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Original Research Article

Antioxidant and Antiulcerogenic Potential of *Aloe barbadensis* and *Carica papaya*: An Integrated Phytochemical, In Vitro and In Silico Study

Raliat A. Aladodo[1], Abimbola L. Adeniji[1], Zainab A. Suleiman[1], Eyiwumi B. Ajao[2] and Mutiu A. Alabi[1],*

[1]*Department of Biochemistry, Faculty of Pure and Applied Sciences, Kwara State University, Malete, Kwara, Nigeria.*
[2]*Department of Environmental Health Science, Faculty of Allied Sciences, Kwara State University, Malete, Kwara, Nigeria.*
*For correspondence: Email: mutiu.alabi@kwasu.edu.ng +2347030428661

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Abstract

Purpose: This study aimed to evaluate the antioxidant and antiulcerogenic potential of ethanolic extracts from *Aloe barbadensis* gel (AEE) and *Carica papaya* seeds (CEE) through integrated phytochemical analysis and computational modeling.
Methods: The phytochemical composition was characterized using Gas Chromatography-Mass Spectrometry (GC-MS). Antioxidant activity was assessed via DPPH, ABTS, FRAP, hydroxyl, and nitric oxide radical scavenging assays. Molecular docking against the H^+/K^+ ATPase target was performed to identify antiulcerogenic leads, followed by ADME, toxicity, and biological activity prediction (PASS) profiling.
Results: GC-MS revealed distinct phytoconstituents, with CEE exhibiting higher antioxidant capacity in all assays. Molecular docking identified two lead compounds: 9,12,15-Octadecatrienoic acid, ethyl ester from AEE and 2,5-Pyrrolidinedione,1-(phenylmethyl)- from CEE, both showing superior binding affinity and stability compared to omeprazole. ADME analysis indicated favourable drug-likeness for the pyrrolidinedione derivative. PASS predictions suggested complementary mechanisms: the fatty acid ester for antiulcer and anti-H. pylori activity, and the pyrrolidinedione for anti-inflammatory and urease inhibition.
Conclusion: The findings scientifically validate the traditional use of both plants, identifying specific lead compounds with high potential as multi-targeted antiulcer agents, warranting further investigation for drug development.

Keywords: *Aloe barbadensis*, *Carica papaya*, antioxidant, gastric ulcer, H^+/K^+-ATPase, docking, SwissADME, PASS.

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INTRODUCTION

Peptic ulcer disease (PUD) remains a significant global health burden, affecting millions and contributing to considerable morbidity and healthcare costs due to complications like hemorrhage and perforation.[1-4] Its pathogenesis involves an imbalance between mucosal defense and aggressive factors, primarily gastric acid hypersecretion, oxidative stress, and Helicobacter pylori infection.[2,5] Current mainstays of therapy, notably proton pump inhibitors (PPIs), are highly effective but associated with adverse effects and potential complications upon long-term use,[6-9] highlighting the need for safer therapeutic alternatives.

Medicinal plants represent a vital reservoir for such novel candidates. *Aloe barbadensis* (Aloe vera) gel and *Carica papaya* seeds are traditionally employed for gastrointestinal ailments,[12,13] with their purported benefits attributed to diverse phytoconstituents, including terpenoids, fatty acid esters, and lactones.[14-16] However, systematic validation of their antiulcer potential through an integrated methodology is lacking. The relevance of our chosen multi-faceted approach is to provide this comprehensive validation: phytochemical profiling identifies the specific bioactive constituents; in vitro antioxidant assays directly evaluate their capacity to mitigate the oxidative stress integral to ulcerogenesis; and in silico molecular docking against the H^+/K^+ ATPase proton pump, complemented by ADME/Tox predictions, offers a rational, mechanism-based screening of these compounds for both efficacy and drug-like properties prior to costly in vivo studies.[17-19]

Consequently, this study aims to characterize the phytochemical composition of *Aloe barbadensis* gel (AEE) and *Carica papaya* seed (CEE) ethanol extracts, evaluate their in vitro antioxidant capacities, and elucidate their molecular interactions with gastric H^+/K^+ ATPase via docking simulations to predict pharmacokinetic and safety profiles. This integrative strategy is designed to establish a mechanistic foundation for their anti-ulcerogenic effects and guide their targeted development as potential phytopharmaceuticals.

MATERIALS AND METHODS

Chemical and Reagents

The chemicals and reagents used included absolute ethanol (96%, v/v, Sigma-Aldrich, USA) as the primary extraction solvent; the radical reagents 2,2-diphenyl-1-picrylhydrazyl (DPPH, analytical standard, purity ≥ 95%, Sigma-Aldrich, USA) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS, purity ≥ 98%, Sigma-Aldrich, USA); the Ferric-Tripyridyltriazine complex contained within the FRAP assay kit (Sigma-Aldrich, USA); and the reference standard butylated hydroxytoluene (BHT, analytical standard, purity ≥ 99%, Sigma-Aldrich, USA), for which a stock solution was prepared in dimethyl sulfoxide (DMSO) and serially diluted to working concentrations.

Plant Collection and Extraction

Fresh *Aloe barbadensis* leaves and *Carica papaya* seeds were collected from Ilorin, Nigeria (8.4966° N, 4.5426° E), and authenticated at the Department of Plant Biology, University of Ilorin, by Mr. Bolu Ajayi. Voucher specimens were deposited in the departmental herbarium with accession numbers UILH/001/945/2025 and UILH/002/1058/2025, respectively. The plant materials were extracted with 70% ethanol (v/v, ethanol:distilled water = 70:30) and concentrated in a water bath at 50 °C.

