Molecular Diversity
https://doi.org/10.1007/s11030-023-10614-w

ORIGINAL ARTICLE

Unravelling the anti-inflammatory mechanism of *Allium cepa*: an integration of network pharmacology and molecular docking approaches

Victor Omoboyede[1,2] · Olugbenga Samson Onile[3] · Bolaji Fatai Oyeyemi[4] · Raphael Taiwo Aruleba[5] · Adeyinka Ignatius Fadahunsi[3] · Grace Ayomide Oke[6] · Tolulope Adelonpe Onile[7] · Ochapa Ibrahim[8] · Tayo Alex Adekiya[9]

Received: 19 December 2022 / Accepted: 25 January 2023
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2023

Abstract

Allium cepa, commonly known as onion, is a widely consumed spice that possesses numerous pharmacological properties. *A. cepa* bioactive components are often explored in the treatment of inflammation-related complications. However, the molecular mechanism via which they exert their anti-inflammatory effects remains unknown. Therefore, this study aimed to elucidate the anti-inflammatory mechanism of *A. cepa* bioactive components. Consequently, the bioactive compounds of *A. cepa* were obtained from a database, while the potential targets of the sixty-nine compounds with desirable pharmacokinetic properties were predicted. Subsequently, the targets of inflammation were acquired from the GeneCards database. The protein–protein interaction (PPI) between the sixty-six shared targets of the bioactive compounds and inflammation was retrieved from the String database and visualized using Cytoscape v3.9.1 software. Gene Ontology (GO) analysis of the ten core targets from the PPI network revealed that *A. cepa* bioactive compounds could be involved in regulating biological processes such as response to oxygen-containing compounds and response to inflammation while Kyoto Encyclopaedia of Genes and Genomes (KEGG) analysis revealed that *A. cepa* compounds might modulate pathways including AGE-RAGE signaling pathway, interleukin (IL)-17 signalling pathway, and tumor necrosis factor signaling pathway. Molecular docking analysis showed that 1-O-(4-Coumaroyl)-beta-D-glucose, stigmasterol, campesterol, and diosgenin have high binding affinities for core targets including EGFR, ALB, MMP9, CASP3, and CCL5. This study successfully elucidated the potential anti-inflammatory mechanism of *A. cepa* bioactive compounds, hence, providing new insights into the development of alternative anti-inflammatory drugs.

✉ Victor Omoboyede
omoboyedebch174299@futa.edu.ng

✉ Olugbenga Samson Onile
olugbenga.onile@elizadeuniversity.edu.ng

Bolaji Fatai Oyeyemi
Oyeyemi_bf@fedpolyado.edu.ng

Raphael Taiwo Aruleba
arulebataiwo@yahoo.com

Adeyinka Ignatius Fadahunsi
adeyinka.fadahunsi@elizadeuniversity.edu.ng

Grace Ayomide Oke
graceoke253@gmail.com

Tolulope Adelonpe Onile
tolulope.onile@elizadeuniversity.edu.ng

Ochapa Ibrahim
ochapa.ibrahim@elizadeuniversity.edu.ng

Tayo Alex Adekiya
Adekiyatalex@gmail.com

[1] Department of Biochemistry, School of Life Sciences (SLS), Federal University of Technology Akure, P.M.B 704, Akure, Nigeria

[2] Computer-Aided Therapeutics Laboratory (CATL), Federal University of Technology Akure, P.M.B 704, Akure, Nigeria

[3] Biotechnology Programme, Department of Biological Sciences, Elizade University, P.M.B, 002 Ilara-Mokin, Ilara-Mokin 340271, Nigeria

[4] Molecular Biology Group, Department of Science Laboratory Technology, The Federal Polytechnic, Ado-Ekiti, Ekiti, Nigeria

[5] Department of Molecular and Cell Biology, Faculty of Science, University of Cape Town, Cape Town 7701, South Africa

[6] Department of Food Science and Technology, Federal University of Technology Akure, P.M.B 704, Akure, Nigeria

