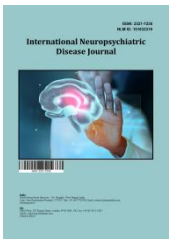

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Association between Age Gain, Parkinsonism and Pesticides: A Public Health Problem?

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Authors' contributions

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ABSTRACT

As life expectancy increases worldwide, so does the time available for prolonged exposure to toxic materials in the environment that have the potential to exert gradual pressure, facilitating the onset of aging in the body.

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Neural/behavioral alterations are linked to age gain, making the understanding of the aging process more complex considering the high complexity of the neural system and, although neuropsychological, pathological and neuroimaging criteria have been established to differentiate between normal and pathological aging, diagnosing the mild cognitive problems of each elderly individual remains a challenge.
Parkinson's disease is recognized as one of the most common neurological disorders in the elderly, whose intrinsic cause is still unknown, but its main molecular basis is the decrease in dopamine produced in the substantia nigra. Studies have suggested that exposure to organophosphate, the glyphosate class, in different organisms, are capable of promoting bodily malformations, neurotoxicity, hepatotoxicity, genotoxicity, metabolic disorders, among others. The effects of pesticides on the environment, associated with their exacerbated permanence in the environment, indicate that more and more people may suffer their deleterious action, which may be the cause of some neurodegenerative disorders. The main objective of this study was to use specific data from the literature on Parkinsonism, correlating it with aging and contamination by pesticides.
In fact, the health risks inherent in the use of pesticides are greater the greater the intensity of exposure to them and, considering the widespread use of pesticides today, the number of poisoning of the human population and animals will increase. Therefore, in terms of literary data, contamination with pesticides may be associated with a public health problem and, therefore, a possible increase in dementia processes, thus Parkinsonism.

Keywords: Aging; parkinsonism; pesticide toxicity; glyphosate.

1. INTRODUCTION

1.1 Aging and Nervous System

It has been known for some years that the increase in the proportion of elderly in the population is a global phenomenon [1], with a negative population growth rate happening nowadays as in South Korea [2]. In Brazil, according to the Brazilian Institute of Geography and Statistics [3], the number of inhabitants aged sixty years or older was 22.34 million in 2012, representing 11.3% of the entire resident population; however, the portion of people over sixty years old reached 14.7% of the total population in the year 2021, surpassing the mark of 31.23 million; this increase of 8.89 million elderly over a period of nine years corresponds to the growth of 39.8% of this age group that has become increasingly representative in Brazil.

Given the increase in population aging, Brazil is ranked as the sixth country in the world with the largest number of elderly people, with the perspective that in 2060 the number will exceed 58 million in the country, representing 25.5% of the total Brazilian population [3]. According to the World Health Organization (WHO, 2015), the world population has shown an accelerated rate of aging, however, it is estimated that in 2060 there will be two billion people over sixty years old worldwide.

In this sense, in terms of public health, there is a concern focused on healthy age gain over aging associated with pathological states (senility) [4,5]. Considering age gain as a time-dependent chronic-degenerative process modulated by genetic and environmental parameters in which the population is destined to suffer [6], and, to date is irreversible, by virtue of the ability of cells to evolve differentiated and irreplaceable [7], the prevention of pathological processes and understanding of healthy aging become the basis for a healthy life in advanced ages, making it essential to seek care and good habits throughout life [8].

According to Lipsky and King [9] aging is a natural process of wear and tear on the body, which is significantly dependent on lifestyle and uneven because organs, tissues, cells, and subcellular structures show differentiated wear and tear over time, that is, when comparing from birth to death, organic functions decline in most organs, in particular, there is a reduction in the renal flow, cardiac output, glucose tolerance, vital capacity of the lungs, body mass, and cellular immunity [10,11].

However, paying attention to biological factors alone, such as genetics, metabolic rate, and caloric intake, may not be enough for healthy longevity, as the link between healthy age gain and psychological factors is associated with longer and better survival, such as satisfying affective attachments, stress tolerance, spontaneity, optimism, and well-being [12].

In physiological terms, it is known that the fragility of reparative and regenerative mechanisms propitiates aging [11], thus, the inherent irregularities of biological systems, such as the modifications by which cells undergo when transforming renewable cells into non-renewable ones, added to the decrease in cell regeneration capacity, are responsible for characterizing the aging of tissues [13], being able to cause a series of alterations in organic and mental functions that result in changes in homeostatic balance and physiological functions due to age gain [14,15].

Other aspects to be considered as a consequence of age gain and cellular changes in tissues are reduced weight and volume in most organs, uneven and disharmonic atrophy, loss of bone density, nutritional and vitamin deficiencies, decreased capillary vascularity, increased body fat and subsequent infiltration of adipose tissue into the liver and muscles, which may correlate with insulin resistance and glucose intolerance, and decreased body water content in the body, leading to dehydration and consequent physical, psychomotor, oculomotor, and cognitive changes in the aging body [16,17,18].

Logically speaking, the incidence of diseases associated with aging becomes more common as a result of the increase in the average lifespan of the population [19], however, not all people of advanced age become senile, although changes occur in the neural system, one cannot assume that senility is a normal consequence of the aging process [8,20], notwithstanding the fact that some dementias are associated with aging, such as Alzheimer's and Parkinson's disease [21,22].

Moreover, a recent study questioned the relationship of aging theories with the disastrous consequences proposed by them in relation to Alzheimer's disease [5], showing the need for more detailed and practical studies with the elderly population so that the understanding of the consequences of aging gain, better understood, provide more comfort to this growing slice of the population [23,24].

Neural/behavioral changes are linked to age gain, making understanding the aging process more complex considering the high complexity of the neural system [25,26], since the central nervous system plays an important role in processing complex information from the environment, being the main mechanism in decoding the aging process, whose anatomical and molecular changes are observed via imaging technologies [27,28,29].

The cortex is the main structure of the neural system with regard to sensory, motor and associative functions [30] and, it is assumed to be responsible for neural mechanisms related to thinking, memory, language, attention, perception and voluntary movements [31]. Since the beginning of the 20th century, several studies have emerged with the intention of clarifying the various questions about the origin, evolution and function of the cortex, however, many questions are still misunderstood [32].

Cortical areas have relatively defined boundaries and functions, differing in cytoarchitectural features and specialized patterns of afferent-efferent connectivity [32,33]. Modifications in brain structures, such as a decreased cortical thickness, are associated with increasing age, and are a promising marker to investigate changes in gray matter during normal aging, nevertheless, variations in the cortical surface area are also closely linked to behavioral changes and pathologies [34,35].

Non-pathological aging may be accompanied by mental changes analogous to those of incipient dementia, and although there are several studies aimed at unraveling the pathophysiology of Alzheimer's disease, little attention has been paid to the cognitive deficits that arise during normal aging, leading to the problems of differential diagnoses. Although neuropsychological, pathological, and neuro-imaging criteria for differentiating between normal and pathological aging have been established in consensus, diagnosing the mild cognitive problems of individual elderly individuals is an ongoing challenge [36,37].

Age gain can result in two different processes, called "senescence" and "senility" [9]. Aging is characterized as senescence which results from a complex interaction between genetic, hormonal, metabolic, immunological, and structural factors, acting on histological, molecular, cellular, and organic levels, i.e., it covers all the changes that occur in the human body without the affliction of diseases; it is characterized by the biological effects of aging when there is a decrease in the biological repair capacity [38,39]. In turn, senility is a process that refers to the pathophysiological changes, including weakness or deterioration of the body

and/or mind in the course of life, reflecting in the gradual reduction of morphofunctional capabilities of the elderly [39,40].

1.2 Aging and Parkinsonism

Parkinson's disease is recognized as one of the most incident neurological disorders in old age, affecting 2-3% of the population aged 65 years and older [41], and it affects mainly the motor system, whose intrinsic cause is still unknown, but which has the decrease of dopamine produced in the substantia nigra as the main molecular basis, leading to insights of specific age-related factors that predispose some individuals to develop such neurodegenerative pathology [42,43].

Studies conducted about the damage caused as a result of advancing age found an acceleration of the brain atrophy process, with dilation of sulci and ventricles, a loss of neurons, deposits of ß-amyloid protein, a granulovacuolar degeneration, a presence of neuritic plaques and neurofibrillary tangles; the authors concluded that the initial phase of Parkinson's disease occurs with involvement of the lower brainstem, specifically in the dorsal motor nucleus of the glossopharyngeal and vagus nerve and the anterior olfactory nucleus, evolving in six neuropathological stages and spreading throughout the neocortex, leading to multiple motor, sensitive-sensory, autonomic, affective, cognitive, behavioral, and sleep alterations [44-47].

In a joint analysis of the associations of aging gain with neural functions, it is necessary to discern between the differential effects of senescence and senility, so that aging is not diagnosed and treated as a disease or that pathologies derived from aging gain do not fail to receive a proper treatment [48], making it necessary to understand some intervening factors in the complex process of aging and its consequences on the brain [19,49].

There are processes that seem to be an indication of normal aging, such as slowness of perception, memory and reasoning [48], however, there is evidence that shows how continuous and moderate physical exercise and cognitive training are effective in achieving beneficial effects on cognition, increasing neuroplasticity, thus preventing a cognitive decline and a delaying some of the dysfunctions common in the old age [50].

The population aging process that has occurred in modern Western societies has generated a social problem, since the affliction of chronic diseases and functional disabilities in the elderly have been increasingly difficult to prevent [39,49]. It is also emphasized that, the care of the elderly population represents a challenge for the health system and the State, which need to adopt a continuous and multidisciplinary organization capable of strengthening healthy aging, since the occurrence of chronic and disabling diseases is more present in old age compared to other age groups [36,50,51].

Parkinsonism (PK) is the second most common neurodegenerative disorder among the elderly, second only to Alzheimer's disease, according to a report by the Parkinson's Foundation [52]. According to Ou, Pan, Tang, Duan, Yu, Nong et al. [53], through a study using data from the Global Burden of Disease 2019, provided a comprehensive overview of the burden of Parkinson's disease (PD) and its trends in the incidence and prevalence at global, regional, and national levels during 1990-2019. Globally, it was observed that the number of PD incidents was nearly 1.1 million, increasing by about 159.73% since 1990 with an annual incidence rate of 14 cases per 100,000 population, while the global prevalent number increased by 155.50% from 1990 reaching an average of 8.5 million in 2019 with an annual prevalence rate of 107 cases per 100,000 population.

Parkinson's disease (PD) was discovered in 1817 by James Parkinson, who defined it as a "chronic progressive disease of the Neural System beginning in middle age" [54]. It is an agitating paralysis that primarily affects the motor system, with a higher prevalence in elderly males over the age of fifty [55]. It is characterized by movement changes such as stiffness tremor, bradykinesia (slowness of movement), hypokinesia (reduced range of motion), akinesia (absence of movement), postural changes, and "freezing" phenomena (periods when the patient stands still with his feet literally planted on the ground) [41,55].

PD is a disorder of the extrapyramidal system, formed by the thalamus, the cerebellum, and the motor structures of the basal ganglia, and is characterized by the loss of dopaminergic function and consequent decreased motor function. The process of degeneration of dopaminergic neurons of the substantia nigra results in decreased levels of dopamine in the

corpus striatum, resulting in characteristic motor changes and determining the appearance of the main signs and symptoms of Parkinson's disease, given that the substantia nigra is an important modulator of the motor circuitry [42,56,57,58].

In this respect, a set of abnormal firing, oscillatory neuronal activity and the loss of sensitivity of the motor circuit are considered to be important factors that cause the onset of involuntary movements. The initial manifestation in PD is a unilateral rest tremor that affects mostly the hands, seen initially in one extremity (sometimes involving only one finger or the thumb). The tremor is slower than a classical essential tremor, but is gross when the limb is in a resting posture, and tends to diminish or stop when the affected part is used for some activity [55,56,57,59].

The Parkinson's disease is a complex neurodegenerative disease that has a number of molecular pathways, all of which may be implicated in the neurophysiology of the disease. Age gain also favors the onset of PD, as the conduction velocity of neural impulses is reduced with aging, in addition to quantitative changes in neurotransmitters. Deficits in the central (CNS) and peripheral nervous systems (PNS), even in normal aging, affect more complex and higher motor, cognitive, and language abilities, and can lead to neurodegenerative disorders [56,60,61].

For some patients, the classic parkinsonian tremor is the only manifestation of the disease, however, there are other symptoms that should be noted. A cognitive impairment is often observed and, when associated with motor disturbances, leads to a disability comparable to that seen in the severe cerebral vascular disease [62,63]. Furthermore, imbalance, gait alteration, and postural abnormalities are frequent in Parkinson's disease [64], signifying an impairment in the systems responsible for proprioception and balance functions [65].

There are two main sensory systems that complement each other to guide a proper balance: the vestibular system, located in the inner ear, and the proprioceptive system; while one monitors the gravitational forces, the other tracks the speed and force of the muscle movement, respectively. The vestibular activity modifies the neuronal bioelectrical conditions in the cerebellum, which in turn influence the motor neurons and interneurons in the brainstem and spinal cord, also the neurons in the superior colliculus and the cerebral cortex, to initiate the muscle contractions and the reflex responses [65-68].

The vestibular system acts on the movements, the somatosensory sensation, the digestion, the balance, and the mental state. Its absence or decreased vestibular responses in patients with Parkinson's disease is associated with symptoms of postural instability and an increased risk of falls, having a substantial impact on the quality of life [69,70]. With aging, dizziness and imbalance become common in the elderly. Dizziness interferes with the daily activities for 30% of people over the age of 70 and, the most common causes have been sensory deficits, such as the bilateral vestibular hypofunction, which is the loss of function on both sides of the inner ear, popularly called the labyrinth [51,70].

Regarding etiology, parkinsonism can be divided into 3 categories: primary or idiopathic Parkinson's disease (PDD); secondary or drug-induced parkinsonism (DIP); and Parkinsonism-Plus or atypical syndrome [71].

