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Review Article

Treatment of Alzheimer's Disease: Synthetic Drugs or Bioactive Compounds?

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Introduction

According to estimates, the number of people with dementia worldwide is expected to increase from 57.4 million in 2019 to 152.8 million in 2050. An uncertainty interval of 95% is considered for the year 2019, with variation from 50.4 to 65.1 million people. For 2050, this range should be between 130.8 and 175.9 million people. Despite the large number of people living with dementia across the globe, age-standardized male and female prevalence will remain stable, according to forecasts, between 2019 and 2050 [1].

One of the main pathological features of Alzheimer's disease is the anabolism of the neurotoxic and synaptotoxic beta-amyloid peptide, consisting of 40-42 amino acids, which tend to accumulate in the brain as extracellular amyloid plaques or within the walls of the cerebral vasculature, subsequently increasing the phosphorylation of TAU, an axonal protein that binds to microtubules to promote their assembly and stability. Cytokines such as brain-derived neurotrophic factor, interleukin-1α and interleukin-6 can stimulate APP expression, while interleukin-1β decreases it [2].

Recognition of the entire pathophysiological process involved with Alzheimer's disease should enable more assertive treatment. The neurodegenerative process of Alzheimer's disease appears to be a consequence of reactions involving neurotransmitters, proteins, and other molecules, some of which were previously unknown. Some questions such as diet, lifestyle, age and comorbidities, in addition to genetic aspects, may be directly related to the disease [3].

In recent years, a series of studies have been carried out in the search for drugs capable of preventing the onset or progression of Alzheimer's disease. They are almost entirely synthetic molecules, developed from strategies created within high-tech laboratories. They involve monoclonal antibodies and even genetic vaccines. Faced with all this progress, unquestionable and important, a question arises: are there cheaper resources available in nature capable of bringing faster, more effective, and cheaper results? Instead of concentrating all actions for the search for treatments and cures for Alzheimer's in synthetic drugs, wouldn't it also be interesting to evaluate bioactive compounds, abundantly available in nature?

Among the bioactive compounds that present very satisfactory preliminary results for the prevention of mild cognitive impairment (MCI) and for a possible treatment of Alzheimer's disease are the phenolic compounds.

Many bioactive food compounds can influence the pathological mechanisms underlying AD. Among them, phenolic compounds, omega-3 fatty acids, fat-soluble vitamins, isothiocyanates and carotenoids seem to be promising. They act not only as antioxidant and anti-inflammatory agents, but also as active modulators of

the pathological molecular mechanisms that play a role in the development of AD, including the formation of amyloid plaques and tau tangles, key features of AD pathology [4].

Phenolic compounds are found in common plant foods, and one of their most important sources is olive oil, which contains oleuropein, hydroxytyrosol and oleocanthal. Oleuropein is a glycosylated seco-iridoid with many beneficial properties; has strong antioxidant potential and protects nerve cells from neurotoxin-induced apoptosis [5].

In an in vitro experiment in Escherichia coli cell culture, [6]. demonstrated that oleuropein prevented the accumulation of a mutated and rapidly aggregating tau protein by 67% compared to the control group. For wild-type tau, the efficiency was 79%, while methylene blue, the reference tau aggregation inhibitor, was 75% effective. These results suggest that oleuropein can prevent the formation of toxic tau aggregates, probably due to the presence of aldehyde groups in the tautomeric forms of its aglycone metabolite. [5,6]. In the digestive tract, oleuropein is hydrolyzed into another phenolic compound, hydroxytyrosol, which is also present in olive oil and has greater bioavailability [5,6]. Hydroxytyrosol is a potent antioxidant and free radical scavenger, it may also activate phase II detoxification enzymes [7].

Another phenolic compound worth mentioning is oleocanthal, a substance responsible for the bitter taste of olive oil. Reduces inflammation by inhibiting the enzyme cyclooxygenase (COX), which participates in the synthesis of pro-inflammatory prostaglandins [5].

Other neuroprotective phenolic compounds are anthocyanins. They belong to the flavonoid group and are responsible for the red, violet and blue color of many fruits and vegetables. According to [8], anthocyanins improve oxidative stress by decreasing free radical production and lipid peroxidation. They also reduce prostaglandin synthesis by inhibiting COX. In addition, anthocyanins increase the activation of the FKBP52 protein, which has an affinity for phosphorylated tau protein and prevents its aggregation. They decrease the concentration of intracellular Ca2+ ions and inhibit caspase-3, which regulates neuronal apoptosis. The neuroprotective effects of anthocyanins were analyzed in vitro by [9] who found that two of these substances, delphinidin and cyanidin, complexed with Aβ peptides to inhibit their aggregation. The authors confirmed these observations in their next experiment, in which mouse neurons were exposed to both Aβ and anthocyanins. Survival was significantly higher among cultures treated with solutions containing delphinidin or cyanidin than in cells exposed to toxic peptides alone. This suggests that anthocyanins can counteract the toxic effects of amyloid and protect nerve cells.

Conclusion

There is a true gold rush in search of solutions for the treatment of various diseases, not only for Alzheimer's disease, but also for Cancer, diabetes, depression, among others. If you look at what a research laboratory was a century ago and what it has become today, it's easy to see the differences. Technology has advanced a lot and has been bringing excellent results, benefiting people's quality of life, and promoting the cure of many diseases. However, in the same way that synthetic drugs emerge after preliminary discoveries in nature, there are many bioactive compounds that still need more investment and research, although they have potential through their therapeutic effects. In the segment of Alzheimer's research, we highlight bioactive compounds such as anthocyanins, phenolic compounds, among others. There are already results of these compounds in the prevention of mild cognitive decline, a phase prior to the onset of the dementia process, thus showing the viability of using these substances as a strategy to shield brain tissue against the formation of senile plaques and neurofibrillary tangles. Only with more research and investigation studies will it be possible to verify these beneficial effects. We hope that there will be an increase in interest in these studies, in order to justify greater investments by institutions interested in discovering new and effective treatment alternatives for Alzheimer's dementia.

Acknowledgement

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Conflicts of interest

None.

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