Silibinin stereochemistry: Why it matters in neurodegenerative diseases

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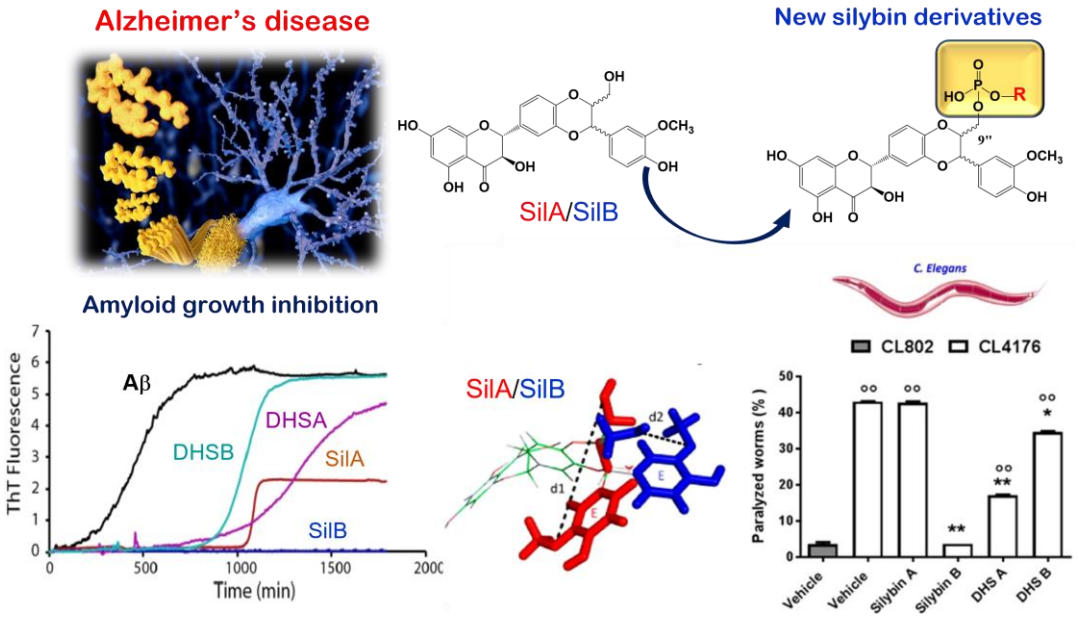
Alzheimer's disease (AD) is the most widespread form of neurodegenerative disorder affecting elderly people worldwide. AD is linked to the abnormal accumulation of amyloid β peptide (Aβ) aggregates in the brain.
Increasing evidence supports the hypothesis that oligomeric Aβ assemblies are the most neurotoxic species of the peptide. [1]
Hence, inhibition of Aβ self-assembly is a promising therapeutic approach for the treatment of AD, and a multitude of compounds have been screened for their antiaggregating properties. Unfortunately, most of them failed in clinical trials due to their limited neuroprotective activities, poor pharmacological profile, and often unwanted side effects. More recently, a number of small hydrophobic molecules isolated from natural sources have been shown to offer a viable alternative for Aβ antiaggregation approaches. Among natural molecules, silibinin, the major component of silymarin, that consist of a diastereoisomeric mixture of two flavonolignans, namely, silybin A (SilA) and silybin B (SilB), has shown promising neuroprotective effects. [2]
In many cases, the optical purity aspect of silibinin have been largely neglected, but their stereochemistry could play an extremely important role with interesting pharmacological implications. In this context, our recent studies have been directed to single out the molecular basis of the antiaggregating properties of these diastereoisomers. The ability of SilA, SilB and its oxidation products (DHSA, and DHSB) to bind Aβ and interfere with its aggregation into toxic assemblies was investigated by biophysical (ThT assays, TEM and AFM imaging) and computational techniques. [3]



This study underscores the pivotal role of stereochemistry in determining the neuroprotective potential of silybins and points to SilB as a promising lead compound for further development in anti-AD therapeutics.
Despite these encouraging results for SilB, its use as a neuroprotective drug is hampered by its poor bioavailability and pharmacokinetics. In order to overcome these limitations, new silybin derivatives have been synthesized [4]. New derivatives present increased water solubility and good stability in blood serum maintaining the antiaggregant ability of silybins.

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