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Analgesic and Anti-inflammatory Activities of Triterpenoid Molecules Isolated from the Leaves of *Combretum glutinosum* Perr. Ex DC (Combretaceae)

Madièye Sene[1], Daouda Ndiaye[2], Abdoulaye Gassama[2], Firmin Sylva Barboza[1], Mbaye Diagne Mbaye[2] and S. Y. Guata Yoro[1*]

[1]Laboratoire de Pharmacologie et Pharmacodynamie, Faculté de Médecine de Pharmacie et d'Odontologie, Université Cheikh Anta DIOP, BP 5005, Dakar, Sénégal.
[2]Laboratoire de Chimie et Physique des Matériaux, Faculté des Sciences et Techniques, Université Assane SECK, Ziguinchor, Sénégal.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MS, DN and AG designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FSB and MDM managed the analyses of the study. Author SYGY managed the literature searches and supervised the study. All authors read and approved the final manuscript.

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ABSTRACT

Combretum glutinosum Perr. Ex DC (COMBRETACEAE) is a traditional medicinal plant, widely distributed in Senegal and Africa. The aim of that study was to investigate the analgesic and anti-inflammatory activities of two triterpenes, betulonic acid (DN7) and cabraleone (DN12), isolated from the leaves of *Combretum glutinosum*. Experiments were performed in acetic acid-induced contortions in mice and carrageenan rat paw oedema. DN7 (3 mg/kg, per os) and DN12 (3 mg/kg, per os) significantly prevent contortions in mice. The number of contortions is respectively 30±10 and 32±7 versus 72.6±6.64 in control group ($p<0.05$, n=5). DN7 (3 mg/kg, per os) significantly prevented the increased rat paw oedema (31.84±6.76 vs 92.72±6.05%) ($p<0.05$, n=5). DN12 (10 mg/kg, per os) induced rat paw oedema prevention similar to that of acetylsalicylic acid (10 mg/kg,

**Corresponding author: E-mail: guata.sy@gmail.com;*

per os) administered in the same conditions (29.28±5.88 vs 30.96±7.25%; ns, n=5). The analgesic and anti-inflammatory activities of triterpenes isolated from *C. glutinosum* leaves are similar to those of non-steroidal anti-inflammatory drugs such acetylsalicylic acid, justifying the use of this plant in traditional medicine to manage pain and inflammation.

Keywords: Combretum glutinosum; betulonic acid; cabraleone; pain; inflammation.

1. INTRODUCTION

Inflammation is a crucial biological process to maintain homeostasis. It is essential to successfully fight pathogens and repair tissue damage [1]. Pain is one of the most important symptoms of inflammatory disease, which is a pathophysiological process that activates defense mechanisms to protect organism against causal agent [2]. However, inflammatory process is linked to deleterious effects, which are an essential components of various diseases such as rheumatoid arthritis, type 2 diabetes, cancer, obesity, asthma, cardiovascular and neurodegenerative pathologies [3-5]. The drugs commonly used to prevent inflammatory response are non-steroidal anti-inflammatory and glucocorticoids. They are efficient, but however result in serious adverse effects [6].

Medicinal plants are alternative for the discovery of new molecules with minimal adverse effects. In fact, bioactive natural products can be regard as very promising ones to develop new therapeutic agents, as well analgesic and anti-inflammatory drugs [7,8].

Combretum glutinosum Perr. Ex DC is a plant of Senegalese traditional pharmacopoeia, and the leaves are used in the treatment of various diseases [9]. In west Africa, several traditional uses of *C. glutinosum* leaves have been described to treat hepatitis, cardiovascular, infectious, gastrointestinal and bronchial diseases [10-17].

Several studies had shown pharmacological properties of *C. glutinosum* leaf extracts [18-23].

Triterpenoid molecules, betulonic acid (DN7) and cabraleone (DN12) were isolated from *C. glutinosum* leaves in previous studies (Fig. 1) [9].

It was shown that triterpenoids are widely distributed in the plant kingdom [24]. Several properties of triterpenes such as anti-inflammatory, wound healing, anti-bacterial, antiviral, hepatoprotective, antidiabetic and anti-tumoral effects, have been also described [25, 26,27,28,29].

The aim of the current study was to investigate anti-inflammatory and analgesic activities of betulonic acid (DN7) and cabraleone (DN12) on acetic acid contortions in mice and carrageenan-induced paw rat oedema.

