Serbian Biochemical Society
Eighth Conference
with international participation

University of Novi Sad – Rectorate Hall
16.11.2018. Novi Sad, Serbia

"***Coordination in Biochemistry and Life***"

PROGRAMME

10:00-10:15	Opening ceremony
10:15-10:45	Tantos Ágnes Institute of Enzymology, Research Center for Natural Sciences, HAS, Budapest, Hungary **Intrinsically disordered proteins: Giving new shapes to cellular networks** (FEBS3+ Lecture)
10:45-11:15	Miloš Filipović Institut de Biochimie et Génétique Cellulaires, Université de Bordeaux, Bordeaux, France **Sulfaging: live longer with H_2S** (Diaspora Lecture)
11:15-11:35	Dimitar S. Jakimov Faculty of Medicine, University of Novi Sad; Oncology Institute of Vojvodina, Sremska Kamenica **Modified steroid compounds with antitumor activity**
11:35-11:45	Natascha Brinskelle-Schmal Thermo Fisher Scientific, Vienna, Austria **eBioscience novel approaches in biomedical analysis – ProQuantum immunoassays (the next generation in protein quantification, ELISA & qPCR) and Luminex technology: ProcartaPlex multiplex immunoassays, QuantiGene multiplex gene expression assays** (Sponsor's Lecture)
11:45-12:30	Coffee break

12:30-12:50 Milica R. Milenković

Department of General and Inorganic Chemistry, Faculty of Chemistry, University of Belgrade

Antitumor and antimicrobial properties of isothiocyanato pentagonal-bipyramidal d metal complexes with dihydrazone of 2,6-diacetylpyridine and Girard's T reagent

12:50-13:10 Jelena Katanić

Department of Chemistry, Faculty of Science, University of Kragujevac

Phytotherapy of cisplatin side effects: A case of two *Filipendula* species

13:10-13:30 Ana Miltojević

Faculty of Occupational Safety, University of Niš

Polypharmacologically active esters of N-methylanthranilic acid from Mexican orange (*Choisya ternata* Kunth): from the discovery to panacea-like properties

13.30-14.30 Poster session

14.00-15.00 Cocktail / Lunch break

15:00-15:20 Goran Miljuš

INEP-Institute for the Application of Nuclear Energy, University of Belgrade

Transferrin/IGFBP-3 complex: Crossroad for the IGF system and iron metabolism

15:20-15:40 Marina Stanić

Department of Life Sciences, Institute for Multidisciplinary Research, University of Belgrade

Transport and metabolism of vanadium in filamentous fungi with emphasis on fungus *Phycomyces blakesleeanus*

15:40-16:00 Dragana Nikolić

Institute of Molecular Genetics and Genetic Engineering, University of Belgrade

Unraveling mechanisms of Si action: modulation of gene expression in plants under abiotic stresses

16:00-16:20 Danijela Savić

Department of Neurobiology, Institute for Biological Research "Siniša Stanković", University of Belgrade

Distribution and role of metals in sclerotic hippocampi of patients with mesial temporal lobe epilepsy

16:20-17:00 Coffee break

17:00-17:15 Poster awards and closing ceremony

Phytotherapy of cisplatin side effects: A case of two *Filipendula* species

Jelena Katanić*

Department of Chemistry, Faculty of Science, University of Kragujevac, Kragujevac, Serbia

**e-mail: jkatanic@kg.ac.rs*

Cisplatin (CP), an inorganic complex of platinum, has been effectively used as a potent chemotherapeutic agent against various malignancies, but it causes a number of side effects, *e.g.*, digestive tract disorders, vomiting, and toxic effects on different organs, particularly on kidneys. Besides that, CP use in cancer chemotherapy may be responsible for secondary malignancies. Therefore, a number of scientific studies are focused on ameliorating potential of medicinal plant products (phytotherapeutics) on reducing or preventing the negative effects of anticancer drugs, namely cisplatin. Especially polyphenolic compounds from plant origin (flavonoids, phenolic acids, tannins, terpenes, etc.) showed significant activity towards modulation of cisplatin-induced toxicity. Genus *Filipendula* Mill. consists of over 20 plant species, two of which are growing in Serbia, *Filipendula ulmaria* (L.) Maxim. and *F. vulgaris* Moench. Both plants are in use in traditional medicine based on their antirheumatic, astringent, diuretic, and anti-inflammatory properties and potential to treat kidney problems. Hence, the effects of aerial parts and roots methanolic extracts of *F. ulmaria* and *F. vulgaris* were investigated against cisplatin-induced kidney and liver injuries in rats along with the determination of their phytochemical composition. The obtained results showed that tested extracts, rich in polyphenolic compounds, attenuate cisplatin-induced liver and kidney oxidative stress, reduce tissue damage, and enhance the antioxidative status of experimental animals during cisplatin application. Therefore, *F. ulmaria* and *F. vulgaris* extracts may be used as supportive agents for the prevention and amelioration of cisplatin side effects.