GC-MS Analysis

Gas chromatography-mass spectrometry (GC-MS) of the ethanol extract was performed on an Agilent 7890A Gas Chromatograph coupled with an Agilent 7000 Triple Quadrupole Mass Spectrometer (Agilent Technologies, USA). Compound separation was carried out using an HP-5MS capillary column (30 m × 0.25 mm i.d., 0.25 µm film thickness). Helium was employed as the carrier gas at a constant flow rate of 1 mL/min. The oven temperature was programmed to rise from 100 to 260 °C at a rate of 4 °C/min. The injector temperature was maintained at 250 °C, and the detector at 230 °C. Compound identification was achieved by matching the acquired mass spectra with those in the NIST 2017 mass spectral library.[20]

Antioxidant Assays

The antioxidant capacity of the extracts was evaluated using five distinct assays, each measuring a different mechanism of action.

DPPH Radical Scavenging Assay

The ability to neutralize stable free radicals was measured using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method.[21] The reduction of the purple DPPH radical to a yellow-colored product was monitored spectrophotometrically at 517 nm.

ABTS Radical Cation Scavenging Assay

Antioxidant activity against the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical cation was assessed.[22] The assay involved the generation of the blue green ABTS•+ cation, with the extent of its decolorization measured at a wavelength of 734 nm.

Ferric Reducing Antioxidant Power (FRAP)

The reducing capacity of the extracts was determined using the FRAP assay.[23] This method quantifies the reduction of ferric-tripyridyltriazine complex to a ferrous form, which produces an intense blue color detected at 593 nm.

Hydroxyl Radical (OH•) Scavenging Activity

The scavenging capacity against highly reactive hydroxyl radicals was evaluated according to a standard protocol, measuring the prevention of radical-mediated degradation.

Nitric Oxide (NO•) Scavenging Activity

The extract's ability to inhibit nitric oxide radicals was similarly tested using an established scavenging protocol.

For all radical scavenging assays (DPPH, ABTS, OH•, NO•), the percentage inhibition was calculated at concentrations ranging from 31.25 to 1000 µg/mL. The half-maximal inhibitory concentration (IC_{50}) was derived from nonlinear regression fits of the dose-response data. Butylated hydroxytoluene (BHT) was used as a reference standard across all assays for comparative purposes.

Molecular Docking

Protein and Ligands

Molecular docking was performed against the gastric H^+/K^+-ATPase enzyme. The ligands included selected phytochemicals identified from Aloe barbadensis gel extract (AEE), Carica papaya seed extract (CEE), and the reference drug omeprazole.

Docking Workflow

Molecular docking simulations were performed using the Glide module (standard precision [SP] and extra precision [XP] modes) within the Maestro 14.3 software suite (release year 2023; Schrödinger, LLC, New York, NY, USA). Subsequent binding affinity refinement was conducted via the Prime Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) rescoring protocol integrated into the Schrödinger suite. Ligand–protein interaction analyses were visualized using both 2D and 3D visualization tools within the Maestro interface.

In silico ADME/Tox and Bioactivity Predictions

Computational pharmacokinetic and toxicity profiling was carried out with SwissADME, PASS, and Protox-3/StopTox. SwissADME was used to evaluate drug-likeness (Lipinski, Ghose, Veber, Egan, and Muegge rules), lipophilicity (logP), topological polar surface area (TPSA), aqueous solubility, and interactions with P-gp efflux transporters and CYP450 isoenzymes. PASS provided probability scores (Pa/Pi) for predicted biological activities. Protox-3 and StopTox were employed to classify compounds according to toxicity endpoints. SMILES notations of candidate ligands were submitted, and the resulting output data are summarized in the Results section.

Statistical Analysis

All data were expressed as Mean ± Standard Mean of Error (SEM) for each animal in each group. All group data were statistically evaluated using SPSS 25.0 software. Hypothesis testing methods included t-test and one-way Analysis of Variance (ANOVA) with subsequent comparisons among groups using Duncan's Multiple Range Test (DMRT). Statistical significance was set at $p \leq 0.05$. The graphs were drawn with GraphPad Prism version 10.0 software.

RESULTS AND DISCUSSION

This study presents an in-depth characterization of the phytochemical constituents, antioxidant properties, and antiulcerogenic potential of ethanol extracts from *Aloe barbadensis* gel and *Carica papaya* seeds. The results confirm the presence of diverse bioactive compounds in both extracts, substantiating their traditional therapeutic applications.

GC-MS Chromatograms

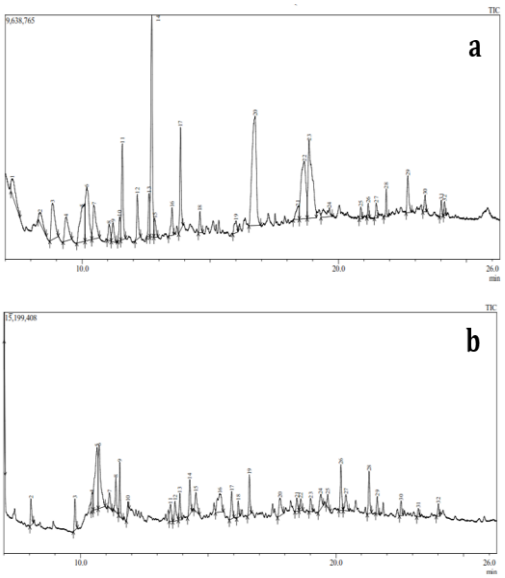


Figure 1: Chromatograph of (a) *Aloe barbadensis* and (b) *Carica papaya* Extracted by Ethanol.

The total ion chromatogram (TIC) of *Aloe barbadensis* ethanol extract (Figure 1a) displays a complex mixture of phytochemicals eluting between 5.0 and 26.0 minutes.

Phytochemical Composition Identified by GC-MS

--The Gas Chromatography-Mass Spectrometry (GC-MS) analysis of the ethanolic extracts of *Carica papaya* and *Aloe barbadensis* revealed a wide range of bioactive constituents differing in chemical structure, polarity, and relative abundance (Tables 1 and 2).

