*Available online www.jocpr.com*

**Journal of Chemical and Pharmaceutical Research, 2014, 6(3):1294-1298**

**Research Article**

**ISSN : 0975-7384**
**CODEN(USA) : JCPRC5**

# Partial agonistic property of new isolated natural compounds

**Aimun AE. Ahmed[1*], Robert Gaspar[2], Arpad Marki[2], M. M. E. Mudawi[1] and George Falkay[2]**

*[1]Department of Pharmacology, Faculty of Pharmacy, Omdurman Islamic University, Sudan*
*[2]Department of Pharmacodynamics and Biopharmacy, Faculty of Pharmacy, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*

---

**ABSTRACT**

*The aim of this study was to validate the partial agonistic property of two natural isolated $\beta_2$-adrenocepotor agonists using rat uteri in vitro functional efficacy test. Our results revealed that the combination of the two agonists exhibited intermediate relaxing effect represented as dose-response curve with 50% $E_{max}$ of terbutaline, which confirmed by the effect of the selective β2-adrenoceptors antagonist ICI118.551, and their significant inhibition of terbutaline relaxing effect in both uteri. Finally, both isolated compounds are considered as partial $\beta_2$-adrenoceptors agonists.*

**Keywords:** $\beta_2$-adrenoceptor agonists, partial agonist, rat uterus, isolated tissue, combination, drug-drug interaction.

---

## INTRODUCTION

Partial agonists were of therapeutic essentials [1-2-3-4], the β-adrenergic partial agonist; alifedrine was implicated in the management of cardiac performance with acute ischemic left ventricular failure [1].

In our previous studies, we isolates two compound from El-hazha herb, 6-methoxykaempferol-3-O-glucoside (6-MKG) [2] and Haplopine-3,3'-dimethylallyl ether (HAP) [3] and investigated their $\beta_2$-Adrenoceptors activity, but we observed that their activities were less than that of terbutaline [4]. These observations encourage us to think about their partial property which was not studied yet. This study aimed to validate this partial activity for both compounds.

## EXPERIMENTAL SECTION

### In vitro functional efficacy test

*Ethical considerations for housing and handling the animals*

The animals were treated in accordance with the European Communities Council Directives (86/609/ECC) and the Hungarian Act for the Protection of Animals in Research (XXVIII.tv.32. §). All experiments involving animal subjects were carried out with the approval of the Hungarian Ethical Committee for Animal Research (registration number: IV/1758-2/2008). Sprague-Dawley rats (Charles-River Laboratories, Hungary) were kept at 22 ± 3 $^oC$; the relative humidity was 30-70% and the light/dark cycle was 12/12 h. They were maintained on a standard rodent pellet diet (Charles-River Laboratories, Hungary), with tap water available *ad libitum*. The animals were sacrificed by $CO_2$ inhalation.

*Uterus preparation*

Uteri were removed from non-pregnant rats (180–200 g) and on pregnancy day 22 from pregnant rats (270–350 g). Muscle rings 5 mm long were sliced from the uterine horns and mounted vertically in an organ bath containing 10 ml de Jongh solution (composition: 137 mM NaCl, 3 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 12 mM $NaHCO_3$, 4 mM $NaH_2PO_4$, 6 mM glucose, pH=7.4). The organ bath was maintained at 37 °C and carbogen (95% $O_2$+5% $CO_2$) was bubbled through it. After mounting, the rings were equilibrated for about 1 h before the experiments were undertaken; with a solution change every 15 min. The initial tension of the preparation was set to about 1.5 g, which was relaxed to about 0.5 g at the end of equilibration. The tension of the myometrial rings was measured with a gauge transducer (SG-02; Experimetria Ltd., Budapest, Hungary) and recorded with a SPEL Advanced ISOSYS Data Acquisition System (Experimetria Ltd., Budapest, Hungary).

