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Investigations on the *in vivo* wound healing potential of *Hypericum perforatum* L.

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- **Abstract**
- Ethnopharmacological relevance
- Olive oil extract of the flowering aerial parts of *Hypericum perforatum* L. (Hypericaceae) is a popular folk remedy for the treatment of wounds in Turkey.
- Aim of the study
- In order to prove the claimed utilization of the plant, the effects of the extracts and the fractions were investigated by using bioassay-guided procedures. For the wound healing activity assessment, *in vivo* excision and incision wound models were applied. For the anti-inflammatory activity, an *in vivo* model, based on the inhibition of acetic acid-induced increase in capillary permeability was used as well. Moreover, a parallel study was run on *Hypericum scabrum* L., which is a widespread species of the gender but not known as a folk remedy for wound healing, to provide a preliminary data to compare and emphasize the selection of correct plant species.
- **Results**
- Initial investigations proved that the olive oil extract of *Hypericum perforatum* has a significant wound healing effect on excision (5.1–82.6% inhibition) and circular incision (20.2–100.0% inhibition) wound models. In order to determine the active wound healing ingredient(s), aerial parts of the plant was extracted with ethanol, noteworthy wound healing activity profile was observed with the wound models; between 18.3% and 95.6% in excision model and from 13.9% to 100.0% inhibitions in incision model were determined. The ethanolic extract was then submitted to successive solvent extractions with *n*-hexane, chloroform and ethyl acetate (EtOAc). Each solvent extract was also applied on the same wound models, consequently, EtOAc subextract was found to be the most active one by inhibiting wounds between 17.9% and 100.0% in excision model, subsequently between 9.4% and 100.0% in incision model. However, all subfractions obtained from the EtOAc subextract using Sephadex LH-20 column chromatography showed wound healing activity not more than the whole EtOAc subextract, which revealed that a possible synergistic activity that might be questioned. Among the active Sephadex fractions, Fr. A further yielded hyperoside, isoquercitrin, rutin and (-)-epicatechin and Fr. B yielded hypericin as the major components. Moreover, a dose-dependent anti-inflammatory activity was found for the ethanol extract, EtOAc subextract and Sephadex fractions of *Hypericum perforatum*. These results suggest that anti-inflammatory activity of the active fractions might have a contributory role in the wound healing effect of the plant.
- **Conclusion**
- Results of the present study have proved that aerial parts of *Hypericum perforatum* possess remarkable wound healing and anti-inflammatory activities supporting the folkloric assertion of the plant in Turkish folk medicine. Flavonoids [hyperoside,

isoquercitrin, rutin and (-)-epicatechin] and naphthoquinones (hypericins) were found as the active components of *Hypericum perforatum*. On the other hand, ethanol extract of *Hypericum scabrum* showed neither remarkable wound healing nor anti-inflammatory activity demonstrating the importance of correct plant species selection in therapeutic applications.

- **Graphical abstract**
- Olive oil extract of the flowering aerial parts of *Hypericum perforatum* L. (Hypericaceae) is a popular folk remedy for the treatment of wounds in Turkey. In order to prove the claimed utilization of the plant, the effects of the extracts and the fractions were investigated by using bioassay-guided procedures. For the wound healing activity assessment, *in vivo* excision and incision wound models were applied. For the anti-inflammatory activity, an *in vivo* model, based on the inhibition of acetic acid-induced increase in capillary permeability was used as well. Moreover, a parallel study was run on *Hypericum scabrum* L., which is a widespread species of the gender but not known as a folk remedy for wound healing, to provide a preliminary data to compare and emphasize the selection of correct plant species.