Cisplatin: activity and toxicity

Cisplatin (cis-$[Pt(NH_3)_2Cl_2]$ (cis-diamminedichlorplatinum(II)) is an inorganic complex with a square planar geometry, which consists of an atom of platinum surrounded with two ammonia groups and two chlorine atoms in *cis* position. This inorganic complex has been in clinical usage for cancer treatments, since 1978 when it was approved by the American Food and Drug Administration [1], and today it is on the World Health Organization's List of Essential Medicines [2]. Cisplatin was first synthesized and described by the Italian chemist Michele Peyrone as early as in 1845, but in 1965 American biophysicist Barnett Rosenberg

managed to characterize the powerful antiproliferative effects of this complex [3–5]. For 40 years cisplatin has been effectively used as a potent and one of the most common chemotherapeutic agents against various malignancies, mainly for testicular, ovarian, head and neck, bladder, cervical, esophageal as well as small cell lung cancer [6,7], but also for breast, stomach, prostate cancers, Hodgkin's and non-Hodgkin's lymphomas, neuroblastoma, sarcomas, multiple myeloma, melanoma and mesothelioma [4].

The mechanism of cisplatin action is based on targeting cancer cell DNA (Figure 1). Upon entering a cell, cisplatin become hydrated, after the dissociation of two chlorides, and a reactive complex is formed and it is then able to interact with nucleophilic molecules within the cell, including DNA, RNA, and proteins. When this positively charged molecule interacts with deoxyribonucleic acids it causes interstrand and intrastrand covalent crosslinking with local denaturation of the DNA chain [8,9]. This process primarily occurs due to the favoring crosslinking between N7 and O6 atoms of the adjacent imidazole ring of the purine base guanine, and to a minor extent via N7 and N1 of the adenine molecules or via N3 atom of the cytosine. The main product responsible for the anticancer activity of cisplatin is intrastrand crosslink 1,2-(guanine deoxydinucleotide) (1,2-GpG, about 65%), where platinum is coordinated to N(7) of two guanine molecules from one DNA strand [9–11]. The final cellular outcome is generally apoptotic cell death, although the pathway(s) from platinum–DNA binding to apoptosis remains incompletely elucidated. The platinum–DNA adducts can impede cellular processes, such as replication and transcription, but also signal-transduction pathways, that control growth, differentiation and stress responses, have also been implicated [5].

Although cisplatin has this very important role in cancer treatment and has had a major clinical impact, it causes a number of side effects, such as vomiting, gastrointestinal tract disorders, and toxic effects on different organs [1]. Cisplatin frequently causes notorious kidney damage (nephrotoxicity) because it is mainly excreted via the kidneys (27-45%). Cisplatin-induced nephrotoxicity can also lead to acute renal failure [4,8,12]. Besides nephrotoxicity, also ototoxicity (adult: 23-50%; children: >50%) and peripheral neurotoxicity (adult: 30-86%, children: ~10%) are considered to be the most serious toxicities associated with cisplatin treatment [9]. Moreover, cisplatin can provoke less frequent toxic effects like hepato- and cardiotoxicity [1]. Since the target of cisplatin is DNA, its use in cancer chemotherapy may be responsible for secondary malignancies. After application of cisplatin, DNA damage may lead to mutagenesis, carcinogenesis, and to apoptotic cell death [13]. Generally, toxic side effects of cisplatin arise because this complex has a high affinity for sulfur-containing compounds like glutathione, and these newly formed compounds are highly reactive and generally responsible for toxic effects in the organism [10,11]. Besides binding of cisplatin to various cytoplasmic molecules, some of the suggested mechanisms of cisplatin-induced toxicity are a generation of reactive oxygen species and inhibition of antioxidant enzymes (superoxide dismutase, glutathione peroxidase, and glutathione S-transferase). Taking this into consideration, oxidative stress plays a significant role in cisplatin-induced toxicity [14].

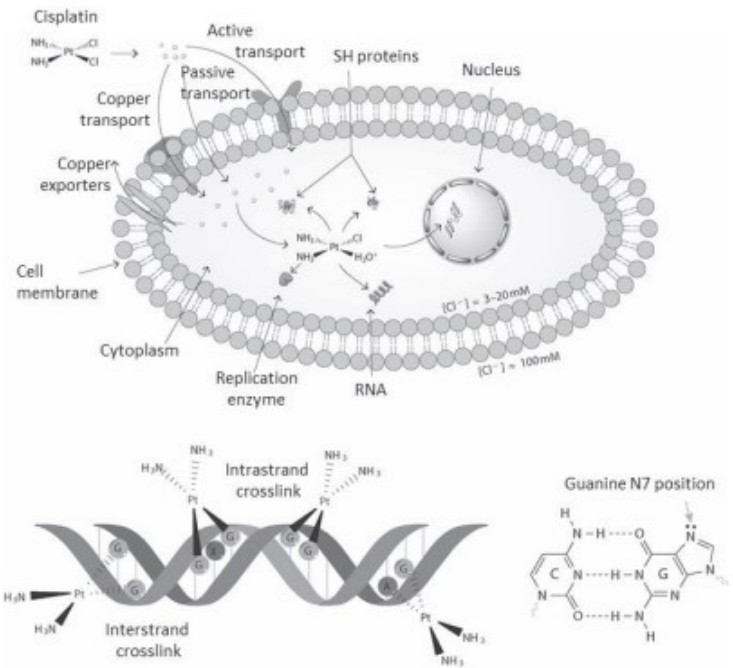

Figure 1. Schematic overview of the mechanism of cisplatin transport/export and targets in the cell and DNA adduct formation with cisplatin moiety. Adapted from Kelland [5] and Gómez-Ruiz et al. [6].

