The Indiscriminate Use of Pesticides could Increase the Prevalence of Alzheimer's Disease? A Systematic Review

ABSTRACT

Aims: This review aims to perform an extensive literature search about the pesticides problems and to associate with AD in qualitative analysis, mainly.
Place and Duration of Study: Biomathematics Laboratory, Institute of Biomedical Sciences, Federal University of Alfenas, Alfenas, Brazil. Entre outubro de 2023 a abril de 2024.
Methodology: For the purpose of this systematic review, articles from 2014 onwards with the descriptors Alzheimer's disease and pesticides; neurodegenerative diseases and pesticides, were sought. Among these, articles considered most pertinent to the objective of the present review were utilized, i.e., those whose subject matter was associated with the effects of pesticides, especially glyphosate, on dementias, particularly Alzheimer's disease (AD).
Results: After analyzed 35,590 articles, and applying exclusion criteria to journals with an impact factor equal to or lower than 4 and including topics most relevant to the objectives of this work, 35,526 articles were excluded, resulting in 64 remaining articles, of which 40were qualitative in scope and 24 were quantitative. The articles considered most suitable for the objective of the present review were utilized, i.e., those whose topic was associated with the effects of pesticides, especially glyphosate, on dementia. The criteria for scrutinizing articles included a journal impact factor equal to or greater than 4 and the removal of duplicate articles using the freely accessible EndNote program from Web of Science. Articles and books on history and those outside the scope of the pesticide/AD relationship did not follow the criterion of having an impact factor equal to or greater than 4.
Conclusion: There appears to be a relationship between the increase in pesticide use, particularly Glyphosate, and the rise in Alzheimer's disease prevalence.

Keywords: Dementia; Alzheimer's disease; pesticides; agrochemicals.

1. INTRODUCTION

1.1 Pesticides

Agrochemicals, pesticides, chemical or agricultural pesticides are synonymous terms referring to substances used in agriculture for the management of agricultural pests. The nomenclature of agrochemicals highlights their toxicity to the environment, humans, and animals [1].

The advent of agriculture as a commercial enterprise trace back to the 16th century [2], propelled by the burgeoning global population and urban density, which precipitated a concurrent demand for increased food supply.

By 2025, there will be an estimated 8.4 billion people dependent on food sourced from rural areas [3], exerting pressure for increased agricultural productivity in technological and organizational terms. This necessitates efforts to mitigate losses from the field to the final consumer, with pesticide usage remaining indispensable [4].

Historically, pesticides were developed and refined in the 20th century by the chemical industry to be used as weapons in World War II [1], particularly in Germany, where scientist Fritz Haber, Nobel Prize winner in 1918 for the synthesis of ammonia from its elements [5], served as a mentor for ammonia production. However, with the end of the war, the chemical weapons industry transformed into the industry of fertilizers and agricultural pesticides [1,4].

In post-war Europe, food poverty prevailed due to the scarcity of food resulting from the destruction of farmlands and pastures, as well as the lack of labor [2]. The "green revolution" was proposed in the 1950s to expand agricultural production in the old continent. However, in Brazil, the encouragement of agriculture arrived in the mid-1960s, as the country did not suffer the consequences of the war on its territory and supplied/exported foods to the European continent [1,4]. Nevertheless, greater agricultural production was deemed necessary to stimulate the economy and foster economic growth [2]. The agrochemical industry was favored by the Brazilian government, which instituted bank financing for the purchase of seeds associated with fertilizers and pesticides [1].

Notwithstanding the significance of pesticides for crop cultivation and food production to sustain the population, human and animal health may be at risk, as various types of pathologies related to the effects of pesticides have been observed [2].

These include an increase in the number of cases of neurological diseases, psychiatric disorders, memory-related disturbances, attention deficits [6,7], and cancer [8].

Indeed, pesticides are substances employed to control and mitigate pests [9], applied in activities targeting fungi, insects, vegetation along roads, gardens, parks, water systems [10], and in agriculture, where pesticide usage stands as the primary source of environmental contamination [11,12].

