A REVIEW ON IMPACT OF GLYPHOSATE ON DEVELOPMENT OF CANCER

ABSTRACT

Pesticides are a vast mixture of compounds used to control pests like plants, moulds, and insects. In agriculture, non-agricultural vegetation management, and crop desiccant harvesting aid, chemicals from every major functional family of pesticides, such as insecticides, herbicides, fungicides, and fumigants, were frequently used. Herbicides are one of the most effective tools for farmers to obtain optimal crop yields when used correctly. Glyphosate (N-(phosphonomethyl) glycine) is a broad-spectrum weed killer that is used all over the world in agriculture and forestry. Glyphosate's herbicidal activity in plants is to disrupt the shikimic acid pathway's generation of branched-chain amino acids by preventing the binding of phosphoenolpyruvate (PEP) to the enzyme 5-enolpyruvylshikimate 3-phosphate synthase. This causes a deficiency in aromatic amino acid synthesis and, as a result, weeds mortality. Glyphosate exposure through food, drinking water, wind, water erosion, and other environmental pathways has been linked to human health issues as a carcinogen, mutagen, and reproductive toxicity. Glyphosate has a wide range of tumorigenic effects in biological systems, and epidemiological evidence suggests that glyphosate use on crops is linked to a wide range of cancers, including liver cancer, breast cancer, thyroid cancer, pancreatic cancer, kidney cancer, bladder cancer, and myeloid cancer. The shikimate pathway enzymes, intermediates, and derivative amino acids, which have been associated to genotoxicity and carcinogenicity, are thought to have a role in most cancer pathologies. This review summarises glyphosate's function in cancer pathology, including the ability of the glyphosate circuit to induce cancer and implications for future therapeutic methods.

KEY WORDS: Glyphosate, Cancer, Herbicides, Roundup, phosphoenolpyruvate

1. INTRODUCTION

Herbicides are one of the most important instruments used by farmers to produce optimal crop yields. Herbicides are weed-control agents that represent a breakthrough in plant breeding science, but they have the potential to harm the environment [1,2] and have negative health consequences because there is a link between diseases, particularly cancer, and occupational exposure to these chemical compounds [3]. Raw fruits and vegetables as weed control plant products expose people to various types of herbicides [4]. Herbicides also known as chemical pesticides are easily absorbed through the gastrointestinal and respiratory tract and skin. Due to their high stability and their affinity to adipose tissue they can metabolize and be stored in human organs mainly in adipose tissue. Herbicide contamination requires special consideration due to the high toxicity of pesticides and their great persistence in the environment [5].

Glyphosate (organophosphorus compound) is a systemic herbicide developed by Monsanto in 1971 [6], and it is the most widely and extensively used herbicide for weed control in agriculture and forestry globally. Glyphosate-based herbicides are sold under the trade names Roundup and Ranger Pro and are frequently mixed with additional materials, such as surfactants as inert additives. These herbicides come in a variety of chemical forms, including isopropylamine salt, ammonium salt, diammonium salt, dimethylammonium salt, and potassium salt, and are the most widely used herbicide class in the world. They increase penetration and efficacy while also having their own side effects [7]. This is also known as N- (phosphonomethyl) Glycine is a broad-spectrum herbicide that inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which blocks the

synthesis of aromatic amino acids such as tryptophan, phenylalanine, and tyrosine by inhibiting the binding of phosphoenolpyruvate (PEP) in the shikimic acid pathway [8]. As a result, this biosynthesis pathway system is found exclusively in plants, bacteria, and some fungi, and glyphosate's claimed low toxicity in mammals has made it the most popular herbicide in recent years [9]. Glyphosate, the designated active ingredient, is a chelating agent that binds macro- and micronutrients, which are necessary for numerous plant processes and disease resistance. As a result, glyphosate treatment may limit plant uptake and availability of macro- and micronutrients therefore potentially affecting many organisms and processes [10]. Human health concerns have been expressed about glyphosate exposure via food, drinking water, wind, water erosion, and other environmental channels as a carcinogen, mutagen, or reproductive toxin [11]. The International Agency for Research on Cancer (IARC) stated in March 2015 that glyphosate is probably carcinogenic to humans, which was later validated by the EU assessment and the latest joint WHO/FAO study [12].

