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Review

An overview of the biological activities of less known wild onions (genus *Allium* sect. *Codonoprasum*)

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Summary. Cultivated forms of *Allium* species, such as onion, garlic, leek and shalot, are widely used in the human diet and are also respected as medicinal plants. In contrast, wild onions, esspecially species from *Codonoprasum*, are less well known and remain understudied, even though they are present in local diets and traditional medicines. Therefore, in recent years, the chemical composition and biological activities of several species of onions from sect. *Codonoprasum* have been intensively studied in order to estimate their potential for applications in medicine. Headspace GC–MS analyses revealed that dimethyl-disulfide is by far the most dominant volatile sulfur compound in fresh bulbs of species from *Codonoprasum* section. LC-MS/MS analysis of phenolic compounds showed that these species are rich in phenolics, particularly in quercetin glycosides and kaempferol 3-*O*-glucoside. *Allium flavum* expressed the highest antioxidant activity in common *in vitro* assays and high anti-inflammatory activity in human platelets. *Allium flavum* and *A. melanantherum* exhibited high levels of antigenotoxic effects by activation of cellular antioxidant defence mechanisms. *Allium flavum* and *A. carinatum* drastically improved the activity of doxorubicin (Dox) against cancer cells. In zebrafish models, *A. flavum* and *A. carinatum* expressed high anti-angiogenic activity and protective effects against Dox-caused cardiac dysfunction and neutropenia. The results of these rewieved studies are indicative of the multiple beneficial pharmacological activities of wild *Allium* species.

Keywords: *Allium*, antigenotoxic, anti-angiogenic, antioxidant, anti-inflammatory, cardioprotective, *Codonoprasum*.

INTRODUCTION

The genus *Allium* is the largest genus of the Alliaceae family, comprising around 1000 species (Khassanov 2018). Some of these species are widely used in the human diet as spices and vegetables (*A. cepa*, *A. sativum*, *A. porrum*). These species are also very reputable medicinal plants, which are rich in biologically active molecules such as organosulfur and organoselenium compounds, phenolics, steroidal saponins, vitamins and amino acids (Brewster and Rabinowich 1990; WHO 1999). A broad spectrum of biological activities has been found for extracts and isolated compounds from these species, including strong antimicrobial, anti-inflammatory, antioxidant, anti-diabetic, hypolipidemic, anti-hypertensive, analgesic and immunoprotective effect (WHO 1999; Božin et al. 2008; Hosseini and Hosseinzadeh 2015; Teshika et al. 2019). However, wild edible onions including species from *Codonoprasum* section, are much less known and under-studied. Until now, 37 small size *Allium* species distributed mainly in the Mediterranean region, are classified in the *Codonoprasum* section. Some of these (*A. flavum*, *A. carinatum*) have a milder smell and taste than onions (*A. cepa*) and are used in the local diet of the Balkan countries. In Serbian flora, eight species from the *Codonoprasum* section are present: *A. flavum* and *A. carinatum* that are widespread, sporadically distributed *A. paniculatum*, *A. fuscum* and *A. oleraceum*, and rare taxa *A. rhodopeum*, *A. pallens* subsp. *tenuiflorum* and *A. melanantherum* (Anačkov 2009). These species have recently become the subject of extensive research, which included chemical composition analysis and

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evaluation of biological activities, and results of these studies are reviewed in this paper.

