Vol. 17(2), pp. 43-51, February 2023
DOI: 10.5897/AJPP2022.5349
Article Number: 4CD654770370
ISSN 1996-0816

http://www.academicjournals.org/AJPP

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African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Anti-inflammatory and analgesic activities of methanolic extract of *Elaeis guineensis* Jacq. leaves (Arecaceae) and its fractions

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Received 28 December, 2022; Accepted 13 February, 2023

***Elaeis guineensis* Jacq. is an arborescent monocotyledon of the Arecaceae family. It is a plant originated from tropical rainforest of West Africa. For centuries, it has been a source of food and a natural remedy against several pathologies. The aim of the present research was to evaluate anti-inflammatory and analgesic activities of methanolic extract *E. guineensis* Jacq. (Arecaceae) leaves and phytochemical groups. Extraction with methanol and various liquid-liquid fractionations were carried out. These extract and fractions were administered orally at different doses. The experiments were performed on models of carrageenan-induced inflammatory edema in rat and acetic acid-induced pain in mouse. The extraction protocols gave a methanolic extract and different fractions, methanolic tannins free, alkaloid, terpenoid, and flavonoid. The methanolic extract administered at doses of 1, 3 and 10 mg/kg significantly prevents inflammatory edema. The percentages of increase in edema 5 h after induction are 38.31±3.55, 37.48±4.98, 40.82±4.14 versus 92.72±6.05 in the control group. The same profiles are observed with the methanolic fractions tannins free, flavonoid and terpene. However, the latter show dose-dependent activities between 1 and 3 mg/kg. The methanol fraction tannins free at 3 mg/kg is better in preventing inflammatory edema. Oral tannin-free methanolic fraction significantly prevents acetic acid-induced pain in mice. *Elaeis guineensis* leaves possess anti-inflammatory and analgesic properties on models of carrageenan-induced inflammatory edema in rat and acetic acid-induced pain in mouse. The anti-inflammatory and analgesic activities could be linked to the combined action of alkaloids, flavonoids and terpenes, on the different targets of the inflammatory reaction.**

Key words: *Elaeis guinensis* Jacq., anti-inflammatory, analgesic, methanolic extract, alcaloïds, flavonoïds, terpenes

INTRODUCTION

Inflammation is an immediate and transient physiological defensive response of vascularized living tissues, triggered by any cellular or tissue damage, due to infectious, chemical, traumatic, and immune stimuli (Kunnumakkara et al., 2018). Pain is thought to be an alarming sign of actual or apparent tissue damage (Shoaib et al., 2016). Different pathways and molecules of inflammation are involved in nociception, defining so-called inflammatory pain (Chen et al., 2013). Several studies had shown the interest of plant extracts on

experimental models of inflammatory and pain processes (Agyare et al., 2013).

Elaeis guineensis (Arecaceae) is a perennial, arborescent, monocotyledonous plant distributed over humid tropical areas (Yehouessi et al., 2019). It is a plant originated from tropical rainforest of West Africa (Erinoso et al., 2020). For centuries, it has been a source of food and a natural remedy against several pathologies (Da Silveira Agostini-Costa, 2018). Bioactive compounds such as phenolic compounds, flavonoids, tannins, coumarins, alkaloids, saponins, terpenoids and steroids have been shown in the leaves of *E. guineensis* (Yin et al., 2013). Flavonoid and phenolic acids are considered the major bioactive compound groups in the *E. guineensis* leaves extract (Sulistiarini et al., 2022). The latter such as flavonoid C-Glycosides (orientin, isoorientin, vitexin, and isovitexin) possess healing activity *in vitro* on 3T3 Fibroblast Cells (Che Zain et al., 2020). Flavonoids from *E. guineensis* leaves would also have antioxidant and antibacterial (Yin et al., 2013), antidiabetic (Rosalina Tan et al., 2011; Kalman et al., 2013), anticancer and anti-inflammatory activities (Gruca et al., 2014; Owoyele and Owolabi, 2014).

