

## Research Article

# Antinociceptive and Anti-inflammatory Effects of the Aqueous Leaves Extract of *Plectranthus glandulosus*. Hook. F. (Lamiaceae) in Mice and Rats

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## Abstract

*Plectranthus glandulosus* (Lamiaceae) is used in traditional Cameroon medicine for the treatment of dermatitis, bellyache, venereal diseases, internal inflammation, lower abdominal and nerve ache. In the present study, we have been evaluated analgesic and anti-inflammatory properties of aqueous extract of *P. glandulosus* in mice (*Mus musculus*) and Wistar strain albino rats. Analgesic property was carried out in experimental animal models of acute pain; acetic acid (1%, 20  $\mu$ L), formalin (1%, 20  $\mu$ L), capsaicin (32  $\mu$ g mL<sup>-1</sup>, 20  $\mu$ L) and hot plate (55 $\pm$ 0.55°C). Anti-inflammatory activity was assessed on carrageenan-induced inflammation. Extract was administrated orally at 200, 400 and 600 mg kg<sup>-1</sup>. The results showed that aqueous extract significantly reduced the pain induced by acetic acid by 38.98% at a dose of 600 mg kg<sup>-1</sup>. In the formalin test, the extract also significantly reduced linking time in both phase of the test ( $p<0.01$ ) by 49.41% (neurogenic phase) and 65.51% (inflammatory phase) at a dose of 400 mg kg<sup>-1</sup>. The aqueous extract of *P. glandulosus* significantly reduced ( $p<0.01$ ) neurogenic pain linking time induced by capsaicin by 83.98% at the highest dose (600 mg kg<sup>-1</sup>). More over the extract significantly increase the reaction time in hot plate test. In the inflammatory test, the plant extract significantly reduced the carrageenan induced rat paw edema from 30 min to 6 h with a maximum percentage inhibition of 80.76% (6 h) at the dose of 600 mg kg<sup>-1</sup>. These results demonstrate that the aqueous extract of *P. glandulosus* may possess analgesic (central and peripheral) and anti-inflammatory effects. These results justify the use of the fresh leaves of *P. glandulosus* in traditional medicine for the treatment of painful and inflammation.

**Key words:** Pain, inflammation, analgesic, *Mus musculus* carrageenan, neurogenic

**Received:** October 01, 2015

**Accepted:** November 27, 2015

**Published:** December 15, 2015

**Citation:** Annie Laure Fongang Magne, Edwige Laure Nguemfo, Calvin Bogning Zangueu, Hélène-Laure Ngando, Phillippe Ebanda Kedi Belle and Alain Bertrand Dongmo, 2016. Antinociceptive and Anti-inflammatory Effects of the Aqueous Leaves Extract of *Plectranthus glandulosus*. Hook. F. (Lamiaceae) in Mice and Rats. *Pharmacologia*, 7: 60-66.

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**Competing Interest:** The authors have declared that no competing interest exists.

**Data Availability:** All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Painful is one of the leading causes of medical consultations features of many diseases and affects individuals of all ages. Pain is a symptom associated with several disorders, including inflammation. The pain treatment involves a number of drug classes for example non-steroidal anti-inflammatory drugs, corticosteroids and narcotics<sup>1,2,3</sup>. The number of new drugs used to treat these both pain and inflammation remains low, despite anti-inflammatory research<sup>4</sup>. These drugs available are expensive and are not accessible to the population especially in developing countries. In addition, their adverse effects (gastric ulcer, addiction and blood pressure elevation) are important. There is consequently the need to search for more active compounds with less adverse effects. Medicinal plants represent an alternative. There is a renewed and increased interest in plants a source of new pharmaceutical drugs. *P. glandulosus* is a climbing herbaceous plant with three meters long, that grows in forested mountains and bush from Mali to Fernando Po, she was found in West Africa, Central Africa and Africa South<sup>5,6</sup>. It is a highly aromatic herb found in Cameroon in the central and west regions. *Plectranthus glandulosus* is used in traditional medicine for the treatment of dermatitis, bellyache, venereal diseases, internal inflammation, lower abdominal<sup>7,8</sup>. Ethnobotanic data indicate some claimed therapeutic uses like nerve ache. Phytochemical investigation of *P. glandulosus* revealed the presence of terpenoids, steroids, tannins and flavonoids<sup>9</sup>. The purpose of the present study was to investigate the possible analgesic and anti-inflammatory activities of the aqueous leaves extract of *Plectranthus glandulosus*.

