



Methanol extract of *Napoleona vogelii* demonstrates anti-nociceptive and anti-inflammatory activities through dopaminergic mechanism and inhibition of inflammatory mediators in rodents

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Abstract

Napoleona vogelii (Lecythidaceae) is used in traditional medicine for the management of pain and inflammatory disorders. This study was conducted to investigate the anti-nociceptive and anti-inflammatory activity of the methanol stem bark extract of *N. vogelii* in rodents. The extract (100–400 mg/kg) was administered 1 h before intraperitoneal and intraplantar injection of 0.2 mL of 0.6% v/v acetic acid and 0.05 mL of 2% v/v formalin, respectively. Anti-inflammatory activity was investigated using the carrageenan-induced paw edema and formalin-induced arthritis models. Mechanistic studies were conducted by exploring opioidergic, dopaminergic pathways, and inflammatory mediators. There was 62.26% inhibition of inflammatory pain at 400 mg/kg in the formalin-induced paw licking test. In the acetic acid-induced mouse writhing assay, the extract produced a dose-dependent inhibition of writhes with peak effect at 400 mg/kg producing 54.87% inhibition compared with diclofenac at 71.09%. The extract produced 90.98% inhibition of the late phase of carrageenan-induced paw edema and 82.81% inhibition in the formalin-induced arthritis test. The anti-nociceptive activity of the extract was blocked by sulpiride (D₂ receptor antagonist; 1 mg/kg) but not by naloxone (opioid receptor antagonist; 5 mg/kg). In addition, pre-treatment of mice with the extract produced 95.08% inhibition of histamine-induced inflammation similar to that of indomethacin at 97.54% and inhibition of serotonin-induced inflammation at 46.79% compared with indomethacin which produced 94.26%. This study demonstrates that the extract possesses anti-nociceptive and anti-inflammatory activity mediated through inhibition of dopaminergic pathways and inflammatory mediators.

Keywords Anti-nociceptive · Anti-inflammatory · Inhibition · Opioidergic · Dopaminergic

Introduction

It has been reported that inflammation is usually triggered by infections of bacterial, viral and fungal nature, and defective immune responses which culminates in damage to living tissues (Oguntibeju 2018). It is a protective response that involves host cells, blood vessels, proteins, and other mediators intended to eliminate the initial cause

of cell injury and the necrotic cells and tissues resulting from the original insult and to initiate the process of repair (Agarwal 2013). Pain, however, is an unpleasant condition arising from intense stimuli, primarily protective in nature and can act as a sensorial indication of the presence of tissue injury (Zendehdel et al. 2011; Bektas et al. 2015).

It is documented in literature that several plants have been explored and used in traditional medicine for treatment and management of pain and inflammatory disorders (Gacche et al. 2011). Medicinal plants provide important sources of new drugs and chemical substances which have the potential for therapeutic effects (Kinghom et al. 2011) and adjunctive solutions to the side effects of conventional analgesics and anti-inflammatory drugs.

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Napoleona vogelii is a tropical flowering plant that is widely distributed in the coastal regions of West Africa. It is found mostly in the rain forest and along the sea shores and mostly prevalent in the southern part of Nigeria (Akah et al. 2007; Adiele et al. 2014). The plant is used in making wooden poles, warps, chewing stick, and mats (Keay et al. 1964). Preparation from the stem bark is used in the management of cancer (Soladoye et al. 2010), and the leaf extract has been used for asthma and wound healing (Akah et al. 2007; Jhansi et al. 2010). Muganza et al. (2012) also reported that the decoction of the stem bark is used in the management of dermatosis and sexual asthenia. The need to discover novel agents for pain and inflammation with little or no side effects necessitates the design of this study to investigate the anti-inflammatory and anti-nociceptive activity of the stem bark extract of *N. vogelii* using standard inflammatory and nociceptive models and establish the various mechanisms of its activity.

Materials and methods

Drugs and chemicals

Methanol (BDH Chemicals, Poole, England), 0.9% normal saline (Unique Pharmaceuticals, Lagos, Nigeria), formalin, carrageenan, acetic acid and naloxone (Samarth Life Sciences PVT. Limited; Ram Mandir Road, Mumbai), morphine (Pfizer Manufacturing Deutschland GmbH, Illertissen, Germany), indomethacin and diclofenac (Clarion Medicals Limited, Ilupeju, Lagos, Nigeria), and sulphiride, histamine and serotonin (Sigma-Aldrich, St. Louis MO, USA).

