DOI 10.32900/2312-8402-2022-128-21-35
UDC 577.1: 577.112.4: 577.115.4: 639.2: 615.322

DOSE-DEPENDENT ALTERATIONS IN THE BIOMARKERS OF LIPID AND PROTEIN OXIDATION IN THE MUSCLE TISSUE OF RAINBOW TROUT (*ONCORHYNCHUS MYKISS* WALBAUM) AFTER *IN VITRO* TREATMENT BY EXTRACTS OF GREAT CELANDINE (*CHELIDONIUM MAJUS* L.)

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Consistent with our previous studies, we continue to evaluate the antioxidant potential of representatives of the Papaveraceae family collected from the northern part of Poland on the model of muscle tissue of rainbow trout. Therefore, in the current study, oxidative stress biomarkers [2-thiobarbituric acid reactive substances (TBARS), aldehydic and ketonic derivatives of oxidatively modified proteins (OMP), and total antioxidant capacity (TAC)] were used to evaluate the antioxidant activity of extracts derived from stalks and roots of great celandine (Chelidonium majus L., CM) at a final dose of 5 mg/mL, 2,5 mg/mL, 1,25 mg/mL and 0,63 mg/mL. Homogenate of muscle tissues derived from rainbow trout was used in this in vitro study. Phosphate buffer was used as a positive control (blank). After incubation of the mixture at 25°C for 120 min with continuous mixing, samples were used for biochemical studies. Our studies have shown that the use of extracts at a final dose of 5 mg/ml and 2.5 mg/ml resulted in a statistically significant increase of lipid peroxidation biomarkers (TBARS levels) in the muscle tissue of rainbow trout. The final dose of extract 1.25 mg/ml caused a statistically significant increase in the levels of aldehydic and ketonic derivatives of OMP, and this is reflected when measuring the levels of TAC. On the other hand, the use of extracts at a final dose of 0.63 mg/ml derived from both roots and stems of CM resulted in statistically significant reduced levels of TBARS, as well as aldehydic and ketonic derivatives of OMP in the muscle tissue of rainbow trout after in vitro incubation. The comparison of these results showed that CM extracts can effectively inhibit the production of oxidatively modified carbonyls by scavenging free radicals. The secondary metabolites of CM, i.e. polyphenols, are most likely responsible for this effect. Screening of species of the family Papaveraceae for other biological activities, including antioxidant activity, is essential and may be effective in the search for preventive measures in the pathogenesis of some diseases, as well as in the prevention and treatment of some disorders in veterinary and medicine.

Keywords: **rainbow trout (*Oncorhynchus mykiss* Walbaum), muscle tissue, oxidative stress, 2-thiobarbituric acid reactive substances (TBARS), aldehydic and ketonic derivatives of oxidatively modified proteins (OMP), total antioxidant capacity (TAC).**

Free radical-induced macromolecular damage has been studied extensively as a mechanism of oxidative stress. Large-scale intervention trials with free radical-cavenging antioxidant supplements show little benefit in animals [1, 2, 36]. Recent advancements and growing attention to free radicals (ROS) and redox signaling enable the scientific fraternity to consider their involvement in the pathophysiology of inflammatory diseases, disorders, and many defects. Free radicals increase the concentration of reactive oxygen species and nitrogen oxygen species in the biological system through different endogenous sources and thus increased the overall oxidative stress [30]. An increase in oxidative stress causes cell death through different signaling mechanisms such as mitochondrial impairment, cell-cycle arrest, DNA damage response, inflammation, negative regulation of protein, and lipid peroxidation. Thus, an appropriate balance between free radicals and antioxidants becomes crucial to maintain physiological function [12, 17].

Oxidative stress, defined as disturbances in the pro- and antioxidant balance, is harmful to cells due to the excessive generation of highly reactive oxygen and nitrogen species [7]. When the balance is not disturbed, oxidative stress has a role in physiological adaptations and signal transduction [7]. However, an excessive amount of reactive oxygen and nitrogen species results in the oxidation of biological molecules such as lipids, proteins, and DNA [4, 18, 31].

Fish represent the largest group of vertebrates and they inhabit a broad range of ecosystems where they are subjected to many different aquatic contaminants. In many cases, the deleterious effects of contaminants have been connected to the induction of oxidative stress. Deciphering molecular mechanisms in responses of organisms to contaminant effects may let prevent or minimize the deleterious impacts of oxidative stress [20].

Recently, research on natural antioxidants has become increasingly active in various fields [11, 24]. Accordingly, numerous articles on natural antioxidants, including polyphenols, flavonoids, vitamins, and volatile chemicals, have been published [3, 19, 27]. Assays developed to evaluate the antioxidant activity of plants and food constituents vary [23, 29]. Phenolic compounds, ascorbic acid, and carotenoids, derived from different plant species, are able to protect the skin by preventing UV penetration, reducing inflammation and oxidative stress, and influencing several survival signaling pathways [28].

Recent studies report the antioxidant properties of plants in the Papaveraceae family and it could be used in veterinary and medicine [25]. *Chelidonium majus* L. (CM, Papaveraceae), or greater celandine, has a long history of being useful for the treatment of many diseases in European countries [39]. This plant is of great interest for its use also in Chinese herbal medicine. This plant contains, as a major secondary metabolite, isoquinoline alkaloids, such as sanguinarine, chelidonine, chelerythrine, berberine, and coptisine [10]. Other compounds structurally unrelated to the alkaloids have been isolated from the aerial parts: several flavonoids and phenolic acids [10]. CM extracts and their purified compounds exhibit interesting antioxidant, antiviral, antitumor, and antimicrobial properties both *in vitro* and *in vivo* [6, 10, 32, 39].