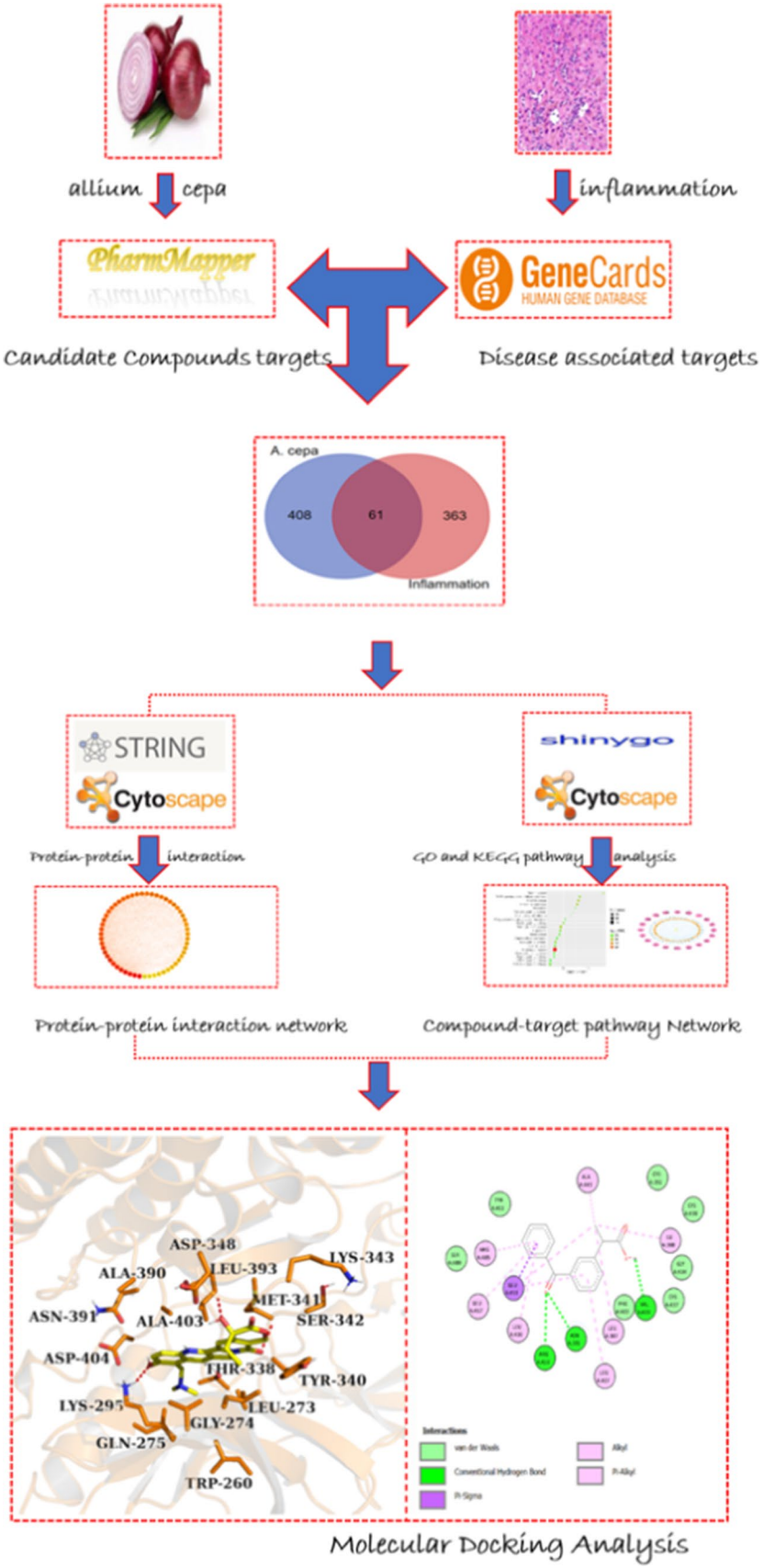
[7] Microbiology Programme, Department of Biological Sciences, Elizade University, Ilara Mokin, P.M.B, 002, Ilara-Mokin 340271, Nigeria

[8] Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna, Nigeria

[9] Department of Pharmaceutical Sciences, Howard University, Washington, DC 20059, USA

Published online: 03 March 2023

Graphical abstract



Keywords Inflammation · Onion · Network pharmacology · Molecular docking · Signaling pathways

Introduction

Inflammation is a process which plays an essential role in the biological response of the immune system against infections [1]. The inflammation cascade, which also plays an essential role in the regulation of tissue homeostasis, involves the activation of the cells of the innate and the adaptive immune system [2]. Generally, inflammatory responses are of two types, the acute inflammatory response is majorly triggered by the cells of the innate immune system, while the chronic inflammatory response, which develops from the acute inflammatory response, is triggered by persistent pathogens. While inflammation is a phenomenon pivotal to the elimination of infections, it also plays a significant role in the pathogenesis of several diseases including cancer. For example, the chronic inflammatory response often leads to the creation of a biological milieu favorable to tumorigenesis and tumor progression [3]. Noteworthy, chronic inflammatory diseases are associated with more than 50% of all deaths worldwide [4].

Currently, the most common treatment for both acute and chronic inflammation is the administration of non-steroidal anti-inflammatory drugs (NSAIDs), with diclofenac and ibuprofen being the most widely used in the world. However, numerous side effects are associated with the administration of NSAIDs. This includes mild effects such as vomiting, dizziness, and headache, and severe ones such as stomach ulcers, stroke, and stomach bleeding [5]. Consequently, naturally-derived small molecules are being explored as viable alternatives to NSAIDs.

Allium cepa, commonly known as onion, is one of the most consumed culinary spices in the world. Onion, belonging to the *Liliaceae,* possesses a plethora of bioactive compounds and pharmacological properties including anti-inflammatory, anti-cancer, and antioxidant properties [6]. Several studies have evaluated the anti-inflammatory properties of *A. cepa*. MareFati *et al*. reported that the anti-inflammatory properties of *A. cepa* are due to the presence of compounds including tannin, flavonoids, and anthocyanin [7]. Yamaguchi *et al*. reported that nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) induced by receptor activator of NF- κB ligand (RANKL) in MC3T3-E1 preosteoblastic cell line was greatly suppressed by quercetin [8]. Similarly, Simin *et al*. reported that some phenolic compounds of *A. cepa* including quercetin-3-O-glucoside, kaempferol-3-Oglucoside, 4-hydroxybenzoic acid, and vanillic expressed inhibitory properties against Cyclooxygenase 1 and 12-lipoxygenase. Furthermore, isorhamnetin-3-glucoside, dipropyl disulphide and dipropyl sulphide of *A. cepa* have also been reported to possess OH^- scavenging effect, hence, showing antioxidant properties [9]. While there have been numerous studies on the anti-inflammatory effects of *A. cepa* compounds, only a few of the compounds have been explored in studies and the interaction between the effective components and their therapeutic targets is still not clear. Furthermore, there could be some unidentified *A. cepa* compounds endowed with anti-inflammatory properties.

Advances in bioinformatics have shifted the one-drug/one-target/one-disease paradigm in drug design and discovery through the integration of network biology and polypharmacology to develop multitarget drugs. Consequently, network pharmacology has emerged as an effective approach for unravelling the pharmacological mechanisms of multitarget compounds in various diseases [10]. Using this approach, this study aims to identify the effective bioactive compounds of *A. cepa*, their potential targets, and the signaling pathways through which they exert their anti-inflammatory effects, hence, establishing a hypothesis for further studies aimed at developing anti-inflammatory therapies.