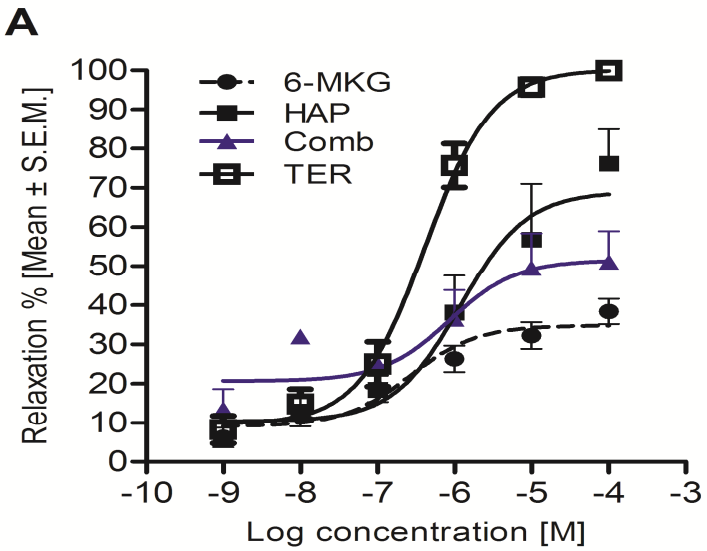
Uteri were pre-contracted with 25 mM KCl and cumulative concentration–response curves were constructed in each experiment for both compound together alone, and then everyone alone with terbutaline on isolated tissue and together with terbutaline in different concentrations (range from $10^{-9}$ to $10^{-4}$ M) in the presence or absence of 3-(isopropylamino)-1-[(7-methyl-4-indanyl)oxy]butan-2-ol (ICI 118,551) ($10^{-5}$ M). Following the addition of each concentration of the tested material, recording was performed for 5 min. Area under the curve were evaluated and concentration–response curves were fitted; $E_{max}$, $EC_{50}$ and $pA_2$ values were determined and compared statistically by using the computer program Prism 5.0. (GraphPad Software, USA).

## RESULTS AND DISCUSSION

6-MKG and HAP alone and together produce intermediate curves on non-pregnant (Fig. 1A) and late-pregnant (Fig. 1B) rat uteri, compared to that of terbutaline.

The calculated $pA_2$ values that indicate affinity of combination of 6-KMG and HAP and standard terbutaline standard with the selective $\beta_2$-adrenoceptors antagonist ICI118.551 in a dose of [10-9M and 10-4 M] for at least six repeated measures were showed in a tabular form (Table 1).

Addition of 6-KMG and HAP to terbutaline decreased significantly its effect and shifted its dose-response curve to the right in NP and LP rat uteri (Fig. 2).



