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Radioprotective action of resurrection plant *Haberlea rhodopensis* Friv. (Gesneriaceae) and role of flavonoids and phenolic acids

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Abstract

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Haberlea rhodopensis Friv. (Gesneriaceae) is a Balkan endemic and resurrection glacial relict plant which is distributed in Bulgaria (Rhodope Mountains, Sredna Gora Mt. and Central Balkan). Currently, there is a huge interest in *Haberlea rhodopensis*, and several scientific studies aimed at the isolation and identification of its active components as well as the investigation of the pharmacological effects and possibilities of the use of *Haberlea rhodopensis* as a medical plant have been conducted. The main effects of *Haberlea rhodopensis* include radioprotective, anti-mutagenic, antioxidant and anti-ageing properties. This review emphasises the radioprotective potential of *Haberlea rhodopensis* and focuses on the biological properties of its ingredients like flavonoid aglycones and glycosides as well as phenolic acids in relation to their capacity to capture free radicals and reduce oxidative stress. More research on animals and humans are needed for clarification of the mechanisms of action and the eventual side effects of *Haberlea thodopensis* and its compounds as radioprotective agents.

Keywords: Resurrection plants, *Haberlea rhodopensis*, radioprotection, flavonoids, phenolic acids

Introduction

It is widely acknowledged that ionizing radiation causes damage to living organisms and induces a wide range of lesions in somatic and germ cells that can bring about mutations, cell inactivation, hereditary diseases and cancer. Irradiation causes an overabundance of reactive oxygen species (ROS) and free radicals that damnify integral macromolecules in the living cells (Cox et al., 1995). The most important target for ionizing radiation is genomic DNA. DNA changes appear as a result of direct ionization leading to injury of both the nucleobases and sugar or indirectly through the generation of ROS (Rehmana et al., 2016). If the repair of DNA is incorrect it may result in mutations, as double strand breaks, cross-links, base modifications, chromosome aberrations, etc. Apart from DNA, ROS attack lipids and proteins and cause oxidation, membrane damage, enzyme inactivation and other disorders (Ghosh et al., 2018). Consequently, since exposure to radiation accidentally or in radiotherapy can produce acute and late effects, it is very important to protect normal tissue by the use of nontoxic and efficient radioprotectors. Although synthetic compounds such as RW-2127 exhibited good protective properties, their toxicity in optimal doses promoted the search for new less

toxic and more effective alternatives (Jageta, 2007). This is why, over the decades a large number of plants and phytochemicals were considered as radioprotectors on account of their pharmacological properties and low toxicity (Cheki et al., 2016; Zbikowska et al., 2016; Ghali et al., 2018).

Resurrection Plants

Resurrection plants are a small group of species belonging to different botanical families. What is typical of them is the high sustainability to extreme conditions like drought or desiccation. They have the ability to survive drought for months and years after which, in the presence of water, they can recover and continue to develop normally (Alpert & Oliver 2002). The mechanism of safekeeping of resurrection plants has been studied by many investigators (Blomstedt et al., 1998; Challabathula et al., 2016; Van Buren et al., 2018) and it is widely believed that defence is provided by a variety of processes including accumulation of different types of sugars, proteins and other substances which work together to substitute water and stabilise the subcellular environment. Via transcriptome analysis it was revealed that the drought induces new genetic programming, which directed resources from growth and development to cell protection (Gechev et al., 2013). Their observations suggested that both constitutive and inducible processes work concomitantly for the persistence during severe desiccation.

Haberlea rhodopensis (Friv.) (Fig.1) is an endemic resurrection plant, within a very small group of poikilohydrate angiosperms, member of the family Gesneriaceae. It is a Balkan Peninsula relic plant that has emerged before the glacial period. Gechev et al., (2014) reported that *Haberlea rhodopensis* under conditions of drying and humidification revealed common genetic pathway with other desiccation tolerant species and has unique genes that may contribute to its desiccation sustainability. *Haberlea rhodopensis* is a unique plant that may serve not only as a model for the study of revitalization mechanisms after surviving strong water loss and as a source of genes involved in regeneration but also as a medicinal plant due to the beneficial properties of the ingredients of its extracts (Gechev et al., 2014).

