






# Protective Role of *Aframomum melegueta* against Monosodium Glutamate-induced Prostate Damage in Rats



Asiat Na'Allah<sup>1</sup> , Umar Muhammad Ghali<sup>2,\*</sup> , Şevki Adem<sup>2</sup> , Nadia Mohammed Salama Kurzama<sup>2</sup> , Qendresa Hoti<sup>3</sup>  and Fatimah Abubakar<sup>1</sup>

<sup>1</sup>Department of Biochemistry, Faculty of Pure and Applied Sciences, Kwara State University, Malete, P.M.B. 1530, Ilorin, Oyo, Kwara State, Nigeria

<sup>2</sup>Department of Chemistry, Faculty of Science, Cankiri Karatekin University, Cankiri-18100, Turkey

<sup>3</sup>Department of Biochemistry, College of Medical Sciences "REZONANCA" Prishtina, Kosovo

## Abstract:

**Introduction:** Prostate cancer is among the most prevalent cancers in men, with increasing incidence, and the limited therapeutic options have stimulated interest in plant-based bioactive compounds as alternatives. *Aframomum melegueta* is widely utilized in ethnomedicine for various health issues and has drawn interest due to its promising therapeutic properties. This study investigated the protective and therapeutic role of ethanol seed extract of *Aframomum melegueta* (ESEAM) against MSG-induced prostate damage in rats, integrating *in vivo* experimental evidence with *in silico* analysis to establish its relevance in prostate-related drug discovery.

**Methods:** Male rats were divided into groups and induced with MSG with or without treatment using ESEAM or finasteride. Biochemical assays and histopathological evaluation were conducted to assess protective and restorative effects. Molecular docking was performed to predict interactions between phytochemicals and prostate damage-associated protein targets. Data were presented as mean  $\pm$  SEM and analyzed using one-way ANOVA followed by Tukey's post-hoc test ( $p < 0.05$ ).

**Results:** MSG exposure induced significant alterations in hematological and biochemical indices, with severe histopathological alterations. Compared with the control, ESEAM significantly ( $p < 0.05$ ) improved hematological indices and lowered liver and prostate markers, with histology confirming notable attenuation of prostate damage. Molecular docking revealed favorable binding interactions between ESEAM phytochemicals (552098, 296573, 5364759, and 296573) to prostate-related molecular targets.

**Discussion:** The observed biochemical, histological, and computational findings suggest that ESEAM exerts protective and restorative effects against MSG-induced prostate injury, possibly through bioactive compound-target interactions that modulate prostate-related pathways.

**Conclusion:** Collectively, these findings indicate that ESEAM displays protective and therapeutic effects and represents a promising drug candidate for further mechanistic and drug development.

**Keywords:** *Aframomum melegueta*, Monosodium glutamate, Prostate cancer, Prostate acid phosphatase, Prostate-specific antigen, Luteinizing hormone.

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\*Address correspondence to this author at the Department of Chemistry, Faculty of Science, Cankiri Karatekin University, Cankiri, 18100, Turkey; E-mail: [umarghali18@gmail.com](mailto:umarghali18@gmail.com)

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## 1. INTRODUCTION

Prostate cancer and other related prostate damage are the significant forms of malignancy in men, especially in developed countries, where most of the cases are diagnosed in men above 50 years of age [1]. There are no known causes of prostate cancer, but reports suggest that dairy factors are major risk determinants [2-4]. Hormones, mainly androgens and estrogens, have been highly involved in prostate carcinogenesis as well, but evidence from human models is also lacking. Nonetheless, the scientific explanation of prostate cancer biology suggests that androgen and possibly estrogen may be responsible. Infections (prostatitis, inflammation of the prostate) are also considered prostate cancer risk factors [5]. In addition, studies from experimental animals have shown that chemical agents, most especially those metabolically activated in the prostate, can trigger prostate carcinogenesis [6].

The sodium salt of glutamic acid, monosodium glutamate (MSG), dissociates in water to yield free sodium ions and glutamic acid [7], which stimulates synaptic receptors (glutamate receptors) on neuronal membranes and plays a central role in excitotoxicity. Its overstimulation by MSG can trigger signaling pathways linked to cell survival and proliferation [8], potentially mimicking mechanisms seen in neurological disorders, where glutamate excitotoxicity causes cellular stress. The toxic effects of MSG on the testis cause significant oligozoospermia and an increase in sperm morphology in a dose-dependent fashion in male Swiss albino rats [9, 10]. It has also been implicated in causing degeneration, testicular hemorrhage, alteration of sperm cell morphology, and population in male infertility [8, 11]. Furthermore, overuse of MSG as a flavor enhancer has been reported to be hepatotoxic [12]. In contrast, in the animal model, chronic MSG intake has been reported to induce kidney damage *via* oxidative stress [13, 14], and ROS formation, both of which contribute significantly to its nephrotoxic effect, thereby causing cellular and functional damage [15]. These suggest MSG can be a useful experimental model for studying chemically induced prostate damage.

Hormone therapy, radiation, surgical treatment, and chemotherapy are the currently available treatment options for prostate cancer and or damage. These treatments have shown remarkable improvement in patients, but have come up with adverse and toxic side effects, creating a need for alternative therapy with improved efficacy and safety profiles [15, 16]. Among available therapies, finasteride is widely used as a reference drug in both human and animal models. It is a selective 5 $\alpha$ -reductase inhibitor that prevents the conversion of testosterone to dihydrotestosterone (DHT), thereby suppressing androgen-driven prostate growth and carcinogenesis. It has been clinically approved for benign hyperplasia and investigated in prostate cancer chemoprevention trials [17]. The use of natural and dietary supplements, such as vitamin E, selenium, lycopene, and

green tea, is widely accepted in prostate cancer treatment [18-21]. According to the World Health Organization, about 65% of the global population feels safe with treating disease(s) with traditional medicine [22, 23] with India, China, and Africa, along with the USA, having an increased usage of complementary and alternative drugs within the last 2 decades [24, 25]. Approximately 80% of anticancer agents are derived from plants and other natural resources; however, they have not been explored in the management of prostate cancer or prostate-related damage [26-28].

*Aframomum melegueta* is a Zingiberaceae family plant spice widely cultivated in Africa for its valuable seeds. It is an herbaceous perennial plant native to swampy habitats along the West African coast. It is commonly known as "grains of paradise," "melegueta pepper," "alligator pepper," "guinea grains," or "guinea pepper" [29, 30]. Apart from their culinary uses, the seeds of *A. melegueta* are claimed to have antioxidant [31], anti-cancer [32-34], anti-diabetic [35, 36], anti-inflammatory [37], and hepatoprotective activity [38]. Okeke *et al.* [39] reported that the seed of *A. melegueta* helps in improving penile rigidity and erectile function. Despite the numerous therapeutic applications and scientific reports on this plant, there is no report on the effectiveness of this plant on prostate cancer or prostate-related damage with respect to prostate markers *in silico*. Given the limitations, we used this plant to evaluate its therapeutic potential for treating prostate damage using experimental and computational approaches.

## 2. MATERIALS AND METHODS

### 2.1. Chemicals

Monosodium glutamate and finasteride were purchased from Sigma Chemical Company (St. Louis, MO, USA). Prostate-specific antigen (PSA) and luteinizing hormone (LH) ELISA assay kit (Calbiotech Inc., CA, USA), interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) ELISA assay kit (Bioassay Tech. Lab. Shanghai, China). All other chemicals and solvents used were of analytical grade and the highest purity.

