

# Phytochemical investigation of *Heliopsis helianthoides*, a North American traditional medicinal plant

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## HELIOPSIS SPECIES

The genus *Heliopsis* Pers. belongs to the Asteraceae family. Members of this genus are cultivated almost anywhere in the world as ornamental plants. Some species of the *Heliopsis* genus have been used by the North American Indians as medicinal plants. One of the most widely applied species, *Heliopsis longipes* has been used to relieve toothache, and for the treatment of inflammations and ulcers. Its analgetic effect has been attributed to the alkylamide content of the root [1, 2]. *Heliopsis helianthoides* (L.) Sweet, a species native to North America, has been applied to relieve lung troubles by the Meskwaki Indians and strengthen limbs by the Chippewa Indians [3]. The species is cultivated in Hungary as an ornamental plant.



## AIM OF THE STUDY

- To discover new biologically active alkylamides and other compounds from the root of *Heliopsis helianthoides* with possible effect on the central nervous system.
- Isolation and structure determination of the compounds



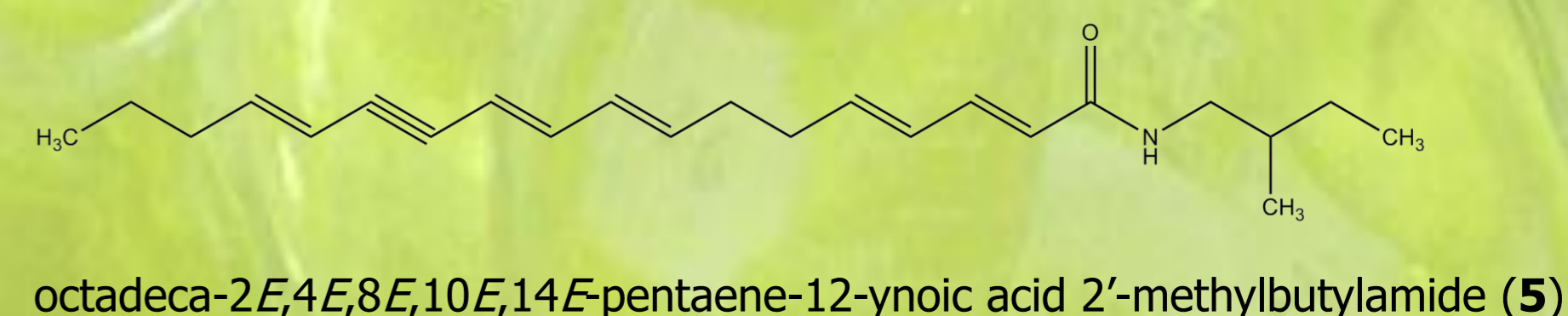
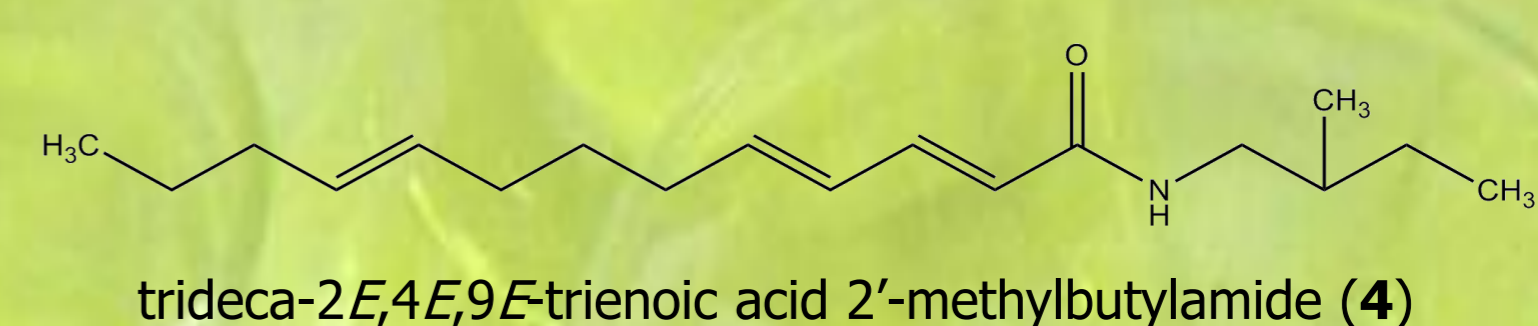
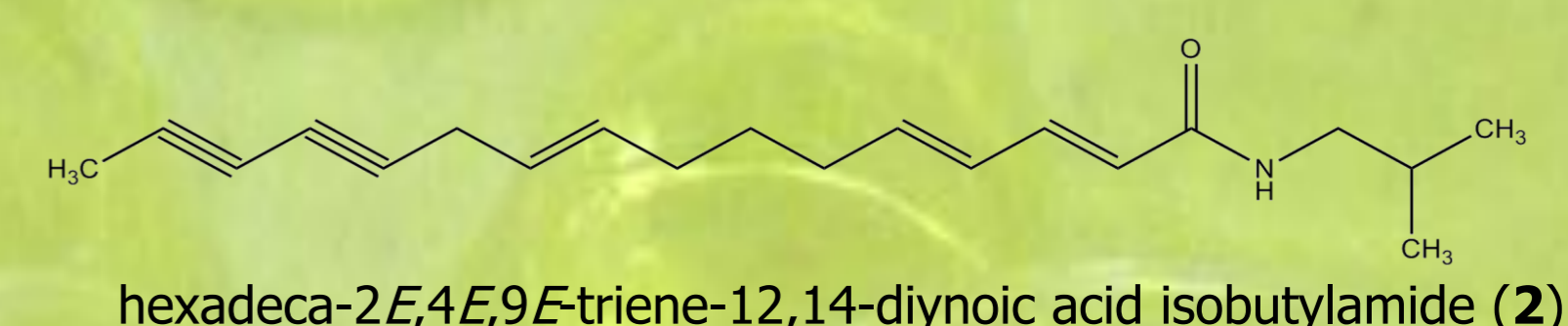
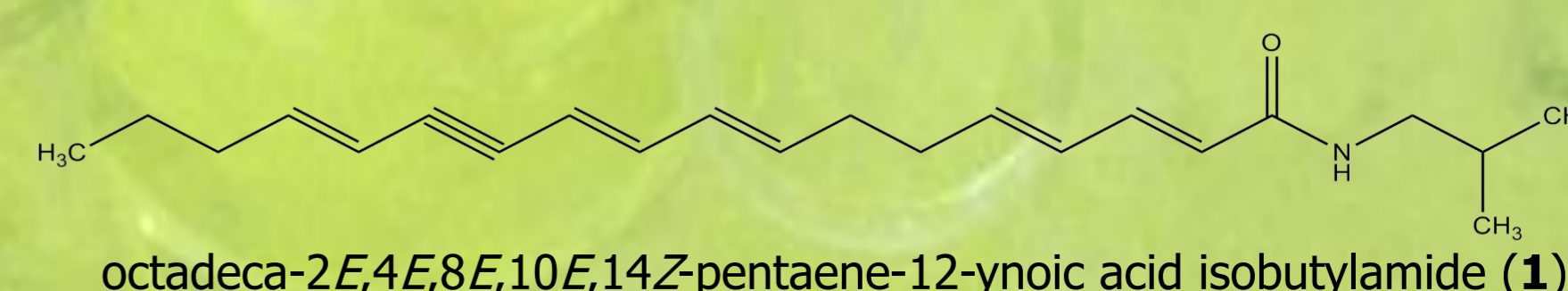
## ISOLATION