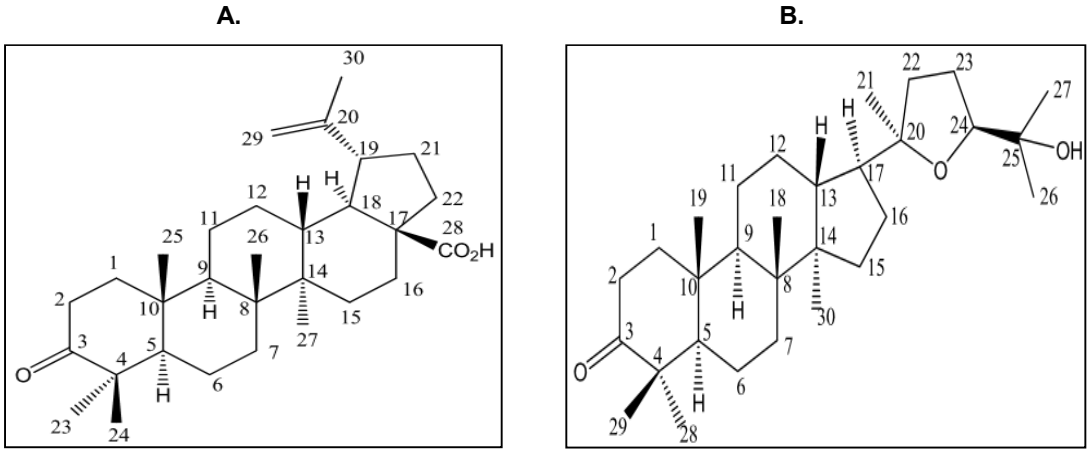


Fig. 1. Structure of betulonic acid (DN7) and cabraleone (DN12) isolated from leaf extracts of *Combretum glutinosum*

A: Betulonic acid, B: Cabraleone

2. MATERIALS AND METHODS

2.1 Drugs and Chemicals

Carrageenan, acetyl salicylic acid, betamethasone, acetic acid were obtained from Sigma. Betulonic acid (DN7) and cabraleone (DN12) were provided by the Laboratory of chemistry and Physics of materials of Assane Seck University of Ziguinchor, Senegal.

Characterization of DN7 and DN12 was performed by exploiting proton ^{1}H, ^{13}C carbon, DEPT 135, HSQC and HMBC correlations of these molecules. The analysis of mass spectra and Infra Red (IR) of DN7 ($C_{30}H_{46}O_3$ = 454 g/mol) and DN12 ($C_{30}H_{50}O_3$ = 454 g/mol) confirmed both structures [9].

2.2 Animals

Adult Wistar KYOTO strain rats (about 180 g) and mice (about 20 g) body weight were used. The animals had free access to food and water. The experimental protocols were conducted in accordance with the guidelines on the care and use of laboratory animals (Senegal National Ethical Committee for Health Research).

2.3 Experimental Procedures

2.3.1 Carrageenan induced rat paw oedema

The anti-inflammatory study was carried out following the method described by Winter [30]. The rats were divided into 8 groups of 5 animals. They were then fasted 12 hours before the experiment.

For each rat, the initial diameter (D_0) of the left hind paw was measured using digital calliper:

- Group 1 (control): Normal saline (10 mL/kg, *per os*)
- Group 2 (reference): Betamethasone (1 mg/kg, *per os*)
- Group 3 (reference): Acetyl salicylic acid (ASA) (10 mg/kg, *per os*)
- Group 4 and 5 (treated): DN7 (1 and 3 mg/kg, *per os*)
- Group 6, 7 and 8 (treated): DN12 (1, 3 and 10 mg/kg, *per os*)

The rat paw oedema was induced by injection of carrageenan solution 1% (100 µL) under neath the planter region of left hind paw of the rats, 1 h after oral administration of different solutions.

The increased oedema was measured using digital calliper at 180 and 300 minutes (T_{3h} and T_{5h}) after carrageenan injection.

The importance of oedema was assessed by determining the mean percentage increase (% INC) of diameter of rat paw according to formula:

$$\%\mathrm{INC} = \frac{\mathrm{Dt} - \mathrm{Do}}{\mathrm{Do}} \times 100$$

Dt: Paw diameter at t time;
D_O: Initial paw diameter

2.3.2 Acetic acid induced writhing in mice

The writhing test in mice was used [31]. Contortions were induced by intraperitoneal injection of 3% acetic acid. Animals were divided into 6 groups of 5 mice each. They were then fasted 12 hours before tests.

Mice were treated with the following solutions:

- Group 1 (control): Normal saline (10 mL/kg, *per os*)
- Groups 2 (reference): Acetyl salicylic acid (ASA) (10 mg/kg, per os)
- Group 3 and 4 (treated): DN7 (3 and 10 mg/kg, per os)
- Group 5 and 6 (treated): DN12 (3 and 10 mg/kg, per os)

Intraperitoneal injection of 3% acetic acid solution was performed 1 h after gavage. The sensitivity to pain was evaluated by the contortions number counted during 30 min after latency time.

