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ORIGINAL ARTICLE

Molecular docking and anti-inflammatory studies on extracts of *Prosopis africana* (Guill. & Perr.) Taubert and *Parkia biglobossa* (Jacq.) Benth (Fabaceae)

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ABSTRACT
Prosopis africana and Parkia biglobossa have been used since ancient times in Sierra Leone, Mali, Uganda and Nigeria in the treatment of anti-inflammatory related diseases. To evaluate the anti-inflammatory potentials of methanolic extracts and fractions of Prosopis africana, and Parkia biglobosa using in vivo and in silico methods. Their pulverized stem barks were extracted with methanol using Soxlet extraction technique. The crude extracts, CMEPR and CMEPK were partitioned into n-hexane, ethylacetate and methanol fractions. The extracts and fractions were subjected to anti-inflammatory studies using egg albumin and Xylene inflammatory models. Molecular docking was carried out on compounds identified via GC-MS with the aid of Vina. Molecular interactions between outstanding compounds and target enzymes was viewed using Discovery Studio Visualizer, 2020. The phytochemical analysis was carried out using standard method. The results obtained from both egg albumin and Xylene inflammatory models revealed dose dependent inhibition of edema in both plants with the greatest inhibition observed at higher doses. CMEPR: 23.65%, 35.89%, 69.23% (egg albumin model); 48.65%, 64.86%, 78.38% (Xylene model), CMEPK: 33.33%, 46.15%, 73.08% (egg albumin model); 67.57%, 78.37%, 91.89% (Xylene model) for 100,200 and 400 mg/kg respectively. The ethylacetate fraction of Parkia biglobosa exhibited the highest edema inhibition (94.59%) comparable with the standard drug Piroxicam (89.18%). Molecular docking revealed l-(+)-ascorbic acid 2,6-dihexadecanote as a potent inhibitor of both cyclooxygenase-2 (Cox-2) and tumor necrosis factor alpha (TNF-α) with a binding affinity of -12.6 and -9.0 kcal/mol respectively compared to standard drugs. This study revealed that methanolic extracts of Prosopis africana, and Parkia biglobosa possess promising anti-inflammatory properties with a mechanism of action that may involve the inhibition of Cox-2 and TNF-α. Further research is needed to identify the active compounds responsible for the activities observed.
***Keywords**: Prosopis africana, Parkia biglobossa, anti-inflammatory studies, In silico analysis, molecular docking.*

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INTRODUCTION

Inflammation, a vital biological process essential for maintaining the body's equilibrium, plays a pivotal role in combating pathogens and facilitating tissue repair. However, it also contributes to the development and persistence of numerous severe disorders, including rheumatoid arthritis, asthma, chronic inflammatory bowel diseases, type 2 diabetes, neurodegenerative diseases, and cancer [14]. Although several approved anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs, glucocorticoids, immunosuppressant drugs, and biologicals, exist, their effectiveness is often insufficient, and they may be accompanied by undesirable side effects. Consequently, scientists in both academia and

industry face an ongoing challenge to discover novel compounds with anti-inflammatory properties [7]. *Prosopis africana* is a remarkable tree species that holds a significant place in various African regions. Commonly known as the African mesquite, it boasts an array of attributes that make it highly valuable and versatile in different domains. In recent times, the medicinal significance of *Prosopis africana* has garnered attention as well. The bark and leaves of the plant have been traditionally used to alleviate inflammation, microbial infection, digestive disorders, respiratory ailments and other related conditions [5, 9, 17]. *Parkia biglobosa*, commonly known as the African locust bean or African mesquite, is a tree highly valued for its medicinal properties in traditional African medicine. Various parts of the tree, including the bark, leaves, seeds, and pods, are utilized for their therapeutic benefits including; indigestion, diabetes, pain relief, wound healing, antibacterial etc. [10, 1]. This study is designed to evaluate the anti-inflammatory potential of methanolic extract of *Prosopis africana,* and *Parkia biglobosa* and to evaluate the inhibitory potentials of compounds identified through GC-MS on cyclooxygenase-2 (Cox-2), and Tumor Necrosis Factor alpha (α) using *in silico* methods.

