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Anti-inflammatory effect of *Abyssinone V-4'-methyl ether* on acute and chronic inflammation models

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Abstract

Plan: *Anti-inflammatory evaluation of abyssinone V-4'-methyl ether.*
Prologue: *The anti-inflammatory activity of abyssinone V-4'-methyl ether, a natural prenylated flavonoid isolated from the bark of Erythrina droogmansiana (Leguminosae) was evaluated using acute and chronic inflammation models in vivo namely carrageenan-induced paw edema in rats, xylene induced-ear edema in mice and cotton pellets-induced granuloma formation in rats.*
Methodology: *Oral administration of abyssinone V-4'-methyl ether at doses of 2.5, 5 and 10 mg/kg produced a dose-related inhibition of edema formation in the carrageenan induced-paw edema test in rats.*
Outcome: *The highest dose (10 mg/kg) of the compound induced an inhibition of 71.43% compared to 61.90% inhibition obtained with dexamethasone (2.5 mg/kg). In the xylene induced-ear edema in mice, abyssinone V-4'-methyl ether also produced a dose-dependent effect with a maximum inhibition of 62.25% obtained with the dose 10 mg/kg. In the chronic test, abyssinone V-4'-methyl ether at similar doses strongly inhibited the granulomatous tissue formation in cotton pellet-induced granuloma model in rats. These results suggest the anti-inflammatory properties of abyssinone V-4'-methyl ether. This is the first time that the anti-inflammatory activity of this prenylflavanone is reported.*
Keywords*: Abyssinone V-4'-methyl ether, anti-inflammatory activity, carrageenan-induced paw edema, xylene induced ear edema, cotton pellet-induced granuloma.*

1. Introduction

Over 50 flavonoids have been obtained during the last three decades from about 15 species of *Erythrina* genus [1-4], with prenylated flavonone, isoflavones and pterocarpans being the major non alkaloid secondary metabolites isolates so far [4,5]. Among these metabolites, there are abyssinones which are prenylated flavonoids isolated from plant *Erythrina abyssinica* [3]. These molecules have gained attention since abyssinone II was reported to show aromatase inhibitory activity [6]. The antioxidant and cytotoxic activities of Abyssinone I, abyssinone II and related compounds have been reported [7].

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The anti-inflammatory and antioxidant activities of prenylflavanones isolated from *Erythrina sigmoidea* have been reported [8]. Some abyssinones especially abyssinone V have recently been reported to inhibit the activity of the protein tyrosine phosphatase-1B (PTP1B), which is directly linked to type-2 diabetes and obesity therapy [9,10] and to exhibit estrogenic properties [4]. The anti-inflammatory properties of Abyssinone V-4- methyl ether has not yet been evaluated.

Therefore, the present study was undertaken to investigate the anti-inflammatory effect of abyssinone V-4'-methyl ether, a prenylated flavonoid isolated from *Erythrina droogmansiana*, using acute and chronic models of inflammation.

2. Materials and Methods

2.1. Plant material

The root bark of *E droogmansiana* T. Durand was collected from Nkomekoui, Yaounde-Cameroon in august 2010. Identification and authentication of the plant material was done at the National Herbarium Yaounde, Cameroon, where a voucher specimen N°4261/SRFK has been deposited.