Effect of the Olive oil extract of *H. perforatum* (HP-Oo) on circular incision wound model

Days	Wound area (mm ²) ± S.E.M. (% Contraction) ^a		
	Negative Control	Vehicle (Olive oil)	HP-Oo
1	311.9 ± 20.5	276.8 ± 24.8	220.3 ± 11.8 (30.3)
4	306.4 ± 21.7	278.2 ± 3.5	180.2 ± 16.1 (41.2) [*]
7	362.9 ± 22.3	303.8 ± 21.4	151.3 ± 17.8 (57.7) ^{**}
10	378.8 ± 16.8	187.8 ± 99.4	71.8 ± 9.0 (81.7) ^{**}
14	337.6 ± 18.4	76.7 ± 18.9	21.5 ± 1.6 (93.8) ^{**}
17	321.5 ± 13.3	13.3 ± 17.7	0.9 ± 0.0 (99.8) ^{***}

^a Statistical evaluation of the experimental results was performed against the vehicle.
HP: *H. perforatum*
S.E.M.: Standard error mean; * : p < 0.05, ** : p < 0.01, *** : p < 0.001

Keywords

- Anti-inflammatory activity;
- Excision wound;
- Flavonoids;
- Hypericaceae;
- *Hypericum perforatum*;
- *Hypericum scabrum*;
- Incision wound;
- Naphthoquinones;
- Tensiometer;
- Wound healing

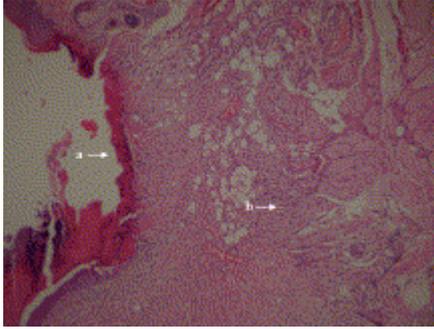


Fig. 1. Photograph of microscopic view of section on 21 day old wound tissue from negative control group (untreated). (a) Area of ulceration and (b) mixed type inflammatory cells.

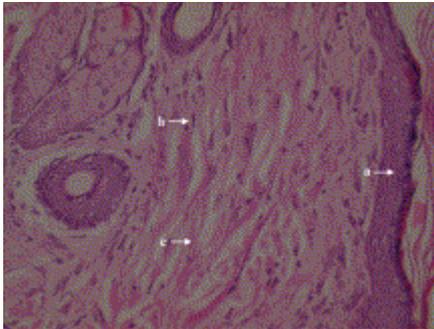


Fig. 2. Photograph of microscopic view of section on 21 day old wound tissue from group treated with HP-EtOAc-Fr. (a) Intact epidermis, (b) fibroblasts and (c) collagen fibers.

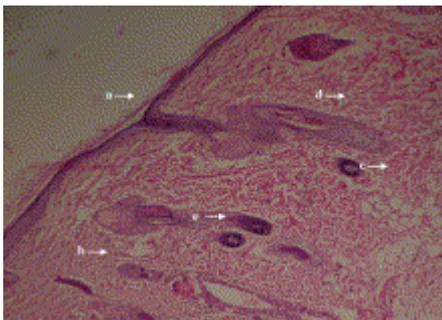


Fig. 3. Photograph of microscopic view of section on 21 day old wound tissue from group treated with Fr.19-85. (a) Intact epidermis, (b) fibroblasts, (c) collagen fibers, (d) edema and (e) hair follicle.

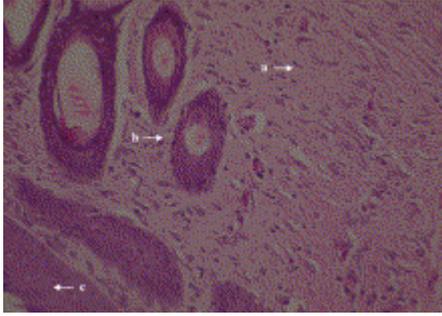


Fig. 4. Photograph of microscopic view of section on 21 day old wound tissue from group treated with Madecassol®. (a) Fibroblasts, (b) hair follicle and (c) intact epidermis.