Fig. 1. Resurrection plant *Haberlea rhodopensis*

Chemical composition of Haberlea rodopensis

The chemical composition of the family Gesnieceae was studied by many authors (Lowry, 1972; Francisco, 1995; Jensen, 1996; Cai et al., 2005; Djilianov et al., 2009) and, as a result, flavonoids, caffeoyl phenylethanoid glycosides, tannins, anthocyanins, zeaxanthin, and ascorbate from various genders of the family have been established.

The availability of myconoside, paucifloside and 3 new flavone C-glycosides, hispidulin 8-C-(2''-O-syringoyl)-b-glucopyranoside, hispidulin 8-C-(6-O-acetyl-b-glucopyranoside), hispidulin 8-C-(6-O-acetyl-2-O-syringoyl-b-glucopyranoside), was reported in *Haberlea rhodopensis* by Ebrahimi et al., (2011). According to Berkov et al., (2011), metabolic profiling (gas chromatography in combination with mass spectrometry, GC–MS) of the polar and apolar fractions from methanolic extracts of *Haberlea rhodopensis*, showed availability of a large quantity of ingredients, including amino acids, fatty acids, several phenolic acids, sterols, glycerides, saccharides, flavonoids and polyphenols.

Microwave-assisted extraction of flavonoid antioxidants from *Haberlea rhodopensis* and evaluation for their total phenolic content also indicated the presence of flavonoid aglycones and glycosides (Fig. 3.) (Mihaylova et al., 2011). More than 100, mostly bioactive compounds have been found in *Haberlea rhodopensis* (Markovska et al., 1992; Djilianov et al., 2011; Moyankova et al., 2014). Recently the content of flavone C–glycosides and caffeoyl phenylethanoid glycosides in *Haberlea rhodopensis* was determined (Zheleva-Dimitrova et al., 2016) and it has been demonstrated that miconoside is the main compound in *Haberlea rhodopensis* extract (332.2 ± 0.7 mg/g dw), reaching to 88.8% from the estimated mixture in leaves, followed by paucifloside (24.8 ± 2.1 mg/g dw). Among the flavone 8-C-glycosides the most abundant was hispidulin 8-C-(6-O-acetyl-glucopyranoside (6.9±0.6 mg/g dw) as the overall content of flavon C-glycosides was 17.1 mg/g dw.

Phenolic acids in Haberlea rhodopensis and their biological activities relevant to radiation protection

According to many investigators, phenolic acids possess therapeutic properties that are due to their ability to capture free radicals and to decrease oxidative stress. They are widely used for the prophylaxis and treatment of cancer, diabetes,

inflammatory diseases and different oxidative stress-related diseases (Griffiths et al., 2016; Mut-Salud et al., 2016; Simoes et al., 2018). Mihaylova et al. (2011) reported that in the *Haberlea rhodopensis* alcoholic extract, the most abundant phenolic acids are ferulic acid (10.882 g/ml), caffeic acid (7.373 g/ml), p-coumaric acid (5.774 g/ml), etc. (Fig.2).

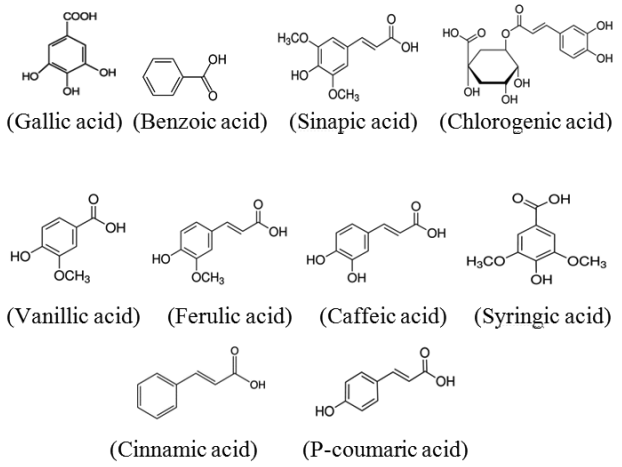

Fig. 2. Chemical structure of phenolic acids in Haberlea rhodopensis

Gallic acid (3,4,5-trihydroxybenzoic acid)

The effects of gallic acid were studied under in vitro and in vivo circumstances and the results showed well defined radioprotective properties (Gandhi and Nair 2005). In their *in vitro* study, the authors tested the protective action of different concentrations of gallic acid in irradiated rat liver microsomes and plasmid pBR322 DNA. The results showed reduction of DNA injury and defence of microsomes against radiation-induced lipid peroxidation by gallic acid administrated during irradiation. At the same time, gallic acid was introduced before whole-body irradiation of mice, resulting in reduction of DNA damage in peripheral leucocytes and protection against lipid peroxidation in vivo (Gandhi & Nair, 2005).