Experimental animals

Healthy albino mice weighing 14–30 g and rats weighing 80–150 g were obtained from the Laboratory Animal Centre, College of Medicine, University of Lagos. The animals were maintained under standard environmental conditions and had free access to standard powdered diet (Livestock Feed PLC, Lagos) and water ad libitum. They were kept in a room under natural conditions and acclimatized for one week prior to the study.

Extraction

The stem bark of *Napoleona vogelii* was collected from Abatadu village about two kilometers off Ikire township of Osun State Southwestern Nigeria. It was duly authenticated by checking with the plants list (<http://www.theplantlist.org/tpl1.1/record/kew-313192>) and at the herbarium of the Department of Botany and Microbiology, University of Lagos, Nigeria where a voucher specimen (LUH 6524) was

deposited. It was washed, chopped, and air-dried at room temperature for 4 months to a constant weight, and the dried stem bark was pulverized into fine powder using a grinding mill. In 7.5 L of 99.9% methanol, 1.5 g of the powder was then macerated. The mixture was stirred and left to stand for 7 days at room temperature. It was filtered using a muslin cloth and a 125 mm Whatman filter paper (GE Healthcare UK Limited, Buckinghamshire, UK). The filtrate was concentrated using a rotary evaporator (Buchi R–215 Rotavapor (pump-) V–700, Flawil, Switzerland) at 45 °C to yield a brown solid extract. The extract was stored in an air-tight container, preserved at 4 °C, and constituted in distilled water before administration to the experimental animals (Ikumawoyi et al. 2018).

Pharmacological models

Anti-inflammatory activity

Carrageenan-induced paw edema

The experimental animals were fasted for 12 h prior to the study and randomly assigned into five groups of five rats each. The treatments include: Group I 10 mL/kg distilled water (DW) P.O., Group II–IV administered 100, 200, and 400 mg/kg of *N. vogelii* (NV) extract P.O., respectively, and Group V indomethacin 10 mg/kg P.O. Edema was induced by injection of carrageenan (0.1 ml; 1% w/v in saline) into the sub-plantar tissue of the right hind paw, 1 h after treatment. The linear paw circumference was measured using a vernier caliper, and measurements were made immediately before the injection of the phlogistic agent, and at 1, 2, 3, 4, 5, and 6 h post carrageenan injection. Afterward, the percentage inhibition was calculated (Gupta et al. 2005) using the formula:

$$\% \text{inhibition} = \frac{[C_t - C_o]_{\text{control}} - [C_t - C_o]_{\text{test}}}{[C_t - C_o]_{\text{control}}} \times 100$$

where

- C_o mean paw size in the control group
- C_t mean paw size in the treated group

Formalin-induced arthritis

The experimental animals were fasted for 12 h prior to the study and randomly assigned into five groups of five rats each. The treatments include: Group I 10 mL/kg P.O. DW, Group II–IV administered 100, 200, and 400 mg/kg P.O. of the extract, respectively, and Group V indomethacin 5 mg/kg P.O. Arthritis was induced by injection of formaldehyde 0.1 ml, 2% v/v in saline into

the sub-plantar tissue of the right hind paw, 1 h after treatment. The linear paw circumference was measured using a vernier caliper, and measurements were made immediately before the injection of formalin. The induction of arthritis with the arthritic agent was repeated on day 3. All extract treatments were administered once daily by oral gavage for 10 days. Paw diameter was subsequently measured on days 3, 7, and 10. The anti-arthritic activity which analyzes the anti-inflammatory response was calculated (Sawadogo et al. 2006) using the formula:

$$\text{Percentage inhibition} = [1 - T/C] \times 100$$

where, T and C are the mean diameters of the treated and control group, respectively.

$$\% \text{inhibition} = \frac{\text{mean reaction time (control)} - \text{mean reaction time (treatment)} \times 100}{\text{mean reaction time (control)}}$$

Acetic acid-induced mouse writhing model

The experimental animals were fasted for 12 h prior to the study and randomly assigned into five groups of five mice each. The treatments include: Group I 10 mL/kg NS P.O., Group II–IV administered 100, 200, and 400 mg/kg of the

$$\% \text{inhibition} = \frac{\text{mean no. of writhes (control)} - \text{mean no. of writhes (treatment)} \times 100}{\text{mean no. of writhes (control)}}$$

Mechanistic studies

Opioidergic system

The experimental animals were fasted for 12 h before the study and randomly assigned into three groups of five mice each. The treatments include: Group I 10 mL/kg NS P.O., Group II 5 mg/kg naloxone I.P., and Group III 5 mg/kg naloxone I.P. + 400 mg/kg P.O. of the extract. After 15 min post-treatment with naloxone (NAL), nociception was induced by injection of acetic acid (0.2 mL; 0.6% v/v in saline I.P.). The number of writhes was recorded in 20 min (Agbaje et al. 2008). Afterward, the percentage inhibition was calculated.

