STUDY OF THE RELATION BETWEEEN AGING AND PESTICIDES

ABSTRACT

Aims: The main aim of this study was to use specific data from the literature on ageing, correlating this with the pesticide contamination, in order to understand the relationship with an increasingly ageing population
Study design: A systematic review was performed.
Place and Duration of Study: Laboratory of Biomathematics of the Federal University of Alfenas, Minas Gerais State, Brazil, between April 2023 and August 2023.
Methodology: A systematic search of articles was performed using the CAPES Periodic plataform, a searcher from the Education Ministry of Brazil that contains Web of Science, Scopus, MedLine, from August 2020 to May 2023. For this review, the subject's "aging theory"; "neuroscience and pathologies to aging"; "aging and aging-associated changes"; "pesticides and pesticide toxicity"; "pesticide toxicity and neurotoxicity"; "longevity and healthy aging"; "aging human and pesticides" were searched together using the type of material "articles" in English language. Some articles about "population growth"; "world population"; "population-aging" were used for epistemological composition of this work content subjects.
Results: From the 19.720 articles after the exclusion and the inclusion criteria made with the subjects most pertinent to the objectives of this work; 19.570 articles were excluded, remaining 150 ones, of which 116 were qualitative in scope and 34 quantitative.
Conclusion: The complex relationship between the pesticide contamination and the condition of the exposed individual may be associated with premature ageing and a greater susceptibility to debilitating age-related diseases. Althoughtechnology is increasingly improved in its innovations, health and environmental regulations have not been able to rid the production processes of their potential to pollute the environment and cause health problems for those exposed to them.

Keywords: Aging theory; precocious aging; pesticide; free radicals; oxidative stress; epigenome.

1. INTRODUCTION

1.1 Theories on Aging

The various studies on the consequences of aging, from visible processes to the molecular level, show the modifications in the body that, so far, are not fully understood, and, because of the intrinsic multidisciplinary nature of the process, the study of the molecular basis has generated theories to explain the phenomenon of age gain, broadly divided into stochastic (1) theories and non-stochastic (2) theories [1,2,3].
Stochastic [1] theories work with the hypothesis that the rising loss of functionality during aging is caused as a result of the random accumulation of molecules with structural and/or functional changes, associated with the environmental action, which interfere with organic and life functions, causing a progressive physiological decline [1]. Stochastic theories

encompass the theory of somatic mutations and DNA repair; error-catastrophe in protein synthesis; free radicals and oxidative stress; linkage breaks and collagen alterations [3,4].
The theory of somatic mutations assumes that the successive changes that occur in the composition of DNA and somatic cells, over the years, would produce mutant cells unable to fulfill their biological functions, which would cause a progressive decline of organs and tissues, favoring cellular aging [5], moreover, the theory was one of the first attempts to understand the aging phenomenon at the molecular level [6]; a recent study using C57BL/6 mice demonstrated a shortened lifespan after the exposure to radiation, corroborating with the first findings that noted links between sublethal radiation and shortened lifespan [7].
The effects of exogenous agents and how the body reacts to their aggression became the basis of study for other theories, such as the DNA repair theory, the error-catastrophe theory, and the oxidative stress theory [5].
The theory on DNA repair consists of essential mechanisms capable of protecting the integrity of the genome, because although the DNA fidelity is highly protected, it can be damaged by being constantly under attack from numerous endogenous and exogenous agents [8], thus, the accumulation of mutations and epigenetic changes can lead to deficiencies in repair systems, being a contributing factor to the biological aging (Fig. 1), as a disruption or dysregulation of DNA repair pathways contribute to a genomic instability, which increases with age [9].

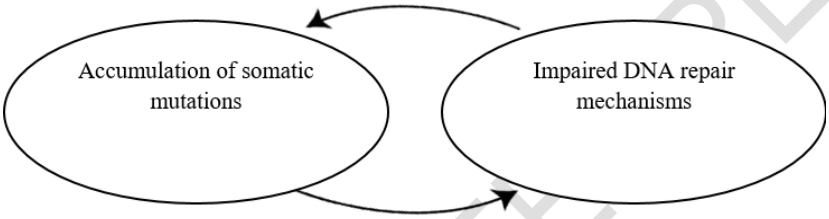

Fig. 1. Somatic mutations and DNA repair.
Caption: The accumulation of somatic mutations and deficiencies in the repair system culminate in genomic instability at levels incompatible with life.

The error-catastrophe theory postulates that errors in a small transcription-translation frequency of a protein can be used in the synthesis of other proteins through self-amplification mechanisms, compromising the protein machinery and leading to a progressive decrease in the fidelity of replicated DNA and the eventual accumulation of potentially lethal proportions of defective proteins (Fig. 2); consequently this would increase the negative consequences to the cell renewal, a fact that would characterize aging [1,10,11].

