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INVASIVE PLANTS AS A SUSTAINABLE SOURCE OF BIOMOLECULES AGAINST NEURODEGENERATIVE DISEASES

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Abstract: The development of neurodegenerative diseases is strongly related to oxidative stress, due to an imbalance in cellular metabolism. There are currently different therapies available to treat these diseases, although they are often not curative and/or have adverse effects. In view of the above, it is necessary to find complementary and/or alternative medicines that replace current treatments, showing fewer side effects. Secondary metabolites synthesized by invasive plants, specifically phenolic compounds, have a great capacity to suppress oxidative stress, neutralizing free radicals. Thus, these compounds can be used as alternative pharmacological treatments for pathological conditions associated with increased oxidative stress. Currently, invasive species are considered one of the greatest threats to the preservation of biodiversity in the world, causing negative impacts at both an environmental and socioeconomic level. Therefore, it is imperative that measures are implemented to control and manage them, ensuring a balanced ecosystem and, at the same time, promoting a sustainable economy. The use of extraction of bioactive compounds from these plants and possible applications in the field of medicine are a futuristic strategy, aiming to implement the 2030 Agenda and some of the sustainable development objectives.
Keywords: Neurodegenerative diseases, invasive species, oxidative stress, bioactive compounds, sustainable economy

INTRODUCTION

Neurodegenerative diseases (ND) comprise a set of pathologies with heterogeneous and complex clinical presentation and pathophysiology, constituting a growing cause of early mortality and morbidity globally. In fact, the field of neurodegenerative diseases is a major challenge in the area of public health and still requires robust preventive measures and disease-modifying treatments, taking into account that these diseases are characterized by the progressive loss of neurons in the central nervous system (CNS) or peripheral nervous system (PNS) (Logroscino et al., 2022). In fact, according to statistical data provided by the World Health Organization (WHO), the increasing prevalence rate of dementia represents a threat to the global health system and society in general. Currently, there are approximately 55 million people with a positive diagnosis of dementia and everything indicates that this number will increase to 78 million by 2030 (WHO, 2023). As an example, consider that, in Europe, approximately 16% of the current population falls into a senior age group, that is, over 65 years of age and, by 2030, this percentage is expected to grow to 25% (Wilson et al., 2023). In fact, dementia is the most prevalent type of ND. The requirement for specialized healthcare and expensive treatments over a period of time between two and ten years makes it possible to predict an investment of around 130 billion euros associated with treatment costs in this group of patients (Keswani, 2020).

The three main NDs are Alzheimer's disease, Parkinson's disease and Hungting's disease. While the first two are related to advanced age, Hungting disease usually appears at an early age, when people are in a highly productive phase of life (Walton et al., 2020).

CAUSES OF NEURODEGENERATIVE DISEASES

The development of clinical conditions associated with NP, diabetes, cardiovascular diseases, sarcopenia and neoplasms are associated with the "free radical theory" of aging (Costanzo et al., 2021; Liguori et al., 2018). This theory is based on the structural

damage hypothesis, claiming that tissue dysfunction due to aging can be attributed to oxidative damage to macromolecules through the presence of free radicals. Oxidative stress results from an imbalance in oxidation and reduction reactions at the cellular level, and the consequences of which imply an increase in chemical imbalance due to the increased production of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS). The consequence of this imbalance promotes the formation of ROS or ERNs, which drive a decrease in the level of antioxidant defense (Sandalio et al., 2023; Aranda-Rivera et al., 2022; Dilberger et al., 2021). According to some authors, the excessive production of ROS has a high contribution to the development of oxidative stress, promoting the death of neuronal cells and, consequently, an alteration in brain function (Aranda-Rivera et al., 2022; Dilberger et al, 2021; Singh et al., 2019). In fact, the central nervous system is vulnerable to oxidative stress, as it requires oxygen and has a lower amount of endogenous antioxidant enzymes when compared to other tissues. Over the last decade, a connection has been created between the "free radical theory" of aging and the "mitochondrial theory" of aging, which are based on the principle that the accumulation of ROS induces mitochondrial dysfunction, contributing to rapid aging. and for the development of diseases related to mitochondria and longevity (Lee and Kim, 2022). Neurodegenerative diseases are often associated with neuroinflammation, a process related to oxidative and nitrosative stress. The inflammatory response is further developed by the activation of glial cells and the modulation of the constitutive expression of extracellular matrix proteins (Kumar et al., 2019).