2.2. Extraction and isolation of the compound

Air-drierd and pulverized root bark of *E. droogmansiana* (1.2 Kg) was extracted successively with ethyl acetate and methanol. The extract was filtered and the solvent evaporated under reduce pressure, 150 g of residue was obtained. This extract was subjected to chromatography over silica gel packed in *n*-hexane. Gradient elution was done using n-hexane, ethyle acetate and methanol in increasing polarity to give 7 series of fractions mixed on the basis of TLC. Repeated column chromatography with hexane-EtAOc (90:10) yielded YG4 and other compounds. The structures have been elucidated using spectral methods (MS, NMR, and element analysis). The compound YD4 was obtained as a white powder (500 mg) and showed a $[M]^+$ at m/z 422.2094 corresponding to molecular formula ($C_{26}H_{30}O_5$). This compound was identified as *abyssinone V-4'-methyl ether* (Figure 1). The presence of a flavonone skeleton was evident from the ^{1}HNMR spectra at 5.33 (1H, dd) and 2.76 (1h, 2q) corresponding to the H-2 and to the H-3 proton of the C-ring of flavonones respectively. From the ^{13}CNMR spectra, the presence of signal at 79.3 and 42.5 respectively indicated the C-2 and C-3 of the C-ring of flavonones (figures 2 to 6). The ^{1}H and ^{13}CNMR spectra data of this compound were compared to those previously published (Tables 1 and 2) [11]. Other compounds obtained were droogmascarpine, phaseollidin, stigmasterol and β-sitosterol.

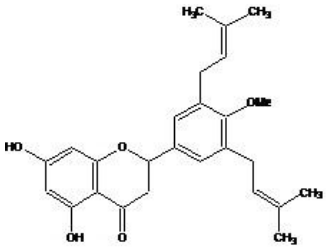

Figure 1: Abyssinone V-4'-methyl ether

2.3. Animals and drug administration

Experiments were conducted using adult male Wistar albino rats (150 – 180 g) and male Swiss mice (20 – 30 g). Animals were housed in standard polypropylene cages, kept under ambient temperature (20-25°C) and illuminated environment of 12:12 h dark/light cycle.

They were provided with standard food pellets purchased from LANAVET, Garoua, Cameroon and tap water *ad libitum*. Experiments were carried out in accordance with the internationally accepted principles for laboratory animal use and as per the experimental protocols duly approved by the Institutional Ethical Committee (No. FWA-IRB00001954) and the current guidelines for the care of laboratory animals for investigations of experimental pain in conscious animals [12].

Abyssinone V-4'-methyl ether and test drugs were given orally to experimental animals after suspending in a mixture of distilled water and 0.5% dimethylsulfoxide (DMSO). The control groups received the same experimental handling as those of the test groups except that the drug treatment was replace with appropriate volumes of vehicle.

2.4. Carrageenan-induced paw edema

Inflammation of the paw in rats was induced as previously described [13]. Rats (n=6, per group) received orally the test compound (Abyssinone V-4'-methyl ether) at doses of 2.5, 5 and 10 mg/kg and dexamethasone (2.5 mg/kg, as positive control) or similar volume of vehicle (10 ml/kg, as negative control), 30 min prior to subplantar injection of 0.1 ml of freshly prepared 1% carrageenan suspension in normal saline into the right hind paw of each rat. The edema (inflammation) was assessed as the difference between zero time linear circumference of the injected paw and its circumference at different times after administration of carrageenan [14]. Measurements were carried out immediately before and thereafter at an interval of 1h for a period of 5h. Edema inhibitory activity was calculated according to the following formula [15]:

$$Percentage\ inhibition = \frac{[(Ct - Co)control - (Ct - Co)treated]}{[(Ct - Co)control]}$$

Where, C_t= mean paw circumference for each group at time t, and C_O= mean paw circumference for each group before carrageenan injection.

2.5. Ear edema induced by xylene

The experiment was conducted based on a previously described method [16]. Mice were divided into five groups of six each. Group 1: vehicle (10 ml/kg); Groups 2, 3 and 4: Abyssinone V-4'-methyl ether (2.5, 5 and 10 mg/kg respectively) and Group 5: Dexamethasone (5 mg/kg), reference drug. The vehicle and drugs were administered orally one hour before xylene application. Ear edema was induced by applying carefully a drop of xylene (0.03 mL) to the anterior and posterior surfaces of the right ear. The left ear remained untreated and considered as control. One hour after xylene application, the animals were killed under ether anesthesia and 9 mm punches were made in the right and left ears of each mouse using a borer. Each ear disc was weighed and the differences in weight of the right and left ear discs of mice were recorded as the edema level.