Nair and Nair (2013) have also found some defensive action of gallic acid on lipid peroxidation in gamma-treated Swiss albino mice, along with raised levels of antioxidant enzymes, glutathione peroxidase and thiol glutathione. Additionally, they reported an anticlastogenic effect, activation of reparative processes in DNA and reduction of mortality and loss of weight in irradiated mice, as a result of gallic acid administration before irradiation.

Other conducted studies confirmed gallic acid as a proven antioxidant with neuroprotective (Mansouri et al., 2013), anticarcinogenic, antimutagenic and antiinflammatory action (Verma et al., 2013).

Caffeic acid (3,4-dihydroxy)-cinnamic acid

Numerous studies have indicated that caffeic acid is a strong antioxidant (Bors et al., 2004; Liu et al., 2019). Through different in vitro antioxidant assays Gülçin (2006) established that caffeic acid is a potent inhibitor of lipid peroxidation and manifested powerful radical scavenging capacity. A significant decrease of the density of chromosome aberrations, micronuclei and comet parameters was observed in human lymph cells administered with 66 μM caffeic acid 30 min. before gamma irradiation (Devipriya et al., 2008).

Hakkim et al., (2014) have conducted an experiment with human skin cells to test the radioprotective action of 5 phenolic acids (caffeic acid, rosmarinic acid, trans-cinnamic acid, p-coumaric acid and hydroxyphenyllactic acid). The comparison of the results has shown that the introduction of caffeic acid, rosmarinic acid and trans-cinnamic acid before irradiation of keratinocytes improved the intracellular antioxidant balance and reduced DNA damage, as the most efficient was caffeic acis.

Sevgi et al., (2015) have explored the mutagenic action of UV and H_2O_2 on plasmid BR322 DNA in the availability and unavailability of several phenolic acids, including caffeic acid. The results showed the defensive effect of caffeic acid against the DNA injury caused by the two mutagens. In addition, caffeic acid was found to be effective against inflammation, mutagenesis, bacterial infections and carcinogenesis, due to its radical scavenging capacity (Genaro-Mattos et al., 2015).

Ferulic acid (4-hydroxy-3-methoxy cinnamic acid)

Ferulic acid is known as a strong antioxidant. Those effects are due to the donation of electrons from hydroxyl and phenoxy groups of ferulic acid that scavenge the free radicals (Srinivasan et al., 2007). For a more detailed explanation of the effects of ferulic acid, Prasad et al., (2006) used 3 different concentrations of ferulic acid and 3 different doses for gamma irradiation of lymphocyte cultures. The results from this experiment showed that administration of ferulic acid prior to exposure of human lymph cells, significantly reduced DNA damage as indicated by the reduced quantity of micronuclei, dicentric aberration and lipid peroxidation and also by the improved antioxidant condition of the cells.

In another experiment, mice were treated with various quantities of ferulic acid (50, 75 and 100 mg/kg body weight) one hour prior exposure to 4.0Gy whole body gamma irradiation. The introduction of ferulic acid induced a concentration-dependent reduction in the DNA injuries in peripheral blood leukocytes and bone marrow cells of mice (Maurya et al., 2005).

Similar evidence for radioprotective action of ferulic acid is presented by Shanthakumar et al., (2012). Their study in *vivo* with irradiated Swiss albino mice indicated that pretreatment with ferulic acid resulted in decrease of inflicted lipid peroxidation and DNA defects, and also improved antioxidant and histopathological amendments in animals. They also reported an antigenotoxic result of ferulic acid *in vitro* expressed by a significant decrease of the comet parameters (% tail DNA, tail length, tail moment and Olive tail moment, comet assay).

P-coumaric acid (4-hydroxycinnamic acid)

Lodovici et al., (2001) investigated the effect of several native phenolic acids on DNA oxidation *in vitro* and found that p-coumaric acid diminished DNA injury caused by Fe and cumene hydroperoxide.

