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Glyphosate and Autoimmune Disease

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Abstract

N-phospho methyl (glycine), another name for glyphosate, is an organophosphorus chemical that competes with other molecules in the shikimate pathway. Both microbes and plants use this process to produce aromatic amino acids. Glyphosate's use in broad-spectrum herbicides like Round UpR has steadily expanded since its 1974 launch. A variety of ecosystems, including soils, water, plants, animals, and food supplies, are subject to glyphosate and its primary metabolite, aminomethylphosphonic acid, monitoring. Glyphosate is often discovered in the blood and urine of people, especially those who deal with it, and is quickly eliminated by the human body. Glyphosate and its derivative herbicides were originally thought to be safe for animals to eat, but they have now been connected to a number of health issues. In 2017, glyphosate was deemed "probably carcinogenic" to humans by the International Agency for Research on Cancer (IARC). In spite of this, glyphosate was approved by numerous national authorities for extended periods of time without more stringent limitations. It is evident that there is currently a lack of international agreement about glyphosate, as several nations have set their own maximum permissible limits.

Keywords: Glyphosate, Immune System, Herbicide, Inflammation

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Introduction

Research and industry in agriculture greatly depend on chemically altered products for the growth and care of crops. These agricultural items are commonly utilized in home settings as well, particularly for lawns and gardens. This category includes fertilizers, herbicides, pesticides, insecticides, and fungicides. In the United States, herbicides are the second most used pesticides, only behind China [1]. However, recent studies indicate that certain widely used products pose significant health risks. Products that contain glyphosate, like Roundup and its equivalents (such as Glyphosate, Touchdown IQ, Touchdown 5), have raised numerous concerns. Grasso sate , known scientifically as N-(phosphonomethyl) glycine, acts as an amino acid substitute that eliminates plants by inhibiting an enzyme called EPSPS, which is crucial for their metabolism [2]. This disrupts the shikimic acid pathway in plants [3]. There is increasing worry that glyphosate, designed to target plant systems, may disrupt similar pathways in mammals, including humans, when they are exposed to or consume items with even small traces of these chemicals. For those working in agriculture, the risks of exposure would rise due to their increased contact with such substances. According to recent research by Connolly et al. [4], glyphosate has a half-life of approximately 3.5 to 14.5 hours based on urine sample analysis from individuals. Soares et al. [5] have identified glyphosate residues in common foods like honey, fruit juice, wheat products (bread and cereals), vegetables, beans, meats, and fish.

According to research, many illnesses and conditions are linked to being around herbicides such as Roundup, which contains glyphosate. These studies suggest that such diseases may be connected to these chemicals. For example, young people exposed to glyphosate have shown signs of liver inflammation, which could increase their chances of getting cancer, diabetes, and heart disease [6]. [7,8] Previous research has also noted connections between glyphosate and certain types of cancer, such as non-Hodgkin's lymphoma, as well as reproductive issues. This evidence repeatedly highlights the risks glyphosate poses to human health. The main aim of this comprehensive study is to investigate how pesticides with glyphosate impact the nervous system. [9,10,12] Several studies have associated herbicides containing glyphosate with neurotoxic and neurodegenerative diseases. Notably, there is strong evidence linking the herbicide Roundup (with glyphosate) to a higher likelihood of developing Parkinson's disease [11]. Recently, new research has emerged looking into whether glyphosate exposure can lead to various neurological disorders such as autism spectrum disorder, seizures, and Alzheimer's disease. Additionally, researchers have begun exploring the relationship between

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Vol.20 No.3 sep 2025

glyphosate exposure and alterations in gut and brain microbiota. Findings from this study could provide insights into the gut-brain axis, a possible mechanism through which glyphosate may affect the central nervous system. This review aims to synthesize existing evidence on glyphosates potential to triggers autoimmune diseases, focusing on mechanisms like immune dysregulation, genotoxicity, and molecular mimicry.

Methods: Articles published in Medline/PubMed were searched with the keyword glyphosate, autoimmune disease. The selected papers included reviews, case reports, retrospective reviews and molecular mechanisms.