Dopaminergic system

The experimental animals were fasted for 12 h before the study and randomly assigned into three groups of five mice each. The treatments include: Group I 10 mL/kg NS P.O.,

Analgesic activity

Formalin-induced nociception

The experimental animals were fasted for 12 h prior to the study and randomly assigned into five groups of five mice each. The treatments include: Group I 10 mL/kg normal saline (NS) P.O., Group II–IV administered 100, 200, and 400 mg/kg P.O. of the extract, respectively, and Group V morphine 5 mg/kg S.C. Nociception was induced by injection of formaldehyde (0.05 mL; 2% v/v in saline) into the sub-plantar tissue of the left hind paw, 1 h after treatment with the extract (and 30 min for morphine). The duration of paw licking was recorded in two phases; phase 1 (0–5 min) and phase 2 (15–30 min). Afterward, the percentage inhibition was calculated (Vasudevan et al. 2007) using the formula:

extract P.O., respectively, and Group V Diclofenac 20 mg/kg P.O. Nociception was induced by injection of acetic acid (0.2 mL; 0.6% v/v in saline) via the intraperitoneal route, 1 h after treatment. The number of writhes was recorded in 20 min. Afterward, the percentage inhibition was calculated (Onasanwo and Elegbe 2006) using the formula:

Group II sulphiride 1 mg/kg in saline I.P, and Group III sulphiride 1 mg/kg in saline, I.P. + 400 mg/kg P.O. After 30 min post-treatment with sulphiride, nociception was induced by injection of acetic acid (0.2 mL; 0.6% v/v in saline I.P.). The number of writhes was recorded in 20 min (Agbaje et al. 2008). Afterward, the percentage inhibition was calculated.

Histaminergic system

The experimental animals were fasted for 12 h prior to the study and randomly assigned into three groups of five rats each. The treatments include: Group I 10 mL/kg P.O. DW, Group II indomethacin 10 mg/kg P.O., and Group III: 400 mg/kg of the extract P.O. All animals were injected with 0.1 mL histamine (10^{-3} mg/mL) into the sub-plantar tissue of the right hind paw, 1 h after administration (Agbaje et al. 2008). The experiment proceeded according to the protocol of Agbaje and Fageyinbo (2012).

Serotonergic system

The experimental animals were fasted for 12 h prior to the study and randomly assigned into three groups of five rats each. The treatments include: Group I: 10 mL/kg P.O. DW, Group II indomethacin 10 mg/kg P.O., and Group III 400 mg/kg of the extract P.O. All animals were injected with 0.1 mL serotonin (10^{-3} mg/mL) into the sub-plantar tissue of the right hind paw, 1 h after administration (Agbaje et al. 2008). The experiment proceeded according to the protocol of Agbaje and Fageyinbo (2012).

Statistical analysis

Data were analyzed using the Graph Pad Prism 6.0 using one- and two-way ANOVA followed by Tukey's post hoc multiple comparison tests. Statistical significance was held at $p < 0.05$.

Results

Phytochemical analysis

According to Ikumawoyi et al. (2017), the extract contains flavonoids, phenols, saponins, tannins, phlobatanin, and cardiac glycoside. Quantitatively, the extract consists of 87.88 ± 0.32 mg/100 g flavonoid, 24.88 ± 0.47 mg/100 g phenol, 35.55 ± 0.19 mg/100 g saponin, and 13.01 ± 0.84 mg/100 g tannin.

Acute toxicity

A study conducted by Ikumawoyi et al. (2017) documented that there was no mortality observed on acute oral administration of the extract at 4000 mg/kg in mice, and hence, the LD₅₀ is greater than 4000 mg/kg.