Materials and methods

Retrieval of active compounds

The active compounds of *A. cepa* were retrieved from the Indian Medicinal Plants, Phytochemistry and Therapeutics curated database (IMPPAT) (https://cb.imsc.res.in/imppat/home) [11]. IMPPAT database is a platform that holds the phytochemical composition, traditional medicinal formulation, and disease interactions of Indian herbal medicines. Subsequently, the chemical structures and PubChem CID of the active compounds were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [12]. Using admetSAR 2.0 webserver (http://lmmd.ecust.edu.cn/admetsar2/) [13], the retrieved compounds were further screened using pharmacokinetic parameters such as absorption, distribution, metabolism, excretion, toxicity, while drug-likeness was evaluated using the Lipinski rule of 5 (RO5) [14].

Prediction of compound targets and inflammation-associated targets

Putative targets of *A. cepa* active compounds were obtained from an online compound targets prediction platform PharmApper (http://lilab-ecust.cn/pharmmapper/) [15]. The chemical structures of the compounds were used as the search input. Subsequently, the predicted compound targets were matched to their standard gene name using the ID mapping tool of Uniprot (https://www.uniprot.org/id-mapping). Similarly, the target genes of inflammation were retrieved from the GeneCards database (https://www.genecards.org/)

[16], using the keyword "inflammation" with a relevance score ≥ 5. The common targets of *A. cepa* active compounds and inflammation were identified using the Venn Diagram Online Tool v2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/index.html).

Construction of protein–protein interaction (PPI) network

The String database (https://string-db.org/) [17] was employed to construct the PPI network of the common targets of *A. cepa* active compounds and inflammation, with Homo sapiens selected as the organism of interest and a medium confidence score of 0.4, as the minimum required interaction score. Subsequently, Cytoscape v3.9.1 software was employed to visualize the PPI network, while the Network Analyzer tool of Cytoscape was utilized to analyse the topological parameters of the network [18].

Gene set enrichment analysis

ShinyGo v0.76 web server (https://bioinformatics.sdstate.edu/go/) [19] was employed to perform the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) of the common targets. Furthermore, the enrichment plots of the significant GO and pathways of the target genes were generated using the in-built graphing tool on the same web server.

Construction of drug-components-disease-targets-pathways network

A network of drug components-disease-targets-pathways was constructed using Cytoscape v3.9.1 software. This was performed to elucidate the anti-inflammatory mechanism of *A. cepa.* In the network, compounds, targets, or disease-correlated pathways, were represented by nodes with different colors and shapes.

Molecular docking simulation and validation

Molecular docking studies were performed to elucidate the binding mechanism of *A. cepa* active compounds against essential inflammation targets. The three-dimensional structure (3D) of the top eleven common targets were retrieved from the protein data bank (https://www.rcsb.org/) and were prepared using the Dock Prep module of USCF chimera v1.10.2 software [20]. Subsequently, the resulting structure of the individual protein targets was subjected to an energy minimization algorithm using the Swiss-PdbViewer v.4.10 software program [21]. This process identifies the missing side chains of protein residues and replaces them. The computation was executed *in vacuo* with the GROMOS 43B1 parameter set and without field reaction. Furthermore, the 3D structure of *A. cepa* active compounds was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). The geometries of the compounds were energy minimized using the universal force field (UFF) in PyRx v0.8 software [22]. The VINA module integrated into PyRx v0.8 software [22] was employed to perform the docking simulation, with default iterations. The prepared proteins and the optimized compounds were the inputs for receptors and ligands respectively, while a standard drug (Ketoprofen) was used as the reference compound. Noteworthy, the space occupied by the cognate ligand of each protein was used to define the binding sites, and a grid box was centered along the x, y, and z axes, to allow the full coverage of the hotspot residues. The docking protocol employed in this study was validated by redocking the cognate ligand of a selected protein and calculating the root mean square deviation (RMSD) of the cognate ligand and the redocked cognate ligand. Following the docking simulation, LigPlot v.2.2.5 and PyMOL v.2.5.2 freeware programs [23, 24] were employed to visualize the 2D and 3D structures of the resulting complexes.

Results

Retrieval of active compounds

187 Unique active compounds, including flavonoids, phenolics, and sulphurous compounds, were retrieved from the IMPPAT database. After a further screening of the retrieved compounds, sixty-nine compounds with desirable ADMET and drug-like profiles were obtained and taken for the next process. The 69 compounds possessed good Lipinski properties and can cross the human intestinal epithelial barrier, Caco-2 permeable, and were also predicted to be non-toxic.

The details of the retrieved compounds and screening results are shown in Table 1.

Acquisition of compound and inflammation-associated targets

A total of 469 unique putative targets were obtained for the 66 active compounds of *A. cepa* using the PharmMapper server. Noteworthy, three of the previously mentioned sixty-nine bioactive compounds were predicted to lack human protein targets by PharmMapper. Similarly, 424 inflammation targets were retrieved from GeneCards with a relevance cut-off ≥ 5. 61 common targets of the compounds and inflammation were identified using the Venn Diagram Online Tool, and these targets were considered the potential targets of *A. cepa* in exerting its anti-inflammatory effects (Fig. 1).

PPI network construction

StringDB was employed to generate a PPI network to uncover the interactive relationship between the 61 common targets. All the 61 targets showed interactions in the PPI network, with a confidence score > 0.4. Visualization and further analysis of the generated PPI network using Cytoscape v3.9.1 showed the network possessed 61 nodes and 570 edges. As depicted in Fig. 2, the varying colors of the PPI network nodes correspond to the degree of interactions between the targets, with the degree of interactions increasing in the order yellow < orange < red. Using the CytoHubba plug-in, the top 10 targets of the network based on the degree of interactions identified are depicted in Fig. 3, these targets were considered the critical targets of *A. cepa* anti-inflammatory effects.

