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ORIGINAL ARTICLE / ÖZGÜN MAKALE

A PRELIMINARY STUDY ON THE ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITIES OF *OPOPANAX HISPIDUS*

OPOPANAX HISPIDUS'UN ANTİOKSİDAN VE ANTİ-İNFLAMATUAR AKTİVİTELERİ ÜZERİNE BİR ÖN ÇALIŞMA

Safa GÜMÜŞOK[1*], Sezen YILMAZ SARIALTIN[2], Tülay ÇOBAN[2], Ceyda Sibel KILIÇ[1]

[1]Department of Pharmaceutical Botany, Faculty of Pharmacy, Ankara University, Tandoğan 06560, Ankara, Turkey

[2]Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Ankara University, Tandoğan 06560, Ankara, Turkey

ABSTRACT

Objective: *Opopanax W. Koch genus is included in Apiaceae family. The genus can be distinguishable with its compound basal leaves, glabrous fruits, yellow flowers, tall stem with glochidate and stellate hairs. It is known with the name "Hercules' all-heal" throughout the world. It was used for the treatment of epilepsy, infertility in women, hemorrhoids and paralysis traditionally. This present research was designed to assess in vitro antioxidant and anti-inflammatory activity of Opopanax hispidus (Friv.) Griseb.*

Material and Method: *Methanol extracts were prepared from the aerial parts and flowers of the plants. Their antioxidant activities were analyzed through a number of chemical assays: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) and 2,2-diphenyl-l-picrylhydrazyl (DPPH) free radical scavenging assays. Anti-inflammatory activities of the extracts were compared and evaluated using human red blood cell membrane stability testing.*

Result and Discussion: *Aerial parts exhibited stronger ABTS and DPPH free radical scavenging activities than flowers. Howver, flowers were found to be more active than aerial parts in terms of anti-inflammatory effects (IC_{50}=3,32 mg/ml and 4,75 mg/ml; respectively). These data suggest that flowers and aerial parts of Opopanax hispidus exhibited antioxidant and anti-inflammatory effects. More research studies are necessary to determine the active ingredients in charge of this activity.*

Keywords: *ABTS, anti-inflammatory, antioxidant, DPPH, Opopanax hispidus*

ÖZ

* **Corresponding Author / Sorumlu Yazar:** Safa Gümüşok
e-mail / e-posta: safagumusok@gmail.com, **Phone / Tel:** +905449674616

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Amaç: *Opopanax W. Koch cinsi, Apiaceae familyasında yer alır. Cins, bileşik bazal yaprakları, tüysüz meyveleri, sarı çiçekleri, gloşidat ve yıldızsı tüyleri olan uzun gövdesi ile ayırt edilebilir. Dünya çapında "Herkül'ün her şeyi iyileştireni" adıyla bilinir. Halk arasında epilepsi, kadınlarda kısırlık, hemoroid ve felç tedavisi için kullanılır. Bu araştırma, Opopanax hispidus (Friv.) Griseb'in in vitro antioksidan ve anti-inflamatuar aktivitesini değerlendirmek için tasarlanmıştır.*

Gereç ve Yöntem: *Bitkinin toprak üstü kısımlarından ve çiçeklerinden metanol ekstreleri hazırlandı. Antioksidan aktiviteleri bir dizi kimyasal deneyle analiz edildi: 2,2'-azino-bis-3-etilbenzotiazolin- 6-sülfonik asit (ABTS) ve 2,2-difenil-l-pikrilhidrazil (DPPH) serbest radikal süpürme deneyleri. Ekstrelerin anti-inflamatuar aktiviteleri insan kırmızı kan hücresi membran stabilite testi kullanılarak karşılaştırıldı ve değerlendirildi.*

Sonuç ve Tartışma: *Toprak üstü kısımları, çiçeklerden daha güçlü ABTS ve DPPH serbest radikal temizleme aktiviteleri sergiledi. Ancak anti-inflamatuvar etki açısından çiçeklerin toprak üstü kısımlardan daha aktif olduğu bulundu (IC50=3,32 mg/ml ve 4,75 mg/ml, sırasıyla). Bu veriler, Opopanax hispidus'un çiçek ve toprak üstü kısımlarının antioksidan ve anti-inflamatuar etkiler sergilediğini göstermektedir. Bu aktiviteden sorumlu aktif içerikleri belirlemek için daha fazla araştırma çalışması gereklidir.*

Anahtar Kelimeler: *ABTS, anti-inflamatuvar, anti-oksidan, DPPH, Opopanax hispidus*

INTRODUCTION

Apiaceae is known as parsley or carrot family having more than 300 genera with not less than 3000 species. They grow naturally in the northern hemisphere [1]. This large family attracts attention due to its diverse secondary metabolites, and also its great economic and medical value [2].