Furthermore, one of the problems associated with cisplatin therapy is tumor resistance to cisplatin, which can develop as a result of decreased influx or increased efflux of drug, glutathione or metallothionein conjugation, drug detoxification, DNA repair, or skipping lesions during DNA replication [3,5,9,15]. Since the 1970s, thousands of platinum analogs have been synthesized and tested to identify other antineoplastic compounds with reduced side effects while retaining tumor toxicity (*i.e.*, carboplatin, oxaliplatin, satraplatin, picoplatin, nedaplatin, heptaplatin, etc.) [5], but cisplatin still holds primacy as the therapy of choice in most tumors [6]. Many current research efforts are focused on the discovery of a drug that provides the excellent anticancer effect, with little or no harmful effect on the organism, but also to find new compounds or formulations which could reduce or prevent the negative effects of anticancer drugs, especially cisplatin side effects.

Phytotherapy of cisplatin side effects

Despite the fact that cisplatin has been used for 40 years as part of the treatment of various solid malignancies its side effects are still unavoidable. Today, besides many synthesized drugs, numerous traditional medicinal plants, dietary vegetables, and fruits, as well as their constituents, still play a key role in the prevention and treatment of different diseases, including the protective role against oxidative stress in the organism [16]. Most of the medicinal plants' constituents, *i.e.*, polyphenolics, alkaloids, carotenoids, vitamins, are known by their significant antioxidant potential [17].

Since the oxidative and nitrosative stresses are main mechanisms involved in cisplatin toxicity [1,8], numerous recent studies are dealing with the beneficial effects of different plant extracts administration on the alleviation of cisplatin-induced toxicity. In particular, plant extracts rich in polyphenols, such as *Zingiber officinale* rhizome extract [18], *Matricaria chamomilla* aerial part extract [19], *Hypericum perforatum* aerial part extract [20], *Stevia rebaudiana* extract [21], as well as standardized extracts like silymarin [22] and ginseng extract [23], showed ameliorating effects on hepato-, oto-, and/or nephrotoxicity caused by cisplatin *in vivo*. The protective activities of these extracts involve, among others, antioxidant and anti-inflammatory mechanisms.

A wide range of pure compounds from plant origin was also tested *in vivo* for the amelioration of cisplatin side effects. Different polyphenolic compounds, *e.g.*, ellagic acid, caffeic acid, rosmarinic acid, ferulic acid, quercetin, rutin, curcumin, resveratrol, chrysin, hesperidin, luteolin, naringenin, epigallocatechin-3-*O*-gallate, cyanidin, genistein, gingerol, terpenes: ginsenosides β-caryophyllene, and artemisinin; alkaloids: berberine, capsaicin, and noscapine; and vitamins C and E showed significant alleviation of oxidative stress parameters during the cisplatin treatment and modulation of cisplatin-induced toxicity on various levels [24–29].

The comprehensive analysis of literature suggests that phytotherapy using herbal medicines and/or plant-derived natural products (phytochemicals) can be widely implemented to prevent the cisplatin-induced toxicity. It is evident that phytomedicines exhibited potentially effective nephro-, oto- and hepato-protection in preclinical studies, primarily based on their antioxidative properties. Substantially, these antioxidant compounds not only target oxidative stress but also other events involved in cisplatin pathology, such as inflammation, mitochondrial damage and endoplasmic reticulum stress [25]. Furthermore, phytomedicines have been widely documented to directly or indirectly target multiple signaling pathways and networks in cancer cells, so a combination of anticancer drugs and polypharmacological plant-derived extracts or compounds may offer a significant advantage in the efficacy of monotherapy and overcoming drug-induced resistance in cancer patients [24].

A case of two *Filipendula* species

Genus *Filipendula* Mill. (fam. *Rosaceae*) is consisted of around 20 plant species that are predominantly widespread the Northern hemisphere. Plants of this genus are growing in

Europe, North America, Siberia, and Asia [30]. The genus name derives from two Latin words: "*filium*" - a thread or a string and "*pendulus*" - hanging, referring to the root of some species that are consisted of rhizomes associated with thin strings [31]. Genus *Filipendula* in the territory of Serbia, as well as on the entire European continent, is represented by two species: *Filipendula ulmaria* (L.) Maxim. (syn. *Spiraea ulmaria* L.) и *Filipendula vulgaris* Moench (syn. *Filipendula hexapetala* Gilib., *Spiraea filipendula* L.) [32–34].