Therefore, in the present study, the oxidative stress biomarkers [2-thiobarbituric acid reactive substances (TBARS), carbonyl derivatives of oxidative modification of proteins (OMP), total antioxidant capacity (TAC)] in the muscle tissue of rainbow trout (*Oncorhynchus mykiss* Walbaum), was used for assessing the antioxidant activity of root and stalk extracts derived from CM collected in urban and rural agglomerations of Kartuzy district (Pomeranian province, northern part of Poland).

Materials and Methods. ***Collection of Plant Material.*** Plant materials (Fig. 1B) were harvested from natural habitats on the territory of the Kartuzy district (54°20′N 18°12′E) in the Pomeranian province (northern part of Poland) (Fig. 1A). Kartuzy is located about 32 kilometers (20 miles) west of Gdańsk and 35 km (22 miles) south-east of the town of Lębork on a plateau at an altitude of approximately 200 meters (656 feet) above sea level on average. The plateau, which is divided by the Radaune lake, comprises the highest parts of the Baltic Sea Plate (http://www.kartuzy.pl/). Plants were collected from urban (n = 5) and rural agglomerations (n = 15) on the territory of the Kartuzy district.

A B

Fig. 1. Location of Kartuzy in the map of Poland (A), where the greater celandine (B) was collected.

Preparation of Plant Extracts. The collected roots and stalks were brought into the laboratory for biochemical studies. Freshly washed samples of plants were weighed, crushed, and homogenized in 0.1M phosphate buffer (pH 7.4) (in proportion 1:19, w/w) at room temperature. The extracts were then filtered and used for analysis. The extract was stored at -20°C until use.

Experimental fish. Clinically healthy rainbow trout with a mean body mass of 80-120 g were used in the experiments. The experiments were performed in water at 14.5 ± 0.5°C and pH 7.2-7.4. The dissolved oxygen level was about 9 ppm with an additional oxygen supply, with a water flow of 25 L/min, and a photoperiod of 12 h per day. The same experimental conditions were used during the whole research. The water parameters were maintained under constant surveillance. The fish were held in square tanks (150 fish per tank) and fed a commercial pelleted diet.

Muscle tissue samples. The muscle tissue samples were homogenized in ice-cold buffer (100 mM Tris-HCl, pH 7.2) using a glass homogenizer immersed in an ice water bath. Homogenates were centrifuged at 3,000 rpm for 15 min at 4 °C. After centrifugation, the supernatant was collected and frozen at −20°C until analyzed. All enzymatic assays were carried out at 22 ± 0.5°C using a Specol 11 spectrophotometer (Carl Zeiss Jena, Germany) in duplicate. The reactions were started by adding the tissue supernatant.

Experimental design. The supernatant of the muscle tissue was used to incubate with extracts derived from stalks and roots of CM at four final concentrations, i.e. 5 mg/mL, 2.5 mg/mL, 1.25 mg/mL. and 0.63 mg/mL, respectively, at room temperature.

The control samples (muscle tissue) were incubated with 100 mM Tris-HCl buffer (pH 7.2). The incubation time was 2 hours. Biomarkers of oxidative stress were studied in the incubated homogenates (control samples and in samples with extracts derived from stalks and roots of CM).

Assay of 2-thiobarbituric acid reactive substances (TBARS). Lipid oxidation was evaluated by TBARS according to the method described by Kamyshnikov [13] with some modifications. TBARS were calculated as nmoles of malonic dialdehyde (MDA) per mg of protein.

The content of carbonyl derivatives of protein oxidative modification (OMP). To evaluate the protective effects of the extracts derived from stalks and roots of CM against free radical-induced protein damage in muscle samples, a carbonyl derivatives content of protein oxidative modification (OMP) assay based on the spectrophotometric measurement of aldehydic and ketonic derivatives in samples was performed. The rate of protein oxidative destruction was estimated from the reaction of the resultant carbonyl derivatives of amino acid reaction with 2,4-dinitrophenylhydrazine (DNFH) as described by Levine and co-workers [15] and as modified by Dubinina and co-workers [8]. DNFH was used for determining carbonyl content in soluble and insoluble proteins. Carbonyl groups were determined spectrophotometrically from the difference in absorbance at 370 nm (aldehydic derivatives, OMP_{370}) and 430 nm (ketonic derivatives, OMP_{430}).

Measurement of total antioxidant capacity (TAC). The TAC level in the samples was estimated by measuring the 2-thiobarbituric acid reactive substances (TBARS) level after Tween 80 oxidation. This level was determined spectrophotometrically at 532 nm [9]. The level of TAC in the sample (%) was calculated with respect to the absorbance of the blank sample.

Statistical analysis. Statistical analysis of the data obtained was performed by employing the mean ± S.E.M. All variables were tested for normal distribution using the Kolmogorov-Smirnov and Lilliefors test ($p > 0.05$). The significance of differences between the levels of oxidative stress biomarkers (significance level, $p < 0.05$) was examined using the Kruskal–Wallis one-way analysis of variance [38].The data were analyzed using a one-way analysis of variance (ANOVA) using STATISTICA 13.3 software (TIBCO Software Inc., Krakow, Poland) [38].

Results and discussion. Figure 2 shows TBARS values in the muscle tissue of rainbow trout after incubation of greater celandine extracts. Using a dose of 5 mg/ml, we observed a statistically significant increase in TBARS levels in the muscle tissue of rainbow trout after *in vitro* incubation with the root extracts by 14.9% ($p < 0.05$) compared to the untreated samples (226.12 ± 1.5 nmol/mg protein *vs*. 196.72 ± 1.34 nmol/mg protein). A similar, yet not statistically significant increase (by 13.7%, $p > 0.05$) in the levels of lipid peroxidation biomarkers was recorded after *in vitro* incubation of the muscle tissue of rainbow trout with stalk extracts of CM compared to the untreated samples (223.73 ± 0.82 nmol/mg protein *vs*. 196.72 ± 1.34 nmol/mg protein). By lowering the final dose of the extract to a value of 2.5 mg/ml, we also recorded a statistically significant increase in the level of lipid peroxidation biomarkers in the muscle tissue of rainbow trout after incubation with both root and stalk extracts (by 13 %, $p < 0.05$ and 14.9 %, $p < 0.05$, respectively), compared to the untreated controls (222.88 ± 0.95 nmol/mg protein *vs*. 196.72 ± 1.34 nmol/mg protein for root extracts; 225.99 ± 1.36 nmol/mg protein *vs*. 196.72 ± 1.34 nmol/mg protein for stalk extracts) (Fig. 2).

