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Original Research Article

Anti-inflammatory Activity and GC-MS Investigation of an Extract of *Capsicum chinense* (Var. Nsukka Yellow Pepper) Fruit

Vincent O. Chukwube[1], Patience N. Ugwu[1]*, Chinenyenwa P. Osigwe[1], Nonhlagabezo Maduba[2], Eleje O. Okonta[1], Charity C. Ezea[3], Fabian I. Eze[4], Charles O. Nnadi[4], Uchenna E. Odo[1]

[1]*Department of Pharmacognosy and Environmental Medicine, Faculty of Pharmaceutical Sciences, University of Nigeria Nsukka, 410001 Enugu State, Nigeria*
[2]*Department of Chemical Sciences, University of Johannesburg, 9 Lewis Road, Johannesburg 2092, Republic of South Africa*
[3]*Department of Pharmacognosy and Traditional Medicine, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, 420007 Anambra State, Nigeria.*
[4]*Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria Nsukka, 410001 Enugu State, Nigeria..*

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ABSTRACT

The edible and non-edible parts of *Capsicum chinense* **(**var. Nsukka yellow pepper) fruit are known for their higher functional compounds content such as polyphenolic which modulate the homeostasis of vital cellular processes such as inflammation. The study evaluated the *in vivo* anti-inflammatory effect and identified important phytochemical content of the extract of *Capsicum chinense* fruit. The powdered sample was cold-macerated in methanol-dichloromethane (1:1). The acute toxicity of the extract was tested using Lorke's method. The GC-MS technique was employed in the phytochemical analysis. The anti-inflammatory activity adopted the egg white albumin-evoked paw and xylene-provoked ear oedema models. The cold-maceration yielded 16%w/w of the dried sample of extract. The acute toxicity test showed that the extract was non-toxic up to 2900 mg/kg in mice with LD_{50} of 3807 mg/kg. The GC-MS analysis identified 23 compounds with 1,2-cyclopentanedione, *n*-hexadecanoic acid, capsaicin and dihydrocapsaicin in significant concentration with peak areas of 0.25, 0.36, 7.76 and 5.26% respectively. The inhibition of egg albumin-evoked inflammation by 200 mg/kg of extract peaked at 4 h and maintained a plateau between 4-5 h while the 50 and 100 mg/kg doses peaked at 3 h with a non-uniform decline in the pattern of inhibition of inflammation. There was no significant difference ($p > 0.05$) between the inhibitory effects of the extract (200 mg/kg) and indomethacin (82.5 vs 87.5 %) in the xylene-induced inflammation. The *n*-hexadecanoic acid, capsaicin and dihydrocapsaicin were detected in significant concentration in the extract and could account for the anti-inflammatory effect of *C. chinenese*

Keywords: Anti-inflammatory, *Capsicum chinense*, gas chromatography-mass spectrometry, phytochemicals, yellow pepper.

Introduction

The medicinal and nutritional benefits of plants often overlap, making them versatile and beneficial to the well-being of man. Many vegetables including *Spinacia oleracea* (with multivitamins and anti-inflammatory activity), *Brassica oleracea* (multivitamin and anticancer), *Allium sativum* (flavour and antimicrobial), *Daucus carota* (vitamin A and antioxidant), *Solanum lycopersicum* (multivitamin and anti-cancer), and *Zingiber officinale* (spice and anti-inflammatory) exemplify how nutritional and medicinal values often overlap, providing synergistic benefits.[1] The overlap may be connected to the roles of the phytochemical constituents and their synergism with the vitamins, minerals and fibre contents, cultural and evolutionary adaptations as well as the traditional and modern medicine integration.[1] *Capsicum chinense* (Nsukka yellow pepper) is an example of the intricate relationship between food and medicine.[2]

***Corresponding author. E mail** patience.ugwu@unn.edu.ng
Tel: +2348064153337

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Edible peppers belong to the capsicum variety of the Solanaceae family with five common species such as *C. baccatum*, *C. annuum*, *C. chinense*, *C. frutescens* and *C. pubescens*.

