based on absence and presence of Ciano group the pyrethroids further sub-divided into two groups namely type-I and type II and claimed to pose relatively low mammalian toxicity. Type-II pyrethroids were proved to be more potent insecticide as compared to type-I due to alpha-Ciano group in its structure (Tabarean and Narahashi, 1998).

Pyrethroids were unlikely to be induced acute toxicity with symptoms like epigastric pain, fatigue, nausea, increased stromal secretion, disturbance in consciousness, convulsive attacks, and pulmonary edema. The symptoms of acute occupational pyrethroid include burning, itching sensation, dizziness, sneezing, broncho spasm, respiratory failure, and corneal damage. Pyrethroids were also found to induce oxidative stress that alters the antioxidant system of an organism. In mice brain, in vivo permethrin exposure resulted in cell stress due to reduced mitochondrial function (Kale et al., 1999; Karen et al., 2001). Some pyrethroids act as endocrine disruptors altered the hormone, mimic and block their action (Ankley et al., 1997), thereby; testicular and prostate cancer, miscarriages and even breast, ovarian and uterine cancer (Hunter et al., 1997). In addition, pyrethroids also induced sister chromatin exchange, chromosomal aberrations, and formation of micronuclei in mammals (Chauhan et al., 2016).

In various studies the pyrethroid pesticides and male infertility has been found to closely associated. Post pyrethroid administration reduced sperm count was observed in mice, rat, and rabbits. Pyrethroids also damage quality of semen and sperm DNA. Testosterone concentration also found to be decreased in rabbits treated with pyrethroids, rats, and mice. Elbetieha et al. (2001) revealed that testes showed atrophy and hemorrhages surrounding seminiferous tubules post pyrethroids treatment. In addition, pyrethroids reduced the expression level of peripheral benzodiazepine receptor and StAR protein, involved in cholesterol transfer via steroidogenesis.

1.5.Oxidative Stress

Cypermethrin's neurotoxicity is believed to be brought about by oxidative stress. Expanded arrangement of receptive oxygen species (ROS) and responsive nitrogen species in cells or tissues

presented to Cypermethrin, or diminished degrees of parts of the cancer prevention agent hardware, are key supporters of oxidative stress. When Cypermethrin is given orally or intraperitoneally, it causes oxidative stress in the nervous system (Rodriguez, 2009). After moderate doses and long-term exposures, there was no discernible change in overall glutathione-S-transferees (GST) activity (Giray B, Gurbay A, Hincal F, 2001); despite considerable changes in the expression of a few GST isoforms. One of the central members in Cypermethrin digestion that produces responsive oxygen species (ROS) and oxidative stress by means of blended capability oxidase is cytochrome P450 2E1 (CYP2E1). Based on Nernst formula, the way back in year 2011 by Sies, oxidative stress generated within the body is an imbalance in their redox coupling. As per Lushchak (2014), transient and chronic elevation in oxidative stress might be due to production of ROS that adversely affects the homeostatic balance between normal cellular metabolism and its regulatory processes. However, in the biological system ROS might be produced due to cellular metabolism at moderate concentration and play a pivotal role in physiological processes; however, its high concentration directly or indirectly targets the DNA, lipids, and proteins (Birben et al., 2012; Weidinger and Kozlov, 2015). Aerobic organisms counteract ROS mediated toxicity by the antioxidant defence system present in their body. However, lack of these antioxidants to scavange the ROS generated creates a stressful condition in the favor of oxidants termed as ‘Oxidative Stress’ that leads to adverse effects (Birben et al., 2012). This stressful condition possesses severe acute to chronic illness and also induces various diseases such as aging, genetic abnormalities, cardiovascular and respiratory diseases, carcinogenesis, autoimmune diseases, cataract, stroke and septic shock and neurodegenerative disorders like Parkinson’s and Alzheimers disease (LukaszewiczHussain, 2008)

1.6.Effect on testes histology, epididymis, and other reproductive organs

The testes, epididymis, and other reproductive organs are susceptible to a variety of side effects when exposed to cypermethrin. These consequences can include the following:

Cypermethrin's ability to impair spermatogenesis, the process by which sperm are produced, can lead to a reduction in sperm production. This can result in a decrease in the number of sperm, as well as their motility and shape.

Cypermethrin's ability to block steroidogenesis, the process by which sex hormones are produced, is one of its most important properties. This can lead to lower testosterone levels, which can have a few impacts, including decreased libido, erectile dysfunction, and infertility. Infertility can also be caused by decreased testosterone levels.