Table 1: Phytochemical Composition of *Carica papaya* Ethanol Extract

S/No	Retention Time	Area (%)	Height (%)	Compound Name	Mol. Weight (g/mol)	Mol. Formula
1	7.014	1.80	7.03	Acetic acid	60	$C_2H_4O_2$
2	8.056	2.40	3.18	Acetamide	59	C_2H_5NO
3	9.777	2.81	3.74	Butyrolactone	86	$C_4H_6O_2$
4	10.445	2.23	2.12	Butanoic acid,3-hydroxy-ethyl ester	132	$C_6H_{12}O_3$
5	10.645	13.72	7.41	Hydroperoxide,1methyl pentyl	118	$C_6H_{14}O_2$
6	10.729	10.72	7.48	2-Hydroxy-gamma-butyrolactone	102	$C_4H_6O_3$
7	11.132	1.79	1.80	1,7-Octadien-3-ol	126	$C_8H_{14}O$
8	11.381	3.47	4.15	2(3H)-Furanone,dihydro-3-hydroxy-4,4-dimethyl	130	$C_6H_{10}O_3$
9	11.536	4.22	6.48	1,5-Hexanediol	118	$C_6H_{14}O_2$
10	11.854	1.01	1.47	2-Pyrrolidinone	85	C_4H_7NO
11	13.522	2.07	2.03	Benzofuran,2,3-dihydro-	120	C_8H_8O
12	13.704	2.60	2.37	1-Pentanol,2,3-dimethyl-	116	$C_7H_{16}O$
13	13.887	2.40	3.21	N-Aminopyrrolidine	86	$C_4H_{10}N_2$
14	14.274	3.74	4.16	2-Coumaranone	134	$C_8H_{16}O_2$
15	14.511	2.74	2.25	L-Asparagine	132	$C_4H_8N_2O_3$
16	15.453	5.36	2.20	4H-Benzo[1,4]oxazin-3-one, 4-(2-morpholin-4-yl-2-oxoethyl)-	276	$C_{14}H_{16}N_2O_4$
17	15.922	3.28	3.27	N-[2-Hydroxyethyl]succinimide	143	$C_6H_9NO_3$
18	16.175	1.53	1.98	3-Hydroxy-pyrrolidine-1carboxylicacid,benz	221	$C_{12}H_{15}NO_3$
19	16.612	3.57	4.78	Dimethyl (1E)-N hydroxyethanimidoyl phosphonate	167	$C_4H_{10}NO_4P$
20	17.811	3.33	2.13	Benzenemethanol.,alpha.-2-propenyl-	148	$C_{10}H_{12}O$
21	18.473	1.56	1.57	Octanal	128	$C_8H_{16}O$
22	18.623	1.28	1.43	Butanoicacid,2,4-diamino	118	$C_4H_{10}NO_2$

23	19.012	1.51	1.57	Cyclohexanol,1R-4-trans-acetamido-2,3-trans-epoxy-	171	$C_8H_{13}NO_3$
24	19.396	2.55	1.79	DL-Proline,5-oxo-methylester	143	$C6H_9NO_3$
25	19.677	1.22	1.55	2,5-Pyrrolidinedione,1-(phenylmethyl)-	189	$C_{11}H_{11}NO_2$
26	20.196	4.83	5.50	3-Methyl-1,4-diazabicyclo[4.3.0]nonan-2,5-dione, N-acetyl	210	$C_{10}H_{14}N_2O_3$
27	20.398	2.47	1.93	3-Methyl-1,4-diazabicyclo[4.3.0]nonan-2,5-dione, N-acetyl	210	$C_{10}H_{14}N_2O_3$
28	21.297	4.51	5.06	Pyrrolo[1,2-a]pyrazine-1,4-dione,hexahydro-3	210	$C_{11}H_{18}N_2O_2$
29	21.621	1.65	2.09	Pyrrolo[1,2-a]pyrazine-1,4-dione,hexahydro-3	210	$C_{11}H_{18}N_2O_2$
30	22.552	1.48	1.78	Pyrrolo[1,2-a]pyrazine-1,4-dione,hexahydro-3	210	$C_{11}H_{18}N_2O_2$
31	23.228	0.89	0.99	11-Octadecenoic acid, methyl ester	296	$C_{19}H_{36}O_2$
32	24.010	1.25	1.51	(E)-9-Octadecenoic acid ethyl ester	310	$C_{20}H_{38}O_2$

Table 2: Phytochemical Composition of *Aloe barbadensis* Ethanol Extract

S/No	Retention Time	Area %	Height %	Compound Name	Mol. Weight	Formula
1	7.275	2.4	1.31	propanoic acid, 2-oxo-, methyl ester	102	$C_4H_6O_3$
2	8.360	1.33	0.86	propanoic acid, 2-oxo-, methyl ester	102	$C_3H_6O_3$
3	8.846	4.17	2.87	Dihydroxylacetone	90	$C_6H_{10}O$
4	9.380	2.82	1.86	Cyclohexanone	98	$C_5H_6O_4$
5	9.990	5.46	2.67	2-butenedioc acid, 2- methyl-,(z)	100	$C_3H_8O_3$
6	10.180	6.04	4.16	Glycerin	92	$C_4H_6O_3$
7	10.464	3.34	2.66	2-hydroxy-gamma-butyrolactone	102	$C_6H_{10}O_2$
8	11.010	1.05	1.29	1,4-dioxin, 2,3-dihydro-5,6-dimethyl	114	$C_6H_8O_3$
9	11.204	1.25	1.49	2,5-dimethyl-4-hydroxy-3(2H)-furanone	128	$C_4H_4O_3$
10	11.460	1.23	1.88	5-oxotetrahydrofuranone	130	$C_7H_{10}O$
11	11.572	4.84	7.54	2-hexanone,3-methyl-4-methylene	114	C_4H_8O
12	12.154	2.28	3.54	cyclopropyl carbinol	72	$C_5H_8O_3$
13	12.612	1.93	3.41	pentanoic acid,4-oxo	116	$C_5H_6O_4$
14	12.716	10.5	17.4	4H-pyran-4-one,2,3-dihydro-3,5-dihydroxy-6	144	$C_4H_8O_3$
15	12.840	1.05	1.44	1,3-dioxolane-4-methanol	104	$C9H_{16}O$
16	13.507	1.59	2.17	3-isopropyl-4-methyl-1-petyn-3-ol	140	$C_6H_6O_3$
17	13.834	4.26	8.09	5-hydroxymethyl furfural	126	$C_6H_{12}O_4$
18	14.593	0.96	1.67	(S)-(-)-1,2,4-butanetriol, 2-acetate	148	$C_{20}H_{44}OSi$
19	16.006	1.01	0.95	1-di(tert-butyl)silyloxy dodecane	288	$C_4H_9NO_5$
20	16.750	14.69	8.58	1,3-propanediol,2-(hydroxymethyl)-2-nitro	151	$C_4H_6O_3$