Due to their highly regarded qualities such as pungency, aromatic spiciness, and their importance as a vegetable, medicine and source of nourishment, they are extensively utilized globally[3]. *Capsicum chinense* (L.) is an indigenized pepper with a long history of usage in Nigeria and is extensively grown in Nsukka due to its pungent flavour, vegetable properties and nutritional benefits.[4] It is used in folk medicine as a nasal decongestant in children and adults. Apart from its culinary use, Nsukka yellow pepper contains minerals (K and Ca), carotenoids (zeaxanthin and lutein), vitamins (A and C), and dietary fibres which contribute to its antioxidant, anti-inflammatory, immune-supportive, cardioprotective and digestive properties.[5] The anti-inflammatory potential of the methanol extract of its subspecies, *C. chinense* has been reported with significant membrane stabilization effect and protection against protein denaturation.[6] Studies have reported a significant pungency level in *C. chinense* higher than previously known sweet pepper (bell pepper), Scotch pepper and Cameroon pepper due to the capsainoids content in capsicum which has also been associated with the anti-inflammatory effect of related species.[7]

Traditionally, the pepper is used as a remedy for various ailments such as colds, respiratory issues and digestive problems.[8] The capsaicin content acts as a natural relief for inflammation and pain, conditions

associated with the body's natural response to injury, infection or irritants. Inflammation is a crucial part of the healing process but can become problematic when chronic, leading to diseases like cancers, arthritis and heart disease.[9] Treatment of inflammatory disorders with NSAIDs, DMARDs or corticosteroids is hampered by drug resistance, immune suppression and the difficulty in targeting inflammation without affecting normal immune functions.[10] Several plants have shown strong potential for the treatment of inflammation due to a plethora of distinct constituents that operate synergistically on specific elements of the complex inflammatory process.[11-13] Therefore, sourcing more potent anti-inflammatory agents from natural products such as edible fruits can provide a good alternative since capsaicin, an anti-inflammatory compound has been reported in the Capsicum genus.[3,14,15] There is a dearth of research regarding the claimed anti-inflammatory potential of the indigenized species of *C. chinense* and its phytochemical profiling. The study, therefore, investigated the phytochemical constituents and anti-inflammatory potential of the extract of *Capsicum chinense*.

Materials and methods

Experimental animals

Both sexes of adult albino Wistar rats (80-120 g) and albino Swiss mice (20-30 g) procured from the Pharmacology and Toxicology Department, University of Nigeria Nsukka were utilized for the studies. They were fed with regular livestock food, provided unrestricted access to water and were subjected to 7 days of acclimatization time before the commencement of treatment. The protocols adopted for the use of animals in the studies were reviewed and approved by the University of Nigeria Ethics Committee (approval number: UN/FPSREC/2024/0023).

Animal grouping for anti-inflammatory studies

The adult albino Wistar rats were randomly allotted into five groups (n = 5). Rats placed in groups B to D were administered doses of 50, 100 and 200 mg of the extract per kg of rat p.o. as treatment groups in the egg white- and xylene-induced models. In both models, groups A and E rats received 10 mg indomethacin per kg of rat as standard, and 0.5 mL distilled water as negative control respectively. They were restricted from access to both food and water for 10 h throughout the experiment to get equal hydration and to limit variability in oedematous reactions.

Collection of plant material

Fresh fruits (10 kg) of *Capsicum chinense* were harvested from Nsukka (N 6 51′ 28.19″, E 7 23′ 44.77″) Nigeria in May 2024 and authenticated by Mr. Chibuoke Onyeukwu, a taxonomist in the Plant Science and Biotechnology Department of the University of Nigeria Nsukka. The fruit specimen was stored at the herbarium of the same Department with a voucher identification number of UN/11774. The fresh fruits were washed, and sliced and the petiole of the fruits and contaminants were removed. They were subsequently air-dried at ambient temperature under the shade and ground to a fine powder using a mechanical iron grinder. The fine powder was preserved under an air-tight environment.

Extraction of plant material

The finely ground fruit (1100 g) was macerated in 5.0 L of methanol/dichloromethane (1:1) for 48 h at 25 ℃ with periodic agitation. The macerate was filtered and the marc was soaked again in 4 L of extraction solvent for 24 h. The combined filtrate was concentrated in a rotary evaporator at 25 ℃ to obtain a viscous extract.[16]

