WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 19, 396-412. Review Article ISSN 2277–7105

TOXIC AND BIOLOGICAL EFFECTS OF GLYPHOSATE IN ANIMALS

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Article Received on
11 September 2023,

Revised on 01 Oct. 2023,
Accepted on 21 Oct. 2023

DOI: 10.20959/wjpr202319-30116

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ABSTRACT

In present review article hazardous and biological consequences of glyphosate herbicide have been discussed in detail. For the suppression of grass, sedge, and broadleaved plants, this is a systemic, nonselective herbicide that is often used in agriculture. Its commercial formulations are offered on the market under a variety of brand names. It affects the function of the kidneys, liver, colon, small intestine, bone, and bone marrow badly after entering the body by the skin, mouth, and inhalation. Following distribution, waste is eliminated by faeces and urine. It damages the hepatorenal system in farmers and has detrimental health implications, such as an increased risk of cancer. This endocrine disruptor may have an impact on reproductive processes. Additionally, it has a negative impact on thyroid and adrenal gland function. The concentrations of luteinizing hormone, prolactin, oestrogen, progesterone, and the testosterone/oestrogen ratio dramatically rose whereas the levels of testosterone and follicle-stimulating hormone significantly dropped in glyphosate-treated rats. Additionally, it displays the onset of behavioural and motor abnormalities as well as neurotoxic consequences like as necrosis or apoptosis. Additionally, it has cytotoxic and genotoxic effects, increases oxidative stress, changes the oestrogen system, impairs a variety of mental abilities, and could be related to some cancers.

KEYWORDS: Herbicides, glyphosate, endocrine disruptor, cytotoxic, xenotoxic effects, hepatotoxic and renal endocrine inhibitor.

INTRODUCTION

In agricultural fields, orchards, and gardens across the world, synthetic herbicides are used to control weeds and grass. But they were shown to be extremely destructive to the environment

and non-target creatures. These exhibited bio-magnifications, entered the food chain, and remained bonded in the soil for a significantly longer period of time. Glyphosate is a nonselective herbicide that is frequently sprayed directly onto agricultural fields in order to eliminate weeds. It offered in the forms of glyphosate, the systemically active N-(phosphonomethyl) glycine, and several grass, sedge, and broadleaf plant species. It interacts with the elements of the soil and spreads to the water, plants, animals, and atmosphere.[1] It is extremely dangerous to human health since it enters the body through the skin, mouth, and respiratory systems.[2]

This is a nonselective herbicide, available in the market in form of glyphosate's isopropylamine.[3] This is an anion at physiological pH values. Its several other glyphosate formulations are also used, including ammonium salt, diammonium salt, dimethylammonium salt, and potassium salt.[4] Its commercial is formulation is also available in market in variety of strengths, from concentrates with 41% or more glyphosate to formulations with 1% glyphosate.[5] To improve the absorption and translocation of the active component in plants, glyphosate is mixed with a number of adjuvants, including surfactants like polyoxyethylene amine (POEA). The popular Roundup® is a POEA-containing product.[6]

Glyphosate and its derivative, aminomethyl phosphonic acid (AMPA), are present in soil and water, thereby impacting water quality and posing a threat to the health of animals and humans. The extensive utilization of glyphosate has resulted in its widespread accumulation in the environment and in consumable products.[6] In the synthesis of aromatic amino acids, both plants and microorganisms employ a seven-step biological procedure.[7]

Glyphosate-based herbicides (GBH) are commonly utilized on a variety of crops, such as edible beans, canola, wheat, barley, soy grain, and maize. Residues of glyphosate-based herbicides have also been detected in food, with its primary metabolite AMPA being found after application. GBH has been found to have adverse health effects on both animals and humans.[8] Prolonged exposure to GBH increases the risk of developing cancer.[9] Exposure to glyphosate in humans can result in irritation of the eyes and skin, while individuals who inhale spray mist from glyphosate-containing products may experience irritation in the nose and throat. Ingesting products containing glyphosate can lead to increased saliva production, burning sensations in the mouth and throat, as well as symptoms such as nausea, vomiting, and diarrhea (Table 1). This article aims to elucidate the toxic effects of glyphosate on humans and other animals.

Source of information

For writing this comprehensive research review on toxic and biological effects of glyphosate on including endocrine various databases were searched. For collection of relevant information specific terms various keywords were used and all published papers, articles and books upto 2023 were searched in MEDLINE. Most relevant bibliographic data was obtained searching databases, including SCOPUS, Web of Science, and EMBASE, Pubmed, PMC, Publon, Swissprot, Google searches" From this common methodology, discoveries and findings were identified and summarized in this final review.