Damage to the testicles: Cypermethrin has been shown to cause damage to the testicles, which can result in infertility.

Inflammation of the epididymis Cypermethrin has been shown to cause inflammation of the epididymis, which can result in pain and swelling of the testicles.

Reduced fertility is a potential side effect of exposure to cypermethrin, which can occur in both males and females.

The length of time a person is exposed to cypermethrin will determine the degree of the effects that it has on the reproductive system. There is a possibility that a brief exposure to low amounts of cypermethrin will not produce any noticeable side effects. On the other hand, research has shown that prolonged exposure to high concentrations of cypermethrin can result in major reproductive issues.

2. PIPER-INE PREVENTS CYPERMETHRIN-INDUCED OXIDATIVE DAMAGE

Estimating free radical production and antioxidant defense has emerged as a critical area of study in mammals in recent years. Antioxidants such vitamin E, isoflavones, and L-ascorbic acid have been demonstrated to protect rats against the oxidative damage brought on by CYP induced toxicity (Raina, 2009). The antioxidant defense mechanism is known to be modulated and scavenged by free radicals, which is how plant compounds achieve their protective benefits. Both long pepper (Flute player longum Linn.) and dark pepper (Flautist nigrum Linn.) contain the alkaloid peperino. Cell reinforcement, bioenhancer, mitigating, and hepatoprotective are only not many of the pharmacologic.

3. ANTIOXIDANTS

The living system is well equipped with the substances capable of counteracting the damage caused by the ROS in response to oxidative stress known as ‘antioxidants defense system’ including antioxidants and antioxidant enzymes. However, ROS mediated oxidative stress induces alterations in lipids, proteins and DNA which was found to be controlled by the antioxidant system of the body by maintaining the balance between ROS and antioxidants (Schieber and Chandel, 2014). In addition, to provide maximum protection to the cell, various scavengers such as antioxidant enzymes are compartmentalized in sub-cellular organelles leading to decline in ROS level; but failure in this defense system results in oxidative stress mediated cell death.

As per Halliwell and Gutteridge (1984), these antioxidant defenses are categorized as primary antioxidants (involved in the impediment of oxidants formation), secondary antioxidants (exhibit scavengers of ROS) or tertiary antioxidants (through sources such as dietary and consecutive antioxidants and repair the oxidized molecules). Various factors disturbing the efficiency of antioxidants include activation energy of antioxidants, oxidation, reduction capability, solubility, and pH stability (Noori, 2012). The antioxidant defense system consists of enzymatic and non-enzymatic components including antioxidant enzymes such as superoxide dismutase (SOD),

catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GSR), glutathione-s-transferase (GST) etc., and non-enzymatic components includes vit C, vit E, zinc, n-acetyl-l-cysteine, glutathione etc. (Birben et al., 2012).

To offset the ROS mediated oxidative stress the antioxidant defense system assists the cells to produce antioxidant enzymes for diminishing their action. The antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GSR), glutathione-s-transferase (GST). Superoxide Dismutase (SOD), an inducible metalloenzymes that catalyzes the dismutation of the superoxide radical (O2-) into hydrogen peroxide H2O2 and oxygen (O2), and act as a first line of defense (Gupta et al., 2008). The reaction catalyzed by SOD maintains the level of O2- in the tissue and is highly efficient.

3.5.Mitigation of Cypermethrin-Induced Reproductive Toxicity with Antioxidants

Antioxidants are substances that can help mitigate oxidative stress by eliminating reactive oxygen species (ROS). (Sharma, et. al., 2014) and (Singh, et. al., 2012) haveinvestigatedwhether antioxidants can reduce the reproductive toxicity of Cypermethrin. Some promising antioxidants for mitigating cypermethrin's effects on reproduction are listed below.

