Research Paper

Aloesin Unveiled: Molecular Docking Investigation of Aloe Vera's Anti-Inflammatory Activity against Tumour Necrosis Factor Alpha

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Aloe vera, historically acclaimed as the plant of immortality, has gained significant attention for its therapeutic potential, particularly in dermatology and anti-inflammatory applications. In this study, we use a computational approach that integrates molecular docking analysis and pharmacokinetic assessment to explore the inhibitory potential of aloe vera phytochemicals against tumor necrosis factor-alpha, a key inflammatory protein implicated in various pathologies, including rheumatoid arthritis. The *in silico* screening identified top-performing compounds, with aloesin emerging as a promising inhibitor. Pharmacological analyses revealed aloesin's favourable toxicity profile, positioning it as a promising candidate for further drug development. This research provides insights into the anti-inflammatory properties of aloesin in Aloe vera, paving the way for future experimental validations and the development of novel therapeutics for rheumatoid arthritis.

Key words: Aloe vera, anti-inflammatory, molecular docking, aloesin, pharmacokinetics

A plant product plays a crucial role in combating human diseases. They contain a variety of bioactive compounds that offer therapeutic benefits through multiple mechanisms. These include antioxidant and anti-inflammatory properties, antimicrobial activities, and immune system modulation[1]. Many plant derived substances also target specific biological pathways involved in disease processes. Furthermore, plant products serve as important sources for novel drug development in modern medicine. Their complex composition often provides synergistic effects, enhancing their overall therapeutic potential against various human diseases.

Aloe vera, recognized for its historical significance as the plant of immortality, holds profound pharmaceutical importance in both traditional and modern medicine. Its gel, containing a diverse array of bioactive compounds, positions aloe vera as a versatile candidate for therapeutic applications, particularly in dermatological formulations, wound healing, and anti-inflammatory interventions. The increasing global demand for natural remedies has driven a substantial rise in aloe vera production and cultivation. Its prevalence spans across arid regions worldwide, contributing significantly to the pharmaceutical and cosmetic industries. Noteworthy cultivation areas include India, Australia, United States of America (USA), Japan, and Europe, attesting to its economic importance and widespread applications. Inflammation, a pivotal aspect of the body's immune response, is intricately regulated by molecular signalling pathways. Tumour Necrosis Factor (TNF), a key inflammatory protein, plays a key role in initiating and perpetuating inflammatory cascades, implicated in various pathological conditions. Rheumatoid Arthritis (RA), a systemic autoimmune disorder, remains a challenge in medical treatment despite current interventions such as Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Disease-Modifying Anti-Rheumatic Drugs (DMARDs), specifically TNF-Alpha (α) inhibitors.

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Aloe vera, renowned for its medicinal properties, has garnered scientific interest for its potential anti-inflammatory effects. Aloe vera's polysaccharides, phenolic compounds, and sterols have emerged as key players in modulating inflammatory pathways. This study employs an *in silico* approach, utilizing molecular docking analyses and pharmacokinetic assessments, to evaluate the inhibitory potential of aloe phytochemicals against TNF-α. This computational analysis aims to provide insights into the therapeutic efficacy of aloe vera constituents against TNF-α, offering a foundation for future experimental investigations.

MATERIALS AND METHODS

Selection of phytochemical compounds in aloe vera and anti-inflammatory drugs:

A curated selection of aloe vera phytochemicals was undertaken through a comprehensive literature review and utilization of the Indian Medicinal Plants, Phytochemistry And Therapeutics (IMPPAT) (https://cb.imsc.res.in/imppat) and ZINC databases. Phytochemicals were chosen based on documented presence in the literature and availability within these databases, ensuring a systematic approach aligned with established knowledge. Approved anti-inflammatory drugs from the therapeutic target database served as benchmarks for comparing the efficacy of bioactive compounds derived from aloe vera. This approach aimed to assess the relative effectiveness of aloe vera compounds against established anti-inflammatory medications (fig. 1).