F. ulmaria (meadowsweet, queen of the meadow) is a perennial herb with creamy-white flowers, a short, pink rhizome and stems 50–120 cm high. *F. ulmaria* is used in traditional European medicine for treatment of various ailments due to its antipyretic, astringent, diuretic, antacid, stomachic, antiseptic, analgesic, antirheumatic, and anti-inflammatory properties [35–38]. Dried flowering tops are used for the treatment of common cold, minor painful articular conditions, and to facilitate renal and digestive elimination functions [35,39]. Based on traditional use and proven pharmacological effects, the herb (aerial parts) of *F. ulmaria* was registered in European Pharmacopoeia 5th Edition (PhEur 5.0) as *Filipendulae ulmariae herba* [40], and now it is an integral part of the latest 9th Edition (PhEur 9.0) from 2017. *F. vulgaris* (dropwort) is up to 80 cm high plant, with pinkish-white flowers and characteristic rhizomes with tuberous roots [32]. *F. vulgaris* is also used in traditional medicine of most European countries [41], and sometimes, it is used as a substitute for *F. ulmaria* due to their similar bioactive effects, in particular, anti-inflammatory properties [38].

Based on the literature data it can be concluded that mentioned *Filipendula* species are characterized by the presence of the three main classes of phenolic compounds: phenolic acids and their derivatives (gallic acid, ellagic acid, salicylic acid, methyl salicylate, salicylaldehyde), flavonoid aglycones and glycosides (quercetin, kaempferol, catechin, epicatechin, rutoside, hyperoside, spiraeoside, quercitrin, apigenin, astragalin), and tannins (mainly tellimagrandins and rugosins) [36,42–45].

Our previous investigations of *F. ulmaria* and *F. vulgaris* aerial part and root methanolic extracts showed that they possessed high antioxidant and anti-inflammatory activity *in vitro*, low genotoxicity, antigenotoxic activity, moderate antimicrobial activity, and good stability at different pH values and thermal conditions [46–49]. The extracts were also subjected to a wide range of spectrophotometric and chromatographic methods (TLC, HPTLC, HPLC, LC-DAD-MS^n) in order to elucidate their phytochemical composition. The results showed that all four extracts had a high content of phenolic compounds, mainly flavonoids (particularly quercetin and its derivatives, *e.g.*, spiraeoside, rutin, hyperoside, quercitrin, isoquercitrin, Figure 2) and phenolic acids in aerial part extracts, along with hydrolyzable tannins in root extracts [46,48–52].

With regard to reported biological activities and traditional uses of *Filipendula* spp., their phytochemical composition, and our previous studies which confirmed potent antioxidant activity of the methanolic extracts of aerial parts and roots of *F. ulmaria* and *F. vulgaris*, we aimed to further investigate those extracts for their potential in amelioration cisplatin-induced toxicity *in vivo*, using albino Wistar rats. All animal procedures were in

compliance with the EEC Directive (86/609/EEC) on the protection of animals used for experimental and other scientific purposes. The study was designed as follows (Figure 3): I - negative control group where animals were treated with normal saline; II - positive control/cisplatin group where toxicity was induced with cisplatin; III-V groups treated with *F. ulmaria* and *F. vulgaris* aerial part extracts (FUA or FVA) *per os* (*p.o.*) at three different concentrations 100, 200, and 400 mg/kg body weight (b.w.); VI-VII groups treated with *F. ulmaria* and *F. vulgaris* root extracts (FUR or FVR) at 100, 200, and 400 mg/kg b.w.; and two last groups were treated only with extracts at the highest concentration (400 mg/kg b.w.). The extracts were administered for 10 days and in groups II-VIII toxicity was induced on the 5th day of treatment by intraperitoneal (*i.p.*) administration of a single dose of CP dissolved in normal saline (7.5 mg/kg b.w.) [50,51].

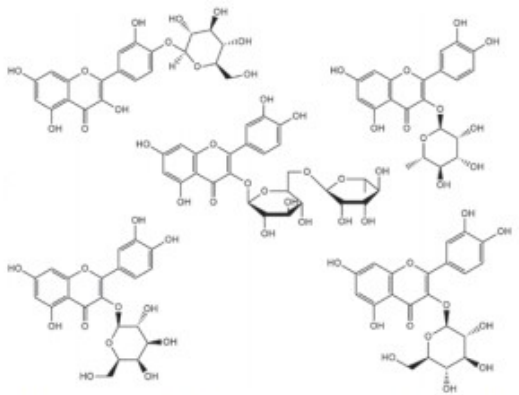

Figure 2. Flavonoid glucosides (derivatives of quercetin) identified in *F. ulmaria* and *F. vulgaris* extracts [36,44–46,50–52]: Spiraeoside (quercetin-4′-*O*-β-D-glucopyranoside); Quercitrin (quercetin-3-*O*-α-L-rhamnoside); Rutin (quercetin-3-*O*-rutinoside); Hyperoside (quercetin-3-*O*-galactoside); Isoquercitrin (quercetin-3-*O*-β-D-glucopyranoside)

The examined parameters and the degree of protective activity of tested extracts on *in vivo* cisplatin-induced hepatorenal toxicity are illustratively shown in Figure 3.

