NEURAL REGENERATION RESEARCH
www.nrronline.org

Historic recurrences in medicinal chemistry: nature-inspired structures as a new opportunity for novel multi-target anti-Alzheimer's drugs

Luca Piemontese*

Downloaded from http://journals.lww.com/nrronline by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 05/15/2023

Alzheimer's disease (AD) is an alarming non-communicable, multi-factorial, and non-treatable disease. Its underlying neurodegenerative events have not yet been fully explained and its early diagnosis is very difficult. The appearance of the disease is associated with clinical features such as the degeneration of several cholinergic nuclei of the brain, causing lower levels of the neurotransmitter acetylcholine and the formation of protein aggregates in the inter-synaptic space (amyloid plaques) or inside the cells (neurofibrillary tangles, Brunetti et al., 2020).

Current therapies focus on enhancing the cholinergic system. The canonical drugs that have been used over the years are cholinesterase inhibitors and memantine (N-methyl-d-aspartate receptor blocker). The efficacy of these molecules concerns just the symptoms and is limited to the first stages of the disease (Brunetti et al., 2020, 2022; Carocci et al., 2022).

Considering the rising prevalence of this pathology and, consequently, its high economic and social costs, large efforts are currently being made both by public institutions and private companies for the development of novel disease-modifying therapeutics. Some attempts in this direction have led to the study of monoclonal antibodies such as Aducanumab, whose actual utility for AD therapy has not yet been unanimously demonstrated (Carocci et al., 2022). Recently, other approaches have focused on joining well-established therapeutic targets to the control of endocannabinoid and inflammatory pathways according to new "metabolic" hypotheses, but none of the tested molecules seem suitable for clinical trials (Brunetti et al., 2020, 2022; Carocci et al., 2022).

These findings highlight the lack of a single theory to explain the onset and progression of AD. For this reason, researchers are increasingly focusing their attention on the development of new drugs such as multi-target directed ligands (MTDLs), capable of interacting with multiple therapeutic targets to fight both the symptoms (like currently marketed drugs such as donepezil and rivastigmine do by inhibiting cholinesterases) and the progression of the disease itself (Poliseno et al., 2021; Brunetti et al., 2022a; Carocci et al., 2022).

In this context, hundreds of papers have been published over the last fifteen years adapting an old but effective strategy: the three main drugs used in the symptomatic therapy of AD, namely tacrine (now discontinued due to hepatotoxicity), rivastigmine, and donepezil, have been repurposed as templates for the design of multifunctional hybrids. The novelty in each work was the combination of different structural motifs, through efficient synthetic strategies such as merging, fusing, or linking, thus endowing the final MTDL with additional biological properties beyond cholinesterase inhibition (Poliseno et al.; 2021; Carocci et al., 2022; Brunetti et al., 2022a). The most common mechanisms studied to define the etiology of AD have most frequently been used to define biological targets for the design of MTDLs, namely the inhibition of aggregation of amyloid proteins and neurofibrillary tangles, the inhibition of enzymes such as monoaminoxidases and beta secretase and fatty acid amide hydrolase (Brunetti et al., 2020, 2022a), but also the reduction of oxidative stress (Carocci et al., 2022), the chelation of heavy metals such as iron, copper and zinc (Poliseno et al., 2021; Brunetti et al., 2022a) and the modulation of glutamatergic, serotonergic, and dopaminergic receptors (De Deurwaerdère et al., 2021). Recently, innovative pathways have also been frequently included in test panels (Piemontese, 2019; Leuci et al., 2022).

An important source of inspiration for the design of hybrid drugs can be secondary metabolites produced by plants or microorganisms (Leuci et al. 2021; Poliseno et al., 2021). In particular, microfungi have historically provided numerous substances useful for medicinal applications, especially as antibiotics (penicillins and in general many beta-lactams, still widely used drugs, can be produced in fermenters using the work of these microorganisms, Leuci et al., 2021). Moreover, recently, other fungal metabolites showed their importance to the pharmaceutical industry, particularly for their effects in the treatment of cardiovascular disorders. This is the case of monacolin K, which is the active substance found in red yeast rice-based food supplements and which can be defined as a "case study" from a legislative point of view (it is a real drug and yet is included in food supplements, with different, rapidly evolving legislation in many European countries, Leuci et al., 2021). However, the implications on consumer perception are also remarkable, considering the widespread belief that "natural is better" that leads patients to prefer functional foods (Piemontese et al., 2022) or food supplements (Leuci et al., 2021) to standard drug formulations, which, in turn, contain much cheaper and, probably, safer active ingredients equally obtained from microorganisms (Leuci et al., 2021; Piemontese et al., 2022). In fact, these "more natural" remedies can be contaminated with harmful chemical substances such as mycotoxins, pesticide residues, or heavy metals (Leuci et al., 2021; Piemontese et al., 2022).

As far as neurodegenerative diseases are concerned, many other natural metabolites might exert neuroprotective effects thanks to their pharmacological properties, including anti-inflammatory and antioxidant activities (Leuci et al. 2021).

