

Original Research Article

Evaluation of topical anti-inflammatory and antipruritic activities of oatmeal with *in silico* validation

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Abstract

Purpose: To investigate the anti-inflammatory and antipruritic potential of *Avena sativa* (Oatmeal) extract using animal model and molecular docking simulation studies.

Methods: About 900 g of Quaker OatTM was extracted with 70 % methanol using Soxhlet method. The topical anti-inflammatory activity of the crude extract was screened by rat paw oedema. The percentage inhibition of oedema compared with that of control (diclofenac) was taken as anti-inflammatory activity as standard. *In vivo* antipruritic activity of the extract was performed using 20 %w/v 2,4-dinitrofluorobenzene, 1 %w/w of Croton oil as standard. Gel without the extract was used as negative control. Systemic molecular docking evaluation of compounds isolated from the extract was carried out against.

Results: Animal studies show that the Oatmeal extract possesses significant anti-inflammatory activities ($p < 0.05$) in comparison with the negative control, with not too promising results ($p > 0.05$) from the antipruritic assay. Docking result for COX-1 receptor antagonists showed 9,12 octadecadienoic acid, octadecanoic acid ethyl ester, methyl stearate with scoring function -7.7 ± 0.0 , -7.3 ± 0.07 , and -7.00 ± 0.08 Kcal/mol, respectively, comparable to Aspirin with scoring function of -7.1 ± 0.01 Kcal/mol. Using phosphodiesterase 4 (PDE4), receptor antagonist as a target for *in-silico* antipruritic validation shows that 9,12 octadecadienoic acid, with scoring function of -7.76 ± 0.08 possess drug-like potential as antipruritic agent, as it had zero violation of Lipinski's rule of 5.

Conclusion: The study showed that compounds isolated from *Avena sativa* crude extract possess high drug-like potential as an anti-inflammatory agent.

Keywords: Anti-inflammatory, Antipruritic, Oedema, *Avena sativa*, Cyclooxygenases-1, Phosphodiesterase-4

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INTRODUCTION

Avena sativa (Family Poaceae; Oat species), the fourth most important crop worldwide, is a cereal widely cultivated in Russia, Canada, United States, Poland, Finland, Australia, Germany,

China, Ukraine, Belarus and many other countries [1]. It is a functional food rich in nutrients like protein, lipids, minerals, and carbohydrates, with reported medicinal uses such as anti-inflammatory, anti-pruritic, antioxidant, immunomodulatory, anti-thrombotic,

and antimicrobial activities [2]. The medicinal uses may be due to its phytochemical contents.

Inflammation and itching are both immunological responses associated with pain, irritation, discomfort and often necrosis [3]. Non-steroidal anti-inflammatory drugs (NSAIDs) are often used in the management of pain and inflammation, but are intolerable in many due to peptic ulcer and allergic reactions [4]. Anti-inflammatory agents like diclofenac, indomethacin, and piroxicam inhibit the action of cyclooxygenase enzymes that catalyze the production of angiogenic substances, for example, prostaglandin, serotonin (5-HT) and adenosine, which are inflammatory mediators [4]. Corticosteroids such as dexamethasone and betamethasone are commonly used in the control of itching both topically and systemically, with often serious and debilitating side effects such as elevated blood sugar, fluid retention, weight gain, and hypothalamic pituitary adrenal (HPA) axis suppression [5].

Bioassay-guided extraction of *Avena sativa* (Oatmeal) was deliberately done to preserve bioactive compounds. This study is therefore aimed at using the methanolic extract of Oatmeal, which is a sort of food, for the possible development of lead compounds that will enhance the discovery of cheap, safe and effective anti-inflammatory and antipruritic drugs, hence a source of medicine.

EXPERIMENTAL

Sample collection

Two 450 g sachets of Quaker Oatmeal – Oat™ (made from 100 % whole Oat grain) were purchased from a supermarket in Abraka, Delta State, Nigeria (GPS lat. 5.7902, log. 6.1047) on the 10th of June, 2024.

Sample extraction

About 900 g of Quaker Oatmeal was weighed using a weighing balance and extracted in 70 % 500 ml methanol using Soxhlet apparatus at a temperature of 60°C for 24 hours. The extract was filtered using Whatman No. 1 filter paper, frozen and then evaporated using Heidolph rotary evaporator by rotating the flask in a heated bath at 60°C. The freeze-dried extract was stored at 4°C until used for further analysis.