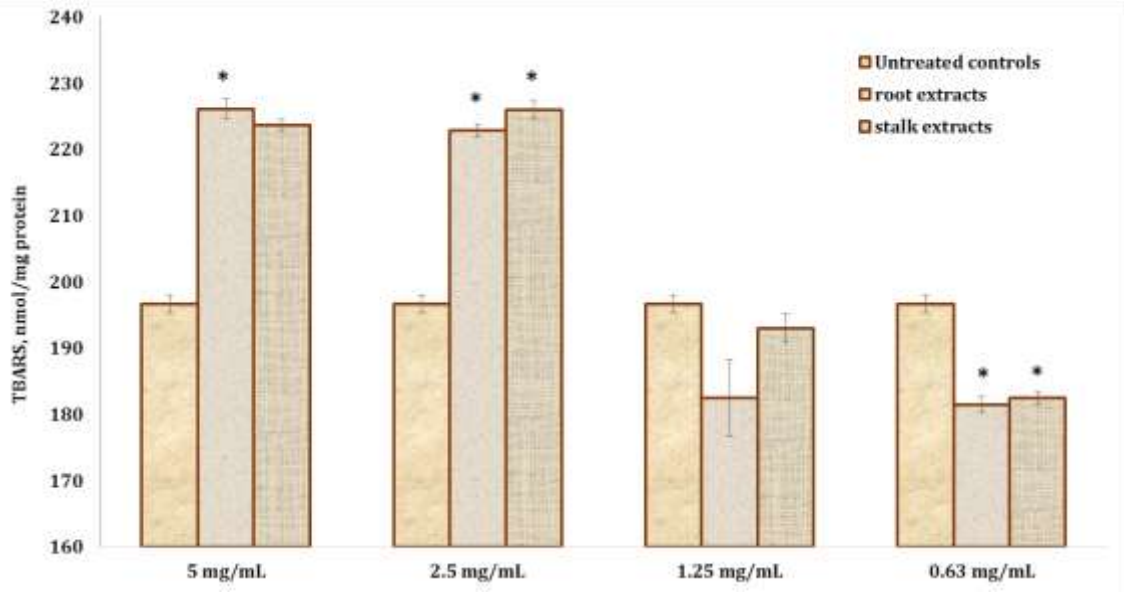

Fig. 2. The content of 2-thiobarbituric acid reactive substances (TBARS) as a biomarker of lipid peroxidation in the muscle tissue of rainbow trout after *in vitro* incubation with extracts in different doses (5 mg/mL, 2.5 mg/mL, 1.25 mg/mL, 0.63 mg/mL) derived from stalks and roots of great celandine (M ± m, n = 8).

*– changes are statistically significant ($p < 0.05$) in relations untreated controls *vs*. extracts derived from roots and stalks of CM.

A different trend was observed after *in vitro* incubation of muscle tissue with both root and stalk extracts of CM at a dose of 1.25 mg/ml, where there was a statistically non-significant decrease in TBARS levels by 7.2 % ($p > 0.05$) and 1.9% ($p > 0.05$), respectively, compared to the untreated controls (182.49 ± 5.84 nmol/mg protein *vs*. 196.72 ± 1.34 nmol/mg protein for root extracts; 192.97 ± 2.11 nmol/mg protein *vs*. 196.72 ± 1.34 nmol/mg protein for stalk extracts). By lowering the final dose of extract to 0.63 mg/ml, we observed a statistically significant reduction in lipid peroxidation biomarkers after *in vitro* incubation of muscle tissue of rainbow trout with both root and stalk extracts by 7.7 % ($p < 0.05$) and 7.2 % ($p < 0.05$), respectively, compared to the untreated samples (181.5 ± 1.23 nmol/mg protein *vs*. 196.72 ± 1.34 nmol/mg protein for root extracts; 182.5 ± 0.97 nmol/mg protein *vs*. 196.72 ± 1.34 nmol/mg protein for stalk extracts) (Fig. 2).

When we incubated the muscle tissue of rainbow trout with root extracts at a final dose of 5 mg/ml, we observed a statistically non-significant increase in the levels of aldehydic derivatives of oxidatively modified proteins (by 2.7 %, $p > 0.05$) compared to the untreated samples (13.02 ± 0.13 nmol/mg protein *vs*. 12.68 ± 0.16 nmol/mg protein). A different trend was observed after incubation of muscle tissues with stalk extracts at a final dose of 5 mg/ml, where there was a statistically non-significant reduction in the levels of aldehydic derivatives of OMP (by 2 %, $p > 0.05$) compared to the untreated samples (12.43 ± 0.13 nmol/mg protein *vs*. 12.68 ± 0.16 nmol/mg protein). Using extracts derived from both roots and stalks of CM at a final dose of 2.5 mg/ml after incubating *in vitro* with muscle tissue, we observed a statistically non-significant reduction in the levels of aldehydic derivatives of OMP (by 2.6 %, $p > 0.05$ and 12.23 %, $p > 0.05$, respectively), compared to the untreated controls (12.35 ± 0.11 nmol/mg protein *vs*. 12.68 ± 0.16 nmol/mg protein for root extracts; 12.23 ± 0.21 nmol/mg protein *vs*. 12.68 ± 0.16 nmol/mg protein for stalk extracts) (Fig. 3).