In the literature, we did not find many data relating only to the anti-inflammatory and analgesic activities of the leaves of *E. guineensis*. However, several works relate the action of the leaves of *E. guineensis* including antioxidant, antibacterial, antihypertensive, antidiabetic, immunomodulatory, diuretic, sun protection, healing, neuroprotective, gastroprotective, and antityrosinase activities (Sulistiarini et al., 2022). Inflammation is a link to most of the mechanisms associated with these pathologies (He et al., 2015).

This study is a continuation of work already carried out on total aqueous and methanolic extracts of leaves. The latter had shown endothelium-depending vasorelaxant (Ndiaye et al., 2010), anti-inflammatory (Sene et al., 2016) and healing (Sene et al., 2020) properties. In this work, the presence of major phytochemical groups such as flavonoids, tannins, alkaloids and sterols/triterpenes had been highlighted.

The aim of this present research was to evaluate the anti-inflammatory and analgesic activities of methanolic extract of *E. guineensis* leaves and its major phytochemical groups.

MATERIALS AND METHODS

The study was carried out at the Pharmacology Laboratory, Faculty of Medicine and Pharmacy, Dakar University, Senegal from October 2019 to July 2020.

Drugs, chemicals and solvents

Carrageenan, acetyl salicylic acid, acetic acid, casein and extraction solvents were obtained from Sigma/BES (Dakar, Senegal).

Plant material

E. guineensis leaves were collected from Casamance, in the southern region of Senegal. Botanical samples were identified at the Department of Botany and Pharmacognosy, Faculty of Medicine and Pharmacy, University of Dakar, where the voucher specimen (DPB/EG-20/01/17) was deposited. The leaves had been dried in the shade at room temperature (25°C) for 4 weeks before being pulverized.

Animals

Wistar Kyoto strain rats weighing between 100 and 300 g and albino mice were used. The rats were obtained from the Pharmacology Laboratory, Faculty of Medicine and Pharmacy. Meanwhile, the mice were obtained from the Pasteur Institute, Dakar and weighed between 20 and 33 g. The animals were housed in a cage under conditions of 25±2°C temperature, 12 h light cycle and provided with food and water as much as desired.

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: approval n° 0372/2019/CER/UCAD).

Experimental procedures

Extractions

Tannin's complexation: Powder leaves (200 g) of *E. guineensis* were mixed with methanol (1.5 L). The mixture had been boiled (70°C) for 30 min after cooling filtered. The operation was repeated a second time. One part of the filtrate has been evaporated giving the methanolic extract (ME), another part was mixed with the casein to complex the tannins, it will give the methanolic extract tannin-free (ME-TF) (Bassene, 2012).

Terpenes and alkaloids extraction: The alkaloids fraction was obtained by the method described by Yubin (Yubin et al., 2014). Powder leaves (300 g) of *E. guineensis* was mixed with alkaline solvent (NaOH:10%, 75 ml) and lipophilic organic solvent extraction (dichloromethane, 1750 ml). The mixture was left in maceration for 72 h and then filtered giving dichloromethane extract (alkaline alkaloids).

The filtrate obtained was acidified with sulfuric acid diluted (7.5

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ml in 1000 ml of physiological water). After decantation, we obtain an acidic aqueous phase (alkaloids salts) and dichloromethane extractive solution. Acidic aqueous phase is taken up in a basic solution of dichloromethane (NaOH:10%, dichloromethane). The liquid-liquid separation gave an acidic aqueous phase and a dichloromethane phase (alkaline alkaloids) that after evaporation gave a total alkaloids fraction (AF). The extractive dichloromethane solution after evaporation gives terpenes fraction (TF).

Flavonoid's extraction: The powder leaves (100 g) of *E. guineensis* were mixed with distilled water (3 L). The mixture had been boiled (80°C) for 1 h and cooling filtered. The aqueous extract obtained was subjected to extraction by liquid-liquid separation with ethyl acetate (300/100/100 ml). We obtained ethyl acetate fraction (genine flavonoids). Extraction by liquid-liquid separation with butanol (300/100/100 ml) of aqueous fraction gave butanolic fraction (salt flavonoids). The flavonoids fraction (FF) regroups ethyl acetate fraction and butanolic fraction after evaporation (Bassene, 2012).