Biological effects

Effect of Glyphosate on endocrine function in vertebrates

Glyphosate based herbicides considered more poisonous than glyphosate due to the nearness of details such as polyoxyethylene fat amine (POEA).[10] Both glyphosate and glyphosate-based herbicides were found dynamic disruptors of endocrine work in man and other creatures. At last these in total influence regenerative capacities in creatures. This herbicide influences regenerative hub and changed the levels of GPR54, GnRH, LH, FSH, estradiol, testosterone. In rodent it too meddling with certain hormonal signaling pathways, which impact on arrangement of hypothalamic-pituitary-gonadal and other organ frameworks.[11] Both glyphosate and glyphosate-based herbicides too influence HPT hub and thyroid function(Table 1). Glyphosate have affect on the forms that lead to iodide oxidation and organification as well as oxidative phosphorylation of ATP.[12] Presentation to glyphosate brought about in altogether diminished ($p \leq 0.05$) the levels of testosterone, 17-estradiol, and add up to protein, which serve as records of endocrine disreputability.[13]

Glyphosate seriously changes the action of the chemical aromatase and brings down blood testosterone levels. It too meddling with the method of masculinization and initiated behavioral adjustments, in females due to endocrine issues in regenerative parameters. Glyphosate uncovered creatures appeared higher gonadal action and sperm generation.[14] In glyphosate treated rats, levels of testosterone and follicle-stimulating hormone altogether diminished and the concentrations of luteinizing hormone, prolactin, estrogen, progesterone, and testosterone/oestrogen proportion essentially expanded. Glyphosate moreover harm pituitary organs in treated rats and forces variations from the norm in its tissues and cells.[15] Glyphosate can have inhibitory impacts on the hypothalamic-pituitary hub, which lower corticosterone generation and impact the adrenal organ as well[16] (Table 1).

Glyphosate-based herbicides are strong carcinogens

Long term introduction of glyphosate salts works as carcinogen in people. It brings out a few sorts of cancer in people, counting non-Hodgkin lymphoma, and could be a potential human carcinogen.[17] Glyphosate is tumorigenic and causes coordinate DNA harm in touchy cells. It causes disturbance of glycine homeostasis, succinate dehydrogenase hindrance, manganese chelation. It does alteration of cancer-causing particles like N-nitrosoglyphosate and glyoxylate, and causes disturbance of fructose digestion system. Bound buildups glyphosate force wide ranges of infections, counting breast cancer, pancreatic cancer, kidney cancer, thyroid cancer, liver cancer, bladder cancer, and myeloid leukemia.[18] Agreeing to George et al. (2010), glyphosate cause carcinogenic movement in a number of organs, counting the thyroid tissues, intestine, liver, kidney, skin, and does quick multiplication of cancer in breast cells in mouse and in human.[19] Glyphosate causes hemangiosarcomas, kidney tumors, and threatening lymphomas and tumors pale skinned person mice[20] (Table 1).

Neurotoxic effects

Glyphosate appears poisonous impact on neurotransmission and to causes oxidative push, neuro-inflammation, and mitochondrial brokenness. Early-life presentation to glyphosate altogether disable ordinary cell advancement by deregulating a few of the signaling pathways alter separation, neuronal development, and myelination. These conditions result within the passing of neurons through autophagy, rot, or apoptosis as well as the development of behavioral and engine clutters.[21] Glyphosate-based herbicides brought about in a more juvenile neuronal profile connected to expanded PAX6, NESTIN, and DCX expression, as well as a alter within the separation prepare toward glial cell destiny at the cost of critical variables in neurogenesis counting PAX6, HES1, HES5, and DDK1[22] (Table 1).

Cytotoxic and genotoxic effects

Glyphosate forces cytotoxic and genotoxic impacts either straightforwardly or by implication through its metabolite, aminomethylphosphonic corrosive (AMPA) in creature models.[23] Intense introduction to tall concentrations of glyphosate and AMPA (over 10 mM) comes about in intense cytotoxic impacts, counting diminished cell practicality, expanded ROS, morphological changes, and impeded mitochondrial work. Lower glyphosate measurements put small or no impact on the reasonability and ROS of H9c2 cells.[24] Glyphosate influences estrogen framework, impede nerve transmission. It seriously influences safe framework and causes irritation of skin epithelial cells.[25] In higher vertebrates like people, it causes

hormone unsettling influence, chromosomal variations from the norm, and DNA harm.[26] Glyphosate based herbicides causes genotoxic impacts on *P. lineatus* erythrocytes and gill cells.[27] Its drawn out introduction actuates DNA harm interior core and[28] create micronuclei in local of *P. cuvieri* and *P. gracilis*[29] (Table 1).