GC-MS evaluation of C. chinense extract

A 50 mg/mL of fruit extract in 70% methanol was prepared for the GC-MS analysis in an electron ionization mode (GC-MS/EI). The instrument was paired with a mass spectrophotometer (triple quadruple) with a fused BR-5MS silica gel capillary column containing diphenyl/dimethyl polysiloxane (95:95%) and length, internal diameter and thickness of 30 mm, 0.25 mm and 0.25 µm respectively. The instrument was run under the following parameters: carrier gas, helium (99.9%); flow rate, 1 mL/min; injection volume, 2 µL (split ratio of 10:1); injector temperature, 250 °C; ion-source temperature was 280 °C; oven temperature gradient, 110 °C (isothermal for 2 min), 10 °C/min increased to 200°C; thereafter 5 °C/min to 280°C, followed by 9 min isothermal at 280 °C; totalling 41 min GC operating time. The MS was run in the +EI mode utilizing an ionization energy of 70 eV. The run was programmed at 0 to 3 min solvent delay; 0.5 s scan interval and m/z 50 to 500 Da fragments; 280 °C intake temperature; 250 °C source temperature. The relative amount (%) of the component of the extract was estimated by the comparison of its mean peak area to the total areas using the MS Workstation 8 and the NIST v.2.0 database of the National Institute Standard and Technology (NIST) including > 62,000 patterns for the identification of the chemical substances.[17]

Pharmacological evaluation

Acute Toxicity test

The test was carried out in two phases according to the Lorke model. In phase I, 9 albino mice were randomized into 3 separate groups and the extract was administered orally at 10, 100 and 1000 mg per kg of mouse. They were disallowed access to food but were granted access to distilled water. The signs of toxicity such as behavioural changes and motility were observed in the mice for 24 h. In phase II, 3 mice were each administered orally with 1600, 2900 and 5000 mg/kg of the extract respectively. They were refused access to food but were allowed access to clean water. The mice were also examined for signs of toxicity and motility up to 24 h period. The LD_{50} was computed as the geometric average of the smallest lethal dose and the greatest non-fatal dose.[18]

Anti-inflammatory activity

Egg white-induced hind paw oedema model

The baseline paw volume of each rat was recorded before the commencement of treatment. Thirty minutes after oral administration of the test and standard and control samples, inflammation of the paw was induced by injecting freshly obtained egg white (0.1 mL, prepared in 10% tween 80) into the sub-plantar tissue of the left hind paw of the rats subcutaneously using a 1 mL syringe. The volumes of the injected paws were determined via the water displacement method at 0, 30, 60, 120, 180, 240 and 300 minutes using a plethysmometer.[12,19] The mean value of oedema at different hours was computed and the % rise in paw inflammation of the treatment groups, B to D was compared with that of the untreated and the inhibitory effects of the medications were evaluated.

Xylene-induced rat ear oedema model

The extract of the fruit of *Capsicum chinense* at a concentration of 50, 100 and 200 mg/mL was smeared two times at 30-minute intervals on the outer surface of the right pinna of the groups B to D rats respectively. Groups A and E rats received 10 mg/kg of indomethacin as standard control and distilled water (0.5 mL) as untreated control respectively. The phlogistic agent, xylene (0.03 mL/ear) was applied topically to the inner surface of the same right ear while the left ear was left untreated and designated a control. After one hour of xylene administration, the rats were euthanized and both ears were removed. Circular portions of both the right and left ear lobes were surgically cut, using a 6 mm diameter cork borer and weighed with an electronic balance.[13,20] The rise in weight of the ear lobe evoked by xylene was assessed by the difference in weight of the left and right ear sections and the level of % inhibition was estimated using equation 1.

$$\text{Inhibition (\%)} = \frac{Weight\ of\ control - Weight\ of\ treated}{Weight\ of\ control} X\ 100$$

Equation 1

Data Analysis

The data was presented as mean ± SEM for each experimental group. The responses were submitted to a one-way analysis of variance (ANOVA). A $p < 0.05$ was regarded as significant when compared with the controls.

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Results and Discussion

The roles played by plants' phytochemical constituents in folk medicine for the management of inflammatory disorders and oxidative stress, especially in developing countries have bridged the gap in healthcare needs among different cultures.[21] These phytochemicals may reduce inflammation by inhibiting the pro-inflammatory cytokine production and enzymes such as nitric oxide synthase or cyclooxygenase-2 or by modulation of mitogen-activated kinases and nuclear factor.[22] Their use