Phytochemical characterizations

Phytochemical characterization of tannins, alkaloids, terpenes and flavonoids was performed on tubes, using the classic methods of characterization of the major chemical families. Aluminium chloride was used to determine flavonoids, ferric chloride for evidence of tannins, Dragendorf's reagent for alkaloids identification and acetic anhydride combined with chloroform and sulfuric acid for terpenes characterization (Bassene, 2012).

Anti-inflammatory activity

The anti-inflammatory activity study was carried out following the carrageenan induced rat paw edema method, described by Winter et al. (1962). The rats were divided into 15 groups of 5 (Table 1). Then, they had been fasted for 12 h before the tests. For each rat, the initial diameter (D0) of the left hind paw was measured using digital calliper.

The rat paw edema was induced by injection of carrageenan solution 1% (1 ml) underneath the planter region of left hind paw of the rats 1 h after oral administration with the different solutions. The increased edema was measured using digital calliper at 60, 180 and 300 min (T1h, T3h and T5h) after carrageenan injection.

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

$$\%INC = \frac{Dt - D0}{D0} \times 100$$

where Dt: paw diameter at t time and D0: initial paw diameter.

Analgesic activity

The writhing test in mice was used (Koster et al., 1959). Contortions were induced by intraperitoneal injection of 3% acetic acid. Animals were divided into 5 groups of 4 mice each. They were then fasted 12 h before tests.

Mice were treated with the following solutions: Group 1 (control): Normal saline (10 mL/kg, *per os*); Group 2 (reference): Acetyl salicylic acid (ASA) (10 mg/kg, *per os*); Group 3 (treated): ME (10 mg/kg, *per os*); and Groups 4 (treated): ME-TF (3 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.

Statistical analysis

All data were expressed as mean ± standard error of mean (SEM) and analysed by GraphPad 6.0 software. The significance was evaluated using one-way Analysis of Variance (ANOVA) followed by Dunett'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.

RESULTS

Phytochemical characterizations

Phytochemical study shows the presence of flavonoids, alkaloids, tannins, sterols and triterpenes in the methanolic extract (ME). Characterization of the methanolic extract tannin-free (ME-TF) revealed the presence of flavonoids, alkaloids, and terpenes. The terpenes were only revealed in the terpenes fraction (TF) (Table 2).

Anti-inflammatory activity

Induction of rat paw inflammatory edema in control group: Carrageenan 1% in rat paw after pre-treatment with normal saline induced edema. The significant increase of rat paw is 34.39±8.81, 67.77±6.79 and 92.72±6.05%, respectively at T1h, T3h, and T5h after carrageenan administration ($p<0.05$ vs baseline, n=5) (Table 3).

Prevention of inflammatory edema by methanolic extract (ME) of *E. guineensis* leaves and acetylsalicylic acid (ASA): Oral administration of ME at doses of 1 and 3 mg/kg significantly prevents inflammatory edema. The prevention of edema is identical in the late phase of inflammation. Indeed, the percentages of increase in edema 5 h after induction are 38.31±3.55, 37.48±4.98 versus 92.72±6.05 in the control group (Table 3).

Prevention of inflammatory edema by different fractions of the methanolic extract of *E. guineensis* leaves: The methanolic extract tannins free (ME-TF), terpenoid (TF) and flavonoid (FF) show the same profile of methanolic extract. However, these fractions dose-dependently prevent edema between 1 and 3 mg/kg. Indeed, the 10 mg/kg dose is not associated with better prevention of edema (Figure 1).

Table 1. Tested products.

