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HABERLEA RHODOPENSIS – EFFECTS AND POTENTIAL APPLICATIONS

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ABSTRACT

In recent years, interest in the plant, natural products as an alternative to the conventional ones has increased. Since ancient times the plant Rhodope silivryak *(Haberlea rhodopensis* Friv.) had been known for the treatment of humans and animals. The plant is also called Orpheus. The flower refers to the "resurrecting" plants and it is spread in the Rhodopes Mountains.

A number of properties have been studied and described: antioxidant, radioprotective, antimicrobial, antimutagenic, anticancer, immunostimulatory, chemoprotective, cytotoxic and anti-aging of Haberlea rhodopensis. Its essential components are myconoside , ferulic acid, caffeic acid, syringic acid, luteolin, quercetin, hesperidin, sinapic acid, etc. *Haberlea rhodopensis* extracts did not show any cytotoxic activity.

The aim of this review is the effects of *Haberlea rhodopensis* and its potential applications in phytotherapy, human and veterinary medicine, and cosmetics.

Key words*: Haberlea rhodopensis*, effects, components, application.

Introduction

In recent years, interest in plant and natural products as an alternative to conventional ones has increased. The researchers are looking for new substances of plant origin that have improved therapeutic efficacy and lower toxicity. The Rhodope silivryak (*Haberlea rhodopensis* – HR) also called the Orpheus flower, refers to the "resurrecting" plants. It is a unique plant with its ability to survive for very long periods of desiccation (up to 31 months dried in a herbarium (Daskalova et al., 2011). The flower of HR, first described by Imre Frivaldszky, was named after the Hungarian botanist Haberle and the Bulgarian mountain of Rhodope, where it was found in 1834 (Szeląg and Somlyay, 2009).

In Bulgaria, *Haberlea rhodopensis* is widespread in the Rhodope Mountains and some regions of the Sredna Gora Mountains and the Stara Planina Mountains. The leaves of *H. rhodopensis* were used in folk medicine for the treatment of wounds and diseases of stock (foot-and-mouth disease and hoof rot) in the Rhodope region of Bulgaria. According to the natives, HR was used for the treatment of *Paronichya contagiosa* by adding it to the food of the animals (Radev et al., 2009).

In folk medicine, the herb is used to cleanse the liver, stomach, kidneys, blood vessels. The herb has a tonic and anti-aging effect (Georgiev et al., 2020).

In recent years *Haberlea rhodopensis* attracted the attention of researchers in terms of its beneficial effects on human and animal health. The aim of this review is to describe the effects of HR and the possibilities for its potential applications in phytotherapy, human and veterinary medicine, and cosmetics.

In *Haberlea rhodopensis* more than 100 compounds such as amino acids, fatty acids, phenolic acids, sterols, glycerides, saccharides, and others were found. The phytochemical research found that the *Haberlea rhodopensis* leaf extract contains some biologically active substances such as flavonoids, tannins, polysaccharides, and phenolic acids with antioxidant, antiradical and antimicrobial activities (Todorova and Atanasov, 2015; Berkov, 2011).

The *Haberlea rhodopensis* extract (HRE) contains high levels of flavonoid antioxidants. Some phenolic compounds were identified: phenolic acids (ferulic acid, stearic acid, caffeic acid, and p-coumaric acid, sinapinic acid, etc.), flavonoid aglycones and glycosides (luteolin, hesperidin, quercetin, myricitin, rutin, etc.). The extensive spectroscopic analyses (HPLC) showed two phenolic glycosides – myconoside and paucifloside, together with three flavone C-glycosides: hispidulin-8-C-(200-O-syringoyl)-bglucopyranoside, hispidulin 8-C-(6-O-acetyl-b-glucopyranoside), and hispidulin 8-C-(6-Oacetyl-2-O-syringoyl-b-glucopyranoside) (Ebrahimi et al., 2011).

The studies of water and alcohol extracts of *Haberlea rhodopensis* showed unique medical and pharmaceutical potential, related to their antioxidant, free radical-scavenging activities, antioxidant skin effect, radioprotective, anticlastogenic, chemoprotective, cytoprotective, antimicrobial, antimutagenic, immunological, anticancer, and anti-aging effects. The *Haberlea rhodopensis* extract lacks any cytotoxic effect and could be used in phytotherapy, human and veterinary medicine, and cosmetics (Todorova and Atanasov, 2015; Todorova et al., 2017).