Gene set enrichment analysis

ShinyGo v0.76 webserver was employed to perform the gene set enrichment analysis of the 61 common targets. In the GO analysis, the biological processes in which the common targets were enriched included the regulation of inflammatory response, regulation of programmed cell death, response to oxygen-containing compounds and regulation of apoptotic processes. Similarly, the molecular functions of the common targets included endopeptidase activity, cytokine receptor binding, protein kinase activity, and signaling receptor binding. The common targets were also localized in the vesicle lumen, membrane raft, cell surface and secretory granule lumen. The top 10 results of the GO analysis were selected for visualization based on an FDR cutoff of 0.05 and depicted in Fig. 4.

KEGG pathway analysis of the common targets revealed the pathway in which the common targets are primarily enriched. The pathways included the relaxin signaling pathway, pathways in cancer, lipid and atherosclerosis, and the IL-17 signaling pathway. The top 20 pathways were identified and visualized based on an FDR cutoff of 0.05 (Fig. 5).

Construction of drug-components-disease-targets-pathways network

The complex relationship between 66 *A. cepa* compounds, 61 common targets, and the 20 core molecular pathways is depicted in Fig. 6. The compounds, represented in orange, interact with one or more inflammation targets, enriched in one or more molecular pathways. Among the compounds, 1-Caffeoyl-beta-D-glucose, with PubChem ID "CID: 5281761" had the highest degree of interaction (20) with the common targets, while pathways in cancer were the molecular pathway in which the common targets are mostly enriched (19).

Molecular docking simulation

To unravel the binding mechanism and affinity of the compounds for the core targets, molecular docking simulation was performed using the VINA module integrated into PyRx v0.8 software. The 66 *A. cepa* compounds were docked with the identified top 10 targets from the PPI network. Analysis of the docking results revealed diosgenin (CID: 99474) as the most selective binder for six of the ten core targets. Compared to our standard drug (Ketoprofen), diosgenin showed the highest binding affinity for targets including SRC ($\Delta = -10.4$ kcal mol^{-1}), PPARG ($\Delta = -9.1$ kcal mol^{-1}), MMP9 ($\Delta = -9.5$ kcal mol^{-1}), MMP2 ($\Delta = -9.0$ kcal mol^{-1}), EGFR ($\Delta = -10.7$ kcal mol^{-1}), and CCL5 ($\Delta = -7.2$ kcal mol^{-1}). Similarly, 1-O-(4-Coumaroyl)-beta-D-glucose (CID: 14,158,117) showed the highest binding affinity for targets ALB ($\Delta = -7.5$ kcal mol^{-1}) and CASP3 ($\Delta = -6.1$ kcal mol^{-1}), while stigmasterol (CID: 5280794) showed the highest binding affinity for AKT ($\Delta = -8.4$ kcal mol^{-1}). Campesterol (CID: 173183) and Cholesterol (CID: 5997) showed the highest binding affinity for target IGF1. Other compounds including 1-Caffeoyl-beta-D-glucose, flavylium, and lophenol, 24-methylenophenol also showed high binding affinities for the targets (Table 2). Noteworthy, lower binding energy corresponds to greater interaction. Validation of the docking protocol via the superimposition of the redocked cognate ligand of ALB on the native ligand showed a RMSD value of 0.044 Å (Fig. 7).

The interactions of 1-O-(4-Coumaroyl)-beta-D-glucose, diosgenin, and the standard drug with the top two targets of the PPI network (ALB and MMP9) were visualized using LigPlot v.2.2.5 and PyMOL v.2.5.2. As depicted in Fig. 8A, Diosgenin exhibited hydrophobic interactions with Tyr179, Leu187, Leu188, Ala189, His190, Ala191, Phe192, Val223, Glu227, His230, His236, Pro246, Met247, and Tyr248 of MMP9. Similarly, some of these residues including Leu188, Ala189, Val223, His226, Pro246, Met247, and Tyr248 were also among the interacting residues in Ketoprofen-MMP9 complex (Fig. 8B).

The comparison of ALB interactions with ketoprofen and 1-O-(4-Coumaroyl)-beta-D-glucose showed both exhibited hydrophobic interactions with Phe 403, Leu407, Tyr411, Leu430, Val433, and Leu453 of ALB and hydrogen bond interactions with Asn391 and Arg410 of ALB (Fig. 8C and D). Conversely, only 1-O-(4-Coumaroyl)-beta-D-glucose interacted with ALB via hydrogen bond with Val433.