Molecular docking studies:

The primary objective in molecular docking was to accurately gauge the scoring function and assess interactions between proteins and ligands. AutoDock Vina, coupled with PyRx, was employed for generating a dataset of bioactive binding poses of ligands within the active site of TNF-α. Additionally, the Discovery Studio 2024 client software was utilized to model nonbonded polar and hydrophobic contacts within the inhibitor site of TNF-α[2].

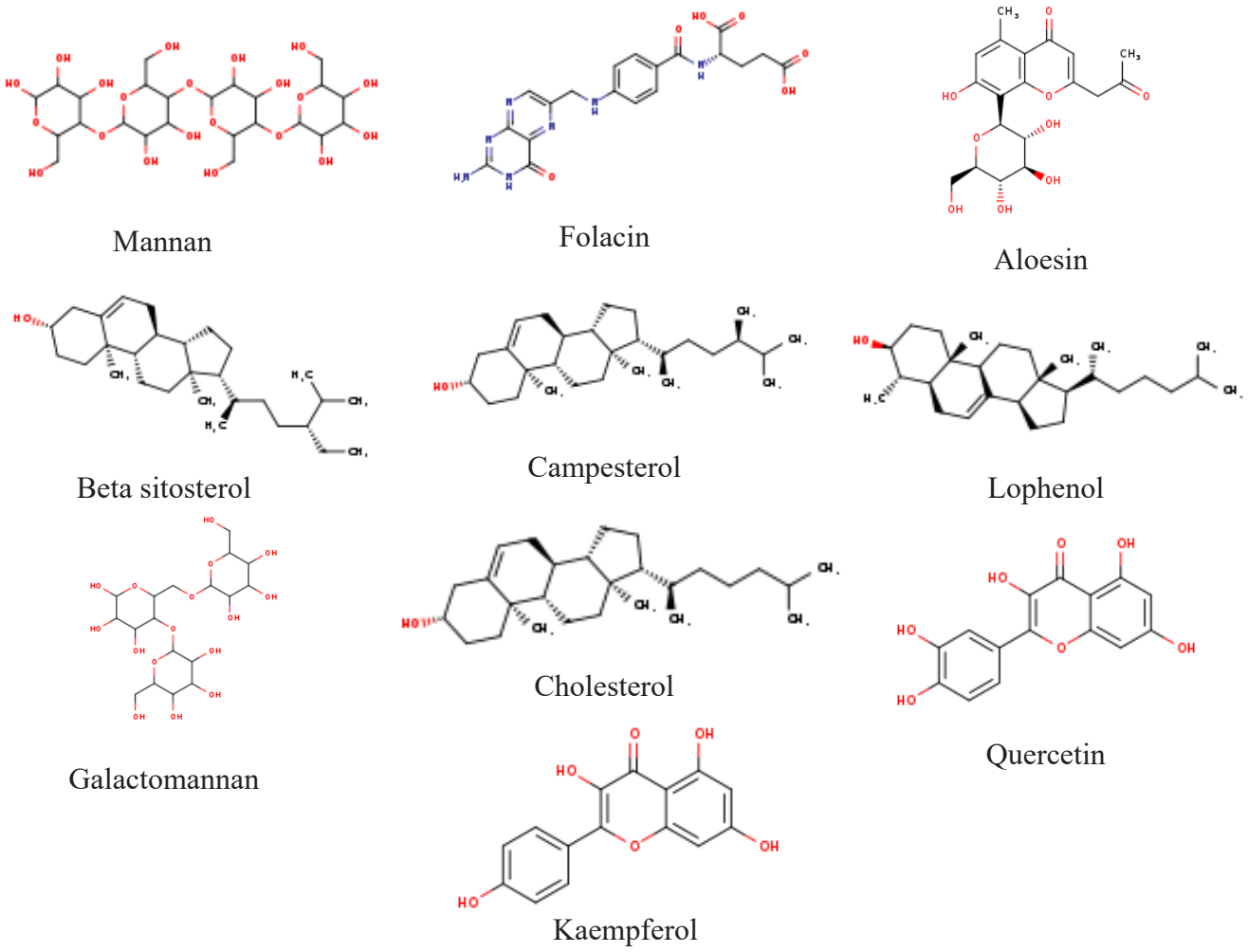

Fig. 1: Chemical structures of top 10 compounds derived from aloe vera

Structure retrieval of compounds:

Three-dimensional structures of bioactive compounds in aloe vera and over-the-counter medicines recommended for inflammation, such as aspirin, hydrocortisone, melaxicam, ibuprofen, celecoxib, and naproxen, along with the three-dimensional structures of the target protein TNF-α, were retrieved from databases such as the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) and PubChem.