Opopanax species are known with the names Kaymakotu, Kaymacık and Kirkozar in Turkey [3] and with the name "Hercules' all-heal" in the world. English name of genus give us a hint about its usage. When etimologically examined the word "*Opopanax*", it is derived from the words "opos" and "panax". The word "opos" means usare (vegetable juice) and the word "panax" (panacea) means all-healing, universal remedy [4].

Opopanax W. Koch, a genus of the Apiaceae family has 4 species: *Opopanax hispidus* (Friv.) Gris., *Opopanax chironium* (L.) W. Koch, *Opopanax persicus* Boiss., and *Opopanax siifolius* (Boiss. & Heldr.) Menemen. *Opopanax* species are traditionally being used both in Turkey and throughout the world due to their medical effects. Gum derived from *O. chironium*'s stem is used in the treatment of epilepsy among people in Iran [5]. *O. chironium* was used in the treatment of epilepsy during the Renaissance period [6]. As a result of an excavation conducted in Cairo, *O. chironium* was found that this species was used in colic and colds, eye diseases, convulsions, tetany and to strengthen erections in the Middle Ages [7]. It has been reported that the ointment prepared with the mixture of fat-gum-resin (oleogumresin) obtained from *O. chironium* used against all cancers in traditional Islamic medicine [8]. *O. chironium* has been used for antinociceptive against headache, joint pain and rhematoid arthritis, as well as, diuretic in traditional Iranian medicine [9]. *O. hispidus* is consumed as food in and around Kazdağı [10]. In a study conducted in the Ilıcalı region of Erzurum, it was reported that the fresh bodies of *O. hispidus* were eaten and thus used to treat female infertility [11]. In the study conducted in Eğirdir, powdered leaves of *O. hispidus* were found to be used in the treatment of hemorrhoids by eating [12].

In Turkey, *O. hispidus* is located in a group of plants known as "Mayasıl otu" and has been reported to be used in the treatment of hemorrhoids [13]. In "Dynameron" writting around 10^{th}-11^{th} centuries, *O. hispidus* was reported to be used as an antidote [14]. It has been reported that the stem, leaf and inflorescence of *O. hispidus* are utilized as antiseptic by smoking [15]. There is information about the resin obtained from *O. persicus* is used to treat paralysis from nasal way, but no more details are given [16]. There is no information about *O. siifolius* (*Crenosciadium siifolium*).

Since these species have been used for antinociceptive effects against headache and joint pain, in this study we aimed to investigate antioxidant and anti-inflammatory activities of *O. hispidus* that grows naturally in Turkey.

MATERIAL AND METHOD

Plant Samples

Plant samples were gathered from the following locality and voucher specimens are kept in AEF (Herbarium of Ankara University, Faculty of Pharmacy):

C3: Akseki, Sadıklar Village entrance, near the fields, 978 m, H. Duman, C.S. Kılıç, 20/6/2016.

O. hispidus' aerial parts and flowers, first macerated with methanol for 8 hours 3 times, were evaporated with a rotary evaporator (Heidolph WB 2000&VV2000).

Chemicals

Trolox, acetylsalicylic acid (ASA), butylated hydroxytoluene (BHT), 2,2-diphenyl-l-picrylhydrazyl (DPPH), 2,2'- azino bis-(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) were bought from Sigma-Aldrich. Dimethyl sulfoxide (DMSO), methanol and the other solvents were bought from Merck.

Antioxidant Activity

$ABTS^{\bullet+}$ Free Radical Scavenging Activity

ABTS radical cation decolorization assay was utilized to measure the total antioxidant activity of the samples [17]. ABTS was prepared by the reaction of 7 mM ABTS+ aqueous solution with 2.45 mM potassium persulfate. The experiment mixture was left to wait for a night (12 to 16 h) in the dark with a temperature of 25°C before usage. To assign an absorbance value of 0.700±0.02 at 734 nm, the resultant strongly-colored ABTS radical cation was diluted with ethyl alcohol, pH 7.4. The compound was diluted 100x with the ABTS solution to a total volume of 1 ml. After addition, the experiment mixture was left to wait 6 min at room temperature. Then the absorbance was measured spectrophotometrically at 734 nm and inhibition percentage was computed. The assay was conducted three times for one extract. On a regular time basis (every five days) fresh stocks of $ABTS^{\bullet+}$ solution were made available for avoiding self-degradation of the radical. Trolox, that is the water-soluble α-tocopherol analogue, was utilized as a standard. The findings were presented as radical scavenging activity percentage (%) of the ABTS,

defined by the below formula:$[(A_o - A_s)/A_o] \times 100$; which is A_o means the absorbance of the control and A_s is the absorbance with the sample or standard. For each plant extract and standard, half-maximal inhibitory concentration (IC_{50}) values were figured from a calibration curve.