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Glyphosate: Mechanism of Action and Environmental Exposure

History of global utilization glyphosate

In weed management, glyphosate is an herbicide that is among the many choices today [13]. The historical significance of this herbicide, along with the expansion of genetically modified crops, has completely revolutionized modern agriculture [14]. It was in 1950 that Henri Martin, a Swiss scientist working for Cilag pharmaceuticals company, discovered that it is a phosphonomethyl derivative of the amino acid glycine [15]. A firm from the field was acquired by a chemical distributor specializing in laboratory research in the late 1950s [16]. Roundup, a glyphosate-based herbicide invented by Dr. John Franz at Monsanto, was first marketed by the company in 1974. This further research led to an evaluation of how effective it was in controlling tough Perennial weeds [17]

Production and use of glyphosate have greatly increased since 1996 [16], when the patent expired and genetically engineered glyphosate-resistant crops were introduced. Just in the United States, 2007 saw a record 80,000 tons of the herbicide spread across fields [18, 19]. Asia was a copycat of the US in 2012, with China, India, and Vietnam together accounting for nearly 70% of total production. According to a 2014 report from Transparency Market Research, it represented approximately thirty percent of global pesticides sales. From 308 tons in 2003-2004 to around 2100 tons by 2007-2008, a Ministry of Chemicals and Fertilizers in India report described how the numbers multiplied. By 2010 at the latest, glyphosate had found its way into the whole world and was accepted as the most widely used herbicide. In table 1, further, as global glyphosate production shows

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Vol.20 No.3 sep 2025

continuing expansion [20] shows how much this crop chemical is being used in nonagricultural and agricultural areas worldwide.

Chemical Characteristics

An amphoteric molecule, glyphosate has a carboxylic acid site at one end and a phosphonic acid site at the other. In the middle of the structure the central focus is a secondary amino group. However, glyphosate has a linear carbon base linked by weaker chemical bond [21] than the other herbicides and as a result, this special property also means that it is likely to decay more quickly in nature.

Toxic Effects of Glyphosate

There are essentially two categories of toxicity. One may have immediate harmful effects if they inhale chemicals, receive them on their skin, consume them, or encounter them through other means related to chemical spraying. Conversely, "chronic toxicity" describes the possible harm that could result from ingesting trace levels of poisonous substances over an extended period that is consistent with one's circumstances.[22]according to EPA guidelines for Category IV herbicides, glypho sate's acute LD50 (the lethal dose for 50% of subjects) is around 5037 mg. Herbici des having an LD50 more than 5000 mg/kg are considered less than mildly hazard ous. Does glyphosate actually qualify as a Category IV toxin based on its LD50? [23].

Environmental Exposure

Since an increase in production that was followed closely by its prolific use led directly into the environment for glyphosate. The biological evidence been examined via paper shows that almost no bioaccumulation of glyphosate takes place naturally. This is because the material is easily decomposed by microbial activity and becomes inert in the soil when absorbed there [24,25]. Though tiny amounts may be found in water bodies where it has been applied, its low vapour pressure (1.84 x 10-7 mm Hg) causes little evaporation since it is capped by the equilibrium; or if not then further interaction from environment and keeps relatively stable under them [2]. Also, glyphosates may get to the atmosphere of a place when it is sprayed in a certain condition of weather. This could then harm 'nontarget' vegetation [23].

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ISSN (print): 2706- 6908, ISSN (online): 2706-6894

Vol.20 No.3 sep 2025

Environmental Contamination and Threats

Reports indicate that glyphosate has been detected in various environments, including soil, agricultural products, animals consuming crop products, humans, and freshwater ecosystems [26]. Research suggests that glyphosate and its byproducts can be spread through soil due to water and wind erosion [27]. Interestingly, even dust from non-agricultural homes has shown traces of glyphosate, implying that exposure isn't limited to agricultural workers [28]. Upon breaking down in the environment, glyphosate results in the formation of ammonia with phosphate (AMPA) and carbon dioxide, and it also lowers the water's pH [29]. Typically, glyphosate can remain in the environment for a period ranging from four to one hundred eighty days, posing significant pollution risks to soil and potentially groundwater [30.31]. Multiple experiments have shown that plants treated with glyphosate can absorb over forty-five percent of it available in the soil [32].

