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The ameliorating effect of *Filipendula hexapetala* extracts on hepatorenal toxicity of cisplatin

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ABSTRACT

The effects of the methanolic extracts of *Filipendula hexapetala* Gilib. aerial parts (FHA) and roots (FHR) against cisplatin induced kidney and liver injuries in rats were investigated as well as determination of genotoxicity and antigenotoxicity of the extracts. Treatment with FHA and FHR significantly decreased levels of urea, uric acid, serum transaminases, alkaline phosphatase and γ-glutamyl transferase, and increased the content of total protein. In addition, treatment with the extracts significantly attenuated the cisplatin-induced oxidative stress in kidney and liver tissues by increasing catalase and superoxide dismutase activities and the content of reduced glutathione and decreasing the content of thiobarbituric acid reactive substances (TBARS). The histopathological studies confirmed the protective effects of the extracts against cisplatin-induced kidney and liver injuries. The extracts ameliorated cisplatin-induced genotoxicity. These results suggest that *F. hexapetala* extracts are effective nephro- and hepatoprotective agents, with potential to reduce oxidative stress and ameliorate cisplatin-induced nephro- and hepatotoxicity.

1. Introduction

There has been an increasing interest in the health enhancing role of functional foods or physiologically-active food compounds. One of the most important traits of some functional food ingredients, in addition to their nutritional values, is their physiological benefit. Many recent studies have reported that components of plant-based diet play a very important role in health promotion (Crozier, Jaganath, & Clifford,

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2009; Farzaneh & Carvalho, 2015). Malignancies are one of the most frequent problems as the consequences of a fast pace life in modern society, unhealthy diet, and everyday stress. A fascinating array of plant and food-derived putative anticarcinogens, which provide aroma, colour and flavour to our diet and may promote good health, was discovered in recent years. Different natural dietary components have a cancer preventive potential which are able to suppress tumour-specific metabolic pathways, but they can also improve efficiency of chemotherapeutics, alleviate the adverse side effects of chemotherapy, and detoxify the body of chemotherapeutics. Thus, cancer patients are advised to have the proper nutrition with needful nutrients already before and during the chemotherapy in order to ensure the best health possible (Gerhauser, 2013; Sak, 2012). Phenolic compounds are the most dominant bioactive compounds identified in plant foods with antioxidant properties and free radical scavenging activities. The consumption of foods rich in phenolic compounds is associated with various physiological effects, such as preventing cancer and some chronic diseases as well as alleviating the harmful effect of drugs and chemotherapeutics (Quirós-Sauceda et al., 2014).

One of the most used anticancer drugs is an inorganic complex called cisplatin – *cis*-[$Pt(NH_3)_2Cl_2$] (*cis*-diamminedichlorplatinum(II)). Cisplatin (CP) in organism interacts with deoxyribonucleic acids causing interstrand and intrastrand crosslinking with local denaturation of the DNA chain (Chirinoa & Pedraza-Chaverri, 2009; Gómez-Ruiz, Maksimović-Ivanić, Mijatović, & Kaluđerović, 2012; Kelland, 2007). Besides this very important anticancer effect of cisplatin, there are also many undesirable side effects such as vomiting, digestive tract disorders, and toxicity like nephrotoxicity, hepatotoxicity, neurotoxicity and ototoxicity (Chirinoa & Pedraza-Chaverri, 2009; Kelland, 2007; Longo, Gervasi, & Lubrano, 2011). Side effects of CP arise because this complex has a huge affinity for sulphur-containing compounds, and that novel compounds are generally responsible for mentioned toxic effects in the organism (Crul, Schellens, Beijnent, & Maliepaard, 1997; Martin, 1999). Besides that, CP use in cancer chemotherapy may be responsible for secondary malignancies (Misra & Choudhury, 2006; Nersesyan & Muradyan, 2004).

