THE PROSPECTS OF THE DRUG DEVELOPMENT ON THE BASIS OF GOUTWEED (*Aegopodium podagraria* L.) HERBAL RAW MATERIAL

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Introduction. Goutweed (GW, *Aegopodium podagraria* L., Apiaceae) is a widely-spread perennial herb that has been used in empirical medicine since time immemorial. Our research work is focused on the obtaining of the gout weed pharmacological preparations (PhP) and verification of their pharmacological properties.

There is a need to expand the possibilities of influence on the pathogenesis of diabetes mellitus (DM) and metabolic syndrome (MS), gout and asymptomatic hyperuricemia, kidney and liver injury, as well as to increase the efficacy and safety of the commonly used drugs. Polytropic action directed towards the pathogenesis of diseases and states mentioned above is inherent in multicomponent herbal drugs. Phenolic compounds, especially hydroxicinnamic acids and flavonoids, are among intensively studied active components of such herbal drugs, and the mechanisms of action of these substances correspond to the modern approaches to their treatment. Potassium compounds are important for herbal drugs activity realization. All these features are inherent in the PhP of GW aerial part which are also characterized by high safety. Moreover, there is a need to verify the effects of the combined use of herbal preparations and commonly used drugs.

The aim of the study. Our studies aimed at verification of goutweed pharmacological properties in order to expand the possibilities of standardized herbal drugs use.

Materials and methods. The generally accepted phytochemical and pharmacological methods (in accordance with the bioethics requirements) were applied as given below.

Note. Тема НДР «Фармакологічне вивчення біологічно активних речовин та лікарських засобів» (номер держреєстрації 0114U000956, 2014–2023 рр.).

Results. The extract and the tincture were obtained from GW aerial part. The standard technology was in accordance with the requirements of State Pharmacopoeia of Ukraine. The quantitative content of hydroxycinnamic acids as one of the main components was measured using direct spectrophotometry and spectrophotometry of the coloured complexes.

In-depth pharmacological studies were done for the mentioned PhPs and, in some cases, for leaves protein-polysaccharide complex and other fractions. Ethyl alcohol was removed before intragastrical administration of the tincture.

The nephroprotective action of GW aerial part extract, which is dose-dependent and most evident in the dose of 1 g/kg, has been proved on the models of ethylenglycole-induced, glycerol-induced, ischemic acute renal failure as well as

gentamicin-induced renal injury. The influence of GW PhP on the excretory renal function (ERF) is realized through the complex and complicated mechanisms. Thus, the tincture (1 and 5 ml/kg) inhibits the tubular reabsorbtion and enhances diuresis. The extract (1 g/kg) substantially increases the glomerular filtration rate (water reabsorbtion enhances), inhibits sodium reabsorption and augments saluresis [1].

The hepatoprotective effect of the extract (1 g/kg), GW PhP leaves protein-polysaccharide complex (200 mg/kg) was established on the models of tetrachloromethane-induced and ischemia-induced liver injury [2].

GW tincture and extract reduce the intensity of hyperuricemia. They also reveal hypoazotemic effect and have antiinflammatory action [1, 2].

The investigation of GW PhPs influence on glucose metabolism [3] have shown a high level of safety in the intact rat with the absence of glycemia changes, except for a moderate hypoglycaemic effect of GW tincture (with the values of glycemia within the normal range) at doses of 0.5; 1.0; 5.0 ml/kg after single administration, 5.0 ml/kg – after course administration. GW tincture (1 ml/kg intragastrically after course administration) counteracted to insulin resistance (IR) induced by low doses of dexamethasone (DEX, 0.125 mg/kg subcutaneously). The antidiabetic action on the severe model of alloxan-induced diabetes (AD) was proven for GW tincture (1.0 and 5.0 ml/kg) and the extract (1 g/kg). The beneficial nephrotropic action under these conditions was inherent in the extract that decreased creatininemia, contributed to proteinuria reduction and kidney structure normalization [3].

GW PhP exerted the antihyperlipidemic effect under the conditions of olive oil loading (the extract at a dose of 1 g/kg, the tincture at a dose of 1 ml/kg), normalized the lipid composition of the liver against the background of the high dose of ethanol (the extract at doses of 100 mg/kg and 1 g/kg, the tincture at a dose of 1 ml/kg). The safety of GW tincture as an antihyperglycemic agent is confirmed by the absence of hypoglycemia after its use against the background of ethanol (there also were no negative shifts in other metabolic values and markers of the liver injury) [3].

GW tincture after extractant removal is promising for the combined use with metformin (METF). In this combination, acute toxicity of METF in mice was decreased, the effect of METF was not blocked in the intact rat, still there was no excessive enhancement of this drug influence on basal glycemia, whereas it became possible to decrease its effective dose in the oral glucose tolerance test (OGTT) from 400 mg/kg to 200 mg/kg and to achieve the significant reduction in the total area under the blood glucose curve against the background of METF at a subtherapeutic dose of 100 mg/kg under the conditions of insulin resistance in rats (DEX, 0.125 mg/kg). GW tincture (1 ml/kg), under the conditions of the severe metabolic disorders caused in rats by DEX at a dose of 5 mg/kg, increased the normalizing influence of METF at a low dose of 50 mg/kg on basal glycemia and partially – on glycemia in OGTT, exerted the permissive effect on the action of this drug on insulin sensitivity, limited the increase in liver glucose-6-phosphatase activity, while the normalizing influence on triglyceridemia

and the level of HDL cholesterol were maintained. The combination, in contrast to monotherapy, did not lead to the further decrease in plasma cortisol level, exerted favourable influence on hyperenzymemia and the values of nitrogen and purine metabolism, whlie there were no signs of hepatotoxicity. It did not cause shifts of the excretory renal function (ERF) and demonstrated advantages compared with monotherapy with METF in regard to proteinuria elimination [3, 4].