In our study, serum parameters in rats treated with cisplatin only clearly showed impaired liver function and renal dysfunction. Serum transaminases (ALT and AST) and other tested serum parameters (ALP and γGT) connected with normal liver function, were significantly elevated in the serum of rats treated only with cisplatin. Since transaminases are located in the cytoplasm and released into the circulation after cellular damage, they are the most sensitive biomarkers which directly indicate cellular damage and toxicity [14].

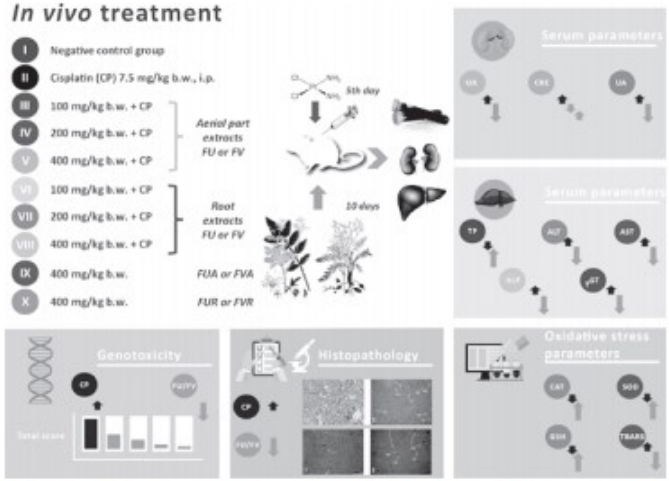

Figure 3. The effects of *in vivo* administration of *F. ulmaria* and *F. vulgaris* aerial part (FUA/FVA) and root (FUR/FVR) extracts along with one dose of cisplatin (CP, 7.5 mg/kg b.w.) on the serum parameters, oxidative stress parameters, histopathological changes, and genotoxicity in renal and hepatic tissues.

The levels of three main serum parameters of kidney function, creatinine (CRE), urea (UR), and uric acid (UA), were significantly increased in rats only treated with cisplatin indicating cisplatin-induced nephrotoxicity, as reported in many recent studies [53–55]. Moreover, cisplatin treatment caused significant body weight reduction that may be caused by gastrointestinal dysfunction, dehydration, reduced appetite, enhanced catabolic rate, and renal tubular injury [55,56]. As stated, one of the most important mechanisms involved in cisplatin toxicity is oxidative stress [1,14]. Under normal physiological conditions generation and elimination of reactive oxygen species in cells are controlled by an endogenous scavenging system including catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH). On the other hand, under cisplatin-induced oxidative stress CAT and SOD activities can be inhibited and another possible mechanism underlying cisplatin-mediated reduction in the level of antioxidant enzymes is diminishing SOD and CAT gene expression [53]. Cisplatin conjugation with glutathione lowers GSH levels and leads to mitochondrial oxidative stress which is related to the toxicity of cisplatin [1,14]. Free radicals generated by cisplatin could react with the membrane lipids resulting in the production of lipid peroxides [53,55], so the alleviation of thiobarbituric acid reactive substances (TBARS) levels is a suitable marker of cisplatin toxicity. In the present study, all examined markers of oxidative stress (CAT, SOD, GSH, and TBARS) in renal and hepatic tissues of rats

treated with cisplatin only, indicated that cisplatin-treatment disrupted normal kidney and liver function. As expected, GSH levels in liver and kidneys were markedly decreased.

The serum and tissue parameters of oxidative stress and tissue damage in rats treated with three different doses of tested *Filipendula* spp. methanolic extracts for 10 consecutive days, in addition to cisplatin (on the 5th day of treatment), indicate a significant beneficial effect, compared to the group treated with cisplatin alone. The extracts were able to markedly reduce serum parameters, in some cases in a dose-dependent manner. Further, they ameliorated the oxidative status in kidney and liver tissues by increasing CAT and SOD activities and reducing the concentration of TBARS, as well as prevent depletion of GSH by cisplatin treatment in liver tissue. In kidneys, GSH was the most affected element of the antioxidative defense. The induction of hepato- and nephrotoxicity by cisplatin were also confirmed by histological analysis of liver and kidney tissues. It was evident that the extracts exerted tissue-protective effects, with a significant reduction of liver and kidney tissue injury caused by cisplatin administration [50,51].

Considering previously reported antioxidant activity and radical scavenging capacity of *F. ulmaria* and *F. vulgaris* [46,47], as well as the high content of antioxidant phenolic compounds, our data strongly imply that their extracts potently protect against liver and kidney toxicity induced by cisplatin via antioxidant activity. The results of phytochemical analysis of all extracts confirmed the presence of a wide range of phenolic compounds, which have been shown to act as antioxidants. Procyanidins (condensed tannins) and catechins, that were detected in all extracts, have been demonstrated to possess an array of beneficial health effects [57–60]. Also, hydrolyzable tannins, detected in aerial parts, have been shown to possess a variety of biological activities, including antioxidant and anticancer effects [61,62]. Flavonoids and flavonoid derivatives detected in all extracts are also highly bioactive and for many of them hepato- and nephroprotective effects *in vivo* were reported [63–67].