Antioxidant potential and free radical-scavenging activity

Under physiological conditions the free radicals formed were maintained at a constant level by endogenous and exogenous antioxidants that neutralize the them (Sies, 1997). Oxidative stress occurs when the production of free radicals exceeds the detoxification capacity, leading to biological damage (Georgiev and Gocheva, 2014). Due to their ability to directly oxidize and damage DNA, proteins, and lipids, free radicals play a key role in the pathogenesis of several diseases such as diabetes mellitus, cataract, respiratory diseases, cardiovascular diseases (hypertension and atherosclerosis), neurodegenerative disorders (Alzheimer's disease, Multiple sclerosis, and Parkinson's disease), rheumatoid arthritis and in various cancers (breast, prostate,,colorectal, bladder, lung cancers) (Phaniendra et al., 2015). Antioxidants are agents that eliminate reactive oxygen species (ROS), prevent their formation, or repair the damage they cause (Odabasoglu et al., 2010). Phenolic compounds, accumulated in high amounts in ressurection plants, are major contributors to the antioxidant activity of HRE (Mihaylova et al, 2014).

The biologically active substances in HRE prevented the formation of free radicals or scavenged them by interacting with them, increased the levels of cellular antioxidant enzymes, enhanced the mechanisms of DNA repair. The antioxidant, antiradical, and antimicrobial activities of HRE may be explained by the presence of phenolic compounds (phenolic acids, flavonoids, and polyphenols) accumulated in high amounts in HR (Todorova and Atanasov, 2015; Mihaylova et al, 2014). It is considered that phenolic compounds in HR can protect the cell membranes against drying and free radical-induced oxidation (Berkov et al., 2011). They are widely used for the prophylaxis and treatment of diabetes, inflammatory diseases, cancer, and different oxidative stress-related diseases (Kumar and Goelb, 2019).

In a study, it was found that antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), peroxidase, ascorbate peroxidase, and guaiacol peroxidase have retained their activity even in dried leaves of HR (Mihailova et al., 2009). They contained also the antioxidants glutathione and the flavonoids tannin and zeaxanthin.

According to Kondeva-Burdina et al., (2013), the total extract of HR showed higher SOD-like activity, compared to TroloxTM (water-soluble vitamin E analog). This is due to the presence of some flavonoids and anthocyanins such as cyanidin and quercetin having strong radical scavenging and antioxidant activities.

According to Berkov et al. (2011), the free radical scavenging activity (DPPH assay) showed that polar fractions of both desiccated and fresh samples had strong antioxidant activity. The fraction from the desiccated leaves was more active due to the presence of phenolic compounds in the extracts.

According to Georgiev et al., (2020) *Haberlea rhodopensis* dried leaf extracts had higher and more specific anti-aging, proliferative and protective effects on cells than fresh leaf extracts.

In an experiment, it was found that methanol extracts from HR leaves showed stronger radical-scavenging (DPPH) activity than the reference compounds L-ascorbic acid and butylated hydroxytoluol (Radev et al., 2008).

Myconoside and three flavone C-glycosides were studied. Their antioxidant activity was measured by: DPPH, FRAP (iron-reducing antioxidant activity) and ABTS (2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) assays. The results showed that the these compounds had antioxidant activity. Myconoside demonstrated the highest DPPH (89.9% ± 0.3%), FRAP (2.49 TE ± 0.01) and ABTS (99.6% ± 0,1%) antioxidant activity similar to that of ascorbic acid. The results showed that these phenolic compounds isolated from HR demonstrated significant antioxidant activity, free radical scavenging potential, cytoprotective effect and inhibit lipid peroxidation (Kondeva-Burdina, et al., 2013).

The HRE stimulates the antioxidant skin defenses. The peroxide-stressed normal human dermal fibroblasts showed increased collagen VI (+822%), collagen XVI (+928%), and elastin (+144%) when treated with HRE. This effect was better for those obtained with retinoic acid and retinol (Dell'Acqua and Schweikert, 2011).

A linear correlation between the cytoprotective effects on rat hepatocytes and *in vitro* free radical scavenge and antioxidant activity of HR phenolic compounds was observed. In combination with tert-Butyl alcohol (t-BuOOH) all tested compounds showed a statistically significant reduction in hepatotoxic agent damage and preservation of cell viability, reduction in lactate dehydrogenase (LDH) leakage (as a marker for apoptotic cell degradation), maintenance of glutathione (GSH) level and reduction of lipid damage (Moyankova et al., 2014).