DIP is one of the most commonly found movement disorders in the elderlies, representing up to 70% of patients seen in specialized clinics worldwide. Its cause remains undefined, however, several studies assume that genetic and environmental exposures are risk factors and play vital roles in the pathogenesis and progression of the disease, such as oxidative stress, mitochondrial defects, neuroinflammation, apoptosis, and ecotoxicity [72-75].

Most individuals are diagnosed over the age of 45, with only a small percentage (10%) of cases considered early onset (under the age of 45). The primary means of identifying the disorder require that two of the four main signs of the disease are present, typically presenting with an asymmetric onset, in addition to the patient history. Among the motor signs bradykinesia, rest tremor, rigidity, and postural instability are included and, related to the non-motor symptoms, a decreased gastrointestinal motility, a loss of olfactory function, sleep disturbance, intense fatigue, weight loss, complaints of depression, and cognitive or behavioral changes are comprised [71,76,77].

In drug-induced (DIP) or secondary Parkinsonism, it is possible to identify its cause, that is, its onset is not idiopathic. It corresponds to the second most common among them, second only to the idiopathic Parkinson's disease (IPD) as a cause of parkinsonism. Generally, the disease arises from the use of drugs that interfere with the levels of dopamine in the brain. The most common are antipsychotics, some calcium channel blockers, stimulants such as amphetamines and cocaine, infections, hexogen poisoning (manganese, cyanide, carbon monoxide, pesticides), expansive processes of the Central Nervous System, encephalitis, traumata and tumors, metabolic and endocrine disorders [78-80].

Clinical features of DIP include bilateral symmetrical parkinsonism, rigidity, and bradykinesia that are more severe than in patients with IPD. Although classic rest tremor is often absent, chin tremor may be observed in some patients. However, these features are not fully diagnostic of DIP, as many patients may present asymmetric symptoms and rest tremor like patients with IPD, leading to difficulties in making a correct diagnosis based on clinical findings alone. One of the commonly used clinical criteria for diagnoses for DIP include the presence of typical clinical symptoms of parkinsonism with onset after the use of an offending drug along with the absence of a previous history of parkinsonism [71,79].

Secondary parkinsonism can also be associated with cerebrovascular diseases, called vascular parkinsonism (PV). It occurs from ischemic or hemorrhagic lesions of the basal ganglia, mesencephalon or their connections with the frontal cortex, triggering tremors and rigidity. According to different investigations, various forms of cerebrovascular disease cause 1% to 15% of parkinsonism cases, however, vascular lesions usually do not produce parkinsonian symptoms immediately after the stroke onset, and it may take weeks to years for the neurodegenerative disorder to develop. Gait abnormalities in PV are characterized by a reduced step speed, length, and height [71,81].

Atypical parkinsonism, also called Parkinson-plus syndrome, occurs when a patient has parkinsonism and additionally has more other features, in other words, it refers to a group of degenerative diseases expressed as kinetic-rigid syndromes associated with other neurological disorders commonly not found in IPD. Clinically, symptoms of atypical parkinsonism, particularly in the early stages of the disease, mimic those of IPD, so it is of great interest to distinguish these different entities early in order to provide appropriate diagnoses and therapies. There are certain features or "warning signs" that help to distinguish atypical parkinsonian syndromes from IPD, such as a rapid disease progression, an early gait instability and falls, absence or scarcity of tremors, or early dementia/hallucination [82-84].

Among the most common causes for the atypical parkinsonism are progressive the supranuclear palsy (PSP), the multiple system atrophy (MSA), and the Lewy body dementia, however, a similarity between the neurodegenerative disorders is the presence of abnormal protein deposits of α-synuclein, ubiquitin, tau, and β-amyloid in the pathological brain tissue [71,83,85].

The progressive supranuclear palsy (PSP) is the most common form of atypical Parkinsonism, comprising about 5% to 6% of patients presenting parkinsonism, with men and women being equally affected. The estimated prevalence and annual incidence of PSP is about 5 per 100,000 in individuals aged 50 to 99 years. The mean age of onset is typically in their sixties (mean age 63 to 66 years), and the mean survival since the diagnosis is reported to be between 5 and 8 years. Characteristics of the disease include a prominent and early postural instability, unexplained falls, vertical supranuclear palsy, and progressive dementia [83,86].

The clinical manifestations of PSP are diverse, the most common (about 40%) being the Richardson's syndrome, with rigid-kinetic symptoms that affect the axial muscles, cause a paresis of the vertical gaze, an early postural instability, and a tendency to fall backward early in the course of the disease. Another syndrome also present is the frontal lobe syndrome and include apathy, impaired executive functions, and a positive "clap signal," meaning the patient is unable to stop clapping [83,86].

The pathophysiological hallmarks of PSP are neuronal loss, star-shaped tufted astrocytes containing abnormal Tau protein aggregates and neurofibrillary tangles.

The Hyperphosphorylation of Tau reduces the ability of Tau protein to stabilize the

microtubules, this leads to aggregate formations and a blockage of the intracellular protein traffic, resulting in a loss or decline in the axonal or dendritic transport in neurons, therefore, the accumulation affects mostly the basal ganglia, the diencephalon, and the brainstem, degenerating the substantia nigra, the subthalamic nucleus, the mesencephalon, the dentate nucleus, the superior cerebellar and the middle cerebellar peduncles [71,87,88].

Multisystemic atrophy (MSA) is a sporadic degenerative disease of the central neural system that generates a dysfunction in the autonomic nervous system providing a range of symptoms that can vary from urinary incontinence, erectile dysfunction, difficulty breathing, motor impairment, among others. In terms of prevalence and incidence, they are approximately 3-5% and range from 0.1-2.4 cases per 100,000 population, respectively. The average age of onset is 58 years, younger than PSP and with a faster progression than in IPD, moreover, the average survival is approximately 6-9 years, considering that the neurodegeneration is more widespread [71,84].

In terms of etiology, inclusions containing the protein α-synuclein accumulated in the cytoplasm of oligodendrocytes added to a neuronal loss involving substantia nigra, the inferior olivary nucleus, and the cerebellum are believed to be largely responsible for MSA, being associated with an oxidative stress and a protein degradation dysfunction. Based on the combination of symptoms, MSA is divided into two subtypes, a classification that follows the occurrence of a predominant clinical abnormality, being MAS-P with a predominant parkinsonism, representing 60% of cases and characterized by an absence of tremors, and MAS-C with predominant cerebellar symptoms, such as ataxia and postural instability, which reach about 40% of the cases [85-88].

Lewy body dementia (LBD) consists of a progressive loss of the mental function, characterized by the development of Lewy bodies in nerve cells, specifically, in the cerebral neocortex, limbic cortex, subcortical nuclei, and brainstem. Its prevalence in the population over the age of 65 is approximately 0.4% and the onset of symptoms usually occurs between the ages of 50 and 80 [83,86].

In addition to the impairment of the dopaminergic system, patients show a characteristic pattern of hypometabolic areas, mainly involving the occipital regions of the primary visual cortex and the visual association cortex, therefore, the initial clinical manifestations are associated with an early cognitive decline with oscillating episodes between poor and better cognitive performances, deficits in executive functions, visuospatial abilities, and visual realistic hallucinations. Moreover, LBD is strongly associated with rapid eye movement behavioral sleep disorder, with a prevalence ranging from 44-55%, negatively affecting the patients' quality of life and safety [71,86,87].

There are no treatments for the aforementioned atypical parkinsonian syndromes whose efficacy could be comparable to levodopa, in IPD. The use of dopaminergic medications, such as levodopa, is unfeasible for these atypical syndromes, because the patient with the Parkinson-plus syndrome presents parkinsonism added to other features, whereas, certain medications can improve the parkinsonian symptoms in the same proportion that worsens the other symptoms. Symptomatic support measures, in addition to a physiotherapeutic care should be performed [83,86].

1.3 Pesticides

Due to the enormous economic development and rapid growth in many fields, such as agriculture and industry, the environment has constantly become more polluted by environmental toxics, among them heavy metals and pesticides [88,90]. The successive growth of global agriculture, currently, is due to the challenges and risks faced to meet the demands of agricultural products and manage to feed the planet [91], since the global demand for food will double by 2050, according to the population growth [92] and, due to climate change scenarios and an increasing competition for land, water, labor and energy [93,94].

The current need to increase the food production maintains pressure on the intensive use of pesticides and fertilizers and, therefore, agriculture has been the largest source of environmental contamination by pesticides [90,95]; pesticides are ubiquitous, being found in waters and soils even after long years of their application, and in the atmosphere, causing adverse effects on biodiversity, natural habitats, and human health [96-98].

Although the use of pesticides appears to be a viable option for feeding the growing population and protecting thousands of people from malaria and other insect-borne diseases [99], they are nevertheless a concern for the environmental sustainability and the global stability [100]. The abuse in the use of pesticides and their potentially serious threats have led to a change in the attitude of organized society and environmental advocacy bodies by some governments to contribute to changes in the actual performance of the purchasing practices and use of these pesticides in order to avoid environmental damages and provide a greater food security [101,102].

The dichotomy (1) feeding humanity and (2) preserving the planet requires, at least at the present moment, a balance that provides for survival and, if it is not possible to zero the environmental damage, to let it be the least [103]; because the society is dependent on a multitude of services provided by ecosystems, including the production of drinking water, the creation of fertile soils and the support of other species that provide food, crop pollination, timber and medicines [104], so it is essential to adopt means that ensure the health of the biosphere.

Pesticides encompass all the compounds that are applied to destroy or regulate pests, describing numerous groups of insecticides (insects), herbicides (weeds) and fungicides (fungi). Currently, there are several classes of pesticides with different active ingredients, forms of biological action and elimination in the environment, so it is important to categorize them based on three commonly recommended approaches, which are (1) as the mode of entry, (2) as to the chemical structure and (3) as to the toxicity of the pesticide and the organisms they kill [105-107].

As for the mode of entry, pesticides can enter the human body by direct chemical contact (dermal route), by ingesting food, especially contaminated fruits, vegetables and water, or by inhaling dust, mist or smoke from pesticides and polluted air; as for chemical toxicity, they can be classified as acute intoxication, arising from exposure in short periods, or chronic intoxication, when adverse effects result from a long period of exposure, both depending on the nature of the toxicant, routes of exposure, dosages and organisms [105-107].

Pesticide poisonings have become ever-increasing, as they have increased worldwide on farms dramatically since the last global assessments made 30 years ago; a recent study by BMC Public Heath revealed that global acute pesticide poisonings have increased from 25 million cases in 1990 to the 385 million mark of cases happening annually worldwide, meaning 44% of farmers if considering only the world's agricultural populations [108].

According to the United Nations report, pesticide poisoning inflicts substantial costs on governments and has catastrophic impacts on the environment, human health, and society; pesticides are a human rights concern because people can be exposed to dangerous levels of pesticides in a variety of ways, from farmers using them on their crops to babies drinking their mothers' contaminated breast milk, furthermore, the report revealed that pesticides were responsible for about 200,000 deaths from acute poisoning each year [109].

According to the report by Pesticide Action Network (PAN-UK), civil society organizations advocating for stricter pesticide rules, hundreds of millions of small farmers and their families in low- and middle-income countries are poisoned by pesticides every year, and an estimated 14 to 16 million people worldwide have died from pesticide ingestion over the past 50 years [110]; all the findings on poisoning data on a global scale highlight an emergency global health issue.

As for the chemical structure of pesticides, they include the classes of organochlorines, organophosphates, carbamates, pyrethroids, dithiocarbamates, organotins, dicarboximides, bipyridyls, dinitrophenols, each of which has distinct toxicity classifications, being determined based on oral, dermal and inhalation toxicity studies, and the duration of exposure [105,107].

Organochlorine (OC) pesticides are synthetic chlorinated compounds widely used worldwide and, belong to the class of persistent organic pollutants (POPs) with a high bioaccumulation and bioamplification potential [111]. They are considered the most hazardous class because they possess metabolites that cause toxicity in higher organisms, and although several of the chlorinated-based formulations have been banned or restricted in several countries over the past 50 years [112], they remain in the environment for decades due to their long half-life, and can biomagnify throughout the food chain and cause high concentrations in top predators, including humans [113,114], often

leading to poisoning of children due to the exposure to pesticide residues found in the breast milk [115].

Among the most commonly used organochlorines, dichlorodiphenyltrichloroethane (DDT) and its main metabolite dichlorodiphenyldichloroethylene (DDE) have been extensively studied in relation to the incidence of the damage caused beyond those found in the ecosystem [116]. They were widely used in the mid-20th century to control insect populations, however, due to growing environmental and wildlife concerns, their use steadily declined until their ban in 1972 when DDT was found to compromise the nervous system [117]. There is limited evidence about organochlorine exposure being related to an impaired cognitive function in general populations, studies showed that elderly people with high DDT had about 3 times higher risks of low cognition and elderly people with high DDE had 2 times a higher low cognition [118].

Some epidemiological evidence shown in several studies suggests that human and animal exposure to organochlorine pesticides can cause potentially harmful effects on the life of the organism [115,119]. Recent studies on the effect of pesticides on animals have shown multiple toxic effects on members of almost all phyla, altering various physiologies of the animal, including nervous, circulatory, and reproductive systems, leading many species to extinction [117,120].

In humans, a recent research has shown that organochlorines adversely affect the uterine development, leading to teratogenic effects, premature labor, and shortened lactation [113,121]. In addition, organochlorine pesticides can damage the central nervous system, causing a hyperexcitable state in the brain, convulsions, tremors, and ataxia, and compromising the other organs such as liver, kidneys, and bladder [115]. Furthermore, environmental exposures to organochlorine in humans have been associated with endocrine, respiratory, immunological, reproductive dysfunctions [122,123], and the risk of developing neurodegenerative disorders, in addition to chronic diseases such as cancer [118,124].

Another class of pesticides commonly used in the environment are organophosphates, which emerged as an alternative to organochlorines due to their easy degradability [125], however, although they are comparatively easier to be degraded than other organic pesticides, studies have shown the presence of organophosphate residues in agricultural land, soil, groundwater, surface water bodies such as rivers, ponds, lakes, and even in snow, fog, and rainwater [126,127] due to their widespread unregulated use practice, generating concerns among environmentalists and governmental agencies [128].