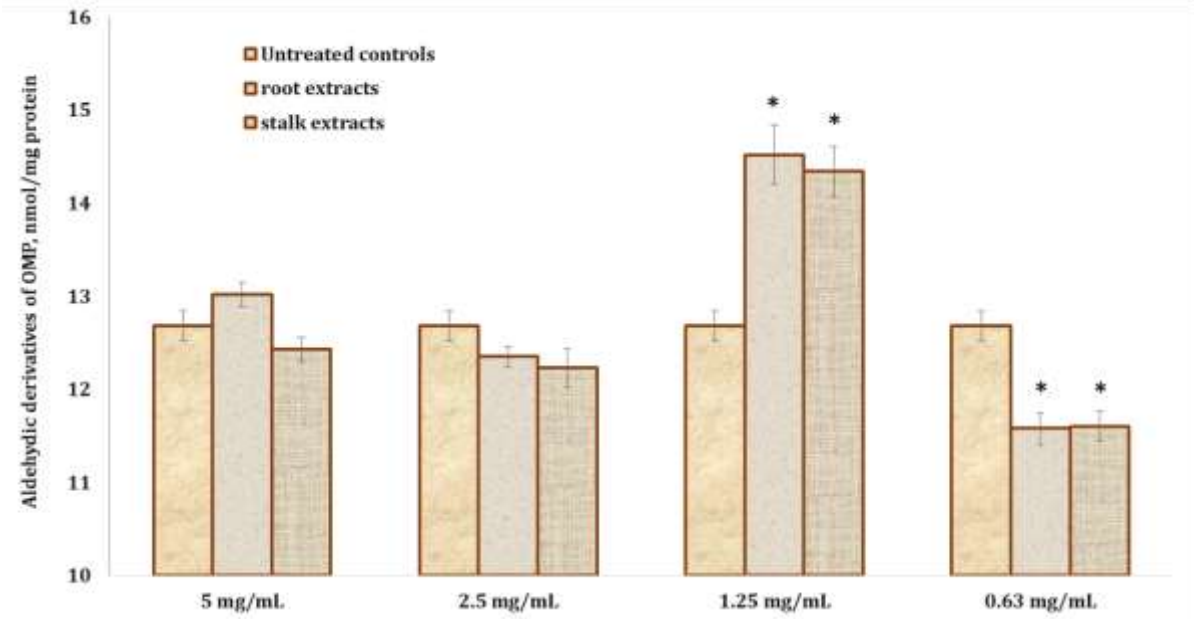

Fig. 3. The content of aldehydic derivatives as a biomarker of oxidatively modified proteins in the muscle tissue of rainbow trout after *in vitro* incubation with extracts in different doses (5 mg/mL, 2.5 mg/mL, 1.25 mg/mL, 0.63 mg/mL) derived from stalks and roots of great celandine (M ± m, n = 8).

*– changes are statistically significant ($p < 0.05$) in relations untreated controls *vs*. extracts derived from roots and stalks of CM.

Other results were obtained after incubation of muscle tissue with extracts derived from both roots and stalks of CM at a final dose of 1.25 mg/ml, where there was a statistically significant increase in levels of aldehydic derivatives of OMP (by 14.5 %, $p < 0.05$ and 14.34%, $p < 0.05$, respectively), compared to the untreated samples (14.52 ± 0.32 nmol/mg protein *vs*. 12.68 ± 0.16 nmol/mg protein for root extracts; 14.34 ± 0.27 nmol/mg protein *vs*. 12.68 ± 0.16 nmol/mg protein for stalk extracts). The trend was different when we incubated *in vitro* muscle tissue of rainbow trout with extracts derived from both root and stalk extracts at a final dose of 0.63 mg/ml. We observed a statistically significant reduction in the levels of aldehydic derivatives of oxidatively modified proteins (by 8.7%, $p < 0.05$ and 8.5%, $p < 0.05$, respectively), compared to the untreated controls (11.58 ± 0.17 nmol/mg protein *vs*. 12.68 ± 0.16 nmol/mg protein for root extracts; 11.6 ± 0.16 nmol/mg protein *vs*. 12.68 ± 0.16 nmol/mg protein for stalk extracts) (Fig. 3).

By incubating *in vitro* the muscle tissue of rainbow trout with root extracts at a final dose of 5 mg/ml, we observed a statistically non-significant increase in levels of ketonic derivatives of oxidatively modified proteins by 12.8 % ($p > 0.05$) compared to the untreated samples (13.99 ± 0.52 nmol/mg protein *vs*. 12.4 ± 0.62 nmol/mg protein). A different trend was noted after incubating the muscle tissue with stalk extracts at a final dose of 5 mg/ml, as there was a statistically significant reduction in the levels of ketonic derivatives of OMP by 9.4 % ($p < 0.05$) compared to the untreated samples (11.24 ± 0.47 nmol/mg protein *vs*. 12.4 ± 0.62 nmol/mg protein). Similarly, yet statistically non-significant reductions in ketonic derivatives of OMP were observed after *in vitro* incubation of muscle tissue with extracts derived from both roots and stalks at a final dose of 2.5 mg/ml, i.e. by 7.3 % ($p > 0.05$) and 11.5 % ($p > 0.05$), respectively, compared to the control (11.49 ± 0.46 nmol/mg protein *vs*. 12.4 ± 0.62 nmol/mg protein

for root extracts; 10.98 ± 0.53 nmol/mg protein *vs*. 12.4 ± 0.62 nmol/mg protein for stalk extracts) (Fig. 4).