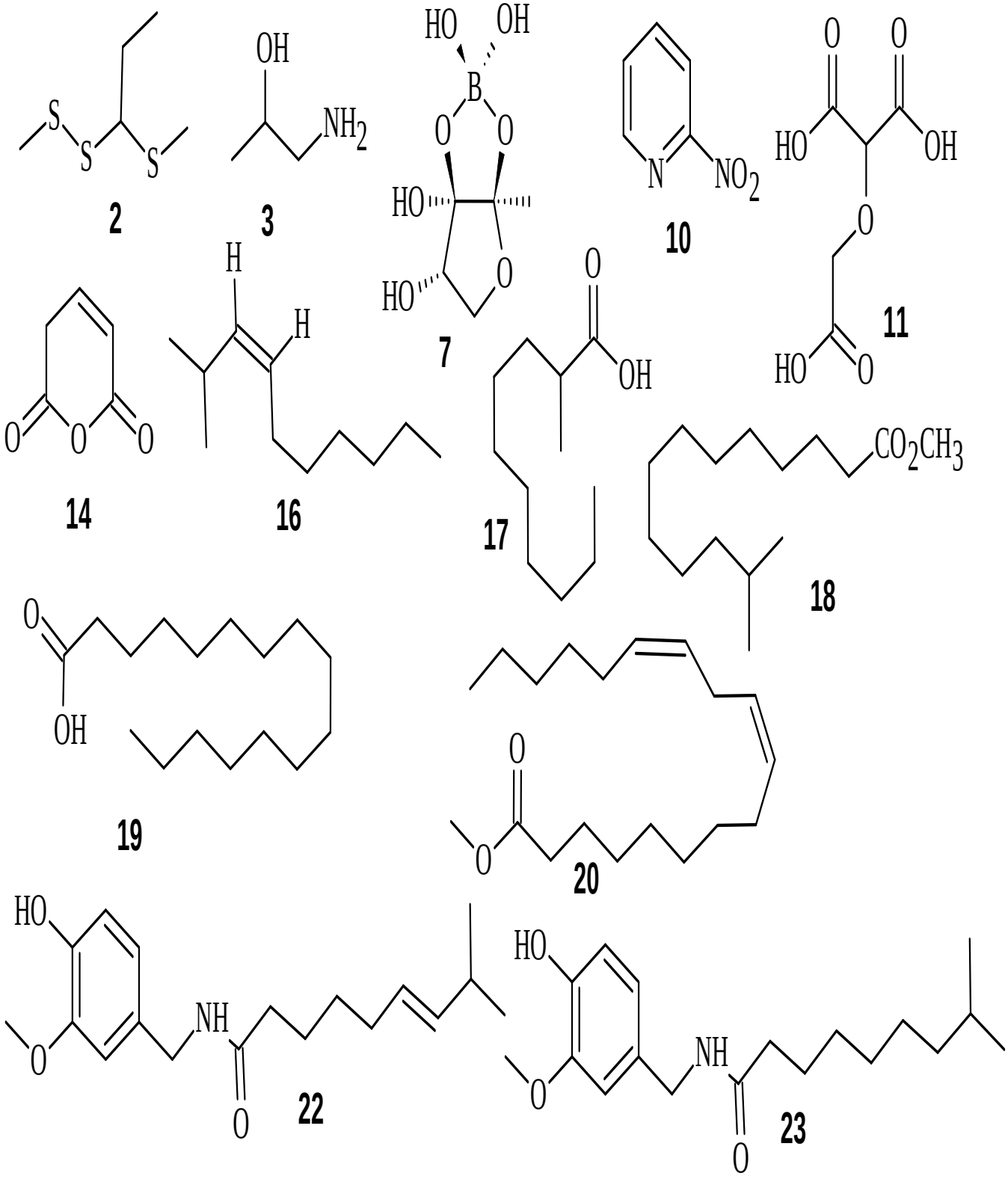

Figure 1. Chemical structures of compounds with anti-inflammatory activity identified from GC-MS analysis; Ethyl (methylthio)methyl disulfide (**2**), 2-hydroxylpropenamide (**3**), tris(trifluoromethyl) methanamine boron (**7**), 2-nitropyridine (**10**), propanedioic acid (**11**), 2H-pyran-2,6-(3H)-dione (**14**), (z)-2-methyl-3-decene (**16**), 2-methyl-decanoic acid (**17**), tridecanoic acid methyl ester (**18**), *n*-hexadecanoic acid (**19**), (*E*,*E*)-9,12-octadecadienoic acid methyl ester (**20**), (*Z*,*Z*,*Z*)-9,12,15-octadecatrienoic acid methyl ester (**21**), capsaicin (**22**) and dihydrocapsaicin (**23**)