OXIDATIVE STRESS

Oxidative stress can be briefly described as a phenomenon resulting from an imbalance between the production and accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in cells and tissues and the inability of cells to eliminate these byproducts. In general, it results from disturbances in the homeostatic mechanisms involved in the pro- and antioxidant balance. ROS/RNS are byproducts of cellular respiration, the process of converting chemical bonds between energy-rich molecules used in vital metabolic processes. In recent years, the accumulation of ROS and RNS has been discovered to be involved in mitochondrial dysfunction, promoting deficits in energy production, alterations in metal homeostasis, and accumulation of toxic protein aggregates that typify many neurodegenerative disorders (Olufunmilayo et al., 2023). As mentioned above, ROS/RNS perform important regulatory and mediating functions in cellular metabolism when in physiological concentrations. However, uncontrolled increases in the levels of these reactive species trigger numerous reactions that generate free radicals as byproducts and subsequently impair cellular function through widespread damage to biomolecules, including lipids, proteins, carbohydrates and nucleic acids. The uncontrolled production of ROS/ERNs exceeds the maximum cellular capacity, causing an unstable pro-antioxidant balance and, eventually, depletion

More quickly a state of oxidative stress. In addition to the endogenous processes that drive oxidative stress, some exogenous processes and factors such as xenobiotics, ionizing radiation, viral and bacterial infections, nutritional imbalance, alcohol consumption and smoking, autoimmune diseases, among others, also contribute to the formation of reactive species (Mannucci et al.,

2021).

GENERAL EFFECTS OF OXIDATIVE STRESS ON THE CENTRAL NERVOUS SYSTEM

The central nervous system (CNS) has a high metabolic rate, which requires a high production of energy by the mitochondria.

This metabolic rate necessary for the production of adenosine triphosphate (ATP) is carried out through the electron transport chain and oxidative phosphorylation, meaning that neurons are more likely to produce large amounts of ROS/RNS (Vinha et al., 2023). Furthermore, neurons and other CNS cells are particularly vulnerable to oxidative stress due to their intrinsic properties (Pardillo-Díaz et al., 2022). The impacts of oxidative stress on the biochemical, cellular and tissue systems vary depending on the impacted region of the CNS. The cumulative effects of long periods of oxidative stress manifest themselves in a variable number of CNS disorders, including neurodegenerative conditions, triggering Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis and frontotemporal diseases (Chung et al., 2023; Zhuang et al., 2020). These diseases share common pathological features, such as induction of oxidative stress, abnormal protein aggregation, disturbances of Ca2+ homeostasis, excitotoxicity, inflammation, and apoptosis (Sharma and Kim, 2021; Zhuang et al., 2020). Some studies indicate that oxidative stress plays a fundamental role in the development and evolution of Alzheimer's disease. For example, elevated ROS production has been shown to initiate the toxic processing of the amyloid precursor protein (peptide called β-amyloid 42 (Aβ42)) (Marucci et al., 2021; Kumar et al., 2015). In the case of Parkinson's disease, there is a loss of dopaminergic neurons, promoting an accumulation of intracellular proteins (synucleins), leading to cognitive and motor deterioration in people with this pathology (Naveen and Bhattacharjee, 2021). It is possible that some chemical processes, such as oxidation, may be responsible for the gradual dysfunction that may occur throughout the disease. Previous studies have reported evidence of triggering oxidative stress through the detection of oxidized deoxyribonucleic acid (DNA), lipids, and proteins in the brain tissues of Parkinson's patients (Chakrabarti and Bisaglia, 2023; Chang and Chen, 2020).

In the case of Huntington's disease, it has been reported that the imbalance of metal homeostasis in the brains of patients with this pathology promotes the formation of free radicals and, consequently, the progression of the disease (Muller and Leavitt, 2016). In fact, the accumulation of iron and copper can catalyze the production of free radicals through the Fenton reaction (free iron) or through a Fenton-like reaction (copper) (Jędrak et al., 2018).