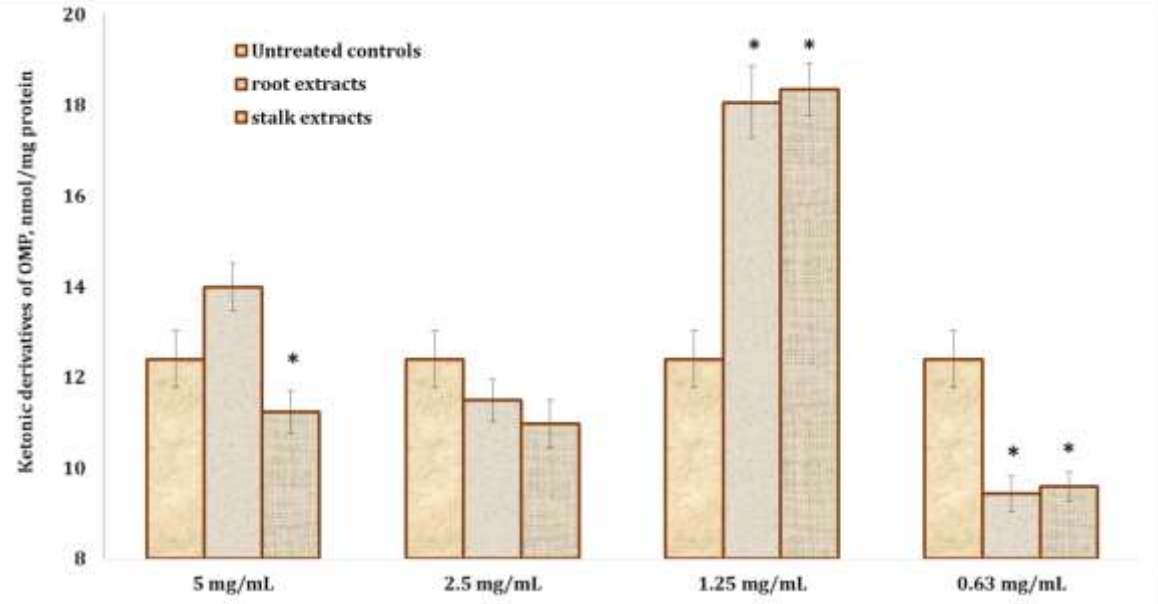

Fig. 4. The content of ketonic derivatives as a biomarker of oxidatively modified proteins in the muscle tissue of rainbow trout after *in vitro* incubation with extracts in different doses (5 mg/mL, 2.5 mg/mL, 1.25 mg/mL, 0.63 mg/mL) derived from stalks and roots of great celandine (M ± m, n = 8).

*– changes are statistically significant ($p < 0.05$) in relations untreated controls *vs*. extracts derived from roots and stalks of CM.

Applying a final dose of 1.25 mg/ml of both root and stalk extracts to muscle tissue after incubation *in vitro*, we recorded statistically significant increases in levels of ketonic derivatives of OMP by 45.6 % ($p < 0.05$) and 48 % ($p < 0.05$), respectively, compared to the untreated control (18.6 ± 0.8 nmol/mg protein *vs*. 12.4 ± 0.62 nmol/mg protein for root extracts; 18.35 ± 0.58 nmol/mg protein *vs*. 12.4 ± 0.62 nmol/mg protein for stalk extracts). A different trend was observed after *in vitro* incubation of trout muscle tissue with extracts derived from both roots and stalks of CM at a final dose of 0.63 mg/ml, where there was a statistically significant reduction in the levels of ketonic derivatives of OMP by 24 % ($p < 0.05$) and 22.6 % ($p < 0.05$), respectively, compared to the untreated control (9.43 ± 0.39 nmol/mg protein *vs*. 12.4 ± 0.62 nmol/mg protein for root extracts; 18.35 ± 0.58 nmol/mg protein *vs*. 9.6 ± 0.32 nmol/mg protein for stalk extracts) (Fig. 4).

Analyzing the total antioxidant capacity (Fig. 5) after incubation of trout muscle tissue with both root and stalk extracts of CM at a final dose of 5 mg/ml, we observed a statistically non-significant reduction in TAC levels (by 8 %, $p > 0.05$ and 6.7 %, $p>0.05$, respectively), compared to the untreated samples (61.69 ± 1.77 % vs. 67.07 ± 1.16 % for root extracts; 62.59 ± 0.58 % vs. 67.07 ± 1.16 % for stalk extracts). Lowering the dose of extracts to 2.5 mg/ml, we recorded a statistically significant reduction in TAC level by 12.5 % ($p < 0.05$) after in vitro incubation of muscle tissue with root extracts compared to the untreated controls (58.7 ± 2.16 % vs. 67.07 ± 1.16 %) (Fig. 5).