### 2.2. Collection and Authentication of the Plant Part

*A. melegueta* seeds were collected from Oja Oba Market in Ilorin, Kwara State. It was identified and authenticated at the Herbarium Unit of the Department of Plant Biology, University of Ilorin, where a voucher number, UILH/001/2019/1166, was assigned and deposited in the University Herbarium. Prior to extraction, the shells of *A. melegueta* seeds were removed and ground into a fine powder (KitchenAid KSB4027PA Countertop Blender, USA). About 3 kg of ground seed was soaked in 3 L of 98% ethanol for 24 hours, then filtered. The ethanol filtrate was concentrated under reduced pressure using a rotary evaporator. The resulting residue, called ethanol seed extract of *Aframomum melegueta* (ESEAM), was transferred to a hot-air oven, where it was dried to constant weight at 40°C, stored in air-tight sample bottles, and kept until used.

**Table 1. Phytochemical constituents of ethanol seed extract of *Aframomum meleguata*.**

S.No.	RT (min)	Name of Compound	MW (g/mol)	Peak Area (%)	Peak Height (%)
1	5.144	2-Nonanol	144.25	0.35	0.42
2	5.374	1-Octene, 3-(methoxymethoxy)	172.26	2.96	1.16
3	6.120	2-Heptanol, acetate	158.24	0.57	1.04
4	6.981	1,6-Octadien-3-ol, 3,7-dimethyl	194.31	0.72	1.84
5	8.183	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	160.12	6.44	1.73
6	8.706	2-Butanone, 4-hydroxy-3-methyl	178.23	2.53	0.91
7	9.021	Thiophene, 2-propyl	126.22	1.14	0.69
8	9.583	Cycloheptane, 1,4-dimethoxy-, trans	158.24	0.11	2.20
9	9.812	Urea, 1-(p-nitrobenzoyl)-3-phenyl	285.25	0.42	0.49
10	10.593	Diethylene glycol monododecyl ether	274.44	0.44	0.35
11	10.894	8-Methyl-6-nonenic acid	170.25	0.61	0.63
12	11.462	Caryophyllene	204.35	5.00	7.82
13	11.830	Humulene	204.35	7.25	9.87
14	12.093	5 $\alpha$ -Androstan-16-one	290.4	0.09	0.39
15	12.376	Toluene-4-sulfonic acid, 2,7-dioxatricyclo[4.3.1.0(3,8)]dec-10-yl	310.4	0.25	1.00
16	12.681	Caprylic anhydride	270.41	2.44	1.36
17	12.965	cis-Z- $\alpha$ -Bisabolene epoxide	220.35	0.23	1.26
18	13.187	12-Oxabicyclo[9.1.0]dodeca-3,7-dien	220.35	0.44	1.95
19	14.346	Octadecanoic acid	284.5	1.75	6.98
20	15.071	Pentadecanoic acid	242.4	7.69	1.80
21	15.962	n-Hexadecanoic acid	256.42	11.32	6.98
22	16.390	Cyclopentadecanone, 2-hydroxy	240.38	2.59	1.78
23	17.039	9,12-Octadecadienoic acid (Z,Z)	296.4	13.18	7.07
24	17.205	Octadecanoic acid	284.5	0.55	2.50
25	17.248	Ethyl 14-methyl-hexadecanoate	298.5	0.23	1.19
26	17.416	Naphthalene, 2-decyldcahydro	278.5	0.38	1.16
27	17.772	Naphthalene, decahydro-1-pentadecyl-	348.6	2.62	2.46
28	17.904	[1,3]Benzodioxolo[5,6-c]phenanthridine, 12,13-dihydro-2,3-dim	712.7	3.06	2.53
29	18.746	Hexadecanal, 2-methyl	254.5	2.98	2.05
30	19.133	Diisooctyl phthalate	390.6	1.54	1.61
31	19.452	Ethyl 9-hexadecenoate	282.5	1.39	1.20
32	19.957	(R)-(-)-14-Methyl-8-hexadecyn-1-ol	252.4	1.97	4.88
33	20.072	Octanoic acid, 2,3-dihydroxypropyl ester	218.29	0.61	2.10
34	21.056	E-11-Tetradecen-1-ol difluoroacetate	290.39	0.66	0.81
35	21.558	d-Norandrostane(5 $\alpha$ ,14 $\alpha$ )	246.4	1.53	2.49

**Abbreviations:** RT = Retention time; MW = Molecular weight.

### 2.3. Phytochemical and GC-MS Analysis of ESEAM

The phytochemical profile of ESEAM has been previously reported in our earlier study (Table 1) [40]. In brief, qualitative phytochemical screening revealed the presence of alkaloids, flavonoids, phenols, saponins, and tannins. At the same time, gas chromatography-mass spectrometry (GC-MS) analysis further identifies some bioactive compounds, notably, caryophyllene, humulene, 5 $\alpha$ -Androstan-16-one, and other lipid compounds. For the current study, the same extraction procedure was adopted to ensure reproducibility. The previously identified phytochemical constituents were also considered as putative ligands for *in silico* docking against enzymes implicated in prostate damage.

### 2.4. Animal Studies

Adult male Swiss albino rats (6 weeks old) weighing  $200.09 \pm 2.20$  g were purchased from the Animal Holding Unit of the Department of Biochemistry, University of Ilorin, Ilorin, Nigeria, and acclimatized for 5 days. Castration was performed according to the method of Dulisch [41], and the rats were left to recover for another week, with constant monitoring for signs of pain, distress, or illness and humane endpoints daily, in accordance with the guidelines of the Animal Care and Use Committee of Kwara State University. Animals were then completely randomized to five (5) groups of ten animals each. All rats were housed in a pathogen-free environment and provided *ad libitum* access to food and water. Our methods were carried out in accordance with international guidelines and regulations on ethical principles for research using laboratory animals, adhering

to the principles of the 3Rs (US NRC's guide). The study was approved and conducted in accordance with the ethical procedures and policies of the Animal Care and Use Committee of Kwara State University, Malete, Nigeria, and an approval number (KWASU/CR&D/REA/2024/050) was assigned.

### 2.5. Sensitization and Treatment

Seventy (70) male rats were castrated and allowed one week of recovery before experimentation. Following castration, fifty (50) rats ( $200.09 \pm 2.20$  g) were divided into five groups ( $n=10$ ) and used for the study. Animals were excluded from the study if they exhibited post-surgical complications, poor recovery following castration, signs of infection, abnormal behavior, or failure to meet the predefined health and physiological criteria required for inclusion. Following the recovery period, only animals that demonstrated complete healing and stable physiological conditions were selected for the study. Consequently, out of the initial 70 mice, 50 met the inclusion criteria and were included in the final experimental analysis. Except for the control group, all rats received 60 mg/kg body weight MSG intraperitoneally in 2 mL distilled water for 28 days to induce and promote prostate damage. Control rats were administered distilled water alone. ESEAM or finasteride was administered to the sensitized rats at 50 mg/kg, 100 mg/kg, or 0.8 mg/kg body weight, respectively, for 28 days. During the experiment, mortality was recorded in the MSG-only group, resulting in a reduction in the number of animals available for analysis. On the 28<sup>th</sup> day, all animals were sacrificed under light anesthesia performed as described previously by Ku *et al* [42], and blood and tissue samples were collected for biochemical estimations and histopathological examination.

### 2.6. Biochemical Analysis

Whole blood samples were collected from rats by cardiac puncture under anesthesia into EDTA sample bottles for hematological studies. At the same time, serum was extracted from whole blood by centrifugation at 5000 rpm using a bench-top centrifuge (Frontier 500 series). Liver, kidney, and prostate tissues were collected and perfused immediately with 0.25 M ice-cold sucrose solution. They were homogenized in sucrose buffer (pH 7.4) to yield a 10% (w/v) homogenate, then centrifuged at 10,000 g for 20 mins. The supernatant (cytosol fraction), after discarding any floating lipid layer and appropriate dilution, was used to assay biochemical analysis. An autohematological analyzer (Shenzhen Mindray, BioMedical Electronics Co., Ltd., China) was used to study hematological indices. AST, ALT, GGT, and ALP were measured using Randox kits (Randox Laboratories Ltd., Antrim, UK). Urea determination was based on the cleavage of urea with urease (Berthelot's reaction) according to Fawcett and Scott [43]. Uric acid was determined using the phosphotungstate method as described by Itiaba [44], and creatinine was measured using Jaffe's modified method [45]. Prostate-Specific Antigen (PSA) and Lutenizing Hormone (LH) were estimated using an ELISA assay kit (Calbiotech Inc., CA,

USA), total acid phosphatase (TACP) and prostatic acid phosphatase (PACP) were assessed as described by Mahmud *et al.* [46], interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were estimated using an ELISA assay kit (Bioassay Tech. Lab. Shanghai, China).