MATERIALS AND METHODS

Collection, Identification and Preparation of Plant Materials

Fresh stem barks of *Prosopis africana* and *Parkia biglobosa* were collected Okpuje, Nsukka in Enugu State, South East Nigeria and were authenticated by Mr A.O.Ozioko, a taxonomist in International Centre for Ethno medicine and Drug Development (InterCEDD), Nsukka. Their voucher specimens, PCG/UNN/0035 *Prosopis africana* (Guill. & Perr.) Taub. (Fabaceae) and PCG/UNN/0397 *Parkia biglobosa* (Jacq.) Benth (Fabaceae) were deposited in the herbarium of the department of Pharmacognosy and Environmental Medicine, University of Nigeria, Nsukka. The stem barks were air dried under shade for one month and ground into powder with a grinding machine.

Extraction and fractionation

The pulverized stem barks *Prosopis africana* (1kg) and *Parkia biglobosa* (1kg) was in each case extracted with 6 litres of methanol (MeOH) for 4 h using soxhlet extraction technique. The extracts were concentrated *in vacuo* using rotary evaporator to yield the crude methanol extract of *Prosopis africana* (CMEPR) and *Parkia biglobosa* (CMEPK). The CMEPR and CMEPK were separately adsorbed on silica gel (60-120 mesh) and fractionated with n-hexane, chloroform, ethyl acetate and methanol to obtain hexane fractions (HFPR, HFPK), chloroform fractions (CFPR, CFPK), ethyl acetate fractions (EFPR, EFPK) and methanol fractions (MFPR, MFPK). The percentage yields of the extracts and fractions were calculated. The crude extracts and their fractions were screened for antimicrobial activities.

Experimental Animals

Albino mice (22-30g) and adult Wister albino rats (170 – 210g) of both sexes were purchasd from the Department of Zoology, University of Nigeria Nsukka. The animals were kept and maintained under laboratory conditions of temperature, humidity, and light, and allowed free access to standard pelletized feed (Top Feeds Nig. Ltd) and water *ad libitum*. The use and care of the laboratory animals were in accordance with internationally accepted best practices as contained in the National Code of Conduct for Animal Research Ethics (NCARE) and approved by the local Ethics Committee of our institution (FPSRA/UNN/23/0055).

Anti-inflammatory Studies

Xylene-induced topical edema in mice

The effect of the compounds on acute topical edema was evaluated by a modification of the previously reported methods by Okoli *et al,* [12]. Adult albino mice (20 ± 5 g) of either sex were divided into groups of 5 animals. The treatment groups received the 100mg/kg, 200mg/kg and 400mg/kg dissolved in xylene (5 mg/ear) applied on the anterior surface of the right ear. Control animals received either equivalent volume of the phlogistic agent (xylene) or Piroxicam dissolved in xylene (5 mg/ear). Two hours after application, the mice were sacrificed and both ears removed. Circular sections (5 mm) of both the right (treated) and (untreated) ears were punched out using a cork borer, and weighed. Edema was quantified as weight differences between the two earplugs. The anti-inflammatory activity was evaluated as percent edema inhibition in the treated animals relative to the control animals using the relation.

$$\%\ Edema\ Reduction = \left[1 - \frac{Rt - Lt}{Rc - Lc}\right] x\ 100$$

Where Rt = mean weight of right earplug of treated animals; Lt = mean weight of left earplug of treated animals; Rc = mean weight of the right earplug of control (vehicle treated) animals; Lc = mean weight of the left earplug of control (vehicle treated) animals.

Egg albumen induced paw edema in rats

The test was carried out as previously reported by Osadebe *et al* and Okoli *et al* [13, 12]. The animals (n = 5, per group) were fasted for 5 h and deprived of water only during the experiment. The extracts, solvent fractions, column fractions solubilized in Normal saline (100mg/kg, 200mg/kg and 400mg/kg) were administered i.p. 30 min before the subplanta injection of the phlogistic agent (0.1 ml of fresh undiluted egg albumen). Control animals received Normal saline (5ml/kg) and Piroxicam (20 mg/kg). Paw volumes were measured by water displacement method at 0, 1, 2, 3 and 4 h after induction of edema. The anti-inflammatory effect was calculated at each time of observation as percent inhibition of edema in the animals treated with the substances under test in comparison with the vehicle treated animals. The percent inhibition of edema was calculated using the formula

$$\%\ Inhibition\ = \frac{(Vo - Vt)}{Vo} x\ 100$$

Vt is the volume of edema at corresponding time and Vo is the volume of edema of vehicle treated rats at the same time.