While there are some physical methods for reducing glyphosate in the environment, their effectiveness is quite limited. Microorganisms in the soil can break down a significant portion of glyphosate, but this process depends on how much oxygen is available in the soil. Additionally, the efficiency of this degradation can change based on soil properties and the pH levels present [33]. Several researchers have noted that glyphosate has a half-life of approximately 47 days in soil, although this can range from 2 to about 200 days depending on soil type and environmental factors [34, 30, 31]. In aerobic environments, the highest amount of AMPA found in soils can reach around 20% of the glyphosate applied. Conversely, in anaerobic conditions, it is limited to about 5% [35]. Due to its strong binding characteristics, some studies have also found adjuvants like POEA in both soil and sediment [36, 37].

Avoiding the release of glyphosate into the environment is advised because of its persistent harmful impact on marine ecosystems and the health information provided [P273 and H411]. Research was conducted by [38] to examine how glyphosate affects the plant tissues of Lemna minor, commonly known as duckweed. The findings indicated that the introduction of glyphosate led to decreased growth and productivity, slowed down the production of carotenoids, as well as chlorophyll a and b, and impaired the photochemical activities of photosystem II.

Impact of glyphosate on ecosystems

Glyphosate enters freshwater ecosystems through diffusion, oxidation, and adsorption, affecting inorganic clays, organic compounds, and sediments. In these water bodies, sediments serve as the main storage for glyphosate [39]. It is

suggested that glyphosate be utilized as a marine herbicide, managing about 30 to 50 percent of a water body at any point in time [39]. This recommendation is based on the glyphosate's long half-life and its potential to harm marine life. Studies show that glyphosate's half-life in water can vary from 12 days to 10 weeks [39]. Notably, the surfactant known as polyoxymethylene amine (POEA) significantly increases the toxicity of Roundup, impacting many fish and invertebrate species within freshwater habitats [40,41]. The toxicity levels of technical-grade glyphosate range from low to highly toxic, with reported LC50 (Lethal concentration) figures exceeding 55 mg/L and a No observable effect concentration (NOEC) of 100 mg/L after a 21-day period [40,41].

In recent years, [42.43] surface waters have shown traces of glyphosate, even though it was originally used to control aquatic plants [44]. It is well known that glyphosate's potential to pollute surface waters is relatively low. Although its method of action targets only plants, various studies from the past few years have shown harmful effects on non-target animals [45]. To help lower glyphosate levels, Limnoperna fortunei has been included in commercially available products. However, reducing glyphosate can lead to increased levels of P-PO4 3- and N–NH4 +. This change may cause eutrophication in natural aquatic environments if glyphosate levels decrease significantly. [46,47]

Potential Mechanisms Linking Glyphosate to Autoimmunity

Multiple Sclerosis (MS)

In addition to MS sugar beet, sugar derived from beets makes up thirty percent of the global sugar supply. However, sugar beets require milder temperatures for growth, while sugarcanethrives in warmer tropical regions. The highest rates of multiple sclerosis (MS) can be found in areas where beet sugar is primarily produced, including the United States, Canada, and western Europe [48]. Consequently, the prevalence of MS is higher in the northern U.S. states than in the southern ones due to the expansion of sugar beet farming. In Canada, Alberta's prairie region, a hub for sugar beet production, holds the record for the country's highest MS occurrence. Studies on migrants show that those who move from areas of lower MS risk to higher risk [49, 50] regions tend to adopt lifestyles that increase their risk, especially if the relocation happens during their childhood. This suggests that local environmental factors prior to adolescence play a role. Interestingly, although only 0.3% of Japan's population [51] resides in Tokachi province, it produces a remarkable 45% of the nation's sugar beets. Additionally, this province exhibits the highest multiple sclerosis rates among all Asian populations [52]. There is also a fascinating theory regarding Aze, a unique noncoding amino acid made by sugar beets. An interesting theory suggests that sugar beets may be linked to the