Among the pesticides used worldwide, glyphosate (N-phosphonomethylglycine) stands as the most consumed. It is an organophosphorus compound derived from glycine and utilized as a non-selective herbicide [13]. Its mechanism of action involves targeting the shikimic acid pathway, inhibiting the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) enzyme responsible for synthesizing phenylalanine, tyrosine, and tryptophan, essential aromatic amino acids for plant survival [12,14], but not produced in animals [15,16].

The herbicidal action of glyphosate was utilized in the formulation of the globally renowned product Roundup®, introduced to the market by the Monsanto Company starting in 1974 [17,18]. It remains one of the most widely used herbicides worldwide [19,20], because that, at least hypothetically, if glyphosate generate health problems it is plausible to conclude that other ones will generate the same since glyphosate is considered less toxic of the used pesticides. Glyphosate is recommended for crops such as soybeans, coffee, sugarcane, citrus fruits, and rice and exhibits persistence in the environment, as it has been detected in both groundwater [21] and surface water [22] long after its application.

Despite being considered a pesticide with low toxicity, both environmentally and for human and animal health, among those available on the market [23], studies have suggested that glyphosate may cause chronic malformations in certain animal species, such as chickens, frogs, and mammals [24,25].

In this regard, the use of glyphosate raises concerns for human and animal health, as it is an environmental contaminant of water, soil, and animals [26]. Furthermore, the extensive application of this pesticide may render organisms capable of developing resistance against other non-selective herbicides [15].

Chronic exposure to Roundup® has been shown to cause human erythrocyte lysis [11] and high genotoxicity in bone marrow cells of Swiss mice [27] within concentrations recommended by the manufacturer. In 2015, the International Agency for Research on Cancer (IARC) [8] concluded that there is strong evidence indicating glyphosate may cause cancer, as pesticides in general [28].

Usually, organophosphates exhibit higher acute toxicity in humans and other mammals [29] compared to organochlorines, that affects neural development and behavior [30] and could increase the dementia risk [31-34]. Several organophosphates pose health risks to workers who apply them and individuals who may come into contact with these pesticides. Intoxication by these substances can occur through exposure to the products via inhalation, ingestion, or absorption through the skin [14].

The dispersion of these pesticides in agriculture occurs through spraying, and due to wind effects, can spread over areas of 1 km to 2 km. Aquatic environments are contaminated through three pathways: I) discharge of industrial waste or effluent discharge into water; II) infiltration of toxic residues into the soil, contaminating water sources; III) surface runoff during product application on the soil [14].

Other studies have indicated that chronic exposure to glyphosate may lead to neurodegenerative disorders, such as Alzheimer's (AD) [28] and Parkinson's diseases [7,35], as well as a decrease in serotonin, norepinephrine, and dopamine levels in the prefrontal cortex, hypothalamus, and hippocampus of rodents [36], which could impair learning and memory processes [37].

1.2 Alzheimer’s Disease

Expenditures on dementia-related care surpass those on prevention efforts, and these diseases not only cause suffering to patients, their families, and caregivers but also necessitate substantial social care. Hence, prevention measures are crucial. It appears that governmental concern regarding Alzheimer's disease (the most prevalent form of dementia) [38], at least in the United States, is diminishing, thereby shifting more responsibility and financial burden onto families [39].

Alzheimer's disease (AD), initially discovered by the German psychiatrist Alois Alzheimer [40] in

1906, is the leading cause of senile dementia, characterized by heterogeneous neurodegenerative effects. It lacks a definitive lifelong diagnosis, and among its various causes, AD is linked to both environmental [41] and genetic factors [38].

Several studies have associated Alzheimer's disease with aging [38], primarily because the majority (approximately 90% of cases) [42] of AD occurs in individuals aged 65 and older. Its prevalence doubles every 5 years, leading to an exponential increase dependent on time [38,43].

Due to its neurodegenerative effects, Alzheimer's disease results in decreased cognition, such as speech impairment, praxis difficulties, memory loss, impaired judgment, and emotional instability, along with personality changes. It involves progressive neuronal loss, increased senile plaques, and neurofibrillary tangles [38], leading to the destruction of neural networks and evident hippocampal atrophy [40].

