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Review Article

Could Lichens Cure Alzheimer's Disease?

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Abstract

Alzheimer's disease is a neurodegenerative illness marked by a gradual memory impairment and certain intellectual (neurocognitive) functions leading to repercussions in the activities of daily living. Until now, there is no drug to treat neurodegenerative disorders; for this, it is preferable to seek to delay the progression of this disease. Lichens show vital therapeutic activity in several neurological diseases, including Alzheimer's disease. Several isolated lichenic compounds have been tested for anti-acetylcholinesterase potency and may play a key role in the prevention of this dementia. This review deals with previous work on the therapeutic activity of some lichens and their bioactive components for them neurodegenerative diseases. Thus, compounds isolated from lichens can be considered favorable and promising for the prevention of neurodegenerative diseases.

Keywords: Lichens; Alzheimer; Anti-acetylcholinesterase; Neurodegenerative; Usnic acid

Introduction

Oxidative stress is an imbalance between the excessive amount of free radicals and antioxidants.

Free radicals are molecules containing oxygen and are the origin of the natural process of oxidation in cells. Too much in the body, they can be harmful to the body and attack fatty tissue, proteins, DNA and all parts of the body. During an antioxidant/free radical imbalance, the body's immune response is weak and therefore the body's coping strategies are damaged.

This anomaly is the root cause of chronic disorders like diabetes, tumor, inflammatory diseases, Alzheimer's disease and Parkinson's. However, it should be remembered that if the balance of antioxidants and free radicals is present, the latter are used by certain white blood cells and contribute to the destruction of bacteria and the regulation of dead cells.

Free radicals are therefore very unstable and chemically reactive molecules, which are at the origin of oxidative stress and can be neutralized by antioxidants [1].

In a normal situation, the antioxidant/prooxidant balance is balanced. However, the body can be faced with over-exposure to oxidizing compounds when the endogenous production of Reactive Oxygen Species (ROS) becomes excessive or following exposure to an exogenous toxic phenomenon. When an imbalance occurs (by overproduction of pro-oxidant compounds or by a deficit in antioxidant substances), we speak of oxidative stress [2]. One of the main causes of Alzheimer's disease is oxidative stress, which is caused by the excess production of free radicals. The main contributing elements are increased formation of Reactive Oxygen Species (ROS) and reactive nitrogen species (RNS). Certain environmental factors (i.e. Contaminants, pesticides, environmental pollutants, and Ultraviolet rays) can lead to the production of free radicals. Lipid peroxidation, which is the major cause of the decrease in membrane phospholipids in Alzheimer's disease, is caused by free radicals reacting with enzymes, transporters, and proteins [3]. Indeed, the antioxidant activity would limit the oxidative damage linked to the neurodegenerative disorders associated with Parkinson's and Alzheimer's diseases [4].

Alzheimer's disease (AD) is the most well-known and widespread neurodegenerative disease that impairs older people's memory and behavior. The clinical manifestation of this neurological disease is the progressive degradation of brain tissue, which is driven by Acetylcholine (ACh) insufficiency [5]. Acetylcholinesterase (AChE) is a key neurotransmission enzyme (Figure 1). By hydrolyzing the cationic neurotransmitter ACh, it allows cholinergic neurons to return to their resting state by hydrolyzing acetylcholine (ACh) (Figure 2). AChE transforms acetylcholine (ACh) into choline (Ch) and acetate [6]. Reduced ACh levels in the hippocampus and cortex have been linked to significant biochemical alterations in Alzheimer's patients [6]. AChE inhibitors (AChEI) are natural compounds that have been tested in clinical trials, primarily for the treatment of Alzheimer's disease. Secondary metabolites have also been found as AChEIs, indicating that they could be used to treat Alzheimer's disease [7]. Acetylcholine levels are particularly low on those suffering from Alzheimer's disease, which explains the cognitive impairment observed. The solution to increasing the level of acetylcholine at the synaptic level is therefore to decrease its degradation by inhibiting the action of acetylcholinesterase [8]. Based on the hypothesis of inhibiting the action of AChE to better treat AD, several inhibitors of this enzyme have appeared on the market [9], such as galantamine, a natural alkaloid from *Galanthus nivalis*, in 2000. Although most of the known AChE enzyme inhibitors are alkaloids, various investigations have lately been conducted to uncover alternative naturally occurring compounds with strong anti-AChE activity. Several substances, other than alkaloids, exhibit a high ability to inhibit the AChE enzyme, according to Houghton et al. [8], including terpenoids, phenolics, flavonoids, and isocoumarins. In addition to secondary metabolites extracted from plants, natural products from lichens have aroused enormous interest from researchers around the world in the search