In many studies, it was found that ferulic acid, caffeic acid, and syringic acid, dihydrocaffeic, vanillic, and p-coumaric acids, luteolin etc. (Todorova and Atanasov, 2015; Berkov et al. 2011) showed strong antioxidant activity. They scavenged reactive oxygen species (ROS), reduced oxidative stress markers, and inhibited lipid peroxidation (Srinivasan et al., 2007).

In a study gallic acid showed an antioxidant protective effect. The administration of gallic acid (100mg/kg bw, orally) one hour prior to whole-body gamma radiation exposure (2–8 Gy) prevented radiation-induced reductions in antioxidant enzyme levels such as glutathione peroxidase (GPx), and glutathione (GSH), and lipid peroxidation inhibition (Nair and Nair, 2013).

It was found that syringic acid to be a powerful antioxidant that effectively inhibits linoleic acid peroxidation. It effective free radical scavenger and reduced oxidative stress markers. Syringic acid is a phenolic compound that shows a wide range of therapeutic applications in the prevention of cardiovascular disease, diabetes, cancer, cerebral ischemia, etc., (Srinivasulu et al., 2018).

Radioprotective effect and anticlastogenic activity

Many experiments described some plants and herbs that, when they administered *in vitro* and *in vivo*, before or after irradiation, they had radioprotective properties. They improve hematological

parameters, prolong life, and reduce the negative effects of radiation on chromosome and DNA levels.

According to Decker (1995), plants containing polyphenols neutralize free radicals and increase the cellular antioxidants in the irradiated system. Polyphenols in plants can regulate the mRNA expression of antioxidant enzymes, such as glutathione peroxidase, glutathione transferase, CAT, and SOD, thus countering oxidative stress caused by ionizing radiation (Popov et al., 2010).

Ionizing radiation induces mutation, chromosomal aberrations, and apoptosis in cells. It may cause cell inactivation, death, cancer, hereditary diseases, etc. in humans and animals (Nair et al., 2001).

Free radical scavengers in *Haberlea rhodopensis* play a key role in radioprotection, as radiation-induced cytotoxicity is mediated mainly by the generation of free radicals and their action on DNA in the biological system (Georgieva et al., 2019).

According to Georgieva et al., (2019) HR has radioprotective potential and anticlastogenic, antimutagenic, antioxidant, and anti-aging effects due to the ability of its flavonoid aglycones, glycosides, and phenolic acids to scavenge free radicals and reduce oxidative stress. The membrane damage to lipids is considered a critical factor for reproductive cell death and radiation-induced cell damage. The extract of *Haberlea rhodopensis* reduces radiation-induced lipid peroxidation products, such as malondialdehyde, which damages DNA and enzyme systems (Von Sonntag, 1991; Popov et al., 2011b).

The *Haberlea rhodopensis* extract acting as a strong antioxidant could protect cells against the negative effects of ionization radiation (oxidative damage to DNA, proteins, and lipids) by initiating cell death or genomic instability. The results showed that the HR extract was effective in counteracting the clastogenic effect of radiation and thus providing radioprotection. The radioprotective properties of the HR are a consequence of its resurrection abilities under stress conditions, where the polyphenol antioxidants are involved in the protection of the photosynthesis apparatus and the antioxidant enzymatic systems (Georgieva et al., 2017).

The biologically active substances in the extract of *Haberlea rhodopensis* prevent the formation of free radicals or scavending them by interacting with them, increase the levels of cellular antioxidant enzymes, enhance the mechanisms of DNA repair. Applied to experimental animals before irradiation with ionizing radiation, the HRE demonstrates an anticlastogenic effect, expressed in a reduction in the frequency of gamma-ray-induced chromosomal aberrations (Georgieva et al., 2012).

According to Popov et al., (2013) the application of *Haberlea rhodopensis* extract (0.24 g/kg) before and after irradiation (2.0 Gy gamma-rays) to New Zealand white rabbits have increased the activity of the antioxidant enzymes such as CAT and SOD and decreased the level of malonic aldehyde (MDA). Thus, HRE had provided radioprotection against radiation-induced reductions in antioxidant capacity and increased lipid peroxidation.

In an experiment, it was found that the treatment of New Zealand rabbits with HRE (120 mg/kg, *i.m.*) before and after gamma irradiation (2.0 Gy) led to a significant reduction in the percentage of aberrant metaphases, as well as the different types of aberrations (Georgieva et al., 2012). The maximal radioprotective effect is achieved with the highest HR dose (Popov, 2011). These results showed the radioprotective and anticlastogenic potential of HR in rabbits. Similar results were obtained by Popov et al. (2011b). The plant flavonoids possess a radioprotective effect in animals when applied before irradiation (Wang et al., 2020).

