

# THE INFLUENCE OF COPTISINE BISULFATE ON THE EVOLUTION OF ACUTE TOXIC HEPATITIS

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## ABSTRACT

In the experiments made on white rats was studied the influence of coptisine bisulfate, alkaloid extracted from *Chelidonium majus*, in the following doses: 10 mg/kg and 20 mg/kg on acute toxic hepatitis cause by carbon tetrachloride. It was established that the researched substance reduced hepatic cytolysis and cholestasis through reestablishment of the transaminases activity and lactate dehydrogenase, while lowering the alkaline phosphatase/alanine aminotransferase ratio and modulated the deflection of the metabolic parameters of acute toxic hepatitis. Coptisine bisulfate corrected the carbon tetrachloride caused hypoproteinemia when administered for 7 days and normalized the albumin level at 14th day of treatment of acute toxic hepatitis.

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**Introduction.** Hepatoprotective activity of *Chelidonium majus* shows benefic influence on the liver functions due to isoquinoline derivatives with antioxidant, choleric, anti-inflammatory and immunomodulatory effects, one of them being coptisine [2, 5]. *Chelidonium majus* ethanolic extract proved the capacity of reducing the hepatotoxicity induced by carbon tetrachloride, through lowering the lipids cumulation, cellular necrosis growth and the lack of [6].

A certain amount of clinical studies that contain extracts from the patients with biliary tract and gallbladder disorders (gallstones, cholecystitis, cholangitis, postcholecystectomy syndrome, alcoholic toxic hepatitis) suggested a significant improvement of the clinical, instrumental and laboratory parameters (bilirubin, transaminases, complete blood count) [6].

Coptisine bisulfate, presented at the Medicine Scientific Centre, USMF "Nicolae Testemitanu" [1] was obtained from Celandine herbs.

Scientific literature analysis allow us to conclude that extract and alkaloids of *Chelidonium majus* manifests hepatoprotective activity through: decreasing the production of the reactive species of Oxygen; inhibition of the lipids peroxidation; glutathione synthesis rise and antioxidant enzyme activity; reduction of the inflammatory process due to decreasing of proinflammatory cytokines production; correction of lipidic metabolism disorders.

Due to the lack of coptisine bisulfate toxicity [3, 4], compared with berberin and other alkaloids of *Chelidonium majus* and considering the hepatoprotective effect, it was established the aim of experimental research of coptisine bisulfate on acute toxic hepatitis (ATH) shaped in white rats by administering carbon tetrachloride.

**Results.** Using coptisine bisulfate in the treatment of ATH, there were studied the influence of this alkaloid on the evolution of acute hepatic lesion when using 10 and 20 mg/kg strenghts for establishing a strengh- hepatoprotective effect dependency.

When shaping ATH using CCl<sub>4</sub> at the 7th day it was observed a growing of AlAT from 56,8±2,4 mmol/l to 190,6±8,2 mmol/l (P<sub>1-2</sub><0,05) and AsAT – from 140,2±5,0 mmol/l to 260,2±20,5 mmol/l (P<0,05). This growing of the transaminase level is still manifesting after 2 weeks after the hepatotoxic was administered (tab.1). In these condition were determined a reduction of Ritis coefficient from 2,46±0,21 to 1,36±0,25. Coptisine bisulfate administration in 10 mg/kg and 20 mg/kg strenghts for 7 and 14 days contributed to maintaining of AlAT and AsAT levels and Ritis coefficient, basically at the position of witness lot (tab. 1).

Tabel 1. Modification of transaminase level in serum in carbon tetrachloride induced HT and coptisine bisulfate 10 and 20 mg/kg usage

Animal groups	Nr.of animals	AlAT mmol/l	AsAT mmol/l	Ritis coefficient
1. Witness lot	10	56,8±2,4	140,2±5,0	2,46±0,21
2. CCl <sub>4</sub> after 7 days	10	190,6±8,2 P <sub>1-2</sub> <0,05	260,2±20,5 P <sub>1-2</sub> <0,05	1,36±0,25 P <sub>1-2</sub> <0,05
3. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 7 days	10	60,0±1,8 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> <0,05	153,1±7,3 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> <0,05	2,55±0,4 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> <0,05
4. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 7 days	10	65,4±4,9 P <sub>1-4</sub> <0,05 P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05	153,2±8,6 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> <0,05 P <sub>3-4</sub> >0,05	2,34±0,18 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> <0,05 P <sub>3-4</sub> >0,05
5. CCl <sub>4</sub> after 14 days	10	223,4±6,9 P <sub>1-5</sub> <0,05	440,4±29,7 P <sub>1-5</sub> <0,05	1,97±0,44 P <sub>1-5</sub> <0,05
6. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 14 days	10	59,6±0,9 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> <0,05	128,1±3,9 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> <0,05	2,15±0,43 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05
7. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 14 days	10	66,6±3,5 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> <0,05 P <sub>6-7</sub> >0,05	144,5±6,1 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> <0,05 P <sub>6-7</sub> >0,05	2,15±0,17 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05