As an example, based on the known chemical structures, my research group recently selected a series of secondary metabolites of natural origin with suitable characteristics to evaluate their potential future role as chemical scaffolds in the design of anti-Alzheimer's agents with innovative profiles (Piemontese et al., 2018; Leuci et al., 2021). In a preliminary *in vitro* screening, some of them showed interesting activities against classic AD targets, chiefly acetylcholinesterase inhibition (IC_{50} = 6.86–86.0 μM), while proving to have other interesting properties such as the ability to chelate metals, e.g., zinc, copper, and iron, which are closely associated with oxidative stress and to the formation of neurotoxic protein aggregates, such as amyloids (Piemontese et al., 2018). Using as a template the structure of one of these scaffolds (tenuazonic acid) and modifying the amino acid used in the reactions, we carried out in the recent past a partial and preliminary structure-activity-relationship total synthesis study (Poliseno et al., 2021) with good results in terms of acetylcholinesterase inhibition (IC_{50} = 42–57 μM), antioxidant activity (EC_{50} = 6.3–10.8 μM), Aβ aggregation inhibition (up to 63.8% at 40 μM), and metal chelation (pFe^{3+} = 16.6, pCu^{2+} = 10.6 and pZn^{2+} = 6.0). The so obtained compounds were then part of the design and preparation of synthetic hybrids with potential multi-target anti-AD activity, with the aim of improving anticholinesterase activity (IC_{50} = 16–24 μM), through the binding with a moiety inspired by the donepezil structure (Poliseno et al., 2021).

Our next goal is even more ambitious.

Very often the preparation of molecules including nature-inspired moieties is hindered by the presence of one or more stereocenters and therefore by the difficulty of chemical and optical resolution of the reaction mixtures; tenuazonic acid itself has two chiral carbons (Piemontese et al. 2018; Poliseno et al., 2021). So, why not use nature itself to obtain these compounds? Fungi and bacteria are able, through their metabolism, to be much more effective than enantio- or diastereo-selective syntheses!

However, a critical point for the synthesis of MTDLs is the availability of appropriate heterocyclic nuclei which must bear functional groups suitable for derivatization, such as a carboxylic acid or a primary amine. Very often, natural secondary

Downloaded from http://journals.lww.com/nrronline by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 05/15/2023

metabolites do not have these attachment points, or they are "masked" by the metabolic processes of the microorganism, probably to prevent their potentially harmful reactivity. In this context, the use of genomic techniques can be crucial: fungi, for example, could be induced to produce different metabolites, perhaps intermediates, through the deletion of some genes or by modifying ecophysiological growth factors (Cervini et al., 2020). Furthermore, through chemical or biotechnological techniques, isolated secondary metabolites could be modified to obtain structures that bear desirable functional groups useful for subsequent derivatizations or, more simply, to confer new biological properties (Ji et al., 2016).

The use of these secondary metabolites as therapeutics or as intermediates in semi-synthetic chemical pathways still requires optimized strategies for their biosynthesis, as well as for their extraction and purification. In many cases, it is not possible to use liquid cultures of microfungi or it is more convenient to exploit specifically inoculated food matrices. On the other hand, if the secondary metabolite is derived from plants, it goes without saying that it is necessary to select the producer species, optimize its biosynthetic capacity, and design a strategy for the isolation of suitable quantities with sufficient purity. These processes may require a long time and high energy consumption (for example high temperatures, which can also damage biologically active substances). Furthermore, they often require the use of large quantities of chemical solvents. To overcome this difficulty, more economical and environmentally friendly extraction methods, which use ultrasound and microwaves, are increasingly being studied. Very interesting advancements have also been made in recent years in the use of alternative extraction media, such as deep eutectic solvents, at least for the extraction step (Brunetti et al., 2022b).

These innovative solvents have recently also been used for the development of sustainable organic synthesis. As an example, several moieties inspired by the structure of donepezil, which were included in hybrid compounds previously developed in my research group, have already been synthesized under green chemistry conditions (Piemontese et al., 2020). This can certainly be a starting point for the optimization of green synthesis of other moieties as well, which could be combined with natural compounds in MTDL design approaches. The industrial scale-up of these intriguing synthetic techniques is also an important breakthrough to be expected in the coming years.

These practices are strongly linked to the objectives of the so-called European Green Deal, whose goal is the achievement of climate neutrality by 2050. It should be added that the European Commission is particularly sensitive to the problem of Alzheimer's disease. In fact, AD is an integral part of the "Healthier Together - EU Non-Communicable Diseases Initiative" program, promoted in June 2022, which describes numerous interventions aimed at managing priorities from the point of view of public health and social problems related to it (EU Commission, 2022).

The lack of a cure for AD underlies the entire program, and all related interventions were planned around this fact. With great effort and large investments by public institutions and private companies, the gloomy predictions about AD incidence and mortality could be corrected for the better, improving the life expectancy and quality of life of hundreds of millions of people. And perhaps nature, thanks to (maybe) the serendipity and (for sure) ingenuity of thousands of researchers, could once again provide the key to solving this long-standing problem, just as it did at the dawn of the history of medicinal chemistry.