### 2.7. Histology

The prostate was collected from euthanized animals and was fixed in 10% paraformaldehyde (PFA), which was routinely processed and paraffin-embedded. This was done according to the method of Ramachandran and Kakar [47].

### 2.8. Molecular Docking

#### 2.8.1. Protein Retrieval and Preparation

The target proteins with PDB IDs: 1ANI, 1IVR, 3IJH, and 4Z9O for alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase 1, respectively, were downloaded from the RSCB Protein Data Bank [48, 49]. All the respective PDB IDs were uploaded to the Molegro Virtual Docker (MVD) 2013 V6.0. Water molecules, cofactors, ligands, and other non-essential molecules in the crystal structures were removed, and protein structural defects were identified for each of the four enzymes. Structural defects in amino acid residues were examined, corrected, and optimized using neighboring residues. The surface was generated for each protein, and a ligand-binding cavity was identified separately for each enzyme after adding hydrogen atoms and assigning charges. Each enzyme was set at a different coordinate along the X, Y, and Z axes. The X, Y, and Z axes were set at 62.78, 31.26, and 26.58 for 1ANI, 46.94, 12.95, and 39.21 for 1IVR, -17.26, 59.32, and 14.00 for 3IJH, -20.80, -26.16, and -10.90 for 4Z9O. Grid resolution was set to 0.30 Armstrong for all PDB IDs, and the maximum energy was minimized.

#### 2.8.2. Ligand Preparation

A total of 30 ligands were downloaded from PubChem in the form of 3D SDF conformers, based on the results of our GC-MS analysis of *A. melegueta* (Table 1) [40]. Finasteride was used as the reference drug for the study. All ligands were uploaded to MVD and prepared to correct any errors present. The preparation options were set to "if missing" for assign bonds, hybridization, create explicit hydrogens, assign tripos atom types, create explicit hydrogens, and assign charges. This was achieved using the Molegro Virtual Docker (MVD) software V2013. Ligands were then docked to each receptor using the Dock Wizard option to obtain docking scores.

### 2.9. Statistical Analysis

Values were presented as mean  $\pm$  SEM. The normality and homogeneity of variance were assessed using one-way analysis of variance, followed by Tukey's post-hoc test for multiple comparisons with variables that showed significant differences ( $p < 0.05$ ) between the groups. All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 16 software (Chicago, IL, USA).

### 3. RESULTS

#### 3.1. Effect of ESEAM on Hematological Parameters

The distribution of some hematological parameters (Table 2) for MSG-induced prostate damage was evaluated. It revealed a significant decrease ( $p < 0.05$ ) in the MSG-treated group compared with the control, and upon treatment with the extract, a substantial increase was observed.

#### 3.2. Effect of ESEAM on Serum and Liver Markers and Kidney Indices

Administration of MSG induced hepatotoxicity by increasing significantly ( $p < 0.05$ ) serum and liver activities of AST, ALT, ALP, and GGT in the MSG-only group compared to the control group. Treatment with the ESEAM at doses of 50 and 100 mg/kg body weight, respectively, induced a significant reduction ( $p < 0.05$ ) (Table 3). Similarly, there was a substantial increase ( $p <$

0.05) in urea, uric acid, and creatinine in animals treated with MSG. Still, upon treatment with ESEAM, there was a significant decrease ( $p < 0.05$ ) in the level of kidney indices (Table 4).

#### 3.3. Effect of ESEAM on Serum and Prostate Markers

The relative serum and tissue activities of prostate markers (PSA, LH, TACP, and PACP) were elevated ( $p < 0.05$ ) in animals treated with MSG when compared with the control (Table 5). Upon treatment with the extract, a significant reduction ( $p < 0.05$ ) was observed.

#### 3.4. Effect of ESEAM on Prostate Tissue Histopathology in MSG-induced Prostate Damage in Rat

The effect of ESEAM on prostate tissue histology in MSG-induced prostate-damaged rats is shown in Fig. (1a-e).

**Table 2. Effect of ESEAM on hematological parameters of MSG-induced prostate damage in rats.**

Enzymes/Organs	Control	MSG (60 mg/kg)	ESEAM (50 mg/kg)	ESEAM (100 mg/kg)	Finasteride (0.8 mg/kg)
Red blood cell ( $\times 10^{12}/l$ )	4.83 $\pm$ 0.42 <sup>b</sup>	3.58 $\pm$ 0.89 <sup>a</sup>	4.98 $\pm$ 0.46 <sup>c</sup>	4.72 $\pm$ 0.59 <sup>b</sup>	4.79 $\pm$ 0.56 <sup>b</sup>
Hemoglobin (g/dl)	7.84 $\pm$ 0.59 <sup>b</sup>	6.82 $\pm$ 1.72 <sup>a</sup>	9.62 $\pm$ 0.88 <sup>d</sup>	9.22 $\pm$ 1.16 <sup>c</sup>	9.26 $\pm$ 1.01 <sup>c</sup>
Packed cell volume (%)	27.20 $\pm$ 2.27 <sup>c</sup>	19.80 $\pm$ 5.01 <sup>a</sup>	27.20 $\pm$ 2.31 <sup>c</sup>	27.20 $\pm$ 3.71 <sup>c</sup>	26.40 $\pm$ 3.23 <sup>b</sup>
Mean cell volume	55.80 $\pm$ 0.97 <sup>c</sup>	44.40 $\pm$ 11.10 <sup>a</sup>	56.40 $\pm$ 2.79 <sup>d</sup>	56.80 $\pm$ 2.78 <sup>e</sup>	54.40 $\pm$ 1.63 <sup>b</sup>
Mean cell hemoglobin (%)	19.04 $\pm$ 0.22 <sup>b</sup>	15.24 $\pm$ 3.81 <sup>a</sup>	19.28 $\pm$ 0.29 <sup>d</sup>	19.22 $\pm$ 0.19 <sup>d</sup>	19.32 $\pm$ 0.26 <sup>c</sup>
Mean cell hemoglobin concentration (%)	33.88 $\pm$ 0.48 <sup>b</sup>	27.20 $\pm$ 6.82 <sup>a</sup>	34.54 $\pm$ 1.07 <sup>c</sup>	35.80 $\pm$ 1.41 <sup>d</sup>	35.44 $\pm$ 1.40 <sup>d</sup>
White blood cell count ( $\times 10^9/L$ )	6.52 $\pm$ 2.12 <sup>b</sup>	8.46 $\pm$ 0.98 <sup>c</sup>	6.03 $\pm$ 1.09 <sup>a</sup>	6.03 $\pm$ 1.09 <sup>a</sup>	6.47 $\pm$ 0.97 <sup>b</sup>
Neutrophils (%)	32.80 $\pm$ 3.48 <sup>c</sup>	23.00 $\pm$ 5.81 <sup>a</sup>	38.40 $\pm$ 3.39 <sup>e</sup>	35.80 $\pm$ 3.99 <sup>d</sup>	29.40 $\pm$ 1.75 <sup>b</sup>
Lymphocytes (%)	63.40 $\pm$ 3.88 <sup>e</sup>	56.40 $\pm$ 14.12 <sup>a</sup>	60.60 $\pm$ 3.71 <sup>c</sup>	62.80 $\pm$ 4.27 <sup>d</sup>	58.80 $\pm$ 14.76 <sup>b</sup>
Monocytes (%)	0.00 $\pm$ 0.00 <sup>a</sup>	1.40 $\pm$ 0.51 <sup>d</sup>	1.00 $\pm$ 0.45 <sup>c</sup>	0.80 $\pm$ 0.37 <sup>b</sup>	0.80 $\pm$ 0.37 <sup>b</sup>
Eosinophils (%)	0.00 $\pm$ 0.00 <sup>a</sup>	0.40 $\pm$ 0.24 <sup>b</sup>	0.00 $\pm$ 0.00 <sup>a</sup>	0.00 $\pm$ 0.00 <sup>a</sup>	0.00 $\pm$ 0.00 <sup>a</sup>
Basophils (%)	0.00 $\pm$ 0.00 <sup>a</sup>	0.20 $\pm$ 0.20 <sup>b</sup>	0.00 $\pm$ 0.00 <sup>a</sup>	0.00 $\pm$ 0.00 <sup>a</sup>	0.00 $\pm$ 0.00 <sup>a</sup>
Platelet ( $\times 10^9/l$ )	202.20 $\pm$ 11.88 <sup>d</sup>	161.60 $\pm$ 40.51 <sup>a</sup>	192.80 $\pm$ 19.04 <sup>b</sup>	212.80 $\pm$ 9.39 <sup>e</sup>	201.00 $\pm$ 13.96 <sup>c</sup>