Molecular docking software:

Molecular docking studies were conducted using PyRx, an open-source tool that employs an iterative approach to predict ligand poses within the protein's binding site, and Discovery Studio, a comprehensive molecular modeling and simulation software integrating various algorithms and scoring functions for accurate prediction of protein-ligand binding affinities.

Docking procedure:

Preparation of protein: The three-dimensional structure of TNF obtained from RCSB PDB was processed to remove water molecules and optimize hydrogen bonds.

Ligand preparation: Aloe vera compounds and commercial drug compounds retrieved from PubChem were prepared by assigning correct bond orders and optimizing conformations. Ligands were loaded into PyRx virtual screening software using Open Babel for conversion to Program Database (PDB) format.

Grid generation: Docking was performed using AutoDock Vina in PyRx virtual screening software with specific grid parameters. The Lamarckian Genetic Algorithm (LGA) was employed to generate 10 docked positions for each ligand. Subsequently, docking results were analyzed and visualized based on docking scores using Discovery Studio 2024 client and PyMOL software.

Scoring and analysis:

Docking scores, binding efficiency, and hydrogen bond interactions were analyzed to evaluate the strength and specificity of ligand binding. Molecular docking results were thoroughly analyzed for binding affinity, and the most promising aloe vera compound was selected based on docking scores and hydrogen bond interactions with TNF (fig. 2a and fig. 2b).