Statistical Analysis

Values of results are presented as mean ± standard error of mean (S.E.M). One-way analysis of variance (ANOVA) followed by Duncans multiple range test used statistical comparison between control and treatment groups. Statistical significance was accepted at $P<0.05$ confidence interval.

Molecular Docking

The crystal structures of cyclooxygenase-2 (Cox-2), and Tumor necrosis factor alpha (TNF-α), with PDB IDs, 5IKV, and 2AZ5, respectively were obtained from protein databank (www.rcsb.org). The existing ligands and water molecules were removed and Hydrogen molecules were added. SDF structures of celecoxib, dexamethasone, and other ligands were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The molecules were converted to mol2 chemical format using Open babel [11]. The protein and ligand molecules were further converted to pdbqt format using Autodock tools. Docking of the ligands to various protein targets and determination of binding affinities was carried out using Vina [15]. Molecular interactions between proteins and the ligands were compared to the reference drug and viewed with Discovery Studio 2020.

Table 1: Results of the anti-inflammatory effects of the crude methanol extracts of *Prosopis africana* and *Parkia biglobosa* stem barks on egg albumin-induced acute paw edema in rats

Treatment	Dose (mg/kg)	Mean edema (ml)			
		1hr	2hr	3hr	4hr
Crude extract *Prosopis africana* (CMEPR)	100	0.68 ± 0.08	0.60 ± 0.08	0.50 ± 0.10	0.38 ± 0.14
	200	0.62 ± 0.07	0.46 ± 0.04	0.30 ± 0.06	0.26 ± 0.24*
	400	0.48 ± 0.10	0.36 ± 0.07	0.24 ± 0.36*	0.16 ± 0.43**
Crude extract *Parkia biglobosa* (CMEPK)	100	0.56 ± 0.14	0.40 ± 0.00	0.34 ± 0.25	0.24 ± 0.18*
	200	0.52 ± 0.31	0.34 ± 0.11	0.30 ± 0.00	0.16 ± 0.66**
	400	0.28 ± 0.09*	0.58 ± 0.36**	0.10 ± 0.04***	0.06 ± 0.50***
Piroxicam	20	0.34 ± 0.06	0.18 ± 0.08**	0.14 ± 0.60***	0.08 ± 0.22***
Normal Saline	5ml/kg	0.76 ± 0.02	0.78 ± 0.37	0.76 ± 0.10	0.74 ± 0.15

Values are expressed as the mean ± S.E.M; n=5; ***P<0.001, **P<0.01, *P<0.05 significantly different compared with control (normal saline)

In egg albumin induced paw oedema model, an increase in paw thickness was seen in all animals throughout the observation period. In this study the paw volume of all the groups treated with CMEPR and CMEPK significantly ($P<0.05$) reduced from the first hour after oedema induction when compared with the control (Table 1). The extent of oedema inhibition increased with time. CMEPR at test doses of 100, 200 and 400mg/kg reduced the egg albumin induced oedema by 48.65%, 64.86% and 78.38% respectively at the 4th hour as compared to the standard drug, Piroxicam (89.18%). CMEPK at the same test doses reduced the egg albumin induced oedema by 67.57%, 78.37% and 91.89% respectively (Table 2). The anti-inflammatory activities of the extracts were observed to be dose dependent which may imply that within the limit of non-toxicity, a higher activity could be achieved at higher dose. In the entire study, the toxicity profile (LD_{50}) of CMEPR (> 5000mg/kg) and CMEPK (4171.33mg/kg) was taken into consideration in dose of the extract administered. At the 4th hour it was observed that higher doses of the extracts exhibited different levels of significant activity ($P< 0.001$, $P< 0.01$) showing high dimension of potency when compared with the control.

