STUDIES ON THE TOXIC EFFECT OF VARIOUS PHARMACEUTICAL PREPARATIONS OBTAINED FROM *HAMAMELIS VIRGINIANA*

STUDII PRIVIND EFECTELE TOXICE ALE UNOR PREPARATE FARMACEUTICE OBȚINUTE DIN *HAMAMELIS VIRGINIANA*

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Abstract. *Hamamelis virginiana L. (witch-hazel) is a shrub from Hamamelidaceae family cultivated in Europe for medical purposes. Due to its high tannins content (gallotannins, polycatechins, non-esterified gallic acid, procyanidins), flavonosides and safrole-rich volatile oil, Hamamelidis folium and Hamamelidis cortex extracts are part of many pharmaceutical products for internal and external use. Aqua Hamamelidis is one of the favourite preparations in cosmetics and dentistry. The experiment presented in this study focuses on monitoring the hepatotoxic effects of pharmaceutical products and aqueous extractive solutions from Hamamelidis folium and Hamamelidis cortex. The trial was conducted on four groups of Wistar rats, to which various pharmaceutical preparations from vegetal products of Hamamelis were administered internally. At the end of the four weeks trial, it was noticed that the biochemical parameters important for the hepatic function and integrity were modified. The hepatotoxic effects are particularly important for the preparations obtained from Hamamelidis cortex.*
Key words: *Hamamelidis folium, Hamamelidis cortex, Hamamelidis oil, hepatotoxicity.*

Rezumat. *Hamamelis virginiana L. (nucul vrajitoarelor), arbust încadrat în familia Hamamelidaceae, este cultivat în scopuri medicinale în Europa. Datorită conținutului ridicat în taninuri (galotaninuri, policatehine, acid galic neesterificat, procianidoli), flavonozide şi ulei volatil bogat in safrol, extractele din Hamamelidis folium si Hamamelidis cortex intră în compoziția a numeroase produse produse farmaceutice destinate administrării interne şi externe. Aqua Hamamelidis constituie un preparat preferat în cosmetologie şi stomatologie. Experimentul detaliat în acest articol ştiințific se axează pe monitorizarea efectelor hepotoxice ale produselor farmaceutice şi soluțiilor extractive apoase din Hamamelidis folium si Hamamelidis cortex. Experimentul s-a efectuat pe patru loturi de şobolani Wistar, cărora li s-a administrat intern diferite preparate farmaceutice din produsele vegetale de Hamamelis. La finalul celor patru săptămâni s-a constat modificarea unor parametri biochimici cu relevanță pentru integritatea şi funcția hepatică. Efectele hepatotoxice sunt*

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deosebit de relevante pentru preparatele obținute din Hamamelidis cortex.
Cuvinte cheie: *Hamamelidis folium, Hamamelidis cortex, ulei de Hamamelis, hepatotoxicitate.*

INTRODUCTION

Hamamelis virginiana is a shrub native from the eastern part of North America. The common name – witch hazel, comes from earlier times when native North Americans ascribed the plant with magic powers, probably due to its flowering characteristic. Witch hazel blooms later than any other native plant, generally in October through December but on occasion may start to bloom as early as September. The flowers have the ability to roll back up if the weather gets too cold and unfurl again when the weather is more favourable (Bone and Mills, 2012).

Over the years the plant has been highly appreciated as an astringent, venotonic, vasoprotective, anti-inflammatory and antibacterial remedy due to its high tannins content. The vegetal products, used in both traditional and modern medicine and cosmetics, are represented by the bark (*Hamamelidis cortex*) and leaves (*Hamamelidis leaves*) (Crellin and Philpott, 1990; Erdelmeier *et al.,* 1996; Hughes-Formella *et al.,* 1998). It is this high tannins concentration which makes the extract of witch hazel suitable mostly for external use. Nevertheless, there are food supplements on the European market administered internally for the improvement of peripheral circulation.

Tannins are generally regarded as safe due to their property of protein precipitation and their high molecular weight that impede their gastrointestinal or dermal absorption into the systemic circulation. Despite this, tannins have shown hepatotoxicity (Williamson and Manach, 2005).

The present study is part of a more extensive series of non-clinical experiments that stress the consumer's health and environmental protection and aims to establish the hepatotoxicity degree caused by ingestion of preparation containing *Hamamelidis* folium, *Hamamelidis* cortex and *Hamamelidis* oleum.

MATERIAL AND METHOD

The experimental model included 4 groups of Wistar rats (average weight of 212.17 g), each group consisting of 5 animals. The experiment lasted 4 weeks (Table 1).

The first group of rats was the reference group which was kept in standard conditions. The animals of the second group were given 5% *Hamamelidis folium* infusion by gavage, in a dose of 2 g. The animals of the third group were administered 5% H*amamelidis cortex* decoction in the same dose and by the same route. The fourth group was treated with Hamamelis oil (2 *guttes* diluted to 2 g with olive oil).

