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Antipyretic and Anti-Inflammatory Effects of *Ocimum gratissimum* in Male Wistar Rats

Bruno Chukwuemeka Chinko [a*] and Confidence Nhachikaru Orlu [b]

[a] Department of Human Physiology, Faculty of Basic Medical Sciences, University of Port Harcourt, Port Harcourt, Nigeria.
[b] Department of Biomedical Technology, School of Science Laboratory Technology, University of Port Harcourt, Port Harcourt, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Ocimum gratissimum (OG), commonly known as clove or African basil has a significant presence in the culinary world and has also been traditionally used as a remedy for a variety of health issues, such as fever and malaria. The present study evaluated the ameliorating effect of OG on fever and inflammation using Wistar rat models. OG used in this study was locally sourced and was extracted using ethanol by the method of Soxhlet to obtain *O.gratissimum* extract (OGE). Twenty (20) male Wistar rats were used for this study and were randomly grouped into four (4) groups of five (5) animals each. Groups I and II served as the negative and positive controls respectively and received distilled water and standard drugs respectively. Groups III, IV and V served as the experimental groups and received OGE at 200, 400 and 800mg/kg respectively. Anti-pyretic activities were determined using the brewer's yeast-induced pyrexia test while anti-inflammatory

**Corresponding author: Email: bruno.chinko@uniport.edu.ng;*

activities were determined using the albumin-induced oedema test. The result from the antipyretic study shows that OGE significantly lowered the rectal temperature in a dose-dependent manner after 1, 2, and 3 hours of treatment (P<0.05). The results reveal that a dosage of 800mg/kg of OGE induced a greater reduction in rectal temperature (8.57%) compared to paracetamol (3.62%). Similarly, the result from the anti-inflammatory study shows that OGE significantly reduced paw thickness in Wistar rats after 1, 2 and 3hrs of treatment in a dose-dependent manner (P<0.05). Data also show that 800mg/kg of OGE produced a greater reduction in paw thickness (41.28%) compared to diclofenac (31.17%). Based on the available data from the current study, it appears that ethanol extracts of *O. gratissimum* possess strong efficacy against fever and inflammation. These findings also show that OGE demonstrated a higher level of anti-inflammatory activity compared to antipyretic activity at a dosage of 800mg/kg. This study offers scientific evidence to support the traditional medicinal use of *Ocimum gratissimum* in treating malaria and other ailments associated with fever and inflammation.

Keywords: Ocimum gratissimum; fever; pyrexia; inflammation.

1. INTRODUCTION

Pyrexia, commonly referred to as fever is an increase in core body temperature above the normal range or thermoregulatory set points. Though the exact set points can vary for individuals, pyrexia is characterized by core body temperature above 38 - 40°C in adults [1-3]. This elevation in the body's internal core temperature is a typical natural or physiological process brought about by infectious causes or non-infectious causes such as inflammation, malignancy, or autoimmune processes [4-6]. These processes involve the release of immunological mediators, which trigger the thermoregulatory centre of the hypothalamus, leading to an increase in the body's core temperature. The physiology of fever involves a complex set of responses by the body, which is triggered by the release of pyrogens (fever-inducing substances) in response to infection or inflammation. While some pyrogens can act directly and immediately on the hypothalamic thermoregulatory centre, others can act indirectly, taking a long time to produce the effect. Exogenous pyrogens act by inducing host cells, such as leukocytes and macrophages, to release fever-producing mediators (e.g interleukin-1), the phagocytosis of bacteria and breakdown products of bacteria present in the blood leads to the release of endogenous pyrogens into the circulation [2,7]. These endogenous pyrogens produce pyrexia by the induction of cyclooxygenase 2 (COX-2), activation of the arachidonic acid cascade, and enhanced biosynthesis of prostaglandin E2 (PGE2) by hypothalamic vascular endothelial cells which affects the set point of the hypothalamic thermoregulatory centre. Pyrexia is also seen in noninfectious disorders such as myocardial infarction, neoplasms and pulmonary embolism due to the action of the injured or abnormal cells to provoke the production of pyrogens [2]. Anti-pyretic agents act by the inhibition of PGE2 synthesis, directing the action on the hypothalamus to inhibit the synthesis of COX-2 or increasing heat dissipation from the body which helps to lower core body temperature [3,8].