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Vol.20 No.3 sep 2025

onset of multiple sclerosis. Both proline and Aze share an uncommon amino acid structure. The side chain in these amino acids loops back to connect with the nitrogen atom, which is a distinctive feature of both. Aze's ring contains three carbon atoms, unlike proline, which has four. Experimental studies indicate that Aze can mistakenly replace proline in proteins [53]. Myelin basic protein, or MBP, interacts with actin, tubulin, calmodulin, and SH3 domains [54]. This protein is vital for maintaining the myelin sheath. Its functions include assembling actin filaments and microtubules, anchoring actin filaments and SH3 domains to membranes, and engaging in signal transduction within oligodendrocytes and the myelin sheath. A significant region within MBP is rich in proline, which plays a crucial role [55,56]. Specifically, this area acts as a binding site for Fyn-SH3, an important regulatory protein [57]. [58] Research indicates that changes in proline reduce the affinity of the SH3 ligand for the Fyn-SH3 domain. Fyn, located in the cytoplasmic side of the oligodendrocyte plasma membrane, is involved in various signaling pathways essential for central nervous system development [59,60]. Phosphorylation at a polyproline structure in the Fyn-binding area affects MBP's structure.

Anxiety is raised about Aze, because more than 90% of sugar beets grown in the U.S. and Canada are now genetically engineered to withstand herbicides. For these beets, greater access to glyphosate is inevitable. Dried sugar beet pulp is permitted to have residues of glyphosate at up to 25 parts per million (ppm) by the electronic Code of Federal Regulations (e-CFR) 180.364 Glyphosate; Tolerances for Residues. In 1999, Monsanto determined that the moisture of digested glucose, genetically engineered with its own Roundup Ready corn and herbicides, surpassed federal Environmental Protection Agency (EPA) maximums by a wide margin. They requested an increase in the upper limit for dry beet pulp from 0.2 to 25 parts per million, an amount 125 times greater. Simultaneously the standard for fresh beets was increased to 10 parts per million, or fiftyfold more.

Additional Autoimmune Conditions Glyphosate and Neuroinflammation

Neuromyelitis Optica and aquaporin

Neuromyelitis optica spectrum disorder (NMOSD) is a rare and severe inflammatory demyelinating disease of the central nervous system that primarily affects the optic nerve and spinal cord. It shares some similarities with multiple sclerosis yet differs in some of its key clinical and pathological features. The chief complaints of patients with neuromyelitis optica are paralysis and injury to the optic nerve [61,62]. The target of autoimmunity in NMO-IgG-seropositive patients

University of Thi-Qar Journal

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Vol.20 No.3 sep 2025

has been conclusively identified as aquaporin-4, which is abundantly expressed on the astrocyte membrane [61,62]. Aquaporins are proteins that play an essential role in the membrane, allowing water molecules to move freely into the cell through their holes while keeping protons from flowing freely in [63]. Therefore, astrocytes make a significant portion of their birth, and one of their main functions is to help the transport of water within the blood-brain barrier to the lymphatic system, where it can be eliminated. Aquaporins have in addition been implicated in the genesis of cerebral edema [64]. A possible explanation for the start of autoimmune sensitivity [65], to this protein could be the similarity between human and plant aquaporins. Plants produce aquaporins as well. Corn, soy, tomato; tobacco and spinach are but a few plants that have been shown to demonstrate aquaporin mimicry [66]. It has been found that multiple sclerosis was associated with an autoimmune sensitivity to aquaporin [66].

Impacts on Human Immune System

Genotoxicity

For a long period, scientists have been studying how glyphosate, its metabolites, and glyphosate-based herbicides (GBHs) can affect the genetic material of human lymphocytes and peripheral blood mononuclear cells (PBMCs). An initial finding by [67] indicated that cells cultured with RoundUpR experienced an increase in sister-chromatid exchanges. The impact of glyphosate on chromosome changes in lymphocytes has been debated since [68, 69] found no effect, while [70] reported a rise based on dosage. It became clear that AMPA led to more chromosomal irregularities in lymphocytes. Furthermore, Santovito and his team observed more micronuclei forming in lymphocytes exposed to low levels of glyphosate. In contrast, [71] could only achieve this outcome with much larger amounts of the substance.