CHEMICAL COMPOSITION OF SPECIES FROM *CODONOPRASUM* SECTION

Volatile sulfur compounds give a specific odor and flavor to *Allium* species and are formed in reactions catalyzed by alliinase. Alliinase is an enzyme released from plant tissue during chopping, which transforms alkyl cysteine sulfoxides (ACSO) into volatiles. Headspace GC–MS analysis of fresh bulbs of *Codonoprasum* section species revealed that dimethyl-disulfide (Fig. 1) is by far the most dominant volatile compound in them, with a relative abundance of 70% to 100% (Simin 2014). Since dimethyl-disulfide is formed in a reaction catalyzed by alliinase from its precursor methiin, it can be concluded that the dominant alkyl cysteine sulfoxide (ACSO) in intact fresh bulbs of *Codonoprasum* section species is methiin (S-methyl-L-cysteine-sulfoxide), in aggreement with previously published results by Fritsch and Keusgen (2006), and Kusterer (2010). Small quantities of three other disulfides (methyl 1-propenyl disulfide, methyl propyl disulfide, methyl allyl disulfide) and dimethyl trisulfide (Fig. 1) were also found in some of the investigated species (*A. pallens*, *A. carinatum* subsp. *carinatum* and *A. fuscum* subsp. *fuscum*). This characteristic volatile profile in species from the *Codonoprasum* section, are very different from the profiles of onion, garlic and other representatives of the typical sect. *Allium* (Kallio and Salorinne 1990; Rose et al. 2005; Božin 2009) could be used for chemotaxonomic purposes. This simple profile is in accordance with the weak odor and flavor of species from *Codonoprasum* section.

The polyphenolics composition of *Codonoprasum* section species was also investigated. The total content of phenolic compounds (TPC) in whole plant methanol extracts was determined using a Folin-Ciocalteu assay. TPC varied between different species (2.15-15.2 mg galic acid eq per g of dw) and also among samples of the same species from different localities (Simin 2014). The highest TPC levels were found in extracts of *A. flavum*, *A. fuscum* and *A. paniculatum* (Simin 2014). However, TPC levels in *Codonoprasum* section species in general were lower in comparison to *A. cepa* (18.8 mg galic acid eq per g of dw, Simin 2014). In addition to TPC determination, quantification of selected phenolic compounds was conducted by LC–MS/MS in whole plant methanol extracts (Simin 2014). The most abundant phenolics in the extracts were flavonoids, particularly glycosides of quercetin and kaempferol (Fig. 2). The common dominant flavonoids for all investigated *Codonoprasum* sect. species from Serbia were isoquercitrin (quercetin 3-O-glucoside) and astragalin (kaempferol 3-O-glucoside) (Simin 2014). Rutin was present in extremely high amounts in *A. melanantherum*, *A. flavum*, *A. fuscum* and *A. paniculatum* (10.5–253 mg/g dw, Simin 2014). Hyperoside (quercetin 3-O-galactoside) was present only in extracts of *A. oleraceum* and *A. pallens* (1.04 mg/g dw and 8.11 mg/g dw, respectively), while aglycones isorhamnetin (3'-metoxi quercetin) and quercetin were detected only in *A. flavum* extracts (0.23–2.47 mg/g dw and 0.19–0.79 mg/g dw, respectively, Simin et al. 2013). The content of phenolic acids in methanol extracts of *Codonoprasum* sect. species were found to be significantly lower compared to flavonoids (Simin 2014). Hydroxycinnamic acids (ferulic, caffeic, p-coumaric and sinapic acid) and four benzoic acid derivatives (*p*-hydroxybenzoic, protocatechuic, vanillic and syringic acid) were present in all investigated samples (Fig. 2). *A. melanantherum* extracts were richest in phenolic acids in general, particularly in hydroxycinnamic acids (3.01–8.15 mg/g dw, Simin 2014).

ANTIOXIDANT ACTIVITY

Oxidative stress plays a crucial role in aging, as well as in the etiology of many diseases, such as different cancers, neurodegenerative disorders including Alzheimer's,