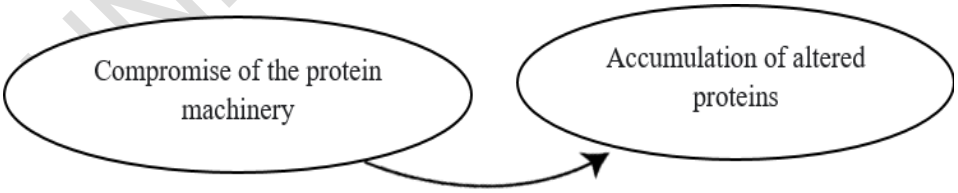

Fig. 2. Error-catastrophe in protein synthesis.
Caption: Accumulation of altered proteins and compromised protein machinery lead to functional and structural changes that culminate in catastrophic damage.

The assumption that the accumulation of modified proteins can lead to a functional impairment of the normal cell has been advocated by the linkage breaking theory and the glycosylation theory [1].
The linkage breakage theory originated from the finding that increased the linkage breakage in DNA and protein molecules during the replication process slows down body functions, impairing cell function [10,12]; furthermore, the glycosylation theory suggests that the modification of proteins by glucose and the association of Maillard reactions lead to the formation of irreversible cross-links in long-lived matrix structural proteins, such as collagen and elastin, induce systemic and tissue-specific effects, causing elevated blood glucose and tissue glucose levels, and loss of elasticity, resulting in the external signs of aging, such as wrinkles [13,14,15].
Many of the reactive agents associated with the DNA cross-linking process and, which are derived from endogenous and exogenous sources, are molecules produced in oxidative metabolism, called free radicals, therefore, because they are highly unstable and reactive, free radicals are the basis of the oxidative stress theory [1]. The oxidative stress theory is associated with the imbalance in the formation of oxidants added to the deficiency of antioxidant defence mechanisms (Fig. 3), triggering a gradual loss of the cell's functional capacity, influencing the degenerative changes associated with aging due to the accumulation of molecular lesions [16,17,18].

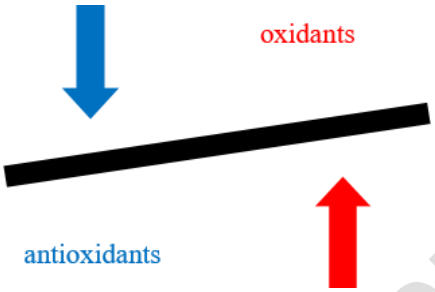

Fig. 3. Error-catastrophe in protein synthesis.
Caption: The excessive production of free radicals or the reduction of antioxidant defenses characterize oxidative damage.

Non-stochastic or genetic theories [2] emphasize the determinant participation of genes in the aging process, that is, they are related to mechanisms programmed in the genome of each organism, but without denying the importance of environmental influences [1,2]. The genetic theories encompass the programmed senescence theory; the telomere theory, the intrinsic mutagenic theory; the neuroendocrine and the immunological theories [19].
The theory of programmed senescence can be understood as a progressive loss of homeostasis capacity, in which the organism would tend to present failures through its time of use, thus, an irreversible arrest of the long-term cell cycle would occur, caused by excessive intracellular or extracellular stress or damage [19,20]. Senescence can be triggered, for example, by oxidative stress, DNA damage, mitochondrial dysfunction, epigenetic dysregulation, and the damage/shortening of telomeres [21].
Telomeres have the function of maintaining the integrity of chromosomes during the cell division, while telomerase is the enzyme responsible for adding DNA repeats to these, being able to restore the capacity of cell multiplication, delaying the aging of tissues [22]. Therefore, the telomere theory has been conditioned on aging, in the sense that the cell ages when it loses its ability to duplicate by the telomere impairment [1]; that is, after successive cell divisions, the tips of the chromosomes damage and suffer a deletion of genes located near the telomeres, occurring a deceleration of cell multiplication and to the lower replacement of cells that die [23].

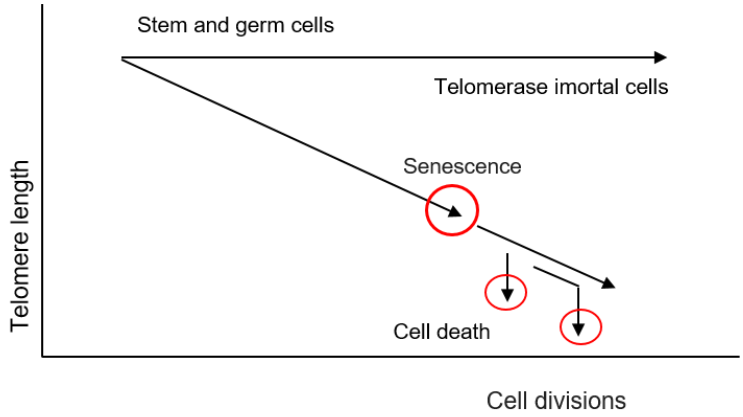

Fig. 4. Programmed senescence and telomere shortening.
Caption: Relationship between the behavior of cells and the length of telomereses that culminate in cell aging and associated pathologies.