Batch	Treated groups	Acronyms	Doses
1	Normal saline	Control	10 ml/kg
2	Acetyl salicylic acid	ASA	10 mg/kg
3	Methanolic extract	ME	1 mg/kg 3 mg/kg 10 mg/kg
4	Methanolic extract tannin-free	ME-TF	1 mg/kg 3 mg/kg 10 mg/kg
5	Alkaloids fraction	AF	10 mg/kg
6	Terpenes fraction	TF	1 mg/kg 3 mg/kg 10 mg/kg
7	Flavonoids fraction	FF	1 mg/kg 3 mg/kg 10 mg/kg

Source: Authors 2022

Table 2. Phytochemical constituents in different fractions.

Extract	Flavonoids	Alkaloids	Tannins		Terpenes
			Condensed	Hydrolyzable	
ME	+	+	+	+	+
ME-TF	+	+	-	-	+
TF	-	-	-	-	+
AF	-	+	-	-	-

+ = presence; - = absence.
Source: Authors 2022.

Table 3. Effect of methanolic extract (ME) on carrageenan-induced paw edema in rats.

Treated groups	Dose (mg/kg)	Increased rat paw edema		
		1 h	3 h	5 h
Control	10 ml/kg	34.39±8.81	67.77±6.79	92.72±6.05
ME	1	27.75±3.13	34.27±5.11*	38.31±3.55****
	3	18.10±3.50	20.36±5.43***	37.48±4.98****
ASA	10	21.79±2.27	33.77±7.08*	30.96±7.25****

*p < 0.05, ***p < 0.001, ****p < 0.0001 vs. control group. ASA: Acetylsalicylic acid. Control group (untreated) 10 ml/kg: 10 ml/kg of rat weight (physiological serum).
Source: Authors 2022