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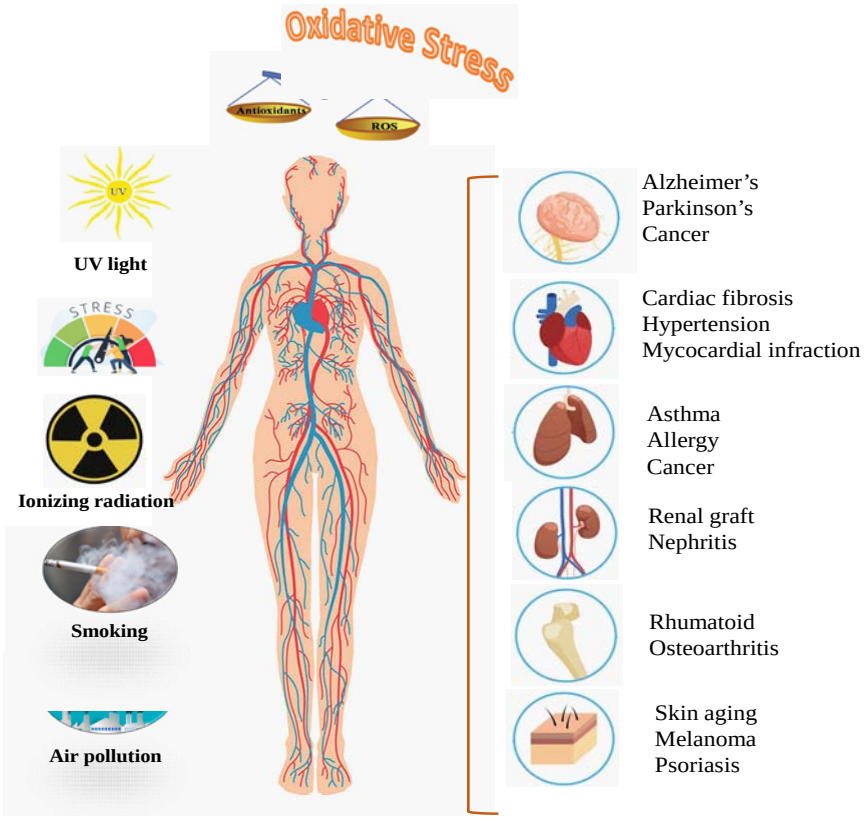

Figure 1: Oxidative stress a leading cause to all chronic diseases.

for new drugs due to their positive effects on bioactivity. With the same objective, this review article focuses on the search for natural alternatives based on lichens that have antioxidant substances that indicate that they can slow the progression of Alzheimer's disease [10]. This review is an attempt to compile information on various ethnomedicinal uses of lichens to fight Alzheimer's disease.

Uses of Lichens

Lichens are the result of a symbiotic association between a fungus (mycobiont) and an alga and/or a cyanobacterium (photobiont) [11]. However, Spribille et al. (2016) revealed that in addition to the mycobiont and photobiont, specific basidiomycetes are systematically found as a third partner [12].

