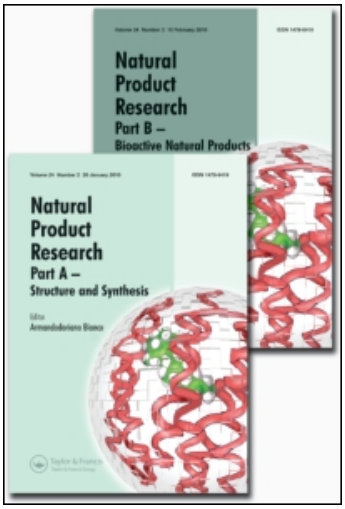


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# New antidepressant drug candidate: *Hypericum montbretti* extract

Özgür Devrim Can[a]; Ismail Bilal Ismail[b]; Yusuf Öztürk[a]; Nilgün Öztürk[c]; İsmühan Potoğlu-Erkara[d]; Gianni Sagratini[e]; Massimo Ricciutelli[e]; Sauro Vittori[e]; Filippo Maggi[e]

[a] Department of Pharmacology, Faculty of Pharmacy, Anadolu University, 26470 Eskisehir, Turkey [b] Department of Basic Science, College of Nursing, Hawler Medical University, Hawler, Iraq [c] Department of Pharmacognosy, Faculty of Pharmacy, Anadolu University, 26470 Eskisehir, Turkey [d] Department of Biology, Faculty of Science and Letters, Osmangazi University, Eskişehir, Turkey [e] School of Pharmacy, University of Camerino, 62032 Camerino, Italy

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# SHORT COMMUNICATION

## New antidepressant drug candidate: *Hypericum montbretti* extract

Özgür Devrim Can[a]*, Ismail Bilal Ismail[b], Yusuf Öztürk[a], Nilgün Öztürk[c], İsmühan Potoğlu-Erkara[d], Gianni Sagratini[e], Massimo Ricciutelli[e], Sauro Vittori[e] and Filippo Maggi[e]

[a]*Department of Pharmacology, Faculty of Pharmacy, Anadolu University, 26470 Eskisehir, Turkey;* [b]*Department of Basic Science, College of Nursing, Hawler Medical University, Hawler, Iraq;* [c]*Department of Pharmacognosy, Faculty of Pharmacy, Anadolu University, 26470 Eskisehir, Turkey;* [d]*Department of Biology, Faculty of Science and Letters, Osmangazi University, Eskişehir, Turkey;* [e]*School of Pharmacy, University of Camerino, 62032 Camerino, Italy*

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This study was designed to investigate possible antidepressant-like effects of the extract prepared from the flowers of *Hypericum montbretti* Spach. (Guttiferae, Clusiaceae). Phytochemical constituents of the methanolic extract were analysed by HPLC method. The main flavonoid component was detected as rutin, and another highly concentrated phenolic compound was quercitrin. Antidepressant activity of the extract was examined by tail suspension and modified forced swimming tests, whereas the motor coordination of the animals was tested by the Rota-Rod apparatus. Reboxetine at a dose of 20 mg kg$^{-1}$ was used as a reference drug. Dose-dependent antidepressant activity was observed in both tests following the administration of extract at 100 and 250 mg kg$^{-1}$ doses. To the best of our knowledge, this is the first study reporting the antidepressant activity of *H. montbretti* extract. Additionally, the results of this work support previous papers reporting the antidepressant activity of rutin.

**Keywords:** *Hypericum*; rutin; modified forced swimming test; tail suspension; Rota-Rod; antidepressant; quercitrin



### 1. Introduction

*Hypericum montbretti* Spach. (Guttiferae, Clusiaceae) is a perennial herb widely distributed in northern Turkey as well as in the Balkans, Syria and Georgia. Naphthoadiantrones (hypericin, pseudohypericin, etc.), phloroglucinol derivatives (hyperforin, adhyperforin), flavonoids (rutin, quercetin, quercitrin, etc.), xanthones, biflavonoids, chlorogenic acid and volatile compounds have been determined in *H. montbretti* extracts (Cirak, Radusiene, & Arslan, 2008; Öztürk, Tunçel, & Potoğlu-Erkara, 2009).

Among the above-mentioned components, hyperforin, hypericin, pseudohypericin and some flavonoids have been reported as constituents responsible for the antidepressant activity of *H. perforatum* extracts (Butterweck et al., 2003;

*Corresponding author. Email: ozgurdt@anadolu.edu.tr

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Butterweck, Petereit, Winterhoff, & Nahrstedt, 1998; Cirak et al., 2008; Müller, Singer, & Wonnemann, 2001; Noldner & Schotz, 2002). Based on its similar chemical constituents to other *Hypericum* species that possess antidepressant activity, we investigated the possible antidepressant activity of *H. montbretti* extract (HME) and discuss herein the probable constituent–activity relationships.