DPPH˙ Free Radical Scavenging Activity

The DPPH free radical scavenging activities of the plant methanolic extracts were assessed by their capacity to decolorize the stable radical DPPH [18]. Various concentrations of the extracts and 100 μM DPPH in methanol constituted the reaction mixture. The mixture was first shaken, then left to wait in dark for half an hour at the aforementioned temperature (25°C). Then at 517 nm, the absorbance was measured and free radical scavenging activity was computed as the percentage of radical reduction. The absorbance of the prepared solution was adapted to 0.700 ± 0.02 at 517 nm. BHT was chosen as a reference compound. Each experiment was conducted in triplicate. Percentage of DPPH radical scavenging activity was computed by the below formula; $[(A_o - A_s)/A_o] \times 100$, which is A_o means the absorbance of the control and A_s is the absorbance with the sample or standard. IC_{50} values were calculated from a calibration curve for each plant extract and standard compound.

Anti-inflammatory Activity (*)

Preparation of Human Red Blood Cells Suspension

A healthy human volunteer without a record of anti-inflammatory or steroidal drug use for the past 2 weeks before the experiment provided fresh whole human blood which was later transmitted to centrifuge tubes. The tubes were centrifuged for 10 min at 3000 rpm. The appropriate volume of sterile isosaline (0.85%, pH 7.2) was used to wash the packed cells. The blood volume was measured and remade as 10% v/v suspension with isosaline [19; 20].

Heat-Induced Hemolysis

The human erythrocyte hemolysis assay which is induced by heat evaluated membrane stabilizing activity of the samples, using previously described methods with slight modifications [19; 20]. Test samples (methanolic extracts) and 10% red blood cell suspension constituted the experiment mixture. The only solvent was used as a negative control. Each centrifuge tube including the experiment mixture was incubated in a water bath for half an hour at 56ºC. At the end of the incubation period, the centrifuge tubes were left for cooling under running water. The available mixture was centrifuged for 5 mins at 2500 rpm, then the supernatant absorbance was measured at 560 nm. This experiment was carried out three times for each sample. ASA was utilized as the reference drug. Percentage of protection was computed by the below formula; $100 - [(A_s/A_o)x100]$, which is A_o means the absorbance of the control and A_s is the absorbance with the sample or standard. The results were represented as IC_{50} for each plant extract and the standard compound.

Statistical Analysis

All of the experiments were conducted three times and the findings were displayed as mean IC_{50}±SD. IBM SPSS Version 25.0 was used to carry out statistical analyses, namely one-way analysis of variance (ANOVA) and post hoc Tukey test with 95% confidence level for normally distributed groups. The results, which were accepted as statistically significant, were p-values less than 0.05.

RESULT AND DISCUSSION

Antioxidant Activity

$ABTS^{\bullet+}$ Free Radical Scavenging Activity

ABTS free radical scavenging activities of the flowers and aerial parts of *O. hispidus* and the reference compound were presented in Table 1. Trolox was found more active than the extracts (p=0.0001). The maximum antioxidant capacity was detected for aerial parts by ABTS free radical scavenging assay with an IC_{50} value of 0,33±0,02 mg/ml. Flowers showed lower ABTS scavenging activity than aerial parts (IC_{50}=0,40±0,02 mg/ml).

Table 1. ABTS free radical scavenging activity of flowers and aerial parts of *O. hispidus*

Plant extract	IC50 (mg/ml) Mean ± SD
Flower	0,3958 ± 0,018
Aerial parts	0,3245 ± 0,016
Trolox	0,0150 ± 0,001

$DPPH^{\bullet}$ Free Radical Scavenging Activity

DPPH free radical scavenging activities of the flowers and aerial parts of *O. hispidus* and the reference compound were presented in Table 2. BHT was found more active than the extracts (p=0.0001). Similar to the findings of previous activity (ABTS), the highest antioxidant potential was detected for aerial parts by DPPH free radical scavenging assay with an IC_{50} value of 0,50±0,01 mg/ml. Flowers showed lower DPPH scavenging activity than aerial parts (IC_{50}=0,54±0,01 mg/ml).