The ability of GW tincture to enhance the antihyperglycemic effect of METF at a low dose was confirmed under the conditions of alimentary hyperlipidemia exacerbated with lipoprotein lipase inhibition in rats. Against the background of the combination, the ability of its components to restore the lipid composition of the liver as well as the histostructure of the kidneys was maintained, while the antiproteinuric effect was achieved only in this group [3].

The safety and moderate protective effect of GW tincture combination with METF were confirmed in the period of maximum damage to the pancreatic β-cells induced by alloxan in rats (72 h). In the late stages (3 weeks) of AD in mice, it normalized glycemia more significantly than METF per se, showed favourable psychotropic effects [3].

According to the complex of data obtained, GW tincture after extractant removal is much more effective on the models of carbohydrate metabolism disorders than GW extract. At the same time, GW extract possessing the favourable combination of potassium compounds high content with hypoazotemic and uricosuric activity is promising for the increase in hydrochlorothiazide (HCTZ) safety. Administration of HCTZ at a dose causing metabolic disorders (80 mg/kg for 16 days) in combination with GW extract (100 mg/kg 1 g/kg) allowed maintaining normokalemia and an adequate potassium excretion, the influence on sodium excretion depended on dose and regimen of kidney function. After a single administration, GW extract dose-dependently changed the natriuretic effect of HCTZ (20 mg/kg), which was maintained against the background of the extract at a dose of 1 g/kg, but not at a dose of 100 mg/kg, while its hydrouretic effect was eliminated [3,5]. During the prolonged (10 weeks) administration of HCTZ (20 mg/kg) with excess fructose, the hypouricemic effect of GW extract was realized, it also contributed to the maintenance of the ERF under the conditions of additional disturbances of purine metabolism (inhibition of uricase) without causing its disordres in normouricemia, it decreased protein excretion. However, exceptionally in this model, the single per day administration of GW extract as source of potassium salts led to adverse changes associated with increased aldosterone control of the ERF. GW tincture (1 ml/kg) ability to reduce glycemia was also evident in this model, it exerted beneficial renal effects. Both PhP did not cause negative shifts in lipid metabolism and normalized the values of the lipid peroxidation / antioxidative system [3,6].

Both GW PhP are promising for the combined use with allopurinol (AL) as one of the main hypouricemic drugs. They decreased AL acute toxicity. GW tincture (1 ml/kg) did not increase the toxic effect of AL at a high dose (50 mg/kg) in rats against the

background of excessive purine derivatives and proteins intake, was neutral in regard to the kidneys histological structure and the ERF values, significantly reduced proteinuria, did not counteract the inhibition of XOD by AL, exerted favourable psychotropic effects. Maintenance or enhancement of AL activity against the background of GW PhP was proven under the conditions of uricase inhibition [3, 7].

A separate area in the studies addresses the possible changes in the functional state of the central nervous system (CNS) which is interrelated with purine metabolism [. Thus, against the background of hyperuricemia in mice (uricase inhibition for 3 weeks), levels of anxiety and depression were decreased that was associated with the changes in uricemia according to correlation analysis results, against the background of hypouricemia (XOD inhibition by AL for 3 weeks) signs of anxiety were also reduced. Under the conditions of hyperuricemia correction by AL, the influence on the anxiety level was maintained, but the depression signs were increased. Under these conditions, GW extract (1 g/kg) and GW tincture (1 ml/kg) did not have a negative effect on the CNS, in combination with AL they reduced depression signs, the extract did not change the anxiety level, the tincture approximated it to that of the intact control (IC) and restored physical endurance.

Hypouricemia is the characteristic feature of the late stages of severe AD. It is important that GW tincture exerted a normalizing effect on purine metabolism not only in hyperuricemia, but also in hypouricemia: the tincture and its combination with METF, unlike METF per se, increased UA blood level in mice after 3 weeks of AD to the intact control value. The influence on UA transport was possible, since the tincture and METF per se suppressed liver XOD. In mice with AD, GW tincture increased locomotor and exploratory activity, reduced levels of depression and anxiety, improved cognition, most of these effects were seen in combination with METF. GW extract (1 g/kg, per se and with METF) exerted the antidepressive effect, improved cognitive functions.

After course administration of the studied GW PhP per se no signs of worsening of the CNS functional state were registered, while they have the favourable type of interaction with the CNS stimulants and depressants (such as ethanol, thiopental sodium, caffeine-sodium benzoate).

Conclusions.

The complex of the results obtained substantiates the expediency of the development of drugs or dietary supplements on the basis of goutweed (*Aegopodium podagraria* L., Apiaceae) raw material as well as their combinations with metformin, allopurinol, hydrochlorothiazide. The solving the health problems arising with the development of urbanized civilization is in all probability possible only through the use of high technologies and on this way it is expedient to rethink the commonly used ideas about an unspecific and uncertain mode of action of phytotherapy and to use the heritage of traditional medicine, the experience of food plants usage for the development of the standardized herbal drugs with proven activity.

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