Effect on Liver

Glyphosate causes blood/urine biochemical changes and shows a lipotoxic impact and cellular harm within the liver and kidney cells.[30] Glyphosate-based herbicides caused greasy liver illness and its movement to steatohepatiosis.[31] Glyphosate intensely aggravates hepatic digestion system and cause noteworthy oxidative harm to the liver tissue. In both male and female mice it causes raised levels of the chemicals ALT, AST, and GOT. Glyphosate caused lipoperoxidation and diminished the amounts of non-protein thiols within the hepatic tissue[32] (Figure 1). GBH poisonous quality causes particle lopsidedness, impede antioxidant protections and contribute liver oxidative harm[33] and cause noteworthy liver congestion.[34] (Table 1) (Figure 1).

Glyphosate introduction in fish appeared vacuolation of hepatocytes, pyknotic cores, corruption of cytoplasm, leukocyte penetration, rot, and noteworthy vasodilation in their liver.[36] It too lift aspartate aminotransferase, alanine aminotransferase, and soluble phosphatase.[37] It moreover murder ruddy blood cells, hemoglobin concentration, lymphocytes, and monocyte checks. Glyphosate influences add up to proteins, antioxidant proteins catalase movement and diminished GSH, and Turf altogether diminished over time and in a dose-dependent way.[38]

Effect on Kidney

Glyphosate-treated rats appeared noteworthy kidney blockage and renal decay.[34] Sublethal glyphosate harming caused kidney irritation and unfavorable histopathological impacts in Nile tilapia.[39] Glyphosate causes glomerular weakening, mononuclear cell penetration and tubular rot.[40] The Bowman's hole expanded and hyaline beads collected within the tubular epithelial cells in glyphosate-tread angle kidney injuries[37] (Figure 1). In HaCaT cells, glyphosate (0.1 mM) altogether expanded ROS generation, diminished [Ca2+], and actuated expansion. Antioxidant N-acetyl-L-cysteine (NAC) pretreatment switched these impacts, demonstrating that glyphosate invigorated cell development by bringing down [Ca2+] levels by means of ROS generation.[41]

Biochemical enzymatic changes

Glyphosate presentation causes expanded levels of AST, ALT, and LDH action which shows hepatocyte damage.[42] Glyphosate causes serious liver harm in both male and female mice and raised levels of certain proteins i.e. ALT, AST, and γ -GT.[32] LDH chemical action altogether expanded while ASAT and ALAT action diminished within the glyphosate-exposed fish's livers.[43] Glyphosate altogether increases AST and ALT within the fish liver.[36] Soluble phosphatase shows stamped decrease in behavior.[44] In Heterobranchus bidorsalis plasma whereas get ALT diminished while kidney ALT values imperceptibly expanded in dose-dependent way.[45] Angle treated with glyphosate had significantly expanded values for ALT, AST.[46] Glyphosate in rats changes the reactions of biomarkers such blood glucose, add up to protein, add up to cholesterol, triglycerides, SGOT, SGPT, and billirubin levels.[47] Glyphosate expanded levels of the proteins glutamate dehydrogenase (GLDH), glutamate oxaloacetate transaminase (GOT), and creatinine kinase (CK) in dairy bovines. It shows nephrotoxicity, hepatoxicity with increased urea levels.[48]

Immune functions

Glyphosate (G) introduction upgrades the levels of IL-4 and IL-17A after its generation, and a decrease of IFN-γ. It improves the activity of G, miRNAs, both in exosome and intracellular zone. After being uncovered to *Beauveria bassiana*, glyphosate presentation expanded silkworm mortality by 4.35 times, which may be credited to diminished PO (phenoloxidase) action and debilitated insusceptibility.[49] The action of common safe components vital to intervene fish resistance to irresistible microorganisms is decreased and blood parameters are modified as a result of glyphosate defilement of water.[50]

Effect on skin cell

Glyphosate extremely influence skin cells, it causes skin carcinogenesis.[51] It causes rot of keratinocytes.[52] Low cytotoxic measurements of glyphosate cause cell layer firmness and the rise of cytoskeleton structures at the subcellular level.[53] Glyphosate causes diminishing of the epidermis and degenerative changes in skin cells and in kidney cells along side vacuolization and harmed capsule in neonate rats[49] (Figure 1).