In general, treatments for neurodegenerative diseases tend to be limited in their therapeutic approach, due to the development of symptoms, but of a non-curative nature (Chaves et al., 2023), and the continuous use of certain conventional medications generates many adverse effects, such as nausea, diarrhea, eating disorders and kidney and liver disorders (Chaves et al., 2023; Ruangritchankul et al., 2021). Therefore, it is necessary to find complementary and/or alternative treatments. Several clinical trials have proven the implication of natural products as antioxidant agents (for example: ferulic acid and p-coumaric acids, resveratrol, catechin, epicatechin, quercetin and ginsenosides (Kim et al., 2018) and, given the relevance of oxidative stress in pathogenesis of neurodegenerative diseases, these compounds could be a good therapeutic alternative against these diseases.

INVASIVE SPECIES

Biological invasions, in addition to impacts on ecosystem services and economic damage, can pose a threat to public health. In fact, changes in geographic distribution affect how plant species interact, and these dynamics allow pathogens to spread (Schatz and Park, 2021). Despite this, the risk of infectious diseases is rarely associated with plant introduction processes, especially when compared to other invasive species, such as arthropods and mammals – which are the agents directly responsible for the transmission of pathogens (Plaza et al., 2018). In a generalized context, the health implications attributed to invasive plants include skin irritation, allergies and poisoning problems, through direct contact or inhalation of pollen and toxins (Daszak et al., 2021; Plaza et al., 2018). Given the potential danger of invasive species to animal and human health, it is imperative that measures are implemented to control and manage them, ensuring a balanced ecosystem and, at the same time, promoting a sustainable economy. The use of extraction of bioactive compounds from these plants and possible applications in the field of medicine are a futuristic strategy, aiming to implement the 2030 Agenda and some of the sustainable development objectives.

Given their easy adaptation to the ecosystem, it is believed that the biochemical metabolism (primary and secondary) of invasive species must be very varied and with an enormous potential for biological activity that remains to be explored. This, of course, implies new studies in this area, focusing on the biological activity of isolated products – most existing phytochemical studies of invasive species focus on the biological activity of extracts and no active ingredient has been isolated (Máximo et al., 2020). It is also desirable that these studies focus on invasive species, rather than native species. Most likely, the prevalence of invasive species over endemic ones depends on a still unknown biological activity of the metabolites they produce; these are certainly responsible for its ease of expansion and dominance of new habitat and, therefore, its chemical profile can certainly be correlated with its ability to survive in different ecosystems. Furthermore, the use of these species as a therapeutic source allows a rational use of social and economic resources that would ultimately mitigate the cost of their removal. In this article, global invasive species were chosen that constitute a threat to Portugal and Brazil, where they are recognized by the government and the scientific community, in order to illustrate their potential as a source of bioactive metabolites with possible applications in the prevention/treatment of neurodegenerative diseases: *Carpobrotus edulis* and Tropaeolum majus.

CARPOBROTUS EDULIS

Carpobrotus edulis, known as ice plant or beach weeping plant (Aizoaceae), it is a perennial subshrub that can reach several meters in height. It was introduced in Portugal for ornamental purposes where it is currently cultivated to maintain dunes and sandy slopes. Native to South Africa, this invasive plant has vigorous growth, leading to the formation of continuous vegetative areas that prevent the existence of native vegetation. At the level of traditional medicine, it is used to treat tuberculosis, throat infections, diarrhea, dysentery, burns, stomach diseases, chilblains, mouth ulcers, sinusitis and diabetes (Akinyede et al., 2020; Hafsa et al., 2016). This species was characterized by containing several secondary metabolites which are related to the various biological functions described above.

In fact, amyrin (triterpene), oleanolic acid (pentacyclic triterpenoid), uvaol (terpenic alcohol), catechin and epicatechin

(flavonoid) and procyanidin B5 (tannin) were identified (Máximo et al., 2020). Sabiu et al. (2021) reported the presence of rutin and luteolin (flavonoids) as well as some phenolic acids, including chlorogenic and sinapic acids and alkaloids, such as cacticin. Some studies emphasize the biological activity of methanolic and aqueous extracts of this species, namely anti-proteus (Cock and Van, 2014) and anti-klebsiella (Cock and Van, 2015) activities, indicating their potential to prevent the development of rheumatoid arthritis and ankylosing spondylitis. These extracts were also effective in inhibiting the growth of Mycobacterium tuberculosis and Staphylococcus aureus, suggesting that this plant can serve as a source of new antimicrobial agents effective against problematic medications (Máximo et al., 2020). However, the diversity of the profile of bioactive compounds present in C. edulis allows us to conclude that the synergism of these compounds enhances the antioxidant, metal chelating and anticholinesterase activities, promoting the use of this invasive species as a candidate natural source for therapeutic purposes, namely in the treatment of neurological disorders associated with low levels of acetylcholine in the brain. The presence of catechin and epicatechin in this species enhances its therapeutic effects. Catechins can help in the prevention and, to some extent, in the treatment of neurodegenerative diseases. It is common knowledge that flavonoids have anti-inflammatory and antioxidant effects by blocking excessive production of cytokines and inflammatory pathways, as well as chelating metal ions and eliminating free radicals (Afzal et al., 2022).