Lichens find applications in a wide range of medical treatments throughout the world, mainly in traditional medicine, to treat wounds and skin disorders, or respiratory and digestive problems. The genus *Usnea* is most commonly used, but other genera such as *Thamanolia* or *Lethariella* are used in Asia or China, respectively [13].

Native Americans, Egyptians, Indians and Chinese used lichens to treat ailments, primarily as expectorants [14]. *Peltigera canina*, a leafy cyanobacterial lichen rich in methionine, was once utilized as a liver cure in India. In different pharmacopoeias, many species of lichens possessing a therapeutic activity are identified such as *Xanthoria parietina*, *Peltigera canina*, *Lobaria pulmonaria*, *Cladonia coccifera*, *Evernia prunastri*, *Cetraria islandica*, and *Usnea plicata* [15]. In Spain, certain species of lichens were used as diuretics (*Ramalina bourgeana*), analgesics (*Xanthoria parietina*), to treat menstrual pain, kidney problems, or even respiratory (*Pseudevernia furfuracea*) [16]. In India, mixtures of at least two species of Parmelia, *Heterodermia tremulans*, *Ramalina subcomplanata*, and *Usnea longissima*, are sold under the name "Chharila" and are used as an astringent, laxative and carminative [17].

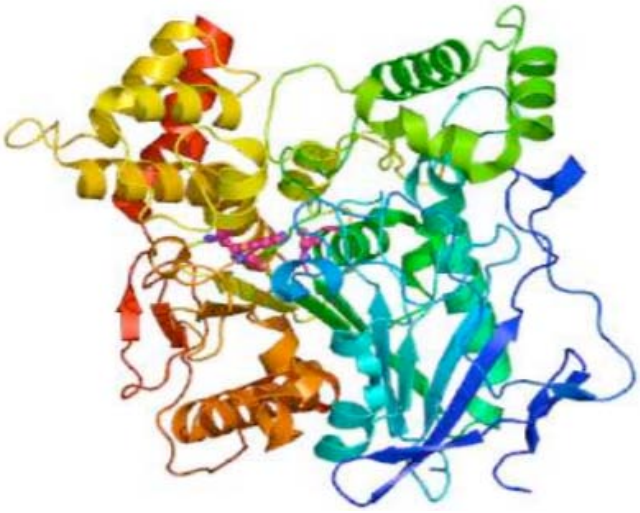

Figure 2: Acetylcholinesterase enzyme.

The *Cetraria islandica* lichen, or "Icelandic moss", has many

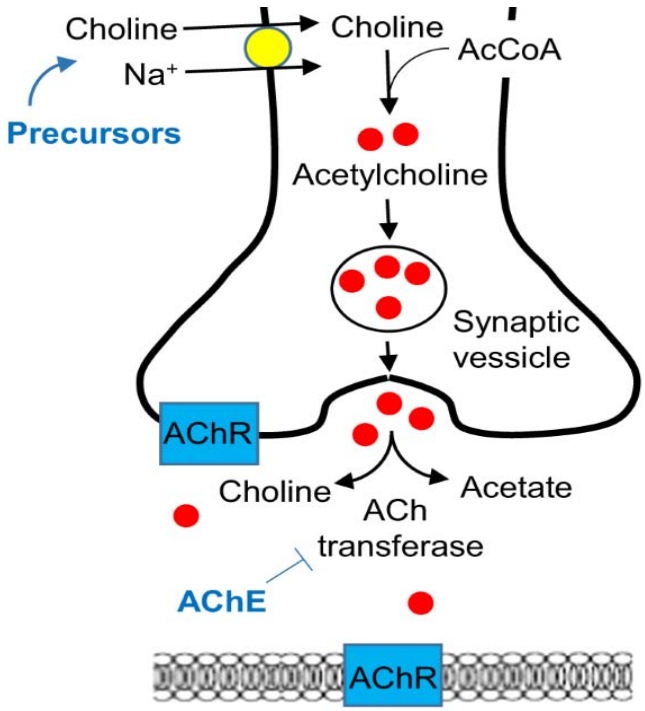

Figure 3: Acetylcholine diffusing across the synaptic cleft.