Formulation of topical gel

About 100 g of Carbopol was placed in a beaker and dispersed in distilled water with constant

stirring using a mechanical stirrer for 30 mins at 1200 rpm. The methanol extract dissolved in 100 ml ethanol was added to the thoroughly dispersed Carbopol in a beaker and mixed. A total of 20 g gel of different strengths (10, 5, and 2 % w/w) of the extract was prepared in duplicate with a gelling agent carbopol and Tween 80, using mechanical stirrer. Dropwise addition of triethanolamine was then added to adjust the pH to neutral, mixed well until a clear, consistent gel was obtained. A gel to be used as control was similarly prepared without the addition of the extracts, filled into sterile bottles and stored in a cool, dry place for topical determination of its anti-inflammatory and anti-pruritic actions [6]. The skin pH was maintained by dropwise addition of triethanolamine with continuous stirring.

Animal handling

Weighed Wistar rats of both sexes (300 – 400 g) were used for *in vivo* determination of topical anti-inflammatory and antipruritic activities of the methanolic extract of Oatmeal, taking into cognizance international principles and local regulations concerning the care and use of laboratory animals. The animals were procured from the animal house in the Department of Pharmacology and Therapeutics, Faculty of Basic Medical Science, Delta State University, Abraka, were allowed to have free access to standard diet and water and were kept in the animal house of Department of Pharmacology and Therapeutics, Faculty of Pharmacy, Delta State University, Abraka at an ambient temperature of about 30 °C and 45 to 55 % of relative humidity with a 12 h light/dark cycle for 2 weeks for acclimatization. Animal experimental protocol was in accordance with the approval of the institutional animal ethical committee of the Faculty of Pharmacy, Delta State University, Abraka, Delta State, Nigeria, with reference no. REC/PHC/DEL/25/07/10.

In vivo anti-inflammatory assay

The anti-inflammatory activities of methanol extract of oatmeal were screened by carrageenan induced raw paw oedema assay. The rats of both sexes were divided into 5 groups of six each. Group 1 was treated with the gel without the Oatmeal extract to serve as negative control, group 2 – 4 were topically treated with 2, 5, and 10 % w/w of methanol extract, respectively. Group 5 was administered with a standard topical anti-inflammatory drug, Diclofenac 1 %w/w (Diclomol manufactured in India by Kremant Pharmacy Ltd) as positive control. Oedema was induced by subcutaneous

injection of 100 µL of 1 % carrageenan solution in the plantar aponeurosis of the right hind paw [7]. One hour after carrageenan injection, oedema was first measured at zero time, coinciding with one hour post carrageenan use and then at 1, 2, 3 and 24 h after injection of drug by a volume displacement method using a digital plethysmometer. The percentage inhibition of Oedema compared with that of the control was taken as anti-inflammatory activity. The percentage inhibition of Oedema was determined using Eq 1 [3].

$$\text{Inhibition (\%)} = (A-B/B)100 \dots\dots\dots (1)$$

Where A represents the paw volume of the control group at the corresponding time and B represents the paw volume of the test group at the same time.

***In vivo* antipruritic determination of oatmeal extract**

Male rat of 8 weeks was used for the behavioural experiment. All the animals were habituated in a room with a 12h light/dark cycle at a temperature of about 30°C. All animal experiments required the approval of the institutional ethical committee of the Faculty of Pharmacy, Delta State University, Abraka, Delta State, Nigeria, with reference no. REC/PHC/DEL/25/07/10.

Pruritic model

A total of 20 rats of both sexes were divided into 5 groups and were painted with 10 mL 20 %w/v 2,4-dinitrofluorobenzene on the necks of the rats, shaved 2 days earlier and the behavior of rat was recorded by video for 1 h. The gel (2, 5, and 10 %w/w), 10 %w/w Croton oil (Eurax cream) manufactured by Thornton and Ross Ltd, UK, gel devoid of the extract was applied topically as positive and negative control, respectively, every 8 hours for 2 days.