1.3 AD and Pesticides

Recent research indicates that neurodegenerative diseases have increased in prevalence in recent years [44,45] due to pesticides effects [46-48]. Specifically, the etiology of Alzheimer's disease remains unclear and the role of the environment as a probable risk factor is significant [38,49-51], nevertheless, some new treatments has been suggested for this affection, at least *in vitro* [52-55]. Of particular concern is the evidence suggesting that prenatal and postnatal exposures to harmful environmental factors predispose individuals to neurodegenerative diseases later in life [56].

In the context of associating pesticide effects with Alzheimer's disease prevalence, exposure of both animals and humans to these substances has been linked to Alzheimer's disease [57] due to their ability to increase beta-amyloid peptide (A-β) [50,51] and protein Tau phosphorylation (P-Tau) [7]. These compounds contribute to the formation of senile/amyloid plaques and neurofibrillary tangles (NFTs), which are common in Alzheimer's disease.

Moreover, epigenetic mechanisms involving maternal nutrient complementation and exposure to metals and pesticides have been proposed to elevate phenotypic diversity and susceptibility to neurodegenerative diseases [35].

One possible cause of the increased prevalence of Alzheimer's disease is that even "mild" environmental factors (such as behavioral or physical stress) and exposure below the recommended limit to pollutants and chemicals, such as pesticides, can elevate the risk of Alzheimer's disease [58].

Considering the current use of pesticides, particularly glyphosate, which has been approved in Brazil without efficient toxicological/environmental analysis by public agencies and environmental assessments via presidential decree [59], it is reasonable to hypothesize that there may be a relationship between the increased use or concentration of pesticides (glyphosate) and the rise in the prevalence of AD.

Therefore, the objective of this study was performing an extensive literature search about the pesticides problems and to associate with AD in qualitative analysis, mainly.

2. MATERIALS AND METHODS

For the purpose of this systematic review, articles from 2014 onwards with the descriptors Alzheimer's disease and pesticides; neurodegenerative diseases and pesticides, were initially searched on the CAPES journals platform, which includes the Web of Science, Scopus, MedLine, PubMed, PubMed Central, Elsevier ScienceDirect Journals, Directory of Open Access Journals, and Google Scholar. This search was conducted during the month of April 2024 to form the epistemological basis of the review, resulting in a total of 35,590 articles.

From these, articles considered most suitable for the objective of the present review were utilized, i.e., those whose topic was associated with the effects of pesticides on dementia, particularly Alzheimer's disease (AD). The criteria for scrutinizing articles included a journal impact factor equal to or greater than 4, firstly, however, other articles with impact factor minor than 4 were used due the importance for the theme, and the removal of duplicate articles using the freely accessible EndNote program from Web of Science. Articles and books on history and those outside the scope of the pesticide/AD relationship did not follow the criterion of having an impact factor equal to or greater than 4. The impact equal or greater than 4 was chosen because the high number of papers, however other considered important articles for this subject were used with impact minor than 4.

Based on this analysis and considering topics closer to the objective of this work, the exclusion