## 2. Results and discussion

The findings of this study showed evidence of antidepressant-like activity of HME, as we hypothesised. Administration of the reference drug reboxetin (Rbx) and two different doses of the extract significantly shortened the immobility times of the animals in the tail suspension test when compared to the control values. The 250 mg kg$^{-1}$ dose was more effective than the 100 mg kg$^{-1}$ dose. In the modified forced swimming test (MFST), the extract at both doses caused significant and dose-dependent reductions in immobility and swimming times, with significant prolongation of the climbing times of the animals (Table 1), indicating that the antidepressant-like effects exhibited in this study might be related to catecholaminergic rather than serotonergic mechanisms on the central nervous system (Cryan, Markou, & Lucki, 2002). However, the involvement of the catecholaminergic system in the exhibited antidepressant activity needs to be confirmed with further detailed studies such as inhibition of catecholamine synthesis by alpha-methyl-para-tyrosine pre-treatment or measuring the levels of catecholamines in limbic areas of brain, etc. In addition, there was no increase in

Table 1. Effects of the extract on different behavioural tests.

| Tail suspension tests | | | |
|---|---|---|---|
| Groups | Immobility time (s) | | |
| Control (physiological saline) | $123.8 \pm 6.3$ | | |
| Rbx (20 mg kg$^{-1}$) | $43.1 \pm 5.24^{c}$ | | |
| HME (100 mg kg$^{-1}$) | $93.1 \pm 5.6^{b}$ | | |
| HME (250 mg kg$^{-1}$) | $67.7 \pm 4.3^{c**}$ | | |
| MFST tests | | | |
| Groups | Climbing time (s) | Swimming time (s) | Immobility time (s) |
| Control (physiological saline) | $45.9 \pm 3.4$ | $105.7 \pm 6.1$ | $99.7 \pm 7.3$ |
| Rbx (20 mg kg$^{-1}$) | $80.7 \pm 4.6^{c}$ | $76.0 \pm 5.5^{a}$ | $68.2 \pm 6.5^{b}$ |
| HME (100 mg kg$^{-1}$) | $62.8 \pm 5.1^{a}$ | $80.1 \pm 6.5^{a}$ | $70.3 \pm 5.1^{b}$ |
| HME (250 mg kg$^{-1}$) | $83.2 \pm 3.2^{c**}$ | $54.9 \pm 6.9^{c*}$ | $44.7 \pm 4.5^{c}$* |
| Rota-Rod tests | | | |
| Groups | Falling latencies (s) | | |
| Control (physiological saline) | $574.5 \pm 17.6$ | | |
| HME (100 mg kg$^{-1}$) | $559.7 \pm 16.0$ | | |
| HME (250 mg kg$^{-1}$) | $497.8 \pm 23.3^{a}$ | | |

Notes: One-way ANOVA, post-hoc Tukey's test, $n = 6$. Significance against control values: $^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$; significance against 100 mg kg$^{-1}$ extract: $^{*}p < 0.05$, $^{**}p < 0.01$.

Rota-Rod performance of the extract-treated animals, which may cause false positive results in the depression tests. Motor coordination parameters of the animals were observed to decrease following a 250 mg $kg^{-1}$ dose of HME. The mechanisms of this effect need to be clarified with further detailed studies.

The main flavonoid component of HME investigated in this study was rutin (1519 ppm). Another highly concentrated phenolic compound in the extract was quercitrin (784 ppm). Chlorogenic acid (49 ppm), isoquercitrin (29.06 ppm), hyperoside (19.45 ppm), hypericin (10.93 ppm), hyperforin (2.91 ppm) and quercetin (0.6 ppm) were detected in lower amounts (Supplementary Table S1 – online only).

The antidepressant activity of *Hypericum* extracts have been attributed to the phloroglucinol derivative hyperforin (Cervo et al., 2005), to the napthodianthrones hypericin and pseudohypericin (Butterweck et al., 1998) and to several flavonoids (Butterweck et al., 2003; Butterweck, Jurgenliemk, Nahrstedt, & Winterhoff, 2000). However, hyperforin, which is suggested to be mainly responsible for the antidepressant action, was found in a trace amount following the phytochemical analysis of the extract tested in this study. Besides hypericin, the other possible active constituents were also detected in quite low amounts. Low concentrations of these bioactive constituents in spite of significant antidepressant action were one of the interesting findings of this study. These results support previous findings suggesting antidepressant activities of hyperforin- or hypericin-free extracts and exhibit the importance of flavonoid content in antidepressant activity (Butterweck et al., 2000, 2003; Öztürk, Aydın, Beis, Başer, & Berberoğlu, 1996).

The major phenolic compound of the HME in this study was determined as rutin with 1519 ppm, quite a high-concentration value. Rutin alone has been recently reported to possess antidepressant activity. Increasing the availability of serotonin and noradrenalin in the synaptic cleft has been suggested as the mechanism responsible for its antidepressant action (Machado et al., 2008). In another study, this flavonoid was also reported for its antidepressant capabilities, with the inhibition of monoamino oxidase suggested at least as part of its mechanism of action (Dimpfel, 2009). In addition, Noldner and Schotz (2002) have suggested that rutin is an essential constituent for the antidepressant activity of *Hypericum* extracts, and that other constituents may act synergistically (Noldner & Schotz, 2002). Therefore, the antidepressant effect exhibited in this study is probably related to the high rutin concentration in the HME. Studies for potential antidepressant-like activities of rutin and quercitrin, the two highly concentrated constituents in the tested extract, are proceeding in our laboratory.

To the best of our knowledge, this is the first study reporting the antidepressant activity of HME. Interpretation of the information based on recent phytochemical and pharmacological investigations of *Hypericum* species is believed to be beneficial for the determination of the active compound/s responsible for the antidepressant activity and the explanation of possible synergic mechanisms.

## 3. Conclusions

This study shows evidence of the antidepressant activity of *H. montbretti* for the first time, and supports previous papers reporting the antidepressant activity of rutin in rodents (Dimpfel, 2009; Machado et al., 2008; Noldner & Schotz, 2002).

## Supplementary material

Experimental details relating to this article are available online, alongside Tables S1–S2.

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