The main mechanism of toxicity of organophosphate pesticides is the inhibition of the enzyme acetylcholinesterase (AChE) and the development of a cholinergic crisis. When inhibited, AChE is prevented from catalyzing acetylcholine, leading to an accumulation of the neurotransmitter at synapses and neuromuscular junctions, and as a consequence, cholinergic hyperstimulation occurs. This excessive stimulation of acetylcholine receptors, the nicotinic and muscarinic ones, are responsible for causing an altered mental status, convulsions, muscle weakness, spasms, and excessive secretory activity [129-132].

Among the different organophosphate pesticides, glyphosate is the most widely used worldwide with the most common use in soybean, coffee, sugarcane, citrus and rice crops [132-134]. It is considered a systemic, non-selective, post-emergent herbicide. From the systemic point of view, it is one that when absorbed, translocate through all the plant tissues of the plant, non-selective means having a broad spectrum of action, being able to kill or damage all the plants and post-emergent is when the herbicide acts on plants at a stage where it is already developed [135,136].

Since the commercialization in 1974, its agricultural uses have increased considerably following the development of genetically modified crops resistant to the effects of glyphosate [137]. Currently, a variety of glyphosate-containing formulations are produced in the United States, Europe, Asia, and South America [138] and registered in more than 100 countries, marketed under different names [139], but all chemical forms present the same mechanism of action, regardless of the salts present, whether they are isopropylamine salt, ammonium salt, diammonium salt, dimethylammonium salt, and potassium salt [136,140].

In 2022, the Food and Agriculture Organization of the United Nations (FAO), offered statistics

and reports on the agricultural consumption of pesticides in the world, the global consumption of herbicides reached almost 1.4 million tons, while the consumption of fungicides and bactericides was around 606 and 471 thousand tons, respectively [141]. In the same year, glyphosate (and its salts) was the most sold agrochemical in Brazil, with the sales of this herbicide totalizing more than 246,000 tons in the country [142].

To form glyphosate-based herbicides that will be used for the Roundup formulation, the active ingredients in the formulations are mixed with other inert ingredients (coformulants), i.e., those that have the function of diluting the active ingredient and facilitating its dispersion or penetration into the target organism. Roundup formulations usually contain about 40% glyphosate and the rest corresponds to the coformulants [141,143,144].

Some studies show that the coformulants of Roundup herbicides are much more toxic than the active ingredient itself, glyphosate, alone. However, because the added coformulants differ between countries and manufacturers, they are confidential, not publicly available, and are not target ingredients in ecotoxicological studies, often the active ingredient alone and the formulation are treated as the same substance, leading to concerns about toxicity misclassifications [143,145,146,147].

Glyphosate in its acid form is less soluble than in its salt form, so the glyphosate-based herbicides, Roundup, feature glyphosate in salt form, with the isopropylamine salt being the most widely used in agriculture. These characteristics allow glyphosate, under environmental conditions, to be highly soluble in water and insoluble in apolar organic solvents such as acetone, ethanol and xylene. Glyphosate exhibits a zwiterionic behavior in water, they are polyelectrolytes that have the overall neutral charge and both ionic states within the same molecule, i.e., depending on pH, glyphosate is able to form cationic and anionic sites within its structure [136,148-152].

Due to the zwitterionic character of glyphosate in the environment, it forms complexes with trivalent and quadrivalent metals, thus the glyphosate-metal junction allows glyphosate to accumulate in waters with high mineral content. These complexes increase the half-life of the herbicide from 90 days to 22 years, as they reduce the bioavailability of glyphosate for microorganisms to degrade; however, all this persistence in the environment represents a major exposure risk factor for the human population [136,153].

The mechanism of action of glyphosate consists in the inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) of the shikimic acid pathway, which is one of the main biosynthesis pathways in higher plants and is involved in the biosynthesis of aromatic amino acids essential for the plant survival, as phenylalanine, tyrosine, and tryptophan and, consequently, phenolic compounds, lignins, tannins, and other phenylpropanols in plants, bacteria, algae, and fungi (Fig. 1). The physiological stress caused by glyphosate induces the production of ethylene, a simple hydrocarbon that is naturally produced in response to environmental stresses, in senescent or maturing organs, possessing an inhibitory effect on the cell expansion. With this, increased ethylene can lead to the membrane destruction, chlorophyll inhibition, and a reduced stomatal closure [154-158]; however, EPSPS is absent in animals [159].

Because the EPSPS enzyme is not found in animals, glyphosate was considered environmentally benign, non-toxic, and safe for use near wildlife and humans [151]. In the year 2015, the World Health Organization and the International Agency for Research on Cancer classified glyphosate as category 2A, as probably carcinogenic in humans [152], while the European Food Safety Authority (EFSA) reported there is no evidence of carcinogenic risk to humans and being safe when used properly [153,154]; moreover, the United States Environmental Protection Agency in 2016 also reviewed the carcinogenic potential and concluded it was not likely for humans [155].

However, the classification of glyphosate for its toxicity in humans is carried out by institutions with different objectives, while IARC is closely linked to WHO, questioning the latest findings with a focus on the health protection, EPA and other agencies have registration purposes and can have strong economic bias, creating a division between the agribusiness industry, which opposes IARC's classification, and those other experts who support it [140,156].

The indiscriminate use of glyphosate brings concerns about the environmental contamination and how it can be harmful to biodiversity,

habitats and human health [157], because like organochlorines, it is also persistent in the environment, as it has been detected in groundwater and surface water [158,159]. The extensive application of this pesticide can make pests able to resist against other non-selective herbicides [160], with a consequent reduction of microorganisms in the soil that perform many important functions, such as nutrient cycling, maintenance of the soil structure, carbon transformation, and regulation of pests and diseases [161,162].

Although the acute toxicity of glyphosate is in category IV, with I being the most toxic and IV being the least toxic [143], studies suggest that glyphosate can cause chronic malformations in some species of animals, such as chickens, frogs, and mammals [114]. Exposures to organophosphate, glyphosate class, in different organisms show its toxic potential, being able to promote body malformations, neurotoxicity, hepatotoxicity, genotoxicity, metabolic disorders, among others [163,164,165].

Researches indicate that its persistence in the environment is underestimated and its toxicity may be more harmful to animals and humans than expected [166]. Studies examining low doses of glyphosate-based herbicides, in the range of what is now generally considered "safe" for humans, show that these compounds impact human health [167]. Symptoms of acute toxicity of glyphosate-based herbicides in humans include abdominal pain, vomiting, excess fluid in the lungs, headaches, loss of consciousness, destruction of red blood cells, heart palpitations, facial numbness, itching, tingling [168-170].

Studies suggest that exposures to neurotoxicants occurring during neurodevelopment trigger a number of neurological disorders, among them the inhibition of acetylcholinesterase (important for the neuronal growth and differentiation) [171,172]. Pre- and postnatal exposures to different doses of glyphosate promote impairments in maternal behavior associated with brain neurotransmission systems, occurring behavioral changes including apathy, repetitive movements, tremors, a reduced social interaction [173,174,175].

Some authors have demonstrated that the herbicide exposure may be associated with menstrual cycle disorders, reduced fertility, a prolonged time to pregnancy, an increased incidence of spontaneous abortions, stillbirths and developmental defects in animals and humans when administered in high doses and for a prolonged period [176-179], becoming potentially toxic considering the bioaccumulation in the body [138]. Studies in rodent models showed evidence of glyphosate and glyphosate-based herbicides bioaccumulation [180] related to osteoporosis and thyroid dysfunction [181], behavioral and cognitive abnormalities [182], growth problems [181], dysplasia in the digestive tract [183].

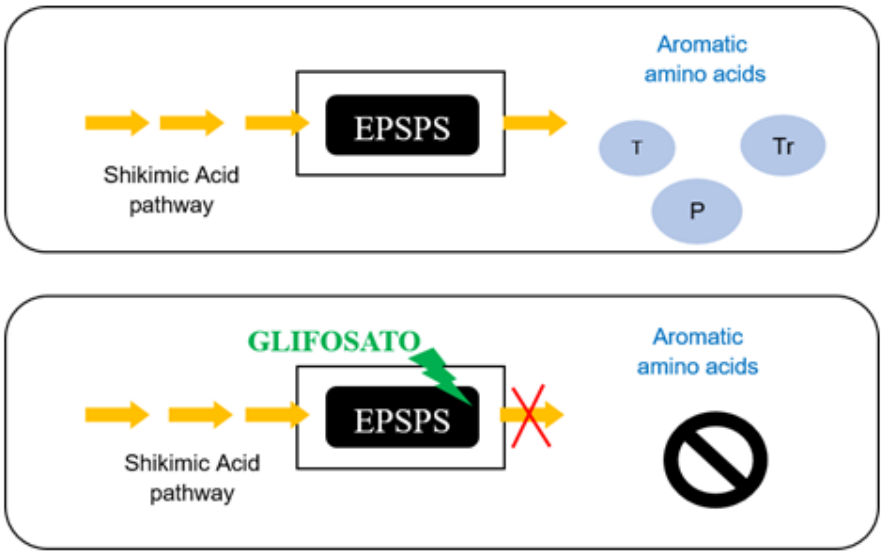

Fig. 1. Mechanism of action of glyphosate
Source: Adapted from Leino, Tall, Helander, Saloniemi, Saikkonen, Ruuskanen et al. [232]

The effects of pesticides on the environment associated with their exacerbated permanence indicate that more and more people may suffer their deleterious action [89]. Studies show that the exposures to these herbicides can lead to silent damage, deleterious effects and a decrease in genes expressed in different brain regions [184]; moreover, chronic exposure to glyphosate and its oral exposure caused the decrease in serotonin, norepinephrine and dopamine levels in brain structures such as the prefrontal cortex, the hypothalamus and the hippocampus in rodents [185,186], which can cause impairment to learning and memory processes [182].

Changes on complex organ systems, such as the neural system, may be the cause of some neurodegenerative disorders, such as Parkinsonism and Alzheimer's disease [187]. Although the causes and origins of neurodegenerative diseases, such as Parkinson's and Alzheimer's still do not have a clear explanation for such phenomena, the environment is believed to have an influence on the onset of neurodegenerative disorders throughout life, since there is evidence of the harm caused by prenatal and postnatal exposures to environmental factors) [174,188]. With this, epigenetic mechanisms by the maternal nutrient complementation as well as the exposure to metals and pesticides have been proposed to elevate phenotypic diversity and susceptibility to neurodegenerative diseases [189].

Considering the wide use of pesticides nowadays, even more with the current governmental policy in Brazil to release their indiscriminate use, an increase in the poisoning of the human and animal population may occur [90,190] and, as Brazil has been among the world's largest agricultural producers and consumers since 2008, marketing highly toxic chemicals that are banned in many countries [191], the worsening of environmental contamination indicates the need for studies and evaluation of the effects of these substances on the human and animal health [192]. The study of a method of elimination/inactivation/filtration of glyphosate can minimize the toxic actions of pesticides via physical-chemical associations [192,193].

Therefore, the general objective of this study was to use specific data from the literature on Parkinsonism, correlating it with aging and with pesticide contamination, to relate the pesticide contamination with the prevalence of Parkinsonism in the Human population; to indicate by logical-scientific means that the indiscriminate use of pesticides may increase the prevalence of neurodegenerative diseases focusing on Parkinsonism; to alert health professionals about a prophylactic care to be developed in order to avoid parkinsonism and related diseases, since no cure exists or is not satisfactorily effective.

2. MATERIALS AND METHODS

For the purpose of this review, articles from 2013 containing the subject's population growth; aging theories; elderly care; longevity and healthy aging; aging, neuroscience and pathologies linked to aging; fundamentals of neuroscience; pesticides and pesticide toxicity; pesticides, pesticide toxicity and neurotoxicity; aging and changes associated to aging; neurodegenerative diseases and Parkinson's disease, and some about norms and regulations. They were searched on the CAPES journal platform that contains the Web of Science, Scopus, and MedLine bases; and on the Google Scholar platform, from August 2020 to January 2023, to form the epidemiological basis of the review for a total of 1. 285,440 articles.

Of these, the articles considered most suitable to the objective of the present review were used, i.e., those whose theme was associated with the effects of pesticides, especially Glyphosate, on dementias, in particular Alzheimer's disease and, especially, Parkinsonism. The basis of scrutiny for choosing articles that dealt with similar subjects was the relevance of the subject.

From this analysis and considering the themes closer to the objective of this work, the exclusion criteria were duplicates within the subjects.

3. RESULTS

From the 1,285,440 articles refined with the exclusion criteria and the inclusion made with the subjects most pertinent to the objectives of this work, 1,285,197 articles were excluded, leaving 243 articles.