Scratching number was defined as the number of times the hind limbs scratched the neck [8]. One bout of scratching was defined as the rat lifting its hind paw towards the painted side of the neck to scratch until it either licked or bit the hind paw or placed it back down on the floor. The percentage inhibition of scratching was calculated using Eq 2.

$$\text{Antipruritic activity (\%)} = (B_v - B_t/B_v)100 \dots\dots (2)$$

Where, B_v is the bout of scratching in vehicle group, B_t is the bout of scratching in treatment group [9].

***In silico* anti-inflammatory activity**

A total of 15 compounds isolated from Oatmeal extract were used for molecular docking evaluation into the binding site of cyclooxygenase (COX)-1 enzyme, a key enzyme that catalyzes the production of prostaglandins responsible for inflammatory responses. This is necessary in developing an insight into the putative intermolecular interaction and evaluating the possible binding pattern responsible for the inhibitory activities of the studied compounds [10].

Retrieval of protein structure

Ligand compound scandium (SCs) bound at the active site of Cox-1 at 2.67 Å resolution retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank and observation of its major role was done. Protein preparation was done by retraining protein in PDB format from protein Databank protein preparation. Wizard Maestro version 11.1 was used for refining the structure, with removal of water and optimization was done. For field, OPLS3 was used for minimization of heavy atom molecules at Root Mean Square Deviation (RMSD).

Ligands were prepared by selecting the isolated compound and downloading them from Pubchem data base. All the structures were downloaded in 2D SDF format. Ligand preparation was done using Ligprep, while force-field OPLS3 was used for energy minimization to convert 3D structure from 2D structure [11].

***In-silico* evaluation of antipruritic activity of bioactive compound of oatmeal extract**

Molecular docking a tool that can help identify potential interactions between bioactive compounds and disease targets by evaluating the best orientation of a ligand and protein binding sites, was used.

Qiwei antipruritic model

The main components of Qiwei model in molecular docking, like Quercetin, Kaempferol and β-sitosterol has good binding ability with targets such as EGFR, ESRI, IL6, PPARG and TP53.

Statistical analysis

Statistical analysis was performed using SPSS version 13 to evaluate significant differences between groups. In all analyses, *p* < 0.05 is

considered to be statistically significant. Data was presented using mean and standard deviation.

RESULT

The results of the *in vivo* topical anti-inflammatory activities of the Oatmeal extract are presented in Table 1.

From Table 1 below, it was observed that there was no significant difference between the topical anti-inflammatory activity of the different concentrations of Oatmeal extract (10 % w/w, $p \leq 0.08$, 5 % w/w, $p \leq 0.003$ and 2 % w/w, $p \leq 0.004$) and diclofenac gel with $p \leq 0.001$. The control had a p-value of 0.736 in comparison with the extract. This result shows that the methanol oatmeal extract has good potential as a topical anti-inflammatory agent. According to some *in vitro* studies, the influence of various concentrations of extracts of medicinal plants and their nanoparticles was verified on the anti-inflammatory effects they exert on cell models [12-14]. Natural substances like crude extracts, isolated compounds, and essential oils obtained from different parts of medicinal plants have traditionally been utilized in medical, nutraceutical, cosmeceutical, and agricultural fields. There is significant and ongoing research interest in these natural products from medicinal plants and their extracts, particularly for their role in treating human inflammatory conditions and creating modern pharmaceuticals [15].

In Table 2, the result shows a notable difference between the anti-pruritic activities of Crothamiton (Eurax cream) and different concentrations of

Oatmeal extract with p -values of 0.056, 0.694 and 0.341 for 10, 5 and 2 %w/w, respectively, with non-significant differences. Crothamiton cream and control have p -values of 0.004 and 0.849, respectively. Chronic itching, or pruritus, is a pervasive and uncomfortable symptom associated with various skin diseases (e.g., atopic dermatitis, hives) and systemic conditions (e.g., kidney failure, liver disease, diabetes). This itch-scratch cycle frequently leads to skin damage and exacerbates the primary illness, particularly in cases like atopic dermatitis. Consequently, preventing itch-driven scratching is crucial for enhancing patient well-being and managing the original disease. Our findings indicate that oatmeal methanol extract is a poor choice for an anti-itch remedy [16]. Table 3 and Table 4 revealed that 9,12 Octadecadienoic acid, Octadecanoic acid ethyl ester, Methyl stearate, with scoring function -7.7 ± 0.0 kCal/mol, -7.3 ± 0.07 kCal/mol and -7.00 ± 0.08 kCal/mol, respectively, are comparable to Aspirin with a scoring of -7.1 ± 0.01 kCal/mol.