Table 2: Results of the Percentage inhibition of acute edema by the methanol extracts of *Prosopis africana* and *Parkia biglobosa* on egg albumin-induced acute paw edema in rats

Treatment	Dose (mg/kg)	Percentage inhibition of edema (%)			
		1hr	2hr	3hr	4hr
Crude extract *Prosopis africana* (CMEPR)	100	10.53	28.57	32.43	48.65
	200	18.42	45.23	59.46	64.86
	400	36.84	57.14	67.57	78.38
Crude extract *Parkia biglobosa* (CMEPK)	100	26.32	52.38	54.05	67.57
	200	31.58	59.52	59.46	78.37
	400	63.16	73.80	86.49	91.89
Piroxicam	20	55.26	78.57	81.08	89.18
Normal Saline	5ml/kg	-	-	-	-

Values are expressed as the mean ± S.E.M; n=5; ***P<0.001, **P<0.01, *P<0.05 significantly different compared with control (normal saline)

Table 3: Results of the anti-inflammatory effects of the crude methanol extracts of CMEPR and CMEPK on Xylene induced ear edema in Mice.

Treatment	Dose (mg/kg)	Edema (mm)	Percentage edema Inhibition (%)
Crude extract *Prosopis africana* (CMEPR)	100	5.80 ± 1.67	25.65
	200	5.00 ± 0.71	35.89
	400	2.40 ± 0.48**	69.23
Crude extract *Parkia biglobosa* (CMEPK)	100	5.20 ± 0.20	33.33
	200	4.20 ± 0.74	46.15
	400	2.10 ± 0.63***	73.08
Piroxicam	20	1.90 ± 0.51***	82.82
Normal saline	5 ml/kg	7.80 ± 1.12	-

Values are expressed as the mean ± S.E.M; n=5; ***P<0.001, **P<0.01, *P<0.05 significantly different compared with control (normal saline)

A dose dependent reduction of oedema was also observed in Xylene induced oedema model. At 100, 200 and 400mg/kg dose, CMEPR and CMEPK reduced the mice ear oedema by 25%, 35%, 69% and 33%, 46%, 73% respectively as compared to the standard drug, Piroxicam 82.82% (Table 3). Egg albumin and Xylene inflammatory models are well known animal models widely used to study anti-inflammatory activities of medicinal plants and anti-inflammatory agents. Egg albumin exerts its inflammatory effect by initiating the discharging of histamine and 5-HT (5- hydroxytryptamine or serotonin) while histamine cause inflammation by activating increased vascular permeability leading to amplified blood flow and vasodilation. This results to inflammatory signs such as redness and swelling [3]. The egg white, a foreign albumin presented to the intercellular space cause inflammation and oedema. Zylene initiate inflammation by the release of histamine, kinin, fibrinolysin and phospholipase A_2. These inflammatory mediators induce edema by vasodilation and increased vascular permeability [16].

Table 4: Results of the percentage inhibition of acute paw edema by the solvent fractions of *Prosopis africana* and *Parkia biglobosa*.

Treatment	Dose (mg/kg)	Inhibition of edema (%)			
		1hr	2hr	3hr	4hr
Ethyl acetate fraction of *Prosopis africana* (EFPR)	400	63.16	73.80	75.68	75.68
Methanol fraction of *Prosopis africana* (MFPR)	400	18.42	45.23	59.46	64.86
Ethyl acetate fraction of *Parkia biglobosa* (EFPK)	400	73.68	85.71	91.89	94.59
Methanol fraction of *Parkia biglobosa* (MFPK)	400	52.63	85.71	86.48	86.48
Piroxicam	20	55.26	78.57	81.08	89.18
Normal Saline	5ml/kg	-	-	-	-

Values are expressed as the mean ± S.E.M; n=5; ***P<0.001, **P<0.01, *P<0.05 significantly different compared with control (normal saline)