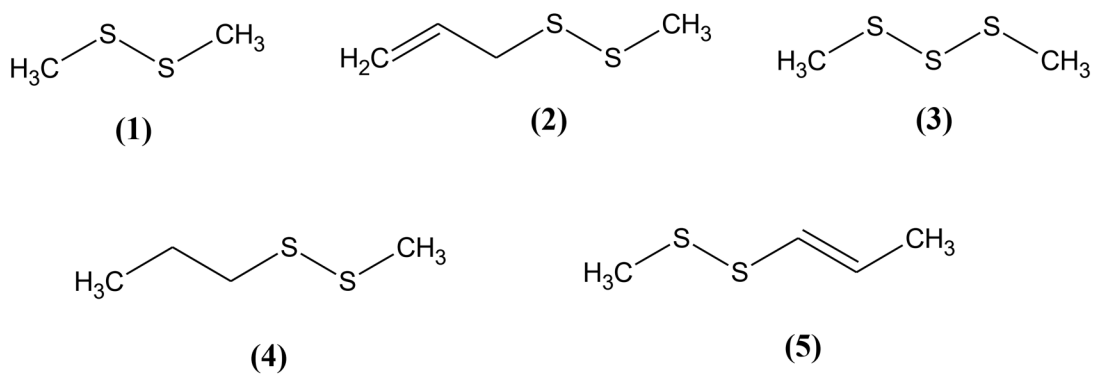

Fig. 1. Volatile sulfur compounds detected in *Codonoprasum* section species. **(1)** dimethyl-disulfide, **(2)** methyl 1-propenyl disulfide, **(3)** dimethyl trisulfide, **(4)** methyl propyl disulfide, **(5)** methyl allyl disulfide.

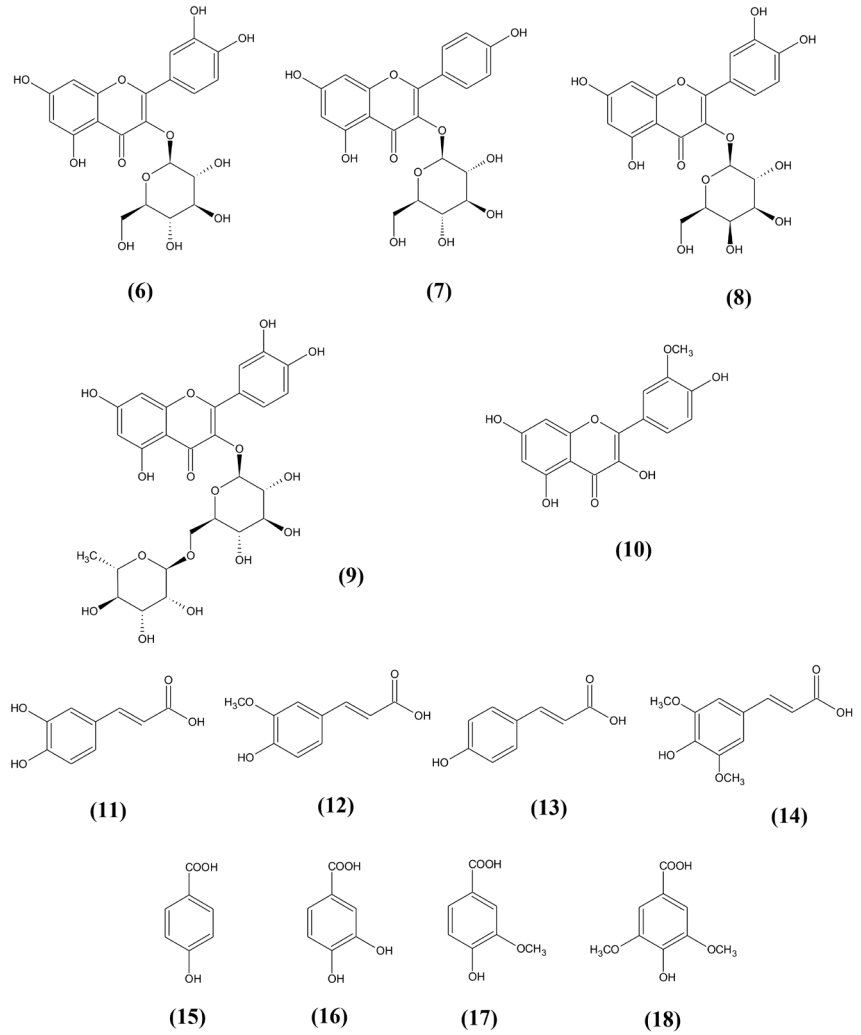

Fig. 2. Phenolic compounds detected in *Codonoprasum* section species. **(6)** isoquercitrin, **(7)** astragalin, **(8)** hyperoside, **(9)** rutin, **(10)** isorhamnetin, **(11)** caffeic acid, **(12)** ferulic acid, **(13)** p-coumaric acid, **(14)** sinapic acid, **(15)** *p*-hydroxybenzoic acid, **(16)** protocatechuic acid, **(17)** vanillic acid, **(18)** syringic acid.