Popov et al., (2011a) was found that the HRE (100 mg/kg for 2 days *i.m.*) inhibited the frequency of sister chromatid exchanges by 43.84%, as well as the number of chromosomal aberrations ($p < 0,001$) by 42.85%, respectively, induced from cyclophosphamide (CP) in peripheral lymphocytes of New Zealand white rabbits. The *Haberlea rhodopensis* extract inhibited the decrease in SOD and GPx activity. The results showed the antimutagenic potential and chemoprotective effect of HR against the CP-induced genotoxicity and clastogenicity in rabbit lymphocytes.

In a study, the application of HRE (0.24 g/kg b.w.) 2 hours before irradiation with 2 Gy significantly reduced radiation-induced histological lesions in testes. These results indicated the radioprotective potential of HR leaf extract against the effects of whole-body gamma irradiation on the rabbit's testicular histostructure (Penchev et al., 2018).

Popov et al. (2010) was found that HRE (at concentrations of 1.0 µl//ml, 4.0 µl/ml, and 8.0 µl/ml) reduced the frequency of chromosomal aberrations, especially double chromosome fragments, and dicentrics, more effectively than vitamin C (1.0 µg/ml) in the rabbit peripheral blood lymphocytes after *in vitro* gamma irradiation (2 Gy). These results showed that HRE has radioprotective and anticlastogenic potential.

The biologically active substances contained in HR also have radioprotective and anticlastogenic effects. When hesperidin was administered orally to mice (25 mg/kg) 7 days before whole-body irradiation (4 Gy), it restored the antioxidant status to almost normal levels and reduced DNA damage, lipid peroxidation levels, and comet parameters. Hesperidin reduced the hepatic damage induced by radiation. The results showed that hesperidin was an effective radioprotector against radiation-induced liver damage in mice (Kalpana et al., 2011).

Gallic acid has an anticlastogenic effect. The administration of gallic acid (100 mg/kg b.w.) 1 hour before gamma radiation (2–8 Gy) resulted in inhibition of micronucleus formation and chromosomal aberrations in leukocytes and bone marrow cells. Activation of reparative processes in DNA and reduction of mortality and weight loss in irradiated mice were observed (Nair and Nair, 2013).

In the experiment, mice were treated with various quantities of ferulic acid (50, 75, and 100 mg/kg b.w. *i.p.*) 1-hour prior to exposure to 4.0 Gy whole-body gamma irradiation. The introduction of ferulic acid induced a concentration-dependent reduction in the DNA injuries in bone marrow cells and peripheral blood leukocytes of mice. It reduced the number of dicentric aberration, micronuclei, and lipid peroxidation and also improved the antioxidant status of the cells. These results showed that ferulic acid exhibits a radioprotective and anticlastogenic effect (Maurya et al., 2006)

According to Devipriya et al. (2008), a significant decrease in the density of chromosome aberrations, micronuclei, and comet parameters was observed in human lymphocytes administered with 66 µM caffeic acid 30 min before gamma irradiation. These results showed that caffeic acid protects lymphocytes against gamma-induced cell damage. Caffeic acid showed to be effective against inflammation, mutagenesis and bacterial infections.

In an experiment in mice receiving luteolin (10 µmol/kg) 2 hours before irradiation with γ-rays (6 Gy) a protective effect was observed against the reduction of endogenous ascorbic acid in their bones. The results showed that luteolin exhibits both *in vivo* and *in vitro* antioxidant activity and that its radioprotective effect may be due to its ability to scavenge free hydroxyl radicals (Shimoi et al., 1996).

Immunostimulatory effects

Most of the synthetic chemotherapeutic agents used today are immunosuppressants and lead to numerous side effects such as diarrhoea, nausea and vomiting (Carr et al., 2008).

The plant-based immunomodulators are employed as supportive or adjuvant therapy to reduce the toxic side effects of chemotherapy. In addition, the plants can have synergistic action in the therapy (Diwanay et al., 2004).