21	18.4	1.23	0.96	alpha,-d-methyl-l-sorboside	360	$C_{12}H_{24}O$
22	18.6	8.72	4.49	3-deoxy-d-mannoic-Lactone	180	$C_6H_{12}O_6$
23	18.8	9.92	6.12	alpha-d-galactopyranoside, methyl	194	$C_7H_{14}O_6$
24	19.6	1.42	0.66	1-eicosanol	298	$C_{20}H_{42}O$
25	20.8	0.49	0.92	1,2-benzenedicarboxylic acid, bis(2-meth ylpropyl	278	$C_{16}H_{22}O$
26	21.1	0.46	1.11	Hexadecanoic acid methyl, ester	270	$C_{17}H_{34}O_2$
27	21.4	0.72	1.17	alpha-d-galactopyranoside, methyl	184	$C_7H_{14}O_6$
28	21.8	0.93	2.19	Hexadecanoic acid, methyl ester	270	$C_{17}H_{34}O_2$
29	22.7	2.02	2.87	l-lyxose	150	$C_5H_{10}O_5$
30	23.8	0.71	1.31	Phytol	296	$C_{20}H_{40}O$
31	24.0	0.70	1.29	9,12-octadecadienoic acid (z,z)-	280	$C_{18}H_{32}O_2$
32	24.1	0.49	1.08	9,12,15-octadecatrienoic acid, ethyl ester	306	$C_{20}H_{34}O_2$

A total of thirty-two (32) distinct phytochemical compounds were identified in the Carica papaya extract, with retention times ranging from 7.014 to 24.010 minutes and peak area percentages varying between 0.89% and 13.72%. The dominant constituent, Hydroperoxide, 1-methyl pentyl ($C_6H_{14}O_2$), exhibited the highest area percentage (13.72%), followed by 2-Hydroxy-γ-butyrolactone ($C_4H_6O_3$, 10.72%) and 4H-Benzo[1,4]oxazin-3-one, 4-(2-morpholin-4-yl-2-oxoethyl)- ($C_{14}H_{16}N_2O_4$, 5.36%). The identified compounds represent diverse chemical classes, including esters, lactones, alcohols, carboxylic acids, nitrogen-containing heterocycles, and aromatic derivatives, underscoring the chemical richness of the *Carica papaya* extract. The detection of compounds such as N-acetyl diazabicyclo-nonanedione, pyrrolidinedione, and benzenemethanol derivatives suggests notable antioxidant and antimicrobial potential, while the presence of octadecenoic acid esters indicates lipid-based constituents typical of plant oils. This complex chromatographic profile confirms the high phytochemical diversity of Carica papaya, supporting its traditional use as a potent antioxidant and anti-inflammatory agent.

Similarly, the GC-MS analysis of the ethanolic extract of Aloe barbadensis revealed a complex mixture of phytochemicals (Table 2). The identification of thirty-two (32) compounds, based on their retention time, mass spectra, and molecular formula, provides a chemical basis for the observed pharmacological properties of this widely used medicinal plant. The extract is characterized by a diverse array of compound classes, including organic acids and esters, sugars and sugar derivatives, furanones, pyrones, and fatty acid esters. The most abundant compound by percentage area (%) was 1,3-propanediol, 2-(hydroxymethyl)-2-nitro (14.69%), followed by 4H-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl- (10.5%), and alpha-d-galactopyranoside, methyl (9.92%). Notably, glycerin (6.04%), a well-known humectant and skin-conditioning agent, was also present in significant quantity, which aligns with *Aloe barbadensis*'s traditional use in cosmetics and dermatology.

GC-MS profiling revealed distinct chemical compositions between the two extracts. *Aloe barbadensis* gel was dominated by oxygenated compounds, including glycerin, dihydroxyacetone, and 5-hydroxymethylfurfural (HMF), consistent with previous reports on aloe gel composition.[24] Notably, HMF and related derivatives have been implicated in the antioxidant and cytoprotective properties attributed to Aloe barbadensis.[25] In contrast, Carica papaya seed extract exhibited a more complex phytochemical profile, featuring hydroperoxides, 1-methyl pentyl derivatives, various lactones, and nitrogenous compounds such as pyrrolidinediones, compounds previously associated with antimicrobial and antioxidant effects in papaya seeds.[26]

Antioxidant Profiling

The antioxidant potential of the ethanolic extracts of *Carica papaya* (CEE) and *Aloe barbadensis* (AEE) was systematically assessed using multiple in vitro assays, including ABTS, DPPH, FRAP, hydroxyl radical (OH•), and nitric oxide (NO•) scavenging activities.

Across all assays, CEE consistently demonstrated higher antioxidant capacity than AEE, although both extracts remained less effective compared to the standard antioxidant, butylated hydroxytoluene (BHT). For the ABTS

assay, CEE exhibited approximately 90% inhibition at 1000 µg/mL, with an IC_{50} of 35.22 µg/mL, whereas AEE achieved about 70% inhibition with a higher IC_{50} value of 97.60 µg/mL. BHT, as expected, showed superior efficacy with an IC_{50} of 26.77 µg/mL (Figure 2a). In the DPPH assay, CEE also outperformed AEE with ~85% inhibition at 1000 µg/mL (IC_{50} = 38.15 µg/mL) compared to ~75% inhibition for AEE (IC_{50} = 102.27 µg/mL). BHT demonstrated the strongest effect, with an IC_{50} of 18.77 µg/mL (Figure 2b). For hydroxyl radical scavenging, CEE achieved an IC_{50} of 57.64 µg/mL compared to 118.88 µg/mL for AEE, while BHT again exhibited superior scavenging activity (IC_{50} = 19.17 µg/mL) (Figure 2c).