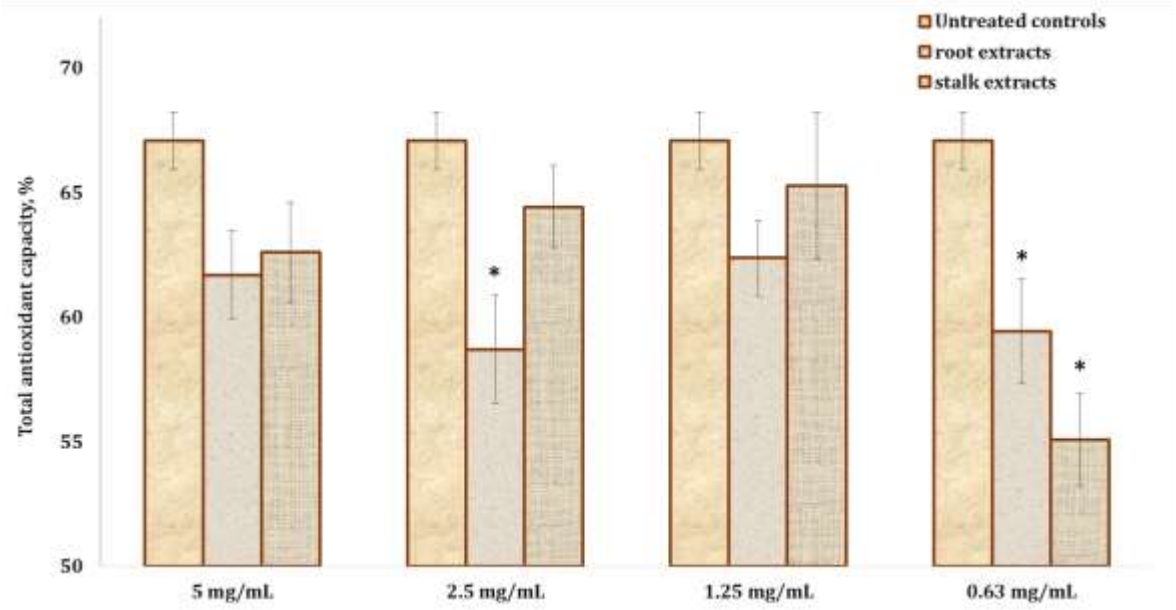

Fig. 5. The total antioxidant capacity in the muscle tissue of rainbow trout after *in vitro* incubation with extracts in different doses (5 mg/mL, 2.5 mg/mL, 1.25 mg/mL, 0.63 mg/mL) derived from stalks and roots of great celandine (M ± m, n = 8).

*– changes are statistically significant ($p < 0.05$) in relations untreated controls *vs*. extracts derived from roots and stalks of CM.

We noted a similar yet statistically non-significant reduction in TAC level after incubating muscle tissue with stalk extracts at a final dose of 2.5 mg/ml (by 4 %, $p > 0.05$) compared to the untreated controls (64.42 ± 1.65 % *vs*. 67.07 ± 1.16 %). Using a dose of both root and stalk extract at 1.25 mg/ml, we recorded a statistically non-significant reduction in total antioxidant capacity after incubation with muscle tissue (by 7 %, $p > 0.05$ and 2.7 %, $p > 0.05$, respectively), compared to the untreated controls (62.36 ± 1.52 % *vs*. 67.07 ± 1.16 % for root extracts; 63.26 ± 2.94 % *vs*. 67.07 ± 1.16 % for stalk extracts). By lowering the final dose of both root and stalk extracts of CM to 0.63 mg/ml and incubating them with trout muscle tissue, we observed a statistically significant reduction in TAC levels by 11.4 % ($p < 0.05$) and 17.9 % ($p < 0.05$), respectively, compared to the untreated controls (59.42 ± 2.12 % *vs*. 67.07 ± 1.16 % for root extracts; 55.09 ± 1.83 % *vs*. 67.07 ± 1.16 % for stalk extracts) (Fig. 5).

In our previous study [35], we also demonstrated the *in vitro* antioxidant activity of CM extracts using the muscle tissue of rainbow trout (*Oncorhynchus mykiss* Walbaum). Our results revealed that extracts derived from CM collected from both urban and rural areas statistically significantly reduced the levels of aldehydic derivatives of OMB (by 18.8 %, $p < 0.05$). The analysis of the levels of ketonic derivatives of OMP showed that extracts of CM collected from both urban and rural areas statistically significantly decreased the levels of ketonic derivatives of OMP (by 20.6 % and 21.5 %, respectively, for urban areas, as well as by 26.7 % and 12.5 % for rural areas). Lower levels of lipid peroxidation biomarkers were observed after incubation with stalk extracts, while those collected from rural areas showed the lowest result. Root extracts of CM collected from urban and rural areas increased TBARS levels. Analysis of oxidatively modified protein levels in the blood of rainbow trout after *in vitro* incubation with root and stalk extracts demonstrated that extracts can inhibit the production of oxidative carbonyls by scavenging free radicals [33].

We also evaluated the effects of extracts derived from stalks and roots of CM collected from rural and urban agglomerations on levels of oxidatively modified pro-

teins in the erythrocyte suspension of rainbow trout after incubation with the extracts *in vitro* [34]. When rainbow trout erythrocytes were incubated with root and stalk extracts obtained from CM plants, the OMP level was significantly decreased. Although the precise mechanisms responsible for the effects of CM on OMP levels remain to be explored more, they might be related to some components such as catechins, flavonols, and phenolic acids of plant pigments. Polyphenols and alkaloids are diverse groups of naturally occurring compounds with different biological functions. Many polyphenols such as catechins can regulate antioxidant reactions.

Based on the broad spectrum of its biological activities, CM has been studied extensively in the medical and veterinary fields. Also, protoberberine compounds derived from CM possess anticancer and antiproliferative activities. The effect of a protoberberine-rich fraction (BBR) of CM on endometriosis regression was investigated by Warowicka and co-workers [37]. BBR was prepared from an ethanolic extract of dry plant CM. Rats with confirmed endometriosis were treated with BBR administered orally (1 g/kg) for 14 days. The metabolomic pattern was compared before and after the protoberberine treatment. The performed analysis showed significant changes in the concentrations of metabolites that are involved in energy homeostasis, including glucose, glutamine, and lactate. Histopathological studies showed no recurrence of endometriosis loci after treatment with BBR. The results of the study found that BBR treatment prevents the recurrence of endometriosis in rats [37].