The subject in the references, after the exclusion criteria, were 2 about the population growth; 5 about the aging theories; 6 about the elderly care; 10 about the longevity and healthy aging; 12 about the aging, neuroscience and

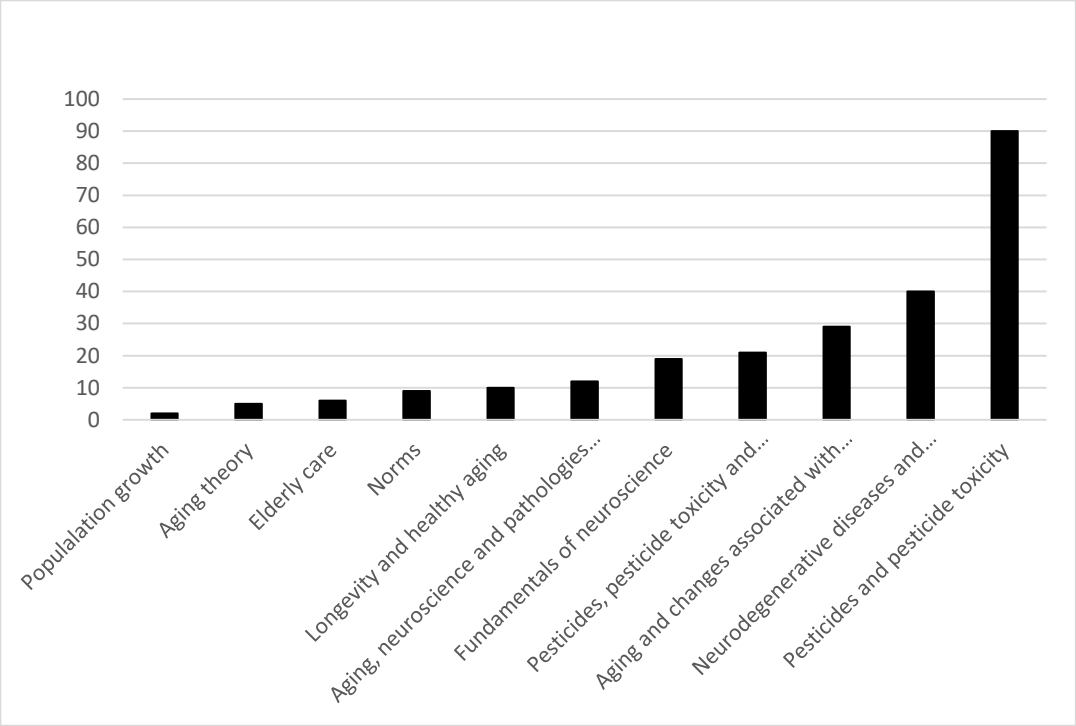

Fig. 2. Number of references associated to subjects
Source: authors

pathologies linked to aging; 19 versa about the fundamentals of neuroscience; 90 versa on the pesticides and pesticide toxicity; 21 about the pesticides, pesticide toxicity and neurotoxicity; 30 were about the aging and changes associated to aging; 40 of them were about the neurodegenerative diseases and Parkinson's disease, and 9 were about norms and regulations, totalizing 243 texts used in this review (Fig. 2).

4. DISCUSSION

Aging is a natural and inevitable process dependent on the interaction between genetic and environmental factors [194]. The various genetic changes that occur from the birth contribute to aging [195], in addition, the low mortality rates at younger ages added to the increase in life expectancy and the decline in fertility rates, lead to a rapid population aging worldwide [196,197] However, aging is a process that varies according to several aspects of each human being [198], being associated with a greater or lesser loss of health depending on the adopted lifestyle, considering the predecessor phases, such as eating behavior, inadequate habits of alcoholism, sedentary lifestyle, among others) [199,200].

The term frailty commonly relates to the transitional phase between a successful aging and the decline in the functional capacity of every system of the human body [201]; it is characterized by declines associated with imbalances in homeostasis, leading to an increased vulnerability to adverse outcomes [202]. So, if we add the weaknesses arising from aging that weaken the body's defense systems, and tissues in general, especially the kidneys, a contact with a contaminant such as a pesticide through water, food, or air, can logically-deductively increase the prevalence of dementias [164,188].

In fact, the health risks inherent in the use of pesticides are greater the greater the intensity of exposure to them, which is increased during the period of their preparation and application, often associated with an occupational exposure [117]. In this case, pesticide contamination occurs repeatedly in farmers, pesticide industry workers, and household pest exterminators [203], as they are routinely exposed to high levels of pesticides, usually much higher than those of consumers [203]. In the case of elderly farmers, one study showed that 73% of them were less likely to read labels, propitiating in potential risks of pesticide handling [204], often underestimated.

The most complex structure of the organism is the neural system, thus, modifications in the intricate network formed by neurons can generate changes in cognitive, motor and sensory functions [205]. In this aspect, in the elderly, who have fewer neurons and these more debilitated, the environmental contamination will be more severe and, considering parkinsonism, its manifestation becomes prominent due to oxidative stresses in CNS neurons and damage to dopaminergic neurons [194,206]. Epidemiological studies have found increased a PD risk associated with the exposure to environmental toxicants, such as pesticides, solvents, metals, and other pollutants [207,208,209].

A population-based case-control study proposed by Narayan, Liew, Paul, Lee, Sinsheimer and Bronstein et al [210], revealed that frequent use of any household pesticide increased the odds of PD by 47%, showing that even a familial exposure can lead to an increased risk of developing PD. Another recent epidemiological study by Kim, Kim I, Sung and Song [211] showed the relationship between the insecticide exposure in a tomato greenhouse and PD. In this study, the diagnosis of occupational PD was confirmed after the patient worked in contact with the pesticide for 12 years and 5 months. Therefore, considering the vulnerability, elderly people should not be close to pesticide application regions and should not reside in this vicinity.

In secondary parkinsonism, pesticides are one of the causes [212], but other diseases with clinical features similar to parkinsonism can be generated by an intoxication of the neural system, such as a multisystem atrophy caused by changes in the cerebellum [213]. Furthermore, a large number of neurotoxins have been associated with secondary parkinsonism, including metals, organic solvents, and illicit drugs [214]. Epidemiological studies have shown that the abuse of illegal stimulants can elevate the levels of reactive oxygen species, leading to the toxicity and death of dopaminergic neurons [215]. Another study associated the use of amphetamines, especially methamphetamine, with clinical signs of parkinsonism [216].

Although PD is characterized by 4 motor symptoms (resting tremor, rigidity, bradykinesia, and postural instability), PD patients have a variety of non-motor symptoms, which may even appear before the motor features and progress in severity as the disease progresses, and include neuropsychiatric problems, cognitive impairments, sleep disturbances, and autonomic dysfunctions [217,218]. The patient with Parkinsonism may not accept the disease and the tremor can create suffering as symptoms begin to interfere with the patient's daily activities and quality of life [219]. Psychological distresses, including anxiety and depression, are common and often comorbid, with a significant impact on health [220]; psychological distress is estimated to have a prevalence of 40% to 50% of Parkinson's disease cases [221].

As there is no effective treatment for parkinsonism, prophylaxis is the best choice [86], and if you consider the environmental contamination factor, this may not depend on the patient, but on the healthcare and the governmental system to prevent the syndromes [222]. The biggest challenge of this century will be caring for a large population of elderly people, most with low socioeconomic and educational levels and a high prevalence of chronic and disabling diseases [223]. Recently, Cieza, Causey, Kamenov, Hanson, Chatterji and Vos [224] have produced a global estimate of the need for rehabilitation services using data from the Global Burden of Diseases 2019. Globally, in 2019, 2.41 billion individuals had conditions that would benefit from rehabilitation, contributing to 310 million of years of life lived with disability, increasing by about 63% from 1990 to 2019.

Under these circumstances, the health care system will face an increasing demand for diagnostic and therapeutic procedures for chronic non-communicable diseases, especially cardiovascular and neurodegenerative diseases, and an even a greater demand for physical and mental rehabilitation services [225,226]. The multidisciplinary team will be most directly responsible for maintaining the individual's health [227], through a psychosocial support, to discuss the caregiver's role with the patient and family, and the psychotherapeutic support, such as a cognitive-behavioral therapy and a strength perspective therapy; both interventions intended to improve care outcomes, such as function, independence, activities of daily living, dietary control, and mental health [228].

In this sense, a caloric restriction (CR), without malnutrition, appears to protect the Central Nervous System, proving to be the single most consistent non-genetic and non-pharmacological

intervention that prolongs useful longevity [229], from yeast to mammals [230]. It is characterized by a delaying functional decline and preventing age-related diseases [231], as it can decrease the oxidative status and damage in lipids, proteins, and especially mitochondrial DNA, and can also decrease mutations in DNA, in addition to inducing an anti-inflammatory mechanism, promoting synaptic plasticity and white matter integrity, resulting in the beneficial effect during aging [229,232,233].

Epidemiological studies in aged mice demonstrated that the caloric restriction increased the animal's life expectancy, leading to preserved energy production, brain structural integrity, and long-term memory [234]. Recently, Singh, Singh AK, Garg and Rizvi [235] evaluated the potential of fisetin, a caloric restriction mimetic, for neuroprotection in rat models of accelerated aging. It was shown that fisetin benefited aging brains by enhancing a mitochondrial membrane depolarization and apoptotic cell death, as well as causing a decreased expression of inflammatory genes. Thus, fisetin, a substance found in strawberries, tomatoes, onions, apples, and grapes, showed a great potential for stimulating brain mechanisms that, in the long term, improve memory.

Calorie restriction can involve different feeding regimens, such as intermittent fasting or eating every other day, and it refers to reducing the total calorie intake by 20-50% without malnutrition [236]. However, studies in various organisms have concluded that a protein restriction, rather than a calorie restriction, appears to have the greatest effect in slowing aging. Mattison, Colman, Beasley, Allison, Kemnitz et al. [237] assessed that monkeys that weighed less and ate less were healthier until later in life; Paoli, Wakeling, Wright and Ford [238] demonstrated that a restriction of the essential amino acids can increase life expectancy in honeybees; Solon-Biet, McMahon, Ballard, Ruohonen, Wu, Cogger et al. [239] concluded that low-protein, high-carbohydrate diets are associated with a longer life expectancy in mice.

Data in humans indicate that a reduced protein intake may become an important component of anti-cancer and anti-aging dietary interventions [240], so a medium to high carbohydrate and a low but a sufficient protein intake or a normal protein intake but a high legume intake contribute to an increase in life expectancy [241,242]. A recent study based on data provided by the Global Burden of Disease 2019, provided evidence in the support of the longevity diet. A sustained shift from the typical Western diet to an ideal diet rich in vegetables, whole grains and nuts with reduced red and processed meats is associated with an increase in life expectancy of 10.7 years in women and 13 years in men if started at age 20, and over 8 years of an increased life expectancy when started at age 60 [243].

It is evident that healthy aging will decrease adverse effects, such as contaminations and any type of activity that influences the deleterious effects of age gain [8,50], because dementias can have their origin in normal aging processes [21,22], and considering the possibility of increased contaminations, the number of people with dementias in general will increase [198]. This argument indicates that any factor that increases the possibility of acquiring dementia should be avoided.

In the case of the objective of this article, it is the study of the effects of glyphosate, as it is the most widely used pesticide in the world [134], it will be the pesticide, in general terms, with the greatest impact on the contamination of people [136] and, even within the range of lower toxicity, it causes direct neural alterations associated with adjuvants [166,167]. Obviously, more toxic pesticides will generate a greater toxicity, but as glyphosate bioaccumulates, the most widely used in the world becomes the most concerning [189], hence, it acts as a deleterious agent to the neural system and therefore it triggers neural pathologies such as dementias [89].

The care of the elderly population will represent a challenge for the health [223,227], since there is a higher occurrence of chronic and disabling diseases in this age group compared to the others [19], especially with the indiscriminate use of pesticides and a decreased government control [90,190]. Therefore, in terms of literary data, pesticide contamination seems to be a public health problem and a possible driver of dementia and Parkinsonism.

5. CONCLUSIONS

Based on the current understanding of the underlying mechanisms involved, it has been hypothesized that there may be a correlation between age gain and environmental stressors associated with the development of

neurodegenerative disorders, particularly parkinsonism; however, despite the understanding of the necessary components of the etiology of aging and Parkinson's disease, much remains unclear.

In terms of the prevalence of Parkinson's disease, it is known that aging is associated with the susceptibility of dopaminergic neurons to undergo the cell death, which would lead to an exponential increase in the disease; nonetheless, there are elderly people who do not show any senility, so one cannot assume that aging means disease, therefore, factors other than aging, such as the environment, should be taken into consideration as major enhancers to develop the pathology, thus, understanding the events and the pathways that drive the onset and the progression of parkinsonism will shed light on potential therapeutic targets for the disease modification.

Several findings have provided evidence of an epidemiological link between cognitive decline and pesticide exposure, suggesting the existence of a relationship between aging, genetic susceptibility, and environmental factors. Because pesticides are a tool for modern agriculture and continue to be constantly used, it is important that there are strategies to reduce their impact, such as integrated pest management programs to decrease the number of applications, leading to less pesticide use, and the use of personal protective equipment so that the farmers' exposure to pesticides is reduced, as well as seeking to adopt more advanced and less harmful technologies such as natural enemies and permaculture.

As aging is the main contributor to a wide spectrum of chronic disorders, all associated with a lower quality of life in the elderly, one of the main issues facing public health will be the global trend of an increasingly aging society, yet some elderly people have a few health problems, a characteristic that should be extended to the general population. With this, the best anti-aging strategy is to intervene in environmental factors, aiming to reduce the incidence of risk factors for poor health.

The changes resulting from aging can be mitigated and decreased with the practice of a regular and well-guided physical activity, which helps to reduce the degenerations and transformations of the body, also a nutrition control improves the living conditions making aging less drastic for the individual, since several studies have shown that a dietary intervention started at the early stage can benefit the cognitive and the mental reserve in aging.

A public health response that guides stakeholders globally is needed. The governmental system needs environmental controls that oversee the purchasing practices and the use of pesticides, in order to reduce their indiscriminate use and to avoid the environmental damage and provide a greater food safety, given its deleterious effects. It is important that the state offer specific policies that ensure survival and quality of life, and that if it is not possible to zero out the environmental damage, or at least to reduce it. Finally, the society needs to become aware of the consequences of the abusive use of pesticides in order to obtain a healthier food production.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Vilela DSD, Dias CMSB, Sampaio MA. Idosos Encarcerados no Brasil: uma revisão sistemática da literatura. Contextos clínicos. 2021;14(1):304-32.
2. Yun J, Kim CY, Son SH, Bae CW, Choi YS, Chung SH. Birth Rate Transition in the Republic of Korea: Trends and Prospects. J Korean Med Sci. 2022;37(42):e304.
3. Instituto Brasileiro de Geografia e Estatística. Características gerais dos moradores 2020-2021. Rio de Janeiro: IBGE; 2022. Available:https://static.poder360.com.br/2022/07/populacao-ibge-2021-22jul2022.pdf. Acesso em: 14 dez. 2022.
4. Organização Mundial de Saúde. Relatório mundial de envelhecimento e saúde. 2015. Disponível em: https://sbgg.org.br/wp-content/uploads/2015/10/OMS-

ENVELHECIMENTO-2015-port.pdf. Acesso em: 14 dez. 2022.