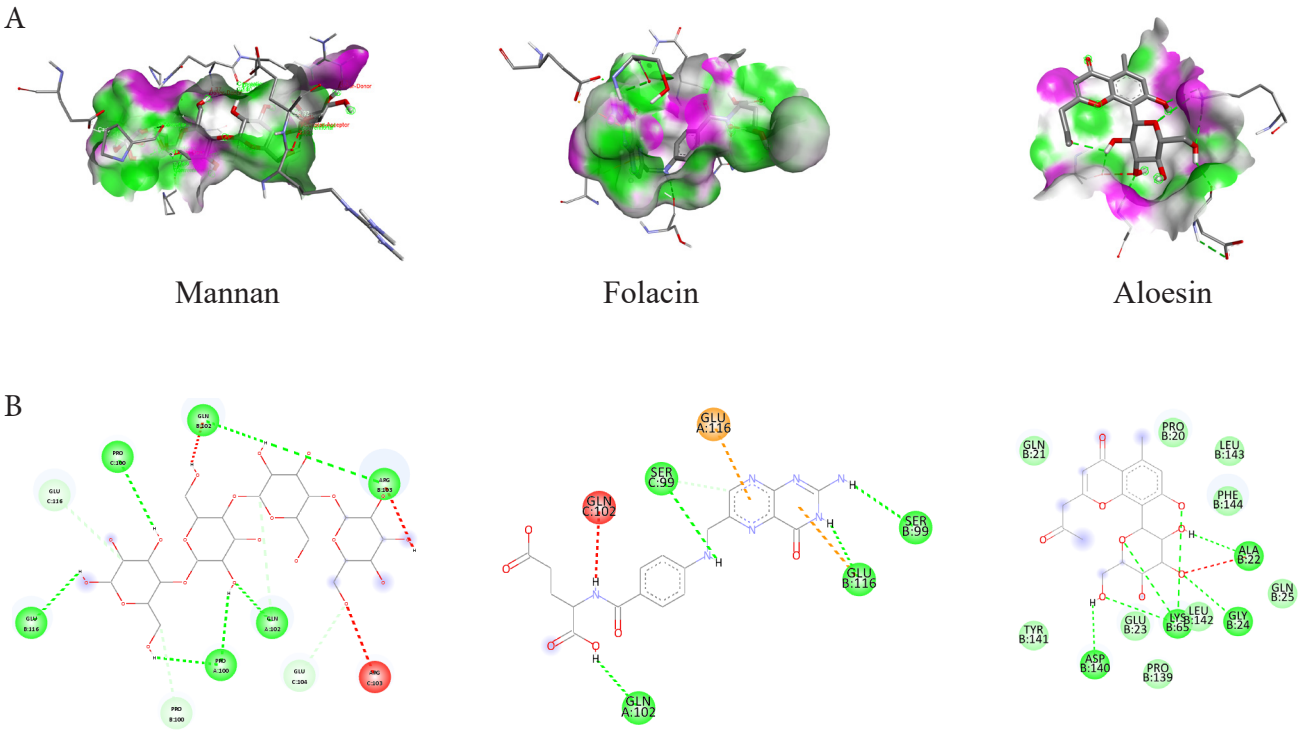

Fig. 2: (a): H-bonding interactions between the best ligands with TNF α protein target and (b): All types of interactions between the best ligands with TNF-α
Note: (A) ( ): Donor and ( ): Acceptor and (B) ( ): Conventional hydrogen bonds; ( ): Unfavourable donor-donor; ( ): Carbon hydrogen bond and ( ): Van der walls force or bond

Pharmacology analysis:

Pharmacokinetic analysis of ligands was systematically performed using the SwissADME server (http://www.swissadme.ch/). This computational tool facilitated the comprehensive evaluation of various pharmacokinetic parameters, encompassing absorption, metabolism, distribution, excretion, and toxicity predictions for the prospective compounds under investigation. Additionally, the SwissADME server provided insights into critical aspects such as bioavailability score, druggability, and synthetic accessibility score, offering a holistic perspective on the pharmaceutical viability of the examined compounds. Ligands were screened according to Lipinski's Rule of Five (RO5), for safety assessment in drug development, and toxicology predictions were performed using the Small-molecule pharmacokinetics prediction (pkCSM) online server. Parameters analyzed included Ames toxicity, maximum tolerance dose, human Ether-a-go-go Related Gene (hERG) inhibition, Lethal Dose 50 (LD_{50}), Lowest Observed Adverse Effect Level (LOAEL), hepatotoxicity, skin toxicity, *Tetrahymena pyriformis* toxicity, and minnow toxicity. This rigorous pharmacological scrutiny aims to inform and guide further exploration of these compounds in drug development endeavours.

RESULTS AND DISCUSSION

The study addresses the considerable socio-economic burden posed by the inflammatory autoimmune disease rheumatoid arthritis, affecting around 1 % of the global population[3,4]. Acknowledging the limitations of current RA treatments, the research aims to explore alternative therapeutic interventions with reduced side effects. Aloe vera demonstrates anti-inflammatory properties by effectively inhibiting the cyclooxygenase pathway, resulting in a diminished synthesis of prostaglandins and, consequently, a reduction in inflammatory processes[5-7]. The bioactive compounds in aloe vera demonstrate an inhibitory effect on the release of pro-inflammatory mediators, such as cytokines and histamine[8,9]. The principal focus of the study was to investigate the potential of phytochemicals to target the cytokine TNF-α, thereby demonstrating their anti-inflammatory activity. In pursuit of identifying active chemical constituents of aloe vera possessing potential interactions with the TNF-α protein, molecular docking studies were conducted for a set of 74 aloe vera chemical constituents (Table 1).