Note: Values are expressed as mean  $\pm$  SEM, n = 6 rats. Analysis of variance ( $p < 0.05$ ).

**Table 3. Effect of ESEAM on serum and liver markers of MSG-induced prostate damage in rats.**

Enzymes (U/L)/Organs	Control	MSG (60 mg/kg)	ESEAM (50 mg/kg)	ESEAM (100 mg/kg)	Finasteride (0.8 mg/kg)
<b>ALP</b>	-	-	-	-	-
Serum	81.87 $\pm$ 1.29 <sup>a</sup>	103.00 $\pm$ 0.72 <sup>b</sup>	96.63 $\pm$ 0.46 <sup>d</sup>	88.63 $\pm$ 0.59 <sup>c</sup>	81.70 $\pm$ 0.63 <sup>b</sup>
Liver	81.57 $\pm$ 0.67 <sup>a</sup>	108.73 $\pm$ 3.10 <sup>b</sup>	93.80 $\pm$ 1.04 <sup>d</sup>	85.33 $\pm$ 0.58 <sup>b</sup>	87.63 $\pm$ 0.46 <sup>c</sup>
<b>AST</b>	-	-	-	-	-
Serum	36.03 $\pm$ 0.30 <sup>a</sup>	61.70 $\pm$ 0.70 <sup>b</sup>	56.67 $\pm$ 2.40 <sup>d</sup>	49.70 $\pm$ 0.50 <sup>c</sup>	45.60 $\pm$ 0.60 <sup>b</sup>
Liver	51.27 $\pm$ 0.72 <sup>a</sup>	68.13 $\pm$ 1.27 <sup>b</sup>	57.70 $\pm$ 1.36 <sup>d</sup>	47.40 $\pm$ 0.64 <sup>c</sup>	43.87 $\pm$ 0.35 <sup>b</sup>
<b>ALT</b>	-	-	-	-	-
Serum	18.70 $\pm$ 0.10 <sup>a</sup>	41.23 $\pm$ 0.50 <sup>b</sup>	35.40 $\pm$ 0.20 <sup>d</sup>	27.90 $\pm$ 0.27 <sup>c</sup>	25.90 $\pm$ 0.28 <sup>b</sup>
Liver	17.83 $\pm$ 0.35 <sup>a</sup>	41.80 $\pm$ 0.58 <sup>b</sup>	38.00 $\pm$ 0.26 <sup>d</sup>	30.67 $\pm$ 0.41 <sup>c</sup>	28.20 $\pm$ 0.47 <sup>b</sup>
<b>GGT</b>	-	-	-	-	-
Serum	20.76 $\pm$ 0.29 <sup>a</sup>	30.86 $\pm$ 0.20 <sup>b</sup>	23.10 $\pm$ 0.34 <sup>d</sup>	17.73 $\pm$ 0.27 <sup>c</sup>	15.93 $\pm$ 0.18 <sup>b</sup>
Liver	36.17 $\pm$ 0.41 <sup>c</sup>	62.37 $\pm$ 0.39 <sup>e</sup>	41.50 $\pm$ 0.64 <sup>d</sup>	23.70 $\pm$ 1.46 <sup>a</sup>	26.30 $\pm$ 0.22 <sup>b</sup>

Note: Values are expressed as mean  $\pm$  SEM, n = 6 rats. Analysis of variance ( $p < 0.05$ ).

**Table 4.** Effect of ESEAM on serum and kidney indices of MSG-induced prostate damage in rats.

Enzymes/Organs	Control	MSG (60 mg/kg)	ESEAM (50 mg/kg)	ESEAM (100 mg/kg)	Finasteride (0.8 mg/kg)
<b>Urea (mg/dl)</b>	-	-	-	-	-
Serum	2.70 ± 0.05 <sup>a</sup>	4.77 ± 0.08 <sup>e</sup>	3.53 ± 0.03 <sup>d</sup>	3.33 ± 0.12 <sup>c</sup>	3.10 ± 0.06 <sup>b</sup>
Kidney	2.50 ± 0.06 <sup>c</sup>	4.10 ± 0.12 <sup>e</sup>	3.67 ± 0.09 <sup>d</sup>	2.23 ± 0.03 <sup>b</sup>	2.13 ± 0.09 <sup>a</sup>
<b>Uric Acid (mg/dl)</b>	-	-	-	-	-
Serum	0.13 ± 0.02 <sup>a</sup>	0.36 ± 0.01 <sup>c</sup>	0.23 ± 0.01 <sup>b</sup>	0.18 ± 0.01 <sup>a</sup>	0.17 ± 0.01 <sup>a</sup>
Kidney	0.15 ± 0.02 <sup>a</sup>	0.38 ± 0.01 <sup>d</sup>	0.31 ± 0.01 <sup>bc</sup>	0.27 ± 0.01 <sup>b</sup>	0.23 ± 0.01 <sup>b</sup>
<b>Creatinine (mmol/l)</b>	-	-	-	-	-
Serum	55.03 ± 0.38 <sup>a</sup>	80.58 ± 0.61 <sup>e</sup>	76.20 ± 1.35 <sup>d</sup>	60.89 ± 0.29 <sup>b</sup>	62.37 ± 0.58 <sup>c</sup>
Kidney	51.70 ± 0.74 <sup>a</sup>	82.23 ± 0.82 <sup>e</sup>	69.53 ± 0.68 <sup>d</sup>	57.20 ± 0.51 <sup>c</sup>	52.53 ± 0.52 <sup>b</sup>