5. Trevisan K, Cristina-Pereira R, Silva-Amaral D, Aversi-Ferreira TA. Theories of Aging and the Prevalence of Alzheimer's Disease. Biomed Res Int. 2019;2019: 9171424. Available:https://doi.org/10.1155/2019/9171424
6. Kaeberlein M. Longevity and aging. F1000prime reports. 2013;5:1-8.
7. Galkin F, Zhang B, Dmitriev SE, Gladyshev VN. Reversibility of irreversible aging. Ageing Res Rev. 2019;49:104-114. Available:https://doi.org/10.1016/j.arr.2018.11.008
8. Tavares RE, Jesus MCP, Machado DR, Braga VAS, Tocantins FR, Meirighi MAB. Healthy aging from the perspective of the elderly: an integrative review. Revista brasileira de geriatria e gerontologia. 2017;20(6):878-89. Available:https://doi.org/10.1590/1981-22562017020.170091
9. Lipsky MS, King M. Biological theories of aging. Disease-a-month. 2015;61(11):460-66.
10. Amarya S, Singh K, Sabharwal M. Ageing Process and Physiological Changes [Internet]. Gerontology. InTech; 2018;276. Available:http://dx.doi.org/10.5772/intechopen.76249
11. Khan SS, Singer BD, Vaughan DE. Molecular and physiological manifestations and measurement of aging in humans. Aging cell. 2017;16(4):624-33.
12. Steptoe A, Deaton A, Stone AA. Subjective wellbeing, health, and ageing. Lancet. 2015;385(9968):640-48. Available:https://doi.org/10.1016%2FS0140-6736(13)61489-0
13. Gladyshev VN. The origin of aging: imperfectness-driven non-random damage defines the aging process and control of lifespan. Trends Genet. 2013;29(9):506-12. Available:https://doi.org/10.1016/j.tig.2013.05.004
14. Belkacem AN, Jamil N, Palmer JA, Ouhbi S, Chen C. Brain Computer Interfaces for Improving the Quality of Life of Older Adults and Elderly Patients. Front. Neurosci. 2020;14:692. Available:https://doi.org/10.3389/fnins.2020.00692
15. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153(6):1194-217. Available:https://doi.org/10.1016%2Fj.cell.2013.05.039
16. Amarya S, Singh K, Sabharwal M. Changes during aging and their association with malnutrition. J Clin Gerontol Geriatr, Taiwan. 2015;6(3):78-84. Available:https://doi.org/10.1016/j.jcgg.2015.05.003
17. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. Nat Rev Endocrinol. 2018;14(9):513-537. Available:https://doi.org/10.1038/s41574-018-0062-9
18. Santos DCA, Bianchi LRO. Envelhecimento morfofuncional: diferença entre os gêneros. Arquivos do MUDI. 2014;18(2):33-46
19. Meinzer M, Lindenberg R, Antonenko D, Flaisch T, Flöel A. Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. J Neurosci. 2013;33(30):12470-8. Available:https://doi.org/10.1523/jneurosci.5743-12.2013
20. Zanjani S, Tol A, Mohebbi B, Sadeghi R, Jalyani KN, Moradi A. Determinants of healthy lifestyle and its related factors among elderly people. J Educ Health Promot. 2015;4:103
21. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. Alzheimer's Disease Neuroimaging Initiative. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog Neurobiol. 2014;117:20-40. Available:https://doi.org/10.1016/j.pneurobio.2014.02.004
22. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL et al. Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol. 2019;15(10):565-581. Available:https://doi.org/10.1038/s41582-019-0244-7
23. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES et al. Geroscience: linking aging to chronic disease. Cell. 2014;159(4):709-13. Available:https://doi.org/10.1016/j.cell.2014.10.039

24. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R et al. The burden of disease in older people and implications for health policy and practice. Lancet. 2015;385(9967):549-62. Available:https://doi.org/10.1016/s0140-6736(14)61347-7
25. Dong X, You Y, Wu JQ. Building an RNA Sequencing Transcriptome of the Central Nervous System. Neuroscientist. 2016; 22(6):579-92. Available:https://doi.org/10.1177/1073858415610541
26. Simonato M, Bennett J, Boulis NM, Castro MG, Fink DJ, Goins WF et al. Progress in gene therapy for neurological disorders. Nat Rev Neurol. 2013;9(5):277-91. Available:https://doi.org/10.1038%2Fnrneurol.2013.56
27. Alcedo, J, Flatt T, Pasyukova EG. The role of the nervous system in aging and longevity. Front Genet, USA. 2013;(4):124, 1-2. Available:https://doi.org/10.3389/fgene.2013.00124
28. Rosso AL, Studenski SA, Chen WG, Eisenstein HJ, Alexander NB, Bennett DA L. et al. Aging, the central nervous system, and mobility. J Gerontol A Biol Sci Med Sci. 2013;68(11):1379-86. Available:https://doi.org/10.1093/gerona/glt089
29. Engelhardt B, Carare RO, Bechmann I, Flügel A, Laman JD, Weller RO. Vascular, glial, and lymphatic immune gateways of the central nervous system. Acta Neuropathol. 2016;132(3):317-38. Available:https://doi.org/10.1007/s00401-016-1606-5
30. Pandya D, Petrides M, Cipolloni PB. Cerebral cortex: architecture, connections, and the dual origin concept. New York: Oxford University Press; 2015.
31. Molnár Z, Clowry GJ, Šestan N, Alzu'bi A, Bakken T, Hevner RF et al. New insights into the development of the human cerebral cortex. J Anat. 2019;235(3):432-451. Available:https://doi.org/10.1111/joa.13055
32. Leopold DA, Strick PL, Basset DS, Bruno RM, Cuntz BH, Harris KM et al. Functional architecture of the cerebral cortex. In: Singer W, Sejnowski TJ, Rakic P, editors. The neocortex. USA: Strüngmann Forum Reports; 2020.
33. Lodato S, Arlotta P. Generating neuronal diversity in the mammalian cerebral cortex. Annu Rev Cell Dev Biol. 2015;31:699-720. Available:https://doi.org/10.1146/annurev-cellbio-100814-125353.
34. Grasby KL, Jahanshad N, Painter JN, Colodro-Conde L, Bralten J, Hibar DP et al. The genetic architecture of the human cerebral cortex. Science. 2020;367(6484): eaay6690. Available:https://doi.org/10.1126/science.aay6690
35. Van Velsen EF, Vernooij MW, Vrooman HA, van der Lugt A, Breteler MM, Hofman A et al. Brain cortical thickness in the general elderly population: the Rotterdam Scan Study. Neurosci Lett. 2013;550:189-94. Available:https://doi.org/10.1016/j.neulet.2013.06.063
36. Cabeza R, Albert M, Belleville S, Craik FIM, Duarte A, Grady CL, et al. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nat Rev Neurosci. 2018;19(11): 701-10. Available:https://doi.org/10.1038/s41583-018-0068-2
37. Ferreira LK, Busatto GF. Resting-state functional connectivity in normal brain aging. Neurosci Biobehav Rev. 2013; 37(3):384-400. Available:https://doi.org/10.1016/j.neubiorev.2013.01.017
38. Da Costa JP, Vitorino R, Silva GM, Vogel C, Duarte AC, Rocha-Santos T. A synopsis on aging-Theories, mechanisms and future prospects. Ageing Res Rev. 2016;29:90-112. Available:https://doi.org/10.1016/j.arr.2016.06.005
39. Stambler I. Recognizing degenerative aging as a treatable medical condition: Methodology and policy. Aging and Disease. 2017;8(5):583.
40. Saraiva EG, Rodrigues WVL, Araújo TO, Araújo ICR, Bertozzo CCMS. Alterações anátomo-fisiológicas na pessoa idosa e a importância da assistência de enfermagem na senescência e na senilidade. In: Da Costa GM, Porto MLS, Orgs. Saúde a serviço da vida 3 ed. Imea: João Pessoa; 2020.
41. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J et al. Parkinson disease. Nat Rev Dis Primers. 2017;3:17013.

Available:https://doi.org/10.1038/nrdp.2017.13
42. Reeve A, Simcox E, Turnbull D. Ageing and Parkinson's disease: why is advancing age the biggest risk factor? Ageing Res Rev. 2014;14(100):19-30. Available:https://doi.org/10.1016/j.arr.2014.01.004
43. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. J Neurochem. 2016;139:318-24.
44. Engelender S, Isacson O. The Threshold Theory for Parkinson's Disease. Trends Neurosci. 2017;40(1):4-14. Available:https://doi.org/10.1016/j.tins.2016.10.008
45. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB; Alzheimer's disease neuroimaging initiative. Brain changes in older adults at very low risk for Alzheimer's disease. J Neurosci. 2013;33(19):8237-42. Available:https://doi.org/10.1523%2FJNEUROSCI.5506-12.2013
46. Harada CN, Natelson LMC, Triebel KL. Normal cognitive aging. Clin Geriatr Med. 2013;29(4):737-52.
47. Holmqvist S, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Björklund T et al. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol. 2014;128(6):805-20. Available:https://doi.org/10.1007/s00401-014-1343-6
48. Watanabe H, Bagarinao E, Maesawa S, Hara K, Kawabata K, Ogura Aya et al. Characteristics of neural network changes in normal aging and early dementia. Front Aging Neurosci. 2021;13:747359. Available:https://doi.org/10.3389/fnagi.2021.747359
49. Miranda GMD, Mendes ACG, Silva ALA. Population aging in Brazil: current and future social challenges and consequences. Rev Bras Geriatr Gerontol. 2016;19(3):507-19.
50. Bamidis PD, Vivas AB, Styliadis C, Frantzidis C, Klados M, Schlee W. A review of physical and cognitive interventions in aging. Neurosci Biobehav Rev. 2014;44:206-20. Available:https://doi.org/10.1016/j.neubiorev.2014.03.019
51. Jahn K. The aging vestibular system: dizziness and imbalance in the elderly. Vestibular disorders. 2019;82:143-49. 52.
52. Marras C, Beck JC, Bower JH, Roberts E, Ritz B, Ross GW et al. Prevalence of Parkinson's disease across North America. NPJ Parkinsons Dis. 2018;4(1):21.
53. Ou Z, Pan J, Tang S, Duan D, Yu D, Nong H et al. Global Trends in the Incidence, Prevalence, and Years Lived With Disability of Parkinson's Disease in 204 Countries/Territories From 1990 to 2019. Front Public Health. 2021;9:776847. Available:https://doi.org/10.3389/fpubh.2021.776847
54. Simon DK, Tanner CM, Brundin P. Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology. Clin Geriatr Med. 2020;36(1):1-12. Available:https://doi.org/10.1016/j.cger.2019.08.002
55. Hayes MT. Parkinson's disease and parkinsonism. The American journal of medicine. 2019;132(7):802-07.
56. DeMaagd G, Philip A. Parkinson's Disease and Its Management: Part 1: Disease Entity, Risk Factors, Pathophysiology, Clinical Presentation, and Diagnosis. P T. 2015;40(8):504-32. PMID: 26236139; PMCID: PMC4517533.
57. Menon NM, Adiga M, Pady AE. Understanding Parkinson's disease (PD) in Ayurvedic Prospective. Int J Ayurveda Pharma Res. 2021;9(6):86-92.
58. Radhakrishnan DM, Goyal V. Parkinson's disease: A review. Neurol India. 2018;66(Supplement):S26-S35. Available:https://doi.org/10.4103/0028-3886.226451
59. Chen W, Hopfner F, Becktepe JS, Gunther D, et al. Rest tremor revisited: Parkinson's disease and other disorders. Transl Neurodegener. 2017; 6:16. Available:https://doi.org/10.1186/s40035-017-0086-4
60. Ashford S, Mcintyre A. The Ageing Body–Body Functions and Structures: Part 1. Occupational Therapy and Older People, Chichester. 2013;120-145.2013. Available:http://dx.doi.org/10.1002/9781118782835.ch6
61. Nikhara V. The aging brain: Recent research and concepts. Gerontol Geriatr Stud. 2017;1:1-11.
62. Schwartz RS, Halliday GM, Soh D, Cordato DJ, Kril JJ. Impact of small vessel disease on severity of motor and cognitive impairment in Parkinson's disease. J Clin Neurosci. 2018;58:70-74.