Luca Piemontese*
Università degli Studi di Bari Aldo Moro, Dipartimento di Farmacia-Scienze del Farmaco, via E. Orabona, Bari, Italy
***Correspondence to:** Luca Piemontese, PhD, luca.piemontese@uniba.it.
https://orcid.org/0000-0002-7980-5818 (Luca Piemontese)

Date of submission: January 2, 2023
Date of decision: February 15, 2023
Date of acceptance: February 19, 2023
Date of web publication: April 20, 2023

https://doi.org/10.4103/1673-5374.373685
How to cite this article: *Piemontese L (2023) Historic recurrences in medicinal chemistry: nature-inspired structures as a new opportunity for novel multi-target anti-Alzheimer's drugs. Neural Regen Res 18(12):2671-2672.*
Open access statement: *This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.*

References

Brunetti L, Laghezza A, Loiodice F, Tortorella P, Piemontese L (2020) Combining fatty acid amide hydrolase (FAAH) inhibition with peroxisome proliferator-activated receptor (PPAR) activation: a new potential multi-target therapeutic strategy for the treatment of Alzheimer's disease. Neural Regen Res 15:67-68.

Brunetti L, Leuci R, Carrieri A, Catto M, Occhineri S, Vinci G, Gambacorta L, Baltrukevich H, Chaves S, Laghezza A, Altomare CD, Tortorella P, Santos MA, Loiodice F, Piemontese L (2022a) Structure-based design of novel donepezil-like hybrids for a multi-target approach to the therapy of Alzheimer's disease Eur J Med Chem 237:114358.

Brunetti L, Leuci R, Colonna MA, Carrieri R, Celentano FE, Bozzo G, Loiodice F, Selvaggi M, Tufarelli V, Piemontese L (2022b) Food industry byproducts as starting material for innovative, green feed formulation: a sustainable alternative for poultry feeding. Molecules 27:4735.

Carocci A, Barbarossa A, Leuci R, Carrieri A, Brunetti L, Laghezza A, Catto M, Limongelli F, Chaves S, Tortorella P, Altomare CD, Santos MA, Loiodice F, Piemontese L (2022) Novel phenothiazine/donepezil-like hybrids endowed with antioxidant activity for a multi-target approach to the therapy of Alzheimer's disease. Antioxidants 11:1631.

Cervini C, Gallo A, Piemontese L, Magistà D, Logrieco AF, Ferrara M, Solfrizzo M, Perrone G (2020) Effects of temperature and water activity change on ecophysiology of ochratoxigenic Aspergillus carbonarius in field-simulating conditions. Int J Food Microbiol 315:108420.

De Deurwaerdère P, Chagraoui A, Di Giovanni G (2021) Serotonin/dopamine interaction: Electrophysiological and neurochemical evidence. Prog Brain Res 261:161-264

EU Commission (2022) Healthier together EU non-communicable diseases initiative. Available at: https://health.ec.europa.eu/system/files/2022-06/eu-ncd-initiative_publication_en_0.pdf. Accessed December 28, 2022.

Ji C, Fan Y, Zhao L (2016) Review on biological degradation of mycotoxins. Anim Nutr 2:127-133.

Leuci R, Brunetti L, Poliseno V, Laghezza A, Loiodice F, Tortorella P, Piemontese L (2021) Natural compounds for the prevention and treatment of cardiovascular and neurodegenerative diseases. Foods 10:29.

Leuci R, Brunetti L, Laghezza A, Piemontese L, Carrieri A, Pisani L, Tortorella P, Catto M, Loiodice F (2022) A new series of aryloxyacetic acids endowed with multi-target activity towards peroxisome proliferator-activated receptors (PPARs), fatty acid amide hydrolase (FAAH), and acetylcholinesterase (AChE). Molecules 27:958.

Piemontese L, Vitucci G, Catto M, Laghezza A, Perna FM, Rullo M, Loiodice F, Capriati V, Solfrizzo M (2018) Natural scaffolds with multi-target activity for the potential treatment of Alzheimer's disease. Molecules 23:2182.

Piemontese L (2019) An innovative approach for the treatment of Alzheimer's disease: the role of peroxisome proliferator-activated receptors and their ligands in development of alternative therapeutic interventions. Neural Regen Res 14:43-45.

Piemontese L, Sergio R, Rinaldo F, Brunetti L, Perna FM, Santos MA, Capriati V (2020) Deep eutectic solvents as effective reaction media for the synthesis of 2-hydroxyphenylbenzimidazole-based scaffolds en route to donepezil-like compounds. Molecules 25:574.

Piemontese L, Brunetti L, Leuci R (2022) Can foods influence the onset and progress of neurodegenerative diseases? Neural Regen Res 17:2443-2444.

Poliseno V, Chaves S, Brunetti L, Loiodice F, Carrieri A, Laghezza A, Tortorella, P, Magalhães JD, Cardoso, SM, Santos MA, Piemontese L (2021) Derivatives of tenuazonic acid as potential new multi-target anti-Alzheimer's disease agents. Biomolecules 11:111.

C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y