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Original Article

Anti-Inflammatory, Anti-pyretic and Acute Toxicity Effects of n-Butanol Extract of *Atractylis flava* Desf in Rats

Melakhessou Mohamed Akram*, Benkiki Naima, Marref Salah Eddine, Bouzidi Soumia

ABSTRACT

Objectives: This study was aimed to explore the antipyretic and anti-inflammatory effects of *n*-butanol etract of *Atractylis flava* Desf *(A. flava)* using experimentally induced inflammation and pyrexia models in rats. **Methods:** In the acute toxicity study, a single oral dose of 2000 mg/kg of *n*-butanol extract was given to rats. The antipyretic activity was evaluated using brewer's yeast induced pyrexia in rats. In addition, albumin induced rat paw edema was performed by the injection of 100 µL undiluted fresh egg albumin to assess the anti-inflammatory effects of the plant. **Results:** The results of the present study revealed that *n*-butanol extract of *A. flava* significantly (P<0.001) reduced fresh egg albumin-induced rat paw edema and also inhibited fever significantly in brewer's yeast induced pyrexia. **Conclusion:** The results of the present study indicated that *A. flava* possesses antipyretic and anti-inflammatory activity in the models studied.

Key words: *Atractylis flava desf,* Pyrexia, Brewer's yeast, Egg albumin, Inflammation.

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INTRODUCTION

The commonly used drugs for management of inflammatory and fever conditions are non-steroidal anti-inflammatory drugs (NSAIDs), which have several adverse effects especially gastric irritation leading to formation of gastric ulcers.[1] As an alternative, plant-based medicines are getting an increased therapeutics market share due to their mild action and fewer adverse effects. According to the World Health Organization nearly 80% of the world population prefers plant-based drugs.[2] The wealth of plant kingdom can represent a current source of newer compounds with significant anti-inflammatory and antipyretic activities. The major merits of herbal medicines seem to be their perceived efficacy, low incidence of serious adverse effects, and low cost.

The species *Atractylis flava* Desf. Belongs to the genus *Atractylis* L. of the family Asteraceae (Compositae).[3] This family, divided into 11 subfamilies and 35 tribes comprises about 1400 genera and more than 25.000 species of herbaceous plants, shrubs, and trees spread throughout the world.[4,5] *Atractylis* plants are distributed worldwide but especially abundant in the Mediterranean zone. *Atractylis flava* Desf. (Syn. *Atractylis carduus* (Forsk.) locally called "assenan aouragh".[3] *Atractylis* plants have been used in folk medicine to treat circulatory disorders, intestinal parasites, ulcers, and snake-bite poisoning, while *A. flava* was particularly known in traditional North African medicine for its diuretic effects.[6,7] Phytochemical investigations of the whole plant revealed the presence of triterpenes, steroids, saponins and flavonoids.[8] Furthermore, the presence of a tiliroside, narcissin, vicenin3, ladaneine and schaftoside was confirmed in the *n*-butanol extract of this plant.[8,9] However, no data were found regarding the pharmacological evaluation of the plant. The aim of the present study is to evaluate the anti-inflammatory and antipyretic properties of the *n*-butanol extract of the whole plant *Atractylis flava* Desf (BEAF).

MATERIALS AND METHODS

Plant material

The whole plant *Atractylis flava Desf* was collected from Biskra Algeria in the month of May 2015. The plant materiel was identified by Prof. Bachir Oudjehih (Agronomic Institute of Batna1 University, Algeria). A voucher specimen number (660/LCCE) was deposited in the herbarium of the mentioned department.

Animals

Experiments were performed using Wistar rats of both sexes, weighing (150 – 180 g). The animals were obtained from the Pasteur institute, Algiers, Algeria. The animals were kept in polypropylene cages under standardized conditions for 8 days before experiments. The animals were fed with standard diet and water *ad libitum*.

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Extraction

The collected whole plant *Atractylis flava* was air-dried and powdered. 500 g powder was macerated with MetOH–H_2O (80:20). After filtration, the filtrate was concentrated under vacuum at room temperature the hydro alcoholic extract was submitted to liquid–liquid fractioning using solvents with increasing polarities (petroleum ether, dichloromethane, ethyl acetate, and *n*-butanol). The *n*-butanol fraction was used for the investigation of the acute toxicity study, anti-inflammatory and anti-pyretic effects.