At the end of the experiment, blood samples were collected for the biochemical analysis which consisted in the assay of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase (GGT).

Table 1

The experimental model

Groups	5% HF[1] infusion	5% HC[2] decoction	Hamamelis oil	Biochemical parameters
Group 1	-	-	-	AST, ALT, LDH, GGT
Group 2	2 g	-	-	AST, ALT, LDH, GGT
Group 3	-	2g	-	AST, ALT, LDH, GGT
Group 4	-	-	2 *guttes*[3]	AST, ALT, LDH, GGT

[1]HF – *Hamamelidis folium*; [2]HC – *Hamamelidis cortex*; [3]diluted to 2 g with olive oil

RESULTS AND DISCUSSION

The results obtained after the biochemical investigation of the parameters characteristic to the hepatic integrity are presented in Figs. 1-4. Transaminases are enzymes with a strictly citosolic localization. This is why they are used as indicators of hepatic cytolisis. They are catalysts of the transamination reaction that allows the synthesis of aminoacids needed by the organism.

The evolution of ALT, as shown in Fig. 1, shows a slight insignificant increase of the activity from 18.123 UI (for the referrence group) to 18.500 UI for group 2 (treated with 5% *Hamamelidis folium* infusion). Of higher significance is the increase of ALT to 20, 670 UI in group which was given the hamamelis oil. This augmentation may be explained by the migration of the enzyme from the cytosolic space to the extracelular liquid due to the hepatocyt membrane damage produced by the tannins from *Hamamelis virginiana*. This phenomenon is more important for the animals treated with decoction from *Hamamelidis cortex.*

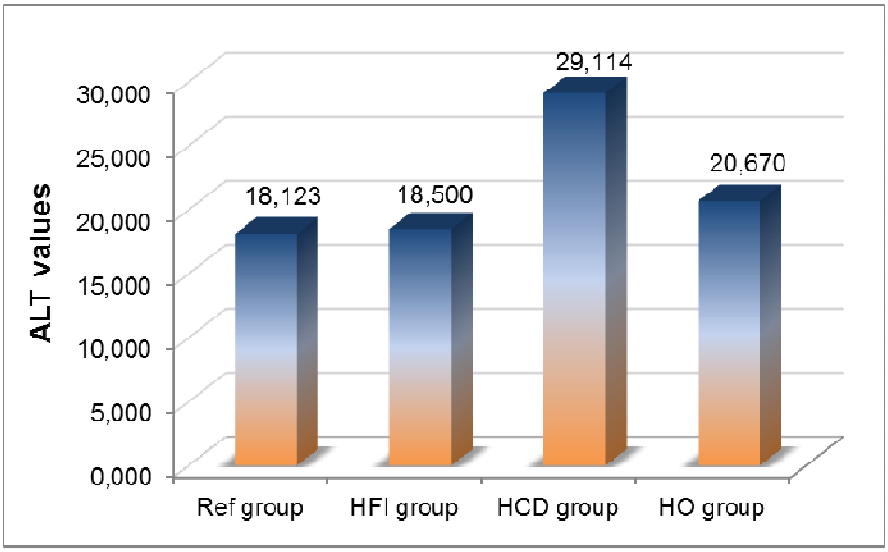

Fig. 1 - Evolution of ALT for the 4 experimental groups

The study of the second aminotransferase (AST) emphasize an increase of the serum activty for the animals that were given the infusion of *Hamamelidis folium* (from 48.999 UI, value characteristic to the reference group to 50.150 UI). Of great importance is the variation of AST in group 3 (treated with *Hamamelidis cortex* decoction), suggesting an increase of the hepatocyte permeability having as result the migration of AST in the serum (Fig. 2).

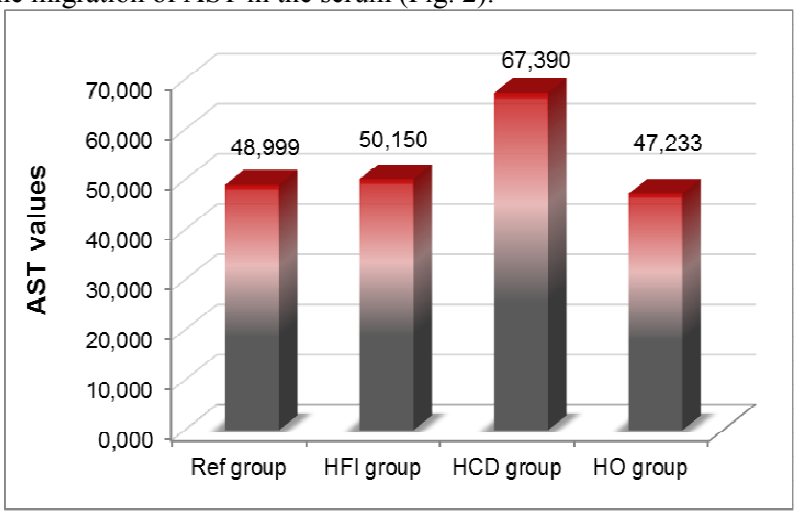

Fig. 2 - Evolution of ALT for the 4 experimental groups

The evolution of the third biochemical parameter (LDH) is in agreement with the evolution of the other parameters, revealing a significant increase of its activity in the serum of the third group which was given the decoction from the bark of witch hazel (2.291 µmols/ml vs 1.557 µmols/ml representing the value for the reference group) (Fig 3).