In vitro and animal research has suggested that glyphosate may cause genotoxicity or carcinogenicity. Glyphosate has a variety of tumorigenic effects on biological systems, including direct DNA damage in sensitive cells, disruption of glycine homeostasis, succinate dehydrogenase inhibition, manganese chelation, modification to more carcinogenic molecules like N-nitrosoglyphosate and glyoxylate, disruption of fructose metabolism, and so on. Strong temporal links between glyphosate use on crops and a variety of malignancies that are reaching epidemic proportions, including breast cancer, pancreatic cancer, kidney cancer, thyroid cancer, liver cancer, bladder cancer, and myeloid leukaemia, are supported by epidemiological studies [13]. Increased risk of massive mammary tumours in the females, along with kidney and liver damage in the males has been observed in rats fed GM maize and/or Roundup in their water over their entire lifespan associated with the increased risk of glyphosate usage [14]. Similarly, in the United States, an increase in glyphosate use is highly connected with an increase in the incidence and/or death rate of a variety of diseases, including many malignancies [15].

Glyphosate as a possible human carcinogen and genotoxin, with a focus on research that reveals mechanisms that would go unnoticed in typical toxicological investigations, such as microbiome disruption and endocrine mimicking at very low concentrations, as well as cancers, which are said to be the leading cause of death in developed countries and the second leading cause of death in developing countries [16,17]. The impact of glyphosate on cancer histology was highlighted in this review, which has implications for treatment perception.

2. GLYPHOSATE ROLE AS HERBICIDE

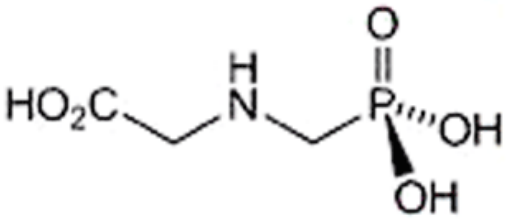

Table 1: Glyphosate properties

Glyphosate properties	
Physical state	Crystalline powder
Colour	White
Odour	None

Molecular Formula	$C_3H_8NO_5P$ or $HOOCCH_2NHCH_2PO(OH)_2$
Molecular Weight	169.07
IUPAC	N-phosphonomethyl-glycine
Melting point	184.5 °C
Specific gravity	1.704
Surface tension	0.072 N/m

Glyphosate (N-(phosphonomethyl) glycine) is a broad-spectrum herbicide used for weed control in agriculture and forestry around the world. It was patented as a herbicide active component in 1971 (US Patent No 3,799,758) and later commercialised by Monsanto Company under the brand name Roundup. Glyphosate Based Herbicides (GBHs) have been on the market since 1974, and are frequently compounded with other components such as surfactants [7,18]. It's frequently utilised in agriculture, non-agricultural vegetation control, and harvesting help as a crop desiccant. The herbicide's use in agriculture has expanded significantly as a result of the advent of glyphosate-resistant GM crop varieties; the herbicide has also been employed to control illegal crops via huge aerial sprays [19]. Glyphosate's herbicidal function in plants is to disrupt plant production of aromatic amino acids in the shikimic acid pathway by inhibiting the binding of phosphoenolpyruvate (PEP) to the enzyme 5-enolpyruvylshikimate 3-phosphate synthase. Glyphosate binds to EPSPS with excellent specificity, and it is thought that this molecule will not bind to the PEP association site of other enzymes in mammals [20].