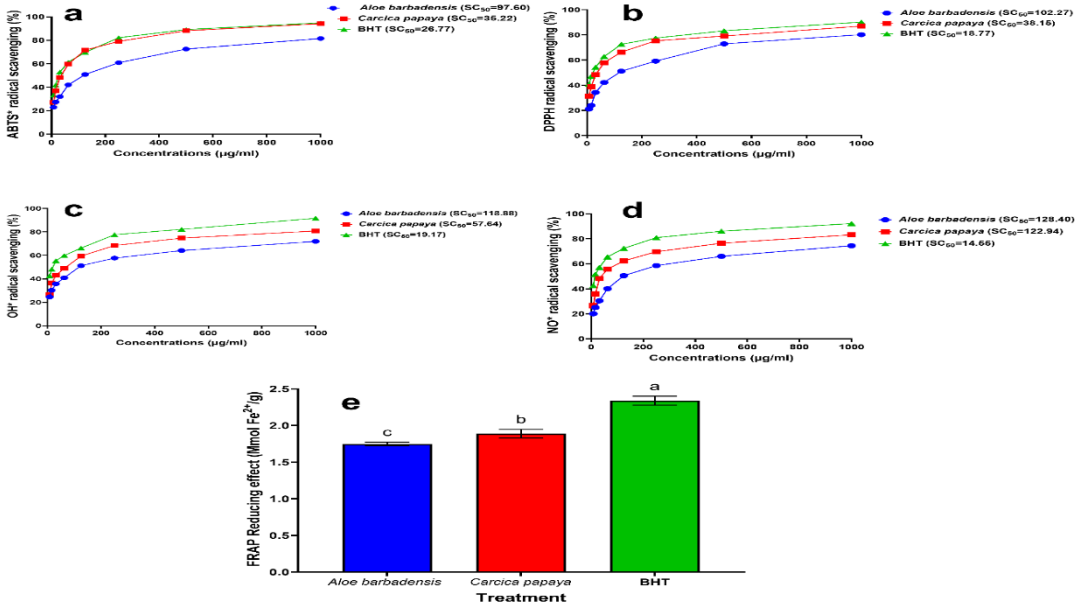


Figure 2: Antioxidant Potential of the Methanol Extracts of *Aloe barbadensis* (AEE) and *Carica papaya* (CEE)

The FRAP assay further supported these findings. At 1000 µg/mL, CEE reached ≈ 2.0 mmol Fe^{2+} equivalents/g, AEE ≈ 1.8 mmol Fe^{2+}/g, while BHT showed the highest value of ≈ 2.3 mmol Fe^{2+}/g (Figure 2d). Lastly, in the nitric oxide scavenging assay, both extracts showed weaker activity relative to other assays, with CEE (IC_{50} = 122.94 µg/mL) and AEE (IC_{50} = 128.40 µg/mL), while BHT remained the most effective scavenger (IC_{50} = 14.55 µg/mL) (Figure 2e).

The antioxidant assays (ABTS, DPPH, FRAP, hydroxyl and nitric oxide radical scavenging) demonstrated a consistently superior activity of *Carica papaya* extract (CEE) over *Aloe barbadensis* extract (AEE), though both were less potent than the synthetic antioxidant BHT. The enhanced antioxidant potential of CEE is attributable to its more diverse phytoconstituent composition, including 2-hydroxy-γ-butyrolactone and other heterocyclic compounds, which aligns with earlier work linking papaya seed extracts' antioxidant activity to their phenolic and flavonoid content.[27] The moderate yet significant antioxidant activity observed in AEE supports prior findings that attribute *Aloe barbadensis*'s antioxidant effects primarily to polysaccharides and low molecular weight compounds like HMF.[28]

Molecular Docking Analysis of *Aloe barbadensis* and *Carica papaya* Ethanol Extracts

Molecular docking simulations were performed to evaluate the inhibitory potential of phytoconstituents identified in the ethanolic extracts of *Aloe barbadensis* (AEE) and *Carica papaya* (CEE) against the gastric proton pump, H^+/K^+ ATPase. The binding affinities and interaction profiles of these ligands were compared to the reference drug omeprazole.

Ten ligands from AEE showed a broad range of binding affinities (Table 3). Glide scores spanned from -5.19 to -0.94 kcal/mol (SP) and -6.56 to -0.90 kcal/mol (XP). Notably, the sugar derivatives α-D-Methyl-L-sorboside (XP: -6.56 kcal/mol) and α-D-Galactopyranoside, methyl (XP: -6.13 kcal/mol) demonstrated superior XP docking scores compared to omeprazole (XP: -6.07 kcal/mol). Post-docking MM/GBSA refinement, which estimates binding free energy, revealed that 9,12,15-Octadecatrienoic acid, ethyl ester formed the most thermodynamically stable complex (ΔGbind: -41.17 kcal/mol). This strong affinity is primarily driven by extensive van der Waals and alkyl-π interactions within a hydrophobic sub-pocket of the binding site, as visualized in Figure 3a. In contrast, smaller polar molecules like (S)-(-)-1,2,4-Butanetriol, 2-acetate exhibited moderate affinity (ΔGbind: -15.66 kcal/mol), correlating with fewer stabilizing contacts

