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The Journal of Phytopharmacology 2025; 14(4):208-214
Online at: www.phytopharmajournal.com

Research Article

ISSN 2320-480X
JPHYTO 2025; 14(4): 208-214
July- August
Received: 25-06-2025
Accepted: 20-08-2025
Published: 30-09-2025

doi: 10.31254/phyto.2025.14401

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Evaluation of anti-nociceptive and anti-inflammatory activities of a folklore medicinal plant (*Gongronema latifolium*) in rodent models

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ABSTRACT

Background: Nociception (pain) and inflammation have adverse impact on health and socio-economic well-being of humans globally. Currently, synthetic opioids and NSAIDs are commonly used in management of pain and inflammation, but certain factors like unavailability, unaffordability and unwanted reactions, have limited their use as anti-nociceptive and anti-inflammatory agents. Natural plants are important source of new drugs for treatment of numerous human ailments, including pain and inflammation. Analysis of folklore herbal plants used in tradomedical management of pain and inflammation is a laudable and logical approach towards development of new therapy. **Objective:** The present work sought to evaluate the anti-nociceptive and anti-inflammatory activities of a folklore medicinal plant (*Gongronema latifolium*) in rodent models. **Method:** This was accomplished by using acetic acid (writhing) and formalin models in albino mice to test for anti-nociceptive activity, while carrageenan and histamine models in albino rats were used to test for anti-inflammatory activity. **Result:** The results of anti-nociceptive activity reveal that treatment with the leaf extract of *Gomgronema latifolium* when compared to negative control, produces significant ($p<0.05$) inhibition of nociception on acetic acid and formalin models. The results of anti-inflammatory activity also indicate significant ($p<0.05$) inhibition of inflammation on carrageenan and histamine models. **Conclusion:** The present work therefore, authenticates the folklore medicinal claim and existing scientific reports on *Gongronema latifoliumas* as an agent for management of pain and inflammation. We recommend further studies to identify the bioactive principle(s) responsible for the observed activities.

Keywords: Plant extract, Anti-nociceptive, Anti-inflammatory, Folklore.

INTRODUCTION

Nociception (pain) and inflammation are health challenges that have great impact on the socio-economic aspect of human activities globally [1]. Pain is a physiological and psychological sensation linked to actual or possible tissue injuries resulting from inflammation [2]. Inflammation, one of the body's adaptive defenses [3] has five classic signs: pain, warmth, redness, swelling and loss of function, produced by inflammatory mediators such as prostaglandins, histamine, serotonin, bradykinin, leukotriene and nitric oxide [4,5]. Unresolved inflammation promotes progression of many acute and chronic diseases such as rheumatoid arthritis, bowel inflammatory disease, multiple sclerosis etc [6], which have pains and persistent inflammation as symptoms that make the patient seek for medical attention [2,7]. From the perspective of pathophysiology, some pains are mediated centrally, while others are mediated peripherally [8].

Currently, pain and inflammation are managed with the use of synthetic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, but problems associated with availability, affordability and unwanted adverse reactions have imposed limitations to the use of these drugs as pain-relieving and anti-inflammatory agents [9], NSAIDs cause gastric ulceration [10], while opioids cause tolerance and dependence especially on long term use [11]. In view of these shortcomings, attention is diverted towards search for novel agents that are devoid of these problems, to replace NSAIDs and opioids as analgesic and anti-inflammatory agents.

Right from ancient time, plants have been used in tradomedicine to treat diseases and infections in human [12-14], and have remained the pillar of medicinal revolution up to recent time [15]. Medicinal plants are not only affordable and readily available to greater proportion of rural and semi-urban population [16], but have advantage of toxicity consideration [17]. Scientific studies have reported medicinal plants as a source for discovery of new drugs [14,18]. A number of medicinal plants have been reported for their efficacy in management of pain and inflammation: they include *Blepharis maderaspatensis* [19],

Tridax procumbens [20], *Alafia barteri* [21], *Annona vepretorum* [22], *Cucumis ficifolius* [23].