## MATERIALS AND METHODS

**Chemicals:** Acetic acid and capsaicin were obtained from Roth, formaldehyde (Polypharma, Douala, Cameroon), carrageenan and aspirin (SIGMA Aldrich, Germany), tramadol (New Divine Favour Pharm IND. Ltd., Nigeria).

**Preparation of plant material:** Leaves of *P. glandulosus* were collected in Bafoussam, West region of Cameroon. The plant material was identified and authenticated by comparison with herbarium voucher specimen N°33879, National Herbarium (Yaoundé, Cameroon). The fresh leaves were cut, dried in the shade and then crushed with a mill. The resulting powder (2.5 kg) was macerating for 24 h in 6 L of distilled water. After filtration, filtrate was lyophilized to obtain crude aqueous extract (brown residue, 80.6 g).

**Animals:** Mice (18-25 g) aged between 75 and 90 days and Wistar albino rats (100-150 g) aged 90 days both sexes were used for investigations. They were bred in the animal house of the Department of Animal Biology and Physiology, University of Douala, Cameroon. They were housed in plastic cages under laboratory conditions (12/12 h light/dark cycle, 22-25°C). They were fed *ad libitum* and have free access to water. After divided animals in group (n = 7), they were fasted 12 h before the experiments. Prior authorization for the use of laboratory animal was obtained from the Cameroon National Ethical Committee.

### Antinociceptive activity

**Writhing test:** The antinociceptive effect of the aqueous extract of *P. glandulosus* was investigated in mice using the method described by Koster *et al*<sup>10</sup>. Animals were pretreated with *P. glandulosus* extract (200, 400 and 600 mg kg<sup>-1</sup>) and the reference analgesic drug, aspirin (200 mg kg<sup>-1</sup>) were orally administered to mice 30 min before acetic acid (10 mL kg<sup>-1</sup>) 1% was administered intraperitoneally. The control animal was treated by vehicle (10 mL kg<sup>-1</sup>). The mice were individually placed into glass (20 × 204). The number of writhing and stretching of the hind limbs was counted over a period of 30 min as previously reported<sup>10,11</sup>. The percentage of analgesic activity was expressed as percentage reduction of the number of stretching in treated animals with respect to the controls as follow: (control mean-treated mean) × 100/control mean<sup>12</sup>.

**Formalin test:** The method used in this test was previously described by Tjolsen *et al*<sup>13</sup>. Animals were pretreated with *P. glandulosus* extract (200, 400 or 600 mg kg<sup>-1</sup>) p.o; distilled water (10 mL kg<sup>-1</sup>) and reference analgesic drug, aspirin (200 mg kg<sup>-1</sup>). Thirty minutes after pretreatment, 20 µL formalin (1%) was injected under the surface of the right hind paw. Mice were individually placed in a transparent plexiglass cage for observation. The total time spent licking and biting the injected paw was recorded with a chronometer in two different time periods (from 0-5 min for the early acute phase and from 20-30 min for a late phase) and was considered as indicative of pain.

**Hot plate test:** The hot plate assay was carried out according to the method described by Eddy and Leimboech<sup>14</sup>. Mice were placed on an hot plate (Ugo basile, Italy, socrel and mod DS-37), maintained at 55 ± 0.5 °C to induce pain. The reaction time of each mouse (licking the forepaw or jumping reaction) was recorded before the treatment and only mice with a control response time of 4-12 sec were included in the study. These mice received, for p.o plant extract (200, 400 or

600 mg kg<sup>-1</sup> p.o, vehicle (distilled water, 10 mL kg<sup>-1</sup>) and Tramadol (20 mg kg<sup>-1</sup>) p.o 30 min before thermal stimulus. Each mouse acted as its own control. Prior to treatment, the reaction time of each mouse was done at 0-10 min intervals. The nociceptive response was measured 15, 30, 45, 60, 90 and 120 min period following the administration of extract. The increase of latency time in relation to the initial time for each group was taken as an index of analgesic activity.