Table 2. DPPH free radical scavenging activity of flowers and aerial parts of *O. hispidus*

Plant extract	IC50 (mg/ml) Mean ± SD
Flower	0,5405 ± 0,0127
Aerial parts	0,5022 ± 0,0075
BHT	0,0188 ± 0,0004

Anti-inflammatory Activity

Human Red Blood Cell Membrane Stabilizing Activity

The cell membrane stabilizing activities of flowers and herbs of *O. hispidus* were presented in Table 3. Contrary to the results of ABTS and DPPH free radical scavenging activities, the maximum membrane stabilization activity was detected for methanol extracts of flowers with an IC_{50} value of 3,32±0,03 mg/ml. Aerial parts exhibited lower membrane stabilizing activity than flowers with IC_{50} values of 4,75±0,003 mg/ml. Flowers of *O. hispidus* are more effective than aerial parts of *O. hispidus*. ASA was more effective on that activity than the extracts significantly (p=0.0001).

Table 3. The cell membrane stabilizing activity of flower and herbs of *O. hispidus*

Plant extract	IC50 (mg/ml) Mean ± SD
Flower	3,3177 ± 0,0255
Aerial parts	4,7533 ± 0,0034
ASA	0,2910 ± 0,008

Opopanax genus has been used in traditional medicine for numerous reasons. In previous studies for methanol extracts of aerial parts of *O. hispidus*, antioxidant capacity was found as follows: ABTS: 0.08 ± 0.032 mmol Trolox equivalent g^{-1} extract [21]. Matejić et al reported that methanolic extracts of inflorescences of *Opopanax hispidus* showed the highest scavenging activities on DPPH and ABTS free radicals compared to aerial parts and fruits (IC_{50}=1.157 mg/mL and 3.14 ± 0.006 Vit C/g, respectively) [22]. Similarly, the greatest total phenolic (89.95 ± 0.005 mg GA/g) and total flavonoid content (24.06 ± 0.004 mg Qu/g) was found in methanol extracts of inflorescences parts [21]. In another study, radical scavenging potentials of the ethanol extracts of aerial parts of *O. hispidus* were found 88.27 ± 0.45 mg Trolox equivalent/g extract for DPPH and 138.07 ± 1.48 mg Trolox equivalent /g extract for ABTS [23].

We examined radical scavenging and erythrocyte membrane stabilization capacities of different parts of *O. hispidus*. To our knowledge, this article is the first report to showing the anti-inflammatory capacity of this plant. ABTS and DPPH radical scavenging activities were found higher for aerial parts than flowers, but not a serious margin. Naturally-occurring plant pigments, phenolic compounds, terpenes are secondary metabolites of plants that are the best known for their ability to scavenge free radicals [17, 24]. Phenolic substances are known to be responsible for the antioxidant effect that medicinal plants possess [25, 26]. The antioxidant effect may be due to its rich content. On the contrary of antioxidant activity, flowers were found to be more effective in anti-inflammatory assay than aerial parts. Flowers and especially yellow flowers are known to be rich in flavonoids [27]. There is strong

evidence suggesting that flavonoids prevent and reduce inflammation by means of multiple mechanisms. This plant secondary metabolites reduce inflammatory cytokine production, decrease inflammation-promoting cells' recruitment, and modulate inflammatory pathways [28]. Therefore, it is not surprising that flowers were found to be more effective than aerial parts in anti-inflammatory activity assay. Further studies should be conducted to clarify the phytochemical content, flavonoid and phenolic profile of this species.

AUTHOR CONTRIBUTIONS

Concept : *S.G., S.Y.S., T.Ç., C.S.K.*; Design: *S.G., S.Y.S., T.Ç., C.S.K.*; Control: S.*G., S.Y.S., T.Ç., C.S.K.*; Sources: *S.G., S.Y.S., T.Ç., C.S.K.*; Materials: *S.G., S.Y.S., T.Ç., C.S.K.*; Data Collection and/or processing: *S.G., S.Y.S., T.Ç., C.S.K.*; Analysis and/or interpretation: *S.G., S.Y.S., T.Ç., C.S.K.*; Literature review: *S.G., S.Y.S., T.Ç., C.S.K.*; Manuscript writing: *S.G., S.Y.S., T.Ç., C.S.K.*; Critical review: *S.G., S.Y.S., T.Ç., C.S.K.*; Other: *S.G., S.Y.S., T.Ç., C.S.K.*

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS COMMITTEE APPROVAL

The Ethics Committees of the Faculty of Medicine of Ankara University, Ankara-Turkey approved the study protocol with acceptance number of 26.10.2015/16-695-15.

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