In an experiment, New Zealand white rabbits were immunized with keyhole limpet hemocyanin (KLH) and treated with *Haberlea rhodopensis extract* (2x120 mg/kg, b.w., *i.m.*) prior to single-dose (2 Gy) irradiation. The non-irradiated control group was also treated with HRE. Rabbits were reimmunized and re-treated with HRE on Day 36. KLH-specific production of total IgM, G, A, and KLH-specific IgG antibody was determined during the primary and secondary antibody response by ELISA. Gamma-radiation induces immunosuppression on the total production of primary antibodies. Administration of HRE restored the primary total KLH-specific antibodies and significantly increased the primary KLH-specific IgG antibodies response. *Haberlea rhodopensis extract* strongly enhanced the production of KLH-specific antibodies after reimmunization. *Haberlea rhodopensis* extract showed *in vivo* immunostimulatory activity, increasing the secondary production of IgG, IgM, and IgA in experimental rabbits, immunized with the KLH. The immunostimulating effect was preserved for more than 23 days after a secondary administration of the HRE and KLH, revealing the potential of the HR to boost the humoral immune response. The results showed that HRE exhibits immunostimulatory properties and may play a radioprotective role against γ-irradiation damaging the immune response (Dobreva et al., 2014).

The immunostimulatory activity of HRE is due to the fact that HR induces the secretion of interferon-γ, thus enhancing the switching of IgG class and IgG memory B cells formation. *Haberlea rhodopensis* stimulates the release of cytokines such as IL-2, IL-6, and IL-10 from antigen-presenting cells and T helper cells leading to increased proliferation of activated memory B cells. It can affect the process of memory B-cell activation by increasing the expression of MHC II (major histocompatibility complex) and costimulatory molecules and thus may lead to improved antigen presentation (Dobreva et al., 2014).

In another experiment, New Zealand white rabbits were immunized with keyhole limpet hemocyanin (KLH). At the same time, rabbits were injected with HRE (100 mg/kg), 50 mg/kg CP, or HRE + CP. The rabbits were reimmunized and treated with HRE and CP on day 44. The specific production of anti-KLH total IgM, G, A, and KLH-specific IgG antibodies was determined on days 0, 15, 22, 28 for primary and days 43, 51, 58, 66 for secondary antibody response by ELISA. The results showed that KLH-specific production of IgG antibodies increased significantly after treatment with HRE during the secondary humoral immune response. At the tested concentration, the HRE showed a well immunostimulatory activity on the secondary IgG and to a lesser extent on the secondary production of IgG, M, A antibodies (Popov et al., 2010).

According to Kandilarov et al., (2014) the treatment of rats with male Wistar rats with HRE (50 mg/kg b.w., *i.p.*) led to a significant increase in the number of hemopoietic progenitor stem cells (CD34+) in the peripheral blood. *Haberlea rhodopensis* increased platelet levels in the peripheral blood compared to controls. The hematopoietic stem cells can differentiate into different immune cells that fight malignant hematological diseases, heart attack, bone fractures, diabetes, multiple sclerosis, and other autoimmune diseases, etc. It is suggested that HRE may be used as a stem-cell liberator.

Haberlea rhodopensis extract was administered orally to 6 healthy volunteers (9 g in compressed gelatin capsules). Two hours after ingestion an increase in the absolute neutrophil count from 19% to 44.18% was observed in all subjects compared to control values taken before HR administration. The percentage change in total blood cell count (white blood cells, red, blood cells, and platelets) varies between 4 and 21%. This is evidence that dry *Haberlea rhodopensis* contains substances, that activate neutrophils, associated with systemic immunity (Todorova et al., 2017).

Anticancer activity

Haberlea rhodopensis was studied as potential cancer modulating drug, where human embryonic (HEK293$^{+/+}$) as well as prostate cancer cell lines (LNCaP (p53$^{+/+}$) and PC3 (p53$^{-/-}$) were used as a model for oxidative and genotoxic stress. In the nonmalignant cell line HEK 293, HR had an apoptosis-protective and cell death-reducing effect when the cells were pre-treated before H2O2-induced oxidative stress. The results showed that HRE had an antioxidative effect in cancer versus normal cell lines and differentially modulate distinct cell lines in genotoxic and inflammatory stress, stimulating NFkB activation in p53$^{+/+}$ cells, while suppressing its signaling in p53$^{-/-}$ cells. *Haberlea rhodopensis* is a potential drug for the treatment of prostate cancer (Hayrabedyan et al., 2013).

The cytotoxicity of HR on MDA-MB-231 (breast cancer), HL-60 (acute myelocytic leukemia), its multidrug-resistant subline HL-60/Dox, SKW-3 (T-cell leukemia) cell lines were tested. After 72 h exposure at concentrations up to 50 mg/ml of HRE were found that they did not cause any significant cytotoxic effects on the studied cell lines and therefore HR can be used in phytotherapy (Berkov et al., 2011).