The plant material was gathered in Hungary from a horticulture in the flowering period. 10 kg of the fresh roots was extracted with methanol. After evaporation, the methanol extract was subjected to solvent partitioning to obtain chloroform- and water-soluble fractions. The alkylamide containing chloroform phase was fractionated by vacuum liquid chromatography (VLC) on silica gel. Selected fractions were further purified by medium pressure liquid chromatography (MPLC), centrifugal planar chromatography (CPC), preparative layer chromatography (PLC), and finally purified by HPLC to afford pure compounds.



## RESULTS

Four alkylamides (**1**, **2**, **4**, **5**) and three lignans (**3**, **6**, **7**) were isolated from the root of *Heliopsis helianthoides*. Compounds **1**, **4**, **5** and **6** are new natural products, but **2** and **3** were isolated earlier from this plant [4]. Although the biological activities of the isolated compounds were not evaluated to date, with regard to the literature data published for structurally similar compounds, it can be supposed that compounds **1-7** may also have promising bioactivities.



## ALKYLAMIDES

### Chemistry

The plant-derived *N*-alkylamides (NAA) mostly contain a polyunsaturated aliphatic fatty acid chain and a shorter substituent at the amine side. Both might include cyclic systems and/or heteromolecules (nitrogen, sulfur, oxygen). At the core is the amide bond, which resembles the peptide link  $-C(=O)NH-$  as observed in polypeptides and proteins.

These secondary metabolites are responsible for different medical properties of several plants, such to relieve pain, toothache, skin and gastric diseases, sexual dysfunctions and viral infections. NAA-containing plants are used in numerous traditional medicinal systems all over the world.

More than 70 NAAs have already been identified in the Heliantheae tribe (Asteraceae). The fatty acid moiety of these compounds contains a  $C_4$ ,  $C_6$ ,  $C_8$ – $C_{16}$  or  $C_{18}$  chain, while the amide residue may be an isobutylamide, 2-hydroxy isobutylamide, 2-methylbutylamide, saturated phenylethylamide or unsaturated phenyl ethylamide (styrylamides).