Huntington's and Parkinson's disease, chronic inflammatory diseases including rheumatoid arthritis and systemic lupus erythematosus, as well as cardiovascular diseases (Olinski et al 2002; Cooke et al. 2003). Since cellular antioxidant mechanisms are often insufficient, the consumption of antioxidative compounds in food or as dietary supplements can protect cells from oxidative damage and improve human health (Dimitrios 2006; Ziech et al. 2012). The antioxidant activity of *Allium* species from *Codonoprasum* sect. was evaluated by standard *in vitro* spectrophotometric assays. Due to the presence of high amounts of phenolic compounds with strong reducing ability, extracts of *A. flavum*, *A. fuscum* and *A. paniculatum* expressed high scavenging capacity toward DPPH$^{\bullet}$, ABTS$^{\bullet+}$ and NO radicals, and strongly inhibited lipid peroxidation (Simin 2014). Since phenolics are mostly located in the aerial parts of investigated plants and not in bulbs, extracts of the aerial parts of *A. flavum* had higher antioxidant capacity than whole plant extracts. This activity was comparable to that of *A. cepa* extract, but lower in comparison to synthetic antioxidant BHA (Simin et al. 2013). Extremely high amounts of rutin in certain extracts, particularly in extracts of *A. melanantherum* and *A. flavum*, did not contribute significantly to antioxidant capacity, since the 3-OH group in the C ring of rutin that is needed for the reduction reaction is occupied in a glycosidic bond (Rice-Evans et al. 1996). In further studies, the protective effects of *A. flavum* and *A. melanantherum* extracts on oxidative DNA damage, as well as modulatory effects on the antioxidant cellular defense system were investigated (Mitić-Ćulafić et al. 2016). Oxidative DNA damage was induced by a latent ROS donor t-butyl hydroperoxide (t-BOOH), in human fetal lung fibroblast cells (MRC-5) and special *Escherichia coli* cells lacking redox-sensitive transcriptional activators of genes encoding antioxidant enzymes. It was found that both extracts reduce t-BOOH-induced DNA damage by 70% in MRC-5 cells, but not in *E. coli* cells. These results indicate that *A. flavum* and *A. melanantherum* extracts do not have direct protective effects against ROS in the cell, but activate cellular

antioxidant defence mechanisms, which then protect cells from oxidative DNA damage. To elucidate the mechanism of activation, the effect of *Allium* extracts on the activity of superoxide dismutase (SOD) and catalase (CAT) in MRC-5 cells was monitored. SOD protects the cells against superoxide anions, while the role of CAT is to eliminate hydrogen peroxide (Das 2002; Davies 2000). The results obtained show that *A. melanantherum* extracts significantlly increase CAT activity (by 34%), which correlate with enchanced enzyme levels, indicating that *A. melanantherum* extracts activate CAT gene expression. *A. flavum* extract slightly increased the activity of both CAT and SOD 1 (Mitić-Ćulafić et al. 2016). The conclusion of the above-mentioned studeies is that species from *Codonoprasum* section have potential to protect from oxidative stress through direct scavenging of free radicals and more importantly by modulation of cell-mediated antioxidant defense.

