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I. Summary

During these stages, a series of activities were carried out in order to evaluate the anti-fibrotic potential of cyclodextrin-associated chrysin-based complexes (CD-RAMEB and HPBCD) enriched with Corylus avellana gemotherapeutic extract (CAG-CHR / Cyclo). In Activity 2.1, the potential of the CAG-CHR / RAMEB and CAG-CHR / HPBCS complexes to interact with the TGFβ signaling pathway involved in stellar liver cell (HSC) activation was evaluated in vitro. Following the analysis of TGF-β fibrotic markers and SMAD molecules, their expression was reduced and the TGF-β1 / SMAD signaling pathway was inhibited, with better results obtained for the RAMEB complex. In activity 2.2, the in vitro anti-fibrotic potential of CAG-CHR / Cyclo complexes was evaluated by investigating the expression of apoptotic markers. CAG-CHR / RAMEB induced HSC apoptosis by inhibiting Bcl-2 and stimulating 3/8/9 caspase expression and cleavage. Based on the in vitro results obtained in activity 2.3, the CAG-CHR / RAMEB complex was selected for in vivo experiments. In the next part of the step, in vivo experiments evaluating CAG-CHR / RAMEB were performed. In Activity 2.4, the experimental design of a CCl_4-induced liver fibrosis model in diabetic mice was performed. CD1 adult male mice with streptozotocin diabetes and CCl_4 liver fibrosis were used. After obtaining mice with diabetes and liver fibrosis, they were given orally CAG, CHR / Cyclo, CHR and CAG-CHR / Cyclo. In Activity 2.5, the anti-fibrotic activity of CAG-CHR / Cyclo was assessed by hematological and biochemical analyzes. Activity 2.6 involved the histopathological analysis of liver biopsies from mice included in the experiment to evaluate the anti-fibrotic activity of the complexes. The samples from the treated mice showed a histo-architecture close to healthy control and less insular collagen, which suggests the effectiveness of the treatment. In activity 2.7, the in vivo antioxidant activity of CAG-CHR / Cyclo was evaluated by analyzing the expression of Nrf2, HemOX1, MMP2 and MMP9 proteins in liver tissue by Western blot. Enzymatic activity of metalloproteinases (MMPs) was also determined by the zymography method. Activity 2.8 involved the evaluation of the in vivo anti-fibrotic activity of the complexes by analyzing the TGFβ signaling pathway. Following analysis of TGF-β expression and SMAD molecules, the TGF-β1 / SMAD signaling pathway was inhibited. The last activity 2.9, involved the dissemination of the results in the form of ISI and abstract articles at national and international conferences.

II. Scientific and technical description

Activity 2.1 In vitro evaluation of CAG-CHR / Cyclo anti-fibrotic activity by TGFβ signaling pathway analysis

In activity 2.1, the in vitro evaluation of the anti-fibrotic activity of the CAG-CHR / RAMEB and CAG-CHR / HPBCD complexes was performed by analyzing the expression of markers (TGF-β1, SMAD 2/3) in the TGF-β signaling pathway. , both at the gene and protein level. The expression of the fibrotic marker TGF-β1 in stellate liver cells (HSC) from the LX2 cell line was analyzed. In latent HSCs, TGF-β1 expression was reduced in protein (Fig. 1a) and gene (Fig. 1b), but upon activation by stimulation with TGF-β1, the expression of this marker was increased (Fig. 1B). Treatment with both complexes investigated, CAG-CHR / Cyclo, significantly reduced TGF-β1 expression compared to activated control, indicating the efficacy of the complexes in inhibiting the TGF-β1 / SMAD signaling pathway and, implicitly, HSC activation. The CAG-CHR / RAMEB complex has been shown to be more effective than CAG-CHR / HPBCD in inducing the reversal of activated HSC cells to a latency state. The results were also confirmed in tgf-β1 gene expression. Following the administration of the two types of complexes, the level of expression was statistically significantly lower than the activated control, with a higher level of statistical significance in the case of the complex with RAMEB ($p <0.01$) compared to HPBCD ($p <0.05$).

The cellular localization of the SMAD 2/3 phosphorylated complex was also analyzed by immunofluorescent labeling (Fig. 2).