Acute toxicity study of the extract

Acute oral toxicity study was performed as per the OECD-423 guidelines.[10] Ten Wistar female rats were used for this study; they were divided into two groups of five animals each. The animals were fasted overnight and allowed free access to water, after *A. flava n*-butanol extract was administered orally in a single dose of 2000 mg/kg body weight. Animals were observed individually after dosing at least once every 30 min, periodically during the first 4 h, with special attention given during the first 24 h.

General symptoms of toxicity and mortality in each group were observed within 24 h. Animals that survived after 24 h were observed daily for any signs of delayed toxicity for two weeks. At the end of 14 days observation period, the animals were anaesthetized, and blood samples were collected through cardiac puncture with and without anticoagulant (EDTA) for hematological and biochemical analysis, respectively.

Hematological analysis

Hematological parameters: white blood cell (WBC), hemoglobin (HGB), red blood cell (RBC), hematocrit (HCT), mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), lymphocyte %, lymphocytes number (lymph no), Red cell distribution width (RDW), mean volume platelets of (VPM) and platelets (PLT)were determined using a hematology analyzer **(ADVIA® 2120i System).**

Biochemical analysis

For biochemical parameters *blood without additive was centrifuged* at 3000 × g at 4°C for 10 min, serum was separated and alanine amino-transferase (ALT), aspartate aminotransferase (AST), total bilirubin, urea, creatinine, glucose, HDL-Cholesterol, LDL-cholesterol, cholesterol and triglycerides were estimated using *automated Analyzer* **(COBAS INTEGRA® 400 plus).**

Egg albumin induced paw edema in rats

The anti-inflammatory activity of the tested extract was evaluated in male Wistar rats by the egg albumin induced paw edema method.[11] the animals were divided in five groups (n = 5).

All groups were kept fasting and allowed free access to water.

Group I was treated orally with normal saline (10 mL/kg), **group II** with diclofenac (30 mg/kg), the rest of groups (**III**, **IV** and **V**) were treated with *Atractylis flava n*-butanol extract at the dose level of 100, 250 and 500 mg/kg p. o. After 1 h, inflammation induced by sub plantar injection of 100µL of undiluted fresh egg albumin into the right hind paw of all rats. The paw thickness of each rat of all groups was measured in mm using digital vernier calipers at 0, 1, 2, 3, and 5 h.

The percentage inhibition of edema by the tested extract and standard drug was calculated in comparison with vehicle control using this following formula:

$$\% \text{ inhibition} = \left[\frac{(tCn - tC0) - (tTn - tT0)}{(tCn - tC0)}\right] \times 100$$

Where **tCn** = paw thickness at particular time point of control animal; **tC0** = paw thickness before induction; **tTn** = paw thickness at particular time point of treated animal; and **tT0** = paw thickness before induction.

Brewer's yeast induced pyrexia

Antipyretic activity was measured by Brewer's induced pyrexia in male Wistar rats.[12] Rats were fasted overnight with free access to water before the experiments. Pyrexia was induced in animals by subcutaneous injection of 20 % brewer's yeast (10 mL/kg) suspended in saline solution into back side of below the nape of the neck. After 17 h of yeast injection, the rectal temperature of each rat was measured using a digital thermometer. Only rats that showed rectal temperature of 38°C and above were selected for the experiments. Rats were divided into five groups. The 1st group was kept as a control (received the normal saline) while the 2nd one was given paracetamol in a dose of 150 mg/kg (standard). The 3rd - 5th groups received orally 100, 250 and 500 mg/kg of the BEAF, and the rectal temperature was measured periodically at 1, 2, 3 and 5 h after drug administration.

Statistical analysis

Data were expressed as the mean ± SEM. The data were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's test. Differences between two means were detected using the Student's t-test (acute toxicity test). Data were considered different at significance level of $p < 0.05$.

RESULTS

Acute toxicity study

The acute toxicity test revealed that the oral administration of a single dose (2000 mg/kg) of BEAF to rats did not bring any signs of toxicity or mortality in treated animals during the 14 days observation period. In addition, there was no significant difference in hematological and biochemical parameters between control and treatment group (Table 1 and 2). This indicates that BEAF was nontoxic in rats up to the dose of 2000 mg/kg of body weight (Table 1 and Table 2).