ANTI-INFLAMMATORY ACTIVITY

It is known that some *Allium* species, particularly garlic and onion, display anti-inflamatory activity both *in vitro* and *in vivo*, through different mechanisms (Srivastava 1986; Ali et al. 2000; Sengupta et al. 2004; Kim et al. 2005; Park 2011), but for members of *Codonoprasum* section, anti-inflammatory activity has only been investigated recently. Extracts of *A. flavum*, *A. rhodopeum*, *A. oleraceum*, *A. paniculatum*, *A. carinatum*, *A. fuscum*, *A. pallens* and *A. melanantherum* were included in the study, and their potential to inhibit the production of eicosanoids in COX-1 and 12-LOX pathways in human platelets was measured (Simin 2014). Eicosanoids formed in these pathways are significant mediators of inflammation (Smith, 1989). Extracts of *A. flavum*, *A. rhodopeum*, *A. oleraceum* and *A. paniculatum* expressed high inhibitory activity toward both COX-1 and LOX-12 enzymes, comparable to the activity of *A. cepa*. It is supposed that *A. rhodopeum*, *A. oleraceum* and *A. cepa* extracts act by inhibiting phospholipase A2, which catalyzes the initial step in arachidonic acid metabolism pathway. Aerial part extracts of *A. flavum* exhibited the highest anti-inflammatory activity compared to all other investigated samples, and more strongly inhibited 12-LOX than COX-1: at concentrations less than 0.25 mg/mL they acted as a selective inhibitor of 12-LOX (Simin et al. 2013; Simin 2014). Thus, aerial part extracts of *A. flavum* could be beneficial for the treatment of pathological conditions related to excessive 12-HETE generation, such as cancer (Nie and Honn 2002), psoriasis (Kragballe et al. 1986), atherosclerosis (Nakao et al. 1982) and rheumatoid arthritis (Liagre et al. 1997).

CYTOTOXIC POTENTIAL

The cytotoxic potential of species from genus *Allium* sect. *Codonoprasum* was investigated in normal (MRC-5) and various cancer cell lines (HeLa, MCF7, HT-29, HCT-116, SW480). Methanol extracts of the aerial parts of *A. flavum* expressed good anti-proliferative activity toward human colorectal carcinoma cells (HCT-116, IC_{50}=28 μg/mL, Curcic et al. 2012), cervix epithelioid carcinoma (HeLa, IC_{50}=36 μg/mL, Simin et al. 2013) and breast adenocarcinoma cells (MCF7, IC_{50}=25 μg/mL, Simin et al. 2013), but was equally cytotoxic for normal cells (MRC-5, IC_{50}=30 μg/mL, Simin et al. 2013); limiting its potential applications. In further research, it was found that three new spirostane-type steroidal glycosides isolated from *A. flavum* exhibited moderate cytotoxicity against a human colorectal cancer cell line (SW480, Rezgui et al. 2014). *A. paniculatum*, *A. melanantherum* and *A. rhodopeum* extracts expressed moderate, but selective antiproliferative activity. Namely, *A. paniculatum* whole plant extracts selectively inhibited proliferation of HT-29 cells, *A. melanantherum* aerial part extracts inhibited only MCF7 cells, while *A. rhodopeum* whole plant extracts exhibited two-fold stronger antiproliferative activity toward HeLa and MCF7 cells over normal cells (Simin 2014). Extracts of *A. carinatum*, *A. fuscum*, *A. pallens* and *A. oleraceum* expressed low and unselective cytotoxicity (IC_{50} values in the range of 250–880 μg/mL), while *A. cepa* and *A. sativum* extracts did not have any effect on cell growth (Simin 2014). Since extracts of species from *Codonoprasum* section did not display very high cytotoxic potential, in future studies the ability of the extracts to modulate the cytotoxic activity of the anticancer drug doxorubicin (Dox) was investigated (Pavic et al. 2019). Dox was applied at a sub-lethal concentrations (survival rate ~80%) to normal and cancer cells in combination with extracts of *A. flavum* and *A. carinatum* subsp. *pulchelum* at different concentrations. The combination treatment greatly reduced the survival rate of both cancer cell lines (up to 8%) compared with Dox alone. On the other hand, the extracts protected normal cells (MRC-5) from Dox toxicity raising their survival rate to 99% (Pavic et al. 2019). While strong synergistic effects were found for extracts and Dox against cancer cells, these effects were antagonistic in MRC-5 cells. The extracts potentiated Dox-induced apoptosis in cancer cells and attenuated Dox cytotoxicity in normal cells by reducing oxidative stress (Pavic et al. 2019).