**Capsaicin test:** This test is performed as described previously by Mesia-Vela *et al.*<sup>15</sup>. The animals were orally treated with vehicle (water, 10 mL kg<sup>-1</sup>) or aqueous extract of *P. glandulosus* (200, 400 and 600 mg kg<sup>-1</sup>), tramadol (20 mg kg<sup>-1</sup>) 1 h before intraplantar injection of 30 µL of capsaicin (32 µg mL<sup>-1</sup>). Animals were observed individually in plexiglass cage. The amount of time spent licking the inject paw was considered as indicative of nociception and recorded from 0-5 min.

**Anti inflammatory activity: carrageenan-induced rat paw oedema:** Carrageenan induced paw inflammation was produced according to the method described by Winter *et al.*<sup>6</sup>. One hour before oral administration of plant extract (200, 400 or 600 mg kg<sup>-1</sup>), aspirin (200 mg kg<sup>-1</sup>), or vehicle (10 mL kg<sup>-1</sup>), oedema was induced by injection of 0.1 mL of 1% suspension of carrageenan in 0.9% sterile saline solution into the right plantar aponeurosis of the rat. Paw volume oedema was measured using Ugo Basile 7510 plethysmometer, before (volume displacement technic carrageenan injection) and 1/2, 1, 2, 4 and 6 h after carrageenan injection. Anti-inflammatory activity was expressed as the percentage reduction in oedema in treated rats by comparison with the controls calculated as percentage of reduction of the oedema in the treated rats compared to control by the formula:

$$\text{Percentage reduction} = \frac{[(v_t - v_o) \text{ control} - (v_t - v_o) \text{ treated}]}{(v_t - v_o) \text{ control}} \times 100$$

where,  $v_t$  is the average volume of each group and  $v_o$  is the average volume obtained for each group before any treatment<sup>17</sup>.

**Statistical analysis:** Data were expressed as mean  $\pm$  standard error of the mean (SEM). Comparisons between experimental and control groups were performed by one-way analyze of variance (ANOVA) followed by Dunnett's tests. The p-value less than 0.05 were considered significant.

## RESULTS

### Analgesic activity

#### Effect of aqueous extract on writhing response induced

**by acetic acid:** Aqueous extract of *P. glandulosus* (200-600 mg kg<sup>-1</sup>) induced a significant reduction ( $p < 0.01$ ) in the number of writhing provoked by an intraperitoneal injection of acetic acid in mice. The maximum percentage of reduction was 38.98% at the dose of 600 mg kg<sup>-1</sup>. The positive control drug, aspirin (200 mg kg<sup>-1</sup>), also provoked significant ( $p < 0.01$ ) protective effect 39.24% against acetic acid-induced pain (Table 1).

#### Effect of aqueous extract on hind paw licking response

**induced by formalin:** Injection of 20 µL formalin (1%) into the surface of the right paw generated classical biphasic nociceptive responses (neurogenic and inflammatory pain) in mice. The plant extract (200-600 mg kg<sup>-1</sup>) significantly ( $p < 0.01$ ) reduced licking time in both phases of the formalin test. The maximum percentage of inhibition was 49.41% (early phase) and 65.51% (late phase) at the dose of 400 mg kg<sup>-1</sup>. A positive control group, aspirin (200 mg kg<sup>-1</sup>) also significantly reduces pain only at the late phase (60.36% inhibition) (Table 2).

**Hot plate test:** The latency of reaction to hot plate stimulus is summarized in Table 3. The aqueous extract of *P. glandulosus* significantly ( $p < 0.01$ ) increased reaction (32.9 sec at 400 mg kg<sup>-1</sup>) and (30.80 sec; at 600 mg kg<sup>-1</sup>) after 45 min compared to control. A central acting reference analgesic drug, tramadol (20 mg kg<sup>-1</sup>), significantly increased reaction (18.70 sec) after 90 min (Table 3).

**Capsaicin-induced neurogenic pain:** As shown in Table 4, the oral administration of *P. glandulosus* (200, 400 and 600 mg kg<sup>-1</sup>) produced significant inhibition of the capsaicin-induced licking in mice by 49.14, 68.60 and 83.98, respectively. Positive control animals which received tramadol showed the decrease of the licking time by 80.10% (Table 4).