Gongronema latifolium belongs to the family Asclepiadaceae. In Nigeria, it is known as "utazi" among the Igbos, "utasi" among the Ibibios and "arokeke" among the Yorubas. It is one of the bitter plants widely used to alleviate pains and swellings by many local communities in South Eastern Nigeria. Some studies on *Gongronema latifolium* reported anti-inflammatory [24], antioxidant [25], antimalarial [26], and antidiabetic [27]. Considering its wide application in management of different types of pain and inflammation in tradomedicine, the present study evaluated the anti-nociceptive and anti-inflammatory activities of leaf extract of *Gongronema latifolium* in rodent models, in order to authenticate, or otherwise, the folklore medicinal claim and other reports on the plant as anti-nociceptive and anti-inflammatory agent.

MATERIALS AND METHODS

Collection, Identification and Authentication of Plant Material

Fresh leaves of the plant were collected from a farm land in South Eastern Region, Nigeria. The plant was presented to the herbarium of Department of Plant Science and Biotechnology, University of Port Harcourt, Nigeria, where it was identified and authenticated as *Gongronema latifolium*, and was assigned a voucher specimen number, UPH/P/1471.

Preparation and Extraction of Plant Material

The leaves were gabbled and thoroughly washed to remove extraneous matters. Thereafter, the leaves were spread in a well-ventilated room and allowed for about two weeks to dry at room temperature until a constant weight was achieved. The dried leaves were milled into coarse powder. About 600 g of coarsely milled leaves was macerated in 2.0 liters 96% ethanol for 72 hours, with 6 hourly agitations. Thereafter, the mixture was filtered through Whatmann's filter papers. The extraction cycle was repeated twice to ensure complete extraction. The obtained filtrates were pooled together in a clean beaker and concentrated by evaporating the extraction solvent (ethanol) in a hot air oven at 40 ºC. The percent yield of the extracted residue was 3.17% (w/w). The residue was stored in a clean air-tight container, and labeled, GLE.

Drugs and Chemicals

Indomethacin (OneHealth, Nigeria), Acetic acid (Sigma Aldrich, USA), Formalin (Fine Chemicals, Pvt Ltd, Surat, India), Carrageenan (Sigma Aldrich, Germany), Histamine (BDH, England), Absolute ethanol (Central Drug House, Pvt. Ltd., New Delhi, India), Tween 80 (Elsie Organics, Nigeria).

Animals

The animals used in this study were male albino mice (22-25 g) and male albino rats (160-180 g). The animals were bred and housed in clean plastic cages at Animal Facility Center of Madonna University, Nigeria. The animals were maintained under ambient room temperature, freely fed with commercial rodent food and clean water. Animal handling procedure adopted in this study was in accordance with the "Public Health Policy on Humane Care and Use of Laboratory Animals", proposed by National Institute of Health [28], and approval (MAU/DRC/HD/E/PHARM/2025/114) granted by Animal Ethics Committee of Madonna University, Nigeria. The animals were fasted from food for 24 hours, and water for 2 hours, prior to experiments.

Acute Toxicity Test

This was conducted according to Guideline 423 (limit test) proposed by Organization for Economic Cooperation and Development [29], with slight modification. A single oral dose, 5000 mg/kg, of *Gongronema latifolium* extract was administered to each of the five fasting mice group, numbered, M_1-M_5. The sixth mouse (M_6) served as negative control and was administered 10 ml/kg Tween 80 (3% w/v), orally. The mice were monitored for general behavioral and physiological changes as well as mortality, at 1, 4, 24 hours, and then daily for 7 days in case of manifestation of any sign of delayed toxicity or mortality.

Experimental Models

Acetic acid-induced Nociception (Writhing Test)

This test was conducted according to procedure described by [30], with slight adjustment. Twenty-five adult albino mice were randomized into five groups (1-5) of n=5, and were treated as follows: Group 1 (negative control) was administered (p.o) with 10 ml/kg Tween 80 (3% w/v). Group 2 (positive control) was administered (p.o) with 20 mg/kg indomethacin. Groups 3, 4 and 5 were respectively administered (p.o) with 100, 200 and 400 mg/kg of crude plant extract. An hour after the respective administration, nociception (writhing) was induced in each mouse by injecting (i.p), 10ml/kg of 0.6 % acetic acid suspended in 0.9% saline solution. After 5 minutes of acetic acid administration (i.e., induction of nociception), the number of writhes for 30 minutes was recorded for each mouse [31]. Writhing was characterized by contraction of the abdomen, back arching, twist of the trunk and/or pelvis ending with elongation of limb [32]. Percent inhibition of writhing, or percent anti-nociceptive activity, was determined using the formula [33,34]

$$\% \text{ Inhibition of Writhing (Anti-nociception)} = [W_{control} - W_{test}/W_{control}]100$$

Where $w_{control}$ = mean writhing in negative control group

W_{test}= mean writhing in test groups.