2.4 Statistical Analysis

The experimental results are expressed as mean ±standard error of mean (SEM). The significance was evaluated using one-way ANOVA followed by Bonferroni's post hoc test compared with the control group. Values of $p<0.05$ were considered significantly different. n is the number of animals in each group.

3. RESULTS AND DISCUSSION

Intraperitoneal acetic acid (3%) induced contortions (72.6±6.64; $p< 0.05$, n=5) in normal mice treated with vehicle only (10 mL/kg, *per os*). Pretreatment with betamethasone (300 µg/kg, *per os*), prevented significantly the writhes induced with acetic acid, compared to control group (24±4 vs 76.6±6.64; $p< 0.05$, n=5). The prevention of contortions induced with

acetylsalicylic acid (10 mg/kg, *per os*) is significant compared with control group, but less potent to that of betamethasone administered at a lower dose (300 µg/kg, per os). It suggests that peripheral pain model of acetic acid induced contortions, also discriminates the profile of analgesic effect between glucocorticoids and the non-steroidal anti-inflammatory drugs (Fig. 2).

Prior administration of DN7 (3 mg/kg, *per os*) and DN12 (3 mg/kg, *per os*), significantly prevents acetic acid induced contrortions in mice. The mean of contortions are 30±10 and 27±7 versus 72.6±6.64 in control group ($p< 0.05$, n=5). The analgesic effect of DN7 and DN12, at 3mg/kg per os, is similar to that of acetylsalicylic acid (10 mg/kg) administered under same conditions (Fig. 2).

The cyclooxygenase 2 (COX2) produces prostanoids that mediate pain, fever and inflammation processes [32]. Ribeiro et al. [33], showed that acetic acid causes nociception by a mechanism involving eicosanoids such as prostaglandins, which also mediate the mechanical hyperalgesia induced by inflammatory stimuli as carrageenan. Several studies had shown the analgesic activity of triterpenes. In fact, asiatic acid, a pentacyclic triterpene compound from *Centella asiatica*, significantly inhibits acetic acid induced writhes. This effect may be caused by inhibition of arachidonic acid metabolites syntheses [34]. It was also shown that many molecules possess both analgesic and anti-inflammatory properties; their mechanism of action involves COX2 inhibition [35]. In this study, the analgesic effect of betulonic acid (DN7) and cabraleone (DN12), similar to that of acetylsalicylic acid, may involve COX2 inhibition such as asiatic acid of *C. asiatica*, a triterpenoid molecule.

Injection of 1% carrageenan into the plantar pad in normal rats induced oedema. Significant increase of the paw volume was 92.72±6.05% ($p< 0.05$, n=5). Pretreatment with betamethasone (1 mg/kg, *per os*) significantly prevented the acute rat paw oedema induced with 1% carrageenan. The increase of paw oedema was only 23.47±3.99%, suggesting a power anti-inflammatory response of glucocorticoids in acute rat paw oedema. In this model, the anti-inflammatory activity of glucocorticoids is more effective than that of non-steroidal anti-inflammatory drugs such acetylsalicylic acid. In fact, pretreatment with acetylsalicylic acid (1 mg/kg, per os), significantly prevented rat paw oedema (30.96±7.25 vs 92.72±6.05%; $p< 0.05$, n=5). DN7 and DN12 dose dependently prevent rat paw oedema induced with carrageenan. At 10 mg/kg per os, the increase of paw oedema is 29.28±5.88 vs 30.96±7.25% in acetylsalicylic acid (10 mg/kg, per os) group, suggesting a similar profile of anti-inflammatory effect between acetylsalicylic acid and triterpenoid molecules from *C. glutinosum* (Table 1).

The development of paw oedema following injection of carrageenan has been characterized as a biphasic event in which various mediators are involved to generate inflammatory response [36]. The acute phase of oedema (0–2.5 h) contributes to the release of histamine, 5-hydroxytryptamine and bradykinin, which are not inhibited by non-steroidal anti-inflammatory drugs [37]. However, a delayed phase of inflammation is correlated with overproduction of prostaglandins in tissues, mediated by COX2 [38].

The anti-inflammatory effect of DN7 and DN12 on carrageenan-induced rat paw oedema is particularly significant in the second phase of inflammation, suggesting a possible prevention of eicosanoids production such prostaglandins, probably by COX 2 inhibition.