Available:https://doi.org/10.1016/j.jocn.2018.10.029
63. Shibata K, Sugiura M, Nishimura Y, Sakura H. The effect of small vessel disease on motor and cognitive function in Parkinson's disease. Clin Neurol Neurosurg. 2019;182:58-62. Available:https://doi.org/10.1016/j.clineuro.2019.04.029
64. Vallabhajosula S, Buckley TA, Tillman MD, Hass CJ. Age and Parkinson's disease related kinematic alterations during multi-directional gait initiation. Gait Posture. 2013;37(2):280-6. Available:https://doi.org/10.1016/j.gaitpost.2012.07.018
65. Casale J, Browne T, Murray IV, Gupta G. Physiology, Vestibular System. [Updated 2022 dez 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available:https://www.ncbi.nlm.nih.gov/books/NBK532978
66. Battilana F. The effect of age and exercise on the proprioceptive and vestibular system. 2019. 129 f. Thesis (Doctorate in Philosophy) - University of Basel, Faculty of Science, Basel; 2019. Available:http://dx.doi.org/10.5451/unibas-007110965
67. Khan S, Chang R. Anatomy of the vestibular system: A review. Neuro Rehabilitation. 2013;32(3):437-43.
68. Murray AJ, Croce K, Belton T, Akay T, Jessell TM. Balance Control Mediated by Vestibular Circuits Directing Limb Extension or Antagonist Muscle Co-activation. Cell Rep. 2018;22(5):1325-1338. Available:https://doi.org/10.1016/j.celrep.2018.01.009
69. Anson E, Jeka J. Perspectives on aging vestibular function. Frontiers in neurology, USA. 2016;6:269. Available:https://doi.org/10.3389/fneur.2015.00269
70. Coto J, Alvarez CL, Cejas I, Colbert BM, Levin BE, Huppert J, et al. Peripheral vestibular system: Age-related vestibular loss and associated deficits. J Otol. 2021; 16(4):258-65. Available:https://doi.org/10.1016/j.joto.2021.06.001
71. Srivanitchapoom P, Pitakpatapee Y, Suengtaworn A. Parkinsonian syndromes: A review. Neurology India. 2018;66(7):15-25.
72. El Sayed ESK, Eissa A, Nofal S, Elmorsy E. Parkinson's Disease: A Review about Pathogenesis, Treatment and Experimental Models. J Adv Pharm Res. 2018;2(3):142-61. Available:https://dx.doi.org/10.21608/aprh.2018.8013
73. Elbaz A, Carcaillon L, Kab S, Moisan F. Epidemiology of Parkinson's disease. Rev Neurol, Paris. 2016;172(1):14-26. Available:https://doi.org/10.1016/j.neurol.2015.09.012
74. Kouli A, Torsney KM,Kuan WL. Parkinson's disease: Etiology, neuropathology, and pathogenesis. Exon Publications. 2018;3-26.
75. Rocha EM, Keeney MT, Di Maio R, De Miranda BR, Greenamyre JT. LRRK2 and idiopathic Parkinson's disease. Trends Neurosci. 2022;45(3):224-236. Available:https://doi.org/10.1016/j.tins.2021.12.002
76. De Miranda BR., Greenamyre JT. Etiology and Pathogenesis of Parkinson's Disease. *In*: Franco R, Doorn JA, Rochet J-C (Eds.). Oxidative Stress and Redox Signalling in Parkinson's Disease, London: Royal Society of Chemistry; 2017.
77. Wong JC, Hazrati LN. Parkinson's disease, parkinsonism, and traumatic brain injury. Crit Rev Clin Lab Sci. 2013;50(4-5):103-6. Available:https://doi.org/10.3109/10408363.2013.844678
78. Bohlega SA, Al-Foghom NB. Drug-induced Parkinson's disease. A clinical review. Neurosciences (Riyadh). 2013;18(3):215-21. PMID: 23887211.
79. Garg K, Rajan R, Singh M. Drug-Induced Parkinsonism. Neurology India. 2021; 69(2):437.
80. Jeong S, Cho H, Kim YJ, Ma HI, Jang S. Drug-induced Parkinsonism: A strong predictor of idiopathic Parkinson's disease. PLoS One. 2021;16(3):e0247354. Available:https://doi.org/10.1371/journal.pone.0247354
81. Levin OS, Chimagomedova AS, Skripkina NA, Lyashenko EA, Babkina OV. Nonmotor Symptoms in Vascular and Other Secondary Parkinsonism. Int Rev Neurobiol. 2017;134:1303-1334. Available:https://doi.org/10.1016/bs.irn.2017.05.016
82. Heim B, Krismer F, Seppi K. Structural imaging in atypical parkinsonism. Int Rev Neurobiol. 2018;142:67-148.

83. Mcfarland NR. Diagnostic approach to atypical parkinsonian syndromes. Continuum (Minneap Minn). 2016;22(4): 1117-142.
84. O'Dowd S, Healy D, Bradley D. Parkinsonism-plus syndromes. Neurodegener Dis. 2016;181-98.
85. Stamelou M, Hoeglinger GU. Atypical parkinsonism: An update. Curr Opin Neurol. 2013;26(4):401-5. Available:https://doi.org/10.1097/wco.0b013e3283632da6
86. Levin J, Kurz A, Arzberger T, Giese A, Höglinger GU. The differential diagnosis and treatment of atypical Parkinsonism. Dtsch Arztebl Int. 2016;113(5):61-9
87. Abbott SM, Videnovic A. Sleep disorders in atypical parkinsonism. Movement Disorders Clinical Practice, USA. 2014;1(2):89-96. Available:https://doi.org/10.1002/mdc3.12025
88. Stamelou M, Bhatia KP. Atypical parkinsonism: Diagnosis and treatment. Neurol Clin. 2015;33(1):39-56. Available:https://doi.org/10.1016/j.ncl.2014.09.012
89. Alengebawy A, Abdelkhalek ST, Qureshi SR, Wang MQ. Heavy Metals and Pesticides Toxicity in Agricultural Soil and Plants: Ecological Risks and Human Health Implications. Toxics, Basel. 2021; 9(3):42. Available:https://doi.org/10.3390%2Ftoxics9030042
90. Frota MTBA, Siqueira, CE. Pesticides: the hidden poisons on our table. Reports in public health, USA. 2021;37(2): e00004321. DOI: 10.1590/0102-311X00004321
91. Sharma N, Singhvi R. Effects of chemical fertilizers and pesticides on human health and environment: a review. Int J Environ Agric Biotechnol. 2017;10(6):675-80.
92. Organização das Nações Unidas. World Population Prospects 2022. 2022. Available:https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/wpp2022_summary_of_results.pdf?_gl=1*jp1gh5*_ga*Mzg1ODk5MTc5LjE2NzM4ODU3MzE.*_ga_TK9BQL5X7Z*MTY3NDQ5MTY1MC4xLjAuMTY3NDQ5MTY1MC4wLjAuMA. Acesso em: 10 dez. 2022
93. Delcour I, Spanoghe P, Uyttendaele M. Literature review: Impact of climate change on pesticide use. Food Res Int, Amsterdam. 2015;68:7-15. Available:https://www.researchgate.net/publication/267544278
94. Matzrafi M. Climate change exacerbates pest damage through reduced pesticide efficacy. Pest Manag Sci. 2019;75(1):9-13.
95. Carvalho FP. Pesticides, environment, and food safety. Food Energy Secur, USA. 2017;6(2):48-60. Available: https://doi.org/10.1002/fes3.108
96. Tang FHM, Lenzen M, Mcbratney A, Maggi F. Risk of pesticide pollution at the global scale. Nat Geosci. 2021;4:206-210.
97. Tudi M, Daniel Ruan H, Wang L, Lyu J, Sadler R, Connell D, et al. Agriculture Development, Pesticide Application and Its Impact on the Environment. Int J Environ Res Public Health. 2021;18(3):1112. Available:https://doi.org/10.3390/ijerph18031112
98. Woodrow JE, Gibson KA, Seiber JN. Pesticides and Related Toxicants in the Atmosphere. Rev Environ Contam Toxicol. 2019;247:147-196. Available:https://doi.org/10.1007/398_2018_19
99. Enserink M, Hines PJ, Vignieri SN, Wigginton NS, Yeston JS. Smarter pest control. The pesticide paradox. Introduction. Science. 2013;341(6147): 728-9. Available:https://doi.org/10.1126/science.341.6147.728
100. Mahmood I, Imadi SR, Shazadi K, Gul A, Hakeem KR. Effects of pesticides on environment. In: Hakeen K, Akhtar M, Abdullah S, editors. Plant, soil and microbes. Cham: Springer; 2016.
101. Mengistie B,Mol APJ, Oosterveer P. Pesticide use practices among smallholder vegetable farmers in Ethiopian Central Rift Valley. Environ Dev Sustain. 2017;19:301-24.
102. Zhao L, Wang C, Gu Haiying, Yue C. Market incentive, government regulation and the behavior of pesticide application of vegetable farmers in China. Food Control. 2018;85:308-17.dark
103. Farswan K. Effects of chemical fertilizer pesticides on human health. Asian J Res Soc Sci Humanit, India. 2021;11(12):77-80. DOI: 10.5958/2249-7315.2021.00323.3
104. Tilman D, Clark M. Food, agriculture & the environment: Can we feed the world &

save the earth? Daedalus. 2015;144(4):8-23.
Available:https://doi.org/10.1016/j.parkreldis.2016.02.019

105. Dar MA, Kaushik G, Chiu J FV. Pollution status and biodegradation of organophosphate pesticides in the environment. In: Singh P, Kumar A, Borthakur A (Eds.). Abatement of environmental pollutants, Amsterdam: Elsevier, 2020:25-66.
Available:https://doi.org/10.1016/B978-0-12-818095-2.00002-3
106. Hassaan MA, El Nemr A. Pesticides pollution: Classifications, human health impact, extraction and treatment techniques. Egypt J Aquat Res. 2020; 46(3):207-20.
107. Weis GCC, Alves AO, Assmann CE, Bonadiman BRS, Costabeber IH. Pesticides: classifications, exposure and risks to human health. Arch Biosc Health. 2019;1(1):29-44.
108. Boedeker W, Watts M, Clausing P, Marquez E. The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review. BMC Public Health. 2020;20: 1875.
Available:https://doi.org/10.1186/s12889-020-09939-0
109. Organização das Nações Unidas. Report of the Special Rapporteur on the right to food. Human Rights Council Thirty-Fourth Session. 2017.
Available:https://digitallibrary.un.org/record/861172?ln=en. Acesso em: 10 dez. 2022.
110. Pan-Uk – Pesticide Action Network Uk. Pesticide poisoning. 2020.
Available:https://www.pan-uk.org/pesticide-poisoning/
Acesso em: 11 dez. 2022
111. Jayaraj R, Megha P, Sreedev P. Organochlorine pesticides, their toxic effects on living organisms and their fate in the environment. Interdiscip Toxicol. 2016; 9(3-4):90-100.
112. Rani M, Shanker U, Jassal V. Recent strategies for removal and degradation of persistent & toxic organochlorine pesticides using nanoparticles: A review. J Environ Manage. 2017;190:208-222.
Available:https://doi.org/10.1016/j.jenvman.2016.12.068
113. Chandra R, Sharpanabharathi N, Prusty BAK, Azeez PA, Kurakalva RM. Organochlorine pesticide residues in plants and their possible ecotoxicological and agri food impacts. Sci Rep. 2021;11(1):17841.
Available:https://doi.org/10.1038/s41598-021-97286-4
114. Qi SY, Xu XL, Ma WZ, Deng SL, Lian ZX, Yu K. Effects of Organochlorine Pesticide Residues in Maternal Body on Infants. Front Endocrinol (Lausanne). 2022;13: 890307.
Available:https://doi.org/10.3389/fendo.2022.890307
115. Pirsaheb M, Limoee M, Namdari F, Khamutian R. Organochlorine pesticides residue in breast milk: a systematic review. Med J Islam Repub Iran. 2015;29:228.
116. Parada H Jr, Wolff MS, Engel LS, White AJ, Eng SM, Cleveland RJ et al. Organochlorine insecticides DDT and chlordane in relation to survival following breast cancer. Int J Cancer. 2016;138(3): 565-75.
Available:https://doi.org/10.1002/ijc.29806
117. Singh NS, Sharma R, Parween T, Patanjali PK. Pesticide contamination and human health risk factor. In: Oves M, Khan MZ, Ismail IMI, editors. Modern age environmental problems and their remediation. Cham: Springer; 2018.
Available:https://doi.org/10.1007/978-3-319-64501-8_3
118. Kim KS, Lee YM, Lee HW, Jacobs DR Jr, Lee DH. Associations between organochlorine pesticides and cognition in U.S. elders: National Health and Nutrition Examination Survey 1999-2002. Environ Int. 2015;75:87-92.
Available:https://doi.org/10.1016/j.envint.2014.11.003
119. Kaur R, Mavi GK, Raghav S. Pesticides classification and its impact on environment. Int J Curr Microbiol Appl Sci. 2019;8(3):1889-897.
120. Keswani C, Dilnashin H, Birla H, Roy P, Tyagi RK, Singh D et al. Global footprints of organochlorine pesticides: a pan-global survey. Environ Geochem Health. 2022; 44(1):149-177.
Available:https://doi.org/10.1007/s10653-021-00946-7
121. Fang J, Liu H, Zhao H, Wong M, Xu S, Cai Z. Association of prenatal exposure to organochlorine pesticides and birth size. Sci Total Environ. 2019;654:678-83.
Available:https://doi.org/10.1016/j.scitotenv.2018.10.384
122. Maurice C, Kaczmarczyk M, Côté N, Tremblay Y, Kimmins S, Bailey J.Prenatal