2.6. Cotton pellet-induced granuloma

Cotton pellet-induced granuloma in rats was conducted according to the method as previously described[17]. Granulomatous lesions were induced by surgically inserting sterile cotton pellets (15 ± 1 mg) subcutaneously in both axilla regions of each rat following a single incision which was thereafter closed by interrupted sutures.

Abyssinone V-4'-methyl ether (2.5, 5 and 10 mg/kg) and Dexamethasone (5 mg/kg) or vehicle (10 ml/kg) were given orally once daily for 7 consecutive days. On day 8, the cotton pellets were dissected out under ether anesthesia, cleaned of extraneous tissue, weighed and dried at 50°C to a constant weight. The mean weights for different groups were determined. The increase in dry weight of the pellets was taken as the measure of the granuloma formation.

2.7. Statistical analysis

The results were expressed as mean±SEM. and the data obtained was statistically analyzed using one-way ANOVA, followed by Dunnett's multiple comparison tests. Differences were considered significant when $P \leq 0.05$.

3. Results

Oral administration of Abyssinone V-4'-methyl ether obtained from *E. droogmansiana*, significantly inhibited in a dose-dependent manner the oedema formation after carrageenan injection to the rat hind paw. The compound at doses of 2.5, 5 and 10 mg/kg respectively produced a 21.88%, 25% and 56.25% inhibition of edema 3 h post carrageenan injection, compared with 46.88% of dexamethasone. The effect was more pronounced at 5 h with a maximal inhibitory ratio of anti-edema effect of 71.43% with the dose 10 mg/kg, compared with 61.90% of dexamethasone (Table 1).

The oral administration of Abyssinone V-4'-methyl ether significantly suppressed xylene-induced ear edema in mice (Table 2). The inhibition percentage at each dose of Abyssinone V-4'-methyl ether (2.5, 5 and 10 mg/kg) were 22.45%, 36.73% and 62.65% respectively compared with control. Dexamethasone (2.5 mg/kg), used as reference drug, exhibited a 59.08% inhibitory rate compared with control.

The effect of Abyssinone V-4'-methyl ether on cotton pellet-induced granuloma formation in rats is shown in Table 3. At doses of 2.5, 5 and 10 mg/kg, Abyssinone V-4'-methyl ether markedly inhibited the granulomatous tissue formation in a dose-dependent manner compared with the control group. The highest dose of the compound (10 mg/kg) exhibited a maximum inhibition of 61.32%, while 39.91% and 45.56% inhibition were observed with doses of 2.5 and 5 mg/kg respectively, when compared with 68.72% for dexamethasone (2.5 mg/kg).

4. Discussion

The present study was undertaken to assess the anti-inflammatory effect of Abyssinone V-4'-methyl ether using acute and chronic models of inflammation in rodents. Results obtained provided evidence that this compound isolated from *E. droogmansiana* possesses anti-inflammatory activity in both inflammation models. In the carrageenan-induced paw edema test in rats, Abyssinone V-4'-methyl ether significantly elicited inhibitory effect on edema formation at all assessment times. Based on this result, it can be suggested that this compound may act by inhibiting the release or synthesis of various inflammatory mediators including histamine, serotonin, bradykinin and prostaglandins.It is well established that carrageenan-induced paw edema formation is a classical model of acute inflammation which involves a biphasic event. The first phase is mediated by the release of histamine and serotonin and the second phase is the result of the release of kinins and prostaglandins [18].

Plants of *Erythrina* genus are known to be a rich source of bioactive flavonoids, mainly isoflavones, pterocarpans, flavonone and isoflavanones [19]. Some of *Erythrina* extracts and isolated compounds have been found to display anti-inflammatory activity [2, 8, 20, 21]. The inhibition of cyclooxygenase activity by *Erythrina* species have been reported [22]. Abyssinones are prenylated flavonoids isolated from different species of *Erythrina* [3].