In the case of HSC control, the protein complex was located in the cytoplasm, throughout the cell, which confirms that this pathway is not activated in latent HSC. Following activation with TGF-β1, the complex was translocated to the nucleus, indicating that the TGF-β1 / SMAD signaling pathway was activated. Treatment with CAG-CHR / CD inhibited the translocation of the complex into the nucleus, an effect better observed in the case of the RAMEB complex. This suggests the superiority of the CAG-CHR / RAMEB complex and the efficiency of the RAMEB in releasing CAG and CHR from the complex. The complexes also acted at the level of gene expression, at the level of the TGF-β1 / SMAD signaling pathway by reducing the expression of smad2, but especially smad3, but not statistically significant, because the effect was best observed at the location of the SMAD 2/3 complex. . The complexes also induced the expression of smad7, a molecule that has an inhibitory role on the TGF-β1 / SMAD signaling pathway (Fig. 3). At this level, too, the RAMEB complex has been shown to be more effective in releasing CAG and CHR which have induced a statistically significant increase in smad expression7.

Activity 2.2 In vitro evaluation of CAG-CHR / Cyclo anti-fibrotic activity by apoptosis analysis

In this activity, the antifibrotic potential of CAG-CHR / Cyclo was evaluated in vitro by analyzing the expression of apoptotic markers (bcl-2, caspase 3/8/9) at the genetic and protein level. In liver fibrosis, HSCs acquire a proliferative profile and their number increases well above the normal number. During liver tissue regeneration, activated HSCs either go through a process of reversal to latency or enter apoptosis and a normal number of HSCs in the liver are restored. BCL-2 is an anti-apoptotic factor, the expression of which indicates signs of pro-cell survival. Caspases 3, 8, 9 represent the effectors of apoptosis, which are activated by cleavage. By marking the nuclei with DAPI (blue) and caspase 3 cleaved with antibody coupled with Alexa Fluor 546 (red), these images were observed under the fluorescence microscope (Fig. 4). LX2 cells were activated by TGF-β1 treatment. In latent and activated HSCs, the expression of cleaved caspase 3 was not observed because these cells are not in the process of apoptosis under normal conditions. Treatment with the two complexes induced apoptosis activation in aHSC, and the presence of the cleaved form of caspase 3 was observed. cleavage of caspase 3 is better highlighted (Fig. 4D).

The expression of apoptotic markers at the gene level was also examined (Fig. 5). In HSCs treated with TGF-β1, increased bcl-2 expression was observed compared to latent control, which confirms that HSC secretes anti-apoptotic factors that allow them to survive and remain active. In CAG-CHR / Cyclo-treated HSCs, bcl-2 expression is reduced, indicating the effect of ADSC-secreted molecules in reducing cell survival. The effect on the apoptosis process is better observed at the protein level, as only cleaved forms of caspases induce apoptosis. However, an increase in the expression of caspases in the case of treatment with the investigated complexes was also observed at the genetic level, which indicates a stimulation of this pathway by treatment. The superiority of the CAG-CHR / RAMEB complex was best observed in the case of caspase 3 and 8, where a greater increase in their expression level is induced compared to the level induced by CAG-CHR / HPBCD. In the case of caspase 9, both treatments induce a similar response in terms of the level of expression, confirming that the two types of complexes can act as possible anti-fibrotic treatments.

Activity 2.3 Selection of the best performing CAG-CHR / Cyclo for in vivo experiments

Based on the in vitro results, by evaluating the anti-fibrotic activity of CAG-CHR / Cyclo by analyzing the TGFβ signaling pathway and apoptosis, the best results were obtained in the case of CAG-CHR / RAMEB. This complex has been shown to be more effective in releasing CAG and CHR that induced HSC reversal and induced apoptosis of activated cells. CAG-CHR / RAMEB further reduced the expression of fibrotic markers and induced a more pronounced response in apoptosis of cells.

Activity 2.4 In vivo experimental design on CCl4-induced liver fibrosis in diabetic mice

The experimental protocol was approved by the Research Ethics Committee of the Western University Vasile Goldis (152 / 02.10.2019).