Table 1 List of *A. cepa* bioactive compounds retrieved from IMPPAT server

S/No.	Compounds	Phytochemical identifier	RO5	Absorption				Metabolism (CYP450 Inhibition)					Toxicity		
				$Cac0_2$	BBB	HIA	P-gp	IA2	2C9	2D6	2C19	3A4	AT	CT	hERG
1.	Riboflavin	CID:493570	+	−	+	+	−	No	No	No	o	No	No	No	No
2.	Alliofuroside A	CID:4,97967	−	−	−	−	+	No	No	No	No	No	No	No	No
3.	**Propanol**	**CID:1031**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
4.	**1-O-(4-Coumaroyl)-beta-D-glucose**	**CID:14158117**	**+**	**−**	**−**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
5.	Dimethyl disulfide	CID:12232	+	+	+	+	−	No	No	No	No	No	No	No	No
6.	Diallyl sulfide	CID:11617	+	+	+	+	−	No	No	No	No	No	No	No	No
7.	**2-Tridecanone**	**CID:11622**	**+**	**+**	**+**	**+**	**−**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
8.	Quercetin 7,4'-diglucoside	CID:11968881	−	−	−	+	−	No	No	No	No	No	Yes	No	Yes
9.	Alliospiroside A	CID:101641343	−	−	−	−	+	No	No	No	No	No	No	No	Yes
10.	Alliospiroside B	CID:101641344	−	−	−	−	+	No	No	No	No	No	No	No	Yes
11.	1-O-feruloyl-beta-D-glucose	CID:13962928	+	−	−	+	−	No	No	No	No	No	No	No	No
12.	Cycloeucalenol	CID:101690	+	−	+	+	−	No	No	No	No	No	No	No	No
13.	**2,3-Dihydroflavon-3-ol**	**CID:147806**	**+**	**+**	**−**	**+**	**−**	**Yes**	**No**	**No**	**Yes**	**No**	**No**	**No**	**No**
14.	**2,3-Dimethylthiophene**	**CID:34295**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**	**No**
15.	**2,4-Dimethylthiophene**	**CID:34296**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
16.	S-Methylthiocysteine	CID:3080775	+	−	+	−	−	No	No	No	No	No	No	No	No
17.	2-Azaniumyl-3-propylsulfinylpropanoate	CID:25202184	+	−	+	−	−	No	No	No	No	No	No	No	No
18.	**Flavylium**	**CID:145858**	**+**	**+**	**+**	**+**	**−**	**Yes**	**No**	**No**	**Yes**	**No**	**No**	**No**	**No**
19.	**Phloroglucinol**	**CID:359**	**+**	**+**	**−**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
20.	**Mevalonic acid**	**CID:439230**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
21.	1-Kestose	CID:440080	−	−	+	−	−	No	No	No	No	No	No	No	Yes
22.	**2-Methylpentanal**	**CID:31245**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
23.	Citric acid	CID:311	+	−	−	+	−	No	No	No	No	No	No	No	No
24.	Calcium oxalate	CID:33005	+	−	−	+	−	No	No	No	No	No	No	No	No
25.	**Cycloartanol**	**CID:12760132**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
26.	**Choline**	**CID:305**	**+**	**+**	**+**	**−**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
27.	**Sinapic acid**	**CID:637775**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
28.	Kaempferol	CID:5280863	+	−	−	+	−	Yes	Yes	No	Yes	Yes	Yes	No	No
29.	**3(2H)-Furanone, 5-methyl-2-octyl-**	**CID:529383**	**+**	**+**	**+**	**+**	**−**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
30.	5-Dehydro-avenasterol	CID:44263331	+	+	+	+	+	No	No	No	No	No	No	No	Yes
31.	**Stearic acid**	**CID:5281**	**+**	**+**	**+**	**+**	**−**	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
32.	Isoalliin	CID:5281112	+	−	+	+	−	No	No	No	No	No	No	Yes	No
33.	Methyl propyl disulfide	CID:16592	+	+	+	+	−	No	No	No	No	No	No	Yes	No
34.	Allyl propyl disulfide	CID:16591	+	+	+	+	−	No	No	No	No	No	No	Yes	No
35.	**2-Methylbutyl 2-methylbutyrate**	**CID:17129**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**

Table 1 (continued)

S/No.	Compounds	Phytochemical identifier	RO5	Absorption				Metabolism (CYP450 Inhibition)					Toxicity		
				$Cac0_2$	BBB	HIA	P-gp	IA2	2C9	2D6	2C19	3A4	AT	CT	hERG
36.	**1-Caffeoyl-beta-D-glucose**	**CID:5281761**	+	−	−	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
37.	**Tianshic acid**	**CID:5321949**	+	−	−	+	−	+	**No**	**No**	**No**	**No**	**No**	**No**	**No**
38.	Diallyl trisulfide	CID:16315	+	+	+	+	−	No	No	No	No	No	No	Yes	No
39.	Levan n	CID:440946	−	−	+	−	−	No	No	No	No	No	No	No	Yes
40.	Brassicasterol	CID:5281327	+	+	+	+	−	No	No	No	No	No	No	No	Yes
41.	Dimethyl trisulfide	CID:19310	+	+	+	+	−	No	No	No	No	No	No	Yes	No
42.	Alloxan	CID:5781	+	−	+	+	−	No	No	No	No	No	No	No	No
43.	**2-Methylpent-2-en-1-ol**	**CID:5362851**	+	+	+	+	−	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
44.	2-Amino-3-(propyldisulfanyl)propanoic acid	CID:560398	+	−	+	+	−	No	No	No	No	No	No	No	No
45.	Dipropyl trisulfide	CID:22383	+	+	+	+	−	No	No	No	No	No	No	Yes	No
46.	**Trigonelline**	**CID:5570**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
47.	Acetal	CID:7765	+	+	+	+	−	No	No	No	No	No	No	Yes	No
48.	Glycolic acid	CID:757	+	−	+	+	−	No	No	No	No	No	No	No	No
49.	**Cholesterol**	**CID:5997**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
50.	Allyl methyl trisulfide	CID:61926	+	+	+	+	−	No	No	No	No	No	No	Yes	No
51.	Ascorbic acid	CID:54670067	+	−	+	+	−	No	No	No	No	No	No	No	No
52.	1 – Propanethiol	CID:7848	+	+	+	+	−	No	No	No	No	No	No	No	No
53.	Gamma – Glutamylmethionine	CID:7009567	+	−	+	−	−	No	No	No	No	No	No	No	No
54.	2-Methyl-2-buten-1-OL	CID:6433417	+	+	+	+	−	No	No	No	No	No	No	No	No
55.	6-Kestose	CID:9914062	−	−	+	−	−	No	No	No	No	No	No	No	+
56.	Oxalic acid	CID:971	+	−	+	+	−	No	No	No	No	No	No	No	No
57.	(3R,5S)-5-Methyl-1-oxo-1,4-thiazinane-3-carboxylic acid	CID:91808874	+	−	+	−	−	No	No	No	No	No	No	No	No
58.	**Nicotinic acid**	**CID:938**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
59.	**Palmitic acid**	**CID:985**	+	+	+	+	−	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
60.	**Propionaldehyde**	**CID:527**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
61.	**Nonadecanoic acid**	**CID:12591**	+	+	+	+	−	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
62.	**Neodecanoic acid**	**CID:62838**	+	+	+	+	−	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
63.	**1-Octanol**	**CID:957**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
64.	Cyanidin	CID:128861	+	−	+	+	−	Yes	No	No	No	No	Yes	No	No
65.	Vitamin E	CID:14985	+	+	+	+	−	No	No	No	No	No	No	No	No
66.	**3,4-Dimethylthiophene**	**CID:79089**	+	+	+	+	-	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**	**No**	**No**
67.	Isorhamnetin	CID:5281654	+	−	−	+	−	Yes	Yes	No	Yes	Yes	No	No	No
68.	**Lophenol**	**CID:160482**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
69.	Cyanidin 3-laminaribioside	CID:44256721	−	−	−	−	−	No	No	No	No	No	No	No	No