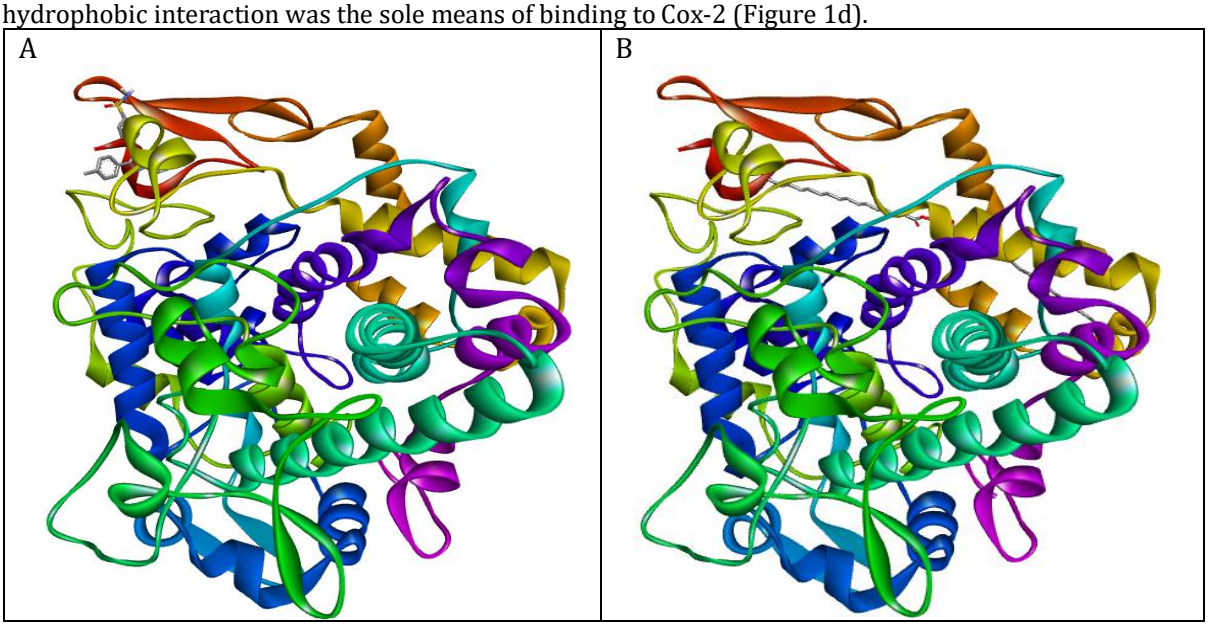
The results of anti-inflammatory activities of the ethylacetate and methanol fractions of CMEPR (EFPR, MFPR) and CMEPK (EFPK, MFPK) showed that at a singular dose of 400mg/kg, EFPR, MFPR, EFPK and

MFPK reduced the egg albumin induced oedema by 75.68%, 64.86%, 94.59% and 86.48% respectively at the 4th hour (Table 4). It is worthy to note that the activities EFPK and MFPK were very significantly ($P<0.001$). The standard drug, Piroxicam has analgesic, antipyretic and anti-inflammatory properties. Like other NSAIDs, its mechanism of action is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). It is a potent inhibitor of prostaglandin (PG) synthesis. Bioactive compounds present in plants account for their biochemical and pharmacological actions. The anti-inflammatory effect of herbal products may be due to the inhibition of the production of inflammatory cells or by suppressing the expression of inflammatory mediators or both. Flavonoids have an anti-inflammatory capacity since they inhibit the production of inflammatory mediators by modulating the arachidonic acid pathway, inhibiting several enzymes such as ATPase, prostaglandin, cyclooxygenase, lipoxygenase, NADH oxidase, protein kinase, hydrolases, peroxidases, tyrosinases and phospholipases. They also act by inhibiting or decreasing inflammatory activity by modulating the induced nitric oxide synthase enzyme and the cells involved with inflammation, inhibiting the production of pro inflammatory cytokines and modulating the activity of arachidonic acid pathways, such as cyclooxygenase (COX), Lipoxygenases (LOX) and phospholipase A_2 [2]. Another metabolite that may account for anti-inflammatory activity of the extracts is presence of Saponins. Saponins are steroid glycosides or polycyclic terpenes used for the synthesis of cortisone an anti-inflammatory agent and sex hormone. Tannins exert anti-inflammatory effects by scavenging of radicals and inhibition of inflammatory mediators, such as cytokines, inducible nitric oxide synthase and COX-2 [6]. This study justifies the use of the decoctions of stem barks of *P.africana* and *P. biglobosa* in treatment of inflammatory related diseases.