Inflammation is a complex physiological process that involves the coordinated response of immune cells and molecules in the body in response to harmful stimuli such as injury, pathogens, toxic chemicals and irradiation [9,10]. The primary goal of inflammation is to eliminate the harmful agent and initiate the repair of the damaged tissue, hence serving as a defence mechanism crucial to optimal health [11,12]. Inflammation can be induced by exogenous or endogenous means. Exogenous inflammation induction refers to the stimulation of the immune system by external factors, such as infectious agents, toxins, or allergens. These external factors trigger an immune response that leads to inflammation. Endogenous inflammation induction, on the other hand, refers to the stimulation of the immune system by internal factors, such as damaged cells, stress, or metabolic imbalances. These internal factors can activate immune cells and signaling pathways, leading to inflammation [13,14]. The inflammatory response involves a coordinated activation and enhancement of various signaling processes that ensure that detrimental stimuli are recognized, appropriate inflammatory pathways are activated, inflammatory markers are released and inflammatory cells are recruited to resolve the cause of the inflammation [10,11]. Chronic inflammation can contribute to the development

of various diseases, including cancer, autoimmune disorders, and cardiovascular disease [11,15]. Anti-inflammatory agents act by reducing or suppressing the inflammatory response in the body by inhibition of pro-inflammatory cytokines, suppression of leukocyte activation, inhibition of PGE-2 and COX-2 synthesis, inhibition of phospholipase A2 (PLA2), modulation of immune response and antioxidant activity [16-18].

The prevalence of side effects associated with synthetic drugs has resulted in a significant surge in interest towards natural products, leading to a rise in research dedicated to exploring their potential benefits [19-21]. Over the past 20 years, the utilization of natural plant products as therapeutic remedies for fever and inflammation has gained increasing recognition thanks to ongoing research and the comparatively lower occurrence of adverse effects compared to synthetic medications [22,23]. Several plants have been screened for their antipyretic [24-26] and anti-inflammatory activities [27-29]. *Ocimum gratissimum* (OG) is a species of plant in the Lamiaceae family, also known as the clove basil or African basil. Mostly valued for its culinary uses, its leaves are commonly used to add flavour to dishes [30,31]. It is native to Africa and southern Asia and is widely used in traditional medicine for various ailments, including respiratory and digestive issues, fever, and malaria. In Nigeria, OG is known by several local names by different ethnic groups. It is known as *Tan-motsungi-wawagi*, *Ireru, Dai doya ta gida*, *Efinrin ajase* and *Nchanwu* by the Nupe, Ebira, Hausa, Yoruba and Igbo respectively [32,33]. *Ocimum gratissimum* is widely applied in the traditional treatment of high fever, epilepsy, stomachache, diarrhoea, haemorrhoids and helminthiasis [30,34-36]. The chemical composition of plants can vary depending on the location in which they are grown due to environmental conditions, such as soil type, climate, and availability of nutrients [37,38]. *Ocimum gratissimum* grown in Nigeria has shown significant quantities of carbohydrates, alkaloids, terpenoids, phenols, tannins, flavonoids, anthraquinones, sterols and saponins and essential oils rich in eugenol, thymol, and β-caryophyllene [31,32,39]. These phytochemical components confer on OG, a wide range of pharmacological activities. Documented scientific reports have highlighted it's antioxidant [34,40], antifungal [41,42], antibacterial [43,44], anti-diabetic [45,46], immunomodulatory [47,48], anti-ulcer [49,50], anti-cancer [51,52], anti-hypertensive [53,54], analgesic [55,56] and anti-inflammatory [57,58] activities. Although the pharmacological activities of our local variety have been mentioned, there is a lack of data on how it affects fever and inflammation. To address this knowledge gap, our study aims to assess the impact of OG on fever and inflammation using Wistar rat models.