Table 1 (continued)

S/No.	Compounds	Phytochemical identifier	RO5	Absorption				Metabolism (CYP450 Inhibition)					Toxicity		
				$Cac0_2$	BBB	HIA	P-gp	IA2	2C9	2D6	2C19	3A4	AT	CT	hERG
70.	Cyanidin 3 – malonylglucoside	CID:10143380	+	–	–	–	–	No	No	No	No	No	Yes	No	No
71.	Allyl mercaptan	CID:13367	+	+	+	+	–	No	No	No	No	No	No	Yes	No
72.	**2,5-Dimethylthiophene**	**CID:12,514**	**+**	**+**	**+**	**+**	**–**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
73.	Dipropyl disulfide	CID:12377	+	+	+	+	–	No	No	No	No	No	No	Yes	No
74.	Propanethial S-oxide	CID:441491	+	+	+	+	–	No	No	No	No	No	No	Yes	No
75.	**24-Methylenecycloartanol**	**CID:94204**	**+**	**–**	**+**	**+**	**–**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
76.	2-Methyl-2-pentenal	CID:5319754	+	+	+	+	–	No	No	No	No	No	Yes	No	No
77.	Lutein	CID:5281243	+	–	+	+	+	No	No	No	+	No	No	No	Yes
78.	**Gibberellic acid**	**CID:6466**	**+**	**–**	**+**	**+**	**–**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
79.	Cycloartenol	CID:92110	+	+	+	+	–	No	No	No	No	No	No	No	Yes
80.	Beta-Tocopherol	CID:6857447	+	+	+	+	–	No	No	No	No	No	No	No	Yes
81.	Alpha-Amyrin	CID:73170	+	+	+	+	–	No	No	No	No	No	No	No	Yes
82.	Diallyl disulfide	CID:16590	+	+	+	+	–	No	No	No	No	No	No	Yes	No
83.	Fucosterol	CID:5281326	+	+	+	+	+	No	No	No	No	No	No	No	Yes
84.	Arachidic acid	CID:10467	+	+	+	+	–	Yes	No	No	No	No	No	No	No
85.	Alpha-Carotene	CID:6419725	–	–	+	+	+	No	No	No	No	No	No	No	Yes
86.	**(2Z,4E)-5-[(1S)-1-hydroxy-2,6,6-trimethyl-4-oxocyclohex-2-en-1-yl]-3-methylpenta-2,4-dienoic acid**	**CID:5280896**	**+**	**+**	**+**	**+**	**–**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
87.	Beta-Carotene	CID:5280489	–	–	+	+	+	No	No	No	No	No	No	No	Yes
88.	**Oleanolic acid**	**CID:10494**	**+**	**+**	**–**	**+**	**–**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
89.	Isorhamnetin 3 – glucoside	CID:44258009	–	–	–	+	–	No	No	No	No	No	No	No	No
90.	Zeaxanthin	CID:5,280899	–	–	+	+	+	No	No	No	Yes	No	No	No	Yes
91.	**Oleic acid**	**CID:445639**	**+**	**+**	**+**	**+**	**+**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
92.	Taxifolin	CID:439533	+	–	–	+	–	Yes	No	No	No	Yes	Yes	No	No
93.	Glutathione	CID:124886	+	–	–	–	–	No	No	No	No	No	Yes	No	No
94.	Raffinose	CID:439242	–	–	+	–	–	No	No	No	No	No	No	No	Yes
95.	Isoquercitrin	CID:5280804	–	–	–	+	–	No	No	No	No	No	Yes	No	No
96.	Adenosine	CID:60961	+	–	+	+	–	No	No	No	No	No	No	No	No
97.	**24-Methylenelophenol**	**CID:5283640**	**+**	**+**	**+**	**+**	**–**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
98.	Sucrose	CID:5988	–	–	+	–	–	No	No	No	No	No	No	No	No
99.	**Campesterol**	**CID:173183**	**+**	**+**	**+**	**+**	**–**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
100.	D-Galactose	CID:6036	+	–	+	–	–	No	No	No	No	No	No	No	No
101.	**4-Hydroxycinnamic acid**	**CID:637542**	**+**	**+**	**–**	**+**	**–**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
102.	**cis-3,5-Diethyl-1,2,4-trithiolane**	**CID:6431294**	**+**	**+**	**+**	**+**	**–**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**

Table 1 (continued)