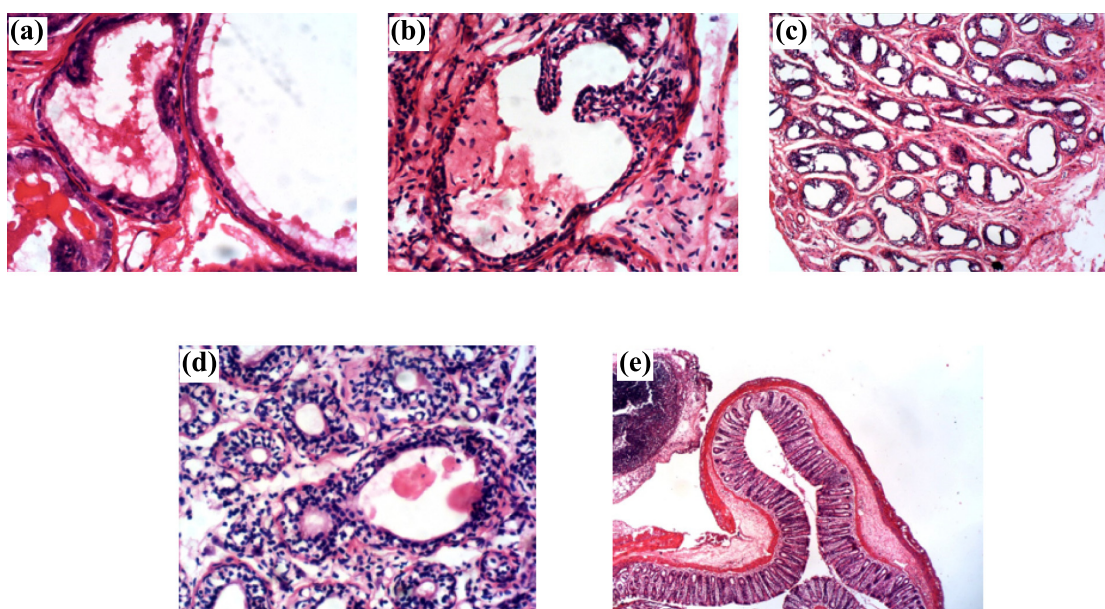
**Note:** Values are expressed as mean ± SEM, n = 6 rats. Analysis of variance ( $p < 0.05$ ).

**Table 5.** Effect of ESEAM on serum and prostate markers in MSG-induced prostate damage in rats.

Enzymes/Organs	Control	MSG (60 mg/kg)	ESEAM (50 mg/kg)	ESEAM (100 mg/kg)	Finasteride (0.8 mg/kg)
<b>PSA (ng/mL)</b>	-	-	-	-	-
Serum	0.35 ± 0.03 <sup>a</sup>	6.48 ± 0.21 <sup>d</sup>	0.88 ± 0.06 <sup>c</sup>	0.85 ± 0.05 <sup>c</sup>	0.57 ± 0.13 <sup>b</sup>
Prostate	0.34 ± 0.01 <sup>a</sup>	3.87 ± 0.42 <sup>e</sup>	0.59 ± 0.04 <sup>c</sup>	0.67 ± 0.04 <sup>d</sup>	0.49 ± 0.06 <sup>b</sup>
<b>LH (IU/L)</b>	-	-	-	-	-
Serum	0.11 ± 0.01 <sup>a</sup>	0.38 ± 0.02 <sup>c</sup>	0.18 ± 0.01 <sup>ab</sup>	0.13 ± 0.01 <sup>a</sup>	0.13 ± 0.02 <sup>a</sup>
Prostate	0.13 ± 0.01 <sup>a</sup>	0.47 ± 0.02 <sup>c</sup>	0.19 ± 0.00 <sup>ab</sup>	0.17 ± 0.01 <sup>a</sup>	0.19 ± 0.00 <sup>ab</sup>
<b>TACP (ng/mL)</b>	-	-	-	-	-
Serum	5.76 ± 0.04 <sup>a</sup>	17.72 ± 1.28 <sup>e</sup>	9.18 ± 0.60 <sup>d</sup>	7.20 ± 0.37 <sup>c</sup>	6.13 ± 0.62 <sup>b</sup>
Prostate	6.41 ± 0.71 <sup>a</sup>	12.66 ± 0.56 <sup>d</sup>	8.20 ± 0.37 <sup>c</sup>	6.72 ± 0.72 <sup>b</sup>	6.41 ± 0.71 <sup>a</sup>
<b>PACP (ng/mL)</b>	-	-	-	-	-
Serum	2.07 ± 0.09 <sup>a</sup>	8.76 ± 0.13 <sup>e</sup>	7.70 ± 0.78 <sup>d</sup>	4.62 ± 0.04 <sup>c</sup>	4.12 ± 0.28 <sup>b</sup>
Prostate	2.95 ± 0.04 <sup>a</sup>	12.05 ± 0.13 <sup>e</sup>	5.38 ± 0.21 <sup>d</sup>	3.27 ± 0.06 <sup>c</sup>	3.03 ± 0.12 <sup>b</sup>

**Note:** Values are expressed as mean ± SEM, n = 6 rats. Analysis of variance ( $p < 0.05$ ).

**Abbreviations:** PSA = Prostate-specific antigen; LH = Luteinizing hormone; TACP = Total acid phosphatase; PACP = Prostate acid phosphatase.

**Fig. (1).** Photomicrograph of the histological evaluation of prostate tissue of MSG-induced prostate damage in rats.

The histopathology showed prostatic tissue composed of glands lined by low columnar epithelial cells with basal nuclei and supranuclear clear cytoplasm. (a) Control group: The prostate gland shows mild epithelial folds, contains secretion, and has no features of hyperplasia or atypia. (b) MSG-only: This group revealed prostatic tissue composed of glands lined by cuboidal epithelial cells and showed mild to moderate epithelial folds featuring glandular hyperplasia with some features of atypia. (c) ESEAM 50 mg/kg: Prostatic tissue is composed of glands lined by cuboidal epithelial cells with mild folds. Dense neutrophilic inflammatory infiltrates were present, but no hyperplasia or atypia were revealed. (d) ESEAM 100 mg/kg. Similar preservation of the glandular architecture with cuboidal epithelial lining and mild folds was seen. Cell infiltrations were noted, but no features of hyperplasia or atypia. (e) The finasteride group showed prostatic tissue composed of glands lined by cuboidal epithelial cells but no features of hyperplasia or atypia.

### 3.5. Molecular Docking Results

The molecular docking analysis of the ligands against the enzymes ALP, AST, ALT, and GGT, as shown in Table 6, reveals their potential inhibitory effects. The ligands with the highest binding affinity for all the enzymes are 552098, 5280450, 5364759, and 280342, particularly showing the highest binding to ALP (-157.696), AST (-140.326), ALT (-115.826), and GGT (-125.851), respectively. In contrast, the standard drug,

10970751, demonstrated the lowest binding affinities across all enzymes, particularly against ALP (-29.1069), suggesting a weaker inhibitory potential.

Ligands 13849 and 552098 exhibited strong binding to the ALP enzyme. Ligand 13849 hydrogen bonds with His 372, Glu 57, and Ser 56, suggesting their crucial role in enzyme binding, while 552098 interacts with Ser 56 via a hydrogen bond, strengthening its stability within the active site (Fig. 2). They also showed steric interactions with some amino acid residues on both chains A and B, possibly contributing to their strong binding affinity and suggesting potential for effective inhibition of ALP activity, as shown in Table 7. The enzyme's active site ligand stabilization may also be due to the interactions of Thr 413 and His 372 residues on both chains.

Ligands 10944926 and 5280450 showed significant binding to the AST enzyme. Both ligands hydrogen-bond to His 181(A), Cys 183(A), Ala 184(A), and Ala 216(A), indicating strong interactions within the catalytic pocket. Other steric interactions (Table 6) may contribute to enhancing ligand stabilization. The participation of residues Arg 378(A), Gly 105(A), and Trp 133(A) in the binding interaction suggests that these amino acids play a crucial role in ligand anchoring and enzyme inhibition. The potential inhibitory role of these ligands in AST function may be due to the consistency of hydrogen bonding and steric interactions highlighted in Table 6 and Fig. (3).