Effect of the BEAF on egg albumin induced paw edema in rats

The percentage rate of effect of BEAF in fresh egg albumin induced rat paw edema test and the average edema for the various groups was

Table 1: Biochemical parameters of control and treated rats; measured during the acute toxicity study.

Biochemical parameters	Control	BEAF 2000 mg/kg BW
Liver profile		
AST(U/L)	131 ± 5.54	122.8 ± 3.36
ALT(U/L)	86.2 ± 7.13	78.4 ± 9.66
Total bilirubin(mg/dL)	0.76 ± 0.04	0.70 ± 0.07
Renal profile		
Urea (mg/L)	0.30 ± 0.01	030 ± 0.01
Creatinine (mg/L)	4 ± 0.01	3 ± 0.0
Lipid profile		
Cholesterol (mmol/L)	0.57 ± 0.04	0.63 ± 0.05
Triglycerides (mmol/L)	0.83 ± 0.10	1.14 ± 0.15
HDL-Cholesterol (mmol/L)	0.50 ± 0.03	0.54 ± 0.06
LDL-Cholesterol (mmol/L)	0.06 ± 0.01	0.06 ± 0.01
Glucose (g/L)	0.67 ± 0.03	0.68 ± 0.05

Values are mean±SEM(n=5). No significant compared to control.

Table 2: Hematological parameters of control and treated rats; measured during the acute toxicity study.

Hematology parameters measured	Control	BEAF 2000 mg/kg BW
RBC(106xμL)	7.35±0.14	7.13±0.06
MCV(fL)	55.68±0.85	57.06±0.67
RDW(fL)	13.18±0.26	13.22±0.25
HCT (%)	40.92±0.48	40.74±0.42
PLT (10^3/μL)	614.8±61.76	645.4±50.75
MPV (fL)	6.18±0.09	6.32±0.13
WBC (10^3/μL)	6.10±0.69	6.92±1.10
HGB(g/dL)	14.5±0.17	14.34±0.11
MCH(pg)	19.74±0.25	20.08±0.22
MCHC(g/dL)	35.46±0.17	35.22±0.13
Lymphocyte no	4.24±0.51	4.82±0.93
Lymphocyte %	69.08±2.43	68.76±2.73

Values are mean±SEM(n=5). No significant compared to control.

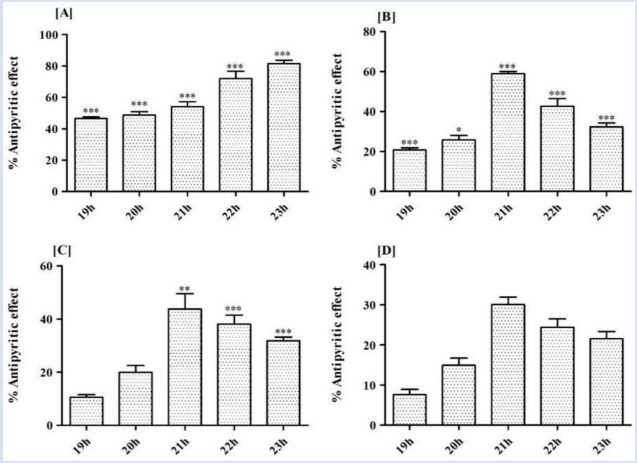

Figure 1: Percent of the antipyretic effect of BEAF in Brewer's yeast induced pyrexia test; [A]paracetamol, 150mg/kg [B] 500mg/kg and [C] 250 [D] 100 mg/kg. Values are reported as mean ± S.E.M (n=5). *P<0.05, **P<0.01, ***P<0.001 compared to control.

Table 3: Effect of the *n*-butanol extract of *A. flava* (BEAF) on egg albumin-induced paw edema in rats.