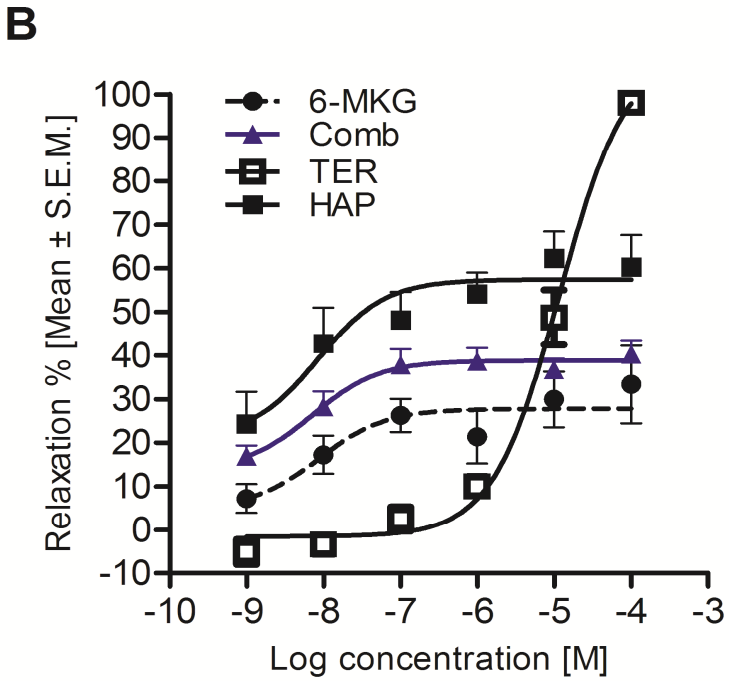
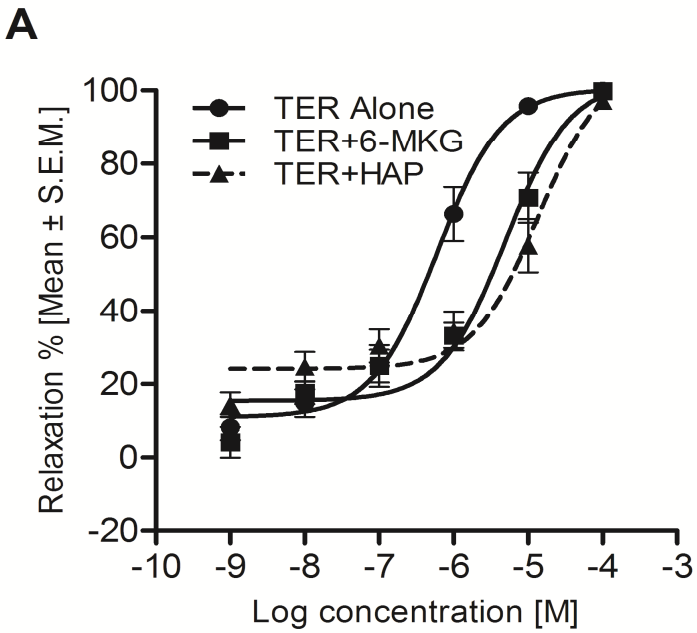



**Fig. 1: Dose-response curves of the relaxing effect of terbutaline, 6-MKG, HAP and their combination on non-pregnant (A) and late-pregnant (B) rat uteri in vitro, pre-contracted with 25 mM KCl**

*Values presented are means of 6-8 observations; vertical bars denote standard errors of the mean (S.E.M.). , *, P<0.05, for HAP against terbutaline*



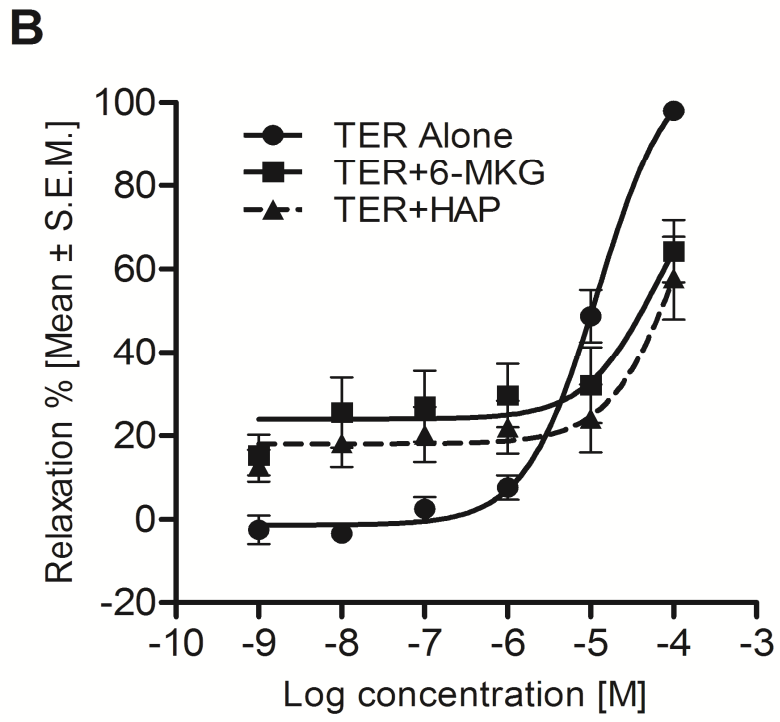



**Fig. 2: Dose-response curves of the effect of HAP+ terbutaline (dotted-line) and terbutaline + 6-MKG (continuous-line) on non-pregnant (A) and late-pregnant (B) rat uterus *in vitro* against KCl-induced control contractions**