Table 5: Binding affinity of compounds identified in CMEPR and CMEPK to TNF-α and Cox-2

		Binding affinity (Kcal/mol)	
S/N	Compounds	Cox-2	TNF-α
R	Celecoxib	-9.8	-
R	Dexamethasone	-	-7.4
1	Metaraminol	-6.9	-5.5
2	L-(+)-Ascorbic acid 2,6-dihexadecanoate	**-12.6**	**-9.0**
3	Histamine, N-benzoyl-2-cyano-	-7.9	-6.1
4	1,2-Dichloro-4,5-dinitrobenzene	-7.2	-5.2
5	m_Guaiacol	-6.1	-4.6

l-(+)-Ascorbic acid 2,6-dihexadecanoate had a higher binding affinity (-12.6 kcal/mol) compared to standard Cox-2 inhibitor (celecoxib, -9.8 kcal/mol) (Table 5). Similarly, l-(+)-Ascorbic acid 2,6-dihexadecanoate had a higher binding affinity (-9.0 kcal/mol) for Cox-2 compared to dexamethasone's -7.4 kcal/mol. Two halogen bonds (Cys36, Pro154) were visualized in the binding of Cox-2 and celecoxib in addition to hydrophobic interactions (Figure 1c). For L-(+)-ascorbic acid 2,6-dihexadecanoate, hydrophobic interaction was the sole means of binding to Cox-2 (Figure 1d).



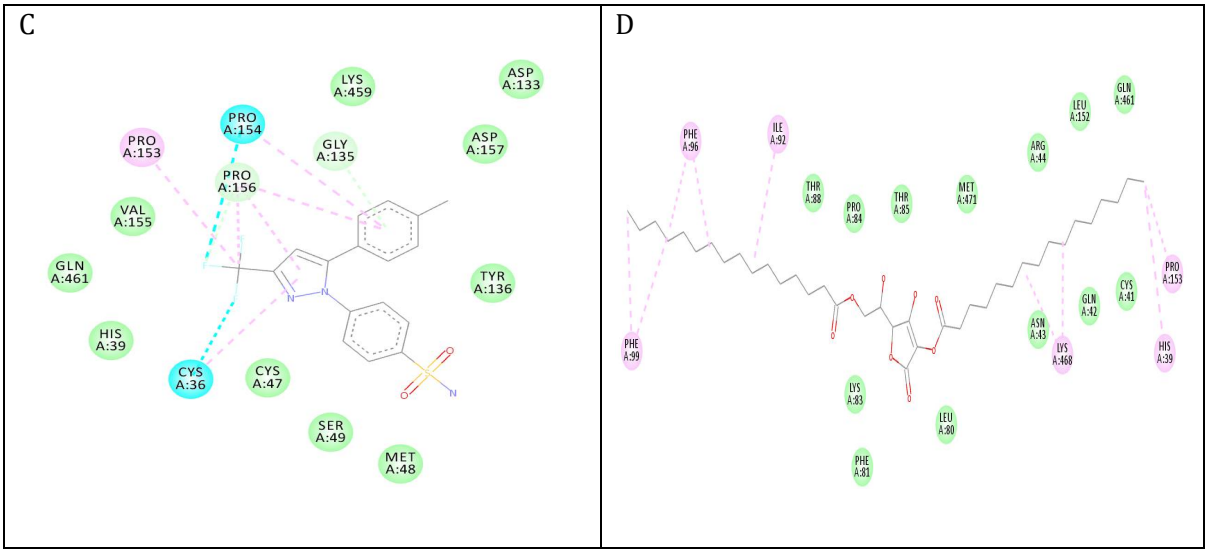


Figure 1: 3D view of the interaction between COX-2 and (a) Celecoxib (b) l-(+)-ascorbic acid 2,6-dihexadecanote. 2D view of the interaction between amino acids in the binding site of Cox-2 and (c) celecoxib (d) l-(+)-ascorbic acid 2,6-dihexadecanote