Anti-inflammatory study

Carrageenan-induced paw edema

The anti-inflammatory effect of the extract as evaluated by carrageenan-induced paw edema model is shown in Fig. 1. Treatment of animals with the extract or indomethacin produced time course and significant inhibition of edema with peak effect observed at 6 h post carrageenan injection. The highest percentage inhibition of edema observed was 90.98% (0.11 ± 0.03 cm) at 400 mg/kg of the extract; similarly, 10 mg/kg indomethacin produced 97.54% (0.03 ± 0.01 cm) inhibition of edema.

Formalin-induced arthritis

Treatment of rats with the extract significantly reduced the arthritic activity in a dose-dependent manner. Inhibition of arthritis was observed as indicated by a reduction in paw circumference. The percentage inhibition observed was 82.81% (0.23 ± 0.03 cm) on day 10 at 400 mg/kg of the extract and 91.11% (0.12 ± 0.01 cm) in 5 mg/kg indomethacin treated animals (Fig. 2).

Anti-nociceptive activity

Formalin-induced nociception

The first phase of formalin-induced pain produced nociceptive response of biting and licking of the paw with a duration of 68.0 ± 6.02 s in the control group. There was no significant inhibition of nociceptive reaction produced by the extract even at the highest dose. In the second phase, the duration of nociceptive reaction in the control group was 186.0 ± 19.55 s. The extract significantly inhibited the biting and licking response in a dose-dependent manner with peak effect at 62.26% (70.2 ± 4.26 s) produced at 400 mg/kg. This effect was less but comparable with that produced by morphine (87.74%; 22.8 ± 2.65 s) in phase two (Fig. 3).

Acetic acid-induced mouse writhing model

Treatment of mice with the extract or diclofenac significantly reduced the number of writhes when compared with the control (35.45 ± 2.04). Treatment with the extract of *N. vogelii* at 400 mg/kg produced 54.87% reduction (16.0 ± 1.55) of writhes compared with diclofenac which produced a reduction of 71.09% (10.25 ± 0.88) (Fig. 4).

Mechanistic studies

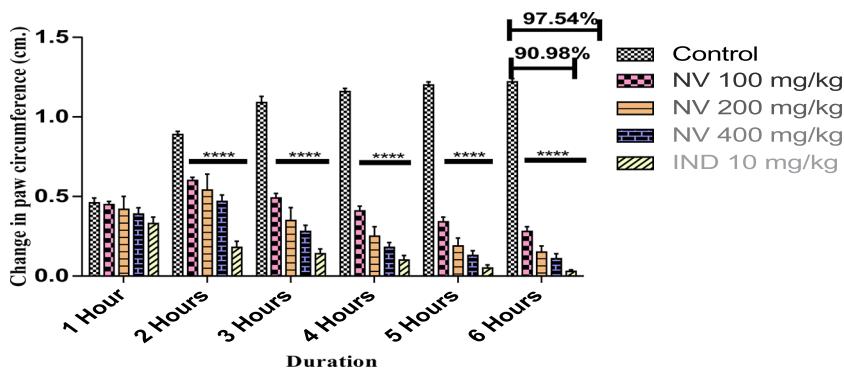
Histaminergic system

The inflammatory effect elicited by histamine (0.1 mL; 10^{-3} mg/mL) was altered after treatment with *N. vogelii* and indomethacin. The anti-inflammatory activity elicited at 400 mg/kg of the extract and 10 mg/kg indomethacin was duration dependent. The extract produced 95.08% inhibition (0.06 ± 0.01 cm) similar to that of indomethacin which produced 97.54% inhibition (0.03 ± 0.01 cm) (Fig. 5).

Serotonergic system

The inflammatory effect elicited by serotonin (0.1 mL; 10^{-3} mg/mL) was ineffectively altered by treatment with *N. vogelii* extract which produced 46.79% inhibition (0.58 ± 0.04 cm), compared with indomethacin treated animals which

Fig. 1 Phasic effects of *N. vogelii* on carrageenan-induced paw edema. Results are mean ± S.E.M (n = 5). **** p < 0.0001 versus control. Two-way ANOVA followed by Tukey’s *posthoc* multiple comparisons test. IND, indomethacin, NV, *Napoleona vogelii*



produced a duration dependent inhibition with a peak effect of 94.26% (0.07 ± 0.01 cm) (Fig. 6).

Opioidergic system

The effect of treatment of animals with naloxone (5 mg/kg, I.P.) on the anti-nociceptive effect elicited by the extract at 400 mg/kg P.O. is depicted in Fig. 7. Naloxone did not block the anti-nociceptive effect of the extract. The extract produced 69.71% inhibition (10.6 ± 1.69) relative to the control (35.0 ± 2.35).