Table 1: Effect of *Plectranthus glandulosus* aqueous extract on pain induced by acetic acid in mice

Treatments	Dose (mg kg <sup>-1</sup> )	No. of writhings	Inhibition (%)
Control	-	79.00 $\pm$ 20	-
Aspirin	200	48.00 $\pm$ 3.72**	39.24
<i>Plectranthus glandulosus</i>	200	53.00 $\pm$ 2.70**	32.91
<i>Plectranthus glandulosus</i>	400	53.00 $\pm$ 3.60**	32.91
<i>Plectranthus glandulosus</i>	600	48.20 $\pm$ 3.58**	38.98

Values are expressed as Mean  $\pm$  SEM of seven individual values, \*\* $p < 0.01$ , significantly difference, when compared to control group

Table 2: Effect of *Plectranthus glandulosus* aqueous extract on formalin- induced pain in mice

Treatments	Dose (mg kg <sup>-1</sup> )	Licking time (min)		Inhibition (%)	
		0-5	20-30	Early phase	Late phase
Control	10	61.18±1.60	43.34±2.69	-	-
Aspirin	200	58.66±2.29**	17.18±3.89**	4.11	60.36
<i>Plectranthus glandulosus</i>	200	34.30±3.27**	21.25±3.62**	40.90	50.95
<i>Plectranthus glandulosus</i>	400	30.96±3.24**	14.94±2.75**	49.41	65.51
<i>Plectranthus glandulosus</i>	600	33.38±3.65**	16.29±2.85**	45.43	62.41

Values are expressed as Mean±SEM of seven individual values. \*p<0.01 significantly difference when compared to control group

Table 3: Effect of *Plectranthus glandulosus* extract on pain induced by hot plate

Treatments	Dose	Reaction time latency (sec)						
		T0	T15	T30	T45	T60	T90	T120
Control	10	5.63±0.73	6.00±10	5.86±2.80	7.30±1.70	7.00±2.41	6.44±1.30	5.64±0.50
Tramadol	20	5.43±1.25	6.22±0.22	14.90±1.65	8.38±1.50	9.02±1.20	18.70±4.60**	15.72±4.60*
<i>Plectranthus glandulosus</i>	200	7.16±1.20	15.02±1.80**	13.12±1.70	11.07±1.14	20.00±2.60**	17.90±2.80*	9.20±1.20
<i>Plectranthus glandulosus</i>	400	8.00±1.44	25.02±1.94**	21.70±0.64**	32.90±6.70**	16.20±1.90*	17.05±2.80*	13.50±1.50
<i>Plectranthus glandulosus</i>	600	8.80±1.21	12.86±1.60*	26.40±3.90**	30.80±3.80**	19.61±1.50**	17.32±1.20*	14.75±0.63*

Values are expressed as Mean±SEM of seven individual values. \*p<0.05, \*\*p<0.01 significantly difference when compared with to control group

Table 4: Effect of *Plectranthus glandulosus* aqueous extract on capsaicin-induced neurogenic pain in mice

Treatments	Dose (mg kg <sup>-1</sup> )	Licking time	
		(0-5 sec)	Inhibition (%)
Control	10	23.27±1.85	-
Tramadol	20	4.63±1.29**	80.10
<i>Plectranthus glandulosus</i>	200	11.83±1.00**	49.14
<i>Plectranthus glandulosus</i>	400	7.30±1.17**	68.60
<i>Plectranthus glandulosus</i>	600	3.72±1.03**	83.98

Values are expressed as Mean±SEM of seven individual values, \*\*p<0.01 significantly difference when compared to control group

**Anti-inflammatory effect of *Plectranthus glandulosus*:** As shown in Table 5, a pretreatment of rats with extract aqueous of *P. glandulosus* significantly decrease paw oedema caused by injection of carrageenan when compare to control group. The highest doses tested (600 mg kg<sup>-1</sup>) reduced inflammation by 80.76% at the 6 h. A non-steroidal drug, aspirin (200 mg kg<sup>-1</sup>), also exhibited an anti-inflammatory effect with anti inflammatory drug inhibition of 63.37 and 67.69% inhibition at ½ and 5 h, respectively (Table 5).

