Review Article

The Pharmacological and Therapeutic Potentials of *Epilobium hirsutum L.*

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ABSTRACT

Bioactive compounds, phytochemicals, have long been analyzed in order to clarify their pharmacological and therapeutic importance. Phenolic and polyphenolic compounds that are founded in plants have a good reputation as they are fulfilling a crucial function to avert and treatment of disparate diseases. Phytochemical analysis and pharmacological studies research therapeutic potential and mechanism of folk medicinal plants about their anti-oxidant, anti-cancer, anti-inflammatory and anti-bacterial activity. *Epilobium hirsutum L.,* having a rich flavonoids content, has been used traditionally for prevention and treatment of some diseases throughout the human history. The present review highlights the chemical components, pharmacological and therapeutic effects *of Epilobium hirsutum L.* and may help researchers in further extensive research and development of new therapeutics based on *Epilobium hirsutum L.*

Keywords: *Epilobium hirsutum* L., ellagic acid, antioxidant effect, anticancer effect, antibacterial effect.

INTRODUCTION

Numerous bioactive phytochemicals are used to be believed as non-essential nutrients and not fundamental for human life. But recent comprehensive studies indicate that they have different activities to combat health problems and increase the life quality[1]. They act as mimicking hormones and antioxidants and stimulating enzymes. They can also destroy bacteria, enhance the immune system and detoxify carcinogens by activating CYP and phase II enzymes[2,3]. As a result of a growing interest and accumulated experience about folk medicinal plants; phytochemical analyses and pharmacological studies increasingly concentrates on beneficial and therapeutic effects, also safeness and toxicity of these plants.

Epilobium (willowherb), one of the genus in Onagraceae family, encompasses annual or perennial herbaceous plants spread all over the world. Especially its most known species are *Epilobium hirsutum, Epilobium angustifolium,* and *Epilobium parviflorum*[4,5,6]. *Epilobium* species have a rich biologically active compound content, related with different areas, climate and soil differences, period of collection, species, plant materials, extraction processes[4]. *Epilobium hirsutum L.* is present in restricted geographical areas such as Eurasia, North Africa, Europe, Southern Australia and United States. It cannot resist unusual weather conditions because it is a softly-hairy herb[7,8]. It gives flowers in July and August[6].

The preliminary phytochemical profile analysis of *E. hirsutum* represented different bioactive compounds including ellagitannins as valoneic dilactone dioxine, 1'-mono-decarboxyvaloneic acid dilactone and 2-O-galloyl 3-O-valoneoyl dilactone- (α/β)-4C1-gluco-pyranose, as well as ellagic, garlic, and p-coumaric acids, quercetin and myricetin [6,9]. Six fatty acids (linoleic,α-linolenic, γ-linolenic, stearic, palmitic, and oleic acids), volatile oils, acidic and neutral saponins, anthocianidins, vitamin C, amino acids (e.g., leucine, isoleucine, cysteine, serine, threonine, phenylalanine, proline, valine, tyrosine) and several minerals and microelements have also been determined [5,9].

Epilobium hirsutum, greathairy willow herb, has been used as a therapeutic agent to treat of prostate diseases, cancer and sleeping disorders by humans for thousands of years[11,12]. The pharmacological studies revealed that extracts this plant have antibacterial, antimicrobial, antioxidative and antiphlogistic effects [8,12,13].

Antioxidant Effect

Phytochemicals known as natural antioxidants are important tools to inhibit oxidation reaction. Reason of formation of toxic compounds and unpleasant flavor, oxidation reactions (Lipid oxidation and protein oxidation) are main threat of meat quality. Myricetin, the most characterized flavonoid in *Epilobium hirsutum*, was determined to have antioxidant properties by displaying an action as a free radical scavenger and hydrogen donor. Phenolics and flavonoids of *E. hirsutum* may produce a negative impact of lipid oxidation on muscle foods contributing increase food quality[14].

Wojdylo et al.[15] had found that *E. hirsutum* has a radical scavenging activity, after investigation of 32 Polish herbs. Also, phytoremediation activity had been found for *E. hirsutum* extract, comparing 146 plants from Sarcheshmeh copper mining region whose soil is rich from copper (Cu)[16]. Moreover, along with high redox potential, there was a usage of *E. hirsutum* in secondary sewage treatment[17].

The methanolic fractions of aqueous and methanolic extracts of *E. hirsutum* demonstrated iron chelating and antioxidant potential. The animals treated with both fractions showed significant organ protection and improved the serum iron profile as compared to control rats[18].

Above all, iron chelating activity can be an alternative strategy for thalassemic patients. Pitfalls of Thalassemia are excess iron deposition in the liver and cumulative cell damage reason of formation of reactive oxygen species (ROS). Because phenolic compound can be used as free radical scavengers, antioxidant therapies help protect red blood cells (RBC) against antioxidant damage. After determination of total phenolic and flavonoid content, *E. hirsutum* and Mentha arvensis had been showed the best chelating activity due to linear relationship between phenolic content and chelatory activity[19].