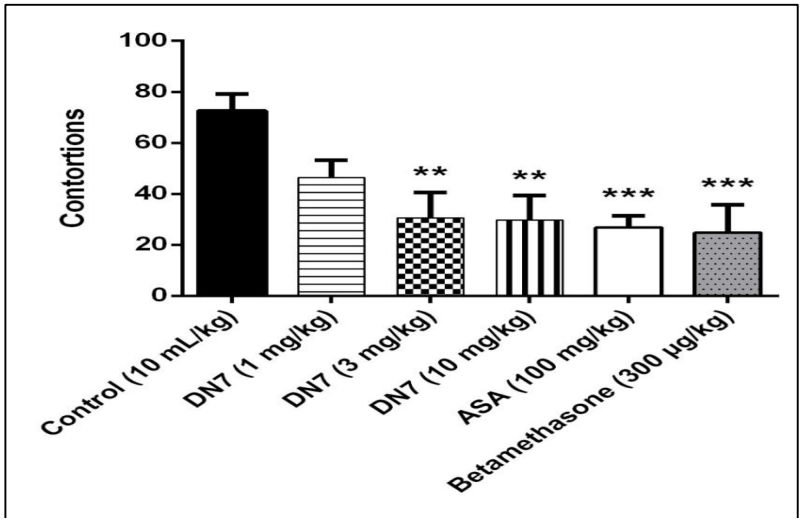
Table 1. Effect of DN7 and DN12 on carrageenan-induced paw oedema test in rats

Treated groups	Dose (mg/kg)	Increased rat paw oedema (%)	
		3H	5H
Control	10 mL/kg	67.77±6.79	92.72±6.05
ASA	10	33.77±7.08**	30.96±7.25****
DN7	1	31.56±7.35***	51.17±4.47***
	3	34.04±4.08**	31.84±6.76****
DN12	1	50.27±6.26**	56.49±8.29***
	3	37.67±4.91**	40.15±4.14****
	10	29.02±3.87***	29.28±5.88****

***p < 0.01, ***p < 0.001, ****p < 0.0001 vs control group. ASA: acetylsalicylic acid, DN7: betulonic acid, DN12: cabraleone*

Several studies had shown the anti-inflammatory activity of triterpenoid molecules, involving the prevention of prostaglandins production. According to Begum et al. [39], coumaroyl lupendioic acid from *Careya arborea* stem barks, inhibits pro-inflammatory mediators on carrageenan induced inflammatory model. The underlining mechanism of action is associated with selective inhibition of COX2. Ursolic acid, pentacyclic triterpenoid, isolated from hexane extract of *Plantago major*, is also anti-inflammatory. This effect has been attributed to inhibition of prostaglandins synthesis associated with COX2 inhibition [40,41]. Tetracyclic triterpenes isolated from gum resins of *Boswellia spp* possess anti-inflammatory activity involving COX2 inhibition [42]. Cabraleone (DN12) and betulonic acid (DN7), are tetra- and pentacyclic triterpenoid molecules from *C. glutinosum*, may involve similar mechanism to prevent both pain and inflammation, justifying their use in African traditional medicine.

A.



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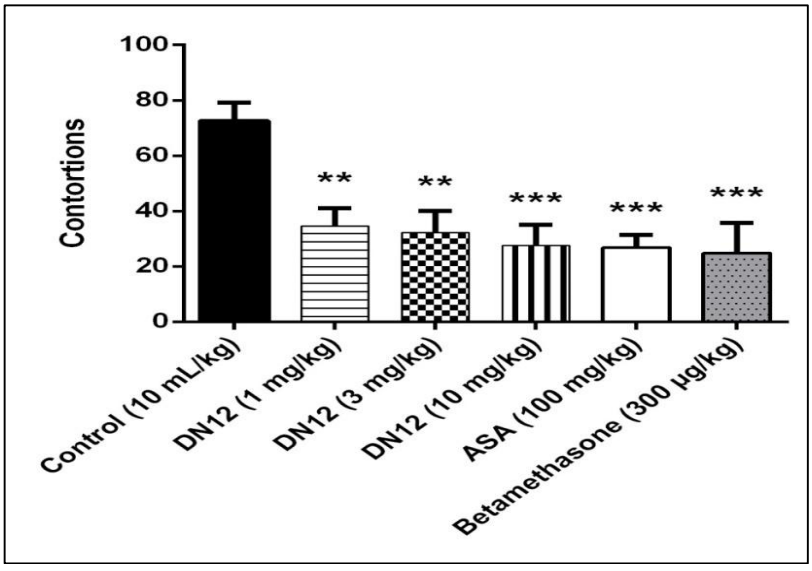

Fig. 2. Analgesic effect of DN7 and DN12 on acetic acid induced contortions in mice

***p < 0.01, ***p < 0.001 vs control group. DN7: Betulonic acid, DN12: Cabraleone*

4. CONCLUSION

Betulonic acid (DN7) and Cabraleone (DN12) possess both analgesic and anti-inflammatory activities, justifying the traditional use of *Combretum glutinosum* leaves to manage pain and inflammation. These results show the potential of triterpenoid molecules to develop analgesic and anti-inflammatory drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The experimental protocols were conducted in accordance with the guidelines on the care and use of laboratory animals (Senegal National Ethical Committee for Health Research).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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