TABLE 1: CHARACTERISTIC OF PHYTOCONSTITUENTS OF ALOE VERA

S.No.	Ligand	PubChem ID	Molecular formula	Molecular weight (g/mol)
1	2(3H)-benzothiazolone	13625	C_7H_5NOS	151.19
2	3,4-dihydrocoumarin	660	$C_9H_8O_2$	148.16
3	7-hydroxy-4-benzopyrone	5409279	$C_9H_6O_3$	162.14
4	15-methylhexadecanoic acid	164860	$C_{17}H_{34}O_2$	270.5
5	Acemannan	72041	$C_{66}H_{100}NO_{49}$	1691.5
6	Allantoin	204	$C_4H_6N_4O_3$	158.12
7	Aloe emodin	10207	$C_{15}H_{10}O_5$	270.24
8	Aloenin	162305	$C_{19}H_{22}O_{10}$	410.4
9	Aloeresin	160190	$C_{19}H_{22}O_9$	394.4
10	Aloesone	5317700	$C_{13}H_{12}O_4$	232.23
11	Aloin A	12305761	$C_{21}H_{22}O_9$	418.4
12	Aloin B	14989	$C_{21}H_{22}O_9$	418.4
13	Aluminum	5359268	Al	26.981
14	anthracene	8418	$C_{14}H_{10}$	178.23
15	anthranol	10731	$C_{14}H_{10}O$	194.23
16	Anthraquinone	6780	$C_{14}H_8O_2$	208.21
17	Ascorbic acid	54670067	$C_6H_8O_6$	176.12
18	Asparagine	6267	$C_4H_8N_2O_3$	132.12

19	Aspirin	2244	$C_9H_8O_4$	180.16
20	Auxin	802	$C_{10}H_9NO_2$	175.18
21	Beta (β)-carotene	5280489	$C_{40}H_{56}$	536.9
22	β-sitosterol	222284	$C_{29}H_{50}O$	414.7
23	Campesterol	173183	$C_{28}H_{48}O$	400.7
24	Carvacrol	10364	$C_{10}H_{14}O$	150.22
25	Caryophyllene oxide	1742210	$C_{15}H_{24}O$	220.35
26	Caryophyllene	5281515	$C_{15}H_{24}$	204.35
27	Celecoxib	2662	$C_{17}H_{14}F_3N_3O_2S$	381.4
28	Cholesterol	5997	$C_{27}H_{46}O$	386.7
29	Chrysophanic acid	10208	$C_{15}H_{10}O_4$	254.24
30	chrysophanol	10208	$C_{15}H_{10}O_4$	254.24
31	Citric acid	311	$C_6H_8O_7$	192.12
32	Creatinine	588	$C_4H_7N_3O$	113.12
33	Cycloartenol	92110	$C_{30}H_{50}O$	426.7
34	Cysteine hydrochloride	25150	$C_3H_8ClNO_2S$	157.62
35	Cysteine	5862	$C_3H_7NO_2S$	121.16
36	D-fructose	2723872	$C_6H_{12}O_6$	180.16
37	D-galactonic acid	128869	$C_6H_{12}O_7$	196.16
38	D-galactose	6036	$C_6H_{12}O_6$	180.16
39	D-glucose	5793	$C_6H_{12}O_6$	180.16
40	D-mannose	18950	$C_6H_{12}O_6$	180.16
41	D-tartaric acid	439655	$C_4H_6O_6$	150.09
42	Danshenxinkun A	149138	$C_{18}H_{16}O_4$	296.3
43	Danthron	2950	$C_{14}H_8O_4$	240.21
44	Docosane	12405	$C_{22}H_{46}$	310.6
45	elgonica dimer A	21582596	$C_{36}H_{30}O_{14}$	686.6
46	Feralolide	5317333	$C_{18}H_{16}O_7$	344.3
47	Folacin	135398658	$C_{19}H_{19}N_7O_6$	441.4
48	Galactomannan	439336	$C_{18}H_{32}O_{16}$	504.4
49	Globulin G	74329879	$C_{36}H_{61}N_7O_{19}$	895.9
50	Hydrocortisone	5754	$C_{21}H_{30}O_5$	362.5
51	Ibuprofen	3672	$C_{13}H_{18}O_2$	206.28
52	Isoaloeresin	76332505	$C_{29}H_{32}O_{11}$	556.6
53	kaempferol	5280863	$C_{15}H_{10}O_6$	286.24
54	L-arabinose	439195	$C_5H_{10}O_5$	150.13
55	Leucine	6106	$C_6H_{13}NO_2$	131.17
56	Linalool	6549	$C_{10}H_{18}O$	154.25
57	Lophenol	160482	$C_{28}H_{48}O$	400.7
58	Lupeol	259846	$C_{30}H_{50}O$	426.7