Another potential route of protection against cisplatin-induced oxidative stress is the proven anti-inflammatory activity of both *Filipendula* species [49,52] since cisplatin-induced oxidative stress leads to the activation of pro-inflammatory mediators [14].

The third mechanism possibly underlying the observed protective effect of tested extracts against cisplatin-induced toxicity may be suppression of DNA damage in normal cells. Cisplatin can react with many structures in the cell, but of course, the most important intracellular target is DNA. DNA damage is a major trigger for cell cycle arrest and apoptosis and cisplatin has demonstrated induction of apoptosis in multiple tissue types [11]. Although the antineoplastic effect of cisplatin is mediated through the binding to nuclear DNA, cisplatin also induces damage of mitochondrial DNA [14]. Results of our study revealed significant cisplatin-induced DNA damage both in the liver and, in particular, kidney cells. Interestingly, the potency of DNA damage reduction in liver and kidneys decreased with increasing concentration of all tested extracts. At lower doses (100 and 200 mg/kg), the extracts were the most effective in reducing cisplatin-induced DNA damage [50,51].

Conclusions and future perspectives

Co-treatment with methanolic extracts of aerial parts and roots of *F. ulmaria* and *F. vulgaris* attenuated cisplatin-induced toxicity in kidneys and liver, regulated serum and tissue parameters related to oxidative stress and tissue damage, and helped to maintain tissue architecture, along with reducing genotoxicity caused by cisplatin. Therefore, it can be concluded that *Filipendula* species may be used as a supportive agent in cancer patients under cisplatin therapy to improve the oxidative stress defense of the organism and to diminish toxic side effects of cisplatin. However, further investigations are still required to completely evaluate their protective effect on the side-effects of cisplatin and obtaining the appropriate therapeutic dose, particularly obtaining evidence of extracts' bioavailability in human subjects. Also, the extracts and phytochemical compounds should be thoroughly investigated in preclinical models for further pharmaceutical development. This approach may offer the best chance of clinically meaningful prevention of cisplatin toxicity.

Acknowledgments

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. III 43004).

References

1. Dasari S, Tchounwou P. Cisplatin in Cancer therapy: Molecular mechanisms of action. Eur J Pharmacol 2014;740:364–78.
2. World Health Organization. "Comparative Table of Medicines on the WHO Essential Medicines Lists from 1977–2011" (XLS). Retrieved. 2011.
3. Galluzzi L, et al. Systems biology of cisplatin resistance: past, present and future. Cell Death Dis 2014;5:e1257.
4. Manohar S, Leung N. Cisplatin nephrotoxicity: a review of the literature. J Nephrol 2018;31:15–25.
5. Kelland L. The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer 2007;7:573–84.
6. Gómez-Ruiz S, Maksimović-Ivanić D, Mijatović S, Kaluderović GN. On the discovery, biological effects, and use of cisplatin and metallocenes in anticancer chemotherapy. Bioinorg Chem Appl 2012;2012:15–7.
7. Jamieson ER, Lippard SJ. Structure, Recognition, and Processing of Cisplatin-DNA Adducts. Chem Rev 1999;99:2467–98.
8. Chirino YI, Pedraza-Chaverri J. Role of oxidative and nitrosative stress in cisplatin-induced nephrotoxicity. Exp Toxicol Pathol 2009;61:223–42.
9. Rabik CA, Dolan ME. Molecular mechanisms of resistance and toxicity associated with platinating agents. Cancer Treat Rev 2007;33:9–23.
10. Bugarčić ZD, Bogojeski J, Petrović B, Hochreuther S, van Eldik R. Mechanistic studies on the reactions of platinum(II) complexes with nitrogen- and sulfur-donor biomolecules. Dalt Trans 2012;41:12329–45.
11. Crul M, Schellens JH, Beijnen JH, Maliepaard M. Cisplatin resistance and DNA repair. Cancer Treat Rev 1997;23:341–66.
12. Jin J, et al. Protective effect of Wuzhi tablet (*Schisandra sphenanthera* extract) against cisplatin-induced nephrotoxicity via Nrf2-mediated defense response. Phytomedicine 2015;22:528–35.