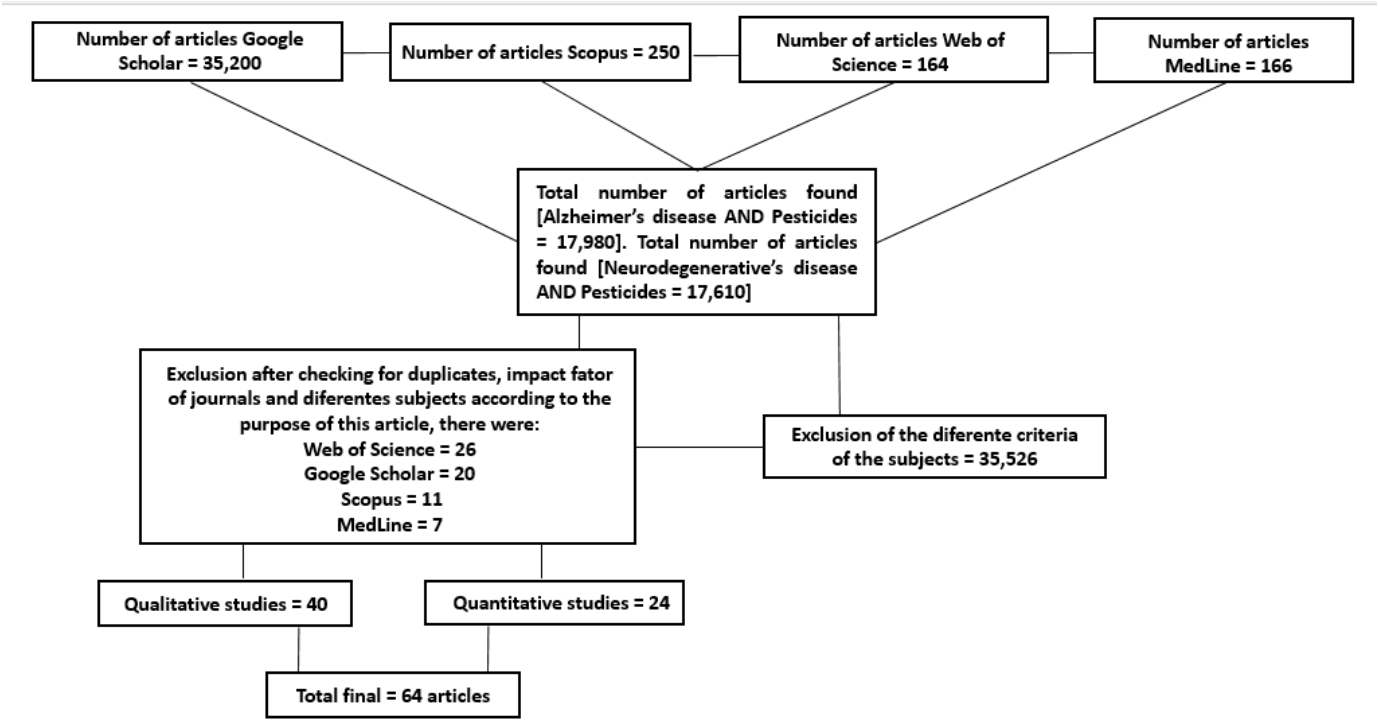
criteria were a journal impact factor lower than 4 and duplicates within the keywords pesticides and dementia (31); pesticides and Alzheimer's disease (28); glyphosate and dementia (5), resulting in 20 articles derived from Google Scholar, 26 from Web of Science, 11 from Scopus, and 7 from MedLine (Graphic 1).