Formalin-induced Nociception (Licking Test)

This test was conducted according to procedure described by [35], with slight adjustment. Twenty-five adult albino mice were randomized into five groups (1-5) of n=5, and were treated as follows: Group 1 (negative control) was administered (p.o) with 10 ml/kg Tween 80 (3% w/v). Group 2 (positive control) was administered (p.o) with 20 mg/kg indomethacin. Groups 3, 4 and 5 were respectively administered (p.o) with 100, 200 and 400 mg/kg of crude plant extract. Following the respective administration, nociception was induced in each mouse 30 minutes later by injecting into sub-plantar region of the right hind paw, 0.05 ml of 2.5 % formalin suspended in 0.9% saline solution. The mice were placed in transparent containers to facilitate observation from various sides. Nociceptive responses in mice were measured in two phases: first phase (neurogenic) was measured for 0 – 5 minutes, while the second phase (inflammation) was measured for 15 – 30 minutes after induction of nociception, i.e., after formalin injection [36,37]. The time (second) spent in lifting, licking or biting the injected paw was recorded for each phase of nociception. Percent inhibition of nociceptive activity, was determined using the formula [38]

$$\% \text{ Inhibition of Nociceptive Activity} = [T_{control} - T_{test}/T_{control}]100$$

Where $T_{control}$ = mean time (second) in negative control group

T_{test} = mean time (second) in test groups

Carrageenan-induced Paw Edema (Inflammation)

This test was conducted according to procedure described by [39], with slight adjustment. Twenty-five adult albino rats were randomized into five groups (1-5) of n=5, and were treated as follows: Group 1 (negative control) was administered (p.o) with 10 ml/kg Tween 80 (3% w/v). Group 2 (positive control) was administered (p.o) with 20 mg/kg indomethacin. Groups 3, 4 and 5 were respectively

administered (p.o) with 100, 200 and 400 mg/kg of crude plant extract. Prior to the above administration in various groups, initial time (t_o) thickness of the right hind paw of each rat was measured in millimeter (mm), using vernier calipers. An hour after the respective administration, paw edema (inflammation) was induced in each rat by injecting into sub-plantar surface of the right hind paw, 0.1 ml of 1% carrageenan suspended in 0.9% saline solution. Thereafter, paw thickness was re-measured at time (t_a) interval of 1 hour for 4 hours using the same vernier calipers, and paw thickness was taken as difference between the value at various time (t_a) and the initial time (t_0) value, (i.e. $t_a - t_0$). Percent inhibition of paw edema (inflammation) was determined using the formula [40]:

$$\% \text{ Inhibition of Inflammation} = [(PT_a - PT_0)_{control} - (PT_a - PT_0)_{test} / [(PT_a - PT_0)_{control}]100$$

Where PT_a represents post-carrageenan mean paw thickness in in the treated and negative control groups, while PT_0 represents pre-carrageenan injection mean paw thickness in treated and negative control groups

Histaminie-induced Paw Edema (Inflammation)

This test was conducted according to procedure described by [41], with slight adjustment. Fifteen adult albino rats were randomized into three groups (1-3) of n=5, and were treated as follows: Group 1 (negative control) was administered (p.o) with 10 ml/kg Tween 80 (3% w/v). Group 2 (positive control) was administered (p.o) with 20 mg/kg indomethacin. Groups 3, was administered (p.o) with 200 mg/kg of crude plant extract. Prior to the above administration in various groups, initial time (t_0) thickness of the right hind paw of each rat was measured in millimeter (mm), using vernier calipers. Following the respective administration, paw edema (inflammation) was induced in each rat 30 minutes later by injecting into the sub-plantar surface of the right hind paw, 0.1 ml of 1% histamine suspended in 0.9% saline solution. Thereafter, paw thickness was re-measured at time (t_a) interval of 30 minutes for 2 hours using the same vernier calipers. Percent inhibition of inflammation was calculated as described in carrageenan model above.