When injected CCl<sub>4</sub> at the 7th day it was determined a growth of alkaline phosphatase activity from 510,2±23,3 UI/l in the witness lot to 1063,7±57,5 UI/l (P<0,05). When using coptisine bisulfate in doses 10 mg/kg and 20 mg/kg for 7 days there was noticed a decreased level of alkaline phosphatase level comparing with the ATH lot, which was non significantly higher than the witness lot. When shaping the experimental hepatitis at 14th day it was noticed that alkaline phosphatase content was 784,4±62,7 UI/l compared to 510,2±23,3 UI/l (P<0,05) in the witness lot, but lower than CCl<sub>4</sub> lot at 7th day - 784,4±62,7 UI/l compared to 1063,7±57,5 UI/l (P<0,05). When coptisine bisulfate was administered in both doses there were no essential changes to the lot with CCl<sub>4</sub> after 14 days determined (tab. 2).

When ATH was shaped at the 7th day was determined a decreasing of the acidic phosphatase from 4,8±0,3 UI/l in the witness lot to 3,7±0,3 UI/l (P<0,05), which was maintained at the same level at 14th day as well. When coptisine bisulfate was administered for 7 days in the doses 10 mg/kg and 20 mg/kg it was established a significant reduction of the acidic phosphatase level in the witness lot, and in the experimental hepatitis one as well. When the alkaloid was used for 2 weeks in both strenghts the acidic phosphatase content increased from 3,7±0,3 UI/l in the lot with CCl<sub>4</sub> to 4,2±0,4 UI/l at the dose of 10 mg/kg and 4,1±0,3 UI/l at the dose of 20 mg/kg (P>0,05).

Tabel 2. The modification of alkaline phosphatase activity, acidic phosphatase and GGTP in serum in carbon tetrachloride induced HT and the coptisine bisulfate 10 and 20 mg/kg usage

Animal groups	Nr.of animals	Alkaline phosphatase (UI/l)	Acidic phosphatase (UI/l)	GGTP
1. The witness lot	7	510,2±23,3	4,8±0,3	3,7±0,4
2. CCl <sub>4</sub> after 7 days	7	1063,7±57,5 P <sub>1-2</sub> <0,05	3,7±0,3 P <sub>1-2</sub> <0,05	3,6±0,3 P <sub>1-2</sub> >0,05
3. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 7 days	7	862,3±49,7 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> <0,05	2,5±0,3 P <sub>1-3</sub> <0,05 P <sub>2-3</sub> <0,05	4,3±0,7 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> >0,05
4. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 7 days	7	783,4±53,3 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> <0,05 P <sub>3-4</sub> >0,05	2,9±0,3 P <sub>1-4</sub> <0,05 P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05	3,4±0,2 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05
5. CCl <sub>4</sub> after 14 days	7	784,4±62,7 P <sub>1-5</sub> <0,05	3,7±0,3 P <sub>1-5</sub> <0,05	6,7±0,7 P <sub>1-5</sub> <0,05
6. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 14 days	7	790,5±47,7 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05	4,2±0,4 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05	4,1±0,4 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> <0,05
7. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 14 days	7	711,9±53,2 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05	4,1±0,3 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05	4,2±0,5 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> <0,05 P <sub>6-7</sub> >0,05

In ATH, induced by CCl<sub>4</sub>, activity of GGTP did not change significantly at the 7th day, but increased a lot at the 14th day (tab. 2). When coptisine bisulfate was administered in the dose of 10 mg/kg the level of the enzyme increased from 3,6±0,3 UI/l in the lot with CCl<sub>4</sub>, to 4,3±0,7 UI/l (P>0,05), while the alkaloid in the dose of 20 mg/kg was decreasing nonsignificantly the content of GGTP (tab. 2). The usage of the alkaloid for 2 weeks contributed to diminishing of the GGTP level from 6,7±0,7 UI/l in the lot with experimental hepatitis, to 4,1±0,4 UI/l and 4,2±0,5 UI/l (P<0,05) in doses of 10 mg/kg and 20 mg/kg accordingly.