medical applications. It's been used for a long time to cure TB, respiratory problems, diarrhea, and infections of the throat and oral cavity, as well as stomach and gastrointestinal disorders, and even the flu. Studies in Iceland and Germany resulted in the creation of capsules and tablets containing lichen extracts, which are now used to treat intestinal blockage, gastric ulcers, osteoarthritis, and asthmatic [18]. Lichens produce unique secondary metabolites of pharmacological interest in addition to the primary metabolites (lipids, proteins, and carbohydrates), the majority of which are phenolic acids from the polyketide group, such as depsides (e.g. evernic acid), depsidones (e.g. lobaric acid), dibenzofurans (e.g. usnic acid), and pulvinic acid derivatives (e.g. vulpinic acid). The mycobiont primarily produces lichenic compounds *via* the acetyl-polymalonyl and shikimate pathways [19]. In addition, as compared to other aromatic and therapeutic plants, lichens have a wealth of natural compounds that are poorly understood from a pharmacological standpoint. Even so, there has been a growing interest in lichens as sources of innovative pharmacologically active biological molecules over the last two decades; their secondary metabolites have been the subject of increasing research for their antibacterial, anti-inflammatory, and cytotoxic activity, but their neuroprotective properties remain unknown [20].

Role of Lichens in Alzheimer's Disease (AD)

The symbiosis between a fungus and a photosynthetic partner gives the lichen a specific metabolism with the production of lichenic secondary metabolites of the complex and original structure [21-23]. There has recently been a surge in attention in lichens that contain bioactivities compounds (Table 1). In 1844, usnic acid was extracted from lichens, especially *Usnea* [24]. Usnic acid, on the other hand, was identified and described from lichens as an active derivative of

Table 1: Lichens against neurodegenerative disorders.

Name of the lichens species	Bioactive compound	References
Cladonia macilenta	Biruloquinone	[42,43]
Evernia prunastri	Evernic acid	[21,54]
Heterdermia sp.	Depsidone	[55]
	Lobaric acid	
Lobaria pulmonaria	Lobaric acid	[49,51-53]
	Stictic acid	
	Deoxystictic acid	
Ramalina capitata	Everninic acid	[48]
	Evernic acid	
	Usnic acid	
	Obtusatic acid	
	Atranorin	
Pertusaria albescens	Perlatolic acid	[50]
Umbilicaria crustulosa	Gyrophoric acid	[46]
Umbilicaria esculenta	Orsellinic acid	[47]
Usnea ghattensis	Usnic acid	[54]

dibenzofuran. Usnic acid is the most well-known and economically valuable lichen metabolite. It's natural ingredient can be found in creams, toothpastes, deodorants, mouthwashes, and sunscreens. It is the most widely used and researched lichen secondary metabolite, including antibacterial and cytotoxic, antiviral, antimicrobial, antiprotozoal, antimycotic, antiparasitic, antipyretic, anesthetic, anti-inflammatory [25] and anti-tumor properties in several cell types [26]. In addition, usnic acid has been shown to have a healing effect [27-30].

Reactive Oxygen Species (ROS) are hazardous biomolecules that occur naturally in living creatures during normal cellular metabolism. They include lipids, carbohydrates, nucleic acids, and proteins [31-33]. Furthermore, ROSs, which have been linked to a variety of illnesses, are created by all living cells as a fundamental immunological defense mechanism [34,35]. Oxidative stress and Reactive Oxygen Species (ROS) have recently been identified as substantial environmental dangers for a variety of chronic diseases, including tumors, aids syndrome, age-related pathologies, cardiovascular disease, arteriosclerosis, diabetes, and obesity [36,37]. Antioxidant components and an antioxidant enzyme make up the antioxidant defense system (Figure 3).