CD1 male mice from the Vasile Goldiș Western University bio-base in Arad were used for the experiment. Mice were injected, ip, with a single dose of streptozotocin (STZ; 65 mg · kg-1 body weight), solubilized in citrate buffer (50 mM, pH 4.5) to induce diabetes. Blood glucose levels were measured after 4 hours of starvation using a glucometer. Following STZ administration, mice with a blood glucose level greater than 2.5 g · l-1 for two consecutive weeks were considered mice with type 2 diabetes and included in the study. Animals with confirmed diabetes were treated intraperitoneally (ip) with CCl_4 dissolved in olive oil (20% v / v, 2 ml / kg), twice a week for 7 weeks, and slaughtered at seventy-two hours. after the last injection to confirm liver fibrosis (Lot 2). Spontaneous resolution of hepatic fibrosis was investigated in diabetic animals treated with CCl4 after two weeks of recovery (Lot 3). To evaluate the antifibrotic effect of Coryllus avelana-nanocomplex CHR / cyclo gemotherapeutic extract, treatment was started at the end of the 7 weeks of CCl4 treatment, using the following daily gavage administration for 14 consecutive days: Coryllus avelana-crisine gemotherapeutic extract / cyclodextrins (CAG-CHR / Cyclo - Lot 4), gemotherapeutic extract Coryllus avelana (CAG - Lot 5), chrysin / cyclodextrin nanocomplex (CHR / Cyclo - Lot 6) and pure chrysin (CHR - Lot 7). All products contain 100 mg / kg of chrysin. Mice belonging to group 1 (control -a.sanatos, b.diabetic), 2 (fibrotic mice) and 3 (de novo resolution of fibrosis) were administered the vehicles of the treated groups. Animals were sacrificed 24 hours under anesthesia after the last dose (lots 1, 3, 4, 5, 6, 7).

Activity 2.5 Evaluation of the anti-fibrotic activity of CAG-CHR / Cyclo by hematological and biochemical analyzes

The analysis of hematological parameters was performed on an automatic hematology analyzer (2900 VetPlus). There is a significant increase in the total number of leukocytes in diabetic mice and experimental groups compared to the healthy control, but at the same time a significant decrease in groups with experimentally induced fibrosis compared to diabetic control.

Analysis of serum biochemical parameters was performed on an automated biochemistry analyzer (BS-120). There is a significant increase in hepatic (TGO, TGP) and renal (Creatinine) markers in diabetic mice and experimental groups compared to the healthy control, and a decrease in LDH. The treated groups had a significant improvement compared to the diabetic control.

Activity 2.6 Evaluation of the anti-fibrotic activity of CAG-CHR / Cyclo by histopathological analyzes

Histological analysis of the liver of the control group indicated a normal lobular architecture with centrolobular vein and cords of radiating hepatocytes, without a proliferation of intralobular connective tissue (Fig.8-V1a) and a slight dilation of sinusoidal capillaries (Fig.8-V1b). Liver samples from the CCl4 group showed severe changes in morphology, obvious collagen deposition, the formation of pseudolobules and the infiltration of inflammatory cells into the interstitial areas of the liver. Numerous hepatocytes with micro- and macro-vesicular steatosis and sinusoidal capillary congestion are also observed (Fig.8-V2). The presence of hypertrophied perivenular "foamy hepatocytes" with a massive accumulation of microvesicular fat is noticeable. After two weeks of de novo recovery, in the absence of a recovery treatment, there is a significant presence of fibrous tissue and pseudo-lobules, accompanied by infiltrates of inflammatory cells, compared to the CCl4 group (Fig.8-V3). Hypertrophied hepatocytes with foamy cytoplasm are present. In the case of the group of mice treated for 2 weeks with the gemotherapeutic extract Coryllus avelana (Fig.8-V5), chrysin / cyclodextrin nanocomplex (Fig.8-V6), ADSC, after the installation of fibrosis, the fibrotic areas were reduced (insular) , compared to those recorded in the case of the CCl4 group. Inflammatory infiltrates in the perivascular areas also maintain sinusoidal congestion. Hepatic microsteatosis is present in these groups. Mice given the Cotherllus avelana-crisine / cyclodextrin gemotherapeutic extract showed a histo-architecture close to that of the control and over group V1b - diabetic control (Fig.8-V4). The weakest structural recovery was recorded for mice given only pure chrysin (Fig. 8-V7).

The formation of perilobular fibrotic septa and pseudolobules was confirmed in trichrome staining for group V2 (Fig.9-V2) and equally in the group of de novo reversal of fibrosis (Fig.9-V3). Insular collagen is also evident in the administration of pure CHR (fig.9-V7), less in CHR / Cyclo (fig.9-V4), of CAG (Fig.9-V5) where the septa are interrupted and the collagen appears more pericentrolobular , and sporadically in the group treated with CAG-CHR / Cyclo, comparable to healthy and diabetic controls (Fig.9-V6).

Activity 2.7 In vivo antioxidant activity of CAG-CHR / Cyclo

Activity A 2.7 (UB) analyzed the level of lipid peroxidation, reduced glutathione concentration, advanced protein oxidation products, the level of Nrf2 protein expression, HemOxygenase1 as well as the expression and activity of MMP2 and MMP9 metalloproteinases.