In the process of shaping the experimental hepatitis at the 7th day there was noticed a tendency of growing the bilirubin total level in rats from 40,1±2,6 mmol/l to 44,2±3,6 mmol/l (P>0,05), direct bilirubin from 23,0±1,4 mmol/l to 26,3±2,7 mmol/l (P>0,05) and indirect bilirubin from 17,1±1,3 mmol/l to 17,9±1,6 mmol/l (P>0,05). When coptisine bisulfate was administered in the doses of 10 mg/kg and 20 mg/kg for 7 days there were no main changes in the total bilirubin content and its fractions (tab. 3). After 14 days there were no significant diversion in total, direct and indirect bilirubin level in comparison with the witness lot, in animals with ATH. Coptisine bisulfate, used for 2 weeks, both strengths, did not influence the content of bilirubin and its fractions (tab. 3).

Tabel 3. The modification of the total, direct and indirect bilirubin level in serum in carbon tetrachloride induced HT and coptisine bisulfate 10 and 20 mg/kg usage

Animal groups	Nr. Of animals	Total bilirubin mmol/l	Direct bilirubin mmol/l	Indirect bilirubin
1	2	3	4	5
1. The witness lot	7	40,1±2,6	23,0±1,4	17,1±1,3
2. CCl <sub>4</sub> after 7 days	7	44,2±3,6 P <sub>1-2</sub> >0,05	26,3±2,7 P <sub>1-2</sub> >0,05	17,9±1,6 P <sub>1-2</sub> >0,05
3. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 7 days	7	42,3±3,4 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> >0,05	25,1±1,9 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> >0,05	17,2±1,9 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> >0,05
4. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 7 days	7	47,2±2,7 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05	27,2±1,2 P <sub>1-4</sub> P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05	20,0±1,7 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05
5. CCl <sub>4</sub> after 14 days	7	39,0±3,7 P <sub>1-5</sub> >0,05	22,9±1,6 P <sub>1-5</sub> >0,05	16,1±2,3 P <sub>1-5</sub> >0,05

Continuation of table 3

1	2	3	4	5
6. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 14 days	7	40,6±2,2 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05	23,1±1,3 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05	17,5±1,0 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05
7. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 14 days	7	38,7±2,6 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05	21,9±1,1 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05	16,8±1,9 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05

When determining the LDH level at the 7th day after shaping ATH it was determined a growth of LDH from 386,2±12,8 UI/l in the witness lot to 1005,7±72,5 UI/l (P<sub>1-2</sub><0,05), following to grow until 1355,7±83,7 UI/l (P<0,05) in the 14th day. Whencoptisine bisulfate in strenghts of 10mg/kg and 20mg/kg was administered for 7 and 14 days, the LDH level was at the position of the animals in the witness lot (tab. 4).

When shaping ATH it was noticed a non esential fall of the glucose level in the 7th day and a non significant increase in the 14th day. Coptisine bisulfate, in 10 mg/kg and 20 mg/kg doses, nearly did not influence after 1 week and after 2 weeks as well, the changes of blood glucose induced by the hepatotoxic substance (tab. 4).

Tabel 4. The modification of LDH activity, glucose level and thymol reaction in carbon tetrachloride induced HT and coptisine bisulfate 10 and 20 mg/kg usage

Animal groups	Nr. Of animals	LDH UI/l	Glucose mmol/l	Thymol reaction
1. The witness lot	7	386,2±12,8	5,2±0,3	4,17±0,1
2. CCl <sub>4</sub> after 7 days	7	1005,7±72,5 P <sub>1-2</sub> <0,05	4,6±0,2 P <sub>1-2</sub> >0,05	3,41±0,08 P <sub>1-2</sub> <0,05
3. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 7 days	7	413,9±20,3 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> <0,05	4,7±0,2 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> >0,05	3,42±0,1 P <sub>1-3</sub> <0,05 P <sub>2-3</sub> >0,05
4. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 7 days	7	375,2±21,6 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> <0,05 P <sub>3-4</sub> >0,05	4,6±0,2 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05	3,43±0,08 P <sub>1-4</sub> <0,05 P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05
5. CCl <sub>4</sub> after 14 days	7	1355,7±83,7 P <sub>1-5</sub> <0,05	5,6±0,1 P <sub>1-5</sub> >0,05	4,19±0,12 P <sub>1-5</sub> >0,05
6. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 14 days	7	392,9±16,6 P <sub>1-6</sub> <0,05 P <sub>5-6</sub> <0,05	5,7±0,3 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05	4,37±0,11 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05
7. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 14 days	7	386,6±19,9 P <sub>1-7</sub> <0,05 P <sub>5-7</sub> <0,05 P <sub>6-7</sub> >0,05	5,7±0,3 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05	4,22±0,12 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05

Carbon tetrachloride did not influence the cholesterol total level in the 7th day, but determined a increase of it in the 14th day from 5,09±0,04 mmol/l in the witness lot to 5,28±0,05 mmol/l (P<0,05). Coptisine bisulfate (10 mg/kg and 20 mg/kg), administered for 7 and 14 days determined a decrease of the total cholesterol content (tab. 5).