Thus, a tissue with many cells containing shortened telomeres has its function compromised by the accumulation of the cell death; therefore, the length of telomeres behave as key molecular markers of cellular aging (Fig. 4), since, when the size of telomeres reaches a certain stage of shortening of its structure, they are no longer able to protect the DNA from certain nuclear enzymes and the cells that stop reproducing, reach a state of aging, such kind of event can be observed in diseases such as Parkinson's and Alzheimer's, where there are large numbers of cells in the process of death in the central nervous system [1,27,28]. 35
Aging evolves through the decline of natural selection forces in the course of age gain [24], since the natural selection selects harmful mutations expressed early in life, but exerts little evolutionary pressure to rid organisms of mutations that cause harmful effects at an older age [5]. Given this, the theory of intrinsic mutagenesis assumes that the longevity of different species will depend on how well the machinery functions in repairing the errors found in DNA [25], thus, those with deficits in the repair systems will be more susceptible in expressing the phenotypes of aging [26].
There are several genetic mutations that affect lifespan, for example, in roundworms, gene mutations that double life expectancy provide clear evidence that genes influence aging and longevity [5]; however, although investigations of gerontogenes is allowing the identification of genes responsible for the development of diseases associated with the age gain, no genes specific to the aging process have been identified [27] corroborating the concepts that the aging phenomenon is a complex and multifactorial process [28].
The immune theory addresses the changes in immune responses associated with age [29], in which the deficiency of the immune system, over the years, would make people more vulnerable and susceptible to aggressions [30]. Such changes in the immune system, such as the formation of autoantibodies with high affinity and decreased T-cell response to antigens, are responsible for the increased incidence of infections, cancer, and autoimmune diseases in age, negatively affecting the functional capabilities of other organ systems and contributing to aging, and subsequently, death [1,29].
The neuroendocrine theory indicates that aging is a result of the decline of several hormones of the hypothalamic-pituitary-adrenal (HPA) axis, which functions as a regulator signaling the beginning and the end of each stage of life. Such changes affect neurons and hormones that regulate functions aimed at preserving and maintaining an internal homeostasis, such as reproduction, growth, development, and stress adaptation, impairing the control of physiological systems' responses to environmental stimuli [1,3,29,30].
Despite the various theories and the very existence of several of them, the aspects linked to the age gain in different contexts pervade biological, psychosocial, intellectual, economic,

functional, chronological processes and lifestyle choices, even if not necessarily linked to the physiological age [31].

1.2 Morpho-Physiological Changes Due to Aging

With an increasing longevity, the prevalence of contracting one or more chronic diseases grows [32]; recent studies using estimates from the Study Global Burden of Disease (GBD) considered arthropathies, systemic arterial hypertension, and heart diseases as the most frequent conditions in the course of aging, in a prevalence ratio of 49.8%, 45.5%, and 30.5%, respectively [33,34]. In other words, there is a close relationship between age gain and functional disabilities, being linked to a tendency to the natural occurrence of pathologies, nevertheless, one cannot assume that aging is a meaning of disease [35,50]; thus, in many cases, it is difficult to distinguish when the change is due to the normal aging process or to pathological manifestations [32,36].

The various changes that occur during the aging process led to the impairment of the neural system's ability to process the vestibular, visual, and proprioceptive signals responsible for maintaining the body balance; consequently, the ability to modify adaptive reflexes is reduced, leading the elderly to present pictures of falls and anxiety [37,38]. Furthermore, symptoms of imbalance and dizziness are associated with sensory changes and, although they appear more frequently after the age of 65 [39], they may be present at other ages.

Regarding brain changes, the age gain is accompanied by an intellectual decline, and may proceed towards the progression of dementia in some cases [40,41]. There is evidence that the cognitive performance peaks in the third decade of life and declines at an estimated rate of 0.02 standard deviations per year [42], showing slight deteriorations in tasks that require a greater speed and flexibility in processing information [43]. According to Ferreira, Correia, Nieto, Machado, Molina and Barroso [44], a memory impairment associated with aging is related to earlier stages of life, since changes in the acquisition and/or retrieval of free memory are also present before the age of 50, although not in a consolidated manner.

Despite causing disorders, memory deficits are considered normal at any age [45]; a study in SAMP8 mice showed an age-related impairment of memory, learning, and behavioral disturbances according to the early onset and rapidly advancing senescence, without any pathological evidence [46]. However, age-related cognitive changes are commonly found in early stages of dementias, so it is important to distinguish when memory loss stems from stress and/or depression pictures and when circumstantial cases are pathological [47,48].