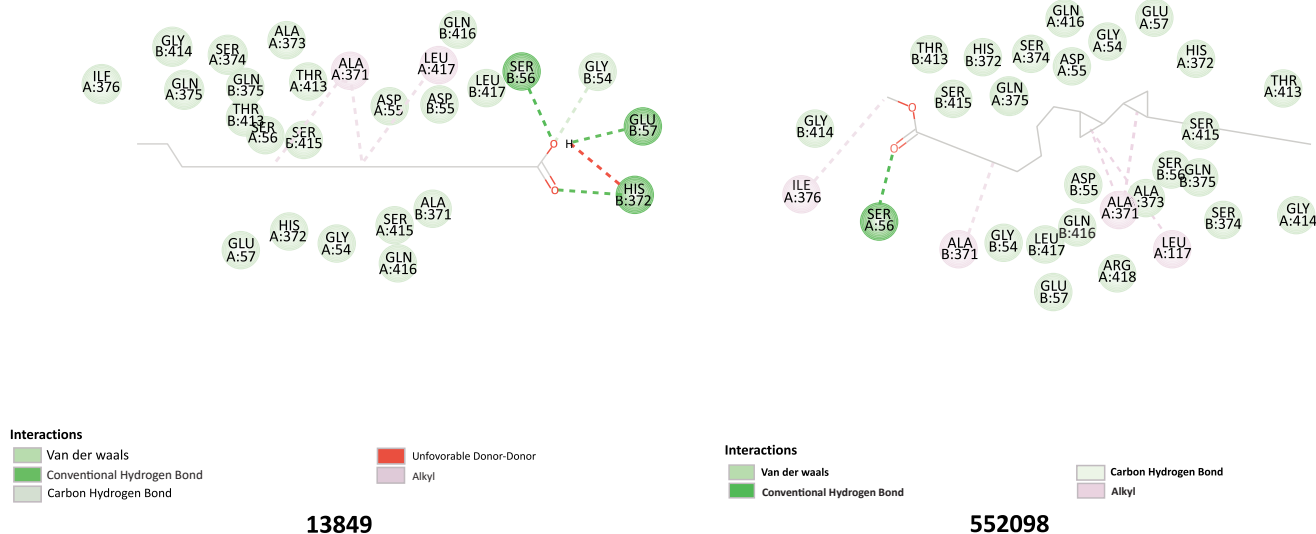
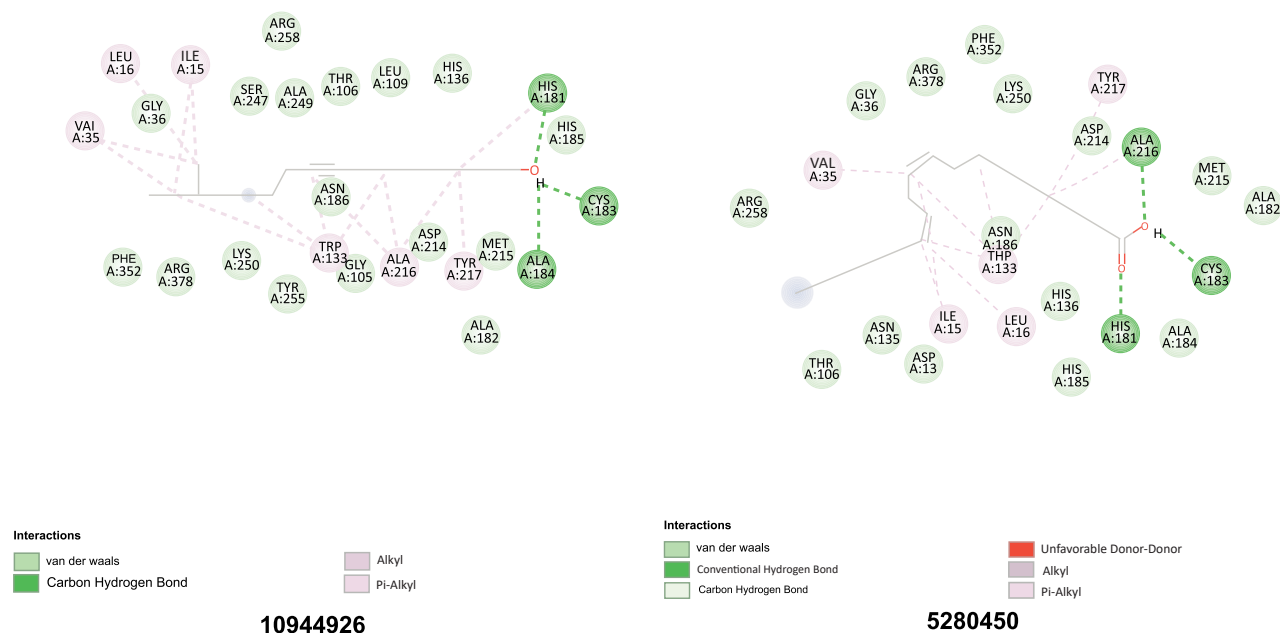


Fig. (2). Binding pose showing interactions of ligands with amino acids in the active pocket of alkaline phosphatase enzyme.



**Fig. (3).** Binding pose showing interactions of ligands with amino acids in the active pocket of aspartate aminotransferase enzyme.

**Table 6.** Binding affinities of ligands against ALP, AST, ALT, and GGT enzymes.

Ligand CID	ALP	AST	ALT	GGT
10944926	-146.857	-122.872	-87.2935	-108.168
5364759	-154.658	-137.115	-115.826	-115.826
5280450	-155.779	-140.326	-106.307	-106.307
586218	-146.955	-119.469	-82.308	-82.3081
552098	-157.696	-137.836	-97.551	-97.551
546976	-137.837	-122.497	-85.9241	-110.574
296573	-135.499	-146.052	-95.601	-129.073
280342	-109.581	-133.32	-98.661	-125.851
69340	-140.73	-125.463	-69.340	-117.761
13849	-133.691	-127.805	-107.984	-108.935
985	-142.008	-134.52	-97.45	-122.407
10970751	-29.1069	-93.9535	-80.6544	-80.6544

Confirming the strongest binding affinity for ALT enzyme, ligand 5364759 established a significant hydrogen bond with Lys 341(A). Moreover, multiple steric interactions with residues such as Ser 350(A), Ser 338(A), Ala 187(A), and Tyr 302(A) further supported its strong binding. The presence of interactions with Asn 268(A), Pro 269(A), and Asn 271(A) suggests that these residues play a role in stabilizing ligand binding. Ligand 5364759 may significantly inhibit ALT activity through interactions with

catalytic residues, particularly Lys 341(A) (Fig. 4), making it a promising candidate for further evaluation.

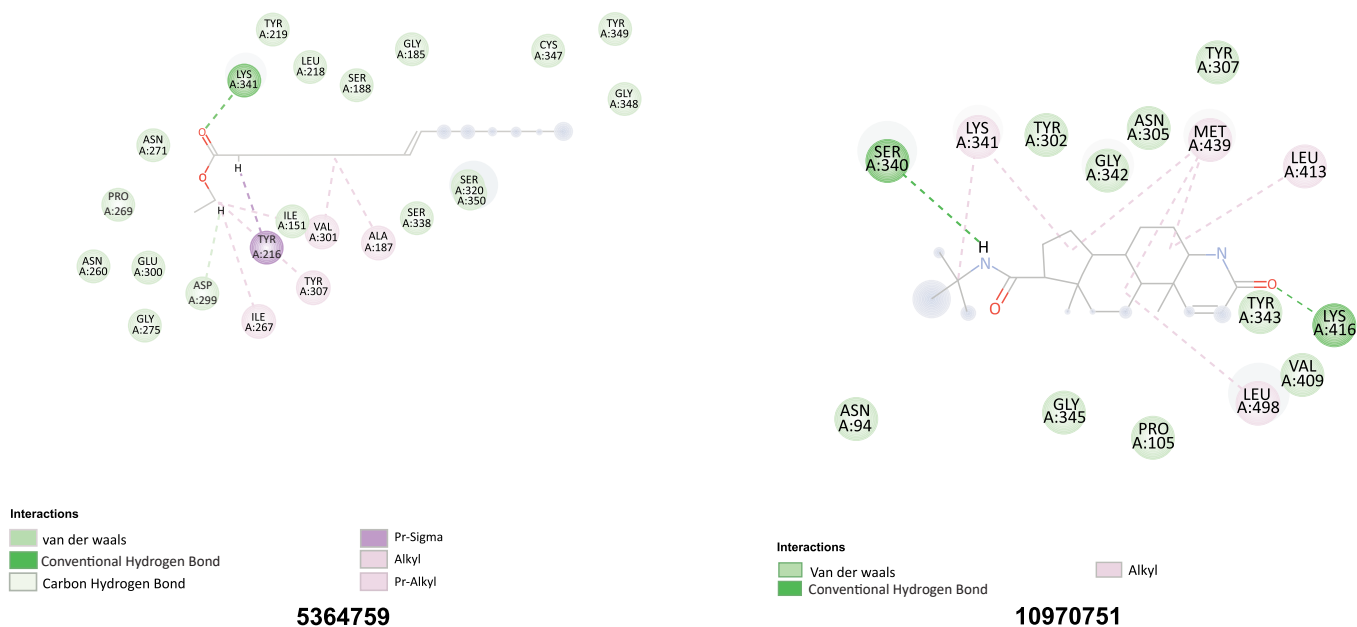
Notable interactions with the GGT enzyme were displayed by ligands 5280450 and 280342. 5280450 hydrogen bonds with Ser 452(B), Thr 381(B), and Thr 399(B), strengthening its stability within the enzyme's active site, while Lys 562(B), Ser 821(A), and Asn 401(B) strongly bond with 280342, emphasizing its potential inhibitory role (Fig. 5). The standard drug, 10970751, indicates a lower