The inhibitory effects of usnic acid have been studied against a number of metabolic enzymes, including Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE), both of which have been associated to neurological disorders. The fact that usnic acid is efficient suggests that metabolic enzyme inhibitory actions are present. In the cosmetic, pharmaceutical, and food industries, enzyme inhibition is the most explored therapeutic medium. They are, however, utilized in therapeutic settings to treat a variety of health issues, including Alzheimer's disease, obesity, and diabetes [38]. Synthetic inhibitors have been linked to gastrointestinal problems and hepatotoxicity, according to reports. Naturally, there is a lot of interest in discovering novel, natural inhibitors that don't have any negative side effects [39].

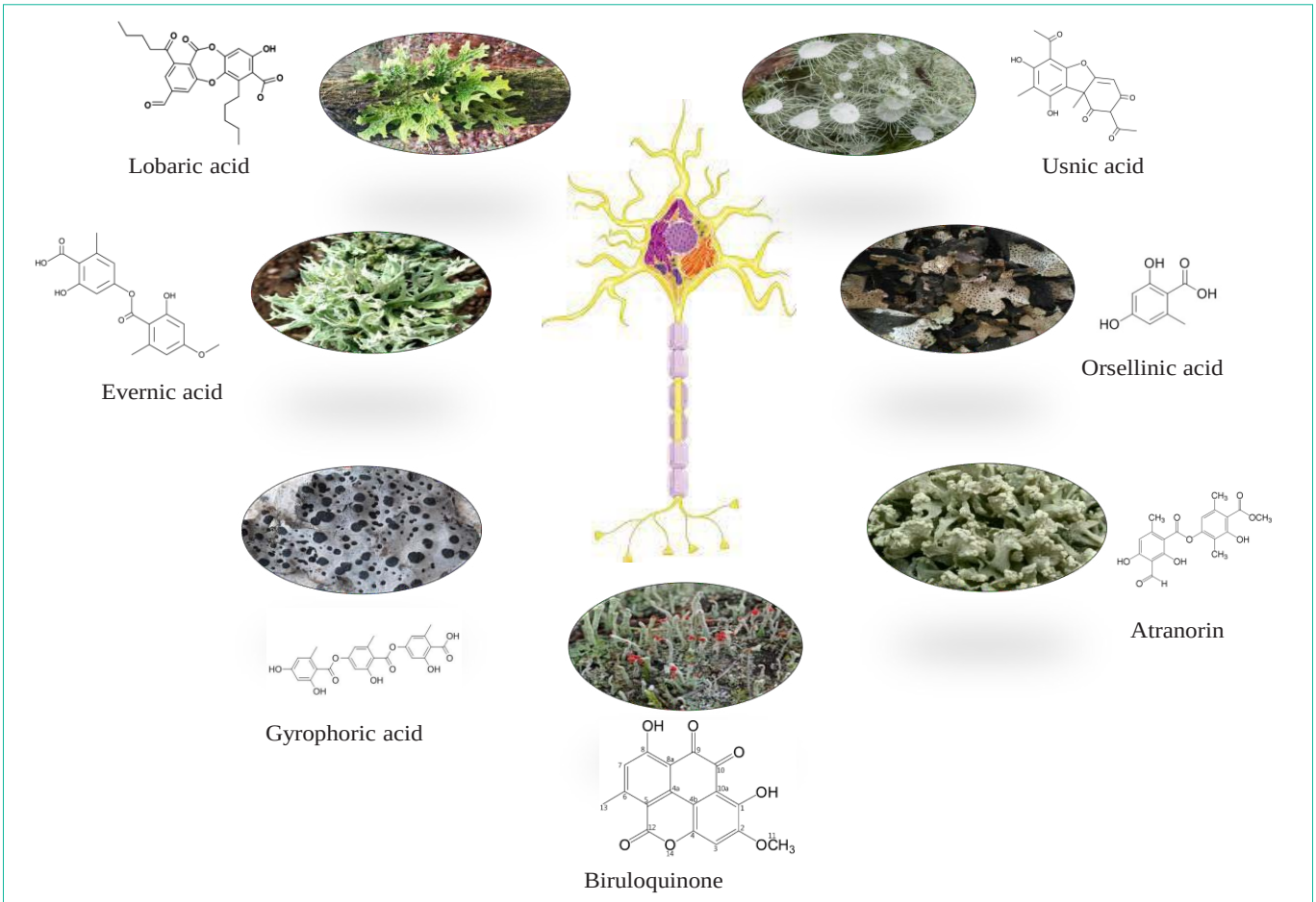

Figure 4: Lichenic acids tested for Alzheimer's disease.

The Ellman technique is used to assess the effect of usnic acid on these enzymes.

In cholinergic synapses, the central nervous system, and autonomic ganglia, both enzymes (AChE and BChE) hydrolyze the neurotransmitter acetylcholine to choline and acetate, which is required for cholinergic transmission. Their inhibitors have been employed in the therapeutic of myasthenia gravis, Alzheimer's disease, apathy, glaucoma, postural tachycardia syndrome, and dementia, among other neurological illnesses [40]. In fact, usnic acid inhibited AChE (IC_{50}: 1.273nM) and BChE (IC_{50}: 0.239nM) enzymes with high potency [41].

Luo et al. [42] determined AChE inhibitory activity and neuroprotective impact using the MTT technique on injured PC12 cells. Extract from the lichen *Cladonia macilenta* exhibited a very strong anti-acetylcholinesterase activity (IC_{50} = 27.1µg/mL), and biruloquinone as an AChE inhibitor was then analysed using Masse