Several macro- and microscopic changes also occur in the encephalon during aging, which include a decrease in the weight and volume of the organ; the number and size of neurons; the extent of dendritic branching; the number of spicules and synapses; the loss of myelin in neural fibers, reducing the impulse conduction velocity; a decline in the ability to generate neurons in the ventricular and subventricular zone; a granulovacuolar degeneration; a morpho functional change of the gyri and sulci; an accumulation of lipofuscin pigment in neurons and glial cells; an appearance of characteristic microscopic modifications, such as senile plaques and neurofibrillary tangles [41,49,50].

Some of the changes that accompany the aging process have pronounced effects on neurodegenerative diseases [43], such as the granulovacuolar degeneration, which degrades the tau protein in lysosomes leading to the blockage of the intracellular protein traffic and, eventually, the onset of dementias; the excessive accumulation of lipofuscin, which affects neuronal RNA causing a reduction in the vital capacity of the cell and, subsequently, the cell death [50,51]. Furthermore, the progressive decrease in the metabolic rates of glucose and oxygen in brain cells is closely linked to normal aging and is further exacerbated in pathologies, such as Alzheimer's and Parkinson's [52,53].

Longevity allows people to live longer, however, as human aging is, markedly, marked by morphological, biochemical, and physiological changes, the population carries the burden of being prone to undergo a cascade of signalling that would result in cell death, causing

neurodegeneration [43,54]. Furthermore, More, Kumar, Cho, Yun and Choi [55] conducted a study using mice to investigate the effects of the toxin exposure and the results showed deficits in learning and memory tasks.
There are indications that strongly contribute to determine an active and longevous aging, which include the ability to solve problems and adapt to changes and losses, which some suffer declines due to the disuse, generating serious adverse consequences to the health of the elderly, such as the risk of falls or morbidity and mortality [56].

1.3 Human Aging and Pesticide

According to World Bank data, the population growth rate fell from 1.2 per cent in 2010 to 1.1 per cent in 2020, indicating an increasingly slow population increase [57]. As a result of this slowdown, population ageing has become increasingly inevitable, mainly due to the demographic transition [58]. The decrease in the fertility rate and the increase in life expectancy are the main factors responsible for the age changes in the population [59], which is marked by a fine line between a decrease in the proportion of children and an increase in the percentage of elderly people [60].
Updated demographic assessments for 204 countries from 1950 to 2019 have shown that the global fertility rate has declined due to the low level of population replacement [61]. The growth rate of the elderly has been higher than all the younger age groups, so the elderly population is expected to reach 994 million in 2030 and 1.6 billion in 2050, so the global share of people aged 65 and over will represent 16%,exceeding twice as many children under 5 worldwide and surpassing the number of children under 12 [62].
Considering that ageing is the greatest risk factor for the majority of chronic diseases that lead to both morbidity and mortality, unhealthy longevity can lead to long-term problems, especially in the elderly [63], also due to their susceptibility to accumulating numerous physiological alterations that lead to a functional impairment of systems and organs, culminating in death [64]. As a result of ageing, the population tends to face a change in the cause of illness and mortality, i.e. the number of deaths will be higher from non-communicable diseases, such as chronic and degenerative diseases, for example Alzheimer's and Parkinson's, than from communicable diseases, such as infections and parasitoses [59,65,66].
Studies have shown the impact of gene-environment interactions on premature ageing and neurodegenerative disorders associated with ageing, as environmental factors contribute to the processes that lead to the emergence of phenotypes that include alterations in the human body, an imbalance in the production and use of energy, a homeostatic dysregulation, a neurodegeneration and loss of neuroplasticity, which result in the accumulation of an unrepaired damage over the course of life and contribute to a differentiation between the real age of the human being (chronological age) and the age that the individual appears to have (biological age) [66, 67,68,69].
In this sense, used in agriculture to combat pests or any agricultural damage that could interfere with the crop productivity [70], pesticides are considered effective in managing weeds, insects and fungi to improve the quality of cultivated products [71]. The chemical additives present in herbicide formulations ensure a greater efficiency in agriculture; however, they are also responsible for amplifying their toxicity beyond the crops [72]. Due to the wide distribution and persistence of pesticides in nature, their contaminating residues can be found in foods of plant and animal origin, such as milk, eggs and meat, in the atmosphere, sediments, soils and in aquatic ecosystems [73], causing adverse effects on non-target organisms [74].
Contrary to the expected effect of being harmful only to pests, the extensive and erroneous applications of pesticides pose risks to health and biodiversity because they have active ingredients that are, in most cases, toxic [75,76]. Pesticides act as endocrine disruptors and are substances of great concern due to their ability to alter the hormonal regulation; they