The main interest of research is now to find a drug that provides excellent anticancer effect, with little or no harmful effect on the organism. Also, many research efforts are focused on finding new compounds or formulations which could reduce or prevent the negative effects of anticancer drugs, especially CP side effects. Today, beside many synthesized drugs, large amounts of medicinal plants which can be used as foods or food ingredients still play a key role in the prevention and treatment of different diseases. It has been reported that many plants and phenolic compounds as their constituents, possess the protective role against CP toxicity. For example, extracts of *Zingiber officinale* (Ajith, Nivitha, & Usha, 2007), *Aloe barbadensis* (Chatterjee, Mukherjee, & Nandy, 2012), and grape seed (Yousef, Saad, & El-Shennawy, 2009) showed nephroprotective effects in CP-induced toxicity. Also, natural compounds like rosmarinic acid (Domitrović, Potoćnjak, Crnčević-Orlić, & Škoda, 2014), *β*-caryophyllene (Horváth et al., 2012), rutin (Arjumand, Seth, & Sultana, 2011) and curcumin (Waseem & Parvez, 2013) attenuate or ameliorate CP-induced nephro- and hepatotoxicity.

Filipendula hexapetala Gilib. (Rosaceae), dropwort, is a perennial herb (up to 80 cm high) with pinkish-white flowers and characteristic tuberous roots, found in dry grasslands of Europe and Asia (Tucakov, 1973). Vračarić et al. (1990) reported that this plant is edible and can be used as a functional food. Young spring leaves can be used in salad, and later on only as cooked vegetables. They have a specific taste, so it is better to mix them with other wild vegetables. The tuberous roots have a bittersweet taste that resembles bitter almonds. They can be eaten fresh and prepared in a lot of different ways, also in combination with other tuberous plants for making porridge and bread, among others. Usage of dropwort in traditional medicine is based on the diuretic, astringent, antirheumatic and anti-inflammatory properties of this plant. Also, it was used for treating breathlessness, sore throats, congestion and kidney-problems (Maksimović, Petrović, Pavlović, Kovačević, & Kukić, 2007; Radulović et al., 2007). In our previous work, we demonstrated high antioxidant potential and antimicrobial activity of *F. hexapetala* aerial part and root extracts. The extracts also showed good stability under different pH and thermal conditions (Katanić, Mihailović et al., 2015). These results suggested that it is necessary to obtain more detailed studies and to evaluate the *in vivo* activity of *F. hexapetala*.

The present study aimed to characterize the phenolic compounds present in the extracts of aerial parts (FHA) and roots (FHR) of *F. hexapetala*. Also, based on traditional usage of *F. hexapetala*, we evaluated the degree of protective activity of *F. hexapetala* extracts on *in vivo* cisplatin-induced nephrotoxicity and hepatotoxicity, with determination of *in vivo* genotoxic effect and antigenotoxic potential.

2. Materials and methods

2.1. Chemicals

All chemicals and reagents were of analytical grade and purchased from Sigma Chemical Co. (St. Louis, MO, USA), Aldrich Chemical Co. (Steinheim, Germany) and Alfa Aesar (Karlsruhe, Germany). Cisplatin was purchased from Sigma-Aldrich Co. Commercial reagent kits for determination of total protein (TP), creatinine (CRE), urea (UR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma glutamyl transferase (γGT) activities were provided by BioSystems S.A. (Barcelona, Spain). Gallic acid, vanillic acid, kaempferol and quercetin were purchased from Sigma–Aldrich, caffeic acid was purchased from Merck KGaA (Darmstadt, Germany), (+)-catechin and ellagic acid from Serva (Heidelberg, Germany), hyperoside and rutin from Carl Roth (Karlsruhe, Germany), epicatechin from Thermo Fisher Scientific (Geel, Belgium) and spiraeoside from Extrasynthese (Genay, France). HPLC-grade acetonitrile, water and trifluoroacetic acid (Merck, Darmstadt, Germany) were used in HPLC analyses. All spectrophotometric measurements were performed on UV–VIS double beam spectrophotometer Halo DB-20S (Dynamica GmbH, Switzerland).

2.2. Plant material and preparation of the extracts

F. hexapetala Gilib. was collected at the locality Šumarice (Kragujevac, Central Serbia), during the flowering season (May