CD-1 white mice were used for in vivo experiments and were divided into 6 groups (6-10 individuals per group): group of mice in which diabetes and fibrosis were induced (group 2), group of Diabetes + mice reversion Fibrosis (group 3), group of mice Diabetes + Fibrosis + CAG / CHR / Cyclo (group 4); group of mice Diabetes + Fibrosis + CAG (group 5); group of mice Diabetes + Fibrosis + CHR / Cyclo (group 6); batch Mice Diabetes + Fibrosis + CHR (group 7). Liver tissue sampling was performed 24 hours after exposure, which was stored immediately at -80 ° C until biochemical tests were performed. Total tissue lysate was obtained by homogenization with a sonicator in 0.1 M Tris-EDTA buffer, pH 7.4, at an extraction rate of 1 g / 10 ml. Protein extracts were determined by the Lowry method (Lowry, 1951) using bovine serum albumin as standard.

Malondialdehyde (MDA) as a marker of lipid peroxidation was evaluated by the method described by Del Rio (Del Rio et al., 2003). Fluorescence measurement was performed at Ex520nm / Em549nm wavelengths using the Jasco FP-750 fluorimeter and the results are expressed in nmol MDA / mg protein.

Determination of low glutathione concentration was performed with the Arbor Assays Detectx ™ Glutathione Colorimetric Detection Kit-K006-H1 (Sigma). Proteins from the samples were removed by precipitation with 10% sulfosalicylic acid (SSA). The results were reported in the protein concentration of the samples and were expressed in nmol / mg protein.Nivelul produsilor de oxidare avansată a proteinelor (AOPP) s-a realizat spectrofotometric conform metodei descrise de Witko (Witko şi colab., 1996), folosind ca standard o curbă de etalonare pe bază de cloramină T. Concentraţia de AOPP a fost calculată prin extrapolarea densităţilor optice ale probelor utilizând curba de etalonare obţinută din Cloramină T 100 μM.

The results of in vivo treatment showed that the level of lipid peroxidation decreased significantly in the batches treated with the CAG-CHR / Cyclo, CAG and CHR / Cyclo complexes compared to the group of fibrotic mice. This demonstrates the beneficial effect of CAG-CHR / Cyclo complexes in attenuating CCl4-induced oxidative stress in CD1 mice. Following the analysis of the concentration of GSH and AOPP, their profile is slightly increased in the case of the group treated with the CAG-CHR / Cyclo complex, followed by a significant decrease in the case of the other groups treated with the CAG, CHR / Cyclo and CHR complexes.

Expression of Nrf2, HemOX1, MMP2 and MMP9 proteins in liver tissue

The Western Blot technique was used to highlight changes in protein expression. The method is based on identifying proteins using specific antibodies.

The first step involved preparing the 10% polyacrylamide gel containing the migration gel and the 4.5% concentration gel. After polymerization of the gel, an amount of 50 µg protein / well was loaded into each well. See Blue Plus2 Prestained Standard was used as the molecular weight marker. Protein migration was performed at 90 V constant for 2 hours at 25 ° C in 1X Tris / Glycine / SDS migration buffer. After migration to the polyacrylamide gel, the proteins were transferred to the polyvinylidene difluoride membrane in the presence of the Tis / Glycine / Methanol transfer buffer at 350 mA for 1 hour and 30 minutes.

After transfer, the membrane was washed twice with distilled water and then blocked in blocking buffer (blocking buffer, secondary antibody, chromogenic substrate and antibody dilution solutions as well as washing solution after exposure to antibodies are included in the Invitrogen kit Western Breeze, Chromogenic Immunodetection System). For protein detection, the membranes were incubated for 1 hour with specific primary antibodies (Santa Cruz Biotechnology), followed by a 30 minute incubation with the secondary antibody. Then the chromogenic substrate BCIP (5 bromo-4-chloro-3-indolyl-1-phosphate) / NBT (nitro blue tetrazolium) was added, which was maintained until the bands appeared. These were visualized and quantified with the ImageLab program from BioRad.

Protein expression of Nrf2, HemOX1 and MMPs was analyzed by Western blot. Sample preparation, migration and transfer were performed according to the aforementioned protocol. Anti-MMP2, anti-MMP9, Nrf2 and HemOX1 primary rabbit polyclonal antibodies were used to detect the proteins of interest. Alkaline phosphatase-conjugated rabbit anti-IgG antibodies were used as secondary antibodies.