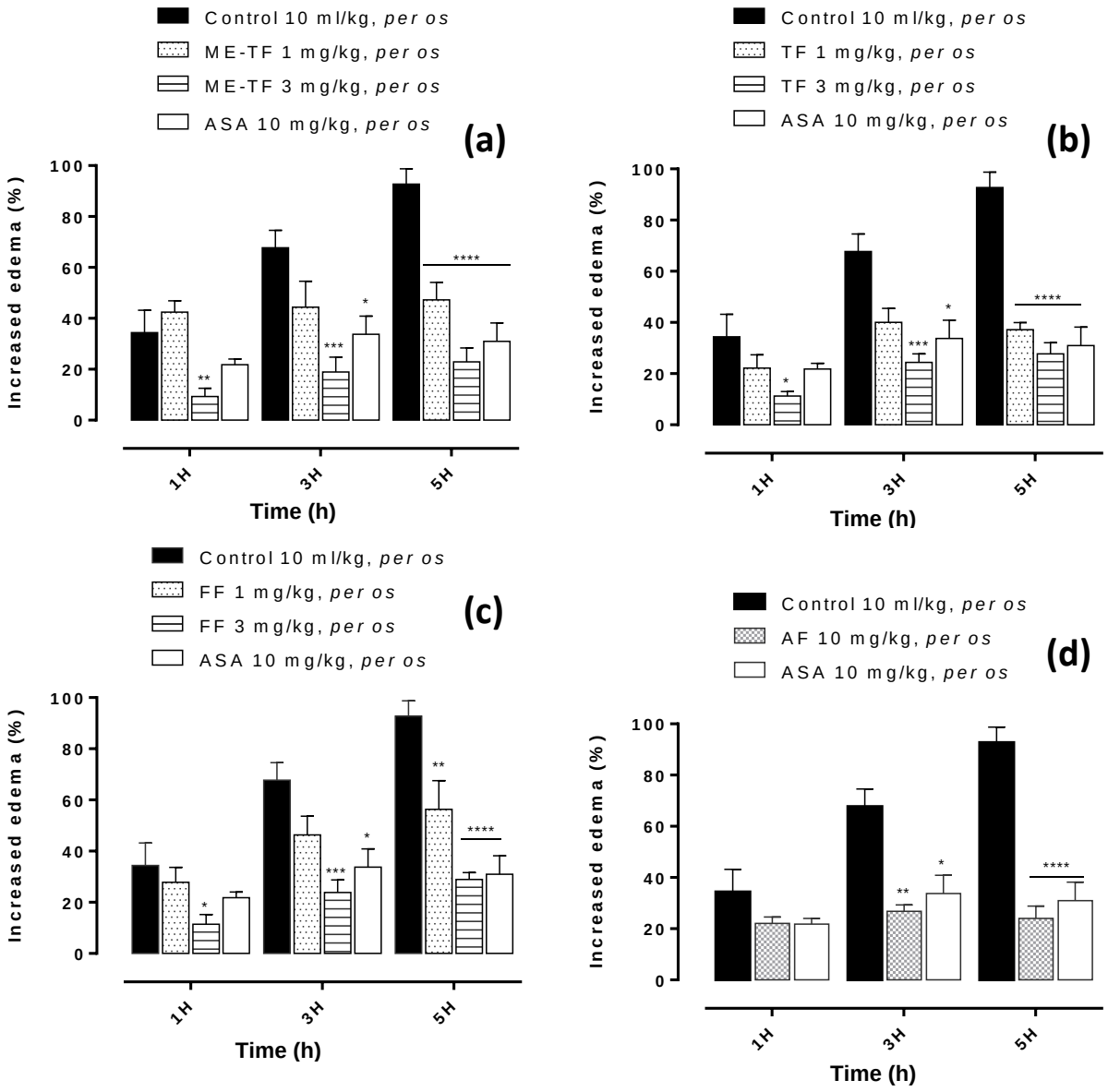

Figure 1. Effect of different fractions of the methanolic extract on carrageenan-induced inflammatory edema in rats. Anti-inflammatory activity was evaluated by the carrageenan induced rat paw edema method. The increase in edema was assessed at doses of 1 and 3 mg/kg, compared to control group. ASA was used as reference molecule. (a) Represents the methanolic extract tannins free (ME-TF), (b) represents the terpenoid fraction (TF), (c) represents the flavonoid fraction and (d) represents the alkaloid fraction (AF). *p<0.05 versus control group, ***p<0.001 versus control group, ****p<0.0001 versus control group. n=5.
Source: Authors 2022

Analgesic activity

Analgesic activity of acetylsalicylic (ASA), methanolic extract (ME) and methanolic extract tannins free (ME-TF) of *E. guineensis* on contortions induced with acetic acid 1% in mice. The administration of ASA (100 mg/kg, *per os*) significantly prevented the occurrence of contortions in mice. The number of contortions is 30.50±3.66. The ME-TF significantly prevented contortions induced by intraperitoneal administration of 3% acetic acid in mice. The analgesic effect of ME-TF (3 mg/kg, *per os*) is similar to that observed with ASA and ME given at a higher

