Session No. 2
What's new in preclinical studies on plant based components?

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4. Health-promoting effects of phenolic acids on the example of protocatechuic acid
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5. Natural substances in the treatment of epilepsy
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6. Phytotherapy of neurodegenerative diseases
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4. Health-promoting effects of phenolic acids on the example of protocatechuic acid

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Protocatechuic acid (PCA) and its derivative - protocatechuiic aldehyde (PAL) are widespread polyphenols found in edible fruits, vegetables and grains. PCA is the major human metabolite of anthocyanin-derived cyanidin glycosides with multidirectional biological activity, incl. antioxidant, anti-inflammatory and neuroprotective properties. The biotransformation of polymerized polyphenols is accomplished by the gut microbiota, and both PCA and PAL affect its profile, contributing to increased health benefits. PCA is a substance with an extremely strong antioxidant effect, significantly exceeding the effect of trolox, protecting cells against oxidation and destruction by free radicals. Depending on the research model, an increase in the concentration of glutathione, an increase in the activity of catalase, superoxide dismutase and heme oxygenase are observed. PCA reduces lipid peroxidation (reducing the concentration of malondialdehyde). In aging-related conditions such as neurodegeneration, inhibition of the aggregation of abnormal proteins such as alpha-synuclein and beta amyloid associated with Alzheimer's disease has been found. Both PCA and PAL have been shown to be antioxidant in vitro and in vivo, and to be beneficial in chronic inflammation. PCA inhibits the production of pro-inflammatory cytokines such as TNF-alpha and IL-1beta, inflammatory mediators such as NO and prostaglandin E2. It inhibits the expression of genes for nitric oxide synthase and cyclooxygenase-2, and also inhibits signaling pathways through NF-κB and MAPK kinase. In mice, PCA inhibited mTOR-induced apoptosis by decreasing the expression of caspase-3 in the liver and the expression of p53 in the liver and brain. PCA has an anti-atherosclerotic effect, moreover, it has anti-aggregating properties, reducing the risk of thrombosis. The prophylactic effect of PCA in experimental models of the metabolic syndrome is of great importance due to the anti-diabetic effect and reduction of obesity. Our research has shown that PCA counteracts the learning disabilities and memory deficits seen in rats chronically administered with D-galactose. It improved episodic memory and recalled information about the spatial location of objects, and was effective in restoring normal serotonergic and dopaminergic transmission in the hippocampus and prefrontal cortex. At the same time, it had a negligible effect on cognitive functions in healthy animals. In preclinical studies, a beneficial effect of PCA on the inhibition of osteoporosis was found. Phenolic acids as food ingredients show anti-cancer properties. PCA has significant influence on all major epigenetic regulation mechanisms, which include regulation of the DNA gene promoter, histone deacetylation, and miRNA expression.

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5. Natural substances in the treatment of epilepsy

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It is well known from numerous animal studies about coumarins as substances with anticonvulsant potential. *In vivo* tests showed that osthole, imperatorin, xanthotoxin, umbelliferone and scoparone exhibit anticonvulsant activity in an animal model of tonic-clonic seizures in mice. Experimental studies have shown that these coumarins, in addition to their anticonvulsant activity *per se*, potentiated the anticonvulsant effect of classic antiepileptic drugs. The anticonvulsant screening showed that many different groups of plant-derived substances have *in vivo* anticonvulsant activity in mice. The conducted studies showed that some naturally-occurring substances used at a constant dose of 300 mg/kg at 4 different pretreatment times have an anticonvulsant effect that protects animals against tonic-clonic seizures. Of course, not all compounds of plant origin (although they have a similar chemical structure) exhibit this anticonvulsant effect - this applies to bergapten or oxypeucedanin, which belong to furanocoumarins and do not have the anticonvulsant activity in mice, or the anticonvulsant effect is weak, such as in isopimpinelin. Therefore, only *in vivo* screening allows the selection of compounds with high anticonvulsant potential. Many natural derivatives isolated from plants have anticonvulsant potential, such as resveratrol, borneol, curcumin. On the other hand, many substances of natural origin do not show these anticonvulsant properties in screening test in mice, such as arbutin, esculetin, esculin, ellagic acid, gallic acid, hesperidin, piperitol, piperonal, quercetin, ursolic acid, alizarin, betulin, diosmin, linalool, mentofuran, α-terpineol, theobromine, β-thujaplicin, or vanillin in the treatment of epilepsy.

6. Phytotherapy of neurodegenerative diseases

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One of the growing and pressing challenges facing healthcare worldwide are neurodegenerative diseases. This is due to overlapping harmful stress factors and the aging of the population. Despite the significant progress of knowledge about Alzheimer's disease, its etiology explaining the molecular basis of the pathomechanism is still mainly based on the cholinergic hypothesis and hypotheses concerning pathological aggregation of proteins (a cascade of beta-amyloid, hyperphosphorylation of tau protein). In the neurodegenerative process of Alzheimer's disease there occur neurochemical (disturbances in neurotransmitters) and neuropathological changes that correlate with each other, although the changes are not in stages of one pathway. It is also considered that in the cascade of biochemical processes of neurodegeneration, several mediators of the inflammatory process released by microglial cells and astrocytes are involved, whereby Alzheimer's disease (and other amyloidosis) is a disease that is associated with long-term inflammation including oxidative stress. Despite extensive studies available today, treatment methods are only symptomatic. So far, AChE inhibitors are the most important group of drugs used in the treatment of cognitive dysfunction in the course of dementia in AD. At the same time, substances of plant origin can be a valuable alternative and may become a new option in complementary medicine in the prevention and treatment of early stages of dementia, which include dementia of the Alzheimer type.
The long history of traditional use of substances of plant origin shows that many medicinal plants affect the central nervous system and are appreciated in the prevention and/or phytotherapy of diseases of this system. Many biologically active compounds (for example carnosic acid, ursolic acid) exert pleiotropic effects on cellular metabolism in diseases of the central nervous system, in both an in vitro and in vivo model. Recently, studies indicate the pharmacological potential for example *Rosmarinus officinalis*, *Melissa officinalis*, *Salvia miltiorrhiza*, *Eryngium planum*, *Scutellaria baicalensis*, *Ginkgo biloba*, *Hypericum perforatum*, *Curcuma longa*, *Lavandula angustifolia*, *Trigonella foenum-graecum* [Hussain et al., 2022; Delerue et al., 2021; Ożarowski et al., 2013]. There has been an increasing research and discussion on the role of spice plants in the neuroprotection process through anti-inflammatory and antioxidant effects i.e. saffron, turmeric and ginger. There is also an increasing number of clinical studies evaluating the effectiveness of *Rosmarinus officinalis* extracts.
The presentation is an up-to-date summary of the results indicating possible preventive and therapeutic solutions.

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