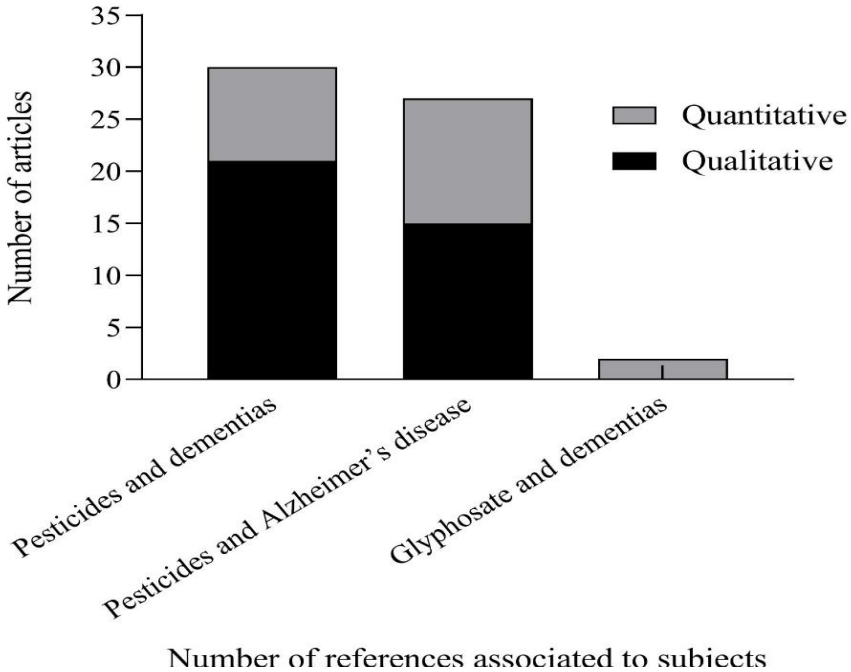
3. RESULTS AND DISCUSSION

3.1 Results

Of the initially analyzed 35,590 articles, after applying exclusion criteria to journals with an impact factor equal to or lower than 4 and including topics most relevant to the objectives of this work, 35,526 articles were excluded, resulting in 64 remaining articles, of which 40were qualitative in scope and 24 were quantitative, as shown in Graphic 1. The exclusion criteria flowchart is presented in Fig 1.

Fig. 1. Diagram of inclusion and exclusion criteria for the articles used in this study





Graphic 1. Association between article identification and its subjects

Graphic 1 associates the identification data of the articles according to the reference system, the themes derived from the keywords and the qualitative and quantitative aspects of the 64 articles after scrutiny.

According to the literature data observed in this article, the relationship between the prevalence of pesticide-related dementia was shown in 40 journal articles derived from qualitative data and 24 from quantitative data with an impact factor greater than 4. The topic of pesticides and dementia (31/64) was the most frequently encountered in the search within this scope.

The lowest number of topics found was for glyphosate and dementia (5/64), indicating that, despite the general concern regarding the association between pesticides and dementia, the effects of glyphosate appear to be underestimated (Fig. 2). This notion is reinforced by the fact that the topic of pesticides and AD (28/64) was the second most frequently encountered for the purpose of this study. In this regard, the data itself justifies the relationship between the most widely used pesticide in the world and one of the dementias affecting the elderly population with high prevalence [40].

The articles that served as the theoretical epistemological basis for this work were chosen to provide more specific and relevant data for the construction of the article. Some of these articles present quantitative data on the effects of glyphosate on erythrocyte osmotic fragility occurring within concentrations recommended by the manufacturer [12,18], as well as aspects that directly associate theories of aging with AD [38,39].

3.2 Pesticides, AD and Environment

As the general population ages, the duration of contact with environmental agents [38], particularly pesticides, increases, contributing to the development of dementia. Therefore, in the impossibility of preventing aging progression, and for the entire population in general, preventive measures are necessary to avoid health risks, especially within the hypothesis that pesticides cause AD, which appears to be the case [35,38] (Graphic 1, Fig 2).

In general, neurodegenerative problems have both familial (genetic) and environmental origins [39,60,61], but they are primarily associated with environmental factors [44,62]. If we combine this information with the increasing global population age [38], it is obvious that the duration of human exposure to degenerative environmental factors will also increase.

