PHYTOPHARMACOLOGY OF URIC ACID METABOLISM – CHALLENGING ASPECTS AND OVERLAP WITH THE COMMONLY USED DRUGS EFFECTS

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Introduction. The problem of uric acid metabolism regulation remains to be an important field of pharmacology which has expanded far beyond the problem of anti-gout and anti-nephrolithiasis interventions. A double-edged role of uric acid [1, 2] as a molecule participating in both deleterious processes (pro-inflammatory role including the inflammasomes activation, involvement into metabolic syndrome and salt-sensitivity development, negative impact of xanthine oxidase (XOD) increased activity with the prooxidants generation, especially on the vessel wall) and beneficial mechanisms including neuroprotection and contributing to the increase in cognitive functions and motivations, cytoprotection and antioxidative activity in certain biological media [3, 4].

Thus, the further studies of the drugs targeting uric acid metabolism are being actively conducted. Verification of the effects of the substances of plant origin is also of high interest as well as of their combinations with commonly used drugs.

The aim and methods of the study. This study aimed at summarization of the own results in the field of pharmacology of uric acid metabolism and elucidating the new areas of research according to the data in the literature.

Results. **1.** At the first stage of our studies, verification of the effects of the plant which antigout properties are indicated in Latin name given by Carl Linnaeus and also in the evidence known from traditional medicine. This plant is goutweed (GW, *Aegopodium podagraria* L.), which is wide-spread in temperate climates including Ukraine. It possesses high safety level and has been long consumed as vegetable and fodder plant. Hydroxycinnamic acids together with flavonoids and potassium salts are the main active components of the plant aerial part. Verification of the effects of crude extracts from this herbal raw material (standardized pharmacological preparations, namely water extract and the tincture after extractant removal) was done [5] and it was proven that they exert antihyperuricemic effect on the model of oxonate-induced hyperuricemia and also suppress inflammation on the standard model of carrageenan-induced rat paw edema.

2. Comparison of the efficacy and mechanisms of action of individual biologically active substances and pharmacological preparations obtained using different types of GW raw material as well as different extractants was done consequently [6]. This biopharmaceutical approach allowed to establish the differences in the intensity of GW preparations effects as well as on their mechanisms. The latter are realized through XOD inhibition, enhancement of the renal uric acid excretion or through combination of both mechanisms. Interestingly, the protein-polysaccharide complex of GW leaves was among the active preparations able to normalize uric acid metabolism.

3.1. Since the preparations of herbal origin are predominantly expected to be used as a part of combined therapy, and besides, studies of potentially synergistic combinations are of great scientific importance, interactions of the most prospective GW pharmacological preparations with commonly used drugs were investigated [7]. Firstly, the interactions with allopurinol (ALL) as the widely used and commonly available hypouricemic drug were assessed. Among the most significant results are the possibility to obtain the statistically significant XOD inhibition using a subtherapeutic dose of ALL combined with GW tincture or extract, maintenance of complete inhibition of XOD by ALL used with these preparations during the 3-weeks period of hyperuricemia, absence of the increase in toxicity of ALL at a high dose combined with GW tincture on the model with aggravated pathogenesis including nephrotoxicity, and, finally, decrease of ALL acute toxicity in mice against the background of the extract and the tincture.

3.2. Modulation of XOD inhibitors effects is the prospective field for further studies, such as using compounds of herbal origin for reducing organotoxicity or decrease in active dose of XOD inhibitors. The latter is especially promising direction since a significant amount of data is available on the mechanism of XOD inhibition by plant polyphenols (of special interest for us are hydroxycinnamic acids and flavonoids), and both competitive and non-competitive inhibitors were found among these compounds [8, 9] At the same time, there are limited data about interaction of these polyphenols and ALL (or other currently used XOD inhibitors) at the level of XOD active site or allosteric sites, and encouraging results could be expected.

