TARIMAD - TO01000078 - Articles – published in 2024

1. **Apolar Extracts of St. John's Wort Alleviate the Effects of β-Amyloid Toxicity in Early Alzheimer's Disease"**

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Abstract: Hypericum perforatum (St. John's wort) has been described to be beneficial for the treatment of Alzheimer's disease (AD). Different extractions have demonstrated efficiency in mice and humans, esp. extracts with a low hypericin and hyperforin content to reduce side effects such as phototoxicity. In order to systematically elucidate the therapeutic effects of H. perforatum extracts with different polarities, APP-transgenic mice were treated with a total ethanol extract (TE), a polar extract obtained from TE, and an apolar supercritical CO2 (scCO2) extract. The scCO2 extract was formulated with silicon dioxide (SiO2) for better oral application. APP-transgenic mice were treated with several extracts (total, polar, apolar) at different concentrations. We established an early treatment paradigm from the age of 40 days until the age of 80 days, starting before the onset of cerebral β-amyloid (Aβ) deposition at 45 days of age. Their effects on intracerebral soluble and insoluble Aβ were analyzed using biochemical analyses. Our study confirms that the scCO2 H. perforatum formulation shows better biological activity against Aβ-related pathological effects than the TE or polar extracts. Clinically, the treatment resulted in a dose-dependent improvement in food intake with augmentation of the body weight, and, biochemically, it resulted in a significant reduction in both soluble and insoluble Aβ (−27% and −25%, respectively). We therefore recommend apolar H. perforatum extracts for the early oral treatment of patients with mild cognitive impairment or early AD.
Keywords: Hypericum perforatum; St. John's wort; Alzheimer's disease; MCI; phytotherapy; silica gel; scCO2 extract; Syloid® XDP3050

2. **Phenoxytacrine derivatives: Lowtoxicity neuroprotectants exerting affinity to ifenprodil-binding site and cholinesterase inhibition**

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Tacrine (THA), a long withdrawn drug, is still a popular scaffold used in medicinal chemistry, mainly for its good reactivity and multi-targeted effect. However, THA-associated hepatotoxicity is still an issue and must be considered in drug discovery based on the THA scaffold. Following our previously identified hit compound 7-phenoxytacrine (7-PhO-THA), we systematically explored the chemical space with 30 novel derivatives, with a focus on low hepatotoxicity, anticholinesterase action, and antagonism at the GluN1/GluN2B subtype of the NMDA receptor. Applying the down-selection process based on in vitro and in vivo pharmacokinetic data, two candidates, I-52 and II-52, selective GluN1/GluN2B inhibitors thanks to the interaction with the ifenprodilbinding site, have entered in vivo pharmacodynamic studies. Finally, compound I-52, showing only minor affinity to AChE, was identified as a lead candidate with favorable behavioral and neuroprotective effects using open-field and prepulse inhibition tests, along with scopolamine-based behavioral and NMDA-induced hippocampal lesion models. Our data show that compound I-52 exhibits low toxicity often associated with NMDA receptor ligands, and low hepatotoxicity, often related to THA-based compounds.