DISCUSSION

Cyclooxygenase 1 (COX-1) plays a major role in anti-inflammatory responses by contributing to the production of prostaglandins, which are important mediators of inflammation, pain and other physiological processes, including homeostasis, blood clotting and neuro-inflammation, where its presence in microglia, which are brain immune cells, is evident. While COX-2 is primarily induced during inflammatory events, COX-1 is constitutively expressed in many tissues even in the absence of inflammatory stimuli.

Table 1: *In vivo* evaluation of anti-inflammatory activity of oatmeal extract

Time (h)	Percentage (%) inhibition of Oedema (mL)				
	Diclofenac gel	10 %w/w	5 %w/w	2 %w/w	Control
0	0.4	0.4	0.4	0.4	0.4
1	0.6	0.7	0.6	0.6	0.7
2	1.0	1.0	1.0	1.0	1.5
3	0.9	1.0	0.9	1.0	1.6
24	0.5	0.6	0.4	0.6	1.0

Results are means of triplicate determinations

Table 2: Determination of antipruritic activity of Oatmeal extract

Time (h)	Mean percentage reduction in scratching time				
	Crothamiton	10 %w/w	5 %w/w	2 %w/w	Control
8	20	18	10	5	1
16	40	35	30	10	5
24	60	55	40	18	7
32	80	70	45	20	8
40	85	80	50	25	9
48	98	90	34	30	11

Key: p -values ≤ 0.05 is not significant

Table 3: *In silico* anti-inflammatory activity determination of bioactive compounds in Oatmeal extracts (Cyclooxygenase-1)

Ligand	Binding energy (kCal/mol)				Mean±SD
	1	2	3	4	
Nimesulide	-8.32	-8.34	-8.28	-8.28	-8.30 ± 0.03
Ibuprofen	-8.05	-8.06	-8.04	-8.07	-8.06 ± 0.01
Naproxen	-8.02	-8.02	-8.01	-8.01	-8.01 ± 0.01
9,12-Octadecadienoic acid (Z, Z)-, methyl ester	-7.70	-7.81	-7.73	-7.78	-7.76 ± 0.05
Octadecanoic acid ethyl ester	-7.37	-7.31	-7.20	-7.33	-7.30 ± 0.07
Aspirin	-7.10	-7.11	-7.11	-7.12	-7.11 ± 0.01
Methyl stearate	-6.94	-7.01	-6.95	-7.11	-7.00 ± 0.08
2-Octylcyclopropene-1-heptanol	-6.90	-6.87	-7.09	-6.85	-6.93 ± 0.11
9,12-Octadecadienoyl chloride	-6.81	-6.75	-6.93	-6.76	-6.81 ± 0.08
Octadecanoic acid, 2-hydroxy-1,3-propanediyl e	-6.64	-6.84	-6.73	-6.65	-6.71 ± 0.10
9-Octadecenoic acid (Z)-, methyl ester	-6.74	-6.74	-6.45	-6.58	-6.63 ± 0.14
Hexadecanoic acid, 1-(2-aminoethoxy) hydro	-6.57	-6.46	-6.58	-6.72	-6.58 ± 0.11
11,14,17-Eicosatrienoic acid	-6.19	-6.42	-6.49	-6.94	-6.51 ± 0.31
Decanamide, N-(2-hydroxyethyl)-	-5.93	-5.85	-5.77	-5.98	-5.88 ± 0.09
Octanamide, N-(2-hydroxyethyl)-	-5.51	-5.41	-5.51	-5.43	-5.46 ± 0.05
Propan-2-ol, 1-(2-isopropyl-5-methylcyclohexy	-3.18	-3.18	-3.18	-3.18	-3.18 ± 0.00

Key: Data are present as Mean ± SD; n = 4

Table 4: *In silico* anti-inflammatory activity determination of bioactive compounds in Oatmeal extracts (Phosphodiesterase 4)