inhibitory potential compared to the ligands, as shown in Table 5, with the weakest binding affinity across all the enzymes. The tested ligands (13849, 552098, 10944926, 5280450, 5364759, and 280342) consistently outperformed ligand 10970751 in binding affinity, consistent with the 2D

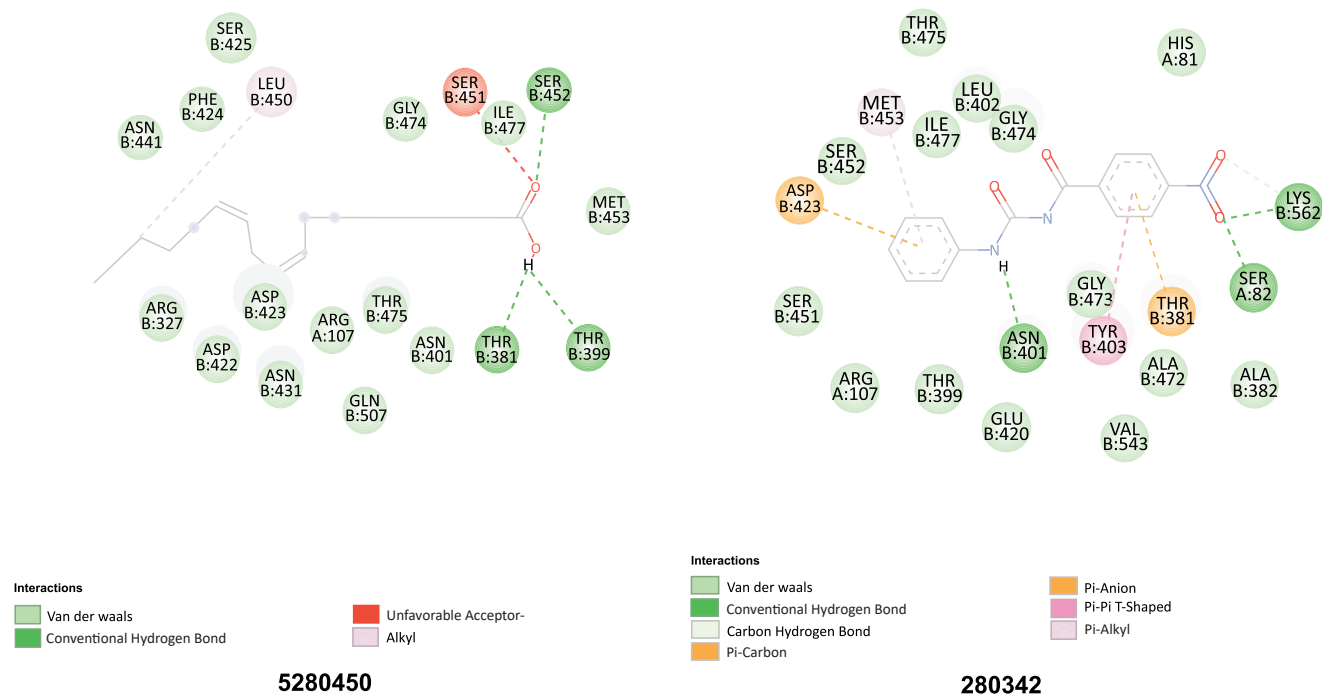
interactions of 10970751 with all the enzymes (Figs. S1-S3). Further validation may be needed to confirm their superior inhibitory properties and potential therapeutic applications *via* molecular dynamics simulation.

**Table 7. Docking interactions of the ligands in complex with ALP, AST, ALT, and GGT enzymes.**

Ligands/Interactions	Hydrogen Bond with Amino Acid Residues	Other Interactions on both Chains A and B
<b>ALP</b> 13849 552098	His 372(B); Glu 57(B); Ser 56(B) Ser 56(A)	Glu 57(A); His 372 (A); Gly 54 (A and B); Ser 415(A and B); Ala 317(B); Gln 416(A and B); Ile 376(A); Gly 414 (B); Ser 374(A); Ala 373 (A); Gln 373 (A and B); Thr 413(A and B); Ala 371(A); Leu 417(A and B); Asp 55 (A and B); Ser 56 (A) Ile 376(A and B); Ala 371(B); Gly 54(A and B); Leu 417(A and B); Gln 416(A and B); Asp 55(A and B); Ala 373(A); Gln 375(A and B); Gly 414(A and B); Ser 374 (A and B); Arg 418(a); Glu 57(B); Thr 413(A and B); His 372(A and B); Ser 415(B)
<b>AST</b> 10944926 5280450	His 181(A); Cys 183(A); Ala 184(A) His 181(A); Cys 183(A); Ala 216(A)	Met 215(A); Tyr 217(A); Ala 182(A); Asp 214(A); Ala216(A); Gly 105(A); Trp 133(A); Tyr 255(A); Lys 250(A); Arg 378(A); Phe 352(A); Val 35(A); Leu 16(A); Asn 186(A); Ile 15(A); Ser 247(A); Arg 258(A); Ser 247(A); Ala 249(A); Thr 106(A); Leu 109(A); His 136(A) Thr 106(A); Arg 378(A); Lys 250(A); Tyr 255(A); Asn 186(A); Trp 133(A); Gly 105(A); Ala 216(A); Asp 214(A); Tyr 217(A); Met 215(A); Ala 182(A); Ala 184(A); His 185(A); His 136(A); Leu 109(A); Thr 106(A); Ala 249(A); Ser 247(A); Ile 15(A); Leu 16(A); Val 35(A); Gly 36(A)
<b>ALT</b> 5364759	Lys 341(A)	Ser 350(A); Ser 338(a); Ala 187(A); Tyr 302(A); Val 301(A); Ile 191(A); Tyr 216(A); Ile 267(A); Asp 299(A); Glu 300(A); Gly 270(A); Asn 268(A); Pro 269(A); Asn 271(A); Tyr 219(A); Leu 218(A); Ser 188(A); Gly 186(A); Cys 347(A); Tyr 348(A); Gly 348(A)
<b>GGT</b> 5280450 280342	Ser 452(B); Thr 381(B); Thr 399(B) Lys 562(B); Ser 82(A); Asn 401(B)	Asn 401(B); Gln 507(B); Thr 475(B); Arg 107(B); Asn 431(B); Asp 422(B); Asp 423(B); Arg 327(B); Asn 441(B); Phe 424(B); Ser 425(B); Leu 450(B); Gly 474(B); Ile 477(B); Met 453(B) Ala 382(B); Thr 381(B); Ala 472(B); Val 543(B); Tyr 404(B); Glu 420(B); Thr 399(B); Arg 107(A); Ser 451(B); Gly 473(B); His 81(A); Gly 474(B); Leu 402 (B); ile 477(B); Met 453(B); Ser 452(B); Asp 423(B)



**Fig. (4).** Binding pose showing interactions of ligands with amino acids in the active pocket of the Alanine aminotransferase enzyme.