Furthermore, lymphocytes grown with greater amounts of glyphosate showed signs of DNA damage in Comet assays, along with an increase in cell death and programmed cell death when they faced high levels of the substance. Conversely, no evidence of DNA base oxidation was found [72]. In lymphocytes, non-toxic levels of glyphosate caused double-strand breaks and the activation of Ku80, whereas AMPA did not. The Ku80 protein plays a role in a DNA repair method called non-homologous end joining, which can result in mistakes. Consequently, the authors expressed concern that ongoing exposure might lead to the development of lymphoma or leukemia [73].

University of Thi-Qar Journal

ISSN (print): 2706- 6908, ISSN (online): 2706-6894

Vol.20 No.3 sep 2025

Except for the highest dose of 'Roundup R', single-strand breaks in PBMCs caused by AMPA, glyphosate, and Roundup Var were repaired within 2 hours. In contrast, both Roundup Var and elevated levels of glyphosate resulted in double-strand breaks [74,75]. The promoter methylation levels of p53, a tumor suppressor gene, increased, while those of p21 decreased, altering their expression [74,75]. Moreover, the Wozniak study reported a rise in the expression of the proto-oncogene Bcl2 and cyclin D (CCDN1), which was linked to a reduction in the expression of the CCDN1 inhibitor, p16. There were no significant changes in methylation levels for these occurrences. Lastly, glyphosate seems capable of altering DNA methylation in PBMCs, thereby influencing the expression of proto-oncogenes, genes related to the cell cycle, and tumor suppressor genes [76].

Genotoxicity Findings: Contradictory Evidence

Evidence for Genotoxicity: Multiple studies report that both pure glyphosate and glyphosate-based herbicides (GBHs) can induce genetic damage (e.g., DNA strand breaks, chromosome aberrations) in vitro and in animal cells, particularly when formulations include certain adjuvants. Comet assays and other DNA damage tests in human lymphocytes show dose-dependent genotoxicity, with commercial formulations often more potent than glyphosate alone[77[.

Evidence Against Genotoxicity: Other research, including various regulatory agency reviews, finds no compelling evidence of genotoxicity for glyphosate at environmentally relevant exposures, especially in animal models. Some comprehensive assays (ToxTracker, micronucleus assay) in mammalian cells find no genotoxicity for glyphosate itself, though some GBH formulations may be cytotoxic and genotoxic due to added adjuvants, not the glyphosate[78,79].

Nature of the Conflict: The contradictory findings are attributed to differences in experimental design—test systems (human vs. animal cells), exposure conditions (acute vs. chronic, high vs. low dose), and whether pure glyphosate or commercial GBHs are assessed. Positive studies are often criticized for using unrealistically high doses or for not clearly distinguishing active ingredient effects from those of other product components [80,81]

Limitations Noted:

Translational Gaps: Animal models may not accurately predict human outcomes due to differences in metabolism, immune responses, and exposure routes. For example, rodents metabolize glyphosate differently from humans, possibly leading to different genotoxic or immune effects[80].

Exposure Levels: Many animal studies use doses/orders of magnitude higher than typical human exposures, limiting real-world relevance. Actual environmental exposures are typically much lower.

Endpoints and Relevance: Animal studies often focus on acute exposures, cancer endpoints, or indirect immune markers, not direct measures of autoimmune disease. Regulatory bodies frequently conclude that results in

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Vol.20 No.3 sep 2025

animal models do not support carcinogenic or autoimmune risk in humans at real-life exposure level [82].

Inflammatory Disorders

Research indicates that people who have come into contact with glyphosate and glyphosate-based herbicides (GBHs) are more likely to develop inflammation-related diseases. [83]One particular study highlighted a woman who experienced acute eosinophilic pneumonia on two separate occasions, both occurring just weeks after she was exposed to Roundup. This happened during a period of four years. Although she smoked, the researchers believed that herbicide may have been responsible for her health issues. Another epidemiological study [84,85] revealed a link between GBH exposure and the onset of both allergic and non-allergic wheezing in male farmers, as well as atopic asthma in female farmers.