In the study of Zou and co-workers [40], larvicidal activity and insecticidal mechanism of CM on *Lymantria dispar* were investigated using bioassays, *in vitro* and *in vivo* enzyme activity assays, determination of the nutritional index, and gene transcription analysis. The results showed that alkaloids are the main insecticidal ingredients in CM. Among the five isoquinoline alkaloids, coptisine was present at the highest concentration (1624.23 mg/L), while tetrahydrocoptisine showed the lowest concentration (0.47 mg/L). Both the crude extract of CM (CECm) and the total alkaloids of CM (TACm) possessed a potent insecticidal activity toward *L. dispar* larvae. TACm had significant effects on the relative consumption rate, efficiency of conversion of digested food into growth, approximate digestibility, and approximate digestibility of *L. dispar* larvae. Enzyme activity assays suggested that both CECm and TACm displayed their strongest inhibitory activity to *in vitro* glutathione S-transferase (GST) and acetylcholinesterase (AChE), and showed the weakest inhibition of *in vitro* carboxylesterase (CarE). Moreover, CECm and TACm affected the *in vivo* activities of five enzymes. The *in vivo* activities of AChE and CarE in *L. dispar* larvae were inhibited significantly by CECm and TACm. Also, qRT-PCR analysis revealed that the transcription of the five enzymes was also affected by TACm. Thus, alkaloids in CM showed prominent toxicity to *L. dispar* by reducing food intake, influencing nutritional indices, and affecting the activity and mRNA transcription of detoxifying and protective enzymes [40].

CM was not hepatotoxic in Wistar rats, in a 4-week feeding experiment. Mazzanti and co-workers [21] have evaluated the effects on the liver function of a CM extract, obtained from the herbal material responsible for one case of hepatotoxicity. Experiments were performed in Wistar rats, after oral administration of doses corresponding to 1.5 and 3g/(kg day) of herbal drug, for 2 or 4 weeks. Blood samples were collected to perform biochemical analysis, whereas liver samples were used for histomorphological and immunohistochemical examination along with the determination of oxidative stress parameters. No significant modification in animal body weight, food consumption, enzyme activities, hepatic histomorphology, and malonic dialdehyde (MDA) formation, at either time or dosage level. Conversely, CM induced a slight but significant decrease in reduced glutathione (GSH) levels and superoxide dismutase (SOD) ac-

tivity, especially at the high dose. The study of these researchers suggested that CM, at doses about 50 and 100 times higher than those generally used in humans, does not alter hepatic function. However, the reduction in GSH levels and SOD activity suggests particular attention to the use of CM or its preparations in situations (pharmacological treatments, physio-pathological conditions, etc.) that can compromise liver function [21].

CM exhibited anti-tumor and anti-oxidative stress potential against artificially induced hepatic tumors and hepatotoxicity in rats. Banerjee and co-workers [2] have analyzed the efficacy of homeopathic *Chelidonium majus* (Chel) 30C and 200C in amelioration of experimentally induced hepatotoxicity in rats. Rats were randomized into six sub-groups: negative control; negative control + ethanol; positive control; positive control + ethanol group; Chel 30; Chel 200. Rats were sacrificed at days 30, 60, 90, and 120; various toxicity biomarkers and pathological parameters were evaluated. Gelatin zymography for determination of metalloproteinases activity and Western blot of p53 and Bcl-2 proteins were also employed. Results of these researchers revealed that chronic feeding of p-dimethyl amino azo benzene (p-DAB) and phenobarbital (PB) elevated the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), triglyceride, cholesterol, creatinine, and bilirubin and lowered the levels of glutathione (GSH), glucose-6-phosphate dehydrogenase (G-6-PD), catalase and HDL-cholesterol. There were statistically significant modulations of these parameters in the treated animals, compared to positive controls. In both treated groups, there was downregulation of metalloproteinases, p53, and Bcl-2 proteins compared to over-expression in the positive control groups [2].

Alkaloids from CM and their inhibitory effects on LPS-induced NO production in RAW264.7 cells were studied by Park and co-workers [26]. A new alkaloid, methyl 2'-(7,8-dihydrosanguinarine-8-yl)acetate (1), together with six known alkaloids, stylopine (2), protopine (3), norchelidonine (4), chelidonine (5), berberine (6), and 8-hydroxydihydrosanguinarine (7), were isolated from CM. The anti-inflammatory activity of the isolates was examined for their inhibitory effects on LPS-induced NO production in macrophage RAW264.7 cells. Among them, compounds 5 and 7 showed strong inhibitory activities toward the LPS-induced NO production in macrophage RAW264.7 cells with IC_{50} values of 7.3 and 4.5 μM, respectively. In addition, compounds 5 and 7 inhibited the inductions of COX-2 and iNOS mRNA in dose-dependent manners, indicating that these compounds attenuated the syntheses of these transcripts at the transcriptional level [26].

Mikołajczak and co-workers [22] have evaluated analgesic activity ("hot plate" test), anti-inflammatory activity (carrageenan-induced paw edema), and locomotor activity in rats under the influence of three fractions of CM herb extract: full water extract (FWE), protein enriched fraction (PEF), and a non-protein fraction (NPF). Effects of the fractions on the level of chosen cytokines and their mRNA levels were also assessed using lipopolysaccharide (LPS) administration as a proinflammatory cue. All fractions and diclofenac did not affect the locomotor activity of rats in comparison with the control group. FWE and PEF three hours after administration showed statistically significant analgesic activities comparable to morphine ($p < 0.05$). A slight reduction in rat paw edema was observed after three (comparable with diclofenac) and six hours in the NPF group. FWE revealed a statistically significant pro-inflammatory effect after three hours in comparison with the control group. Peripheral IL-1 and IL-4 cytokine concentrations were reduced under FWE and NPF, PEF fractions. The combination of FWE, PEF, and NPF together with LPS showed only the effects of LPS. We suggest that pro-

tein-enriched fraction (PEF) produced centrally mediated (morphine-like) analgesic action, whereas the anti-inflammatory potential was shown only after LPS-induced inflammation. The precise mechanisms involved in the production of anti-nociceptive and anti-inflammatory responses of studied fractions are not completely understood, but they may be caused rather by the presence of protein more than an alkaloids-enriched fraction [22].