interfere with the neural processes by inhibiting neurotransmitters and contribute to an increase in free radicals and oxidative stress, culminating in premature ageing [76].
In this way, a constant exposure to pesticides, whether intentional, accidental, occupational, environmental or through food, is responsible for the elimination of pollinating insects and the contamination of soil and water resources, as well as compromising for the epigenetic processes in human beings [77,78,79], leading to successive failures in the establishment or maintenance of biological functions, such as hormonal, metabolic, immunological and neural changes that are responsible for causing alterations in the phenotype [80].
Considering that a greater exposure to an environment is capable of affecting internal biological pathways and triggering chemical changes that alter the gene expression [72], it is presumed that the human exposome contributes to the ageing process and the emergence of serious diseases, being closely linked to a higher incidence of acute and chronic health problems, whether in producers, consumers or nearby communities [81]. Human health problems vary depending on the contamination, causing nausea, vomiting, muscle spasms, gastrointestinal and dermal problems in acute exposure, while chronic problems are related to psychiatric, neurological, endocrine, teratogenic, mutagenic and carcinogenic problems [82].
Pesticide sprayers have had higher levels of 8-hydroxydeoxyguanosine (8-OHdG), an oxidative by-product used as a highly mutagenic and carcinogenic biomarker of oxidative stress [83]; DNA damage in children in rural areas exposed to pesticides have showed the genotoxic and cytotoxic effect of these substances [84].
Exposure to pesticides has been associated with brain neurodegeneration and a higher risk of developing Alzheimer's disease and Parkinson's disease, both intensified by the age factor [85], since environmental stressors and ageing itself are capable of promoting a neuropathology through processes that over time generate senescence in brain neurons and, subsequently, senility [86]. Non-demented individuals who have lived in areas close to sprayed fields have had a lower cognitive performance compared to those who have never lived in such areas, showing a worse performance in executive functioning, visuospatial perception, language, attention and a greater risk of developing neurodegenerative diseases [87].
Various studies have shown that pesticides can be correlated with an increase in health problems as a result of the alterations caused by the contact with the contaminant, whether during the application or the consumption. Therefore, the various factors to which humans are exposed throughout their lives, whether they are reinforcing factors or wear and tear factors, interfere in the ageing process, delaying or accelerating it; data that refers to the objective of this article.

2. MATERIAL AND METHODS

For the purpose of this review, articles from 2013 containing the subjects *aging theory*; and the associations between *aging, neuroscience and pathologies to aging*; *aging and aging-associated changes*; *pesticides and pesticide toxicity*; *pesticide toxicity and neurotoxicity*; *longevity and healthy aging*; and *aging human and pesticides*, mainly because subjects such as *population growth*; *world population*; and *population-aging* were also used in this article; they were searched on the CAPES journal platform that contains the Web of Science, Scopus, MedLine bases, from August 2020 to March 2024, to form the epidemiological basis of the review for a total of 19.720 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 about the changes that lead to human aging. 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

Of the 19,720 articles refined with the exclusion criteria and the inclusion made with the subjects most pertinent to the objectives of this work, 19,570 articles were excluded, leaving 150 articles, of which 116 were qualitative in scope and 34 quantitative, shown in figure 5, in which the themes are associated with the articles.