Nrf2 is a basic leucine-zipper transcription factor (bZIP), which regulates the expression of many genes, which encode antioxidants and detoxifying enzymes by binding to the antioxidant response elements (AREs) found in the promoters of these genes. Nrf2 increases hemoxygenase 1, leading to an increase in phase II enzymes in vitro.

Hemoxygenases (HO) are essential enzymes that degrade heme into carbon monoxide (CO), biliverdin and free iron with anti-inflammatory and anti-apoptotic properties.

Figure 2 shows the profile and densitometry of the results obtained in the case of protein expression Nrf-2, HemOX1, MMP2, respectively MMP9 following in vivo treatment with various complexes. The level of Nrf2 expression decreases significantly after treatment with CAG-CHR / Cyclo, CAG, CHR / Cyclo and CHR complexes in all groups analyzed compared to the group of fibrotic mice. In contrast, HemOX1 expression showed an increasing profile. Protein expression analysis (Figure 2) indicates a significant decrease in MMP9 level compared to the group of fibrotic mice, while MMP-2 expression is maintained in the first batch, followed by a significant decrease in the group treated with CHR complex.

The zymography method was used to determine the enzymatic activity of metalloproteinases (MMPs). This method was performed batchwise on a 4% polyacrylamide concentration gel and a 7.5% polyacrylamide migration gel under denaturing conditions (SDS-PAGE). A 2% gelatin solution was added to the migration gel composition. 80 µg protein / well was loaded for zymography gelatin.

Migration was performed at 4 ° C in 1X electrophoresis buffer at a constant voltage of 90 V. After migration, the gels were washed with distilled water and then incubated twice for 15 minutes with Triton X-100 renaturation buffer to allow the enzymes to regain their enzymatic activity. After renaturation, a new wash with distilled water was performed, and then the gels were incubated with stirring overnight at 37 ° C in 1X incubation buffer. Subsequently, the gel was stained with Coomasie Brillant Blue solution for 1 hour at room temperature. The discoloration of the gels was done with 10% methanol and 10% acetic acid solution in distilled water, twice for 30 minutes, until the bands appeared. The gels were visualized using the Image Lab BioRad program, and the resulting strips were densitometered using the Image J program.

Analyzing Figure 12, it can be seen that the pro-MMP2 and MMP2 activity decreased significantly in all groups treated with the CAG-CHR / Cyclo, CAG, CHR / Cyclo and CHR complexes compared to the group of fibrotic mice. Also, the enzymatic activity of MMP9 decreases significantly in batches treated with CAG-CHR / Cyclo, CHR / Cyclo and CHR complexes.

Statistical analysis

Data were statistically analyzed with GraphPad Prism 8.0.2 using the one-way ANOVA method and the Tukey test. The results were represented as the mean of the replicates (n = 6-10) ± standard deviation and considered statistically significant at a value of $p < 0.05$. All samples were compared with each other and the statistical significance was represented by (*) compared to the Diabetes + fibrosis sample; (#) compared to the Diabetes + Fibrosis reversal test; (&) compared to Diabetes + Fibrosis + CAG-CHR / Cyclo test; (∞) compared to the Diabetes + Fibrosis + CHR / Cyclo test.

References**:**

- Lowry O H, Rosebrough N J, Farr A L & Randall R J. Protein measurement with the Folin phenol reagent. J. Biol. Chem. 193:265, 1951.
- Del Rio D., Pellegrini N., Colombi B., Bianchi M., Serafini M., Torta F., Tegoni M., Musci M., Brighenti F., *Rapid fluorimetric method to detect total plasma malondialdehyde with mild derivatization conditions*, Clin. Chem., 49, 690–692, 2003.
- Witko-Sarsat, V., Nguyen, A.T., Descamp, S., Latsha, B. Microtitre plate assay for phagocyte derived taurine chloroaminea. J. Clin. Lab. Annals 1992, 6: 47-53.

Activity 2.8 Evaluation of the in vivo anti-fibrotic activity of CAG-CHR / Cyclo by analysis of the TGFβ signaling pathway

Analysis of αSMA gene expression revealed a significant overexpression of all experimental groups compared to the healthy control. Induction of fibrosis resulted in a significant additional increase in αSMA gene expression and remained high for 2 weeks after induction of fibrosis compared to the diabetic group ($p < 0.001$). The treated groups had a significant decrease compared to the diabetic group and diabetes-fibrosis ($p < 0.001$) (Fig.13). The same pattern was confirmed for the immunohistochemical expression of αSMA in liver tissues (Fig. 14).

