children with leukemia and 1 (11.1%) of a patient with a solid tumor.

The median vitamin D supply in children from 0 to 3 years old was 16.6 [9.7–21.7] ng/ml, from 4 to 10 years old – 19.8 [14.7–24.8] ng/ml, from 11 to 18 years old – 16.8 [10.5–17.2] ng/ml. Vitamin D deficiency (less than 20 ng/ml) was detected in 6 (54.6%) children under 4 years old, in 8 (50.0%) children from 4–10 years old and 7 (77.8%) adolescents of 11 years old and older ($p < 0.05$); insufficiency with the level from 20 to 30 ng/ml was detected in 3 (27.3%), 6 (37.5%) and 1 (11.1%) children, and the level of more than 30 ng/ml was found in 2 (18.1%), 2 (12.5%) and 1 (11.1%) children, respectively.

Conclusions in the south of Russia, the majority (86.0%) of children and adolescents with cancer have a 25 (OH) D level of less than 30 ng/ml. Level of 25 (OH) D did not significantly depend on the type of cancer. Adolescents with cancer are at risk for vitamin D deficiency (less than 20 ng/ml).

315 INTEGRATING SAFFRON METABOLOMICS INTO THE TREATMENT OF PEDIATRIC CANCERS

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Natural plant extracts are an important source of antitumor agents, and still provide promising approaches for discovering new drugs. *Crocus sativus* (saffron) is endowed with anticancer, differentiating, antioxidant and genoprotective properties. Its pharmacological properties are attributed to biologically active substances, crocins (CRCs) which are hydrophilic carotenoids. They are glycosyl-esters of the amphiphilic natural carotenoid crocetin (CRT), which exhibits extensive distribution and penetration through lipid bilayers. The hemisynthetic derivative dimethylcrocetin (DMCRT) is similar to CRT and is soluble in many organic solvents. With regards to safety, saffron and its constituents are considered practically non-toxic substances. The current research aims to study the in vitro cytotoxic effect of the natural carotenoids CRCs and DMCRT on a medulloblastoma cell line.

CRCs are diluted to nuclease and protease free water and DMCRT to 10% DMSO.

For the biological assays TE-671 medulloblastoma cells are incubated in 96-well plates at a range of concentrations of CRCs (0.18–22.85 mg/ml) and DMCRT (0.18–11.43 mg/ml) for 24, 48 and 72 hours. Analysis of cell viability is performed with Alamar Blue and MTT viability assays.

CRCs manifest a cytotoxic effect in a dose and time-dependent manner ($p < 0.001$ for exposed cells to any concentration at 24, 48 and 72 hours versus cells not exposed); as their concentration increases, cell viability is reduced for all time points. For the same concentration, as the time of exposure increases, the inhibitory effect is increased. The antiproliferative effect of DMCRT is less pronounced, observed only at concentrations higher than 5.71 mg/ml at 24 and 48 hours and higher than

1.43 mg/ml at 72 hours, whereas for lower concentrations the effect is not statistically significant. IC₅₀ values for each time point are calculated as 3.230, 2.14 and 1.72 mg/ml for

CRCs and 5.9, 5.6 and 3.712 mg/ml for DMCRT at 24, 48, and 72 hours, respectively.

The results of our study could afford the basis of research, regarding the use of natural carotenoids as an alternative solution to the toxicity of retinoids, especially for the vulnerable pediatric population and during pregnancy, while retaining the anticancer properties of retinoids.

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316 INTEGRATING NON PSYCHOACTIVE PHYTOCANNABINOIDS AND THEIR CYCLODEXTRIN INCLUSION COMPLEXES INTO THE TREATMENT OF NEUROBLASTOMA

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The non-psychotropic cannabidiol (CBD), deriving from *Cannabis sativa* is endowed with anticancer, antioxidant and genoprotective properties, which along with its safe profile suggest it as a promising approach in cancer therapy. The low solubility of CBD hampers its therapeutic potential.

Cyclodextrins (CDs) are cyclic oligosaccharides used in pharmaceutical industry to incorporate apolar molecules inside their hydrophobic cavity, increasing their stability, water solubility and bioavailability.

CBD-inclusion complexes with CDs are a good nanomedicine-based formulation strategy to improve CBD's properties. The current research aims to study the potential cytotoxic effect of CBD and CBD-CDs complexes CBD-RMβCD (randomly methylated β-cyclodextrin) and CBD-HPβCD (hydroxypropyl-β-CD) on neuroblastoma cells.

CBD is diluted in 10% DMSO and CBD/CDs solutions are prepared by mixing solid CBD, solid CDs and dH₂O. Phase solubility studies are conducted to determine improvement in CBD's solubility from CDs' addition. For the biological assays SH-SY5Y and BE(2)-M17 neuroblastoma cells are incubated at a range of concentrations (0.03125–4 mg/ml) of CBD, CBD-RMβCD, CBD-HPβCD, RMβCD and HPβCD for 24, 48 and 72 hours. Analysis of cell viability is performed with Alamar Blue viability assay.