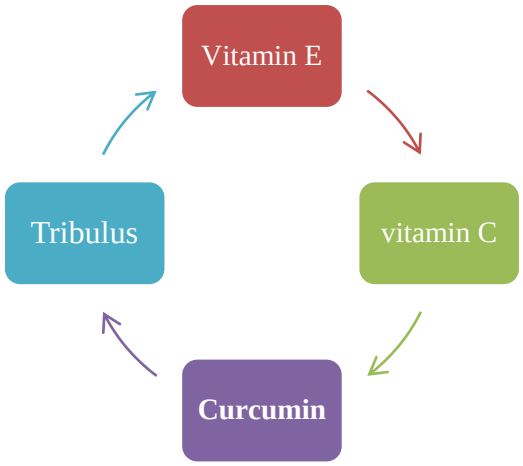

Figure 5: Mitigation of Cypermethrin-Induced Reproductive Toxicity

3.6.Various antioxidants for Cypermethrin reproductive toxicity

3.6.1. Curcumin

Estimating free radical production and antioxidant defense has emerged as a critical area of study in mammals in recent years. It has been shown that including specific vegetables and plant products in one's diet can mitigate the harmful effects of numerous toxicants and environmental pollutants. The antioxidant defense mechanism is known to be modulated and scavenged by free radicals, which is how plant compounds achieve their protective benefits. A radiant orange color called curcumin (CMN) (diferuloylmethane) is separated from the rhizomes of the turmeric plant, Curcuma longa (Maheshwari, 2006). Curcumin is an antioxidant and anti-inflammatory that has been shown to be

very effective at preventing the production of reactive oxygen species (Biswas, 2005). Researchers found that CMN effectively removed both superoxide anion and hydroxyl radicals from their respective samples. CMN treatment has been displayed to safeguard rodents from oxidative stress created by arsenic, gentamicin, and acetaminophen (Ambali, S. 2011). Similarly, CMN inhibits free radical production in paraquat-induced lung damage and rat models of myocardial ischemia (Fatma, 2009). The current investigation aimed to find out if CMM could prevent or lessen the serum biochemical changes and oxidative stress caused by the sub-acute dose of CYP in rats.

3.6.2. Vitamin E

This study was embraced in view of mounting proof connecting receptive oxygen species (ROS) to the toxicity of various pesticides; explicitly, Cypermethrin, Sort II pyrethroids. Raised degrees of Thio-barbituric corrosive receptive substances (Ski lifts) in the mind and liver of rodents were noticed 4 and 24 hours after a solitary (170 mg/kg) or rehashed (75 mg/kg each day for 5 days) oral organization of Cypermethrin, separately. Contrasted with the benchmark group, single-portion consequences for the liver were considerably more articulated, rising from 60% at 4 h to almost multiple times the control at 24 h. The presence of an oxidative affront was likewise recommended by diminished degrees of complete glutathione (all out GSH; up to 20%) and expanded degrees of formed dienes (around 60% in liver by single measurement at 4 h). Be that as it may, in both mind and liver tissues, glutathione S-transferase (GST) movement was not unique in relation to control values at any portion or time point. Treatment of rodents with allopurinol (100 mg/kg, ip) or vitamin E (100 mg/kg each day, ig, for 3 days and a portion of 40 mg/kg on the fourth day) for 4 hours before a solitary high-portion oral organization of Cypermethrin fundamentally diminished the rise of Ski lifts levels in cerebral and hepatic tissues. Expanded lipid peroxidation in the mind and liver after Cypermethrin organization in rodents is steady with free revolutionary intervened tissue harm; this was alleviated by pretreatment with allopurinol and vitamin E (Giray, B., 2001).

3.6.3. Vitamin C

Vit C, as an important water-soluble antioxidant, mitigated the oxidative stress generated; thereby counteracting the ROS, by easily reacting with them in extracellular body fluids. Vit C causes reduction in abnormal sperm (Greco et al., 2005), several apoptosis characteristics attribute in the testicular germinal epithelium; thereby maintaining the physiological integrity of the testes. In addition, Vit C also exhibited effective attenuation on endo-sulphone and atrazine induced goat testicular toxicity (Sharma et al., 2010b, c). Supplementation of Vit C also reduced MDA level (as a by-product of lipid peroxidation) in the tissues after chronic exposure to organophosphates (Ambali et al., 2011). A previous study marked the cadmium induced toxicity in thyroid gland that was found to be ameliorated by ascorbic acid. However, Vit C also modulated the genotoxicity induced

by various pesticides in the primary spermatocytes (Khan and Sinha, 1994b). Along with this, Vit C also decreased the lipid per-oxidation and increased antioxidant enzymes such as CAT, SOD and GST and thereby decreasing methomyl toxicity resulting in modulation of key stress and apoptosis related four genes such as Cas-3, Cas-9, Tp53 and Bcl-2 in the rats (Heikal et al., 2014). Whereas Vit E, as a lipid-soluble antioxidant, caused reduction in pyknotic nuclei, chromoly is and fragmented nuclei after exposure to endo-sulphone. Diazinon induced hepatotoxicity was also found to be mitigated by Vit E supplementation. Vit E efficiently protects the cell against lipid peroxidation by its antioxidative action of chain breaking, where the Vit E is transformed to weak free radicals which converted back to its active state by the ameliorative action of Vit C. Supplementation to Vit E ameliorated the DEHP induced male reproductive toxicity by modulating the peroxisome proliferator-activated receptor (PPAR)-dependent mechanisms (Wang et al., 2017). In addition to their independent effects, studies have also showed the synergistic effects of Vit C and Vit E. DDT exposure elevated the ROS content resulting in activation of NF-κB. Whereas, supplementation to Vit C and E reduces DDT induced toxicity via the ROS mediated NF-κB/Fas-ligand and mitochondrial apoptotic pathways (Jin et al., 2014). Therefore, employing Vit C and Vit E as ameliorants against testicular cells apoptosis due to pesticide poisoning has high potential.