Dopaminergic system

Figure 8 shows the effect of sulpiride (1 mg/kg; an antipsychotic antagonist of dopamine D₂ and D₃ receptors) on the anti-nociceptive action elicited by the extract at 400 mg/kg P.O.

Sulpiride effectively blocked the anti-nociceptive activity of the extract. Treatment with the extract produced 16.85% inhibition (30.6 ± 1.21) relative to the control (36.8 ± 2.20).

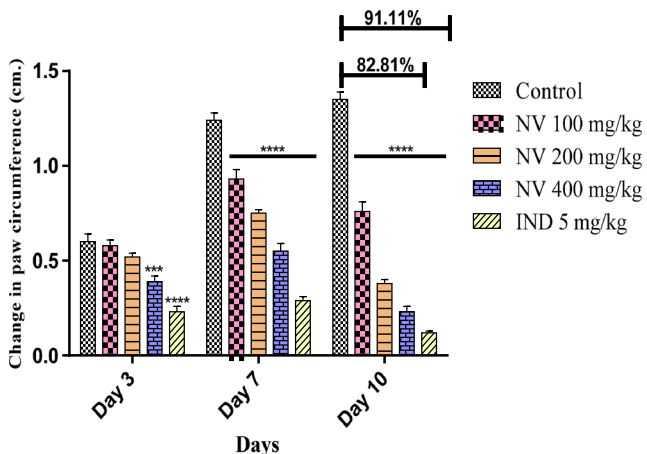


Fig. 2 Effect of *N. vogelii* on formalin-induced arthritis. Results are mean ± S.E.M (n = 5). *** p < 0.001, **** p < 0.0001 versus control. Two-way ANOVA followed by Tukey’s *posthoc* multiple comparisons test. IND, indomethacin, NV, *Napoleona vogelii*

Discussion

Medicinal plants are used by 80% of the developing world population, making it imperative to investigate the acclaimed ones for their possible therapeutic benefits (Adedapo et al. 2008).

This study was conducted to investigate the anti-nociceptive and anti-inflammatory activity and mechanisms of the methanol stem bark extract of *Napoleona vogelii* using standard pharmacological models.

Findings from this study showed that the extract possesses anti-inflammatory and anti-nociceptive properties. The carrageenan-induced paw edema test and formalin-induced arthritis model were used to evaluate the anti-inflammatory activity of the extract. Carrageenan-induced paw edema consists of three distinct phases, including an induction of vasoactive peptides (initial release of histamine and serotonin), a second phase mediated by plasma kinins and leukotrienes, produced by tissue macrophages (sub-acute; due to infiltration by leukocytes), and a third phase associated with the activation of tissue prostaglandins due to tissue degeneration (Unnisa and Parven 2011). It is the most widely used test to screen new anti-inflammatory agents and measures the ability

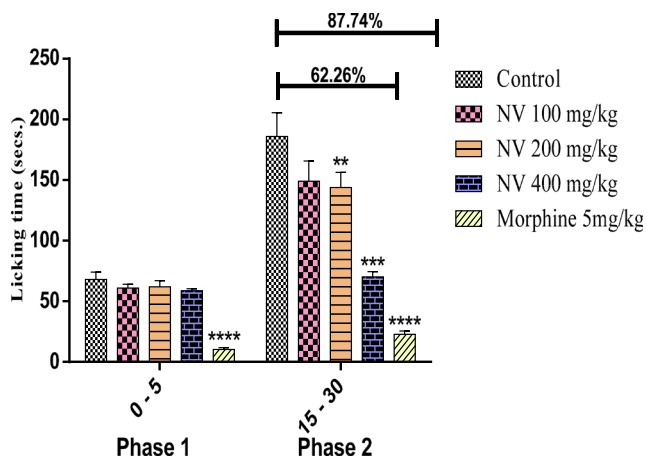
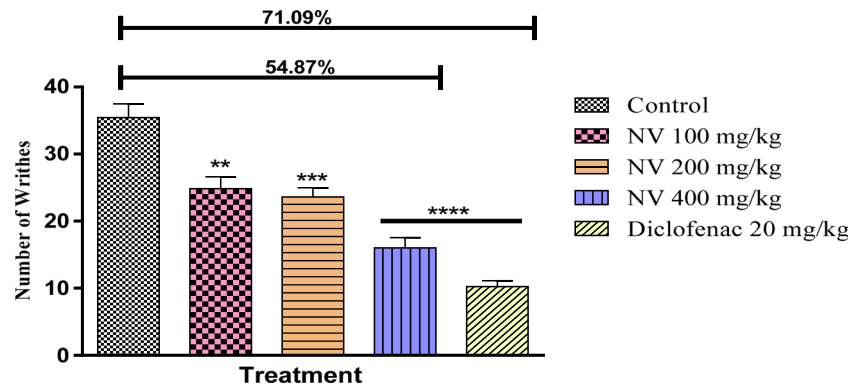