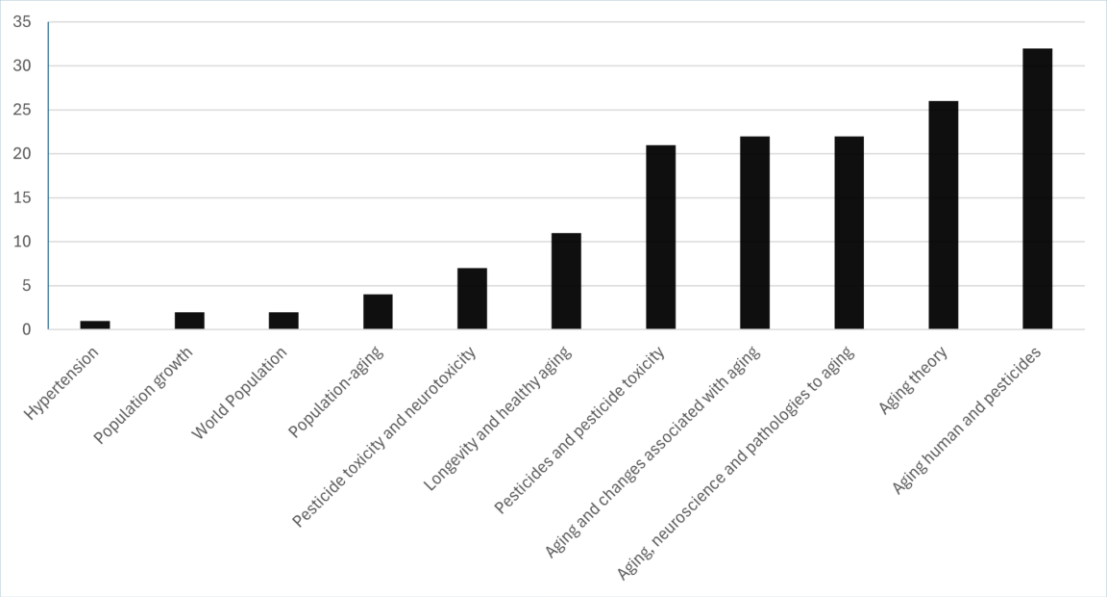

Fig. 5. Number of references associated to subjects

4. DISCUSSION

With the advancing of the age, the society aspires to increase its life expectancy, but it is beneficial when it adds quality, because nowadays, reaching the old age is considered an expected reality even in developing countries, becausequality of life does not depend solely on care during the old age [88]. Individuals build up their homeostatic reserves in order to reverse problems such as illnesses and disabilities. However, with the increasing age, these reserves begin to diminish, establishing a condition of dependence on the individual based on the quality of life throughout his existence [89,90].

Ageing consists of a progressive decrease in the individual's ability to survive as a result of the slow and continuous process of deterioration of the systems intensified by external factors that affect the organism and, consequently, lead to the acceleration of the biological clock causing premature ageing, which is why the likelihood of death generally tends to increase as we get older [69,91,92,93].

There are several different mechanisms that interact to influence ageing, ranging from genetic susceptibility to the exposure to physical and chemical agents [64]; however, one of the most widespread models that presupposes unplanned ageing is correlated with the accumulation of molecular, cellular and tissue damage caused by free radicals, which are responsible for continuously affecting the integrity of DNA, progressively leading to dysfunctions in the body and a subsequent weakening of the immune system, thus ageing [16,94,95].

Free radicals are reactive molecules that are produced during the mitochondrial energy metabolism [96] and their production is a consequence of being alive [97], but their excessive production causes damages to the organism [16].

Defects in the mitochondrial function initially cause increases in the levels of (reactive oxygen species) ROS in the cell and dysfunctions in the electron chain [98,99,100]. Mitochondrial dysfunctions can be caused by mutations in mitochondrial DNA and by environmental causes [102], which in the long term can cause oxidative stress, damaging the mitochondria and resulting in an energy crisis that accelerates ageing due to changes in the cell morphology and function [100,103], and can trigger neurodegenerative diseases as a result of inefficient cell functions and a consequent apoptosis [99,100].

With the progression of age, there is an accumulation of oxidized proteins, lipids, carbohydrates and DNA compared to younger organisms, because although the body owns mechanisms to minimize the harmful effects of free radicals, they are not 100% effective [104]. A study using fruit flies showed that stimulating the production of antioxidant enzymes increased the life expectancy of these individuals by 16% compared to the control group, because dietary antioxidants have an anti-aging activity, probably by increasing the endogenous enzymatic defense capacity and stopping the formation of free radicals [105]. β-caryophyllene (BCP), a compound that has anti-inflammatory and antioxidant effects, generates a neuroprotection against the oxidative stress induced by the pesticide rotenone and protects the body from neuroinflammation in a rat model of PD [106].

Oxidative damages to proteins, for example, can cause changes in them, aggregating them, and although cells have their own structures for the protein degradation, many of the protein clusters are resistant, leading to the accumulation of aggregates [104,107]. Several studies have shown how these aggregates can cause various diseases associated with ageing, including cardiovascular and neurological diseases, such as Alzheimer's and Parkinson's, which are more frequent in the elderly population [108,109].

In this context, several studies have reported that cells stimulated to perform better in proteosomal activities show a greater health and survival, such as in human mesenchymal stem cells [110], mice [111], mole rats [112] and flies [113], suggesting that the proteosomal activity may be correlated with the lifespan of an organism and the appearance of late-onset neurodegenerative diseases [109], making it important to stimulate protease in ageing organisms [114]; However, this is a subject that needs further study.

Among the external factors that cancontribute to the formation of an excess of free radicals that can cause irreparable damages to the human body there are: pesticide residues and theirseepage into water sources and food crops, in substances present in foods and drinks,sun exposure, heavy metal toxicity, atmosphericpollutions, bisphenol-A used in the production ofplastics, smoking, alcohol and drug consumption, among others [115].

The pesticide industry, together with theEnvironmental Protection Agency (EPA) is constantly trying to prove that pesticidesdo not present toxic potentials for humans if used in adequate concentrations [116].However, a study carried out by theEuropean Environmental Agency (EEA) reported the detection of one or more pesticides abovethe limits in 22% of all the monitoring sites in rivers and lakes, in 83% of the agricultural soils,as well as being present in the bodies of 84% of thesurvey participants [117]. Science has increasingly shown the causal relationship between the use of pesticides and a series of chronic diseases, such as cancer, heart, respiratory and neurological diseases [117,118].