**Fig. (5).** Binding pose showing interactions of ligands with amino acids in the active pocket of gamma-glutamyl transferase enzyme.

#### 4. DISCUSSION

The results of this study demonstrate that intra-peritoneal administration of ESEAM for 28 days suppressed the induction of MSG-induced prostate damage in Swiss Albino rats. Administration of ESEAM at doses of 50 and 100 mg/kg body weight conferred a significant increase in the hematological parameters of the MSG-treated groups as compared to the MSG-only group. This result agreed with the work of Eweka *et al.* [50], who reported that MSG adversely altered hematological indices, including lymphocyte and neutrophil counts, as well as other hematological parameters, with a corresponding increase in white blood cell counts, indicative of immune suppression and systemic toxicity. The reversal of this compromised immune status by ESEAM treatment is consistent with the study by Akpanabiatu *et al.* [51], who concluded that *A. melegueta* seed has the potential to ameliorate hematological indices in a rat model of benign prostatic hyperplasia (BPH). Also, MSG exposure led to a marked elevation of serum and hepatic marker enzymes (AST, ALT, ALP, and GGT), consistent with systemic inflammation and oxidative stress, both of which are recognized drivers of hepatocellular injury [52], consistent with previous reports of hepatocellular injury and prostate damage [44]. Oxidative stress, through ROS generation, can induce DNA damage and mutations, initiating malignant transformations [52]. Treatment with ESEAM significantly decreases the activity

of these enzymes, indicating a hepatoprotective effect and mitigating ROS-associated damage, thereby interfering with pathways that predispose to malignancy. This finding is supported by the work of Kokou *et al.* [53], who reported that *A. melegueta* seed extract exerts hepatoprotective potential, likely mediated through antioxidant and anti-inflammatory mechanisms. Since ALP and GGT are clinically linked with prostate-related damage, the observed reduction suggests that ESEAM may confer protective benefits beyond hepatotoxicity, potentially modulating pathways relevant to prostate pathology.

The study also revealed that kidney indices (urea, uric acid, and creatinine) increased significantly in the MSG-treated groups compared with the control group. Although ESEAM and finasteride did not completely normalize these parameters, both treatments attenuated the MSG-induced elevations, suggesting a nephroprotective effect. In addition, MSG exposure significantly elevated serum and prostate markers (PSA, LH, TACP, and PACP) when compared with the control group. These elevated levels are indicative of androgen dysregulation, a hallmark of prostate disease. PSA is transcriptionally regulated by the androgen receptor (AR), which plays a central role in tumor initiation and progression [54]. Increased levels of these markers are consistent with the development of prostate damage and agree with the work of Ito *et al.* [55] who reported that serum and marker concentrations of 4.0 ng/mL and above are indicative of prostate malignancy or

damage. ESEAM treatment ameliorated these changes, thereby supporting its protective role against MSG-induced prostate alterations. This is consistent with previous findings that plant phytochemicals from *Aframomum melegueta* may exert AR-modulatory or inhibitory effects [56]. However, while elevated prostate markers and histopathology changes suggest prostate damage in this model, further studies incorporating definitive cancer biomarkers are necessary to exclude benign conditions.

Molecular docking analysis further revealed the inhibitory potential of selected ligands from ESEAM (552098, 5280450, 5364759, and 280342) against key enzymes, specifically ALP, AST, ALT, and GGT. While AST and ALT are the major circulating enzymes in the serum and are traditionally used as indicators of hepatocellular damage, emerging evidence suggests that their dysregulation may also accompany malignant progression in several cancers, including pancreatic and breast cancer [57-59].  $\gamma$ -Glutamyltransferase (GGT), an oxidative stress biomarker, has been linked to poor survival in various malignancies in elevated conditions [60], whereas ALP is frequently elevated in prostate pathologies and bone metastasis [61]. The interactions observed in the docking results, including strong binding affinities, consistent hydrogen bonding, and steric interactions, suggest that these phytochemicals may contribute to therapeutic effects by modulating enzymatic activity associated with tissue damage in prostate disease, even though docking studies provide only predictive insights.

## CONCLUSION

Ethanol seed extract of *Aframomum melegueta* (ESEAM) intraperitoneal administration has been revealed in this study to significantly alleviate the adverse effects of MSG-induced prostate damage in rats. In addition to improving hematological parameters, administration of ESEAM (at doses of 50 and 100 mg/kg body weight) effectively reversed MSG-induced prostate damage, enhanced serum and liver marker profiles, and suggested its potential as a protective agent against MSG-induced toxicity. Also, ESEAM administration positively influenced kidney indices, reflecting its potential renoprotective effects. Molecular docking studies revealed that the tested ligands (13849, 552098, 10944926, 5280450, 5364759, and 280342) exhibited strong binding interactions with the active sites of the enzymes ALP, AST, ALT, and GGT, suggesting their potential to inhibit enzyme activity. The highest binding affinities to ALP and ALT were observed with ligands 552098 and 5364759, compared with the standard drug, indicating their promising potential for enzyme inhibition. This shows the potential of ESEAM as a therapeutic agent for the management of prostate damage, with promising molecular interactions and its efficacy demonstrated through hematological, hepatic, and renal improvements. Further studies, including molecular dynamics simulations and network pharmacology, are warranted to validate these findings and explore the clinical applications of ESEAM and its active ligands.

## AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: S.A., N.K.: Study conception and design; Q.H.: Methodology; F.A.: Investigation; A.N., U.G.: Draft manuscript. All authors reviewed the results and approved the final version of the manuscript.

## LIST OF ABBREVIATIONS

ALT	= Alanine Aminotransferase
ALP	= Alkaline Phosphatase
AST	= Aspartate Aminotransferase
AR	= Androgen Receptor
BPH	= Benign Prostatic Hyperplasia
DHT	= Dihydrotestosterone
EDTA	= Ethylene Diamine Tetraacetic Acid
ESEAM	= Ethanol Seed Extract of <i>Aframomum Melegueta</i>
GC-MS	= Gas Chromatography-Mass Spectrometry
GGT	= Gamma-Glutamyltransferase
IL-6	= Interleukin-6
LH	= Luteinizing Hormone
MSG	= Monosodium Glutamate
MVD	= Molegro Virtual Docker
MW	= Molecular Weight
PACP	= Prostatic Acid Phosphatase
PSA	= Prostate-Specific Antigen
ROS	= Reactive Oxygen Species
RT	= Retention Time
TACP	= Total Acid Phosphatase
TNF- $\alpha$	= Tumor Necrosis Factor- $\alpha$

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved and conducted in accordance with the ethical procedures and policies of the Animal Care and Use Committee of Kwara State University, Malete, Nigeria, and an approval number (KWASU/CR&D/REA/2024/050) was assigned.

## HUMAN AND ANIMAL RIGHTS

All animal experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals.

This study adheres to internationally accepted standards for animal research and follows the 3Rs principle. The ARRIVE guidelines were employed for reporting experiments involving live animals, promoting ethical research practices.

**CONSENT FOR PUBLICATION**

Not applicable.

**AVAILABILITY OF DATA AND MATERIALS**

All the data and supporting material is available within the article.

**FUNDING**

None.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

**ACKNOWLEDGEMENTS**

Declared none.

**SUPPLEMENTARY MATERIAL**

Supplementary material is available on the publisher's website along with the published article.

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