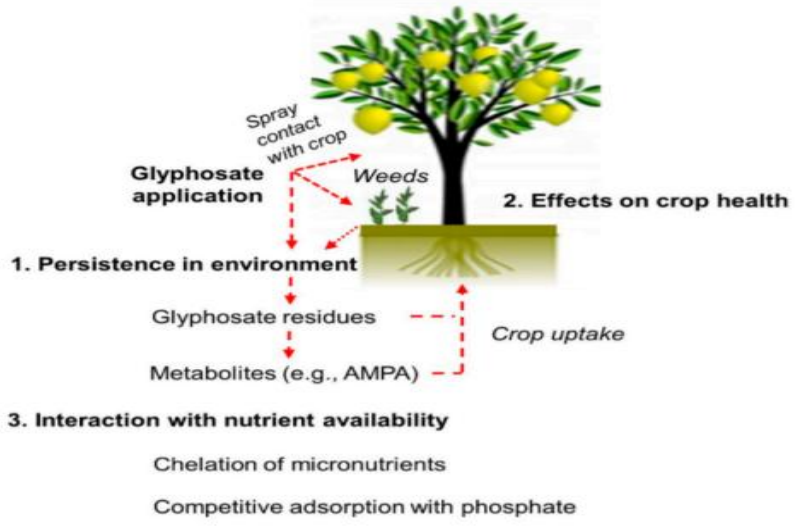

Fig.1:Glyphosate role in plants [21]

The global use of glyphosate has increased 15-fold since 1996, adoption of glyphosate tolerant (GT) crops also been very faster. Hence, the recent report by the USDA [2019] states that 94% of planted soybean and 90% of planted corn in the US is of a GT variety, which further suggests a large amount of GT crops found in animal feed. An estimated 77% of the global soybean production comes from GT soybean and the dominant soy producing countries of USA, Brazil and Argentina have a 94%–100% adoption rate of GT soy [22]. Import, glyphosate residues are frequently found in the food chain due to either being sprayed on cereals to accelerate ripening, facilitate more uniform drying of the grain and thus expedite harvesting of the crop, or to clear weeds during cultivation of Roundup-tolerant

genetically modified crops [23]. Glyphosate residues are commonly discovered in human urine at concentrations of roughly 1 g/L, with some investigations revealing concentrations as high as 10 g/L in non-occupationally exposed population [24].

2.1. GLYPHOSATE TOXICITY

Glyphosate-containing goods are hazardous to animals, including humans, causing eye and skin irritation, headaches, nausea, numbness, raised blood pressure, and heart palpitations as acute symptoms. The surfactant in a popular glyphosate product (Roundup) is more acutely hazardous than glyphosate alone, and the two together are even more harmful. Despite the fact that glyphosate herbicides are considered safe, laboratory research have discovered negative consequences in all conventional categories of toxicity testing [25]. These include long-term toxicity (inflamed stomach linings), medium-term toxicity (salivary gland lesions), genetic damage (in human blood cells), reproductive effects (reduced sperm counts in rats; increased frequency of abnormal sperm in rabbits), and carcinogenicity (increased frequency of liver tumours in male rats and thyroid cancer in female rats) [26]. According to most studies, farmers exposed to glyphosate herbicides had a greater rate of miscarriages, premature births, and malignancies such as non-lymphoma and Hodgkin's disease [27]. Strong temporal links between glyphosate use on crops and a variety of malignancies that are reaching epidemic proportions, including breast cancer, pancreatic cancer, kidney cancer, thyroid cancer, liver cancer, bladder cancer, and myeloid leukaemia, are supported by epidemiological studies [28].

3. GLYPHOSATE IN CANCER

Pesticides are a broad category of chemicals that are used to manage pests such as plants, moulds, and insects. Pesticides are frequently employed in agricultural, commercial, and residential contexts, resulting in widespread exposure to the general public. Herbicide production, use, and discharge into the environment have all increased as a result of agricultural developments. Chemicals from every major functional class of pesticides, including insecticides, herbicides, fungicides, and fumigants, have been linked to a wide range of cancer sites. Glyphosate, a herbicide, has been studied for its potential to cause cancer in mice (five studies) and rats (nine studies). The majority of authority have determined that the evidence does not point to a human cancer risk. However, the International Agency for Research on Cancer (IARC) assessed some of the available evidence and found that glyphosate is likely carcinogenic to humans [29]. This review examines the role of glyphosate in cancer pathophysiology.