TROPAEOLUM MAJUS

Tropaeolum majus, commonly known as nasturtium or nasturtium, it is an invasive species from the American continent, namely from the regions of the Andean mountain range between Bolivia and Colombia. It is a creeping, perennial species, with succulent and very branched stems, reaching around 50 cm in height. As it is highly appreciated by insects, especially caterpillars, it can be used to control pests, preventing predation from other species grown together.

It is also very common in disturbed areas, being considered a very aggressive ruderal plant species, due to its rapid growth and easy spread. In traditional medicine, Tropaeolum majus has recognized pharmacological properties, including expectorant, antispasmodic, antiseptic, antihypertensive, anti-inflammatory, diuretic, sedative, antibacterial and antifungal activities (Musolino et al., 2022; Jurca et al., 2018; Gasparotto et al., 2011). This species has a variety of bioactive compounds, including flavonoids, namely quercetin, kaempferol, myricetin, rutin, catechin, cyanidin and delphinidin (Gonçalves et al., 2019) and hydroxycinnamic acids such as dicaffeoylquinic and chlorogenic acids (Izcara et al., 2022). The leaves of this plant also contain fatty acids, tetracyclic triterpenes and glucosinolates (benzyl glucosinolate and sinobine) (Jakubczyk et al., 2018). There are no studies of this species associated with the prevention of neurodegenerative diseases, however, due to the panoply of bioactive compounds that it presents, everything indicates that it can be an asset in the therapy of certain pathologies. For example, some pharmacological studies have reported the beneficial effects of rutin in many neurodegenerative disease conditions (Enogieru et al., 2018; Ganeshpurkar and Saluja, 2017). Likewise, anthocyanins, a group of natural pigments that make up the

flavonoid group, have shown increasing evidence of improving neurodegenerative diseases (Mattioli et al., 2020). According to Shishtar et al. (2020), anthocyanins or dietary supplementation of foods rich in anthocyanins can reverse cognitive deficits and neurological functions related to neurodegenerative diseases. Another group of promising phytochemicals in terms of neuroprotective effects are glucosinolates (Giacoppo et al., 2015). Tropaeolum majus has considerable levels of benzyl glucosinolate and sinobine. This way, this invasive species could be even more valued due to the diversity of groups of bioactive compounds it presents, enhancing its value in the area of pharmacology.

CONCLUSION

In this review, two invasive species were reported (*Carpobrotus edulis* and Tropaeolum majus) to illustrate the varied chemical and pharmaceutical potential of invasive plants, particularly in the prevention of neurodegenerative diseases.

Although little studied from the point of view of beneficial attributes, extracts from these species present interesting biological activities, ranging from antioxidant, antimicrobial and antifungal, to neuroprotective and neuritogenic, including antiproliferative and cytotoxic, anticholinesterase, allelopathic and viral growth inhibition. The chemical potential of these invasive species was referenced here, a potential that is suggested to be further explored – invasive plants represent a current problem that must be transformed into a profitable resource. The use of invasive species as a source of active metabolites could help reduce real and future control and management costs, making this a value-added resource. As such, additional efforts must be directed towards the phytochemical study of these species in their invasive habitat. These studies must be complemented with a broad-scope analysis of the bioactivities of isolated products, such as antioxidant, anticancer/antiproliferative and anti-inflammatory activities, among others. Humanity must act together decisively through equitable and sustainable partnerships to rethink and accelerate actions towards the 2030 Agenda and the broader goals of health equity, while remaining within "planetary boundaries", i.e. the environmental limits within which humanity can operate safely. Invasive plants are, therefore, a valid and promising strategy for the development of medicine, improving social and economic impact and balancing the global ecosystem.

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