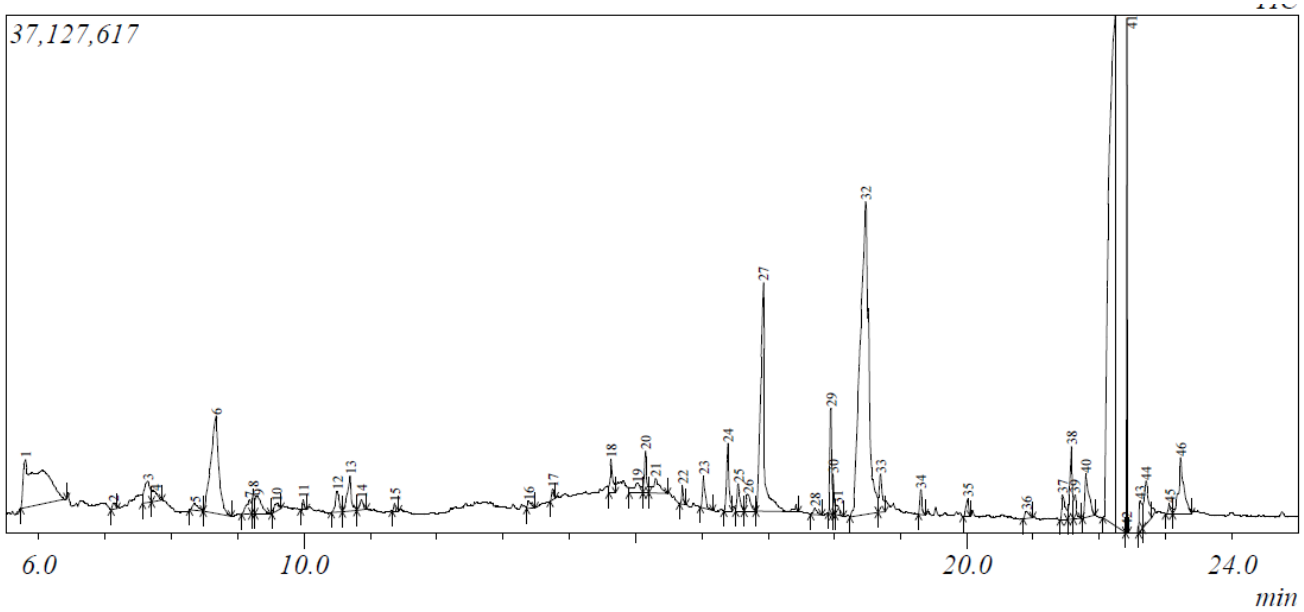

Figure 2. GC-MS spectrum of *C. chinense* extract (peak numbering shown here differs from the compound numbering in Table 1)

has also increased due to the problems associated with orthodox anti-inflammatory agents such as organ damage, hypotension, gastritis and allergic reactions.[23] *Capsicum chinense*, an edible yellow pepper is reputed for its wide use as an anti-inflammatory reagent which has complemented other activities including antioxidant, anti-inflammatory, immune-supportive, cardioprotective and digestive properties.[3-10] The fruit is consumed as a routine diet in foods, and spices or used as fresh or in dried form as other plant parts. The fruit can be extracted by various methods to provide its vitamins and minerals.[4-7]

Extraction of plant material

The extraction of powdered plant samples with a methanol/dichloromethane mixture by cold maceration yielded 176 g of dry viscous extract. The yield represents 16% w/w of dry powdered sample. The cold maceration of dried fruit of *Capsicum chinense* yielded 176 g of dried extract representing 16.0%w/w. Extraction method and extracting solvents are crucial in herbal medicine and drug discovery considering their significant effects on biological activities and phytochemical contents. This study employed a bipolar solvent combination of dichloromethane and methanol with the potential to extract phytochemicals of varying polarities from terpenes to flavonoids. The use of the cold-maceration technique in this study could also be advantageous considering the heat- or photosensitivity of the constituents of the fruit.[24] The effects on the bioactivity of the extract are a consequence of the phytochemical content of the extract. Extraction techniques affect the concentration, stability, selectivity and toxicity of phytochemicals which control the biological potential of plants.[25] Understanding the relationship between the extraction solvents and methods and biological activity of *Capsicum chinense* is important for the optimization of the use of plant secondary metabolites in cosmetics, pharmaceuticals and nutraceuticals.