exposure to an environmentally relevant mixture of Canadian Arctic contaminants decreases male reproductive function in an aging rat model. J Dev Orig Health Dis. 2018;9(5):511-18.
123. Ye M, Beach J, Martin JW, Senthilselvan A. Pesticide exposures and respiratory health in general populations. Journal of Environmental Sciences. 2017;51:361-70.
124. Köhler HR, Triebskorn R. Wildlife ecotoxicology of pesticides: can we track effects to the population level and beyond? Science. 2013;341(6147):759-65. Available:https://doi.org/10.1126/science.1237591
125. Kumar S, Kaushik G, Villarreal-Chiu JF. Scenario of organophosphate pollution and toxicity in India: A review. Environ Sci Pollut Res Int. 2016;23(10):9480-91. Available:https://doi.org/10.1007/s11356-016-6294-0
126. Chandra, R; Kumar, V. Biotransformation and biodegradation of organophosphates and organohalides. Environmental waste management, Sydney. 2015;475-524. Available:http://dx.doi.org/10.1201/b19243-17
127. Upadhiay Lata SB, Dutt A. Microbial Detoxification of Residual Organophosphate Pesticides in Agricultural Practices. In: Patra J, Vishnuprasad C, Das G. (Eds). Microbial Biotechnology. 2017:225-242.
128. Ajiboye TO, Oladoye PO, Olanrewaju CA, Akinsola GO. Organophosphorus pesticides: Impacts, detection and removal strategies. Environ Nanotechnol Monit Manag, USA. 2022;17. Available:https://doi.org/10.1016/j.enmm.2022.100655
129. Chowdhary S, Bhattacharyya R, Banerjee D. Acute organophosphorus poisoning. Clin Chim Acta. 2014;20(431):66-76. Available:https://doi.org/10.1016/j.cca.2014.01.024
130. Piermartiri T, Pan H, Figueiredo TH, Marini AM. α-Linolenic Acid, A Nutraceutical with Pleiotropic Properties That Targets Endogenous Neuroprotective Pathways to Protect against Organophosphate Nerve Agent-Induced Neuropathology. Molecules. 2015;20(11):20355-80. Available:https://doi.org/10.3390%2Fmolecules201119698
131. Robb EL, Baker MB. Organophosphate toxicity; 2017.
132. Worek F, Thiermann H, Wille T. Organophosphorus compounds and oximes: A critical review. Arch Toxicol. 2020;94(7):2275-2292. Available:https://doi.org/10.1007/s00204-020-02797-0
133. Alcántara-de La Cruz R, Oliveira GM, Carvalho LB, Silva MFGF. Herbicide resistance in Brazil: status, impacts, and future challenges. *In:* Kontogiannatos D, Kourti A; Mendes KF (eds.). Pests, weeds and diseases in agricultural crop and animal husbandry production. London: IntechOpen. 2020;153-178. DOI: 10.5772/intechopen.91236
134. Benbrook CM. Trends in glyphosate herbicide use in the United States and globally. Environ Sci Eur. 2016;28(1):3. Available:https://doi.org/10.1186%2Fs12302-016-0070-0
135. Das SK, Mondal T. Mode of action of herbicides and recent trends in development: A Reappraisal. Int. J. Agric. Soil Sci. 2014;2(3):28-32. Available:https://www.researchgate.net/publication/303130418
136. Soares D, Silva L, Duarte S, Pena A, Pereira A. Glyphosate Use, Toxicity and Occurrence in Food. Foods. 2021;10(11): 2785. Available:https://doi.org/10.3390%2Ffoods10112785
137. Duke SO. The history and current status of glyphosate. Pest Manag Sci. 2018;74(5): 1027-34. Available:https://doi.org/10.1002/ps.4652
138. Martins-Gomes C, Silva TL, Andreani T, Silva AM. Glyphosate vs. glyphosate-based herbicides exposure: a review on their toxicity. J Xenobiot. 2022;12(1):21-40.
139. Yalsuyi AM, Vajargah MF, Hajimoradloo A, Galangash MM, Prokić MD, Faggio C. Evaluation of Behavioral Changes and Tissue Damages in Common Carp (*Cyprinus carpio*) after Exposure to the Herbicide Glyphosate. Vet Sci. 2021; 8(10):218. Available:https://doi.org/10.3390/vetsci8100218
140. Gillezeau C, Gerwen MV, Shaffer RM, Rana I, Zhang L, Sherppard L et al. The evidence of human exposure to glyphosate: A review. Environmental Health. 2019;18(2)1-14.
141. FAO – Organização das Nações Unidas para Alimentação e Agricultura. Global

pesticide agricultural use 2020, by type. FAO; 2022.
Available:https://www.statista.com/statistics/1263206/global-pesticide-use-by-type/
Acesso em: 22 abril 2022.

142. FAO – Organização das Nações Unidas para Alimentação e Agricultura. Brazil: top-selling agrochemicals sales volume 2020. FAO; 2021.
Available:https://www.statista.com/statistics/879039/brazil-sales-volume-top-selling-agrochemicals/
Acesso em 22 abril 2022.
143. Novotny E. Glyphosate, roundup and the failures of regulatory assessment. Toxics. 2022;10(6):321.
144. Saleh SMM, Elghareeb TA, Ahmed MAI, Mohamed IA, El-Din HA. Hepato-morpholoy and biochemical studies on the liver of albino rats after exposure to glyphosate-Roundup®. J Basic Appl Zool. 2018;79(1):1-11.
145. Defarge N, Takács E, Lozano VL, Mesnage R, Spiroux de Vendômois J, Séralini GE, et al. Co-Formulants in Glyphosate-Based Herbicides Disrupt Aromatase Activity in Human Cells below Toxic Levels. Int J Environ Res Public Health. 2016;13(3):264.
Available:https://doi.org/10.3390/ijerph13030264
146. Mesnage R, Defarge N, Spiroux de Vendômois J, Séralini GE. Major pesticides are more toxic to human cells than their declared active principles. Biomed Res Int. 2014;2014:179691.
Available:https://doi.org/10.1155%2F2014%2F17969
147. Séralini G. Why glyphosate is not the issue with Roundup. J Biol Phys Chem. 2015; 15(3):111-19.
148. Do MH, Dubreuil B, Peydecastaing J, Vaca-Medina G, Nhu-Trang TT, Jaffrezic-Renault N, et al. Chitosan-Based Nanocomposites for Glyphosate Detection Using Surface Plasmon Resonance Sensor. Sensors (Basel). 2020;20(20) 5942.
Available:https://doi.org/10.3390%2Fs20205942
149. Jayasumana C,Gunatilake S, Senanayake P. Glyphosate, hard water and nephrotoxic metals: are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in Sri Lanka?. Int J Environ Res Public Health. 2014;1(2): 2125-147.
150. Maqueda C, Undabeytia T, Villaverde J, Morillo E. Behaviour of glyphosate in a reservoir and the surrounding agricultural soils. Sci Total Environ. 2017;593-594:787-795.
Available:https://doi.org/10.1016/j.scitotenv.2017.03.202
151. Poiger T, Keller M, Buerge IJ, Balmer ME. Behavior of Glyphosate in Wastewater Treatment Plants. Chimia (Aarau). 2020; 74(3): 156-160.
Available:https://doi.org/10.2533/chimia.2020.156
152. Romano RM, de Oliveira JM, de Oliveira VM, de Oliveira IM, Torres YR, Bargi-Souza P, et al. Could Glyphosate and Glyphosate-Based Herbicides Be Associated With Increased Thyroid Diseases Worldwide? Front Endocrinol (Lausanne). 2021;12:627167.
Available:https://doi.org/10.3389/fendo.2021.627167
153. Ulrich JC, Ferguson PL. Development of a sensitive direct injection LC-MS/MS method for the detection of glyphosate and aminomethylphosphonic acid (AMPA) in hard waters. Analytical and Bioanalytical Chemistry. 2021;413:3763-774.
154. Azania CAM, Rossini LP, Adriano RC, Perecin D, Padua A. The Use of Glyphosate in Sugarcane: A Brazilian Experience [Internet]. Herbicides - Current Research and Case Studies in Use. In Tech. 2013;153-173.
Available:http://dx.doi.org/10.5772/54958
155. Da Silva Ramos N, Bandeira SB, Gonçalves FB, Medieros JH, Dotto MC, Andrade DIO, et al. Physiological and Biochemical Changes in Acacia Mangium Seedlings under Glyphosate Application. Int J Appl Eng Res, India. 2020;15(4):321-7.
156. Firdous S, Iqbal S, Anwar S, Jabeen H. Identification and analysis of 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) gene from glyphosate-resistant Ochrobactrum intermedium Sq20. Pest Manag Sci. 2018;74(5):1184-96.
Available:https://doi.org/10.1002/ps.4624
157. Fuchs B, Saikkonen K, Helander M. Glyphosate-Modulated Biosynthesis Driving Plant Defense and Species Interactions. Trends Plant Sci. 2021;26(4): 312-323.
Available:https://doi.org/10.1016/j.tplants.2020.11.004

158. Leino L, Tall T, Helander M, Saloniemi I, Saikkonen K, Ruuskanen S et al. Classification of the glyphosate target enzyme (5-enolpyruvylshikimate-3-phosphate synthase) for assessing sensitivity of organisms to the herbicide. J Hazard Mater. 2021;408:124556.
Available:https://doi.org/10.1016/j.jhazmat.2020.124556
159. Solomon K, Gil JLR; Prosser R. Ecotoxicology of formulated glyphosate: The role of the active and the formulants. Local organizing committee association of greek chemists regional department of central and western Macedonia. 2019;642-44.
160. Tarazona JV, Court-Marques D, Tiramani M, Reich H, Pfeil R, Istace F et al. Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. Archives of toxicology. 2017;91:2723-743.
Available:https://doi.org/10.1007/s00204-017-1962-5
161. International Agency for Research on Cancer. Monographs on the evaluation of carcinogenic risks to humans, v. 112. Evaluation of five organophosphate insecticides and herbicides. Lyon, France: IARC; 2015.
Available:https://www.iarc.who.int/wp-content/uploads/2018/07/MonographVolume112-1.pdf
Acesso em: 17 fev. 2022.
162. European Food Safety Authority (EFSA). Glyphosate report. 2015;4.
Available:https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/efsaexplainsglyphosate151112en.pdf
Acessed 12 december, 2022.
163. European Union – Glyphosate: EFSA updates toxicological profile; 2015.
Available:https://www.efsa.europa.eu/en/press/news/151112
Acessed 12 december 2022.
164. Environmental Protection agency (EPA). Draft Human Health and Ecological Risk Assessments for Glyphosate. US: EPA; 2016.
Available:https://www.epa.gov/ingredients-used-pesticide-products/draft-human-health-and-ecological-risk-assessments-glyphosate
Acessed 10 december 2022.
165. Richmond ME. Glyphosate: A review of its global use, environmental impact, and potential health effects on humans and other species. J Environ Stud Sci, USA. 2018;8:416-34.
Available:https://doi.org/10.1007/s13412-018-0517-2
166. Sharma A, Kumar V, Shahzad B, Tanveer M, Sidhu GPS, Handa N et al. Worldwide pesticide usage and its impacts on ecosystem. SN Applied Sciences. 2019;1:1-16.
167. Huang J, Gao Z, Hu G, Su G. Non-target screening and risk assessment of organophosphate esters (OPEs) in drinking water resource water, surface water, groundwater, and seawater. Environ Int. 2022;168:107443.
Available:https://doi.org/10.1016/j.envint.2022.107443
168. Vasseghian Y, Alimohamadi M, Khataee A, Dragoi EN. A global systematic review on the concentration of organophosphate esters in water resources: Meta-analysis, and probabilistic risk assessment. Sci Total Environ. 2022;807(2):150876.
Available:https://doi.org/10.1016/j.scitotenv.2021.150876
169. Green JM. Current state of herbicides in herbicide-resistant crops. Pest Management Science. 2014;70(9):1351-357.
170. Gunstone T, Cornelisse T, Klein K, Dubey A, Donley N. Pesticides and soil invertebrates: A hazard assessment. Front Environ Sci. 2021;9:122.
171. Prashar P, Shah S. Impact of fertilizers and pesticides on soil microflora in agriculture. Sustainable Agriculture Reviews. 2016;19;331-61.
172. Bailone RL, Aguiar L, Roca RO, Correa T, Junke H, Silva Fukushima HC. ?Zebrafish as an animal model for food safety research: trends in the animal research? Food Biotechnol. Philadelphia. 2019;33(4):283-302.
Available:http://hdl.handle.net/11449/197537
173. Costas-Ferreira C, Durán R, Faro LRF. Toxic Effects of Glyphosate on the Nervous System: A Systematic Review. Int J Mol Sci. 2022;23(9):4605.
Available:https://doi.org/10.3390/ijms23094605
174. Mesnage R, Arno M, Costanzo M, Malatesta M, Serálini GE, Antoniou MN. Transcriptome profile analysis reflects rat liver and kidney damage following chronic

ultra-low dose Roundup exposure. Environmental Health. 2015;14:1-14.
175. Kissane Z, Shephard JM. The rise of glyphosate and new opportunities for biosentinel early-warning studies. Conserv Biol. 2017;31(6):1293-1300. Available:https://doi.org/10.1111/cobi.12955.
176. Myers JP, Antoniou MN, Blumberg B, Carroll Lynn, Colborn T, Everett LG et al. Concerns over use of glyphosate-based herbicides and risks associated with exposures: A consensus statement. Environmental Health. 2016;15(1): 1-13.
177. Ahmed AI, Abd-El-Hameed B. Histopathological changes in the tongue, palate and parotid gland after exposure to glyphosate. Al-Azhar Assiut Dental Journal, Egypt. 2018;1(1):17-22. Available:https://dx.doi.org/10.21608/aadj.2018.53926
178. Eddleston M. Poisoning by pesticides. Medicine, Amsterdam. 2020; 48(3): 214-7. Available:https://doi.org/10.1016/j.mpmed.2019.12.019
179. Vukotić M, Paleksić V, Narić S. Acute poisoning with herbicide glyphosate. Scripta Medica. 2018;49(2):141-44.
180. Muñoz-Quezada MT, Lucero BA, Barr DB, Steenland K, Levy K, Ryan PB et al. Neurodevelopmental effects in children associated with exposure to organophosphate pesticides: A systematic review. Neurotoxicology. 2013;39:158-68. Available:https://doi.org/10.1016%2Fj.neuro.2013.09.003
181. Syed F, John PJ, Soni I. Neurodevelopmental consequences of gestational and lactational exposure to pyrethroids in rats. Environmental Toxicology. 2016;31(12):1761-770.
182. Antonelli MC, Pallarés ME, Ceccatelli S, Spulber S. Long-term consequences of prenatal stress and neurotoxicants exposure on neurodevelopment. Prog Neurobiol. 2017;155:2-35. Available:https://doi.org/10.1016/j.pneurobio.2016.05.005
183. Modgil S, Lahiri DK, Sharma VL, Anand A. Role of early life exposure and environment on neurodegeneration: Implications on brain disorders. Transl Neurodegener. 2014;3:9. Available:https://doi.org/10.1186/2047-9158-3-9
184. Neuwirth LS, Phillips GR, El Idrissi A. Perinatal Pb2+ exposure alters the expression of genes related to the neurodevelopmental GABA-shift in postnatal rats. Journal of Biomedical Science. 2018;25(45):1-11.
185. Cao M, Wang Y, Yang F, Li J, Qin X. Melatonin rescues the reproductive toxicity of low-dose glyphosate-based herbicide during mouse oocyte maturation via the GPER signaling pathway. J Pineal Res. 2021;70(3): e12718. Available:https://doi.org/10.1111/jpi.12718
186. Fucic A, Duca RC, Galea KS, Maric T, Garcia K, Bloom MS et al. Reproductive Health Risks Associated with Occupational and Environmental Exposure to Pesticides. Int J Environ Res Public Health. 2021; 18(12):6576. Available:https://doi.org/10.3390/ijerph18126576
187. Gupta PK. Herbicides and fungicides. In*:* Gupta RC. Reproductive and developmental toxicology. Academic Press. 2017;657-679.
188. Parvez S, Gerona RR, Proctor C, Friesen M, Ashby JL, Reiter JL et al. Glyphosate exposure in pregnancy and shortened gestational length: A prospective Indiana birth cohort study. Environmental Health. 2018;17(23):1-12. Available:https://doi.org/10.1186/s12940-018-0367-0.
189. Panzacchi S, Mandrioli D, Manservisi F, Bua L, Falcioni L, Spinaci M et al. The Ramazzini Institute 13-week study on glyphosate-based herbicides at human-equivalent dose in Sprague Dawley rats: study design and first in-life endpoints evaluation. Environ Health. 2018;17(1):52. Available:https://doi.org/10.1186/s12940-018-0393-y
190. Hamdaoui L, Oudadesse H, Lefeuvre B, Mahmoud A, Naifer M, Badraoui R et al. Sub-chronic exposure to Kalach 360 SL, Glyphosate-based Herbicide, induced bone rarefaction in female Wistar rats. Toxicology. 2020;436:152412. Available:https://doi.org/10.1016/j.tox.2020.152412.
191. Ait-Bali Y, Ba-M'hamed S, Gambarotta G, Sassoé-PognettoM, Giustetto M, Bennis M. Pre-and postnatal exposure to glyphosate-based herbicide causes behavioral and cognitive impairments in adult mice: Evidence of cortical ad

hippocampal dysfunction. Arch Toxicol, Berlin. 2020;94:1703-23.
Available:https://doi.org/10.1007/s00204-020-02677-7