S/No.	Compounds	Phytochemical identifier	RO5	Absorption				Metabolism (CYP450 Inhibition)					Toxicity		
				$Cac0_2$	BBB	HIA	P-gp	IA2	2C9	2D6	2C19	3A4	AT	CT	hERG
103.	**Stigmasterol**	**CID:5280794**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
104.	Daucosterol	CID:5742590	−	−	+	−	+	No	No	No	No	No	No	No	Yes
105.	Cyanidin 3-glucoside	CID:12303220	+	−	+	−	−	−	−	−	−	−	+	−	−
106.	D-Glucose	CID:5793	+	−	+	−	−	No	No	No	No	No	No	No	No
107.	D -Fructose	CID:2723872	+	−	+	−	−	No	No	No	No	No	No	No	No
108.	Quercetin-3-glucoside	CID:25203368	−	−	−	+	−	No	No	No	No	No	No	No	No
109.	**2,4,6-Trihydroxybenzoic acid**	**CID:66520**	+	+	−	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
110.	**Linoleic acid**	**CID:5280450**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
111.	Rutin	CID:5,280805	−	−	−	+	−	No	No	No	No	No	Yes	No	No
112.	1-Propyltrithiopropane	CID:119097326	+	−	+	+	−	No	No	No	No	No	No	Yes	No
113.	L-Rhamnose	CID:25310	+	−	+	−	−	No	No	No	No	No	No	No	No
114.	Alliospiroside C	CID:4638509	+	−	−	−	+	No	No	No	No	No	No	No	Yes
115.	D-Ribose	CID:10975657	+	−	+	−	−	No	No	No	No	No	Yes	No	No
116.	Alliospiroside D	CID:13939861	+	−	−	−	+	No	No	No	No	No	No	No	Yes
117.	Xylitol	CID:6912	+	−	−	+	−	No	No	No	No	No	No	No	No
118.	Allyl propyl sulfide	CID:98781	+	+	+	+	−	No	No	No	No	No	No	Yes	No
119.	D-Xylose	CID:135191	+	−	+	−	−	No	No	No	No	No	Yes	No	No
120.	Allyl propyl trisulfide	CID:525330	+	+	+	+	−	No	No	No	No	No	No	Yes	No
121.	**Melatonin**	**CID:896**	+	+	+	+	−	**Yes**	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**
122.	DL-Methionine sulfone	CID:69961	+	−	+	−	−	No	No	No	No	No	No	No	No
123.	Hexadecen-1-ol	CID:6442614	+	+	+	+	−	Yes	No	No	No	No	No	Yes	Yes
124.	Methyl propyl tetrasulphide	CID:528709	+	+	+	+	−	No	No	No	No	No	No	Yes	No
125.	Eicosen-1-ol	CID:6365348	+	+	+	+	−	Yes	No	No	No	No	No	Yes	Yes
126.	Methyl propyl trisulfide	CID:5319765	+	+	+	+	−	No	No	No	No	No	No	Yes	No
127.	Dipropyl tetrasulfide	CID:104285	+	+	+	+	−	No	No	No	No	No	No	Yes	No
128.	1 – Propene – 1-thiol	CID:5366351	+	+	+	+	−	No	No	No	No	No	No	Yes	No
129.	Dimethyl pentasulphide	CID:81772	+	+	+	+	−	No	No	No	No	No	No	Yes	No
130.	Selenohomocystine	CID:24496	+	−	+	−	−	No	No	No	No	No	No	No	No
131.	(2S)-2-amino-3-methylsulfinylpropanoic acid	CID:99483	+	−	+	−	−	No	No	No	No	No	No	No	No
132.	Tuliposide B	CID:441643	+	−	+	−	−	No	No	No	No	No	No	No	No
133.	Tuliposide A	CID:108011	+	−	+	−	−	No	No	No	No	No	No	No	No
134.	s-Propyl cysteine sulfoxide	CID:129704175	+	−	+	+	−	No	No	No	No	No	Yes	No	No
135.	Selenomethylselenomethionine	CID:129845685	+	−	+	−	−	No	No	No	No	No	No	No	No
136.	Seleno-methyl-seleno cysteine	CID:129712298	+	−	+	−	−	No	No	No	No	No	No	No	No

Table 1 (continued)