Statistical Analysis

The data obtained in the study are presented as mean±standard error of mean (i.e., ± SEM). One-way analysis of variance (ANOVA) was used to determine statistical significance followed by post-hoc Duncan's comparison test. Probability less than 0.05 (i.e., $p<0.05$) is considered significant relative to negative control, while probability greater than 0.01 (i.e., $p>0.01$) is considered insignificant relative to positive control.

RESULTS

Oral Acute Toxicity

A single oral administration of *Gongronema latifolium* extract at 5000 mg/kg did not cause any sign of toxicity, nor caused mortality within 24 hours observation as well as within 7 days follow up period.

Acetic acid-induced Writhing

Oral administration of *Gongronema latifolium* extract into mice, in dose-dependent manner, significantly ($p<0.05$) reduces the number of writhing when compared to negative control as shown in Table 1. The largest dose (400 mg/kg) of the plant extract produces 68.62 % inhibition of writhing, which is insignificant ($p>0.01$) with respect to inhibition (73.33 %) exhibited by 20 mg/kg indomethacin.

Formalin-induced Licking

As shown in Table 2, *Gongronema latifolium* extract significantly ($p<0.05$) reduced the mean time the mice spent licking the injected paw in both the early and late phases, but more reduction in the late phase. In the late phase, the percentage inhibition of nociception is 26.69%, 33.56% and 45.95%, for extract doses at 100, 200 and 400 mg/kg respectively.

Carrageenan-induced Paw Edema

From the result in Table 3, the test doses of the plant extract exhibit non-dose-dependent inhibition of inflammation (paw edema), with 200 mg/kg producing highest percent inhibition of 64.15%, 63.87%, 59.00% and 53.94% in 1, 2, 3 and 4 hours respectively. With exception of inhibition produced by 100 mg/kg extract at 1 hour, all other inhibition is significant ($p<0.05$) relative to negative control.

Histamine-induced Paw Edema

Paw edema induced by histamine was significantly ($p<0.05$) inhibited by plant extract (200 mg/kg) in 90 and 120 minutes. The inhibition is more pronounced at 120 minutes (51.61%), but insignificant ($p>0.01$) at 60 minutes (47.65%) relative to positive control (53.02%).

Table 1: Effect of *Gongronema latifolium* Leaf Extract on Acetic acid-induced Nociception (Writhing Test) in Albino Mice

Group	Mean Number of Writing Per 30 minutes	% Inhibition of Writhing
1.	32.66±1.83	-
2.	8.71±3.16[a]	73.33
3.	19.35±4.11[a]	40.75
4.	12.08±2.25[a]	63.01
5.	10.25±3.07[a,b]	68.62

Values represent mean ±SEM of n=5; [a] significant ($p<0.05$) relative to negative control; [b] insignificant ($p>0.01$) relative to positive control.

Table 2: Effect of *Gongronema latifolium* Leaf Extract on Formalin-induced Nociception in Albino Mice

	Mean Licking time (seconds) and Percent Inhibition of Nociception			
Group	Early Phase	% Inhibition of Nociception	Late Phase	% Inhibition of Nociception
1.	61.12±3.83	-	76.47±3-28	-
2.	40.74±5.41[a]	33.34	29.72±2.63[a]	61.14
3.	56.46±3.64[a]	7.62	56.06±5.75[a]	26.69
4.	54.34±2.92[a]	11.09	50.81±0,88[a]	33.56
5.	52.53±3.68[a]	14.05	41.33±2.07[a,]	45.95

Values represent mean ±SEM of n=5; [a] significant ($p<0.05$) relative to negative control

Table 3: Effect of *Gongronema latifolium* Leaf Extract on Carrageenan-induced Inflammation in Albino Rats