Table 1: Compounds obtained from the GC-MS of the extract

Compound	RT (min)	MF and MW (Da)	PA (%)
R-(-)-2-propanediol (**1**)	17.3	$C_3H_8O_2$, 76.0944	0.02
Ethyl (methylthio)methyl disulfide (**2**)	0.09	$C_4H_{10}S_4$, 186.4	0.03
2-Hydroxyl propenamide (**3**)	16.8	$C_4H_9NO_2$, 103.12	0.02
Methoxyacetaldehyde (**4**)	6.8	$C_3H_6O_2$, 74.08	0.09
Propylene glycol (**5**)	4.0	$C_3H_8O_2$, 76.09	0.02
2-Fluoro-2-methylpropane (**6**)	4.0	$C_4H_9F_7$, 190.10	0.23
Tris(trifluoromethyl) methanamine boron (**7**)	6.0	B_6O, 80.87	0.03
Hydroxyl acetic acid (**8**)	24.0	$C_4H_6O_5$, 134.09	0.02
1-Chloro-2-nitro-ethane (**9**)	2.0	C_2H_4ClNO,109.51	0.03
2-Nitropyridine (**10**)	15.3	$C_5H_2N_2O_2$, 124.1	0.01
Propanedioic acid (**11**)	4.68	$C_5HH_6O_7$, 178.1	0.003
1,2-Cyclopentanedione (**12**)	3.75	$C_5H_6O_2$, 98.101	0.25
Dihydro-3-methylene-2,5-furandione (**13**)	6.0	$C_5H_4O_3$, 114.09	0.03
2H-Pyran-2,6-(3H)-dione (**14**)	7.105	$C_5H_4O_3$, 126.11	0.005
2-Methoxy-4-vinyl phenol (**15**)	8.57	$C_9H_{10}O_2$, 156.18	0.03
(*Z*)-2-methyl-3-decene (**16**)	13.10	$C_{11}H_{22}$, 154.29	0.02
2-Methyl-decanoic acid (**17**)	15.25	$C_{11}H_{22}O_2$, 186.29	0.05
Tridecanoic acid methyl ester (**18**)	13.16	$C_{14}H_{28}O_2$, 228.37	0.03
n-Hexadecanoic acid (**19**)	20.92	$C_{17}H_{34}O_2$, 256.42	0.36
(E,E)-9,12-Octadecadienoic acid methyl ester (**20**)	23.09	$C_{19}H_{34}O_2$, 294.	0.0023
9,12,15-Octadecatrienoic acid methyl ester (**21**)	60.0	$C_{19}H_{32}O_2$, 292.5	0.05
Capsaicin (**22**)	0.06	$C_{18}H_{27}NO_3$, 305.4	7.76
Dihydrocapsaicin (**23**)	4.25	$C_{18}H_{29}NO_3$, 305.41	5.2607

Molecular weight (MW), retention time (RT), molecular formula (MF), peak area (PA)

Acute toxicity of the extract

The administered doses of *Capsicum chinense* (10-1000 mg/kg) to the mice in phase I of the acute toxicity test showed variable treatment-related behavioural changes. There was a generalized reduced activity with writhing among the mice that received 100 mg/kg of *Capsicum chinense*. The 1000 mg/kg group exhibited general depression and

writhing with abdominal pain. In phase II of the test, 1600 mg/kg-treated mice exhibited confusion, hyperactivity and intense hopping. The 2900 and 5000 mg/kg-treated mice exhibited confusion, hyperactivity, and intense jumping within 10 minutes of administration and the mice treated with 5000 mg/kg finally died after 10 min. The geometric mean of 2900 mg/kg and 5000 mg/kg gave the LD_{50} of 3807 mg/kg. The increase in abdominal writhes is typical due to the presence of capsaicin which opens the transient receptor potential vanilloid receptor-1 (TRPV) calcium channels, increasing muscle contraction and general excitation.[26] This may pose a barrier in the herbal formulation of *C. chinense* extract or routine use for dietary purposes especially if used for a long duration.