## DISCUSSION

The intraperitoneal injection of acetic acid causes pain characterized by abdominal writhing. This pain induced by acetic acid is either direct consequence of stimulation chemo-sensitive nociceptors<sup>18</sup> or indirectly by irritation of visceral surface; causing release of algogenic substances such as histamine, bradykinin, prostaglandins and serotonin<sup>19,20</sup>. Acetic acid also acts by releasing endogenous mediators that stimulate the nociceptive neurons and induce capillary permeability<sup>21,22</sup>. As in report, they are local peritoneal

receptors to nociceptive stimulus which seem to be related with the prostanoid system<sup>23</sup>. Acetic acid-induced abdominal constriction can also be related to release of cytokins like TNF $\alpha$ , interleukin 1 $\beta$  and interleukin 8 and they are released from resident peritoneal macrophage and mast cells<sup>24</sup>. The results demonstrate that the aqueous extract of *P. glandulosus* produced an inhibition of the number of abdominal constrictions induced by acetic acid, a typical model used to search for new drugs with analgesic properties<sup>25</sup>. It antinociceptive effects could occur via peripheral or central sites action. Aspirin, the known inhibitor of COX (COX1, COX2), provoked inhibition of abdominal constrictions induced by acetic acid.

In the present study, the hot plate, formalin and capsaicin tests were used to evaluate-the central analgesic effects of *P. glandulosus* extract. The subcutaneous injection of formalin is characterized by two distinct phases of nociception. The first phase (0-5 min) or neurogenic phase begins immediately after formalin injection and resulting to direct activation of nociception neuron (C fibers) and release of P substance<sup>26,27,28</sup>. Whereas, second phase or inflammatory phase (20-30 min) is the consequence of acute injure tissue and is characterized by the release of chemical mediators such as histamine, serotonin, kinin and prostaglandin<sup>26,27</sup>. The aqueous extract of *P. glandulosus* (200, 400 and 600 mg kg<sup>-1</sup>) significantly decreased pain on both phases. It's well known that, centrally acting drugs such as opioid, inhibit equally both phases<sup>29</sup>. Aspirin (200 mg kg<sup>-1</sup>) used as reference drug significantly inhibited the formalin-induced pain only during the inflammatory phase. Aspirin, peripheral acting drug alleviated pain only at the late phase by inhibited

Table 5: Anti-inflammatory effect of *Plectranthus glandulosus* extract on carrageenan-induced paw oedema in rats

Treatments	Dose (mg kg <sup>-1</sup> )	Inflammation (ΔV, mL)							
		0 h	1/2 h	1 h	2 h	3 h	4 h	5 h	6 h
Control	10	0.77±0.05	0.99±0.03	0.95±0.01	0.98±0.03	0.95±0.03	0.97±0.05	0.9±0.04	0.95±0.01
Aspirin	200	0.72±0.05	0.80±0.04 (67.37)*	0.83±0.04 (43.75)	0.82±0.01 (55.91)*	0.81±0.06 (55.81)*	0.83±0.04 (55.32)*	0.77±0.03 (67.69)*	0.79±0.01 (65.82)*
<i>Plectranthus glandulosus</i>	200	0.72±0.07	0.86±0.04 (41.05)	0.85±0.03 (36.25)	0.91±0.04 (21.50)	0.86±0.03 (33.03)	0.83±0.04 (56.38)*	0.81±0.03 (47.69)*	0.83±0.02 (48.10)
<i>Plectranthus glandulosus</i>	400	0.68±0.03	0.81±0.08 (47.37)*	0.78±0.04 (52.50)*	0.79±0.03 (52.68)*	0.74±0.03 (69.69)**	0.76±0.04 (68.08)*	0.74±0.02 (64.61)*	0.73±0.02 (74.68)**
<i>Plectranthus glandulosus</i>	600	0.77±0.04	0.88±0.05 (52.84)*	0.83±0.03 (69.00)**	0.87±0.04 (55.27)*	0.87±0.03 (47.47)*	0.85±0.04 (62.55)*	0.85±0.04 (44.61)	0.80±0.04 (80.76)**

Values are expressed as Mean ± SEM of seven individual values, \*p<0.05, \*\*p<0.01 significantly difference when compared to control group. The percentage of inhibition against carrageenan-induced, Paw oedema is given in parentheses

cyclooxygenase involved in prostaglandin synthesis<sup>30</sup>. These results suggest that the *P. glandulosus* aqueous extract mechanism may be similar in part to that of aspirin and/or contain compounds which acted in both phases<sup>18</sup>.