Analysis of Smad gene expression 2 and 3 revealed a significant overexpression of all experimental groups compared to the healthy control. Induction of fibrosis resulted in a significant additional increase in gene expression of Smad 2 and 3 and which remains elevated at 2 weeks after induction of fibrosis compared to the diabetic group ($p < 0.001$). The treated groups had a significant decrease compared to the diabetic group and diabetes-fibrosis ($p < 0.001$) (Fig.15). The same pattern was confirmed for the immunohistochemical expression of Smad 2 and 3 in liver tissues (Fig. 16).

Analysis of TGFβ gene expression revealed a significant overexpression of all experimental groups compared to the healthy control. Induction of fibrosis resulted in a further significant increase in TGFβ gene expression and remained high for 2 weeks after induction of fibrosis compared to the diabetic group ($p < 0.001$). The treated groups had a significant decrease compared to the diabetic group and diabetes-fibrosis, especially for the GAG-CHR / Cyclo group ($p < 0.001$) (Fig.17). The same pattern was confirmed for the immunohistochemical expression of TGFβ in liver tissues (Fig. 18).

Activity 2.9 Dissemination

ISI articles:

- Ciceu, A., Balta, C., Herman, H., Gharbia, S., Ignat, S. R., Dinescu, S., Váradi, J., Fenyvesi, F., Gyongyosi, S., Hermenean A., Costache, M. (2021). Complexation with Random Methyl-β-Cyclodextrin and (2-Hidroxypropyl)-β-Cyclodextrin Enhances In Vivo Anti-Fibrotic and Anti-Inflammatory Effects of Chrysin via the Inhibition of NF-κB and TGF-β1/Smad Signaling Pathways and Modulation of Hepatic Pro/Anti-Fibrotic miRNA. International Journal of Molecular Sciences, 22(4), 1869.

The results were also presented at conferences in the form of oral presentations or posters at national and international conferences.:

- Ignat, S. R., Gharbia, S., Dinescu, S., Balahura, R., Fenyvesi, F., Hermenean, A., & Costache, M. (2021). Human adipose-derived stem cells secretome and hepatocyte growth factor (HGF) exhibit a beneficial effect on hepatic fibrosis reversion. The 45th FEBS Virtual Congress, 3-8 iulie 2021, FEBS OPEN BIO, Vol. 11, p. 346-346. **Poster**

- Ignat, S. R., Dinescu, S., Fenyvesi, F., Váradi, J., Costache, M., Hermenean, A. (2021). *In vitro* biocompatibility of *Corylus avellana* gemmotherapic extract reinforced with chrysin/cyclodextrin nanocomplexes. 42nd Anniversary Symposium Of The Institute Of Cellular Biology And Pathology "Nicolae Simionescu" and 38th Annual Scientific Session Of The Romanian Society For Cell Biology. Virtual. Book of abstracts, p. 39 **Prezentare orală**
- Ignat, S. R., Dinescu, S., Fenyvesi, F., Váradi, J., Costache, M., Hermenean, A. (2021). Antifibrotic effects of *Corylus avellana* gemmotherapic extract reinforced with chrysin/cyclodextrin nanocomplexes on hepatic stellate cells. 42nd Anniversary Symposium Of The Institute Of Cellular Biology And Pathology "Nicolae Simionescu" and 38th Annual Scientific Session Of The Romanian Society For Cell Biology. Virtual. Book of abstracts, p. 38 **Prezentare orală**
- Olah N.K, Pripon-Furtuna, Burtescu R.F., Kelemen I., Chișe E., Turcuș V., Herman H., Ciceu A., Hermenean A, Morpho-anatomical and phytochemical study of the *Corylus avellana* L. species (buds), 42nd Anniversary Symposium Of The Institute Of Cellular Biology And Pathology "Nicolae Simionescu" and 38th Annual Scientific Session Of The Romanian Society For Cell Biology. Virtual. Book of abstracts, p. 37 **Prezentare orală**
- Olah N.K, Burtescu R.F., Chișe E., Herman H., Ciceu A., Balta C, Gharbia S, Rosu M, Mladin B., Hermenean A., Phytochemical study of the gemmotherapic extract from Hazel buds (Corylus avellana L.) enriched with chrysin/cyclodextrins, 42nd Anniversary Symposium Of The Institute Of Cellular Biology And Pathology "Nicolae Simionescu" and 38th Annual Scientific Session Of The Romanian Society For Cell Biology. Virtual. 04-06.11.2021, Poster abstracts, p. 27 **Poster**