Effect on digestion

Glyphosate causes dysplasia within the throat, little and expansive digestive tract, and expanded micronucleus generation. Glyphosate-based herbicides have the potential to be genotoxic and actuate oral allergies, dysplastic injuries within the throat, small and huge

digestive system, and verbal hypersensitivities.[54] Within the duodenum and jejunum, introduction to glyphosate decreased the extent of villus stature to sepulcher profundity. Glyphosate diminished antioxidant chemical movement (T-SOD, GSH, and GSH-Px).[55] Both male and female rats uncovered to glyphosate show critical morphological changes to their ileal structures, with female rats being more seriously affected.[56] Glyphosate increment the level of corrosive protease, trypsin, chymotrypsin, and amylase action expanded.[57] Glyphosate uncovered fish gill confront extreme harm, shrinkage, and degeneration of the pentagonal cellular form of stratified epithelial cells. Furthermore glyphosate causes rot of columnar epithelial cell and disintegration of the apical surface of mucosal folds. Glyphosate treatment diminish the movement of the proteins protease and amylase in stomach and digestive system and diminished within the throat and digestive system of the fish uncovered to the chemical. Glyphosate in fish irritate lipase movement in their stomach and digestion tracts as well.[58]

Reproductive inhibition

Glyphosate altogether changed testicular architecture, diminished sperm motility, and expanded sperm deformity proportion.[59] It too forces maternal poisonous quality but had negative impacts on male descendant rats' capacity to duplicate. Glyphosate increments the rate of anomalous sperms and a dose-related diminish in serum testosterone levels amid adolescence, and signs of person spermatid degeneration.[60] Glyphosate exceedingly destructive to Sertoli cells basically cause rot. It causes apoptosis at more noteworthy measurements in co-cultures of Sertoli and germ cells as well as in germ cell lines.[61] Glyphosate causes oxidative push and early apoptosis and disable the advancement of mouse oocytes.[62] Glyphosate presentation amid pregnancy actuates testosterone in females.[63] Furthermore, glyphosate modifies steroidogenesis and lifting oocyte ROS levels.[64] It has been illustrated that glyphosate treatment has considerable negative impacts ($P<0.05$) on sperm parameters such as morphology, sperm cell number, and quality. It diminishes the cellular astuteness of the gonads and is adversely affected by glyphosate introduction, changing the phenotype of the sperm and testicular cells.[65] Glyphosate shows disabled sperm motility, reasonability, mitochondrial movement, and acrosome integrity[66] (Figure 1).

Effect on embryonic development or neonatal life

Glyphosate is additionally transported to uterus and influence fetal / embryonic improvement in human. Glyphosate causes DNA harm in C. latirostris embryos. Its critical peril seriously

influences embryonic improvement.[67] It forces changes in endometrial decidualization and restrain implantation of developing life into the uterus divider.[68] In feathered creatures, it seriously influences improvement of brain tissue and cause higher lipid harm in nerve cell film.[69] It diminishes expression of Wnt5a and Wnt7a quality in rats and interferometer arrangement of uterine signaling[70] (Figure 1).

Glyphosate cause skeletal changes in wistar rats. The foremost common skeletal changes taken note are lacking cranium solidification and an extended fontanel, which was more predominant within the test, bunches than within the control bunches.[71]

Effect on blood parameters

Glyphosate-based pesticides radically changed the biochemical and hematological profiles in test creatures.[72] Fish uncovered to all glyphosate-based herbicide bunches shown a noteworthy decrease in hematocrit, hemoglobin, and ruddy blood cell levels.[73] [74] It causes diminishes in RBC, hematocrit, and hemoglobin as well as a noteworthy rise in cruel corpuscular volume both in male and female rats.[32] In glyphosate treated rats lymphocyte levels get increased.[75] Both intense and incessant presentation to glyphosate essentially diminished the granulocyte and erythrocyte check, hemoglobin level, hematocrit, cruel corpuscular volume, and platelet checks in common carp *Cyprinus carpio L.*[74] Glyphosate causes vascular poisonous quality, which raises the plausibility of an atherosclerotic risk.[76] Glyphosate-based herbicides display morphological variations from the norm and cause muscle degeneration and influenced the shape of muscle filaments and neuromuscular intersections within the stomach[77] (Figure 1).

Table 1: Toxic and biological effects of glyphosate on animal tissues and cells.