Treatment Dose (mg/kg)	Δ paw edema (m m) and % inhibition				
	1h	2h	3h	4h	5h
Normal saline10(mL/kg)	5.43±0.11	4.92±0.21	4.64±0.15	4.09±0.17	3.80±0.13
BEAF 100	5.19±0.11 (4.42%)	4.46±0.21 (9.50%)	3.83±0.16** (17.49%)	2.78±0.11*** (31.83%)	2.35±0.10*** (38.12%)
BEAF 250	5.02±0.09 (7.53%)	4.28±0.19 (13.07%)	3.66±0.15*** (21.11%)	2.57±0.10*** (36.96%)	1.79±0.06*** (52.67%)
BEAF 500	4.76±0.10** (12.40%)	3.89±0.17** (20.93%)	3.18±0.08*** (31.37%)	2.25±0.087*** (44.59%)	1.61±0.05*** (57.54%)
Dichlofenac 30	4.85±0.07** (10.65%)	3.87±0.16** (21.43%)	2.71±0.08*** (41.59%)	1.94±0.07*** (52.31%)	1.24±0.03*** (67.28%)

Values are mean±SEM(n=5). *P<0.05, **P<0.01, ***P<0.001compared to control.

demonstrated in (Table 3). Pre-treatment with BEAF exhibited significant anti-inflammatory activity during various assessment times (1–5 h) in a dose dependent manner. The highest inhibition of edema was obtained with 500 mg/kg dose (57.54%) at the 5th hour of drug administration. (Table 3).

Antipyretic effect of BEAF in Brewer's yeast induced pyrexia test

The results presented in Table 4 show that pyrexia was induced at 18 h after the injection of Brewers' Yeast to rats. The oral administration of BEAF (500 and 250 mg/kg) significantly inhibited (P<0.01) hyperthermia induced by yeast. The antipyretic effect of BEAF (500 mg/kg) manifested from the 1st h and was remained significant up to 5th h of the post-treatment, while at the dose of 250 mg/kg the antipyretic effect appeared after 3rd h of the treatment and remained significant up to 5th h. A non-significant antipyretic effect at the dose 100 mg/kg was also observed. The percent pyrexia inhibition of all the tested groups is shown in (Figure 1)(Table 4).

DISCUSSION

Plants exhibit various pharmacological activities because of the presence of diverse kinds of constituents. It is compelling evidence that many chronic diseases such as inflammatory disorders, rheumatism, diabetes, cardiovascular and many neurodegenerative disorders have been treated by plants or their bioactive compounds used in the traditional medicine those can be a new therapeutic source for the treatment of chronic disorders.[13]

The safety studies on medicinal plants were conducted by performing acute and sub-acute toxicity tests in laboratory animals.[14] Acute toxicity study showed that the n-butanol extract of *Atractylis flava* Desf possessed high safety profile, as BEAF did not present noticeable signs of toxicity or mortality at the dose of 2000 mg/kg, in any animal during the entire observation period. No significant differences on hematological and biochemical parameters when compared to the control group. These results indicated high margins of safety and explain the traditional use of the plant.

Egg albumin induced rat paw edema is one of a commonly used primary test to evaluate the anti-inflammatory effect of natural products. Edema formation results from the synergistic action of inflammatory mediators such as histamine, serotonin and bradykinin produced under the effect of cycloxygenase-2 (COX-2) at the site of a local inflammatory insult leading to increased vascular permeability and blood flow.[15,16] Edema formation due to egg albumin in the rat paw is a biphasic event; the early phase of edema, which begins immediately after the administration of

Table 4: Antipyretic effect of BEAF in Brewer's yeast induced pyrexia test.

Treatment	Dose(mg/kg)	Rectal temperature in rats after drug administration						
		T0	After 18 h	19h	20h	21h	22h	23h
Normal saline	10(ml/kg)	36.56±0.23	38.88±0.18	38.74±0.17	38.56±0.17	38.32±0.12	38.50±0.14	38.56±0.15
	100	36.16±0.12	38.88±0.18	38.74±0.17	38.56±0.17	38.32±0.12	38.50±0.14	38.56±0.15
BEAF	250	36.32±0.37	39.36±0.04	39.04±0.05	38.82±0.05	38.1±0.04**	38.24±0.10***	38.38±0.12***
	500	36.08±0.21	38.82±0.11	38.24±0.09***	38.10±0.07*	37.22±0.09***	37.68±0.05***	37.94±0.06***
Paracetamol	150	35.96±0.23	38.58±0.15	37.36±0.14***	37.3±0.15***	37.15±0.09***	36.70±0.22***	36.44±0.22***

Values are mean±SEM(n=5). *P<0.05, **P<0.01, ***P<0.001compared to control.

the irritant and lasting up to 2 h, is probably due to the release of histamine and serotonin. While the latter phase, occurring from 3 to 5 h after the administration of the irritant is induced by bradykinin, protease, prostaglandins and lysosome.[17]

The results of this study showed that BEAF significantly inhibited the formation of the paw edema during the first phase and significantly maintained in the second one. It can be suggested that this anti-inflammatory effect probably might be attributed to the inhibition of the release of pro-inflammatory mediators of acute inflammation, especially the prostaglandins.