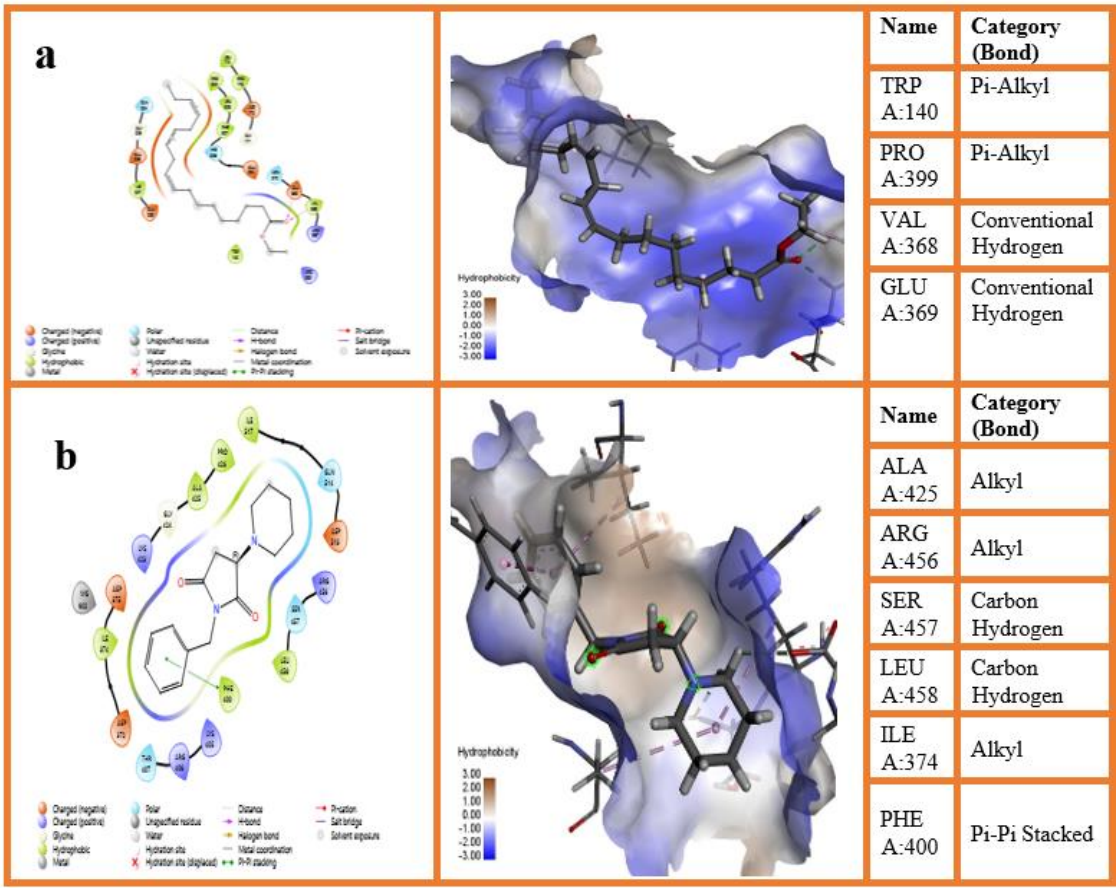
Table 3: Standard and Extra Precision Molecular Docking of AEE Hit compounds against H+/K+ ATPase Receptor

S/No	Compound	Glide SP Score (kcal/mol)	Glide SP MMGBSA (kcal/mol)	Glide XP Score (kcal/mol)	Glide XP MMGBSA (kcal/mol)
1	9,12,15-Octadecatrienoic acid, ethyl ester	-2.75	-30.89	-1.02	-41.17
2	Omeprazole (Reference)	-5.12	-29.53	-6.07	-39.30
3	Phytol	-1.42	-28.66	-1.90	-32.71
4	Hexadecanoic acid, methyl ester	0.94	-33.32	-1.15	-32.65
5	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	-1.25	-28.96	-0.90	-29.90
6	(S)-(-)-1,2,4-Butanetriol, 2-acetate	-3.22	-15.66	-3.35	-29.78
7	Omeprazole	-5.19	-27.13	-4.06	-28.84
8	9,12-Octadecadienoic acid (Z,Z)-	-0.20	-23.71	-1.72	-27.80
9	α-D-Methyl-L-sorboside	-4.68	-26.73	-6.56	-26.74
10	α-D-Galactopyranoside, methyl	-4.91	-29.78	-6.13	-25.87

Table 4: Standard and Extra Precision Molecular Docking Of CEE Hit Compounds Against H+/K+ ATPase Receptor

S/No	Compound	Glide SP Score (kcal/mol)	Glide SP MMGBSA (kcal/mol)	Glide XP Score (kcal/mol)	Glide XP MMGBSA (kcal/mol)
1	2,5-Pyrrolidinedione,1-(phenylmethyl)-	-5.76	84.76	-4.71	-35.13
2	2,5-Pyrrolidinedione,1-(phenylmethyl)-	-6.33	58.58	-4.87	-32.87
3	Omeprazole (Reference)	-5.76	95.39	-3.32	-30.46
4	11-Octadecenoicacid,methyle Ster	-0.95	4.99	-1.31	-28.39
5	Cyclohexanol,1R-4-trans-acetamido-2,3-trans-epoxy	-6.44	60.85	-3.86	-25.70
6	Butanoic acid,3-hydroxy-ethyl ester	-4.00	42.26	-3.41	-25.14
7	Benzofuran,2,3-dihydro-	-4.46	20.68	-3.88	-24.36
8	N-Aminopyrrolidine	-3.82	-7.36	-2.55	-10.72
9	Benzenemethanol.,alpha.-2-propenyl-	-3.96	57.72	-4.50	-5.79
10	4H-Benzo[1,4]oxazin-3-one, 4-(2-morpholin-4-yl-2-oxoethyl)-	-6.31	-6.31	-4.64	2.48

Docking results for CEE compounds also indicated significant receptor engagement (Table 4). SP scores ranged from -6.44 to -0.95 kcal/mol, while XP scores varied from -4.87 to -1.31 kcal/mol. Cyclohexanol, 1R-4-trans-acetamido-2,3-trans-epoxy achieved the most favourable SP score (-6.44 kcal/mol). However, MM/GBSA analysis identified 2s,5-Pyrrolidinedione, 1-(phenylmethyl)- as forming the most stable complex (ΔGbind: -35.13 kcal/mol), which was more favourable than that of omeprazole (ΔGbind: -30.46 kcal/mol). The binding pose of this compound (Figure 3b) shows a dual interaction mechanism: the pyrrolidinedione core forms a conventional hydrogen bond with a key polar residue, while the phenylmethyl group stabilizes the complex via π-π stacking and π-alkyl interactions with adjacent aromatic and aliphatic residues.