This applies equally to both male and female farmers. Based on the findings of the studies, it was concluded that breathing in GBH for long periods could over time cause different kinds of inflammation in the airways. Additionally, a review indicated that regularly consuming GBHs, particularly RoundUp R, could pose a risk for developing endometriosis. This connection was highlighted in the review because the development of this chronic inflammatory condition is linked to oxidative stress and issues with the estrogen pathway [86]. These two factors are crucial in this context. Considering the observations made so far, it suggests that exposure to GBH might influence the onset of inflammatory syndromes in people, whether those syndromes are short-term or long-term.

Harm to The Kidneys

Based on the results from tests with glyphosate on rats and mice by Monsanto [87,88], we can categorize the different types of kidney damage that indicate renal disease. In the research, most of the kidney issues seen in male mice are associated with chronic progressive neuropathy; however, some female mice from both the control and treatment groups showed similar issues. Additionally, signs of mineralization and mineralized debris appeared in the pelvic epithelium of the kidneys, primarily affecting the female subjects. After the study was submitted, the Environmental Protection Agency (EPA) asked Monsanto to re-examine the histology of the male mice that had received low and mid-level doses of glyphosate. This led to determining the 'no observable effect level' (NOEL)[89,90].

University of Thi-Qar Journal

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Vol.20 No.3 sep 2025

Cancerigenicity

A lengthy investigation carried out by Bio/dynamics over 26 months uncovered numerous tumors in the glands and organs of rats [87]. The effects of organs included the pituitary gland, thyroid, thymus, mammary glands, testes, kidneys, pancreas, liver, and lungs. The frequency of these tumors varied greatly. When the pituitary, thyroid, and thymus glands, which play crucial roles in regulating the body and immune system, are disrupted, it can result in several health issues like cancer. These glands produce many vital hormones that influence a range of biological processes. Additionally, the emergence of tumors can hinder the normal operations of the glands and organs where they develop. A confidential document from Monsanto [87] indicated a significant presence of C-cell thyroid tumors alongside a notable increase in lymphocytic hyperplasia in the thymus. Thymus lymphoid hyperplasia, commonly linked to Graves' disease, often appears in CT scans of patients with thyroid cancer [91]. Moreover, conditions such as myasthenia gravis, lupus erythematosus, scleroderma, and rheumatoid arthritis have been connected to thymus hyperplasia [92].

The Infiltration of Glyphosate into The Brain Leads to Increase the Inflammatory Cytokine TNFα.

TNFα is an inflammatory cytokine released primarily by macrophages and monocytes throughout the body. Macrophages and monocytes are vital immune cells that can be activated in response to cytokines, bacterial lipopolysaccharide, extracellular matrix proteins, and other chemicals In the central nervous system (CNS), TNFα is largely produced by microglia (the macrophages of the CNS). However, astrocytes have also been shown to produce TNFα, which is consistent with their involvement in modulating the neuroimmune response. Aberrant TNFα signaling has been implicated in numerous pathological conditions including cancer, rheumatoid arthritis, psoriasis, multiple sclerosis, as well as immune, inflammatory, and neurodegenerative diseases like Alzheimer's disease (AD). In the healthy brain, TNFα expression is low in adulthood, while in contrast, adult neurodegenerative. diseased brains show very high levels of TNFα. Neuroinflammation plays a central role in AD pathogenesis and TNFα specifically has been strongly implicated in the progression of AD. The TNFα death domain pathway is progressively activated in the AD brain and contributes to cellular degeneration. Interestingly, TNFα inhibition has been shown to reduce generation of monomeric Aβ in a murine model of AD and TNFα inhibitors produce sustained clinical improvement in patients with AD.

We exist in a world where herbicides are commonly used [93]. Since the introduction of glyphosate-tolerant crops in 1996, glyphosate has become the most

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Vol.20 No.3 sep 2025

utilized herbicide worldwide (N-(phosphonomethyl) glycine) [94]. In the United States, approximately 113 million kg of glyphosate is applied each year for farming [95]. This herbicide works by targeting weeds and unwanted plants, effectively blocking an enzyme in the shikimate pathway known as enolpyruvylshikimate-3-phosphate synthase (EPSPS). A critical part of this process is the interruption of aromatic amino acid production, which is vital for plant growth [95]. Recent studies indicate that glyphosate could pose risks to human health [96, 97], calling for deeper inquiries into this issue. Although the United States Environmental Protection Agency (EPA) and the European Food Safety Authority (EFSA) currently consider glyphosate safe, there is a pressing need for further exploration of its effects. While much research has focused on the immediate impacts of herbicides, their long-term effects remain less understood [98]. Although laboratory studies have shown that glyphosate can cross the blood-brain barrier, there is insufficient data from studies involving human brains. Therefore, caution is advised in this matter [99,100].