13. Nersesyan A, Muradyan R. Sea-buckthorn juice protects mice against genotoxic action of cisplatin. Exp Oncol 2004;26:153–5.
14. Karasawa T, Steyger PS. An integrated view of cisplatin-induced nephrotoxicity and ototoxicity Toxicol Lett 2015;237:219–27.
15. Sarin N, et al. Key players of cisplatin resistance: towards a systems pharmacology approach. Int J Mol Sci 2018;19:E767.
16. Atanasov AG, et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv 2015;33:1582–614.
17. Shahidi F, Ambigaipalan P. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects – A review. J Funct Foods 2015;18:820–97.
18. Ajith TA, Nivitha V, Usha S. *Zingiber officinale* Roscoe alone and in combination with α-tocopherol protect the kidney against cisplatin-induced acute renal failure. Food Chem Toxicol 2007;45:921–7.
19. Abad ANA, Nouri MHK, Gharjanie A, Tavakoli F. Effect of *Matricaria chamomilla* Hydroalcoholic Extract on Cisplatin-induced Neuropathy in Mice. Chin J Nat Med 2011;9:126–31.
20. Shibayama Y, Kawachi A, Onimaru S, Tokunaga J, Ikeda R. Effect of pre-treatment with St John's Wort on nephrotoxicity of cisplatin in rats. Life Sci 2007;81:103–8.
21. Potočnjak I, Broznić D, Kindl M, Kropek M, Vladimir-Knežević S, Domitrović R. Stevia and stevioside protect against cisplatin nephrotoxicity through inhibition of ERK1/2, STAT3, and NF-κB activation. Food Chem Toxicol 2017;107:215–25.
22. Cho S Il, Lee JE, Do NY. Protective effect of silymarin against cisplatin-induced ototoxicity. Int J Pediatr Otorhinolaryngol 2014;78:474–8.
23. Yousef MI, Hussien HM. Cisplatin-induced renal toxicity via tumor necrosis factor-α, interleukin 6, tumor suppressor P53, DNA damage, xanthine oxidase, histological changes, oxidative stress and nitric oxide in rats: Protective effect of ginseng. Food Chem Toxicol 2015;78:17–25.
24. Cheng YT, Yang CC, Shyur LF. Modulating oxidative stress and the tumor microenvironment for cancer therapy. Pharmacol Res 2016;114:128–43.
25. Gómez-Sierra T, Eugenio-Pérez D, Sánchez-Chinchillas A, Pedraza-Chaverri J. Role of food-derived antioxidants against cisplatin induced-nephrotoxicity. Food Chem Toxicol 2018;120:230–42.
26. Domitrović R, Potočnjak I, Crnčević-Orlić Ž, Škoda M. Nephroprotective activities of rosmarinic acid against cisplatin-induced kidney injury in mice. Food Chem Toxicol 2014;66:321–8.
27. Domitrović R, Cvijanović O, Pugel EP, Zagorac GB, Mahmutefendić H, Škoda M. Luteolin ameliorates cisplatin-induced nephrotoxicity in mice through inhibition of platinum accumulation, inflammation and apoptosis in the kidney. Toxicology 2013;310:115–23.
28. Shahid F, Farooqui Z, Khan F. Cisplatin-induced gastrointestinal toxicity: An update on possible mechanisms and on available gastroprotective strategies. Eur J Pharmacol 2018;827:49–57.
29. Ojha S, Venkataraman B, Kurdi A, Mahgoub E, Sadek B, Rajesh M. Plant-Derived Agents for Counteracting Cisplatin-Induced Nephrotoxicity. Oxid Med Cell Longev 2016;4320374:1–27.
30. Shimizu T. Taxonomical notes on the genus *Filipendula* Adans. (Rosaceae). J Fac Text Sci Technol 1961;26:1–31.
31. Giebelmann R. Kulturgeschichtliches zu Rosengewächsen. 2004;71:54–63.
32. Tucakov J. Lečenje biljem. Izdavačka radna organizacija RAD, Beograd, 1984.
33. Josifović M. Flora of Serbia I-X. Serbian Academy of Sciences and Arts, Belgrade, 1973.
34. Jarić S, et al. An ethnobotanical study on the usage of wild medicinal herbs from Kopaonik Mountain (Central Serbia). J Ethnopharmacol 2007;111:160–75.
35. Barros L, Cabrita L, Boas MV, Carvalho AM, Ferreira ICFR. Chemical, biochemical and electrochemical assays to evaluate phytochemicals and antioxidant activity of wild plants. Food Chem 2011;127:1600–8.