2. MATERIALS AND METHODS

2.1 Source and Preparation of Plant Materials

Freshly harvested leaves of *Ocimum gratissimum* were purchased from the local Rumuoduomaya market in Port Harcourt, Nigeria. The leaves were authenticated at the Plant Science and Biotechnology Department of the University of Port Harcourt. The fresh leaves were air-dried for 2 weeks and crushed into a coarse powder, ready for extraction. The coarse powder was then extracted by the method of Soxhlet [59] using ethanol (99.5%). *Ocimum gratissimum* extract (OGE) was refrigerated at 5ºC pending administration.

2.2 Research Animals

For the study, a total of 20 male Wistar rats (weighing between 180 and 200g) were obtained from the Animal house of the Department of Human Physiology. The rats were kept in standard rat cages under hygienic conditions, with temperature maintained at 25-28ºC and humidity at 40-60%. Additionally, a 12-hour light/dark cycle was maintained. The rats were given access to standard rat chow and water ad libitum, and they were allowed to adjust to their new surroundings for four (4) weeks. The rats were made to fast overnight (12 hrs) before the start of the experiments.

2.3 Experimental Design

Twenty (20) male Wistar rats were randomly grouped into three (4) groups of five (5) animals each. Groups I and II served as the negative and positive controls respectively and received distilled water and standard drugs respectively. Groups III, IV and V served as the experimental groups and received OGE at 200, 400 and 800mg/kg respectively.

2.4 Brewer's yeast-induced Pyrexia Test

Before animal experimentation, the rectal temperature of the Wistar rats was measured

using a well-lubricated digital thermometer (CONTEC HK-908). Brewer's yeast (NOW Brewer's yeast, NOW foods, USA) was locally sourced from a retail store and used to induce pyrexia using a previously established protocol [60,61]. The Wistar rats were administered a subcutaneous injection of 20 ml of brewer's yeast (containing 20% brewer's yeast in normal saline), which resulted in the induction of fever. Post-induction rectal temperatures were taken after 1, 2 and 3 hrs. The animals were then treated as follows: Group I (negative control) received distilled water, Group II (positive control) received paracetamol (Emzor Pharmaceuticals, Nigeria) at 15mg/kg while Groups III, IV and V received OGE at 200, 400 and 800mg/kg respectively by oral gavage. Post-treatment rectal temperatures were after 1, 2 and 3 hrs.

2.5 Albumin-induced Oedema Test

Before animal experimentation, the animal's right hind paw thickness was recorded using a digital Vernier calliper (LT-YB06-1 Jinhua Longtai Tools Co., Ltd, China). Egg albumin was used to induce oedema using an established protocol [62,63]. The Wistar rats were administered a sub plantar injection of 0.1ml of egg albumin which resulted in inflammation of the hind paw. Post-induction rat's hind paw thickness was recorded after 1, 2 and 3 hrs. The animals were then treated as follows: Group I (negative control) received distilled water, Group II (positive control) received diclofenac (Hovid, Malaysia) at 1.5mg/kg while Groups III, IV and V received OGE at 200, 400 and 800mg/kg respectively by oral gavage. Post-treatment paw thickness was recorded after 1, 2 and 3 hrs.

2.6 Statistical Analysis

Data obtained from antipyretic and anti-inflammatory studies were analyzed using IBM Statistical Product and Service Solutions (SPSS version 25). The mean and standard error of the mean were calculated for rectal temperature and paw thickness. The means were compared using the analysis of variance (ANOVA) followed by a least significant difference (LSD) post hoc analysis (ANOVA). A p-value less than 0.05 ($p<0.05$) was considered statistically significant.

3. RESULTS

Table 1 presents the effect of orally administering an ethanolic extract of *O.gratissimum* on the rectal temperature of rats with pyrexia induced by brewer's yeast. The findings demonstrate that OGE significantly lowered the rectal temperature of the pyretic rats in a dose-dependent manner after 1, 2, and 3 hours of treatment ($P<0.05$). Moreover, the results reveal that a dosage of 800mg/kg of OGE induced a greater reduction in rectal temperature (8.57%) compared to paracetamol (3.62%).

The impact of oral administration of ethanolic extract of *O.gratissimum* on the paw thickness of egg albumin-induced paw oedema in Wistar rats is presented in Table 2. The result indicates that OGE significantly reduced the paw thickness of the animals after 1, 2 and 3hrs of treatment in a dose-dependent manner ($P<0.05$). Data also show that 800mg/kg of OGE produced a greater reduction in paw thickness (41.28%) compared to diclofenac (31.17%).