59	Mannan	25147451	$C_{24}H_{42}O_{21}$	666.6
60	Meloxicam	54677470	$C_{14}H_{13}N_3O_4S_2$	351.4
61	Naproxen	156391	$C_{14}H_{14}O_3$	230.26
62	Niacin	938	$C_6H_5NO_2$	123.11
63	Phenylalanine	6140	$C_9H_{11}NO_2$	165.19
64	Potassium	5462222	K	39.098
65	Proline (PRO)	145742	$C_5H_9NO_2$	115.13
66	Quercetin	5280343	$C_{15}H_{10}O_7$	302.23
67	Rhababerone	12310964	$C_{15}H_{10}O_5$	270.24
68	Salicylic acid	338	$C_7H_6O_3$	138.12
69	Serine	5951	$C_3H_7NO_3$	105.09
70	Sorbitol	5780	$C_6H_{14}O_6$	182.17
71	Spathulenol	92231	$C_{15}H_{24}O$	220.35
72	Threonine	6288	$C_4H_9NO_3$	119.12
73	Thymol acetate	68252	$C_{12}H_{16}O_2$	192.25
74	Tricosane	12534	$C_{23}H_{48}$	324.6

The use of AutoDock Vina facilitated the determination of molecular interactions and binding energy between aloe vera phytoconstituents and TNF-α protein, contributing valuable insights for drug discovery endeavours. Molecular docking revealed significant interactions between aloe vera compounds and TNF-α. The measure of the affinity in a ligand-protein complex is termed as binding energy. It represents the difference between the energy of the complex (ligand bound to the protein) and the sum of the energies of each molecule separately (ligand and protein considered as independent entities). In other words, it quantifies the stability and strength of the interaction between the ligand and the protein in a molecular complex. A lower binding energy typically indicates a more favourable and stronger binding interaction. Table 2 summarizes the binding energies and key interactions of the top-performing compounds, thus revealing several high-energy interactions between aloe vera compounds and TNF-α. The observed binding affinity values range from -10 to -9.1 kcal/mol. Mannan exhibited the highest binding affinity with a docking score of -10.0 kcal/mol, forming multiple hydrogen bonds with PRO 100C, Glutamine (GLN) 102B, Arginine (ARG) 103B, Glutamine (GLN) 102A, PRO 100A, and Glutamic acid (GLU) 116B. It also engaged in hydrophobic interactions with GLU 116C, ARG 103A, GLU 104C, and PRO 100B. Folacin and aloesin both demonstrated strong binding with docking scores of -9.8 kcal/mol. Folacin formed hydrogen bonds with SER 99B, SER 99C, GLU 116B, and GLN 102A, while also engaging in hydrophobic interactions with GLN 102C and GLU 116A. Aloesin, interestingly, formed four hydrogen bonds with Alanine (ALA) 22B, Glycine (GLY) 24B, Lysine (LYS) 65B, and Aspartic acid (ASP) 140B, without any notable hydrophobic interactions. β-sitosterol and campesterol both showed binding energies of -9.6 kcal/mol, with β-sitosterol forming hydrogen bonds with GLU 116C and LYS 98B, and campesterol with GLU 116B. Both compounds shared a hydrophobic interaction with ARG 103B. These high-energy interactions suggest strong binding potential between the aloe vera compounds and TNF-α. The stability of the ligand-receptor complex is attributed to hydrogen bonds formed by OH and C=O groups, with the ligand playing a dual role as acceptor and donor[10]. This interaction, coupled with dispersion forces[11], π-π interactions, and hydrophobic interactions, particularly involving polar amino acids, contributes to the overall stability of the complex[12,13].