When adult rats are exposed to herbicides with glyphosate at doses ranging from 0.05 to 250 mg/kg, it can lead to inflammation throughout the body [101]. Following this exposure, the liver shows increased levels of C-reactive protein (CRP) and other cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor alpha (TNFα) [101]. Studies have confirmed that glyphosate raises TNFα levels in the peripheral blood [101, 102]. TNFα, an inflammatory cytokine, is released by monocytes and macrophages found throughout the body [103]. Activation of macrophages and monocytes, which are critical immune cells, can occur due to various stimuli, including cytokines, bacterial lipopolysaccharides, and extracellular matrix proteins [104]. These immune cells are closely associated with the immune system. In the central nervous system (CNS), microglia, which are the macrophages of this area, are primarily responsible for producing TNFα [105].

In contrast, studies indicate that astrocytes are capable of producing TNFα, which aligns with their role in regulating the neuroimmune response [106]. Abnormal TNFα signaling has been associated with various medical conditions, including cancer, rheumatoid arthritis, psoriasis, multiple sclerosis, and several neurological and inflammatory disorders, particularly Alzheimer's disease (AD) [107, 108]. Reference 108 notes that a healthy adult's brain normally displays low levels of TNFα expression. Conversely, individuals with neurodegenerative diseases exhibit significantly elevated TNFα levels in their brains [110]. Neuroinflammation plays a crucial role in the progression of Alzheimer's disease (AD) [109], with tumor necrosis factor alpha (TNFα) being closely linked to the advancement of this condition [110]. People with Alzheimer's disease experience a gradual activation of the TNFα death domain

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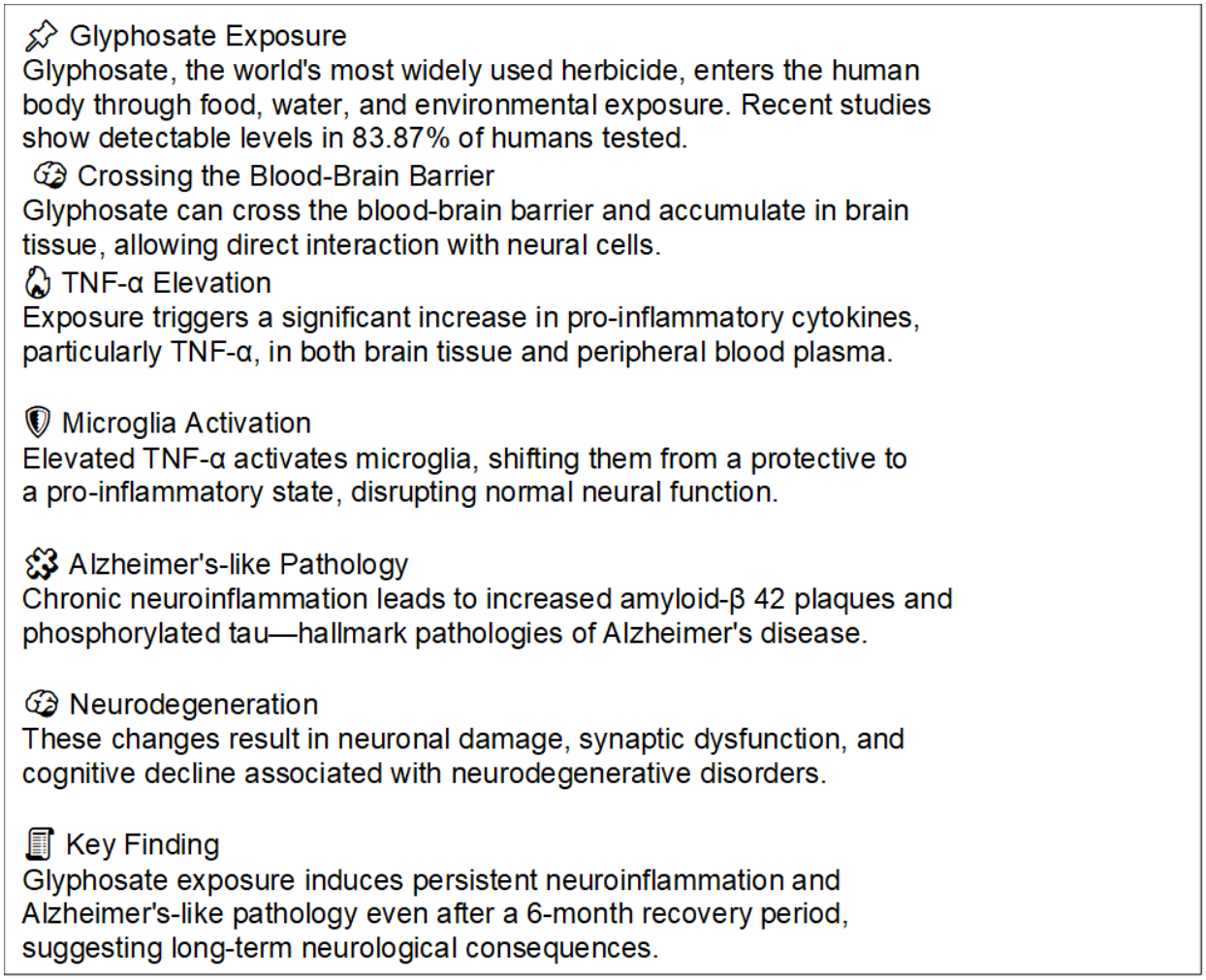
Vol.20 No.3 sep 2025