Tetrahydrocoptisine (THC) is one of the main active components of CM and has been described to be effective in suppressing inflammation. The protective effect of THC on LPS-induced acute lung injury (ALI) in rats was evaluated by Li and co-workers [16]. These researchers found that in vivo pretreatment with THC to rats 30 min before inducing ALI by LPS markedly decreased the mortality rate, lung wet weight to dry weight ratio, and ameliorated lung pathological changes. Meanwhile, THC significantly inhibited the increase of the amounts of inflammatory cells, total protein content, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) secretion in the bronchoalveolar lavage fluids (BALFs). Furthermore, THC inhibited myeloperoxidase (MPO) accumulation in lung tissue and alleviated TNF-α and IL-6 production in serum. Additionally, immunohistochemistry showed that THC efficiently reduced nuclear factor-kappa B (NF-κB) activation by inhibiting the translocation of NF-κBp65. Thus, THC possesses a protective effect on LPS-induced ALI through inhibiting NF-κB signaling pathways, which may involve the inhibition of the pulmonary inflammatory process [16].

Treatment with CM extract has natriuretic and antidiuretic effects against cadmium-induced nephrotoxicity in rats. The natriuretic and antidiuretic effects of methyl alcohol extracts of CM leaves in the kidneys of cadmium-intoxicated rats were evaluated in the study of Koriem and co-workers [14]. There was a decrease in kidney weight and serum electrolytes, but an increase in urinary volume, excretion of electrolytes, serum urea, and creatinine, after 9 weeks of cadmium chloride intoxication. Treatment of CM methyl alcohol extract for 10 weeks starting 1 week before cadmium administration shifted the above parameters towards the normal values. These results were supported by molecular and histological investigations [14].

Conclusions. Our studies have revealed that the use of extracts derived from CM at a final dose of 5 mg/ml and 2.5 mg/ml resulted in a statistically significant increase of lipid peroxidation biomarkers (TBARS levels) in the muscle tissue of rainbow trout in vitro incubation. The final dose of 1.25 mg/ml caused statistically significant increases in the levels of aldehydic and ketonic derivatives of oxidatively modified proteins, and this was reflected when measuring the levels of total antioxidant capacity (TAC). On the other hand, the use of extracts at a final dose of 0.63 mg/ml derived from both roots and stalks of CM resulted in statistically significantly reduced levels of TBARS, as well as aldehydic and ketonic derivatives of OMP in the muscle tissue of rainbow trout after in vitro incubation. This may suggest that the presence of secondary metabolites such as alkaloids and polyphenols, among others, at such doses may induce such biological responses. These results demonstrated that there is a further need to search for an alternative dose of CM extracts for exhibiting therapeutic effects. This could find application in veterinary and other medical fields.

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ДОЗОЗАЛЕЖНІ ЗМІНИ БІОМАРКЕРІВ ОКИСНЕННЯ ЛІПІДІВ ТА БІЛКІВ У М'ЯЗОВІЙ ТКАНИНІ РАЙДУЖНОЇ ФОРЕЛІ (ONCORHYNCHUS MYKISS WALBAUM) ПІСЛЯ ІНКУБАЦІЇ IN VITRO З ЕКСТРАКТАМИ ЧИСТОТІЛУ ВЕЛИКОГО (CHELIDONIUM MAJUS L.)

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Відповідно до наших попередніх досліджень, ми продовжуємо оцінювати антиоксидантний потенціал представників родини Papaveraceae, зібраних у північній частині Польщі, на моделі м'язової тканини райдужної форелі. Тому у цьому дослідженні, для оцінки антиоксидантної активності екстрактів чистотілу великого використовували біомаркери окиснювального стресу [реактивні речовини, які взаємодіють з 2-тіобарбітуровою кислотою (TBARS), альдегідні та кетонові похідні окиснювально-модифікованих білків (OMP) та загальна антиоксидантна активність (TAC)]. У дослідженні використовували екстракти, отримані з стебел і коренів чистотілу великого (Chelidonium majus L., CM) у кінцевій дозі 5 мг/мл, 2,5 мг/мл, 1,25 мг/мл та 0,63 мг/мл. У цьому дослідженні in vitro використовували гомогенат м'язової тканини, отриманих з форелі. Як позитивний контроль використовували фосфатний буфер. Після інкубації суміші при 25°C протягом 120 хв при безперервному перемішуванні, проби використовували для біохімічних досліджень. Наші дослідження показали, що застосування екстрактів у кінцевій дозі 5 мг/мл та 2,5 мг/мл призводило до статистично істотного підвищення рівня біомаркерів перекисного окиснення ліпідів (рівня TBARS) у м'язовій тканині райдужної форелі. Кінцева доза екстракту 1,25 мг/мл викликала статистично істотне підвищення рівнів альдегідних і кетонових похідних OMP, що відображалося при вимірюванні рівнів TAC. З іншого боку, використання екстрактів у кінцевій дозі 0,63 мг/мл, отриманих як з коренів, так і зі стебел CM, призвело до статистично істотного зниження рівнів TBARS, а також альдегідних та кетонових похідних OMP у м'язовій тканині райдужної форелі після інкубації in vitro. Порівняння цих результатів показало, що екстракти CM можуть ефективно інгібувати продукцію окиснювально модифікованих білків шляхом поглинання вільних радикалів. Швидше за все, за цей ефект відповідальні вторинні метаболіти CM, тобто поліфеноли. Скринінг видів родини Papaveraceae на інші види біологічної активності, у тому числі антиоксидантної, має важливе значення і може бути ефективним при пошуку профілактичних заходів у патогенезі деяких захворювань, а також при профілактиці та лікуванні деяких патологічних порушень у ветеринарії та медицині.

Ключові слова: райдужна форель (Oncorhynchus mykiss Walbaum), м'язова тканина, окиснювальний стрес, реактивні речовини, що взаємодіють з 2-тіобарбітуровою кислотою (TBARS), альдегідні та кетонові похідні окиснювально-модифікованих білків (OMP).