Name	Category (Bond)
TRP A:140	Pi-Alkyl
PRO A:399	Pi-Alkyl
VAL A:368	Conventional Hydrogen
GLU A:369	Conventional Hydrogen

Name	Category (Bond)
ALA A:425	Alkyl
ARG A:456	Alkyl
SER A:457	Carbon Hydrogen
LEU A:458	Carbon Hydrogen
ILE A:374	Alkyl
PHE A:400	Pi-Pi Stacked

Figure 3: Representation of 2D and 3D ligand-target interaction between the lead compounds against H+/K+ ATPase Receptor. a - 9,12,15-Octadecatrienoic acid, ethyl ester from *Aloe barbadensis* ethanol extract and b - 2,5-Pyrrolidinedione,1-(phenylmethyl)- from Carica papaya ethanol extract.

The pivotal finding concerns the antiulcerogenic potential elucidated via molecular docking to the gastric proton pump H^+/K^+ ATPase receptor. Two lead compounds were identified based on Glide XP MMGBSA binding free energies: 9,12,15-octadecatrienoic acid, ethyl ester from the AEE, and 2,5-pyrrolidinedione,1-(phenylmethyl)- from the CEE. The fatty acid ester demonstrated a strong binding affinity (−41.17 kcal/mol), surpassing that of the reference drug omeprazole, indicating a highly stable interaction that could effectively inhibit gastric acid secretion.[29] Such fatty acid derivatives have previously been proposed as gastroprotective agents acting through proton pump inhibition.[30]

Similarly, the pyrrolidinedione derivative exhibited a favourable docking score (-6.33 kcal/mol) and MMGBSA value (-35.13 kcal/mol), comparable to omeprazole. The aromatic and rigid structure likely enhances binding to key active site residues. Pyrrolidinedione scaffolds are known for diverse pharmacological activities including enzyme inhibition in medicinal chemistry.[31] PASS predictions further supported these findings, with the fatty acid ester forecast to have anti-ulcerative and anti-Helicobacter pylori properties, and the pyrrolidinedione predicted as a urease inhibitor and anti-inflammatory agent. This suggests a promising multi-targeted mechanism against ulcer

pathophysiology, combining acid suppression and microbial virulence factor inhibition, a contemporary approach in ulcer therapy.[32]

ADME, Drug-likeness, Predicted bioactivity, and Toxicity

A comprehensive in silico Absorption, Distribution, Metabolism, and Excretion (ADME) analysis of the two lead compounds identified from the ethanol extracts of Aloe barbadensis and Carica papaya: 9,12,15-Octadecatrienoic acid, ethyl ester, and 2,5-Pyrrolidinedione,1-(phenylmethyl)- was presents Table 5

Table 5: ADME analysis of the lead compounds in *Aloe barbadensis* and *Carica papaya* ethanol extract

S/No	Descriptors	9,12,15-Octadecatrienoic acid, ethyl ester	2,5-Pyrrolidinedione,1-(phenylmethyl)-
Physicochemical properties			
1.	Formula	$C_{20}H_{34}O_2$	$C_{16}H_{20}N_2O_2$
2.	Molecular weight (g/mol)	306.48	272.34
3.	Number of heavy atoms	22	20
4.	Number of aromatic heavy atoms	0	6
5.	Fraction Csp3	0.65	0.50
6.	Number of rotatable bonds	15	3
7.	Number of H-bond acceptors	2	3
8.	Number of H-bond donors	0	0
9.	Molar refractivity	98.12	84.46
10.	Topological polar surface area (Å²)	26.30	40.62
Lipophilicity			
11.	Log Po/w (iLOGP)	-	2.63
12.	Log Po/w (XLOGP3)	-	1.65
13.	Log Po/w (WLOGP)	6.14	0.89
14.	Log Po/w (MLOGP)	-	2.10
15.	Log Po/w (SILICOS-IT)	-	2.16
16.	Consensus log Po/w	-	1.88
Water solubility			
17.	Log S (ESOL)	-	-2.59
18.	Solubility (mg/ml)	-	0.6971
19.	Class	-	Soluble
20.	Log S (Ali)	-	-2.12
21.	Solubility (mg/ml)	-	2.08
22.	Class	-	Soluble
23.	Log S (SILICOS-IT)	-	-3.52
24.	Solubility (mg/ml)	-	0.0824
25.	Class	-	Soluble
Pharmacokinetics			
26.	GI absorption	-	High
27.	BBB permeant	-	Yes
28.	P-gp substrate	-	No
29.	CYP1A2 inhibitor	-	No
30.	CYP2C19 inhibitor	-	Yes
31.	CYP2C9 inhibitor	-	No
32.	CYP2D6 inhibitor	-	No
33.	CYP3A4 inhibitor	-	No
34.	Log Kp (skin permeation) (cm/s)	-	-6.79
Drug-likeness			
35.	Lipinski	-	Yes; 0 violation
36.	Ghose	-	Yes
37.	Veber	-	Yes

38.	Egan	-	Yes
39.	Muegge	-	Yes
40.	Bioavailability score	-	0.55
Medicinal chemistry			
41.	PAINS	-	0 alert
42.	Brenk	-	1 alert: phthalimide
43.	Lead likeness	-	Yes
44.	Synthetic accessibility	-	2.40

The analysis reveals distinct molecular characteristics between the two compounds. The fatty acid ester exhibits a higher molecular weight (306.48 g/mol) and a significantly greater number of rotatable bonds (15), suggesting higher flexibility. In contrast, the pyrrolidinedione derivative possesses an aromatic ring system and a more rigid structure with only 3 rotatable bonds, reflected in its higher topological polar surface area (40.62 Å²).