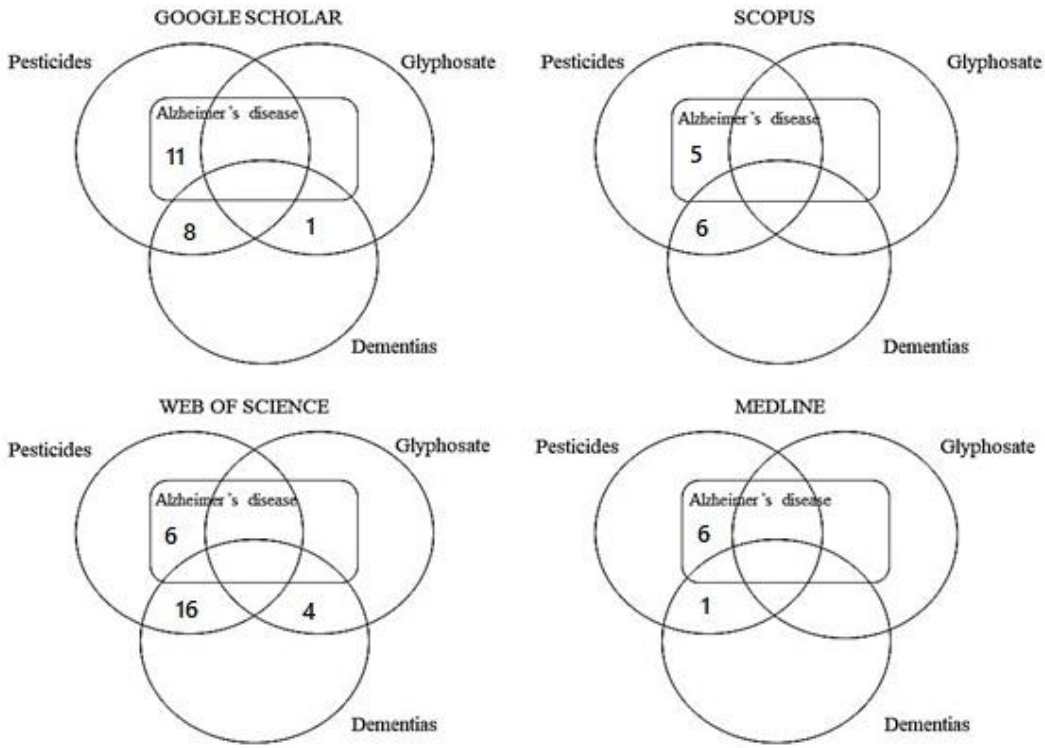


Fig. 2. Venn diagram of articles found in google scholar, Scopus, web of science, and MedLine after considering the exclusion and inclusion criteria

Current scientific studies have raised the hypothesis that exposure to environmental factors may increase the prospective risk of neural system diseases [63,64]. Indeed, variables as genetic elements [65], neurodegenerative disorders can be sporadic in nature and are generally influenced by a range of environmental factors [66,67] and lifestyle [38,68].

Environmental factors can play a crucial role in slowing down or accelerating the progression of AD [38], with prolonged exposure to various heavy metals such as aluminum, lead, and mercury; pesticides; and metal-containing nanoparticles standing out as particularly significant [53,69,70].

The link between pesticide residues and AD is not clear and is difficult to establish [71]. However, studies conducted with mice have investigated the effects of pesticide residues on pathological markers of AD, revealing that serum concentrations of pesticides in the blood strengthened pre-existing pathological markers [11,72,73].

Dementia tends to increase in prevalence with advancing age [38] due to neuronal deterioration caused primarily by circulatory factors, which transport toxins and may decrease the supply of oxygen and nutrients to tissues [39]. In this regard, the increased erythrocyte fragility induced by glyphosate suggests decreased oxygen pressure in individuals, with repercussions on neural tissue [11,18] and those with higher metabolic rates.

Indeed, pesticides adversely affect human health [71], as environmental toxins have been implicated in neurodegenerative diseases, and pesticide exposure is a suspected environmental risk factor for AD [74], particularly because epidemiological analyses confirm the existence of a link between pesticides and the incidence of sporadic AD [75]. Elevated serum levels of pesticides are associated with an increased risk of AD [76]. Pesticides, especially glyphosate, elevate levels of the β-amyloid precursor protein, providing plausibility for the association of pesticide exposure with AD [77,78].

3.3 Pesticides Actions on AD

The action of pesticides on the neural system increases the concentration of β-amyloid peptide (Aβ) along with the hyperphosphorylation of Tau protein, both persistent pathological markers in AD, forming senile plaques and neurofibrillary tangles that involve neural system cells, resulting in neuronal death [79,80,81]. In addition to the inhibition caused in the acetylcholinesterase enzyme, organophosphate pesticides can also cause disruptions in microtubules, another characteristic evidenced in AD [82-84]. This association is important for public health, given the increasing prevalence of dementia and the increasingly common use of pesticides [71].

The mechanism of acute toxicity of pesticides such as glyphosate in target and non-target organisms is mainly attributed to inhibitory actions on various forms of cholinesterase, leading to excessive peripheral and central cholinergic activities [63,85]. Cholinesterase is classified into two types: acetylcholinesterase and pseudocholinesterase [64]. Acetylcholinesterase is synthesized in nervous tissue, skeletal muscles, and the liver, and plays an indispensable role in the destruction of acetylcholine at nerve synapses. Pseudocholinesterase, or nonspecific butyrylcholinesterase, is produced in various organs such as the liver, pancreas, small intestine, and in lower concentrations, the central and peripheral nervous systems [63,64].