CYPs possess numerous substrates both endogenous and exogenous compounds, which possesses a vital role in biological and clinical processes[20,21]. A group from Turkey, Adalı and Şen's mentorships, observed an antioxidant activity in *E. hirsutum* by making animal experiments. In the first study, it was investigated *in vivo* effects of *E. hirsutum* on CYP2E1, CYP1A1, NQO1 and GPx activities, protein and mRNA expressions in liver. CYP1A1, is well known member of CYPs, activates polycyclic aromatic Hydrocarbons to reactive carcinogenic and mutagenic metabolites. CYP2E1 bioactivates certain carcinogens and toxins. The elevated activity of CYP1A1 and CYP2E1 are associated with lung and breast cancer. NADPH quinone oxidoreductase 1 (NQO1) and glutathione peroxidase (GPx) have a crucial defense control function to regulation of ROS generation. Reduction of the CYP1A1 and CYP2E1 and acceleration of GPx and NQO1 enzyme activity might be a cancer chemoprevention strategy. *E. hirsutum* decreased CYP1A1 and CYP2E1 enzyme activity, while increased NQO1 and GPx enzyme activities. Protein and mRNA results supported enzyme activity results[3].

Ellagic acid is one of the most studied phenolic acids and it is found in pomegranate, strawberries, and grapes as well *E. hirsutum*[22]. Another comprehensive research from same group concluded that the ellagic acid makes contribution on the antioxidant impact of *E. hirsutum*. The antioxidant enzymes like superoxide dismutases (SOD), glutathione peroxidase (GPx), NADPH quinone oxidoreductase 1(NQO1) and glutathione S-transferases (GSTs) have a protective role for cancers, cardiovascular diseases etc. After treat with water extract of *E. hirsutum* and ellagic acid, rat liver glutathione peroxidase (GPx) and superoxide dismutases (SOD)] and [NADPH quinone oxidoreductase 1 (NQO1) and glutathione S-transferases (GSTs)] enzyme activities and protein and mRNA expressions were investigated. Albeit NQO1, GPx and SOD enzyme activity importantly increased, GST enzyme activity significantly decreased compared to control groups. Western blot and qRT-PCR studies emerged significantly induction of protein and mRNA expressions of NQO1 and GPx enzymes. They suggested increased antioxidant (NQO1, GPx and SOD) enzyme activities regarding free radical scavenging potential was quite good on a protection against pathophysiological alterations and cardiovascular diseases. GST is an important function in the detoxification of xenobiotics but also it is responsible for production of reactive or toxic compounds. Inhibition of GST activity because of treatment with *E. hirsutum* and ellagic acid, may be a protection way from cancer[23].

In the another study to research antioxidant potential and dose-dependent impact of ellagic acid from *E. hirsutum* examined activity as well as protein and mRNA expressions of CYP1A1/CYP1A2, CYP19, NAD(P)H:quinone oxidoreductase 1 (NQO1), catalase (CAT), glutathione peroxidase (GPx) and glutathione S-transferases (GSTs) enzymes. Two different doses (10 and 30 mg/kg) of ellagic acid was administered intragastrically to animals. The different doses showed different effects when compared control groups. Lower concentration of ellagic acid did not produce any significant effect on worked enzymes but higher concentration was enough to be effective. While Treatment with 30 mg/kg of ellagic acid caused a significant induction enzyme activity of the NAD(P)H:quinone oxidoreductase 1 (NQO1), catalase (CAT), glutathione peroxidase (GPX), and glutathione S-transferase (GST), a reduction enzyme activities of CYP1A, 2B, 2C, 2E, and 19. They concluded that ellagic acid exerts an anticancer and chemo preventive roles by making suppression of CYP1A, CYP2E, and CYP19 and the induction of GSTs, NQO1, GPX, and CAT enzymes and a chemical carcinogen role by making reductions in CYP2B, 2C, and 3A[24]. Similar study about antioxidant features of *E. hirsutum* and ellagic acid, concluded that *E. hirsutum* is an inhibitor of drug-metabolizing CYP2C6, CYP2B1, CYP2D2, and CYP3A1 enzymes due to the ellagic acid content. In the light of the inhibition of drug clearance enzymes, usage of *E. hirsutum* leads toxicity by its ellagic acid constituents[25]. However, in another study, cytotoxic effects of hydro-alcoholic extracts of three popular *Epilobium* species (*Epilobium hirsutum, Epilobium angustifolium* and *Epilobium parviflorum*) was investigated in rat brain, hypophysis, adrenals, liver, kidney, thymus and spleen after treatment 10 days with 1.5 ml/day for each species. *E. hirsutum* and *E. angustifolium* induced lactate dehydrogenase, succinate dehydrogenase and cytochromoxidase enzyme activity in liver and kidney. Also all *Epilobium* extracts decreased lipoperoxidation activity in the brain, liver and kidney. It conducted *in vivo* confirm that three popular *Epilobium* species did not show any cytotoxic activity[1].