Although the greatest health risks are due to the occupational exposure, as it directly contaminates those who produce or handle the product, concerns about the rest of the population should not be minimized, as the contamination of water resources, air, soil and food, both fruit and vegetables and animals that are lower down the human food chain, are routes that carry pesticide residues to consumers [77,119]. Therefore, the toxic potential of these agents affects the physical constitution and health of the individual, since the damage caused to non-target species can be widespread and serious [120].

Every pesticide that is sprayed and distributed on the surface contaminates the water resources and it is estimated that 98% of non-target organisms are directly or indirectly affected [77]. According to data from the US National Academy of Sciences (PNAS), more than 50% of the pesticide concentrations detected exceed the regulatory limits, indicating

that the pollution of surface waters resulting from the current use of pesticides constitutes an excessive threat to the aquatic biodiversity, as well as harms to the human health, since this water will be abstracted and, although much of it undergoes a treatment, the residues of the chemical products are not completely eliminated, so the water that is destined for a domestic consumption becomes a source of contamination [121].

For example, the fungicide imazalil penetrates beyond the apple skin in just seven days, reaching up to 3 centimeters of flesh in apples grown using conventional methods [122, 123].

Before the industrial revolution, when agriculture was modernized on a global scale, there was no exposure to contaminants like there is today [124]; but today the use of pesticides in agriculture has disastrous consequences for the environment and for the health of animals and humans, as it has intensified the contact of non-target species with these chemical agents [125].

The exposure to pesticides can induce the process of oxidative stress in the animal organism by varying the amount of ROS and the activities of antioxidant enzymes [79], so the longer the exposure to harmful agents, the greater the amount of free radicals that will accumulate in the organism, without the ability to neutralize or eliminate them [126]. In addition, pesticides act as endocrine disruptors in the body and, in some way, mimic or block the function of endogenous hormones [76,127].and may involve epigenetic mechanisms [127].

Recently, many effects caused by pesticides have been associated with abnormalities in the reproductive system, which can result in a decrease in the volume of seminal fluid and the number, motility and viability of sperm [128]; while exposures in women are correlated with irregularities in the menstrual cycle, impaired folliculogenesis, a decrease in the number of live fetuses and pregnancy rates, an increase in spontaneous abortions, endometriosis and other birth defects [128,129]. In both genders, fertility rates and the body's reproductive physiology are directly affected, which can lead to an ageing population due to a drop in fertility.

The entire regulation of endogenous hormones is very fragile and the presence of an endocrine disruptor generates other substances and metabolites capable of affecting metabolism through various mechanisms that interfere with the hormonal control, directly impacting organs such as the thyroid, breast, prostate, testicles, uterus, ovary, pancreas and adrenals [130,131].

In fact, the exposure of male flower growers to pesticides has been shown to decrease serum levels of testosterone and inhibin B, both produced by the testicles. Inhibin B correlates with the testicular volume and the sperm concentration, so very low levels indicate minimal or no sperm production, and an abnormal spermatogenesis, infertility and cancer of the male genitalia are common, due to the action of pesticides in favoring an increase in hormones in regions such as the testicle and prostate [132], impacting on procreation.

In women, for example, endocrine-disrupting pesticides bind to estrogen receptors without activation and, because it is not a hormone itself, it affects the pituitary gland's signaling, changing the sequence of the hormonal functioning in the body.Consequently, these hormones begin to act in the breast, uterus and ovaries, generating an exacerbation of hormones in these organs which, over the long term, can generate ovarian cysts and aggravate the polycystic ovary syndrome, as well as causing fibroids, breast, uterine and ovarian cancers, infertility, among others [133,134].

In this sense, the recurrent oxidative stress induced by endocrine disrupting substances (EDC) leads to ovarian ageing and, consequently, contributes to a premature and early menopause associated with an increased risk of cardiovascular diseases and dementia [135].

Exposure to pesticides causes early menopause, as women exposed to EDC were up to 6 times more likely to enter menopause than unexposed women, and consequently a greater susceptibility to Alzheimer's, due to the ability of pesticides to cause an imbalance in the

hypothalamic-pituitary-gonadal axis which is responsible for the interconnection between the endocrine and neural systems [136]. In addition, pesticides can increase beta-amyloid peptide (Aβ) and Tau protein phosphorylation, causing senile/amyloid plaques and neurofibrillary tangles characteristic of Alzheimer's disease [137].