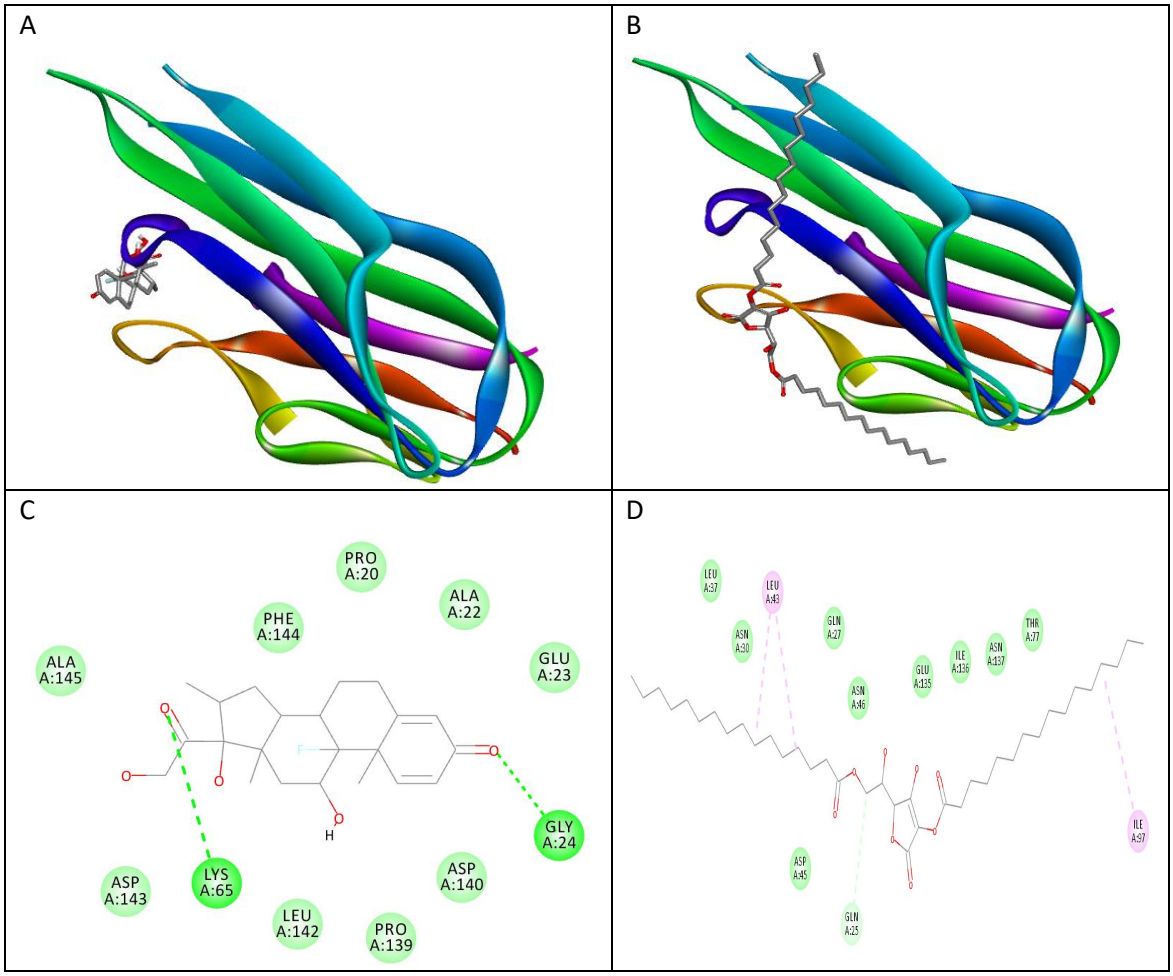


Figure 2: 3D view of the interaction between TNF-α and (a) dexamethasone (b) l-(+)-ascorbic acid 2,6-dihexadecanote. 2D view of the interaction between amino acids in the binding site of TNF-α and (c) dexamethasone (d) l-(+)-ascorbic acid 2,6-dihexadecanote

Dexamethasone formed two hydrogen bonds with Gly24, and Lys65 of TNF-α (Figure 2c). However, L-(+)-ascorbic acid 2,6-dihexadecanoate interacted with TNF-α via hydrophobic interactions with Leu43, Ile97

and carbon-hydrogen bond with Gln25 (Figure 2d). Ascorbic acid is widely recognized as a molecule with versatile anti-inflammatory properties [8]. Ascorbic acid has been reported to improve the body's resistance to oxidative stress and anti-inflammatory capacity by regulating the expression of antioxidant genes HO-1, GSH, SOD2 and inflammation-related genes NF-κB, IKKα, IL-6, TNFα, IL-8, IFN-γ at different time points (Du et al., 2022). This corroborates findings from this research and explains the remarkable binding affinity recorded for L-(+)-ascorbic acid 2,6-dihexadecanoate.

CONCLUSION

Methanolic extract of *Prosopis africana,* and *Parkia biglobosa* are possesses promising anti-inflammatory properties through its reduction of acute oedema and may exhibit other anti-inflammatory activity by inhibiting Cox-2 and TNF-α. These plants may therefore be further examined for consideration as alternative therapy for inflammatory related diseases

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CONFLICT OF INTEREST

The authors hereby declare that there is no conflict of interest.

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