spectrometry, and 1H- and 13C-NMR. Biruloquinone is an AChE inhibitor, according to the inhibitory kinetics test. Biruloquinone, on the other hand, enhanced the viability of PC12 cells that had been damaged by H_2O_2 and amyloid. The high antioxidant properties of biruloquinone are thought to be responsible for the protective effects. These findings suggest that biruloquinone could be used as an anti-disease Alzheimer's agent [43]. Inhibition of AChE by biruloquinone is dose-dependent.

In fact, the percentage of inhibition increased rapidly with the increase in the concentration of biruloquinone from 0 to 100µg/mL. The concentration required for 50% enzyme inhibition (IC_{50}) is 27.1µg/mL (83.1µM). Compared with other AChE inhibitors, biruloquinone exerted weaker inhibition than tacrine, which has been used in the treatment of neuronal disorders, and much lower potency than donepezil, an anti-Alzheimer drug [44], but its activity is comparable to that of many other AChE inhibitors isolated from natural extracts [45].

The results clearly show that biruloquinone attenuates intracellular oxidative stress in PC12 cells. Therefore, biruloquinone's high antioxidant activities could be a probable explanation for its neuroprotective effects. As a result, biruloquinone may not only help people with Alzheimer's disease by enhancing their memory, but it may also help to reduce or stop symptoms by shielding harmed neurons. As a result, biruloquinone has a lot of potential as a multifunction anti-AD agent [43]. Luo et al. [42] also found that the extract of *C. macilenta* has a high cholinesterase inhibitory activity of 60.5%, while Zlatanović et al. [46] found a similar activity to acetone extract from *Umbilicaria crustulosa*, and Lee et al. [47] showed that methanolic extracts of *U. esculenta* had the highest inhibition of AChE activity of 22.4%.