In this study, hot plate test was used to confirm the inhibition of neurogenic phase observed in formalin-induced pain in mice, further more. It's a central model that has selectivity for opioid-derived analgesic<sup>31</sup>. In our study, previous administration of *P. glandulosus* aqueous extract significantly increased the latency time in hot plate test suggesting the central analgesic of this extract and confirms the results observed in formalin-induced pain.

Capsaicin induced neurogenic pain was used to evaluate the effect of the extract. In order to determine the central mechanism. The subcutaneous injection of capsaicin induce pain which is manifested by licking of the injected paw. This phenomenon lasts about 5 min and result to the vanilloid VR1 receptor stimulation of ionotropic channel type that once opened, let in calcium and other cations within the cell, triggering the cell excitation process leading to the perception of the pain message<sup>32,33,34</sup>. The extract significantly decreased the licking time as compared to control. Our results show that oral administration of the *P. glandulosus*. This produced significant reduction of the nociceptive response caused by intra plantar injection of the capsaicin into mice hind paw. The antinociceptive response effect of this extract could be by regulating the VR1 receptor activation, which in turn reduces the neurogenic inflammation and the glutamate release, contributing to the modulation of nociceptive transmission. Tramadol inhibits pain as an opioid with low affinity for the micro receptor and almost negligible for other endogenous opioid receptor (kappa and delta); it also inhibits the receptor of serotonin<sup>35,36</sup>.

Inhibition of the second phase of formalin-induced pain (inflammatory pain) by the aqueous extract of *P. glandulosus* suggests strongly the presence in this plant compounds with anti-inflammatory activities. This reason motivated the testing

of anti-inflammatory property of the aqueous extract of leaves of *P. glandulosus* was conducted carrageenan-induced rat paw edema.

Inflammation is the response of living tissues to injury. It involves the activation of an enzyme release of mediators, extravasation of fluid, cell migration, destruction and tissue repair<sup>37</sup>. The carrageenan-induced paw edema in rats is the appropriate model for assessing anti-edematous effect of natural products or the steroids and non-steroidal anti-inflammatory<sup>20</sup>. The development of inflammation after injection of carrageenan is a three-phase process; the initial phase about 1 h after induction and is attributed to the release of histamine and serotonin<sup>38</sup>, the second phase which runs after 2 h from the the third time may to be the release of kinins; the third phase begins 3 h after injection of carrageenan and is due to the synthesis of prostaglandins and leukotriens<sup>39</sup>. The aqueous extract of *Plectranthus glandulosus* significantly inhibited all three phases of inflammation induced by carrageenan. Maximum inhibition was 80.76% (6 h) at a dose of 600 mg kg<sup>-1</sup> body weight. These results suggest that the extract possess inhibitory effects on the release of histamine, serotonin, bradykinin, prostaglandin and leukotrien which are the main mediators of inflammation, pain and fever<sup>40</sup>. Aspirin has also inhibited the three phases of inflammation with a maximum inhibition of 67.69% (5 h). This inhibitory effect of aspirin is related to the inhibition of the synthesis of inflammatory mediators such as prostaglandin synthesis in peripheral tissues, because aspirin inhibits the activity of COX1 and COX2<sup>41</sup>. In addition phytochemical analysis demonstrated that *P. glandulosus* possess flavonoids, terpenoids and tannins. It has been reported that flavonoids and terpenoids have analgesic and anti-inflammatory effects. Previous studies suggested that flavonoids may interact directly with the prostaglandin system<sup>42,43</sup>. The effect of this plant extract could be attributed partially to the present of these secondary metabolites.

## CONCLUSION

In conclusion, the aqueous extract of *Plectranthus glandulosus* has significant peripheral and central analgesic activity on pain models induced by acetic acid, formalin, capsaicin and a significant anti-inflammatory activity on acute inflammation induced by the carrageenan. Our results support the therapeutic activities of *Plectranthus glandulosus* proclaimed by naturopath and justifies its use in traditional medicine.

## ACKNOWLEDGMENT

This study was supported by Alexander Von Humboldt foundation.

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