4. DISCUSSION

In the last two decades, natural plant-based products have become increasingly recognized as therapeutic remedies for fever and inflammation due to continuous research and their lower incidence of adverse effects when compared to synthetic drugs. The rise in adverse effects linked with synthetic medications has resulted in a considerable increase in interest in natural products, leading to a surge in dedicated research to explore their potential benefits. The present study evaluated the effect of O*.gratissimum* on fever and inflammation using Wistar rat models.

4.1 Effects on Pyrexia

The experimental induction of fever using brewer's yeast is mediated by the action beta-glucan which is found in the cell walls of the yeast. It activates the immune system leading to the production of cytokines such as interleukin-1 (IL-1), tumour necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) which act on the hypothalamus to enhance the production of PGE2, a pyrogen which raises the body temperature [64,65]. Data from the present study shows that intrapleural injection of brewer's yeast was effective in inducing fever as indicated by a gradual rise of post-induction rectal temperature as shown in Table 1. Also, it was observed that oral administration of ethanolic extract of O*.gratissimum* (OGE) caused a significant reduction in rectal temperature of rats with brewer's yeast-induced pyrexia in a dose-

Table 1. The effect of *Ocimum gratissimum* on the rectal temperature of Wistar rats

Treatment	Initial Temp (ºC)	Post-induction rectal temperature (°C)			Post-treatment rectal temperature (°C)		
		1 hr	2 hrs	3 hrs	1 hr	2 hrs	3 hrs
Control	34.62±0.61	35.92±0.52	36.52±0.64	36.84±0.60	35.48±0.35	36.22±0.19	37.28±0.34
Para (15mg/kg)	36.40±0.17	36.94±0.07	37.34±0.18	37.04±0.32	35.50*±0.24	35.76*±0.20	35.70*±0.29
OGE 200mg/kg	35.48±0.14	36.66±0.19	36.64±0.23	37.02±0.02	36.10*±0.22	35.78*±0.31	35.92*±0.36
OGE 400mg/kg	36.02 ±0.25	36.56±0.27	36.00±0.22	36.86±0.29	36.32±0.24	35.96*±0.18	35.38*±0.42
OGE 800mg/kg	35.92 ±0.15	36.74±0.25	36.18±0.48	36.86±0.14	35.80±0.34	34.88*±0.33	33.70*±0.20

Values expressed as mean ± standard error of the mean

**Significant difference compared to 3 hrs post induction rectal temperature (P<0.05)*

Table 2. The effect of *Ocimum gratissimum* on the paw thickness of Wistar rats

Treatment	Initial Paw diameter (mm)	Post-induction paw thickness (mm)			Post-treatment paw thickness (mm)		
		1 hr	2 hrs	3 hrs	1 hr	2 hrs	3 hrs
Control	3.55±0.12	3.55±0.12	8.86±0.27	8.45±0.19	8.11±0.13	7.94*±0.12	7.68*±0.09
Diclo (1.5mg/kg)	3.68±0.12	8.43±0.30	8.42±0.52	8.31±0.38	6.75*±0.20	6.08*±0.24	5.72*±0.19
OGE 200mg/kg	3.89±0.13	8.70±0.11	8.89±0.11	8.76±0.14	7.28*±0.20	6.88*±0.22	6.44*±0.31
OGE 400mg/kg	3.44±0.08	8.57±0.12	8.74±0.10	8.43±0.11	6.95*±0.04	6.39*±0.09	6.02*±0.06
OGE 800mg/kg	3.98±0.09	8.78±0.22	8.92±0.21	8.43±0.25	6.66*±0.10	5.39*±0.17	4.95*±0.05