Another *in vivo* study from the same group is the assessment of relationship between on bile acid metabolizing Cytochrome P450 enzymes (CYP7A1, CYP27A1, CYP7B1and CYP8B1) and *E. hirsutum* and its major polyphenolic ingredient, ellagic acid. Total cholesterol levels significantly decreased after treatment

of *E. hirsutum* and ellagic acid extracts. *E. hirsutum* (37.5 mg/kg) caused a decrease in protein and mRNA expression of CYP7A1 enzyme while 20 mg/kg ellagic acid caused an induction of production of CYP7A1 when compared to control groups. The results indicated that *E. hirsutum* and ellagic acid may be used as a regulator for bile acid metabolizing enzymes[26].

Anticancer Effect

Early research has provided some initial biological evidence for the use of *Epilobium* extracts in benign prostatic hyperplasia. *Epilobium* water extracts, (*hirsutum, palustre, rosmarinifolium*, *spicatum*, and *tetragonum*) incubated to research antiproliferative effect in PZHPV-7 human prostatic epithelial cells in-vitro. *Epilobium* extracts inhibit PZ-HPV-7 human prostate cells proliferation due to inhibition of the cell cycle process (G0/G1 phase)[27].

Cell culture studies on *E. hirsutum* aqueous extracts has postulated its antiandrogenic activity. Prostate cancer cell growth and proliferation and benign prostatic hyperplasia (BPH) are related with High level of prostate specific antigen (PSA) and increased arginase activity. EHT Treated-potent prostate cancer (LNCaP) cells showed reduced PSA secretion and inhibited arginase activity. Ellagitannins from *E. hirsutum* herb aqueous extract are metabolized to urolithins. Urolithin C showed the significant reduction of cell proliferation, PSA secretion and arginase activity[28]. One study on the evaluation of anti-tumor effect of *E. hirsutum* alcohol extracts (of 1 mg/kg and 3 mg/kg) prolonged the life span of tumor models in mice[29].

Antibacterial Effect

Several studies indicated that *Epilobium hirsutum* has antibacterial efficiency. Methanolic extracts (a range of concentrations between 10 and 650 g/ml of dry extract) of the *E. hirsutum*, *E. angustifolium, E. palustre, E. tetragonum and E. rosmarinifolium* showed a bactericidal effect on Gram-positive and Gram-negative bacteria, yeasts and fungi[30]. Also *E. hirsutum* whole extracts and aqueous, ethyl acetic and chloroformic fractions demonstrated a bactericidal effect on both Staphylococcus aureus standard strains and methicillin–resistant Staphylococcus aureus (MRSA) strains. Moreover, *E. hirsutum* whole extracts and fractions showed synergism with Ampicillin or Tetracycline antibiotics and an increase of the antimicrobial effect against *Staphylococcus aureus* standard strains[2]. Ethanolic extracts of *E. hirsutum* showed a strong antibacterial activity against both Gram negative and Gram positive bacteria[31]. Furthermore, the essential oil from the aerial parts of *E. hirsutum* displayed antimicrobial activity against *Staphylococcus aureus, Bacillus cereus, Salmonella enterica* and *Escherichia coli*[32]. But the measured minimum inhibitory concentration (MIC) and inhibition zone values were different [2,30,31].

Herbal extracts, including high antioxidant and antimicrobial properties, can be utilized the treatment of Diabetic Foot Syndrome. For this aim The crude extract of *E. hirsutum* were tested for analyze the anti-fungal activity on *Candida glabrata* and anti-microbial activity on *Staphylococcus aureus*, and Methicillin-resistant *Staphylococcus aureus*. Also to assessment of antioxidant activity (DPPH) assay ABTS) radical scavenging assay were tested. Antimicrobial and antioxidant activities showed evidence that the usage of *E. hirsutum* can be helpful for to treatment of Diabetic Foot Sydrome[33].

CONCLUSION

Several novel extracts of *E. hirsutum* have been analyzed. A clearer picture of many *in vivo* and *in vitro* studies has revealed that *E. hirsutum* showed different biological activities. *E. hirsutum*, which has the best content in flavonoids, had the most favorable effects and phytotherapeutical perspectives on *E. hirsutum* and its major component, ellagic acid, have been evaluated as antioxidant, anticancer and antimicrobial agent. Although initial studies reveal that the great willow herb is a promising source for natural antioxidant, anticancer and antibacterial products, the clinical application results remain unknown. It is envisioned that *E. hirsutum* can be used as pharmaceutical formulation to application of different conditions.

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