In another *in vivo* experiment, rats were treated for 2 weeks with p-coumaric acid in the diet (25 or 50 mg/kg) and results revealed that p-coumaric acid (50 mg/kg) decreased effectively the basic level of oxidative DNA injury in rat colonic mucosa (Guglielmi et al., 2003). Because of its powerful anti-oxidant and anti-apoptotic potential p-coumaric acid manifested neuroprotective action in a rat model of embolic cerebral ischemia (Guven et al., 2015). P-coumaric acid effectively scavenges free radicals, diminishes lipid peroxidation, and also possesses antibacterial, antimutagenic and immunoregulatory activities (Andreicuţ et al., 2019; Shen et al., 2019).

Chlorogenic acid - 3-(3,4-dihydroxycinnamoylquinate

Cinkilic et al. (2013) investigated *in vitro* by comet assay the safeguarding effect of different quantities of chlorogenic acid administrated in human lymphocytes in the presence and lack of X radiation. They observed a lack of genotoxicity in lymphocytes treated with chlorogenic acid only and effective protection against X-ray induced genomic instability. The most effective dose of chlorogenic acid, diminishing by 48.15% the DNA damage was 4 μg/ml. Other authors in the experiments with gamma-irradiated mouse bone marrow cells and human lymphocytes reported that chlorogenic acid acts as a strong antioxidant, free radical neutralizer and anticlactogen (Hosseinimehr et al., 2007; Cheki et al., 2016). Likewise, it was found that chlorogenic acid inhibited MAM acetate-caused carcinogenesis in colon and liver of hamsters (Mori et al., 1986).

Sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid)

Sinapic acid is revealed to have strong antioxidant capacity and free radical scavenging potential to catch superoxide anion ($O2^{-}$), hydroxyl radicals (·OH) and other free radicals (Chen, 2016). According to Thiyam et al., (2006) sinapic acid has the potential to inhibit the products of lipid peroxidation. Hameed et al., (2016) analysed the usefulness for humans of the sinapic acid and its derivatives, particularly 4-vinylsyringol, and established safeguarding effect of sinapic acid against inflammation, mutagenesis and cancer.

Cinnamic acid (3-phenylacrylic acid)

The radioprotective effectiveness of cinnamic acid has been tested in X-ray irradiated human blood lymph cells *in vitro*. Initially, in this experiment it was found out that cinnamic acid did not exhibit genotoxic activity on non-irradiated lymphocytes and then it was revealed that cinnamic acid administrated to irradiated lymphocytes cultures decreased DNA injuries caused by X-rays, as indicated by a reduced quantity of micronuclei (16-55%) and DNA breaks (17-50%) in contrast with irradiated lymphocytes (Cinkilic et al., 2014). Sova (2012) also reported that cinnamic acid has low toxicity and a broad spectrum of biological activities, due to its strong ability to capture free radicals.

As we have already mentioned, the extraction of flavonoid antioxidants from *Haberlea rhodopensis* and evaluation of their total phenolic content was shown the presence of significant quantities of flavonoid aglycones and glycosides (Fig. 3) (Mihaylova et al., 2011).

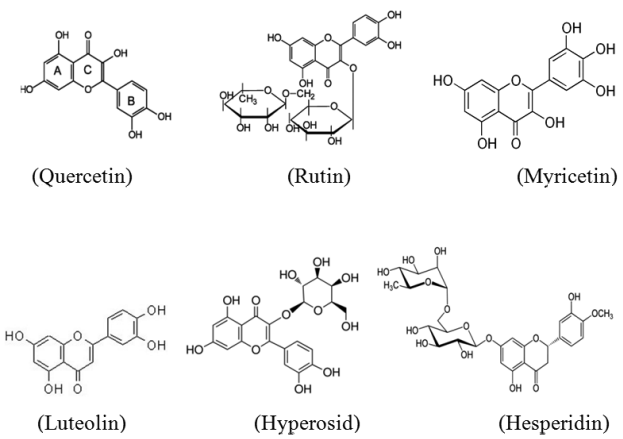

Fig. 3. Flavonoid aglycones and glycosides in *Haberlea rhodopensis*

According to Mihaylova el al., (2011) among the flavonoid aglycones and glycosides in *Haberlea rhodopensis* the most abundant is luteolin (55.118 g/ml) followed by hesperidin (10.122 g/ml), myricetin (11.7 g/ml), rutin, quercetin, etc.