Fig. 3 Effect of *N. vogelii* on formalin-induced nociception. Results are Mean ± S.E.M (n = 5). ** p < 0.01, *** p < 0.001, **** p < 0.0001 versus control. Two-way ANOVA followed by Tukey’s *posthoc* multiple comparisons test. NV, *Napoleona vogelii*

Fig. 4 Effect of *N. vogelii* on acetic acid-induced nociception. Results are Mean \pm S.E.M (n = 5) ** $p < 0.01$ *** $p < 0.001$ **** $p < 0.0001$ versus control. One-way ANOVA followed by Tukey's *posthoc* multiple comparisons test. NV, *Napoleona vogelii*



of a compound to reduce local edema induced in the rat paw by injection of a phlogistic agent (Ravi et al. 2009).

The effect of indomethacin (10 mg/kg) on carrageenan-induced paw edema was more pronounced 2 h after injecting the phlogistic agent (79.78%), while the extract showed higher activity 3 h after administration (74.31%). It could be deduced that the extract showed significant inhibitory effect on rat paw edema in the later phase of the carrageenan-induced inflammation. This anti-edematogenic effect of the extract on paw edema induced by carrageenan is indicative of its benefits in inflammation.

Formalin-induced arthritis test is useful in detecting orally active anti-inflammatory agents acting by inhibiting the mediators of sub-acute inflammation and the activation of tissue prostaglandins (Schiotis et al. 2016). Pre-treatment of rats with the extract or indomethacin significantly reduced the arthritic activity in a dose-dependent manner. Inhibition of arthritis was observed as indicated by a reduction in paw circumference (Gupta et al. 2005). Indomethacin produced a more profound inhibitory effect of arthritis on day 3 (61.87%) after repeated administration of formalin, but the inhibitory effect of the extract was relatively lower (34.45%). However, on day 10, the extract and indomethacin produced greater effect on arthritis, with a percentage inhibition of 82.81% and 91.11%,

respectively. This is suggestive of the significant anti-arthritic activity of the extract.

The involvement of different pathways in the mechanism of anti-inflammatory action was elucidated. The serotonergic system modulates so many physiological processes including inflammation (Agbaje and Fageyinbo 2012). In the serotonin-induced inflammation assay, the anti-inflammatory activity of the extract was highest at 90 min (46.79%). This suggests a partial inhibition of inflammation induced by serotonin. The inhibition of this mediator could be a mechanism of the anti-inflammatory effect of the extract.

Histamine is also an important neurotransmitter that modulates inflammatory response at various stages in the inflammatory pathway (Agbaje et al. 2008). The anti-inflammatory effect elicited by the extract was highest at 180 min (95.08%). This suggests the inhibition of this mediator and portends an important mechanism of the anti-inflammatory effect of the extract.

The formalin-induced paw licking test evokes distant quantifiable behavior, indicative of pain (Agbaje and Fageyinbo 2012). This test representing a model of persistent pain is used to assess the potential of new drugs or compounds to affect central or peripheral nociceptive pathways due to its biphasic nociceptive characteristics, referred to as the early and late

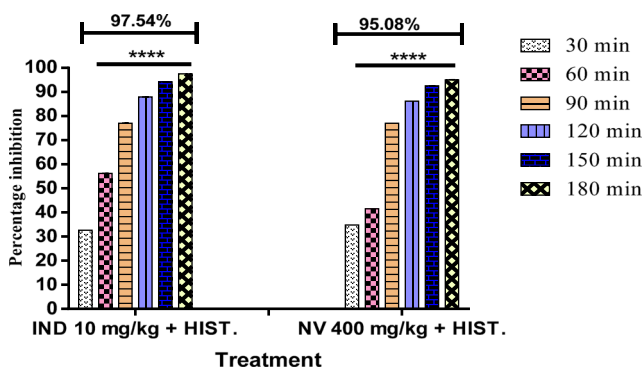


Fig. 5 Effect of *N. vogelii* on histamine-induced inflammation. Results are Mean \pm S.E.M (n = 5) **** $p < 0.0001$ versus 30 min. Two-way ANOVA followed by Tukey's *posthoc* multiple comparisons test. HIST, histamine; IND, indomethacin; NV, *Napoleona vogelii*