CBD's solubility is enhanced in the presence of both CDs. CBD and all CBD/CDs exert significant cytotoxicity in a dose and time-dependent manner; as their concentration and time of exposure increase, cell viability is reduced. The cytotoxic effect is more pronounced in cells exposed to CBD-HPβCD for all concentrations and time-points. RMβCD and HPβCD at the highest concentration of 4 mg/ml exert antitumor action per se. IC₅₀ values are calculated as 0.29, 0.21, 0.06 mg/ml for CBD, 0.046, 0.035, 0.03 mg/ml for CBD-RMβCD, and 0.029, 0.023, 0.021 mg/ml for CBD-HPβCD at 24, 48, and 72 hours, respectively for SH-SY5Y cells. For BE(2)-M17 cells IC₅₀ values are 0.3, 0.27, 0.19 mg/ml for CBD, 0.1655, 0.1644, 0.1534 mg/ml for CBD-RMβCD, and 0.1086, 0.1020, 0.071 for CBD-HPβCD at 24, 48, and 72 hours, respectively.

The results of our study could afford the basis of research regarding the use of natural products and their inclusion complexes as anticancer agents and the shift to targeted therapy with higher efficacy and limited toxicity.

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317

L-ASPARAGINASE ACTIVITY MONITORING IN PAEDIATRIC HEMATOLOGICAL CANCER PATIENTS – CROATIAN EXPERIENCES

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L-asparaginase has been an essential component of paediatric-based multiagent therapy for children diagnosed with haematological cancer.

Drug's effect is based on depletion of asparagine in the circulatory system thus depriving unmatured malignant cells of amino acid. However, some children are faced with silent inactivation or, in worst cases, an allergic reaction to the drug and is recommended to monitor drug activity levels in order to detect these patients and modify the therapy. We had set up the first laboratory for asparaginase-activity testing in Croatia at the Department of Laboratory diagnostics, Children's Hospital Zagreb. Our aim is to present the first experiences in asparaginase monitoring from March 2018 till October 2020 from the 2 pediatric centers (Zagreb and Split).

Children between 1 and 18 years old with diagnosed pediatric acute lymphoblastic leukemia (ALL) or lymphoma (NHL) were included in the prospective L-asparaginase study. Blood samples were collected prior to and during treatment. Serum was separated and frozen prior to shipping. Over 100 samples were processed, among which some were repeatedly measured in order to determine the inter-day precision due to sample thawing. Activities of three commercially available drugs, *E. coli*-derived asparaginase or *Erwinia chrysanthemi* asparaginase or *E.coli* pegylated, PEG-asparaginase were measured in intervals as recommended. Laboratory measurements used plate reader-based indoxine method where L-aspartic beta-hydroxamate (AHA) was a substrate for the enzyme. The reading time was optimized to ensure the best results.

41 patients (38 ALL and 3 lymphoma cases) were included in the study. Among thirty native *E. coli* asparaginase-treated patients, three (10%) of them developed an allergy and four (13%) of them showed silent inactivation.

Patients without hypersensitivity to native drug had serum median trough levels of 281,3 U/L after 48 h. Six patients were treated with *Erwinia* asparaginase; one developed an allergy and none silent inactivation while others had median through levels 90,3 U/L after 48 h. The PEG asparaginase

therapy was given to 4 patients where median trough decline was observed (938,4 U/L, 479,5 U/L, 170,3 U/L for 7, 14 or 21 days, respectively).

Serum samples were stabile after second thawing as were no significant difference in asparaginase level after re-testing. Additionally, the absorbance results showed no significant difference between the 10 minutes reading intervals.

Here we conclude that therapeutic drug monitoring is important for pediatric patients with hematological cancer. The spectrophotometric-based method showed precise performance and has been added to our routine clinical protocols.

318

HAIRY POLYP OF THE NASOPHARYNX – THE IMPORTANCE OF TEAM WORK

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Hairy polyps are rare benign congenital dermoid tumors consisting of both mesodermal and ectodermal elements. They appear as soft, fleshy, pedunculated masses typically located in nasopharynx or oropharynx, usually at birth or soon after birth. Clinical manifestations include respiratory distress, shortness of breath, cyanosis, and difficulties with oral intake. On histology, hairy polyps comprise an outer keratinizing squamous epithelium with adnexal tissue, including hair follicles, and central fibroadipose and cartilaginous tissue. The imaging of choice is magnetic resonance imaging (MRI). MRI is helpful in characterizing the lesions and providing preoperative diagnosis. Further, it delineates the site of origin of these lesions, which can facilitate surgical planning and exclude an intracranial component. This is of the major importance if trans-nasal approach with endoscopy is planned in order to avoid injury to critical structures, such as the internal carotid artery.

We present a case of a 6-week-old full-term female baby presented with intermittent upper airway obstruction. On otolaryngologic examination, an oval, smooth mass was visible in the left side of oropharynx, appeared to descend from the lateral wall of nasopharynx. MRI revealed a lobular mass 10 x 4.8 mm on the left nasopharynx, spanning from torus tubarius to pharyngeal recess. Four days later a complete surgical excision was performed. On histology the lesion demonstrated adnexal skin structures overlying mesenchymal tissue, comprised mostly of fat and cartilaginous nodules. Two smaller parts of 0.4 cm in diameter were covered with stratified squamous epithelium and consisted of muscle cells and seromucous glands. The findings were consistent with the hairy polyp. MRI repeated after 2 months was normal. At 1-year follow-up, the child is in a good condition and without breathing or oral intake difficulties.

This case emphasizes the importance of multidisciplinary approach in neonates with nasopharyngeal masses, in order to provide timely and accurate diagnosis as well as the optimal treatment.