Flavonoid aglycones and glycosides in Haberlea rhodopensis and their biological activities relevant to radiation protection

Luteolin (3',4',5,7-tetrahydroxyflavone)

Early experimental research of Shimoi et al. (1996) have shown strong anticlastogenic and antioxidative effect of luteolin. In this article luteolin was revealed as the most effective anticlastogen (micronucleus test) among the 12 tested flavonoids from rooibos tea (*Aspalathus linearis*). In addition, gastric administration of luteolin before high dose gamma irradiation led to an increase of endogenous antioxidants and a decrease of lipid peroxidation in mouse bone marrow and spleen. Anticlastogenic activity of luteolin against X-rays was also established in mouse bone marrow cells by Benavente-García et al., (2004).

The flavone luteolin exhibited a high protective effect against the t-BHP-induced DNA strand breaks with a reduction in DNA damage, evaluated by the Comet assay (Silva, et al., 2008). Materska et al. (2015) reported that luteolin manifested radioprotective activity against X-rays. They also determined the high coefficient of the correlation between the X-rays radioprotective effect of phenolic glycosides and their scavenging activities against O2− generated in the NADH/PMS system.

Lien et al. (1999) reported that luteolin acts against ROS through its own oxidation, and restricts ROS-generating oxidases (Nagao et al., 1999).

Many other investigators have established that luteolin has a multiplicity of medical properties, including antioxidant, antimicrobial, anti-inflammatory, anti-cancer activity and possibilities to enhance endogenous antioxidants (Leung et al., 2006; Lin et al., 2008; Moga et al., 2016).

Hesperidin (4'-methoxy-3',5,7-trihydroxyflavanone)

Studies have shown the antioxidant potential of hesperidin and its safeguarding action against H_2O_2-induced oxidative damage on pBR322 DNA and shielding effect to human lymph cells and RBC cellular membranes against radiation-induced damage (Kalpana et al., 2009 a,b).

The protective effect of IP administration of hesperidin in different doses prior to gamma irradiation (2 Gy) of mice was proven by the dose-dependent reduction of radiation-induced DNA damage in PCEs of mice (Hosseinimehr & Nemati 2006). Hesperidin was also found to reduce oxidative stress and decrease hepatocellular damage in Sprague–Dawley rats (Pradeep et al., 2008).

The positive effects of hesperidin were evaluated in experimental animals by different methods: 30 days of survival study, biochemical assay, comet assay, DNA fragmentation assay and histopathological alterations in the mouse liver (Kalpana et al., 2011). The authors established an antioxidant effect, defence against DNA damage and protection against liver damage in irradiated mice, pre-treated with hesperidin.

In general, hesperidin has been proven to have a broad spectrum of pharmacological effects, which also include anti-inflammatory, anti-allergic, hypolipidemic, vasoprotective and anti-carcinogenic action (Emin et al., 1994; Haddadi et al., 2017).

Myricetin (3,3',4',5,5',7-hexahydroxyflavone)

Different investigations have indicated that myricetin has an antioxidant, anti-inflammatory and efficient anticancer effect (Ross & Kasum, 2002; Sun et al., 2012; Semwal et al., 2016; Arruda et al., 2018; Jariala et al., 2018). Aherne & O'Brien (1999) in their study examined the effect of the 3 flavonoids – myricetin, quercetin, and rutin, on DNA *in vitro*. They used Caco-2 and Hep G2 cell lines exposed to H_2O_2. After pre-incubation with myricetin and the other 2 flavonoids followed by H_2O_2 exposure of cell lines, they found a significant diminution of DNA injury in both cell lines.

Abalea et al., (1999) also investigated the protective effect of different concentrations of myricetin against iron-induced DNA damage in cultures of rat hepatocytes. They reported that simultaneous administration of myricetin and iron protects against DNA base oxidation and activates the expression of DNA repair enzymes in a dose-dependent manner.