To contextualize our findings, we compared the binding energies of aloe vera compounds with those of standard anti-inflammatory drugs (Table 3). Notably, all of the top-performing aloe vera compounds exhibited higher binding affinities than the standard anti-inflammatory drugs. This suggests that these compounds, particularly mannan, folacin, and aloesin, may have significant potential as TNF-α inhibitors. This inhibition could play a crucial role in reducing inflammation associated with conditions like rheumatoid arthritis. However,

the anti-inflammatory effects of aloe vera likely extend beyond simple TNF-α inhibition. Recent studies have highlighted the importance of crosstalk between Interleukin (IL-9) and TNF-α in modulating inflammatory responses, playing a crucial role in the anti-inflammatory pathway[4]. This interaction involves reciprocal regulation, shared signalling pathways, and cell-specific effects, contributing to the complexity of inflammatory regulation in different tissues. In the context of our study on aloe vera compounds targeting TNF-α, understanding this crosstalk is crucial. The potential inhibition of TNF-α by aloe vera phytochemicals may not only directly reduce inflammation but also indirectly modulate IL-9 signalling, potentially contributing to the overall anti-inflammatory properties of aloe vera observed in various studies. The complex interplay between different inflammatory mediators underscores the potential advantages of multi-target therapeutic approaches, such as those offered by plant-derived compounds. Aloe vera, with its diverse array of bioactive molecules, may be particularly well-suited to modulate these intricate inflammatory networks.

Our investigation also extended to assessing the pharmacokinetics and toxicity properties of molecules exhibiting promising results, positioning them as potential drug candidates. The selection of potential inhibitors or optimal docked ligands was based on their binding energy, a critical factor in determining their efficacy. However, in the context of drug development, the evaluation of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties is essential.

TABLE 2: MOLECULAR DOCKING RESULTS OF ALOE VERA COMPOUNDS AGAINST TNF-α AND THE INTERACTING AMINO ACIDS

Compound name	Docking score (Kcal/mol)	Amino acids with hydrogen bonds	Amino acids with hydrophobic interactions
Drug references			
Aspirin	-5.6	GLN 102B	GLN 102A
Celecoxib	-7.6	ARG 103B, GLU 104B	GLN 102A, GLN 102B, GLN 102C, GLU 104A
Hydrocortisone	-6.3	ALN 33A, ASN 34A, ARG 82C	
Ibuprufen	-6.5	TYR 115A, SER 99C, CYS 101A	PRO 100A
Meloxicam	-6.3	ARG 103C, GLU 104A, GLU 104B, GLU 104C, GLN 102B, ARG 103A	ARG 103B
Naproxen	-7.1	LYS 65B, LEU 142B	PHE 144B
Aloe vera compounds			
Mannan	-10	PRO 100C, GLN 102B, ARG 103B, GLN 102A, PRO 100B, GLU 116B	GLU 116C, ARG 103C, GLU 104C, PRO 100B
Folacin	-9.8	SER 99B, SER 99C GLU 116B, GLN 102A	GLN 102C, GLU 116A
Aloesin	-9.8	ALA 22B, GLY 24B, LYS 65B, ASP 140B	-
β-sitosterol	-9.6	GLU 116C, LYS 98B	ARG 103B
Campesterol	-9.6	GLU 116B	ARG 103B
Lophenol	-9.4	GLU 116A	ARG 103B
Galactomannan	-9.4	THR 105B, ARG 103B, ARG 103A, GLN 102A, GLN 102B, GLU 104A, GLU 104B	GLU 107B
Cholesterol	-9.3	GLU 116B, LYS 98C	ARG 103B, LYS 98B
Quercetin	-9.1	GLN 102A, PRO 100A, GLU 116C, GLN 102C	
Kaempferol	-9.1	ASN 34A, GLN 125C, THR 7A, LEU 37A	LEU 36A

TABLE 3: LIPINSKI PARAMETERS FOR DATASET FROM SWISSADME

S. No.	Compound	Molecular weight (Da)	LogP	Hydrogen Bond Donor (HBD)	Hydrogen Bond Acceptor (HBA)	Violation	Yes/No	Solubility	LogS (mol/l)
1	Mannan	666.58	0.53	14	21	3	No	Highly soluble	2.5
2	Folacin	441.4	0.04	6	9	2	No	Soluble	-2.91
3	Aloesin	394.37	0.92	5	9	0	Yes	Very soluble	-1.53
4	β-sitosterol	414.71	5.05	1	1	1	Yes	Poorly soluble	-9.67
5	Campesterol	400.68	4.97	1	1	1	Yes	Poorly soluble	-9.11
6	Lophenol	400.68	5.06	1	1	1	Yes	Poorly soluble	-9.02
7	Galactomannan	504.44	0.13	11	16	3	No	Highly soluble	1.38
8	Cholesterol	386.65	4.89	1	1	1	Yes	Poorly soluble	-9.02
9	Quercetin	302.24	1.63	5	7	0	Yes	Soluble	-3.91
10	Kaempferol	286.24	1.7	4	6	0	Yes	Soluble	-3.86