In the experimental hepatitis were not ascertained esential changes of the total protein level, both in 7th and 14th day (tab. 5). In the same time the hepatotoxic determined a decrease of the albumin content from 5,28±0,05 g/l in the witness lot to 30,6±0,8 g/l (P<0,05). Coptisine bisulfate in doses of 10 mg/kg and 20 mg/kg, when administered for 7 days, corrected the CCl<sub>4</sub> induced hypoproteinemia. The albumin level in the 14th day in animals with ATH and the ones treated with coptisine bisulfate was at the level of the witness lot (tab. 5).

Tabel 5. The modification of the cholesterol level, total proteins and albumin in serum in carbon tetrachloride induced HT and coptisine bisulfate 10 and 20 mg/kg usage

Animal groups	Nr. Of animals	Total cholesterol mmol/l	Total protein g/l	Albumin
1. The witness lot	7	5,09±0,04	58,3±0,5	35,5±0,8
2. CCl <sub>4</sub> after 7 days	7	5,03±0,07 P <sub>1-2</sub> >0,05	58,3±0,6 P <sub>1-2</sub> >0,05	30,6±0,8 P <sub>1-2</sub> <0,05
3. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 7 days	7	4,97±0,07 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> >0,05	60,3±0,8 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> >0,05	34,3±0,4 P <sub>1-3</sub> >0,05 P <sub>2-3</sub> <0,05
4. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 7 days	7	4,98±0,02 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05	58,5±0,9 P <sub>1-4</sub> >0,05 P <sub>2-4</sub> >0,05 P <sub>3-4</sub> >0,05	33,2±0,6 P <sub>1-4</sub> <0,05 P <sub>2-4</sub> <0,05 P <sub>3-4</sub> >0,05
5. CCl <sub>4</sub> after 14 days	7	5,28±0,05 P <sub>1-5</sub> <0,05	59,2±0,7 P <sub>1-5</sub> >0,05	35,1±0,3 P <sub>1-5</sub> >0,05
6. CCl <sub>4</sub> + coptisine bisulfate 10 mg/kg 14 days	7	5,06±0,03 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> <0,05	60,3±1,4 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05	34,3±1,3 P <sub>1-6</sub> >0,05 P <sub>5-6</sub> >0,05
7. CCl <sub>4</sub> + coptisine bisulfate 20 mg/kg 14 days	7	5,18±0,11 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05	58,9±0,6 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05	35,1±0,7 P <sub>1-7</sub> >0,05 P <sub>5-7</sub> >0,05 P <sub>6-7</sub> >0,05

According to the obtained results, coptisine bisulfate, one of *Chelidonium majus* alkaloids is a component that lacks in systemic toxicity, owns hepatoprotective properties through re-establishing the transaminases activity, reducing the Ritis coefficient and normalizing the cholestasis in acute toxic hepatitis induced by carbon tetrachloride. This fact indicates its contribution to pharmacological effects of celandine extracts and the possibility of using of this product in the complex treatment of toxic hepatitis.

#### Conclusions.

1. Coptisine bisulfate, in doses of 10 mg/kg and 20 mg/kg, in a dose dependent way, annihilated the cytolysis syndrome by reestablishing the transaminases activity, especially ALAT, and the obvious decrease of the Ritis ratio.

2. It was established the reduction of cholestasis under the influence of coptisine bisulfate by non essential growth of alkaline phosphatase activity and of total, direct and indirect bilirubin level, (decrease of FA/ALAT ratio) and modulated the metabolic parameters deflection of acute toxic hepatitis.

3. When administered for 7 and 14 days, coptisine bisulfate in strenghts of 10 mg/kg and 20 mg/kg, normalises the LDH content at the level or witness lot animals, but the blood glucose level induced by the hepatotoxic substance was not influenced.

4. Coptisine bisulfate corrected the hypoproteinemia caused by CCl<sub>4</sub>, when administered for 7 days and normalised the albumin level in the 14th day of treatment of the ATH animals.

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