pathway in their brains, which leads to cell damage [16]. Studies have demonstrated that inhibiting TNFα can decrease the formation of monomeric Aβ in mouse models of Alzheimer's disease (AD) [111]. Furthermore, research has found that TNFα inhibitors can lead to significant and lasting improvements in the clinical status of patients with Alzheimer's disease [112].

This Flow Chart Highlights Glyphosate Exposure and Neuroinflammatory Disorders



University of Thi-Qar Journal

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Vol.20 No.3 sep 2025

Concluding Remark

Glyphosate's Potential to Disrupt Immune Function via **Elevated TNF-α Production:** Multiple studies demonstrate that glyphosate exposure can increase the levels of tumor necrosis factor alpha (TNF-α), a central pro-inflammatory cytokine in both blood and brain tissue. This elevation has been observed in animal models, cell cultures, and human cell lines, and occurs in a dose-dependent manner. Mechanistic Implications: TNF-α is primarily produced by activated macrophages and monocytes in the immune system and by microglia and astrocytes in the central nervous system. Overexpression of TNF-α is implicated in various immune and neurodegenerative diseases, including Alzheimer's disease, by promoting neuroinflammation, demyelination, and mitochondrial dysfunction. Aquaporin Mimicry and Molecular Autoimmunity, **Molecular Mimicry:** There is emerging evidence suggesting that glyphosate may act as a non-coding amino acid analog of glycine, leading to its erroneous incorporation into proteins during synthesis. This can create neoantigens or defective proteins that are not properly degraded and that resemble normal human proteins such as aquaporins—water channel proteins present in many tissues this molecular mimicry could theoretically trigger an immune response against self-aquaporins, potentially leading to the development of autoantibodies and promoting autoimmune diseases. Similar mechanisms have been proposed for other environmental peptides and analogs that are associated with autoimmune disorders.

Myriads of limitations noticed through this review one of them is lack of longitudinal human diseases). Several questions remained to be answered via research actions (e.g., strict glyphosate regulation, studies on auto immune biomarkers in exposed population). While glyphosate carcinogenic and neurotoxic effects are documented ,its role in auto immune disease remains unstudied, particularly regarding mechanism like molecular mimicry and chronic inflammation.

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Vol.20 No.3 sep 2025

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