Quercetin (3,3',4',5,7-pentahydroxyflavone) and rutin (3,3',4',5,7pentahydroxyflavone-3-rutinoside)

Lots of experimental outcomes revealed that quercetin and its derivative rutin are excellent in vitro antioxidants. The antioxidant and radiodefensive activity of both flavonoids was investigated in mice treated with gamma radiation by Patil et al., (*2013*). The results revealed that the application of rutin and quercetin caused elevation of endogenous antioxidants, reduction of lipid peroxidation and inhibition of various free radicals in a dose-dependent way. They also determined radical scavenging activity in vitro by different assays (2,2-diphenyl-1-picrylhydrazyl (DPPH), O2, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS)+, and OH) and concluded that the radioprotective action of rutin and quercetin is probably due to their antioxidant features and high ability to capture free radicals.

In agreement with the previous authors Londhe et al., (2009) reported the defensive effect of rutin and quercetin expressed through diminished lipid peroxidation and protein oxidation in rat liver mitochondria. They also established reduction of radiation-induced DNA damage and more specifi-

cally diminishing in single-strand breaks in plasmid DNA. According to those authors the described effects can be explained by the strong hydroxyl radical scavenging activity of the phytochemicals.

The antigenotoxicity of rutin and quercetin was demonstrated by Patil et al., (2014). In their investigation the introduction of rutin and quercetin before exposure led to a significant diminution in the chromosome aberrations in mice bone marrow cells, micronuclei in PCE and olive tail movement (OTM) in blood leukocytes and those effects are an indicator for anticlastogenicity and antigenotoxicity of rutin and quercetin.

The antigenotoxic effect of quercetin and rutin was also proven on hep G2 cells exposed to H_2O_2 by Barcelos et al., (2011). Some protection against H_2O_2 -induced oxidative stress was found by the administration of both phytochemicals at low non-toxic doses, although at higher concentrations an increase in intracellular ROS was observed.

According to Silva et al., (2008) quercetin protected DNA against oxidative damage of PC12 cells, as the repair of DNA reached 24.7%. In an *in vivo* experiment, the defence by quercetin against radiation-induced DNA injury and apoptosis in kidney and other tissues of rats was proven by Özyurt et al. (2014). Sancar et al., (2004) reported a protective effect of quercetin against DNA strand breaks, enhancement of the repair of MMS-induced damage and excision of damaged nucleotides. Quercetin also showed high radioprotective action (50% vs control) on human lymph cells in response to X ray-induced oxidative damage (Materska et al., 2015) and reduction of percentage mortality and cytogenetic damage in gamma irradiated Swiss mice (Patil et al., 2014).

The anti-cancer activity of quercetin has been examined *in vitro* and *in vivo* by Gibellini et al., (2010) and Hashemzaei et al., (2017). Quercetin at the proper concentrations was found to induce the apoptosis of some tested cancer cell lines and to cause a significant reduction in tumour volume in mice bearing tumours. In addition, quercetin depleted intracellular glutathione and increased intracellular ROS in cancer cells to a level that can cause cell death.

According to Kondareva-Burdina et al. (2013) along with the above mentioned compounds of *Haberlea rhodopensis* with useful properties, the caffeoyl phenyl-ethanoid glycoside myconoside and flavone-C-glycosides hispidulin 8-C-(2-O-syringoyl-glucopyranoside), hispidulin 8-C-(6-O-acetyl-2-O-syringoyl-glucopyranoside), and hispidulin 8-C-(6-O-acetyl-glucopyranoside) isolated from *Haberlea rhodopensis* have shown a good relationship between the cyto-protection of rat hepatocytes, free radical scavenging and antioxidant effect. The authors also reported that myconoside possesses the strongest DPPH radical scavenging and antioxidant potential in the linoleic acid system.

Radioprotective effects of Haberlea rhodopensis extract

A number of medicinal plants and their ingredients have been studied and their radioprotective effect was established *in vivo* and *in vitro* (Taheri et al., 2016; Chandrasekaraa & Shahidi, 2018; Shaikh & Shah, 2018). The results showed that plant extracts that exhibit radioprotective effects contain a variety of compounds with antioxidants, free radical scavenging, anticlastogenic, antigenotoxic, antimicrobial, and immunomodulatory properties.