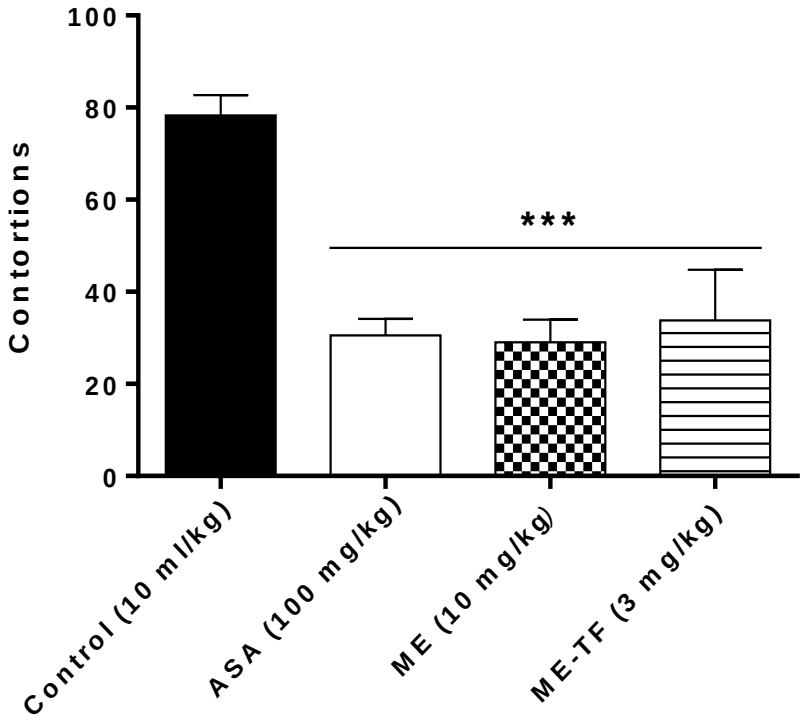

Figure 2. Effect of ME-TF on contortions acetic acid induced with acetic acid 3% in mice. Analgesic activity was evaluated by acetic acid induced contortions model in mice. Pain prevention was assessed by comparing the number of contortions in each treated group versus the control group. ASA was used as reference molecule, ***p<0.001 versus control group, n=4.
Source: Authors 2022

dose. The number of contortions after ME-TF administration is 33.75±11.01 (Figure 2).

DISCUSSION

E. guineensis Jacq. is a plant originated from tropical rainforest of West Africa (Erinoso et al., 2020). In traditional medicine, it is used as natural remedy against several pathologies (Da Silveira Agostini-Costa, 2018). Previous studies had shown the interest of *E. guineensis* Jacq. (Arecaceae) leaf extracts in an inflammation model (Sene et al., 2016).

Phytochemically, the methanolic extract of *E. guineensis* leaves and its tannin-free fraction contain alkaloids, flavonoids and terpenes. Phytochemical screening by other teams revealed the presence of these same major phytochemical groups in the methanolic extract of *E. guineensis* leaves (Sasidharan et al., 2010; Yin et al., 2013; Ajayi et al., 2016).

In this study, we showed that methanolic extract of *E. guineensis* leaves as well as the tannin-free methanolic (ME-TF), terpenoid (TF) and flavonoid (FF) fractions exhibit the same anti-inflammatory and analgesic profile in carrageenan-induced rat paw inflammation and acetic acid-induced pain models in mice. These fractions prevent oedema in a dose-dependent manner between 1 and 3 mg/kg. The 10 mg/kg dose was not associated with improved prevention of oedema. These effects were significant in both the early and late phases of the inflammatory model. The tannin-free methanol fraction also prevents acetic acid-induced pain in mice. The analgesic action of this fraction is superior to that of aspirin.

Inflammation and pain responses induced by carrageenan and acetic acid include the production of eicosanoids, mainly prostacyclins (PGI2) and prostaglandin-E (PG-E). The release of prostaglandins is secondary to the release of pro-inflammatory cytokines and increased expression of cyclooxygenase (COX) (Ferreira et al., 1978; Ahn and Aggarwal, 2005; Attiq et al., 2018). Many medicinal plants are found in Africa with their extracts, fractions and isolates which possess anti-inflammatory and analgesic properties (Agyare et al.,

2013). This is the case for several plants of the Arecaceae family, whose studies have reported anti-inflammatory and analgesic activities in animal models. Indeed, alcoholic extracts of *Areca catechu* (Arecaceae) are anti-inflammatory and analgesic in carrageenan-induced inflammatory oedema in rats and in acetic acid-induced pain in mice (Lee et al., 2014; Barman et al., 2011). Similar results have been described with methanolic leaf extracts of *Cocus nucifera*, *Hyophorbe verschaffeltii* and *Caryota mitis* (Lima et al., 2015; Aly et al., 2016; Tona et al., 2020). Also, ethanolic leaves extract of *Phoenix loureiroi* Kunth (Arecaceae) possesses anti-inflammatory and analgesic effects in dose dependent manner in animal models (Mondal et al., 2021).

The methanolic extract of *E. guineensis* leaves, like other species of the same family, has anti-inflammatory and analgesic properties.