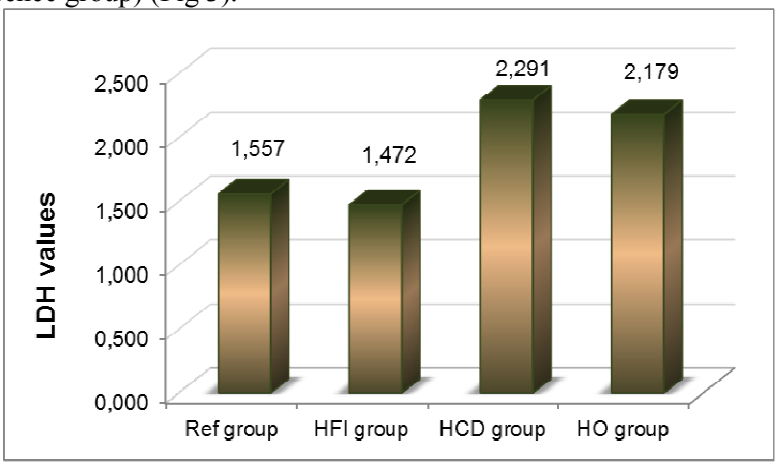

Fig. 3 - Evolution of LDH for the 4 experimental groups

The last of the studied parameters (GGT) is an enzyme that interferes the glicoproteic transport and is represented by five isoenzymes that have multiple diagnostic values (parameter of hepatic cytolisis, marker of ethylism and indicator of an oncogenic process). The evolution of this parameter (Fig. 4) sustains the previous results, the heighest value being reached by the third group (*Hamamelidis cortex* decoction).

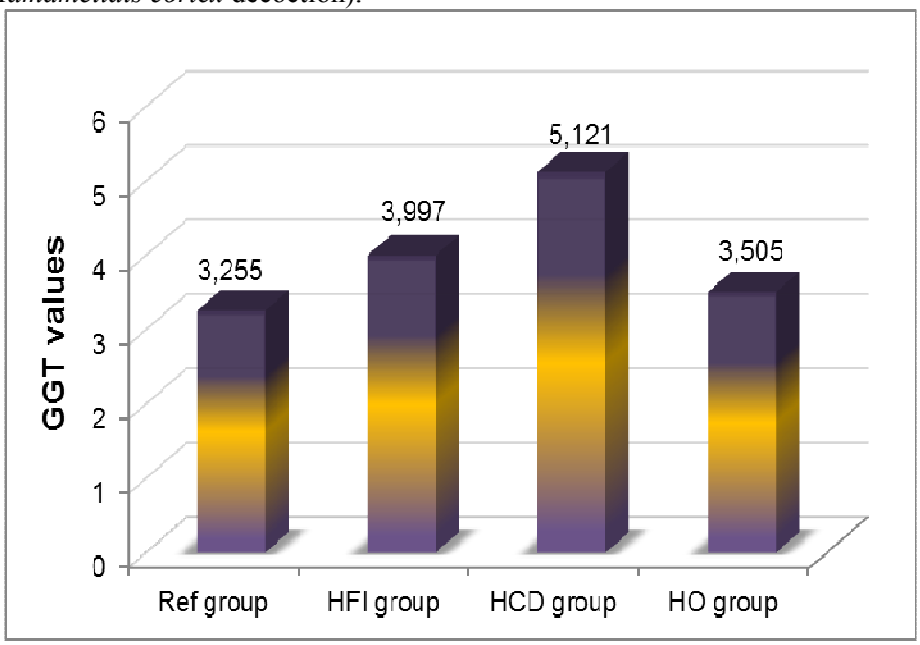

Fig. 4 - Evolution of GGT for the 4 experimental groups

CONCLUSIONS

1. The 5% decoct of *Hamamelidis cortex* showed the highest hepatotoxic potential of all the studied preparations, inducing an increase of all the four biochemical parameters (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and gamma-glutamyl transpeptidase).

2. The oil extract of *Hamamelidis folium* is the second preparation when it comes to hepatotoxicity, producing a slight increase of aspartate aminotransferase and gamma-glutamyl transpeptidase activity.

3. The third studied preparation - 5% infusion of *Hamamelidis folium*, exerted its toxic potential only upon gamma-glutamyl transpeptidase.

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