The assessment of physicochemical properties, a key parameter influencing efficacy, safety, and metabolism, was carried out employing appropriate methodologies, emphasizing the significance of these properties in the drug development and discovery processes. In evaluating the physicochemical properties using RO5, which includes criteria such as molecular mass, hydrogen-bond donors, hydrogen-bond acceptors, and logP, the results demonstrated that among the top ten ligands, only 3 ligands fully complied with Lipinski's rule. Lipinski's screening serves as a crucial filter in the drug design process, determining the suitability of a compound for further development[14]. The polysaccharides mannan and galactomannan, along with the steroids campasterol, β-sitosterol, cholesterol, and lophenol, exhibited a noteworthy affinity for TNF-α. However, their potential use as drugs is hindered by a failure to comply with essential pharmacological parameters and a violation of the Lipinski rule of drug-likeness. In contrast, the chromone aloesin, and the flavonoids quercetin and kampferol, emerged as promising TNF-α inhibitors. These compounds not only demonstrated high affinity but also met all pharmacological parameters, showing potential for effective drug development. Importantly, these compounds adhered to pharmacological rules and displayed lead-like properties, as outlined in Table 3. This suggests a potential avenue for the development of these phytochemicals into drug molecules specifically targeting the cytokine TNF-α. Table 4 presents the pharmacokinetic and toxicity properties of the three potential inhibitors such as mannan, folacin, and aloesin. The Ames test (Ames_test), assessing mutagenicity, indicates that all 3 ligands are non-mutagenic. Carcinogenicity in rats (carcino_rat) is negative for all ligands, suggesting no carcinogenic potential. None of the ligands are predicted to permeate the Blood-Brain Barrier (BBB non-permeant). Mannan and folacin show hERG type 1 (hERG1) inhibition, indicating a potential risk for cardiac arrhythmia, while aloesin does not inhibit hERG I. All ligands are non-substrates for P-glycoprotein (P-gp), suggesting a low likelihood of causing drug interactions related to P-gp. Folacin and aloesin are predicted to have hepatotoxicity, while mannan is absence. None of the ligands show skin sensitization. Regarding cytochrome P450 inhibition, all ligands exhibit no inhibitory effects on the assessed isoforms (1A2, 2C19, 2C9, 2D6, 3A4). Overall, these results suggest that aloesin demonstrates a more favourable toxicity profile compared to mannan and folacin, making it a promising candidate for further drug development.

TABLE 4: PHARMACOKINETICS AND TOXICITY PROPERTIES OF THE 3 POTENTIAL INHIBITORS

Ligand	Ames_test	Carcino_rat	BBB permeant	hERG I	hERG II	P-gp	Hepatotoxicity	Skin sensitization	1A2	2C19	2C9	2D6	3A4
Mannan	No	Negative	No	No	Yes	Yes	No	No	No	No	No	No	No
Folacin	No	Negative	No	No	No	No	Yes	No	No	No	No	No	No
Aloesin	No	Negative	No	No	No	No	Yes	No	No	No	No	No	No

In addressing the global burden of rheumatoid arthritis, this study investigates the anti-inflammatory potential of aloe vera phytochemicals targeting TNF-α. Molecular docking studies identified promising compounds, such as aloesin, quercetin, and kampferol, exhibiting high affinity for TNF-α. Despite Lipinski's rule violations for some compounds, aloesin stands out for its superior binding energy and drug like properties. Future directions include *in vivo* studies, biological assays, compound optimization, exploring combination therapy, and progressing to clinical trials. These findings suggest a potential avenue for developing novel and effective therapeutics for rheumatoid arthritis.

Conflict of interest:

The authors declared no conflict of interests.

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