Ligand	Binding energy (kCal/mol)			Mean±SD
	1	2	3	
N-benzyl-2-{6-((3,5-dichloropyridin-4-yl) acetyl)-2,3-dimethoxyphenoxy} acetamide	-9.19	-9.15	-9.22	-9.19 ± 0.04
9,12-Octadecadienoic acid (Z, Z)-, methyl ester	-7.14	-7.20	-7.11	-7.15 ± 0.05
11,14,17-Eicosatrienoic acid, methyl ester	-6.54	-6.55	-6.22	-6.44 ± 0.19
Octadecanoic acid ethyl ester	-6.50	-6.32	-6.48	-6.43 ± 0.10
Methyl stearate	-6.41	-6.42	-6.37	-6.40 ± 0.02
Octadecanoic acid, 2-hydroxy-1,3-propanediyl e	-6.19	-6.40	-6.53	-6.37 ± 0.17
9,12-Octadecadienoyl chloride	-6.31	-6.25	-6.54	-6.37 ± 0.15
9-Octadecenoic acid	-6.08	-6.15	-6.37	-6.20 ± 0.16
9,12-Octadecadienoyl chloride, (Z, Z)-	-6.10	-6.40	-6.10	-6.20 ± 0.17
Hexadecanoic acid, 1-(2-aminoethoxy) hydro	-5.95	-6.27	-6.21	-6.14 ± 0.17
Decanamide, N-(2-hydroxyethyl)-	-5.92	-6.11	-6.14	-6.05 ± 0.12
Octanamide, N-(2-hydroxyethyl)-	-5.70	-5.77	-5.82	-5.76 ± 0.06
Propan-2-ol, 1-(2-isopropyl-5-methylcyclohexy	-3.14	-3.14	-3.14	-3.14 ± 0.00

COX-1 is a target for non-steroidal anti-inflammatory drugs (NSAIDs) like Aspirin, Ibuprofen, and Diclofenac (non-selective inhibitors of cyclooxygenase), which inhibit activity and reduce prostaglandin production.

Aspirin has been used for many years as an analgesic and anti-inflammatory drug, but its use is currently limited to the prevention of cardiovascular diseases at a low dose as a result of its adverse effect including peptic ulcer, GIT perforation and bleeding. These 3 compounds: 9,12 Octadecanoic acid, Octadecanoic acid ethyl ester and Methyl stearate are therefore potential lead compounds for further investigation as anti-inflammatory drugs. Phosphodiesterase 4 (PDE4) plays a key role in pruritus (itching), especially in inflammatory skin conditions like atopic dermatitis, contact dermatitis and eczema that come with underlying symptoms like itching. PDE4 inhibitors such as crisaborele for atopic

dermatitis increase levels of cyclic AMP (cAMP) and thus may reduce inflammation and relieve itching. PDE4 inhibitors, such as crisaborele for atopic dermatitis, are a therapeutic class of drugs that can be used in the management of pruritus (itching) associated with inflammatory skin conditions like atopic dermatitis. They act by increasing levels of cyclic adenosine monophosphate (cAMP) in skin cells, which helps to reduce inflammation and relieve itching. Propan-2-ol, 1-(2-isopropyl-5-methylcyclohexy with binding energy of -7.15 possesses high drug-like potential as an anti-pruritic agent, as it had zero violation of Lipinski's rule of 5.

CONCLUSION

Many compounds of medicinal value isolated from plants have been widely reported, but only a few have been subjected to pharmacological and

chemical studies. This study is aimed at validating the anti-inflammatory and antipruritic activities of Oatmeal using standard animal models and in-silico approaches commonly used in the prediction and confirmation of drug design. From statistical evidence, this study shows that Oatmeal may have significant anti-inflammatory activity but possesses insignificant antipruritic effect using animal studies.

In silico evaluation shows that compound 9,12 octadecanoic acid, octadecanoic acid ethyl ester and methyl stearate were found to be good candidates for further investigations as anti-inflammatory drugs. These compounds are most probably devoid of GIT side effects associated with NSAIDs and are suitable for use by peptic ulcer patients. In the *in – silico* anti-pruritic assay, 9,12 octadecadienoic acid possesses high drug-like potential as an antipruritic agent, as it had zero violation of Lipinski's rule of 5.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

The Research and Ethics Committee, Faculty of Pharmacy, Delta State University, Abraka, Nigeria, approved the study (approval no. REC/PHC/DEL/25/07/10).

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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