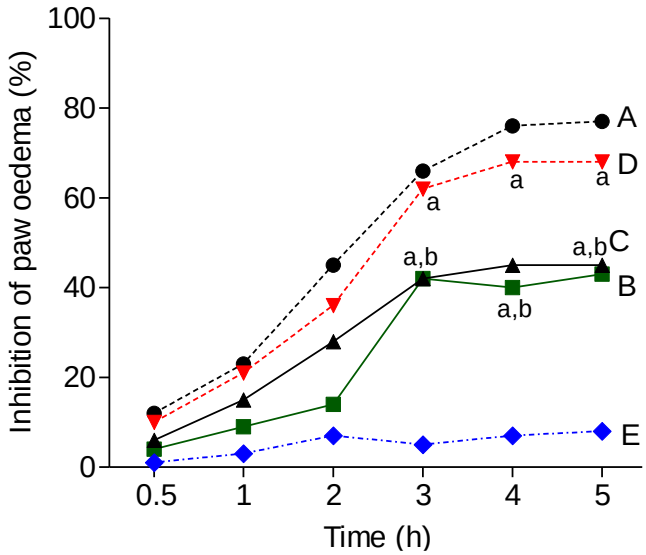

Figure 3. Effect of *Capsicum chinense* extract on egg albumin-induced inflammation. Group A-E represent standard (indomethacin, 10 mg/kg), 50, 100, and 200 mg/kg *C. chinense*, and untreated groups respectively; Statistically significant compared with [a]group E and [b]group A

GC-MS analysis of the extract

The GC-MS analysis of the extract of *C. chinense* identified several compounds whose molecular formula (MF), retention time (RT) and weight (MW) correspond with identical compounds in the database of NIST. Two important compounds, capsaicin and dihydrocapsaicin with peak areas of 7.8 and 5.2% respectively were identified in abundance in the extract. Thirteen compounds identified from the analysis have been associated with anti-inflammatory properties (Figure 1).

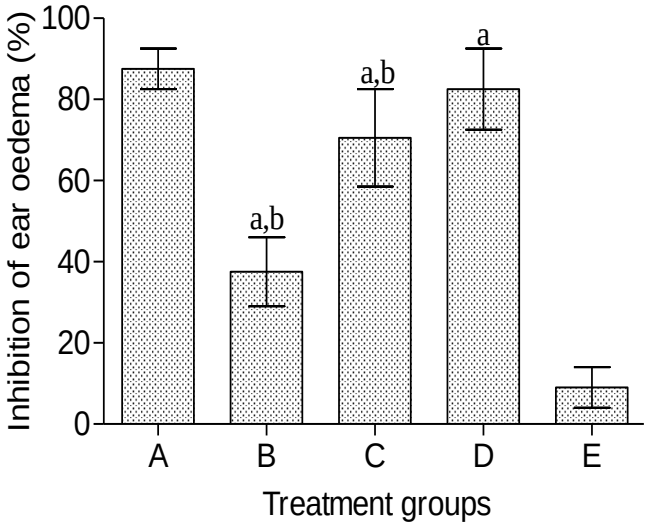

Figure 4. Effect of *Capsicum chinense* extract on xylene-induced inflammation; Group A-E represent standard (indomethacin, 10 mg/kg), 50, 100, and 200 mg/kg *C. chinense*, and untreated groups respectively; statistically significant compared with [a]group E and [b]group A

Of the twenty-three compounds identified from the GC-MS spectrum (Figure 2) evaluation of the extract, capsaicin (**22**) and dihydrocapsaicin (**23**) were the most abundant with relative abundance of 7.76 and 5.62% and retention times of 4.25 and 0.06 mins (Table 1). The GC-MS analysis of *Capsicum chinense* was performed to identify and understand the diversity and complexity of their bioactive secondary metabolites. The GC-MS evaluation of *C. chinense* fruit identified four compounds; 1,2-cyclopentanedione (**12**), *n*-hexadecanoic acid (**19**), capsaicin (**22**) and dihydrocapsaicin (**23**) in significant concentration with peak areas of 0.25, 0.36, 7.76 and 5.26% respectively. Capsaicin and dihydrocapsaicin are phenolic glycosides that provide about 90% of the pungent essence of hot pepper and have been previously described as anti-inflammatory.[27]

Capsaicin is hypothesised to diminish pain via reduction of compound P, a type of neuropeptide that regulates the transfer of signals for pain from the nerve endings to the cerebral cortex and the production of inflammatory cytokines in joints.[28] Ethyl (methylthio) methyl disulfide (**2**) is a natural flavouring agent that has not been quantified in the fruits and could be a biomarker for the pepper.[27] It possesses anti-oxidative, anti-mutagenic, anti-inflammatory and anti-carcinogenic properties linked with its capacity to control essential cellular enzymatic function while the *n*-hexadecanoic acid blocks phospholipase A2 thus eliciting an anti-inflammatory effect.[29] Capsaicin from *C. chinense* and its derivatives dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin possess anti-inflammatory activity via a conventional pharmacological and functional desensitization.[29]

Anti-inflammatory effect of extract

The anti-inflammatory effect of *Capsicum chinense* fruit was evaluated using two models- egg albumin-induced hind paw oedema and xylene-induced ear oedema models.