Fever is a surrogate marker for disease activity in many infectious and inflammatory disorders. According to the classical view, the genesis of fever is induced by inflammatory mediators (i.e., cytokines, namely interleukin-1, interleukin-6, tumor necrosis factor, and others) that are predominantly released by activated peripheral mononuclear phagocytes and other immune cells.[18,19] Antipyretic activity is commonly considered as a feature of drugs or compound which have an inhibitory effect on the biosynthesis or release of prostaglandins.[20]

The subcutaneous injection of brewer's yeast evoked pyrexia by ultimately increasing synthesis of prostaglandin and is considered as a valuable *in vivo* screening test for the assessment of antipyretic potential.[21,22,23] The inhibition of prostaglandin synthesis could be the possible mechanism of antipyretic action as that of paracetamol and the inhibition of prostaglandin can be achieved by blocking the cyclooxygenase enzyme activity.[24,25,12] The antipyretic effect of BEAF may be due to inhibiting the enzyme cyclooxygenase and reducing the level of prostaglandin within the hypothalamus in pyrexia rats.

Phytochemical study of the whole plant *Atractylis flava* showed abundance of flavonoids triterpenes, steroids, and saponins. Furthermore, the presence of a tiliroside, narcissin, vicenin 3, ladaneine and schaftoside were detected in the *n*-butanol extract.[8, 9]

Flavonoids have been demonstrated that they are able to inhibit a series of enzymes, which are activated in the course of the inflammatory process.[26] Also, flavonoid such as vicenin-2, Tiliroside, Schaftoside, have been recognized as potent inhibitors of pro-inflammatory mediators in different studies.[27,28,29,30] Anti-inflammatory and antipyretic action of BEAF may be due to the presence of above phytoconstituents. Hence, the effect may be due to the synergistic effect or than single constituent.

CONCLUSION

Based on the results of the current study, it could be confirmed that the *n*-butanol extract of *A. flava* contained secondary metabolites that showed outstanding anti-inflammatory and antipyretic activity. The plant therefore could be regarded as a natural source of anti-inflammatory and antipyretic compounds and could be used as an alternative remedy for treatment of inflammatory related disorders and disease. So, further studies are needed to identify and isolate the chemical constituents responsible for these activities and to understand its mechanism of action.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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ABBREVIATIONS

BEAF: n-Butanol Extract of *Atractylis flava* Desf; **MeOH:** Methanol ; **EDTA:** Ethylene diamine tetraacetic acid.

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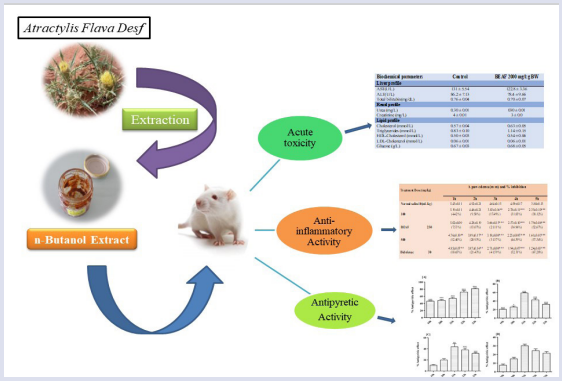
GRAPHICAL ABSTRACT



SUMMARY

- The present study has highlighted on the pharmacological investigation of the n-butanol extract of *Atractylis flava* Desf for the first time.
- The acute toxicity test revealed that BEAF was nontoxic in rats up to the dose of 2000 mg/kg of body weight.
- This study revealed that n-butanol extract of *A. flava* significantly reduced fresh egg albumin-induced rat paw edema and also inhibited fever significantly in brewer's yeast induced pyrexia.
- from the above results, we concluded that the n-butanol extract of *Atractylis flava* Desf have an anti-inflammatory and antipyretic activity.

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