A detailed pharmacokinetic profile was obtained for 2,5-Pyrrolidinedione,1-(phenylmethyl)-. The compound is predicted to have high gastrointestinal absorption, be a blood-brain barrier permeant, and is not a substrate for P-glycoprotein. In terms of metabolism, it is predicted to act as an inhibitor of the CYP2C19 isoenzyme but not of other major CYPs (1A2, 2C9, 2D6, 3A4). The compound demonstrates a favourable drug-likeness profile, complying with all rule-based filters (Lipinski, Ghose, Veber, Egan, Muegge) with zero violations and a bioavailability score of 0.55. Furthermore, it showed no structural alerts for pan-assay interference (PAINS) and was flagged with only one alert (phthalimide) in the Brenk filter, while also exhibiting good lead likeness and a high synthetic accessibility score (2.40).

Overall, the ADME profiling suggests that 2,5-Pyrrolidinedione,1-(phenylmethyl)- possesses promising physicochemical and pharmacokinetic properties warranting further investigation as a potential drug candidate.

The analysis reveals distinct and complementary therapeutic profiles for the two compounds. 9,12,15-Octadecatrienoic acid, ethyl ester demonstrates a high predicted probability for Anti-ulcerative activity (Pa = 0.662), supported by concurrent predictions for Anti-H. pylori (Pa = 0.412) and moderate Antioxidant (Pa = 0.269) effects (Table 6). This suggests a multi-faceted mechanism beneficial for gastrointestinal protection. In contrast, 2,5-Pyrrolidinedione,1-(phenylmethyl)- shows a stronger predicted efficacy for Anti-inflammatory applications, particularly for ophthalmic conditions (Pa = 0.161). It also indicates potential as a Urease inhibitor (Pa = 0.090) and for the general treatment of Gastrointestinal disorders (Pa = 0.040) (Table 6).

Table 6: Predicted Biological activity of selected phytochemicals in AEE using PASS

Biological activity	**9,12,15-Octadecatrienoic acid, ethyl ester**		**2,5-Pyrrolidinedione,1-(phenylmethyl)-**	
	Pi	Pa	Pi	Pa
Anti-ulcerative	0,007	0,662	-	-
Urease inhibitor	0,273	0,051	0,209	0,090
Anti-inflammatory, intestinal	0,438	0,015	0,296	0,074
Anti-inflammatory, ophthalmic	0,406	0,009	0,257	0,161
Cyto-protective agent	0,725	0,004	-	-
Antioxidant	0,030	0,269	-	-
Anti-H. pylori	0,009	0,412	-	-
Gastrointestinal disorders treatment	-	-	0,142	0,040
Gastrointestinal motility stimulant	0,263	0,020	0,240	0,031

Both compounds are predicted to have a minor effect as a Gastrointestinal motility stimulant. Collectively, the PASS predictions suggest that while the fatty acid ester is a promising candidate for antiulcer and anti-H. pylori therapy, the pyrrolidinedione derivative may be more relevant for managing inflammatory conditions and supporting gastrointestinal health through a different mechanism.

According to the PROTOX 3 analysis for oral toxicity, 9,12,15-Octadecatrienoic acid, ethyl ester is predicted to have an LD_{50} of 2,000 mg/kg, placing it in toxicity class 6, which is classified as "non-toxic" or "harmful if ingested" in large

amounts. In contrast, 2,5-Pyrrolidinedione,1-(phenylmethyl)- is predicted to have a lower LD_{50} of 3,500 mg/kg, corresponding to toxicity class 5 ("practically non-toxic") (Table 7).

Table 7: Toxicological Analysis of the Hit Compounds in CEE

Phytochemicals		**9,12,15-Octadecatrienoic acid, ethyl ester**	**2,5-Pyrrolidinedione,1-(phenylmethyl)-**
Oral toxicity of phytochemicals (PROTOX 3)	Predicted LD50 (mg/kg)	2,000	3,500
	Predicted toxicity class	6	5
Acute Toxicity of Phytochemicals (StopTox)	Acute Inhalation Toxicity	-	-
	Acute Oral Toxicity	-	+
	Acute Dermal Toxicity	-	-
	Eye irritation & Corrosion	-	+
	Skin sensitization	+	+
	Skin irritation & Corrosion	-	-

The StopTox analysis for acute toxicity revealed a more favourable profile for the fatty acid ester, which showed a positive alert only for skin sensitization. The pyrrolidinedione derivative, however, was flagged for multiple endpoints, including acute oral toxicity, eye irritation/corrosion, and skin sensitization (Table 7). ADME and toxicity analyses revealed excellent drug-likeness for the pyrrolidinedione candidate, displaying high gastrointestinal absorption, blood-brain barrier permeability, and adherence to major drug-likeness parameters, with a single Brenk filter alert for phthalimide moiety that merits further examination but does not preclude development. The fatty acid ester showed a favourable preliminary toxicity profile with low predicted toxicity except for skin sensitization, whereas the pyrrolidinedione flagged potential acute oral toxicity and eye irritation, suggesting a need for careful toxicological validation.[33]

Collectively, this study provides strong evidence for the phytochemical richness and therapeutic potential of *Aloe barbadensis* gel and *Carica papaya* seed extracts, highlighting novel lead compounds that warrant further preclinical and clinical investigations as antiulcer agents.

CONCLUSION

In conclusion, this integrated in vitro and in silico study delineates the antioxidant and antiulcerogenic potential of *Aloe barbadensis* and *Carica papaya extracts*, identifying two lead compounds, 9,12,15-octadecatrienoic acid ethyl ester and 2,5-pyrrolidinedione,1-(phenylmethyl)-, with strong binding affinity to H^+/K^+ ATPase, favourable ADME properties, and multi-mechanistic predicted bioactivities. These findings validate the ethnopharmacological uses of these plants and provide a robust foundation for future research, which should prioritize the in vivo isolation and efficacy validation of these compounds, detailed preclinical toxicological assessment, and the development of standardized phytopharmaceutical formulations targeting ulcer pathogenesis through dual acid suppression and anti-*H. pylori* mechanisms.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS DECLARATION

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

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