4. CONCLUSION

The present study aimed to investigate the role of antioxidants in mitigating the reproductive toxicity induced by Cypermethrin exposure. Our extensive literature review and analysis of various studies have provided valuable insights into the potential benefits of antioxidants in safeguarding reproductive function and countering the harmful effects of Cypermethrin on the reproductive system in rats and potentially in other species as well. Cypermethrin, a synthetic pyrethroid widely used as an insecticide in agriculture and veterinary medicine, has raised concerns due to its widespread toxicity. The absence of an antidote for Cypermethrin poisoning has highlighted the need for alternative approaches to combat its devastating effects on the body. Our findings demonstrate that Cypermethrin not only affects essential physiological processes like magnesium and ATPase, but it also disrupts sodium channel activity and induces the production of microsomal enzymes in the liver. These neurotoxic and hepatotoxic effects emphasize the urgency of exploring potential therapeutic strategies. One significant consequence of Cypermethrin exposure is its ability to induce oxidative stress. This can lead to the generation of reactive oxygen species (ROS) and subsequent damage to cellular structures and biomolecules, including the reproductive system. However, our research reveals that antioxidants play a pivotal role in alleviating oxidative stress and preventing the associated reproductive damage. Antioxidants such as Vitamin E, Vitamin C, Curcumin, Resveratrol, and the extract of the plant Tribulus Terrestre's have shown promise in

counteracting the harmful effects of Cypermethrin. Vitamin E and Vitamin C are well-known antioxidants that scavenge ROS and protect cells from oxidative damage. Studies have shown that supplementation with these vitamins can enhance the antioxidant defense mechanisms in the reproductive system and restore reproductive function in Cypermethrin-exposed rats. Similarly, Curcumin, a bioactive compound derived from turmeric, exhibits potent antioxidant properties, and has demonstrated the ability to mitigate reproductive toxicity caused by Cypermethrin. Resveratrol, a natural polyphenolic compound found in certain plants, has also shown potential in protecting against Cypermethrin-induced reproductive toxicity. It exerts antioxidant effects by activating various cellular pathways involved in detoxification and reducing oxidative stress. Furthermore, the extract of Tribulus Terrestre's, a medicinal plant with antioxidant properties, has demonstrated beneficial effects in restoring reproductive function in Cypermethrin-exposed rats. Collectively, the evidence supports the notion that antioxidants effectively mitigate the reproductive toxicity induced by Cypermethrin. By neutralizing ROS and enhancing the cellular antioxidant defense mechanisms, these compounds help maintain cell integrity and prevent damage to the reproductive system. This is crucial for the recovery of reproductive capabilities in animals exposed to Cypermethrin. The implications of our research are far-reaching, as they offer potential solutions to combat the reproductive toxicity associated with Cypermethrin exposure. By understanding the mechanisms through which antioxidants protect against oxidative stress and aid in the restoration of reproductive function, we can potentially develop therapeutic interventions to mitigate the adverse effects of Cypermethrin in both animals and humans. However, further research is warranted to delve deeper into the specific molecular pathways involved in the protective effects of antioxidants against Cypermethrin-induced reproductive toxicity. Additionally, investigations into the appropriate dosages and treatment regimens of these antioxidants would be crucial to optimize their efficacy.

The study highlights the critical role of antioxidants in mitigating the reproductive toxicity caused by Cypermethrin exposure. The use of antioxidants, such as Vitamin E, Vitamin C, Curcumin, Resveratrol, and the extract of Tribulus Terrestre's, holds promise as a potential therapeutic strategy to protect and restore reproductive function in animals exposed to Cypermethrin. By harnessing the power of antioxidants, we may be one step closer to addressing the harmful effects of Cypermethrin and promoting reproductive health and sustainability in both wildlife and agricultural settings.

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