	Mean paw thickness (mm) and Percent Inhibition of inflammation				
Group	**0 hour**	**1 hour**	**2 hours**	**3 hours**	**4 hours**
1.	2.75±2.61	3.81±5.15 (0.00)	3.94±1.84 (0.00)	4.36±2.81 (0.00)	4.4±2-02 (0.00)
2.	2.71±4.08	3.01±2.95 (71.69)[a]	3.08±1.36 (68.91)[a]	3.13±2.48 (73.91)[a]	3.29±1.65 (64.85)[a]
3.	2.73±1.96	3.48±3.64 (29.92)	3.47±2.29 (37.81)[a]	3.84±6.06 (31.06)[a]	3.90±3.33 (29.09)[a]
4.	2.69±3.88	3.07±4.41 (64.15)[a]	3.12±2.77 (63.87)[a,b]	3.35±3.05 (59.00)[a]	3.45±4.47 (53.94)[a]
5.	2.77±2.32	3.25±3.06 (54.72)[a]	3.30±5.14 (55.46)[a]	3.55±1.70 (51.55)[a]	3.59±3.50 (50.30)[a]

Values represent mean ±SEM of n=5; [a] significant ($p<0.05$) relative to negative control; [b] insignificant ($p>0.01$) relative to positive control. Figures in the bracket represent percent inhibition of inflammation.

Table 4: Effect of *Gongronema latifolium* Leaf Extract on Histamine–induced Inflammation in Albino Rats

	Mean paw thickness (mm) and Percent Inhibition of inflammation				
Group	**0 minute**	**30 minutes**	**60 minutes**	**90 minutes**	**120 minutes**
1.	2.55±2.31	3.21±1.77 (0.00)	3.53±4.12 (0.00)	4.04±1.73 (0.00)	4.10±2.37 (0.00)
2.	2..62±1.74	3.08±2.03 (30.30)[a]	3.24±0.80 (36.37)[a]	3.23±3.05 (53.02)[a]	3.22±0.89 (61.29)[a]
3.	2.59±1.81	3.23±2.76 (3.03)	3.42±3.59 (15.31)	3.37±2.58 (47.65)[a,b]	3.34±1.40 (51.61)[a]

Values represent mean ±SEM of n=5; [a] significant ($p<0.05$) relative to negative control; [b] insignificant ($p>0.01$) relative to positive control. Figures in the bracket represent percent inhibition of inflammation.

DISCUSSION

This study evaluated the anti-nociceptive and anti-inflammatory activities of ethanol leaf extract of a folklore medicinal plant (*Gongronema latifolium*) in rodent models of pain and inflammation. Screening for anti-nociceptive activity was conducted using acetic acid-induced (writhing) and formalin-induced paw licking tests in albino mice, while screening for anti-inflammatory activity was conducted using carrageenan-induced and histamine-induced hind paw edema in albino rats. Acetic acid-induced writhing test in mice is non-specific but sensitive model widely employed in screening anti nociceptive agents [34] especially those that possess peripheral anti-nociceptive attributes [42,43]. Intraperitoneal administration of acetic acid causes the release of endogenous pain mediators such as prostaglandins E_2 and F_2(PG E_2 and PG F_2), histamine, serotonin, bradykinin, substance P etc., into the peritoneal fluid where they stimulate the nerve ending that results to inflammatory pain [34,44,45] characterized by abdominal muscle constriction (writhing) with fore limb extension and/or body elongation [46]. From the result of this study (Table 1), the *Gongronema latifolium* extract when compared to the control, significantly ($p<0.05$) produced dose-dependent reduction in number of writhing, hence indicating peripheral anti nociceptive activity that could perhaps be mediated via peripheral mechanism involving suppression of prostaglandins release. This finding corroborates other reports that anti-nociceptive agents lower the number of writhing via suppression of synthesis and release of peripheral inflammatory pain mediators [47,48]