3.1 Liver cancer

Hepatocellular carcinoma (HCC) is the most common type of cancer that results in death. Stimulation by chemicals and viruses are two important risk factors, but the molecular processes underlying their variations are unknown [30]. The study by Pandey et al. [31] is the first to describe the impact of a subacute glyphosate exposure on the development of multi-organ inflammation and non-alcoholic fatty liver (NAFL) disease. Increased expression levels of inflammatory markers were detected in liver tissues of treated rats after a 2-week oral exposure to herbicide concentrations substantially below LD50 (0, 5, 10, 25, 50, 100, and 250 mg/kg bodyweight [bw] glyphosate) every day for 14 days. In the liver of rats subjected to higher (100 and 250 mg/kg bw/d) glyphosate dosages, C-reactive protein, cytokines IL-1b, TNF-a, IL-6, and an inflammatory response marker were all increased. At larger doses, liver tissue revealed symptoms of glycogen storage imbalance, fibrosis, inflammation, and nonalcoholic steatohepatitis (NASH). This NASH is a fatty liver disease connected to glyphosate inhibiting the shikimate pathway, which results in reduced generation of aromatic amino acids due to disturbance in gut fructose metabolism [Lim et al., 2010]. Instead, excess fructose supplied to the liver induces cirrhosis and raises the risk of liver cancer by converting it to fat for local storage or distribution within low-density lipid particles (LDL) [32]. Increased serum alanine aminotransferase

(ALT) and aspartate aminotransferase (AST) levels cause irreversible hepatocyte damage and a large deposition of reticulin fibres containing collagen type III, indicating liver fibrosis, in herbicide Glyphosate-Biocarb-exposed wistar rats over a 75-day period. Glyphosate's role in inflammation, liver fibrosis, and non-alcoholic fatty liver (NAFL) disorders in shot increases the risk of liver cancer [33].

3.2. Adipose cancer

At dosages of 10, 50, 100, and 250 mg/kg bw/d, the effects of glyphosate on adrenal gland steroidogenesis and the signalling system linked with steroid synthesis were studied. The condensed circulatory corticosterone levels, cholesterol receptor (low density lipoprotein receptor) expression, de novo cholesterol synthesis enzyme (3-hydroxy-3-methylglutaryl-coenzyme A synthase), hormone-sensitive lipase, steroidogenic acute regulatory protein (StAR) mRNA, and phosphorylated form were all clearly shown. However, there was no change in the expression of the adrenocorticotropic hormone receptor (ACTH), corticotropic hormone receptor (ACTH), or melanocortin-2 receptor. Circulatory ACTH levels and adrenal cortex protein kinase A (PKA) activity, on the other hand, were lower. According to this study, glyphosate may suppress the hypothalamic–pituitary axis, resulting in decreased cAMP/PKA pathway activity, StAR phosphorylation, and corticosterone production in the adrenal tissue [34]. In the adipose tissue of rats subjected to higher (100 and 250 mg/kg bw/d) glyphosate dosages, the cytokines IL-1b, TNF-a, IL-6, and inflammatory response marker, as well as prostaglandin–endoperoxide synthase, were elevated [30]. Thus, glyphosate cytotoxicity in human cells is mediated in part by inhibition of succinate dehydrogenase (SDH), a key enzyme in mitochondrial complex II [35]. SDH is a tumour suppressor, as glyphosate suppressed SDH enzyme activity three to fourfold in an Escherichia coli study [36]. This mechanism of inhibition suggests that glyphosate binds at the succinate binding site with a higher binding energy than succinate, thus blocking substrate bioavailability [37]. Hence, mutations in SDH lead to the development of phaeochromocytoma a type of neuroendocrine tumours of the adrenal glands.

3.3. Breast cancer

The herbicide glyphosate has been studied for its effect on cancer incidence, and its influence on the estrogen-regulated pathway makes it an obvious target for breast cancer research. Glyphosate caused a considerable drop in DNA methylation; however unlike the potent demethylating agent and cancer promoter UP peptide, it did not cause tumour formation in glyphosate-treated cells. Unlike UP, which operates through the DNMT1/PCNA/UHRF1 route, glyphosate boosted the activity of the ten-eleven translocation (TET) 3 pathway. Glyphosate combined with increased expression of the breast cancer-associated microRNA (miR) 182-5p resulted in tumour formation in 50% of mice. In response to glyphosate-miR182-5p treatment, primary cells from resected tumours showed a luminal B (ER+/PR-/HER2-) phenotype with tamoxifen sensitivity and invasive and migratory capability. Tumor formation could be averted by inhibiting miR 182-5p directly or treating glyphosate-miR 182-5p-cells with dimethyloxallyl glycine, a TET pathway inhibitor that primes cells for an oncogenic response in the presence of another possible risk factor [38]. Glyphosate has been shown to induce cellular proliferation via oestrogen receptors in breast cancer (BC) cell lines by affecting survival due to cell cycle deregulation and metabolism changes that may alter mitochondrial oxygen consumption, increase ROS levels, induce hypoxia, damage DNA repair, cause mutation accumulation, and eventually cell death. Glyphosate may also increase the risk of breast cancer indirectly by impairing the metabolism of toxic phenolic compounds like nonylphenols, also known as alkylphenols, which are known to be xenoestrogenic and are widely used as additives in laundry detergents, lubricating oils, paints, pesticides, personal care products, and plastics.