Scientific studies show that pesticides alter the normal functioning and physiology of the nervous system by modulating signaling pathways, with a predilection for different types of disorders [138]. The toxicity of certain classes of pesticides is associated with their ability to inhibit the activity of acetylcholinesterase (AChE), the enzyme responsible for hydrolyzing the neurotransmitter acetylcholine (ACh), which is responsible for the transmission of impulses in the central and peripheral nervous system and is directly associated with AD [1]. As a result of the inhibition, there is an accumulation of acetylcholine in the neuronal synapses and neuromuscular junctions which, when recurrent, can cause a cholinergic crisis that manifests itself with an altered mental state, increased secretions, convulsions, muscle weakness, spasms and, finally, death due to respiratory paralysis and the accumulation of secretions in the airways [139].

Due to their high potential for bioaccumulation and bioamplification, pesticides accumulate along the food chain and are stored in the fat of fish, cattle, poultry, breast milk, fruit, plants and water that have been exposed to these substances [140,141], as the body does not have adequate mechanisms to remove them, pesticide residues can persist for up to decades in humans near the end of the food chain [142], which can lead to a series of undesirable health effects, creating an ecological and public health problem [143].

Exposure can occur in different ways, but it is estimated that more than 90% of the endocrine disruptors are absorbed via the digestive tract and can also be transferred from a mother to her child during the pregnancy or breastfeeding. A systematic study compiled several articles related to the presence of two or more organochlorine pesticides in samples collected from breast milk and showed that breast milk can be an important biomarker for estimating these residues in the human body [144].

Both the period and duration of the exposure are important in determining their effects, which is why it is important to pay special attention during critical phases of life, as these are groups with a greater vulnerability and, in most cases, the central and peripheral damage that occurs early in life and/or childhood is noticed at a later age due to the long latency period between the exposure and the consequence [145]. In addition, the effects of endocrine disrupters can affect up to the third generation, i.e. the fetus can suffer alterations to its genome during pregnancy and pass it on to its children, grandchildren, great-grandchildren and beyond, in a devastating effect because by affecting germ cells, pesticide residues can still be passed on for generations even years after the substance has decomposed or been eliminated [146,147].

5. CONCLUSIONS

The toxicity of pesticides to human health leads to a great deal of oxidative damage to cells, tissues and organs which, over the years, contributes to premature ageing [93]. Oxidative stress caused by the accumulation of free radicals is responsible both for mutations in the mitochondrial genome that have the potential to lead to dysfunctions of the mitochondrial complex, reducing ATP production and predisposing the cell to ageing [148], and for the accumulation of damaged proteins that give rise to lipofuscin, a biomarker pigment of ageing and dementia that accumulates in the brain, liver and other organs or tissues [104].

In addition, pesticides accumulate in the body and alter the gene expression causing a telomere shortening, which is associated with a greater number of senescent cells that can accelerate aging and favor the pathogenesis of chronic diseases, due to the increased accumulation of genetic damage and reduced genomic repair [21,149]. A recent study showed that the exposure to pesticides modified 612 gene expressions inducing a

senescent and premature aging profile in exposed mesenchymal stem cells, contributing to the acceleration of pathologies such as obesity, degenerative diseases and cancers [150].
Therefore, studies suggest that aging is under genetic-environmental control, so that the oxidative stress leading to alterations in the epigenome, resulting from the exposure to pesticides, play a fundamental role in the aging phenotype through diverse and complex cellular and molecular mechanisms. Thus, the increased production of reactive species and the decrease in antioxidant enzymes, together with its potential as an endocrine and metabolic, carcinogen, neurotoxic, hepatotoxic and genotoxicdisruptor, are responsible for altering the regulatory structure, accelerating the ageing process and the appearance and progression of diseases [107,93,138].
Several scientific studies have found that the effects of pesticides as a contributing factor to premature aging contribute to a wide range of health-related problems, all of which are associated with a lower quality of life in the elderly, as they are more prone to debilitating diseases and their consequences. As a result, population aging can be accompanied by senile conditions, especially when it is enhanced by environmental factors, making it increasingly necessary for there to be an oversight of farmers and their agricultural practices and a government monitoring of the rates of pesticide residues present in food and the best practices for reducing the consumption and the application in order to minimize the environmental damage and the deleterious effects on humans and animals.
There is currently an inability of the health system to meet the current demands of the elderly [143], which is why, in order to slow down ageing and allow the personalization of the prevention of multiple diseases linked to ageing, from the earliest stages of life, it is necessary to break away from the hospital-centric vision and invest more in care, because keeping elderly people close to independence is ideal, but it is also a public health challenge. In addition, it is essential to look for solutions that provide well-being and quality of life, such as adopting a healthy lifestyle, which involves eating a balanced diet, practicing physical activity, staying mentally active, socializing and avoiding environments that pose health risks and contact with harmful substances that tend to accumulate free radicals and oxidative stress, in order to develop clinical instruments for the benefit of the elderly.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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