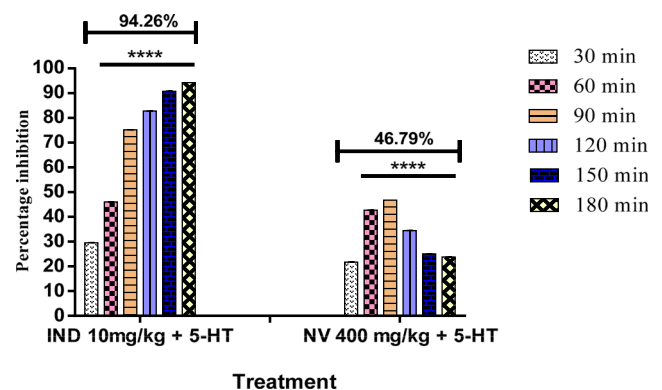
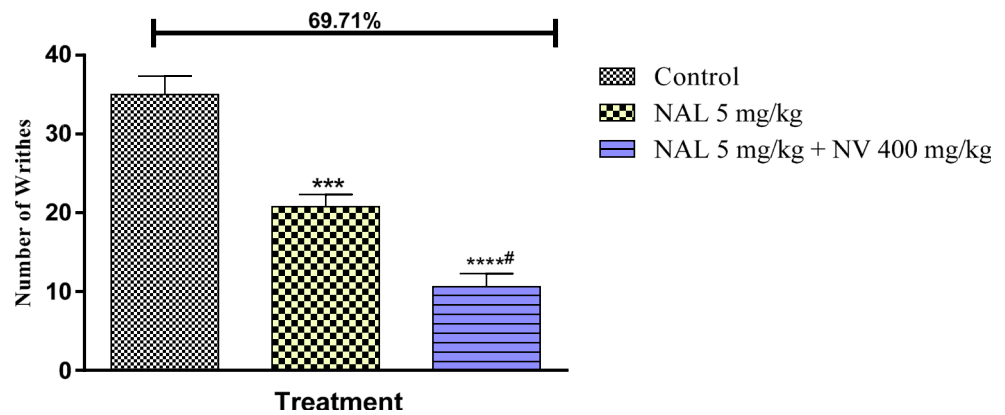


Fig. 6 Effect of *N. vogelii* on serotonin-induced inflammation. Results are mean \pm S.E.M (n = 5) **** $p < 0.0001$ versus 30 min. Two-way ANOVA followed by Tukey's *posthoc* multiple comparisons test. 5-HT, serotonin; IND, indomethacin; NV, *Napoleona vogelii*

Fig. 7 Effect of pretreatment with naloxone on the anti-nociceptive activity of *N. vogelii*. Results are Mean ± S.E.M (n = 5). *** $p < 0.001$, **** $p < 0.0001$ versus control, # $p < 0.01$ versus naloxone. One-way ANOVA followed by Tukey's *posthoc* multiple comparisons test. NAL, naloxone; NV, *Napoleona vogelii*



phase, resulting from formalin administration (Gupta et al. 2005). The early phase which is classified as the neurogenic pain is an acute response observed immediately after the administration of formalin and lasts for 0–5 min. It reflects a direct effect of formalin on nociceptors (non-inflammatory pain), whereas the late phase reflects inflammatory pain (Sawadogo et al. 2006). The late phase is the manifestation of a tonic response brought about by inflammatory processes subsequent to the action of inflammatory mediators such as bradykinin, histamine, prostaglandin, and serotonin (Agbaje et al. 2008). Centrally acting drugs (e.g., opioids) inhibits both phases, while peripherally acting drugs (e.g., NSAIDs) inhibits the late phase only. This is justified by the percentage inhibition of nociception produced by morphine during the early (84.71%) and late (87.74%) phases in this study. The extract significantly inhibited only the late phase, suggesting its ability to majorly inhibit peripheral nociceptive pathways and hence inflammatory pain (Schiotis et al. 2016).