In our studies, the *Haberlea rhoropensis* leaf extract has been tested as an antioxidant and radioprotector in experimental animals - New Zealand rabbits. The radioprotective property of *Haberlea rhoropensis in vitro* was first reported by Popov et al. (2010). The effect of *Haberlea rhoropensis* was investigated in the blood lymphocytes of rabbits after exposure to gamma irradiation and the results showed that *Haberlea rhoropensis* pre-treatment of lymphocyte cultures effectively diminished the quantity of aberrant cells and chromosome aberrations. The comparison of the anticlastogenic effect of *Haberlea rhoropensis* with vitamin C indicated that both the reduction of aberrant cells, the density of chromosome fragments and dicentrics are highly expressed after *Haberlea rhoropensis* treatment.

In other *in vivo/in vitro* studies, the genetic deteriorations in peripheral blood lymphocytes exposed to gamma rays (1.0-3.0 Gy) indicated that radiation-induced increase of chromosome aberrations is dose-dependent. Pre-treatment with different concentrations of *Haberlea rhoropensis* extract strongly diminished the quantity of aberrant cells and chromosomal aberrations, including dicentrics and rings, in a dose-dependent manner (Popov et al., 2011; 2012; 2013).

The alkaline single cell gel electrophoresis analysis of lymph cells from the whole body irradiated rabbits, pretreated with *Haberlea rhoropensis* indicated a reduction in induced cellular DNA damage, like the formation of alkali-labile sites and single and double breaks (Georgieva et al., 2012).

In addition, a biochemical and cytogenetic assay has been carried out to detect the modifying effect of *Haberlea rhoropensis* against radiation-induced oxidative stress. It was observed that *Haberlea rhoropensis* pre-treatment significantly increased the activity of the antioxidant enzymes SOD and CAT (compared between the control and irradiated groups). At the same time the anti-lipid peroxidative effect of *Haberlea rhoropensis* was registered through the reduction of MDA level in blood plasma (Georgieva et al., 2013). Furthermore, cytokinesis blocked micronucleus assay (CBMN) in peripheral lymphocytes revealed a significant reduction of the quantity of MN events in lymphocytes protected with *Haberlea rhoropensis* (Georgieva, 2014).

These observations and the information about the compounds in *Haberlea rhoropensis* and their biological activities relevant to radiation protection provide information on the mechanism of the action of the extract. Fig.4

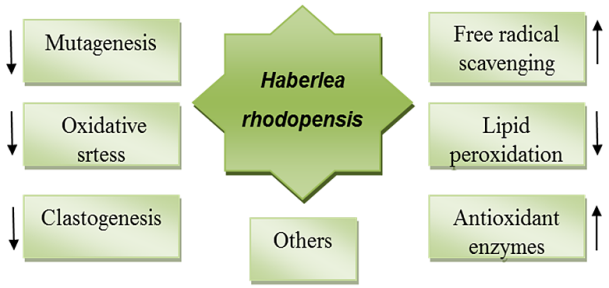

Fig. 4. Mechanism of action of *Haberlea rhoropensis* extract

Many authors have reported a linear correlation between the content of all phenolic compounds and their antioxidant capacity (Katalinic et al., 2006; Chen et al., 2016; Sricharoen et al., 2017; Verma et al., 2018).

The results obtained for *Haberlea rhoropensis* evaluated by reducing power assay activity showed a good positive correlation R^2 0.8286, which suggested that the major antioxidant activity was due to phenolic compounds, which determined its pharmacological properties (Michaylova et al., 2011). In addition to that, to evaluate the usefulness of *Haberlea rhoropensis* for application in phytotherapy Berkov et al., (2011) investigated the cellular viability and cell survival of five cell lines and a lack of any toxicity in tested lines has been found.

Conclusion

The possibilities of using the extracts of medicinal plants, including *Haberlea rhoropensis*, depend on their phytochemical spectrum. Polyphenols such as phenolic acids, flavonoid aglycones and glycosides manifest their action through complex mechanisms. They may capture free radicals, improve the antioxidant balance, regulate the genes responsible for DNA repair and influence the expression of mRNAs of antioxidant enzymes, thus restoring the disequilibrium in cells exposed to ionizing radiation. The presence of an intense antioxidant, free radical scavenging and radioprotective potential as well as the lack of cytotoxic activity of *Haberlea rhoropensis* indicates that it may be used in phytotherapy and radiotherapy, but only after further research has been done and when the mechanisms of its action are basically studied.

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