Biological effect	Mechanism of action	Reference
Effect on endocrine function	Cut down levels of testosterone, 17-estradiol, and total protein, Increased gonadal activity and sperm production, lower corticosterone production	[10], [13], [14], [16]
Act as carcinogens	Evoke Non-Hodgkin lymphoma, Causes skin tumor and Hemangiosarcomas	[17],[18],[19],[20]
Effect on nerve cells	Affect neurotransmission and cause oxidative stress, neuro-inflammation, and mitochondrial dysfunction	[21],[22]
Effect on liver	Increased levels of ALT, AST, and –GT, lipoperoxidation , liver oxidative damage, liver congestion, necrosis,	[32],[33],[34]
Effect on kidney	Renal congestion and atrophy, glomerular deterioration and tubular necrosis	[34], [40]

Effect on calcium regulation	Lowering [Ca2+] levels via ROS production.	[41]
Effect on skin cell	Skin carcinogenesis, apoptosis, cell membrane stiffness and thinning of the epidermis	[51], [53]
Effect on embryonic development	DNA damage in embryos, make changes in endometrial decidualization,	[67],[68],[70]
Effect on blood cells	In fish and rat reduction in hematocrit, hemoglobin, and red blood cell levels.	[32], [73],[74]
Effect on muscle cells	Vascular toxicity, muscle degeneration and affected the morphometry of muscle fibers	[76], [77]

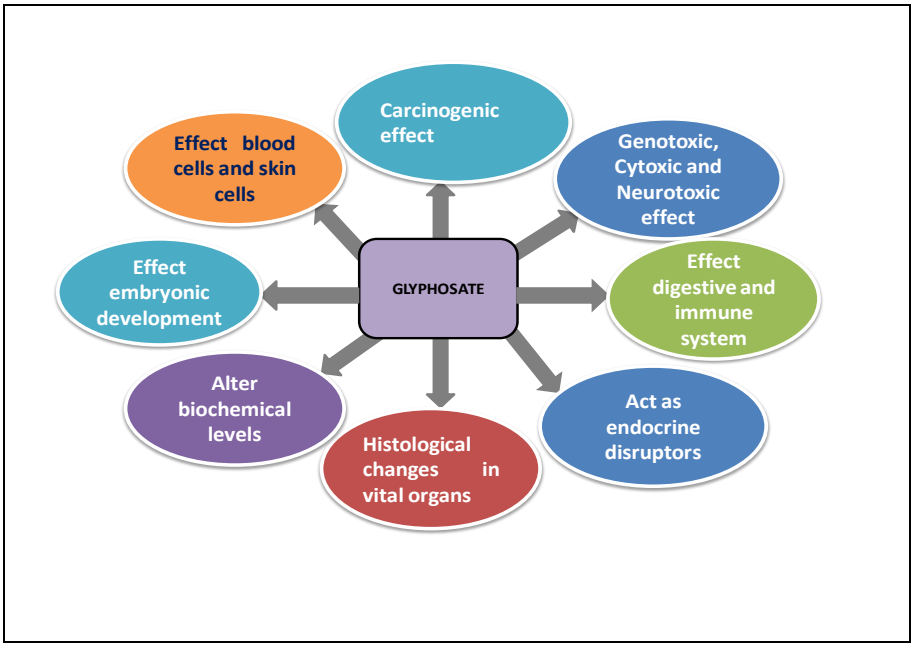

Figure 1 showing toxic and biological effects of glyphosate.

CONCLUSION

The herbicide glyphosate is widely used in crop fields and orchards to control weeds, mostly grasses. The toxicity of glyphosate as an organic pollutant has received a great deal of attention because to its widespread use. Fish and other freshwater creatures are particularly harmed by it. The environmental spread of this kills non-target creatures in soil and water and enters the food chain. In exposed fish, it produces ROS, raises the amount of total proteins, and has a time- and dose-dependent effect on the antioxidant enzymes catalase, reduced GSH, and SOD. Haematological, renal, hepatic, and pulmonary issues are brought on by it. Higher doses reduce lymphocyte and monocyte numbers, damage red blood cells, and lower haemoglobin concentration. Furthermore, glyphosate-based herbicides may cause oral allergies, dysplastic lesions in the oesophagus, small and large intestines, and genotoxic

effects. As a result of glyphosate pollution of the water, the activity of natural immune components essential to mediate fish resistance to pathogenic bacteria is lowered and blood cell parameters are changed. It is very damaging to foetal and natal life, with a 50% mortality rate among newborns as evidence of its teratogenicity. GBH is hazardous when supplied at high doses, altering cell viability, morphology, and mitochondrial health; however, effects are less pronounced at low concentrations.

ACKNOWLEDGEMENTS: Authors are thankful to H.O.D., Department of Zoology for research facilities.

CONFLICT OF INTERESTS

Declared none.

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