The anti-oedematous activity of Abyssinone V-4'-methyl ether observed in this study may in part be mediated by the inhibition of cycloxygenase path way. Other pharmacological properties of Abyssinone V have recently been reported [4,9,10].

Xylene-induced edema is an acute inflammation model mediated by histamine, serotonin and bradykinin. In the present study, the increases in ear weight were dose-dependently inhibited by Abyssinone V-4'-methyl ether treatment. This compound may interfere with the secretion or the action of the above inflammatory mediators and thus confirming the anti-inflammatory effect observed during the first phase in the carrageenan-induced rat paw edema.

Cotton pellet-induced granuloma is an established chronic inflammatory model [23]. In the present study, Abyssinone V-4'-methyl ether exhibited marked antiproliferative activity at different doses. This isolated compound may act by inhibiting neutrophils and macrophages migration or may inhibit the activity of fibroblasts and the synthesis of collagen, which are natural proliferative events of granuloma formation [24]. The inhibition of neutrophils affluence into the skin and the reduction of leukocytes infiltration in the mouse ear inflammation induced by multiple topical applications of 12-*O*-tetradecanoylphorbol 13-acetate (TPA), have been reported with erycristagallin, a pterocarpane isolated from *E. mildbraedii*, have been reported [2].

These results provide evidence that Abyssinone V-4'-methyl ether has acute and chronic anti-inflammatory properties. Further studies are needed to determine the exact mechanism of this action. This study opens additional perspectives for the study of the therapeutic action of abyssinones and provides the basis for the search of novel and safe drugs against inflammatory diseases.

Acknowledgments

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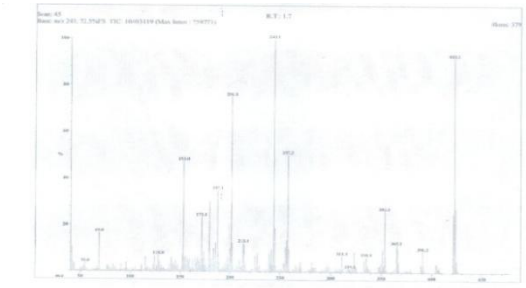

Figure 2: Mass Spectroscopy by IE spectrum of YG4

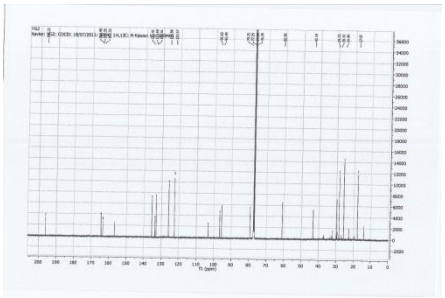

Figure 3: Carbon NMR spectrum of YG4

Table 1: YG4 proton NMR compared with literature data

H	*YG_4 Spectral data*	*literature data* [11]
2	5.27 *dd*	5.33 *dd*
3	2.75 *dd*	2.76 *dd*
	3.08 *dd*	3.11 *dd*
6	5.97 *s*	5.98 *s*
8	5.92 *s*	5.98 *s*
2’	7.09 *s*	7.09 *s*
6’	7.09 *s*	7.09 *s*
1’’	3.37 *d*	3.39 *d*
2’’	5.21 *t*	5.29 *t*
4’’	1.71 *s*	1.73 *s*
5’’	1.73 *s*	1.74 *s*
1’’’	3.3 *d*	3.39 *d*
2’’’	5.21 *t*	5.29 *t*
4’’’	1.71 *s*	1.73 *s*
5’’’	1.73 *s*	1.74 *s*
4’-OMe	3.73 *s*	3.80 *s*
5-OH	12.05 *s*	12.05 *s*