3.4. Prostate cancer

The most prevalent cancer diagnosed in men is prostate cancer. The disease's clinical aggressiveness varies greatly. Prostate cancer metastasizes quickly in some people, killing them within a year of their initial clinical presentation, but other patients may live for years with localised

illness and no visible metastases [39,40]. Sarcosine, an N-methyl derivative of the amino acid glycine, is how glyphosate works in prostate cancer. Sarcosine dehydrogenase can convert sarcosine to glycine, and glycine N-methyltransferase can convert glycine to sarcosine (N-methylglycine). As a result, sarcosine was identified as a unique metabolite that was found to be greatly enhanced during the progression of prostate cancer to metastasis and can be detected non-invasively in urine. Importantly, in many microbial pathways some bacteria break down glyphosate by using carbon-phosphorus lyase (C-P lyase) to produce sarcosine as an immediate breakdown product [41]. These nitrosylated sarcosine or nitrosyl glyphosate are exceedingly toxic and carcinogenic, with raised sarcosine levels as a possible metabolic mediator of prostate cancer cell invasion and aggressiveness [42].

3.5. Thyroid cancer

Selenocysteine is the twenty-first amino acid synthesised from Selenium, which produces twenty-five selenoproteins in turn. In addition to thyroid function, selenium insufficiency can affect immunological function and spermatogenesis [43]. Glyphosate, on the other hand, impairs selenium uptake in plants, just as it depletes sulphur, and both sulphur and selenium are found in the same column of the periodic table [44].

3.6. Non-Hodgkin lymphoma

The recent review of human epidemiological data on glyphosate was published by the International Agency for Research on Cancer (IARC) in 2015 [45]. Positive evidence of a link between glyphosate exposure and non-Hodgkin lymphoma has been found in some case-control studies but not in cohort studies. Agricultural workers have a higher risk of Non-Hodgkin lymphoma than the general population, but it's difficult to separate the effects of glyphosate from the myriad other toxic chemicals, as a Canadian study found a link between glyphosate exposure and the risk of Non-Hodgkin lymphoma [46].

3.7. Other cancer

Folic acid (folate) is a cofactor in a number of key biological activities, including methionine remethylation and DNA biosynthesis single carbon unit donors. The shikimate pathway [47,48] is the route for glyphosate, and it is given not just by diet but also by commensal microorganisms. As a result, it appears to impair folic acid production in both exposed plant food sources and the human gut, resulting in deficits that promote colorectal carcinogenesis and a variety of malignancies, including colorectal, breast, ovarian, pancreatic, brain, lung, and cervix cancers [49]. Glyphosate exposure impairs tryptophan bioavailability to the human host, resulting in tumours in the lung, colon, liver, breast, and skin melanoma [13,50].

4. CONCLUSION

Glyphosate, a broad-spectrum herbicide commonly used in agriculture and non-agricultural settings to eliminate undesired plants, has been shown to be harmful to human health. The shikimate pathway is the method of glyphosate herbicidal activity in plants. Aside from that, the shikimate pathway is found only in plants, bacteria, and some fungi, with negligible toxicity in mammals. Humans are exposed to glyphosate through a variety of sources, including plant products as food, soil, water, and water erosion. Exposure to glyphosate herbicides has been linked to a higher incidence of miscarriages, premature birth, and a variety of cancers, including breast cancer, pancreatic cancer, kidney cancer, thyroid cancer, liver cancer, bladder cancer, and myeloid leukaemia. The current review summarises the mechanism by which glyphosate causes cancer.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is

absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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