3.3. Moreover, further studies of XOD inhibitors activity are far from being limited to these aspects. For instance, withdrawal of XOD inhibitors led to a significant rise in cardiovascular events in patients with cardiovascular diseases. This phenomenon was profoundly explained in light of biochemical events after XOD inhibition, namely increased reutilization of hypoxanthine through the purine salvage pathway to resynthesize adenine nucleotides, including ATP. In this case, XOD inhibitor withdrawal leads to a sudden decrease of ATP levels with the subsequent cardiovascular complications [10] Further studies of other XOD inhibitors including those of herbal origin and possessing other mechanism of influence on energy metabolism is expedient.

3.4. Uric acid is not indifferent molecule for CNS and moderately high levels of uricemia are generally considered as neuroprotective factor [4], and partly for this reason global hypouricemic interventions are not recommended [11] Nevertheless, XOD inhibitors display ambiguous properties in this context not causing cognitive decline which could be expected from decreased uricemia. Even more so, the benefits of these compounds for CNS function were shown and they were partially associated with the limiting of oxidative stress (through blocking XOD as a generally recognized source of free radicals) [12]. The analysis of databases about the prescribed drugs by the criterion on their mechanisms showed that xanthine dehydrogenase/XOD is among the most efficient targets for neurodegenerative disease prevention [13]. Flavonoids are among the herbal compounds considered as prospective XOD inhibitors possessing prospects for mental disorders treatment [14]. In our previous research, we also explored the potential modulation of anxiety,

depression levels, and endurance through changes in uricemia including those induced by XOD inhibition [15]. And in the studies of GW preparations combined use with ALL, functional state of the CNS was also assessed [7]. In the case of hyperuricemia correction by ALL combined with GW extract and the tincture, no negative effect on the CNS were seen; in combination with ALL, GW preparations counteracted the increase in depressive signs, the tincture also favourably decreased anxiety signs.

4.1. The other aspect of our studies dealt with the possibility of correction of the side effects of the thiazide diuretics, namely hydrochlorothiazide (HCTZ) by GW preparations (experiments in rats). It is well known that hyperuricemia and hypokalemia are among the most important links of these side effects (also causing aggravation of metabolic syndrome, insulin resistance and changes within vascular endothelium), and they were effectively eliminated by GW extract, which favourably combines the ability to eliminate potassium deficiency with normouricemic and uricosuric effects.

4.2. Moreover, the problem of modulation of the effects of the commonly used diuretics by compounds of herbal origin is not limited to counteraction to hypokalemia and hyperuricemia. The involvement of influence of uricemia on the CNS can also be analysed in this situation and an extremely admirable continuum exists within the effects of diuretics on cognition. Thus, a meta-analysis [16] has shown the beneficial influence of diuretics on cognitive health and for thiazides that could be linked specifically to hyperuricemia. It is indeed an example of multidirectionality of the biological effects. At the same time potassium-sparing diuretics also exert a beneficial effect on cognitive health during aging, but the mechanism is completely different and involves maintaining adequate potassium blood level and a possible favourable influence on amyloid formation [16]. Possible targets could be found here for the herbal preparations which are able to modulate both hypokalemia and uricemia.

5. Finally, uric acid metabolism modulation at the level of the gut, microflora and transport systems is being actively studied nowadays. It is also applicable to herbal drugs: for instance, antihyperuricemic influence of chicory in quail model was partially realized through increasing the gastrointestinal excretion of uric acid, normalizing the permeability of intestinal barrier and the balance of gut microbiota [17]. These data shed light on the mechanisms of efficacy of plant polysaccharides which due to low or zero bioavailability hardly could be explained in another way, and this question has always belonged to the problematic ones. High activity of protein-polysaccharide complex of GW leaves mentioned above could have similar explanations (though we have not addressed these aspects directly).

Conclusion. The summarized data illustrate the diversity of mechanisms and pharmacological targets associated with uric acid metabolism and elucidate the prospective areas of research within this field.

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