PROTECTIVE EFFECTS FROM DOXORUBICIN TOXICITY IN ZEBRAFISH EMBRYOS

Doxorubicin (Dox) is a highly effective, first-line chemotherapeutic used for the treatment of haematological malignancies and solid tumours, particularly hepatocellular, breast

and lung carcinoma. However, due to low selectivity, Dox also targets normal tissues where it induces oxidative stress and impairment of antioxidant defence, leading to severe cardiotoxicity, hepatotoxicity and myelosuppression. Thus, potential adjuvant therapies are needed that can reduce the harmful side effects of Dox. To examine the possible protective effect of *Allium* extracts on Dox caused toxicity, zebrafish embryos were pre-treated with Dox and then exposed to *A. flavum* and *A. carinatum* extracts. Results indicate that the extracts provide complete protection of the embryos from the cardiotoxic and teratogenic effects of Dox: however, the timing of extract administration is very important – they should be administered before irreversible damages of heart muscle occur (Pavic et al. 2019). Additionally, *A. flavum* and *A. carinatum* extracts demonstrated strong protective effects against Dox-caused neutropenia in zebrafish embryos. This is particularly important because Dexrazoxane, the only FDA-approved cardioprotective agent for Dox chemotherapy, worsens myelouppression in cancer patients (Langer 2014). The obtained results suggest that *A. flavum* and *A. carinatum* extracts have potential to be used as adjuvants in Dox chemotherapy.

ANTI-ANGIOGENIC ACTIVITY

The growth, invasion and metastasis of cancers are fully dependent on neovascularization (Folkman 1995). Because of this, several anti-angiogenic drugs have been approved for use in combination with chemotherapy, which increase survival rates in cancer patients (Cesca 2013). The potential of *A. flavum* and *A. carinatum* extracts to suppress angiogenesis was studied in Tg(fli1:EGFP) transgenic zebrafish embryos, in which endothelial cells expressing EGFP were directly observed by fluorescence microscopy (Pavic et al. 2019), and effects were compared with approved antiangiogenic drugs - auranofin and sunitinib-malate. The extracts displayed higher anti-angiogenic activity than both auranofin and sunitinib, while causing no developmental defects in zebrafish embryos. On the other hand, both auranofin and sunitinib induced serious cardiotoxic effects, retarded embryo growth and reduced survival (Pavic et al. 2019). In combination treatments (*A. flavum* and *A. carinatum* extracts with Dox), suppression of neovascularization was even higher than in single treatments (Pavic et al. 2019). All the mentioned results strongly support the potential use of extracts of wild edible onions *A. flavum* and *A. carinatum* as complementary therapy alongside Dox treatment.

CONCLUSIONS

Here we provide a short overview of the chemical composition and biological activities of less known wild onions from sect. *Codonoprasum* of genus *Allium*. These onions have characteristic profiles with respect to sulfur volatiles, that are very different from onion and garlic, with dimethyldisulfide being the dominant compound. They are rich in phenolic acids and flavonoids, particularly quercetin and kaempferol glycosides. The species from *Codonoprasum* sect. have high protective potential vs. oxidative stress by direct scavenging of free radicals or by modulation of cell-mediated antioxidant defenses. Some of these species, especialy *A. flavum*, express high anti-inflamatory potential. In combination with doxorubicin, these extracts potentiated Dox-induced apoptosis in cancer cells and attenuated Dox cytotoxicity in normal cells by reducing oxidative stress. *A. flavum* and *A. carinatum* extracts completely protected zebrafish embryos from the cardiotoxic and teratogenic effects of Dox, as well as from Dox-induced neutropenia, and expressed strong anti-angiogenic potential. All of the above results suggest that species from *Codonoprasum* section of genus *Allium* have high potential for applications in medicine.

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