Recent findings indicate that pre- and post-transcriptional mechanisms controlling AChE signaling coordinate the identity, functioning, dynamics, and communication between the brain and the body, allowing for the homeostatic maintenance of ACh signaling between the brain and body [86-89].

The main action of organophosphates, a class to which glyphosate belongs, involves the inhibition of the enzyme acetylcholinesterase (AChE) and various molecular targets such as hormones, neurotransmitters, neurotrophic factors, enzymes related to the metabolism of β-amyloid protein, and inflammatory changes [85,90], in general, could increases neuropsychiatric conditions [91].

Neuronal death is directly linked to dementia, which occurs in AD mainly in areas where the neurotransmitter is acetylcholine [39,92,88,89]; glyphosate alters the level of neurotransmitters in the cortex, hypothalamus, and hippocampus [37], reducing cognitive and mnemonic processes [38], and in the peripartum, affects maternal brain plasticity and behavior [93].

In this scope, if glyphosate is the most widely used pesticide worldwide [14], the population will be more susceptible to experiencing its effects in the environment [94], which persist with this substance in biogeochemical cycles such as in soils, springs [22,95], surfaces [23], air [83], and directly or indirectly in plant-origin foods or animal-origin foods [27,96].

Assuming the data from studies so far indicating that pesticides is toxic to the neural system, which is strongly suggested considering here the experimental research and less speculative studies, it is reasonable to indicate that exposure to it should be avoided as a way to prevent AD and dementia in general. AD, due to the strong environmental aspect associated with its prevalence, should be viewed with greater concern. Therefore, it can be said that there should be a relationship between the increase in the use or concentration of pesticides (glyphosate) and the increase in the prevalence of AD, as suggested in the hypothesis in this work.

3.4 Actions of Prevention

In this regard, governmental actions in general should focus their attention on reducing the use of pesticides, notwithstanding the need for large-scale food production [2]; to stimulate research and production of biological inputs (bio pesticides); and to promote family farming, a type of agriculture developed on small properties that in Brazil sustains about 70% of the population [3]. Family farming is more closely linked to sustainability processes because it generates fewer environmental damages and less harm to the health of animals and humans, as managing small properties requires fewer industrial pesticides and allows for the use of natural defenses [1,2].

In addition, the dementia prevention process involves a multidisciplinary family medicine team to raise awareness about the dangers and risks, demonstrate care and detoxification processes for those who work in the field and/or live near pesticides [97]. Environmental surveillance with prevention-focused management is a determining factor in avoiding the exacerbated use of chemical pesticides [3,59]. As proposed by Trevisan et al. (2019), individuals should start preventing AD and other dementias from youth, and in this regard, avoiding indiscriminate

contact with pesticides can reduce health problems, especially considering that healthcare expenditures are greater than those allocated for prevention [40].
Indeed, a public health responsibility is necessary added a governmental policy on the environmental controls in the use of pesticides, *inter alia*, to reduce indiscriminate use of the pesticides to prevent environmental disorganization, however, providing food safety.

In this way, specific policies must ensure survival and quality of life for humans and animals; nevertheless, if it is not possible for now, at least, to reduce the damages, and the society could become aware about the abusive use of pesticides [98].

Future research could be directed for specific studies linking dementia, mainly AD, to pesticides indiscriminate use, in epidemiological terms for humans and laboratory tests, *in vitro* or using animal models.

4. CONCLUSION

Considering the data studied thus far, which strongly suggests that pesticides is toxic to the neural system based on experimental research observed from studied literature, it is compelling to indicate that there is, at least, a qualitative relationship between the increase in pesticide use and the increase in the prevalence of AD. Exposure to it should be avoided as a means of preventing AD and dementia in general by using the methods of prevention indicated against toxicity of pesticides with a rigid government policies and attention of health professionals in a preventive care.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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