Some compounds found in HRE were registered to possess antitumor activities.

According to Lin et al. (2008) luteolin has anti-inflammatory, anti-allergic, and anti-cancer properties. It acts as an antioxidant or prooxidant. Luteolin was found to inhibit ROS-induced damage of lipids, DNA, and proteins. The anti-cancer property of luteolin is associated with the induction of apoptosis and inhibition of cell proliferation, metastasis, and angiogenesis. Luteolin sensitizes cancer cells to drug-induced cytotoxicity by suppressing cell survival pathways such as phosphatidylinositol 3'-kinase (PI3K)/Akt, nuclear factor kappa B (NF-kappaB), and X-linked inhibitor of apoptosis protein, and stimulating apoptosis pathways, including those that induce the tumor suppressor p53. Luteolin is thought to have anti-cancer properties in various cancers. Luteolin inhibits DNA synthesis and proliferation in mammary epithelial cells and breast cancer cells induced by estrogens, both *in vitro* and *in vivo*. Luteolin suppresses the proliferation of prostate cancer cells. It eliminates the transformed cells by inducing apoptosis. Luteolin inhibits cancer cell proliferation and suppresses tumor angiogenesis. Luteolin can arrest the cell cycle during the G_1 phase in prostate and human gastric cancer, and in melanoma cells. *In vivo* experiments in nude mice with tumors showed that luteolin inhibits the growth of tumors formed from human skin carcinoma, hepatoma, and human ovarian cancer cells in a dose-dependent manner. In addition, recent studies showed that it prevents cancer.

In an experiment, it was observed that hesperidin had a significant cytotoxic effect against some breast (MCF7), larynx (HeP2), cervix (HeLa), and liver (HPg2) carcinoma cell lines. Its inhibitory concentration (IC_{50}) values for the these cell lines were 1.67, 3.33, 4.17, 4.58 μg/ml compared to 0.4, 0.85, 0.7, 0.6 μg/ml for standard doxorubicin respectively. The anticancer potential of hesperidin may be due to its antioxidant activity, increased inhibition of cell proliferation, and antimutagenic effect (Al-Ashaal and El-Sheltawy, 2011).

According to Tanaka et al. (1997), hesperidin acted as a chemopreventive agent against colon carcinogenesis, by suppressing cell proliferation in the colonic crypts. According to Stanisic et al. (2018), hesperidin showed anti-cancer activity in bladder, prostate, and liver cancer.

According to Prasad et al., (2011) caffeic acid showed a potent anticancer effect in the human fibrosarcoma cell line HT-1080. Increased oxidative DNA damage and apoptotic morphological changes were observed in the caffeic acid-treated groups.

According to Tao et al. (2015) quercetin has an inhibitory effect on MCF-7 and MDA-MB-231 human breast cancer cell lines through induction of apoptosis, up-regulation of miR-146a expression, activation of mitochondrial-dependent pathways, activation of caspase-3, and down-regulation of the expression of epidermal growth factor receptor.

Dihydrocaffeic acid have cancer chemoprevention, antimutagenic and anticarcinogenic activities (Santana-Gálvez et al., 2020).

Antibacterial effects

Radev et al., (2009) studied the antibacterial activity of total water-alcoholic extract of Haberlea rhodopensis using the disk-diffusion method. The results showed that the herb inhibited the bacterial growth of both methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA *Staphylococcus aureus)* more strongly than that of *Pseudomonas aeruginosa* and *Escherichia coli.* Scientists are discussing the possibility of antibacterial activity of *Haberlea rhodopensis.*

Anti-aging effects

According to Dell'Acqua and Schweikert (2011), 3% *Haberlea rhodopensis extract* protected UV-induced dermis oxidation by 100% ($P < 0.01$) in human skin biopsies. Cream containing 3% HRE was applied to human volunteers. An increase in skin elasticity ($P < 0.0002$) and skin radiance ($P < 0.05$) was observed after 15 days of treatment. These results confirm the antioxidant and anti-aging effects of HRE.

Haberlea rhodopensis extract had a very strong antioxidant and anti-aging effect. It is involved in the synthesis of collagen and elastin genes in human skin by increasing mRNA activity substance by myconoside. HRE improved skin elasticity and is used in anti-wrinkle cosmetics (Hooda, 2015).

This review showed the main effects of HR and its potential applications in human and veterinary medicine and cosmetics. More studies of HR are needed for its use in pharmacy and medicine as a drug.

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