*Values presented are means of 6-8 observations, while vertical bars denote standard errors of the mean (SEM), *, P<0.05, for HAP against terbutaline*

**Table 1: Effect of ICI118,551 on the relaxing activities of combination of 6-MKG and HAP on non-pregnant and late pregnant rat uteri *in vitro***

| Rat uterus | $pA_2$ [mean ± SEM], N=8 | Emax [mean ± SEM]%, N=8 | |
|---|---|---|---|
| | | without ICI | with ICI |
| Non-pregnant | 6.8 ± 0.6 | 51.5 ± 5.5 | 35.7 ± 2.6 |
| Late-pregnant | 6.0 ± 0.5[a] | 38.8 ± 1.6 | 27.4 ± 2.1 |

*$pA_2$: negative logarithm of the competitive antagonist concentration at which the agonist concentration should be doubled to reach the same effect that without the antagonist; N: total number of observations; ICI: ICI18,551 [a]: p>0.05, ns: not significant.*

Literature survey revealed that, there is increasing importance of natural products in the areas of drug discovery [5]. Although information regarding the binding sites of partial agonists is still not sufficient to explain why they cannot fully activate the receptor, partial agonists still were of therapeutic essentials [6-7-8-9-10-11].

This study serves as functional efficacy test or pharmacodynamic drug-drug interactions of two isolated compounds that possesses $\beta_2$-Adrenoceptors agonist activity [2-3]

The resulted intermediate curve of combination was in line with our hypothesis, indicating the partial feature for 6-MKG against the HAP, whilst the combination effect regard terbutaline.

The total combination maximum effect was approximately 50% which represent atypical partial agonist property [12], because partial agonist is a compound that can activate receptors but is unable to elicit the maximal response of the receptor system.

These findings were confirmed by the ICI effects on combination comparable to terbutaline, which can be taken as an evidence regard the partial agonistic feature of our compounds.

**REFERENCES**

[1] [1] P Metzenauer, R Dedecke, H Gobel, PA Martorana, F Stroman, I Szelenyi. *J Cardiovasc Pharmacol*., **1989**, 14(1): 103-108.
[2] AAE Ahmed, M Arpad, G Ropert., V Andrea, MME Mudawi, V Judit, Jojart B., Hohmann, Falkay G. *Eur J Pharmacol*., **2011**, 667 (1-3): 348-354.
[3] AAE Ahmed, A Marki, R Gaspar, A Vasas, MME Mudawi, B Jójárt, R Minorics, J Hohmann, Falkay G.. *Medicinal Chemistry Research*., **2012**, 21(12): 4100-4107.
[4] AAE Ahmed, R Gaspar, A Marki, A Vasas, MME Mudawi, J Humman, G Falkay,. *Am. J. Biochem. and Biotech.*, **2010**, 6 (3 ): 231-238.
[5] TM Olaleye, K Komolafe, AA Akindahunsi. *Journal of Chemical and Pharmaceutical Research*., **2013**, 5(1): 213-220
[6] K Cahill, LF Stead, T Lancaster. *Cochrane Database Syst Rev* , **2008**, (3): CD006103.
[7] K. Ismail. *British Journal of Psychiatry*, **2005**, 186: 354 - 357.
[8] CA Tamminga. *J Neural Transm.*, **2002**, 109(3): 411-420.
[9] M Launer. *Hosp Med* , **2005**, 66(5): 300-303.
[10] WWM Zuurmond, TF Noorduin, H.. *Acta Anaesthesiol Belg*., **2002**, 53(3): 193-201.
[11] Leskova, G. F. A. I., V. *Vopr Med Khim*., **2002**, 48(5): 497-502.
[12] LD Homer, TB Nielsen. *Am J Physiol* , **1987**, 253(1): 114-121.