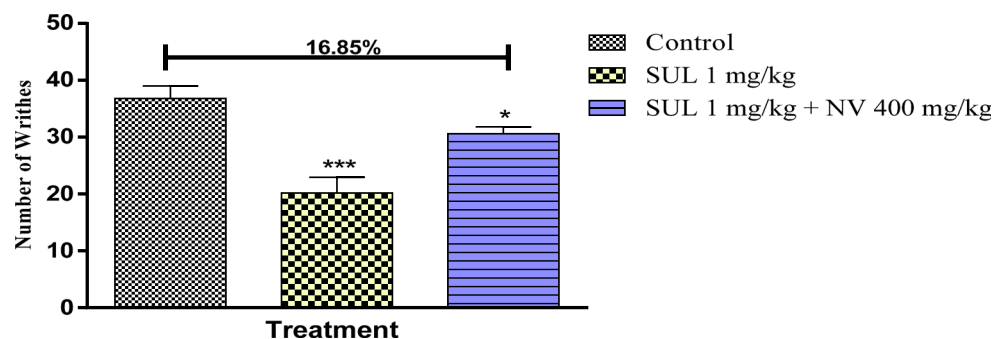
In the acetic acid-induced mouse writhing model, pretreatment with the extract or diclofenac significantly reduced the number of writhes when compared with control. Several chemicals (e.g., phenylquinone, acetic acid) could induce writhing response in laboratory animals (Onasanwo and Elegbe 2006). Intraperitoneal injection of acetic acid in this model produced abdominal writhing responses as a result of the activation of

chemo-sensitive nociceptors in the animals (Adedapo et al. 2008). The percentage inhibition of nociception produced by the extract (54.87%) at 400 mg/kg is comparable with that produced by diclofenac (71.09%). Hence, the extract alleviated visceral pain and suggests its ability to inhibit nociceptive pathways.

Results obtained in this study correlates to findings by other researchers on the anti-nociceptive and anti-inflammatory activities of medicinal plant extracts. Alemu et al. (2018) reported the analgesic and anti-inflammatory effects of *Leonotis ocymifolia* using the acetic acid-induced mouse writhing and the carrageenan-induced paw edema models. In addition, Sofidiya et al. (2014) also documented the anti-nociceptive and anti-inflammatory activities of *Alafia barteri* using the formalin-induced paw licking, acetic acid-induced mouse writhing, and the carrageenan-induced paw edema models.

The involvement of different pathways in the mechanism of anti-nociceptive response was elucidated. The opioid system modulates physiological processes including significant anti-nociceptive responses via activation of opioid receptors (Agbaje and Fageyinbo 2012). Intraperitoneal injection of naloxone (5 mg/kg; a non-selective opioid receptor antagonist) did not block the anti-nociceptive effect of the extract suggesting non-

Fig. 8 Effect of pretreatment with sulphiride on the anti-nociceptive activity of *N. vogelii*. Results are Mean ± S.E.M (n = 5). *** $p < 0.001$ versus control, * $p < 0.05$ versus SUL. One-way ANOVA followed by Tukey's *posthoc* multiple comparisons test. SUL, sulphiride; NV, *Napoleona vogelii*



opioid system involvement (Vasudevan et al. 2007). Dopamine as a neurotransmitter is involved in modulation of nociceptive responses (Agbaje et al. 2008). Sulpiride (an antagonist at dopamine D₂ and D₃ receptors) effectively blocked the anti-nociceptive effect of the extract suggesting that the extract acts via the dopaminergic pathway to elicit anti-nociceptive effects (Schiotis et al. 2016).

One or a combination of the phytochemicals present in the extract may be responsible for the observed analgesic and anti-inflammatory activities in this study. Saponins, phenols, flavonoids, tannins, and some glycosides have been reported to possess anti-nociceptive and anti-inflammatory activities (Akkol et al. 2007; Mohammed et al. 2014).

In conclusion, the findings from this study suggest that the methanol stem bark extract of *Napoleona vogelii* possesses peripheral anti-nociceptive activity through interaction with dopamine D₂ receptors, a late phase anti-inflammatory activity possibly mediated by peripheral and central mechanisms involving the inhibition of the release of chemical mediators of inflammation. The results obtained justify the use of the plant in traditional medicine for the treatment of pain and inflammatory conditions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The procedures employed in this study were in conformity with *The Principles of Laboratory Animal Care (NIH Publication No 8023, revised 1978)* for studies involving experimental animals. Ethical approval was granted by the Health Research Ethics Committee, College of Medicine University of Lagos (CMUL/HREC/02/18/334).

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