Anti-nociceptive activity of *Gongronema latifolium* extract was further evaluated using formalin-induced paw licking test in order to establish the possible mechanism of action. Formalin test ascertains the effectiveness of anti-nociceptive agents on behavioral responses [49,50]. When compared to other models, formalin model is known for its attributes such as validity, reliability and sensitivity to various classes of anti-nociceptive agents [51]. It also has some advantages such as minimal or no restraint, uninterrupted observation of complete behavioral responses, as well as producing pain that mimics clinical condition [52,53]. Formalin-induced nociception has two distinct phases; the early (neurogenic) phase and the late (inflammatory) phase. The early phase which occurs in first 5 minutes after formalin injection, is assumed to be due to direct stimulation of sensory and C-fiber activation by prostaglandins, while the late phase manifests after 15-30 minutes, and it is caused by release of histamine, serotonin, bradykinin substance-P etc. which to some extent sensitizes nociceptive neurons [35,44,50,54,55]. The late phase can be inhibited by drugs such as: (i) NSAIDs, through their peripheral activity against (ii) prostaglandins (iii) steroids (iv) centrally acting narcotic analgesics [22,23,51]. From the result of this study (Table 2), *Gongronema latifolium* extract demonstrates significant ($p<0.05$) inhibition of nociception (licking time) in both phases, but more pronounced in the late phase, hence implying that its anti-nociceptive activity of is both peripherally and centrally mediated. This finding is in agreement with other reports on anti-nociceptive activities exhibited by other plants like *Alafia barteri* [21], *Malva parviflora* [56] and *Cucumis ficifolius* [23]

Carrageenan-induced paw edema model is widely employed for evaluating anti-inflammatory/anti-edematous activities of new compounds, especially phytopharmaceuticals [57-59]. Injection of carrageenan produces edema in biphasic manner: the early phase which lasts between 1-2 hours is attributed to the release of histamine, serotonin and bradykinin, while the late phase lasts between 3-4 hours and it is characterized by release of prostaglandins and nitric oxide [57,60]. The second phase is sensitive to anti-inflammatory agents, steroids and NSAIDs [61], which produce their action by inhibiting the release of mediators of acute inflammation [62]. The result of this study (Table 3) demonstrates that *Gongronema latifolium* leaf extract, in non-dose dependent manner exhibits significant inhibitory effect on both phases, but more on first phase. Greater inhibitory effect is observed at 200 mg/kg than at 400 mg/kg. This situation may likely be due to saturation of the bioactive principles at the target receptor or proteins involved in inflammatory mechanisms. This implies that *Gongronema latifolium* extract at dose greater than 200 mg/kg may not elicit any reasonable increase in anti-inflammatory response. Similar findings are reported on dichloro-methanolic root extract of *Clutiaabyssnica* [63], and on methanolic extracts of *Pistaciaaethiopica* and *Warbugia ugandensis* [64], where smaller dose exhibits higher effect compared to larger dose. The reduction in pharmacological effect beyond optimal dose can also be ascribed to natural pharmacokinetic mechanism within the animal that initiates excretion and clearance of the drug in order to avoid toxic effects by limiting their biological actions [64,65].

Histamine and serotonin are vasodilators that can increase vascular permeability [66,67]. *Gongronema latifolium* extract having shown highest anti-inflammatory activity at 200 mg/kg in the histamine-mediated early phase of carrageenan-induced paw edema model, was further evaluated at this dose (i.e, 200 mg/kg) on histamine-induced paw edema model to confirm whether histamine was involved or not. From the result of this study (Table 4), *Gongronema latifolium* extract

having significantly ($p<0.05$) inhibited edema produced by histamine at 90 and 120 minutes, but more pronounced at 120 minutes, may be pointing that anti-inflammatory activity of *Gongronema latifolium* extract is mediated by inhibiting the synthesis and/or release of histamine.

CONCLUSION

Considering the results of different models of nociception and inflammation in mice and rats respectively, it can be concluded that ethanol leaf extract of *Gongronema latifolium* possesses anti-nociceptive and anti-inflammatory activities. These observations validate, at least in part, the folkloric use of the plant in management of painful and inflammatory conditions. Moreover, the observations of this study not only concur with existing reports on this plant as an anti-nociceptive and anti-inflammatory agent, but also provide empirical data on the plant's efficacy which is the first step towards elucidating the actual bioactive principle(s) responsible for the observed activities.

Conflict of interest

The authors declared no conflict of interest.

Financial Support

None declared.

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HOW TO CITE THIS ARTICLE
Onwudiwe TC, Azudialu BC, Obi IM, Madubuogwu NU, Ogbuagu EO. Evaluation of anti-nociceptive and anti-inflammatory activities of a folklore medicinal plant (*Gongronema latifolium*) in rodent models. J Phytopharmacol 2025; 14(4):208-214. doi: 10.31254/phyto.2025.14401