The inflammatory mechanism of edema induced by carrageenan manifests itself in two phases. In the initial phase, the release in the periphery of the injured site of mediators such as histamine, serotonin and bradykinin is noted (Maity et al., 1998). The second phase involves the overproduction of prostaglandins in the tissues, mediated by cyclo-oxygenase (Gilligan et al., 1994). The anti-inflammatory action of the methanolic fraction tannins-free is dose-dependent between 1 and 3 mg/kg and greater than that of acetylsalicylic acid. Unlike acetylsalicylic acid, the anti-inflammatory activity of the methanolic fraction tannins-free appears earlier in the first phase of inflammation. It is also pronounced in the second phase of inflammatory edema.

The constituents of the methanolic extract of *E. guineensis* leaves, such as flavonoids, terpenoids and alkaloids, may play a major role in the anti-inflammatory and analgesic processes observed in this study. However, further phytochemical studies are needed to isolate the active compound(s) responsible for these pharmacological activities.

The alkaloid fraction of *E. guineensis* leaves is anti-inflammatory on the second phase of inflammation. In contrast to the methanolic fraction tannins free, the alkaloid fraction has no effect on the initial phase of the inflammatory edema, a profile identical to that of acetylsalicylic acid. This result suggests that the alkaloids in the leaves of *E. guineensis* would interfere with the production of inflammatory mediators such as prostaglandins. Alkaloids are very present in plants, some exhibit anti-inflammatory and analgesic activities. Their diverse structures make them potential compounds or candidates for the design and discovery of new anti-inflammatory and analgesic drugs (Bai et al., 2021).

Previous work had reported the involvement of certain alkaloids isolated from plants in the prevention of the production of inflammatory mediators. Indeed, aristolochic aristolochic acid, an alkaloid of *Aristolochia* species, has been shown to inhibit phospholipase A2, a key enzyme in the release of the substrate required for eicosanoid biosynthesis (Chandra et al., 2002). Also, Mitragynine an alkaloid compound isolated from methanolic extract leaves of *Mitragyna speciosa* suppressed PGE2 production by inhibiting COX-2 expression (Utar et al., 2011). The alkaloid fraction could, like these molecules, oppose inflammatory oedema by the same mechanisms.

The flavonoid and terpene fractions are also anti-inflammatory on the carrageenan model. These fractions prevent the appearance of edema on the two phases of inflammation with an activity greater than that of acetylsalicylic acid. Flavonoids have been widely used for their analgesic and anti-inflammatory effects (Ferraz et al., 2020; Al-Khayri et al., 2022). Flavonoids are also considered the major bioactive compound groups in the *E. guineensis* leaves extract (Sulistiarini et al., 2022). Several studies have characterized the effects of flavonoids and terpenes on the production of PGE2 and on the expression of COX 2. Mondal et al. (2019), demonstrated that quercetin-3-methoxy-40 -glucosyl-7-glucoside isolated from *Melothria heterophylla*, exhibited analgesic activity against nociceptive responses triggered in mice by acetic acid injection. It also showed anti-inflammatory activity against carrageenan-induced paw edema. It reduced the amount of arachidonic acid transformed to prostaglandins by suppressing COX level (Mondal et al., 2019). Also, curcumin a natural compound present in the rhizomes of plant *Curcuma longa* Linn., demonstrated its anti-inflammatory action. Curcumin was found to inhibit arachidonic acid metabolism, cyclooxygenase, lipoxygenase and cytokines (Kohli et al., 2005). Flavonoid compounds isolated to methanol extract of *E. guineensis* leaves such as catechins and epigallocathechin are anti-inflammatory at high dose (Anyanji et al., 2013). Several studies had previously reported the interest of terpenes in the prevention of the inflammatory process by mechanisms involving the prevention of the production of inflammatory mediators such as prostaglandins and cytokines (Vega et al., 2018; Sene et al., 2018).

Conclusion

E. guineensis leaves possess anti-inflammatory and analgesic properties on models of carrageenan-induced inflammatory edema in rat and acetic acid-induced pain in mouse. The anti-inflammatory and analgesic activities could be linked to the combined action of alkaloids, flavonoids and terpenes, on the different targets of the inflammatory reaction such as arachidonic pathway. Further pharmacological studies will be needed to confirm these hypotheses.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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