36. Bijttebier S, et al. A first step in the quest for the active constituents in *Filipendula ulmaria* (Meadowsweet): Comprehensive phytochemical identification by liquid chromatography coupled to quadrupole-orbitrap mass spectrometry. Planta Med 2016;82:559–72.
37. Harbourne N, Jacquier JC, O'Riordan D. Optimisation of the aqueous extraction conditions of phenols from meadowsweet (*Filipendula ulmaria* L.) for incorporation into beverages. Food Chem 2009;116:722–7.
38. Barros L, et al. Characterization of phenolic compounds in wild medicinal flowers from Portugal by HPLC–DAD–ESI/MS and evaluation of antifungal properties. Ind Crops Prod 2013;44:104–10.
39. Assessment report on *Filipendula ulmaria* (L.) Maxim., herba and *Filipendula ulmaria* (L.) Maxim., *flos*. European Medicines Agency. 2011, pp. 1–18.
40. Papp I, et al. Monitoring volatile and non-volatile salicylates in *Filipendula ulmaria* by different chromatographic techniques. Chromatographia 2008;68:125–9.
41. Vogl S, et al. Ethnopharmacological *in vitro* studies on Austria's folk medicine - An unexplored lore *in vitro* anti-inflammatory activities of 71 Austrian traditional herbal drugs. J Ethnopharmacol 2013;149:750–71.
42. Fecka I. Qualitative and quantitative determination of hydrolysable tannins and other polyphenols in herbal products from meadowsweet and dog rose. Phytochem Anal 2009;20:177–90.
43. Olennikov DN, Kruglova MY. A new quercetin glycoside and other phenolic compounds from the genus *Filipendula*. Chem Nat Compd 2013;49:610–6.
44. Pukalskienė M, Venskutonis PR, Pukalskas A. Phytochemical composition and antioxidant properties of *Filipendula vulgaris* as a source of healthy functional ingredients. J Funct Foods 2015;15:233–42.
45. Pukalskienė M, Venskutonis PR, Pukalskas A. Phytochemical characterization of *Filipendula ulmaria* by UPLC/Q-TOF-MS and evaluation of antioxidant activity. Rec Nat Prod 2015;9:451–5.
46. Katanić J, et al. Bioactivity, stability and phenolic characterization of *Filipendula ulmaria* (L.) Maxim. Food Funct 2015;6(4):1164–75.
47. Katanić J, et al. Dropwort (*Filipendula hexapetala* Gilib.): Potential role as antioxidant and antimicrobial agent. EXCLI J 2015;14:1–20.
48. Matić S, et al. *In vitro* and *in vivo* assessment of the genotoxicity and antigenotoxicity of the *Filipendula hexapetala* and *Filipendula ulmaria* methanol extracts. J Ethnopharmacol 2015;174:287–92.
49. Katanić J, et al. *In vitro* and *in vivo* assessment of meadowsweet (*Filipendula ulmaria*) as anti-inflammatory agent. J Ethnopharmacol 2016;193:627–36.
50. Katanić J, et al. The ameliorating effect of *Filipendula hexapetala* extracts on hepatorenal toxicity of cisplatin. J Funct Foods 2015;18:198–212.
51. Katanić J, et al. *Filipendula ulmaria* extracts attenuate cisplatin-induced liver and kidney oxidative stress in rats: *In vivo* investigation and LC-MS analysis. Food Chem Toxicol 2017;99:86–102.
52. Katanić J, et al. Phytochemical analysis and anti-inflammatory effects of *Filipendula vulgaris* Moench extracts. Food Chem Toxicol 2018; In press.
53. Almaghrabi OA. Molecular and biochemical investigations on the effect of quercetin on oxidative stress induced by cisplatin in rat kidney. Saudi J Biol Sci 2015;22:227–31.
54. Yamabe N, et al. Protective effects of protocatechuic acid against cisplatin-induced renal damage in rats. J Funct Foods 2015;19:20–7.
55. Sinha S, Jothiramajayam M, Ghosh M, Jana A, Chatterji U, Mukherjee A. Vetiver oil (Java) attenuates cisplatin-induced oxidative stress, nephrotoxicity and myelosuppression in Swiss albino mice. Food Chem Toxicol 2015;81:120–8.
56. Hassan I, Chibber S, Naseem I.Ameliorative effect of riboflavin on the cisplatin induced nephrotoxicity and hepatotoxicityunder photoillumination. Food Chem Toxicol 2010;48:2052–8.
57. Lluís L, et al. Toxicology evaluation of a procyanidin-rich extract from grape skins and seeds. Food Chem Toxicol. 2011;49:1450–4.

58. Spranger I, Sun B, Mateus AM, Freitas V de, Ricardo-da-Silva JM. Chemical characterization and antioxidant activities of oligomeric and polymeric procyanidin fractions from grape seeds. Food Chem 2008;108:519–32.
59. Zanwar AA, Badole SL, Shende PS, Hegde M V., Bodhankar SL. Antioxidant Role of Catechin in Health and Disease. in Polyphenols in Human Health and Disease. Elsevier Inc., London, 2013, pp. 267-271
60. Sutherland BA, Rahman RMA, Appleton I. Mechanisms of action of green tea catechins, with a focus on ischemia-induced neurodegeneration. J Nutr Biochem 2006;17:291–306.
61. Koleckar V, et al. Condensed and hydrolysable tannins as antioxidants influencing the health. Mini-Reviews Med Chem 2008;8:436–47.
62. Kähkönen M, Kylli P, Ollilainen V, Salminen JP, Heinonen M. Antioxidant activity of isolated ellagitannins from red raspberries and cloudberries. J Agric Food Chem. 2012;60:1167–74.
63. Ham Y-M, et al. Quercitrin protects against oxidative stress-induced injury in lung fibroblast cells via up-regulation of Bcl-xL. J Funct Foods 2012;4:253–62.
64. Babujanarthanam R, Kavitha P, Mahadeva Rao US, Pandian MR. Quercitrin a bioflavonoid improves the antioxidant status in streptozotocin: induced diabetic rat tissues. Mol Cell Biochem 2011;358:121–9.
65. Choi J-H, et al. Protective effects of hyperoside against carbon tetrachloride-induced liver damage in mice. J Nat Prod 2011;74:1055–60.
66. Arjumand W, Seth A, Sultana S. Rutin attenuates cisplatin induced renal inflammation and apoptosis by reducing NFkB, TNF-a and caspase-3 expression in wistar rats. Food Chem Toxicol 2011;49:2013–21.
67. Valentová K, Vrba J, Bancířová M, Ulrichová J, Křen V. Isoquercitrin: Pharmacology, toxicology, and metabolism. Food Chem Toxicol 2014;68:267–82.