Values expressed as mean ± standard error of the mean

**Significant different compared to 3 hrs post induction paw thickness (P<0.05)*

dependent manner after 1, 2, and 3 hours of treatment (P<0.05).OGE at 200, 400 and 800mg/kg reduced fever by 2.97, 4.02 and 8.57% respectively. It was also observed that when compared to a standard drug, paracetamol (3.62%), OGE at 800mg/kg caused a greater reduction in rectal temperature (8.57%). The possible mechanisms of action could be attributed to its major phytochemical, eugenol which may have blocked the production of cytokines involved in fever response. Eugenol acts as an antipyretic agent by inhibiting the synthesis of prostaglandins, which are responsible for inducing fever and blocks the enzyme cyclooxygenase (COX), which is responsible for the synthesis of prostaglandins. It has also been shown to act on the central nervous system (CNS) depressant, acting on the hypothalamus to reset the thermoregulatory set point [66-68]. In addition to eugenol, O. *gratissimum* also contains other compounds that have been shown to have antipyretic effects, such as flavonoids and terpenoids. These compounds, similarly reduce fever by inhibiting the activity of COX-2, which reduces the production of prostaglandins that cause inflammation and fever [69,70]. This finding supports previous studies on the antipyretic activity of O. *gratissimum* [71,72].

4.2 Effects on Inflammation

Egg albumin is typically used in experimental models to cause inflammation. It is recognized by the immune system, triggering an immune response which involves the activation of immune cells such as macrophages, neutrophils, and T cells. These cells release various cytokines and chemokines that promote inflammation and attract other immune cells and inflammatory mediators such as prostaglandins, leukotrienes, and histamine. Hence, these mediators contribute to the development of inflammation, causing symptoms such as swelling, redness, and pain [73,74]. Data from the present study shows that the sub-plantar injection of egg albumin was effective in inducing inflammation as evidenced by a gradual rise of post-induction paw thickness shown in Table 2. Also, it was observed that oral administration of ethanolic extract of *Ocimum gratissimum* (OGE) caused a significant reduction in paw thickness in a dose-dependent manner after 1, 2, and 3 hours of treatment (P<0.05). OGE at 200, 400 and 800mg/kg paw thickness by 26.48, 28.48 and 41.28% respectively. It was also observed that a standard drug, diclofenac, caused a lesser reduction (31.17%) in paw thickness when compared with OGE at 800mg/kg (41.28). The anti-inflammatory activity of O. *gratissimum* is attributable to its bioactive constituents: eugenol, thymol, flavonoids and terpenoids. Eugenol and thymol, similar to their antipyretic effects inhibit the synthesis of prostaglandins which are inflammatory mediators involved in pain and inflammation [68,75,76]. Also, O. *gratissimum* has been shown to inhibit the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) [77-79]. These cytokines play a key role in the inflammatory response, so inhibiting their production can help reduce inflammation. Additionally, flavonoids and terpenoids are able to reduce fever by inhibiting the activity of COX-2, which reduces the production of prostaglandins. Furthermore, O. *gratissimum* has also been demonstrated to inhibit of nuclear factor kappa B (NF-κB) which is a transcription factor that regulates the expression of many pro-inflammatory genes. Hence, inhibiting NF-κB signalling can help reduce inflammation [69,70]. It is worth noting here that the antioxidant nature of O. *gratissimum* could have also played a part in its ability to reduce fever. Antioxidants scavenge reactive oxygen species (ROS) which cause oxidative stress and promote inflammation. By scavenging ROS, antioxidants can reduce oxidative stress and inflammation [80,81]. They may also arrest inflammation by inhibiting cytokine production and modulating inflammatory signalling pathways such as the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt pathway [82,83]. This finding supports previous studies on the anti-inflammatory activity of O. *gratissimum* [57,58].

5. CONCLUSION

The use of medicinal plants-derived natural products as therapeutic remedies for fever and inflammation has continued to gain attention due to their wide range of acceptability, availability, affordability and attendant minimal or no side effects. Based on the available data from the current study, it appears that ethanol extracts of *Ocimum gratissimum* possess strong efficacy against fever and inflammation. These findings also show that OGE demonstrated a higher level of anti-inflammatory activity compared to antipyretic activity at a dosage of 800mg/kg. This study offers scientific evidence to support the traditional medicinal use of *Ocimum gratissimum*

in treating malaria and other ailments associated with fever and inflammation.

ETHICAL APPROVAL

Animals used for the study were housed and handled in compliance with standard guidelines and care of the use of laboratory animals [30,31]. The research design and protocol were approved by the institutional research ethic committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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