The anti-inflammatory effect of *Capsicum chinense* on the egg albumin-evoked hind paw oedema was expressed as the inhibition (%) using the average paw volume of the treatment group relative to the untreated as shown in Figure 3. The extract significantly ($p < 0.05$) elicited a dose-dependent inhibition of inflammation with higher doses causing higher inhibition. The inhibition by 200 mg/kg dose of extract peaked at 4 h and maintained a plateau between the 4th and 5th hour while the 50 and 100 mg/kg doses peaked at 3 h with a decline in the pattern of inhibition of inflammation. The anti-inflammatory activity of *C. chinense* was evaluated by egg albumin-induced hind paw and xylene-induced ear oedema models in experimental rats. In the egg albumin-induced hind paw oedema model, the extract (200 mg/kg) elicited 68% inhibition of hind paw oedema, slightly lower than indomethacin, 10 mg/kg and significantly ($p < 0.05$) higher than the inhibitory effect of the 100 and 50 mg/kg doses with 3 to 4 h of treatment. The maximum effects were obtained at 4 and 3 h for 200 mg/kg and other doses respectively. Induction of inflammation using egg albumin is mediated by the initial secretion of histamine and serotonin during the mast cell degranulation phase. This is followed by the release of bradykinin and pain within 1-2 h and subsequent release of eicosanoids at 3-4 h.[30] The inhibitory effect of doses of *C. chinense* (50-200 mg/kg) with 3-4 h of treatment marked by the significant down-regulation in the release of vasoactive agents implicated in paw oedema suggested that *C. chinense* possesses a delayed anti-inflammatory activity.[28]

The xylene-elicited ear oedema test further validated this observed anti-inflammatory effect. The anti-inflammatory effect of *C. chinense* extract using the xylene-evoked ear oedema model showed a dose-dependent inhibition of ear oedema (Figure 4). The 100 and 200 mg extract per kg doses elicited significant effects ($p < 0.05$) when compared with the untreated. There was no significant difference between the anti-inflammatory effect of 200 mg/kg dose compared with indomethacin control in this model. The result also revealed that there was no significant difference between the inhibitory effects of *C.*

chinense (200 mg/kg) and the standard indomethacin. During the xylene-induced ear oedema phase, bradykinin and substance P which cause vasodilation and enhance vascular permeability are released.[31] The swelling of the ear caused by neurogenic inflammatory marker (substance P) is inhibited by the extract. Therefore, the overall anti-inflammatory effect of *C. chinense* may have been facilitated by the blockage of the release or action of substance P, bradykinin, serotonin or histamine.

The study identified several compounds with reported anti-inflammatory activity from the GC-MS analysis. More importantly, was that the compounds were of high relative abundance compared with other compounds. It is plausible, therefore, that the compounds **19**, **22** and **23** were responsible for the observed anti-inflammatory activity of *C. chinense*. However, these and other compounds fingerprinted in this study were not isolated, characterized, quantified or tested for their anti-inflammatory effect. The link between the anti-inflammatory effect of *C. chinense* extract and the compounds identified from the GC-MS investigation remains hypothetical until the isolation of the active constituents (which is currently in progress), characterization of the compounds by NMR and HRMS as well as the quantification of the anti-inflammatory compounds are completed.

Conclusion

The extract of *C. chinenese* possesses anti-inflammatory properties in egg albumin hind paw and ear oedema models. The GC-MS analysis identified many important compounds in the extract. The *n*-hexadecanoic acid, capsaicin and dihydrocapsaicin were detected in significant concentration in the extract and may account for the anti-inflammatory effect of *C. chinenese* fruit. The observed anti-inflammatory activity may have been via the inhibition of the release or action of inflammatory mediators such as substance P, bradykinin, serotonin or histamine.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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