Spilanthol (or affinin) is the best known NAA of several *Spilanthes* species, and together with homospilanthol can be found in *Heliopsis longipes*. *Heliopsis buphthalmoides* and *H. helianthoides* contain  $C_{18}$  NAAs with the rarely occurring pentaene acids.

*Echinacea* NAAs always possess a  $C_2$  unsaturation in their acid chain and have a relatively longer chain acid moiety, starting from  $C_{11}$  up to  $C_{16}$ .

Hydroxy cinnamamides were found in *Helianthus annuus*. [5]

## Pharmacology

Application of NAAs might result in a tingling but also a burning sensation. The characteristic "tingling" activity of some NAAs, called "tingle compounds", has been established for decades. This tingling effect can be described as producing a buzzy, numbing anesthetic, pungent, pin and needles effect.

Despite the obvious effect on the central nervous system of certain NAA-containing plants, the investigation of these compounds focused mainly on their anti-inflammatory and immuno-modulatory activities.

Especially for *Echinaceae* NAAs, the anti-inflammatory and immuno-modulatory properties have been well investigated, confirmed and patented. However, the immune effects of *Anacyclus pyrethrum* and anti-inflammatory effects of *Spilanthes*, *Heliopsis*, *Piper* and *Achillea* species are also established. For the anti-inflammatory properties, different targets have been identified. Spilanthol inactivates NF- $\kappa$ B, shows significant topical anti-inflammatory effects in the mouse ear edema test and is the only NAA that has a marked influence on the transcription and translation of the COX enzymes.

Numerous studies deal with the antibacterial and antifungal, but also with the antiparasitic, molluscicidal and insecticidal activities of NAAs.

NAAs can exhibit analgesic effect through central GABA release e.g. spilanthol, by interfering with voltage-gated sodium channels or *via* desensitization of the TRPV1 receptor. [5]

## STRUCTURE ELUCIDATION

The structures of the compounds were established by UV/VIS spectroscopy, mass spectrometry, advanced two-dimensional NMR methods, including  $^1H$ -NMR, JMOD,  $^1H$ ,  $^1H$ -COSY, HMQC, HMBC experiments and by comparison with literature data. Stereochemical studies and conformational analysis were performed by means of NOESY experiments.

## ACKNOWLEDGEMENTS

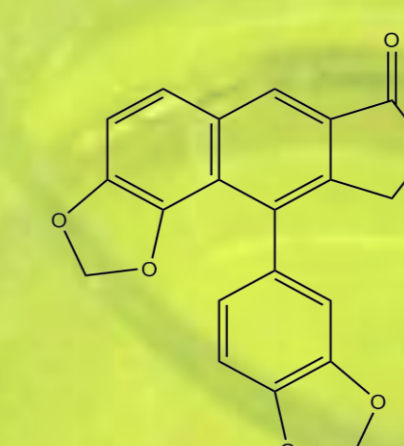
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## FURTHER OBJECTIVES

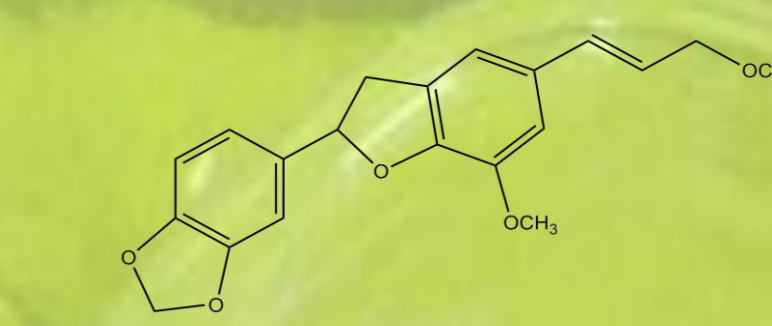
- To find more alkylamides in the species
- Discover the biological effects of the isolated alkamides and lignans
  - Determination of the anti-inflammatory effect (COX-1, COX-2, LOX models)
  - Receptor binding experiments with alkamides

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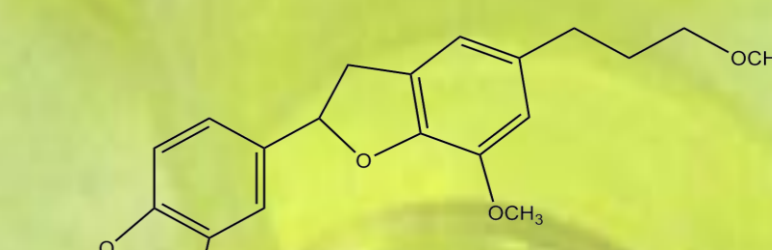
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helioxanthin (**3**)



dehydroegonol methylether (**6**)



egonol methylether (**7**)