Table 2: YG4 carbon NMR compared with literature data

C	*YG_4 Spectral data*	*literature data* [11]
2	79.3	79.3
3	43.2	43.0
4	196.2	196.3
5	163.3	164.2
6	96.6	96.6
8	164.5	165.3
9	95.5	95.3
10	103.0	103.0
1’	133.7	133.7
2’	125.9	125.9
3’	135.4	135.4
4’	156.4	156.4
5’	135.4	135.4
6’	125.9	125.9
1’’	28.4	28.4
2’’	122.6	122.5
3’’	133.0	133.0
4’’	25.8	25.7
5’’	17.9	17.9
1’’’	28.4	28.4
2’’’	122.6	122.5
3’’’	133.0	133.0
4’’’	25.7	25.7
5’’’	17.9	17.9
OMe	60.9	60.9

Table 1. Effect of Abyssinone V-4'-methyl ether on carrageenan-induced rats paw edema.

Group	*Dose*	*Difference in paw circumference, cm (% of inhibition)*				
	(mg/kg)	*1 h*	*2 h*	*3 h*	*4 h*	*5 h*
Control	-	0.26 ± 0.04	0.22 ± 0.02	0.32 ± 0.03	0.14 ± 0.02	0.21 ± 0.03
Abyssinone V-4'-methyl ether	2.5	0.21 ± 0.02 (19.23)	0.17 ± 0.03 (23.73)	0.25 ± 0.04 (21.88)	0.11 ± 0.03 (21.43)	0.14 ± 0.02* (33.33)
	5	0.20 ± 0.03 (23.08)	0.16 ± 0.02* (27.27)	0.24 ± 0.02* (25.00)	0.10 ± 0.01* (28.57)	0.12 ± 0.02$^{\#}$ (42.86)
	10	0.14 ± 0.02$^{\#}$ (46.15)	0.12 ± 0.04$^{\#}$ (45.45)	0.14 ± 0.03$^{\mu}$ (56.25)	0.07 ± 0.03$^{\mu}$ (50.00)	0.06 ± 0.04$^{\mu}$ (71.43)
Dexamethasone	2.5	0.15 ± 0.04$^{\#}$ (42.31)	0.13 ± 0.03$^{\#}$ (40.91)	0.17 ± 0.04$^{\mu}$ (46.88)	0.07 ± 0.03$^{\mu}$ (50.00)	0.08 ± 0.03$^{\mu}$ (61.90)

Each value is the mean difference of paw circumference ± S.E.M. in cm (n=6). % inhibition of paw edema is shown in parenthesis. $^{*}p<0.05$; $^{\#}p<0.01$ and $^{\mu}p<0.001$ when compared with control at the same time point.

Table 2. Effect of Abyssinone V-4'-methyl ether on xylene-induced ear edema in mice.

Group	Doses (mg/kg)	Ear edema (mg)	Inhibition (%)
Control	0	9.80 ± 0.60	-
Abyssinone	2.5	7.60 ± 0.54*	22.45
	5	6.20 ± 0.64$^{\#}$	36.73
	10	3.60 ± 0.53$^{\mu}$	62.65
Dexamethasone	2.5	4.01 ± 0.36$^{\mu}$	59.08

Each value is the mean ± S.E.M. (n = 6). $^{*}p<0.05$; $^{\#}p<0.01$ and $^{\mu}p<0.001$ when compared with control group.

Table 3. Effect of Abyssinone V-4'-methyl ether on cotton pellet-induced granuloma in rats.

Group	Doses (mg/kg)	Granuloma weight (mg)	Inhibition (%)
Control	0	48.60 ± 0.86	-
Abyssinone	2.5	29.21 ± 0.74$^{\#}$	39.91
	5	26.60 ± 0.65$^{\mu}$	45.26
	10	18.80 ± 1.02$^{\mu}$	61.32
Dexamethasone	2.5	15.20 ± 0.72$^{\mu}$	68.72

Each value is the mean granuloma weight ± S.E.M. (n = 6). $^{\#}p<0.01$ and $^{\mu}p<0.001$ when compared with control group.

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