192. De Maria Serra F, Parizi JLS, Odorizzi GASM, Sato GMRH, Patrão IB, Chagas PHN, et al. Subchronic exposure to a glyphosate-based herbicide causes dysplasia in the digestive tract of Wistar rats. Environ Sci Pollut Res Int. 2021; 28(43):61477-96.
Available:https://doi.org/10.1007/s11356-021-15051-6
193. Samsel A, Seneff S. Glyphosate, pathways to modern diseases III: Manganese, neurological diseases, and associated pathologies. Surg Neurol Int. 2015;6(45).
194. Gladyshev VN. Aging: progressive decline in fitness due to the rising deleteriome adjusted by genetic, environmental, and stochastic processes. Aging cell. 2016; 15(4):594-.
195. Jones MJ, Goodman SJ, Kobor MS. DNA methylation and healthy human aging. Aging cell. 2015;14(6):924-32.
196. Beard JR, Officer A, de Carvalho IA, Sadana R, Pot AM, Michel JP et al. The World report on ageing and health: a policy framework for healthy ageing. Lancet. 2016;387(10033):2145-54.
Available:https://doi.org/10.1016/s0140-6736(15)00516-4
197. Reynaud, C; MiccolI, S. Depopulation and the aging population: The relationship in Italian municipalities. Sustainability, Basel. 2018;10(4):1004.
198. Franceschi C, Garagnani P, Morsiani C, Conte M, Santoro A, Grignolio A et al. The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates. Front Med (Lausanne). 2018;5:61.
Available:https://doi.org/10.3389/fmed.2018.00061
199. Quach A, Levine ME, Tanaka T, Lu AT, Chen BH, Ferrucci L et al. Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. Aging (Albany NY). 2017; 9(2):419-446.
Available:https://doi.org/10.18632/aging.101168.
200. Cesari M, Prince M, Thiyagarajan JA, De Carvalho IA, Bernabei R, Chan P, et al. Frailty: An Emerging Public Health Priority. J Am Med Dir Assoc. 2016;17(3):188-92.
Available:https://doi.org/10.1016/j.jamda.2015.12.016
201. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752-62.
Available:https://doi.org/10.1016/s0140-6736(12)62167-9
202. Damalas CA, Koutroubas SD. Farmers' Exposure to Pesticides: Toxicity Types and Ways of Prevention. Toxics. 2016;4(1):1.
Available:https://doi.org/10.3390%2Ftoxics4010001
203. Damalas CA, Khan M. Farmers' attitudes towards pesticide labels: implications for personal and environmental safety. Int J Pest Manag, USA. 2016;62(4)319-25.
Available:https://doi.org/10.1080/09670874.2016.1195027
204. Paraskevoudi N, Balcı F, Vatakis A. "Walking" through the sensory, cognitive, and temporal degradations of healthy aging. Ann N Y Acad Sci. 2018;1426(1): 72-92.
Available:https://doi.org/10.1111/nyas.13734.
205. Ball N, Teo W-P, Chandra S, Chapman J. Parkinson's Disease and the Environment. Front. Neurol. 2019;10:218.
Available:https://doi.org/10.3389/fneur.2019.00218
206. Anselmi L, Bove C, Coleman FH, Le K, Subramanian MP, Venkiteswaran K, et al. Ingestion of subthreshold doses of environmental toxins induces ascending Parkinsonism in the rat. NPJ Parkinson's Disease, USA. 2018;4(1):30.
Available:https://doi.org/10.1038/s41531-018-0066-0
207. Cattani D, de Liz Oliveira Cavalli VL, Heinz Rieg CE, Domingues JT, Dal-Cim T, Tasca CI, et al. Mechanisms underlying the neurotoxicity induced by glyphosate-based herbicide in immature rat hippocampus: involvement of glutamate excitotoxicity. Toxicology. 2014;5(320):34-45.
Available:https://doi.org/10.1016/j.tox.2014.03.001
208. De Miranda BR, Castro SL, Rocha EM, Bodle CR, Johnson KE, Greenamyre JT. The industrial solvent trichloroethylene induces LRRK2 kinase activity and dopaminergic neurodegeneration in a rat model of Parkinson's disease. Neurobiol Dis. 2021;153:105312.

Available:https://doi.org/10.1016/j.nbd.2021.105312

209. Ilieva NM, Wallen ZD, De Miranda BR. Oral ingestion of the environmental toxicant trichloroethylene in rats induces alterations in the gut microbiome: Relevance to idiopathic Parkinson's disease. Toxicol Appl Pharmacol. 2022; 451:116176.
Available:https://doi.org/10.1016/j.taap.2022.116176.
210. Narayan S, Liew Z, Paul K, Lee PC, Sinsheimer JS, Bronstein JM et al. Household organophosphorus pesticide use and Parkinson's disease. Int J Epidemiol. 2013;42(5):1476-85.
Available:https://doi.org/10.1093/ije/dyt170
211. Kim Y, Kim I, Sung JM, Song J. Parkinson's disease in a worker exposed to insecticides at a greenhouse. Ann Occup Environ Med. 2021;33.
212. Eriguchi M, Iida K, Ikeda S, Osoegawa M, Nishioka K, Hattori N et al. Parkinsonism Relating to Intoxication with Glyphosate. Intern Med. 2019;58(13):1935-8.
Available:https://doi.org/10.2169%2Finternalmedicine.2028-18
213. Keener AM, Bordelon YM. Parkinsonism. Seminars in neurology. 2016;36:330-34.
214. Taba P. Toxic-induced Parkinsonism. Movement Disorders Curricula. 2017;225-32.
215. Mursaleen LR, Stamford JA. Drugs of abuse and Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2016;64:209-17.
216. Todd G, Pearson-Dennett V, Wilcox RA, Chau MT, Thoirs K, Thewlis D et al. Adults with a history of illicit amphetamine use exhibit abnormal substantia nigra morphology and Parkinsonism. Parkinsonism Relat Disord. 2016;25:27-32.
Available:https://doi.org/10.1016/j.parkreldis.2016.02.019.
217. Kwok JYY, Kwan JCY, Auyeung M, Mok VCT, Lau CKY, Choi KC et al. Effects of Mindfulness Yoga vs Stretching and Resistance Training Exercises on Anxiety and Depression for People With Parkinson Disease: A Randomized Clinical Trial. JAMA Neurol. 2019;76(7):755-763.
Available:https://doi.org/10.1001/jamaneurol.2019.0534.
218. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci. 2017;18(7):435-450.
Available:https://doi.org/10.1038/nrn.2017.62.
219. D'Iorio A, Vitale C, Piscopo F, Baiano C, Falanga AP, Longo K, et al. Impact of anxiety, apathy and reduced functional autonomy on perceived quality of life in Parkinson's disease. Parkinsonism Relat Disord. 2017;43:114-7.
Available:https://doi.org/10.1016/j.parkreldis.2017.08.003
220. Landau S, Harris V, Burn DJ, Hindle JV, Hurt CS, Samuel M, et al. Anxiety and anxious-depression in Parkinson's disease over a 4-year period: A latent transition analysis. Psychol Med. 2016;46(3):657-67.
Available:https://doi.org/10.1017/s0033291715002196.
221. Kwok JYY, Auyeung M, Chan HYL. Examining factors related to health-related quality of life in people with Parkinson's disease. Rehabil Nurs. 2020; 45(3):122-130. Available:https://doi.org/10.1097/rnj.0000000000000179.
222. Prado JB, Mulay PR, Kasner EJ, Bojes HK, Calvert GM. Acute pesticide-related illness among farmworkers: Barriers to reporting to public health authorities. J Agromedicine. 2017;22(4):395-405.
Available:https://doi.org/10.1080/1059924x.2017.1353936.
223. Fang EF, Scheibye-Knudsen M, Jahn HJ, Li J, Ling L, Guo H et al. A research agenda for aging in China in the 21st century. Ageing Res Rev. 2015;24(Pt B):197-205.
Available:https://doi.org/10.1016/j.arr.2015.08.003
224. Cieza A, Causey K, Kamenov K, Hanson SW, Chatterji S, Vos T. Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet, USA. 2020; 396(10267):2006-17.
Available:https://doi.org/10.1016/S0140-6736(20)32340-0
225. Crocker T, Forster A, Young J, Brown L, Ozer S, Smith J, et al. Physical rehabilitation for older people in long-term care. Cochrane Database Syst Rev. 2013; 2:CD004294.

Available:https://doi.org/10.1002/14651858.cd004294.pub3

226. Reid GA, Darvesh S. Butyryl-cholinesterase-knockout reduces brain deposition of fibrillar β-amyloid in an Alzheimer mouse model. Neuroscience. 2015;298:424-35.
Available:https://doi.org/10.1016/j.neuroscience.2015.04.039

227. Lachs MS, Pillemer KA. Elder Abuse. N Engl J Med. 2015;373(20):1947-56.
Available:https://doi.org/10.1056/nejmra1404688.

228. Hickman LD, Phillips JL, Newton PJ, Halcomb EJ, Al Abed N, Davidson PM. Multidisciplinary team interventions to optimise health outcomes for older people in acute care settings: A systematic review. Arch Gerontol Geriatr. 2015;61(3):322-9.
Available:https://doi.org/10.1016/j.archger.2015.06.021.

229. Parikh I, Guo J, Chuang KH, Zhong Y, Rempe RG, Hoffman JD et al. Caloric restriction preserves memory and reduces anxiety of aging mice with early enhancement of neurovascular functions. Aging (Albany NY). 2016;8(11):2814-826.
Available:https://doi.org/10.18632%2Fagin g.101094.

230. Taormina G, Mirisola MG. Calorie restriction in mammals and simple model organisms. Biomed Res Int. 2014;2014: 308690.
Available:https://doi.org/10.1155/2014/308690

231. Chung KW, Kim DH, Park MH, Choi YJ, Kim ND, Lee J, et al. Recent advances in calorie restriction research on aging. Exp Gerontol. 2013;48(10):1049-53.
Available:https://doi.org/10.1016/j.exger.2012.11.007

232. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: An update. Ageing Res Rev. 2017;39:36-45.
Available:https://doi.org/10.1016/j.arr.2016.08.005

233. Testa G, Biasi F, Poli G, Chiarpotto E. Calorie restriction and dietary restriction mimetics: a strategy for improving healthy aging and longevity. Curr Pharm Des. 2014;20(18):2950-77.
Available:https://doi.org/10.2174/13816128113196660699

234. Guo J, Bakshi V, Lin AL. Early Shifts of Brain Metabolism by Caloric Restriction Preserve White Matter Integrity and Long-Term Memory in Aging Mice. Front Aging Neurosci. 2015;7:213.
Available:https://doi.org/10.3389%2Ffnagi.2015.00213.

235. Singh S, Singh AK, Garg G, Rizvi SI. Fisetin as a caloric restriction mimetic protects rat brain against aging induced oxidative stress, apoptosis and neuro-degeneration. Life Sci. 2018;193: 171-179.
Available:https://doi.org/10.1016/j.lfs.2017.11.004

236. Solon-Biet SM, McMahon AC, Ballard JW, Ruohonen Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. J Endocrinol. 2015;226(1):R17-28.
Available:https://doi.org/10.1530/joe-15-0173

237. Mattison J, Colman R, Beasley T, Allison DB, Kemnitz JW, et al. Caloric restriction improves health and survival of rhesus monkeys. Nat Commun. 2017;8(1): 14063.

238. Paoli PP, Wakeling LA, Wright GA, Ford D. The dietary proportion of essential amino acids and Sir2 influence lifespan in the honeybee. Age (Dordr). 2014;36(3):9649.
Available:https://doi.org/10.1007%2Fs11357-014-9649-9.

239. Solon-Biet SM, McMahon AC, Ballard JW, Ruohonen K, Wu LE, Cogger VC, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. Cell Metab. 2014;19(3):418-30.
Available:https://doi.org/10.1016/j.cmet.2014.02.009

240. Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, Cheng CW, Madia F et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metab. 2014; 19(3):407-17.
Available:https://doi.org/10.1016/j.cmet.2014.02.006.

241. Erbersdobler H, Barth C, Jahreis G. Legumes in human nutrition Nutrient content and protein quality of pulses. Ernährungs Umschau. 2017;64(9):134-9.
Available:http://dx.doi.org/10.4455/eu.2017.034

242. Mariotti F,Gardner CD. Dietary protein and amino acids in vegetarian diets—A review. Nutrients. 2019;11(11):2661.

243. Fadnes, LT, Økland J-M, Øystein AH, Kjell AJ. Estimating impact of food choices on life expectancy: A modeling study. PLoS Med, USA. 2022;19(2): e1003889.
Available:https://doi.org/10.1371/journal.pmed.1003889

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