Zrnzević et al. [48] showed that an acetone extract of *Ramalina capitata* has anti-acetylcholinesterase activity, which varies according to the concentration, tested. Indeed, the extract with a concentration of 1.0mg/mL showed a weak activating effect on cholinesterase up to 2.8%, while the more concentrated extract (10mg/mL) showed a slight inhibitory effect (5.2%) on combined human serum. From these results, it can be assumed that increased concentrations of extracts increase the ability to inhibit cholinesterase activity. In one trial, neostigmine bromide (as a standard cholinesterase inhibitor) inhibited cholinesterase by 96.6%.

A mixture of acetyl dipsidone with a moderate inhibitory activity against acetylcholinesterase was isolated from a leafy lichen (*L. pulmonaria*) by Pejin et al. [49]. Perlatolic acid, a compound derived from lichen, also shows promising activity to inhibit acetylcholinesterase [50], as does the depsidone compound isolated from Lobaria pulmonaria [51,52]. Lobaric acid, isolated from *Heterodermia* sp., also showed an inhibitory activity against acetylcholinesterase with an IC value of 26.86 M and butyryl cholinesterase with an IC value of 36.76 M [50]. The isolation of a combination of acetylated depsidones from *Lobaria pulmonaria* demonstrated moderate activity (0.5g) in an acetylcholinesterase inhibition test on a thin layer chromatography plate [49]. Another mixture of methylated depsidones isolated from Lobaria pulmonaria showed acetylcholinesterase inhibitory activity (2µg). In the quest for inhibitors, depsidones and methylated depsidones, highly specific metabolites of lichen species, remain the finest medications now available for the treatment of Alzheimer's disease [51-52]. Acetylcholinesterase inhibitors (AChE) are still the finest Alzheimer's disease treatments currently available. A novel depsidone 1 with moderate AChE activity (1g) was isolated after a lichenochemical investigation [53]. The active depsidone molecule 1 and galanthamine, both isolated from Lobaria pulmonaria, had greater HOMO energies than the inactive depsidones 2-4. Due to the enhanced HOMO energy value, the amino depsidone derivative 7, whose structure was postulated using computational techniques, is expected to be a more active AChE inhibitor than the depsidone 1. Furthermore, the chemical analysis revealed that compound 7 has the ability to interact with the active site of the enzyme in the same way that powerful AChE inhibitors do. The findings suggest that novel AChE inhibitors based on the depsidone scaffold could be developed [53]. Indeed, the findings could lead to the identification of a novel depsidone track with enhanced AChE inhibitory efficacy [53].

The ability of biruloquinone, usnic acid, and, in particular, evernic acid (Figure 4) as actual therapeutic candidates in neurodegenerative illnesses warrants further investigation in different *in vitro* and *in vivo* models [54].

Many research has shown that the lichen phenolic compounds have anti-acetylcholinesterase properties; for example, depsidone lobaric acid obtained from *Heterdermia* sp. and perlatolic acid extracted from *Pertusaria albescens* both had IC_{50} values of 26.86µM and 6.8µM, respectively [55,50].

Recently Ben Salah et al. [56] study the inhibition of acetylcholinesterase activity by biosynthesized silver nanoparticles from lichen *Roccella phycopsis*. The results showed this lichen were potent in inhibiting acetylcholinesterase enzyme with IC_{50} value of 1.65mg/mL.

Silver nanoparticles also have an inhibitory effect on the acetylcholinesterase enzyme [57]. They do, in fact, have binding affinities for the enzyme, which makes their communication possible [58].

Conclusion

Lichens are a source of bioactive molecules that may be a promising alternative natural treatment to delay the progression of AD. Future research may elucidate the role of depsidones, depsides and dibenzofurans, which may be safe and potent neuroprotective agents that could improve the quality of life for patients. The different lichenic acids could provide new hope for new drugs for Alzheimer's disease. However, to use biruloquinone as a novel anti-AD agent as a dietary supplement or in the pharmaceutical industry, a series of *in vivo* studies should be conducted in the future, as the ability of this compound to cross the blood barrier-encephalic is still unclear; naturally, *in vivo* toxicity tests would also be necessary to ensure its safety.

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