S/No.	Compounds	Phytochemical identifier	RO5	Absorption				Metabolism (CYP450 Inhibition)					Toxicity		
				$Cac0_2$	BBB	HIA	P-gp	IA2	2C9	2D6	2C19	3A4	AT	CT	hERG
137.	Hexadecane	CID:11006	+	+	−	+	−	Yes	No	No	No	No	No	Yes	No
138.	Peonidin-3-glucoside	CID:443654	+	−	−	−	−	No	No	No	No	No	No	No	No
139.	**Diphenylamine**	**CID:11487**	**+**	**+**	**+**	**+**	**−**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**No**	**No**
140.	Octadecane	CID:11635	+	+	+	+	−	No	No	No	No	No	No	Yes	No
141.	**Tsibulin 2**	**CID:14,391671**	**+**	**+**	**+**	**+**	**−**	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
142.	**1-Hexadecanol**	**CID:2682**	**+**	**+**	**+**	**+**	**−**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
143.	**Lauric acid**	**CID:3893**	**+**	**+**	**+**	**+**		**Yes**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
144.	**4-Octylcyclopentane-1,3-dione**	**CID:180441**	**+**	**+**	**+**	**+**	**−**	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
145.	**Diosgenin**	**CID:99474**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**
146.	**(−)-Isopulegol**	**CID:170833**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
147.	**Catechol**	**CID:289**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**
148.	L-(+)-Arabinose	CID:5460291	+	−	−	+	−	No	No	No	No	No	No	No	No
149.	Quercetin 3,4'-diglucoside	CID:5320835	−	−	−	−	+	No	No	No	No	Yes	Yes	No	Yes
150.	Quercetin	CID:5280343	+	−	−	+	−	Yes	No	Yes	No	Yes	Yes	No	No
151.	Myricetin	CID:5,281672	+	−	−	+	−	Yes	No	No	No	Yes	Yes	No	No
152.	**2,4,6-Triethyl-1,3,5-dithiazinane**	**CID:547350**	**+**	**+**	**+**	**+**	**−**	**Yes**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
153.	Folic	CID:6037	+	−	−	−	−	No	No	No	No	Yes	No	No	Yes
154.	**Furfuryl alcohol**	**CID:7361**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
155.	Furfural	CID:7362	+	+	+	+	−	Yes	No	No	No	No	Yes	No	No
156.	Allicin	CID:65036	+	+	+	+		No	No	No	No	No	No	Yes	No
157.	Heptadecane	CID:12398	+	+	+	+	−	Yes	No	No	No	No	No	No	No
158.	Nonadecane	CID:12401	+	+	+	+	−	Yes	No	No	No	No	No	Yes	No
159.	(E)-1-Propene-1-sulfenic acid	CID:20371837	+	+	+	+	−	No	No	No	No	No	No	Yes	No
160.	1-Heptadecene	CID:23217	+	+	+	+	−	Yes	No	No	No	No	No	Yes	No
161.	Spiraeoside	CID:5320844	−	−	−	−	−	No	No	No	No	Yes	Yes	No	No
162.	**Thiosulfinate**	**CID:58219327**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
163.	**Beta-Amyrin**	**CID:73145**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**
164.	**Linolenic acid**	CID:5,280934	**+**	**+**	**+**	**+**	**−**	**Yes**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
165.	1-Hexadecene	CID:12,395	+	+	+	+	−	Yes	No	No	No	No	No	Yes	No
166.	5-Methoxypyrimidin-4-ol	CID:581046	+	−	+	+	−	Yes	No	No	No	No	No	No	No
167.	**4-Hydroxybenzoic acid**	**CID:135**	**+**	**+**	**−**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
168.	**Ferulic acid**	**CID:445858**	**+**	**+**	**+**	**+**	**−**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
169.	3,4-Dihydroxybenzoic acid	CID:72	+	−	−	+	−	No	No	No	No	No	Yes	Yes	No
170.	3-(Allylsulphinyl)-L-alanine	CID:87310	+	−	+	+	−	No	No	No	No	No	No	No	No

Table 1 (continued)

S/No.	Compounds	Phytochemical identifier	RO5	Absorption				Metabolism (CYP450 Inhibition)					Toxicity		
				$Cac0_2$	BBB	HIA	P-gp	IA2	2C9	2D6	2C19	3A4	AT	CT	hERG
171.	Pyruvic acid	CID:1060	+	−	+	+	−	No	Yes	No	No	No	No	No	No
172.	**2,6-Dihydroxybenzoic acid**	**CID:9338**	+	+	−	+	−	**No**	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**
173.	**(4aR,6aR,6aS,6bR,8aR,10S,12aR,14bS)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid**	**CID:45,483610**	+	+	−	+	−	**No**	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**
174.	**Beta-Sitosterol**	**CID:222284**	+	+	+	+	−	**No**	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**
175.	**Cyclopentadecanone**	**CID:10409**	+	+	+	+	−	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
176.	S-Methyl-L-cysteine sulfoxide	CID:182092	+	−	+	−	−	No	No	No	No	No	No	No	No
177.	Cyanin	CID:441688	−	−	−	−	−	No	No	No	No	Yes	Yes	No	Yes
178.	**2-Hydroxycinnamic acid**	**CID:637540**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
179.	**Myristic acid**	**CID:11005**	+	+	+	+	−	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
180.	**Thiamine**	**CID:1130**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
181.	**Menthol**	**CID:1254**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
182.	**2-Ethylbutanal**	**CID:7359**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
183.	**Vanillic acid**	**CID:8468**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
184.	Ceposide D	CID:14,283960	−	−	−	−	−	No	No	No	No	Yes	No	No	Yes
185.	**2,4,6-Triethyl-1,3,5-trithiane**	**CID:12,487714**	+	+	+	+	−	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
186.	**1,4-Benzoquinone**	**CID: 4650**	+	+	+	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
187.	**Caffeic acid**	**CID:689043**	+	+	−	+	−	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**

Compounds in bold font are the 69 compounds with desirable ADMET and drug-like profiles

BBB Blood Brain Barrier, *HIA* Human Intestinal Absorption, *P-gp* P-glycoprotein inhibition, *hERG* Human ether a-go-go gene inhibition, *AT* Ames toxicity, *CT* Carcinogenicity test

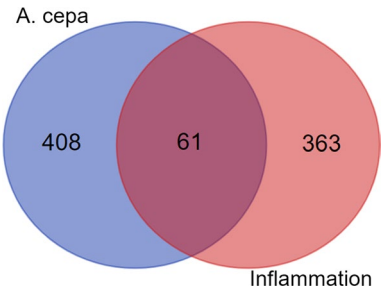


Fig. 1 Venn diagram showing the intersection of *A. cepa* targets and inflammation targets

Discussion

Inflammation is a biological phenomenon that serves protective functions. However, uncontrolled inflammation has been implicated in the etiology of several diseases with high morbidity and mortality [25]. Numerous side effects are associated with current therapies, hence, necessitating the search for better therapies. *A. cepa* is a plant widely known for its numerous physiological properties which include anti-inflammatory properties [6], but the details of the molecular mechanism via which it exerts many of its pharmacological effects are lacking [7]. This study aims to investigate the potential therapeutic targets and anti-inflammatory

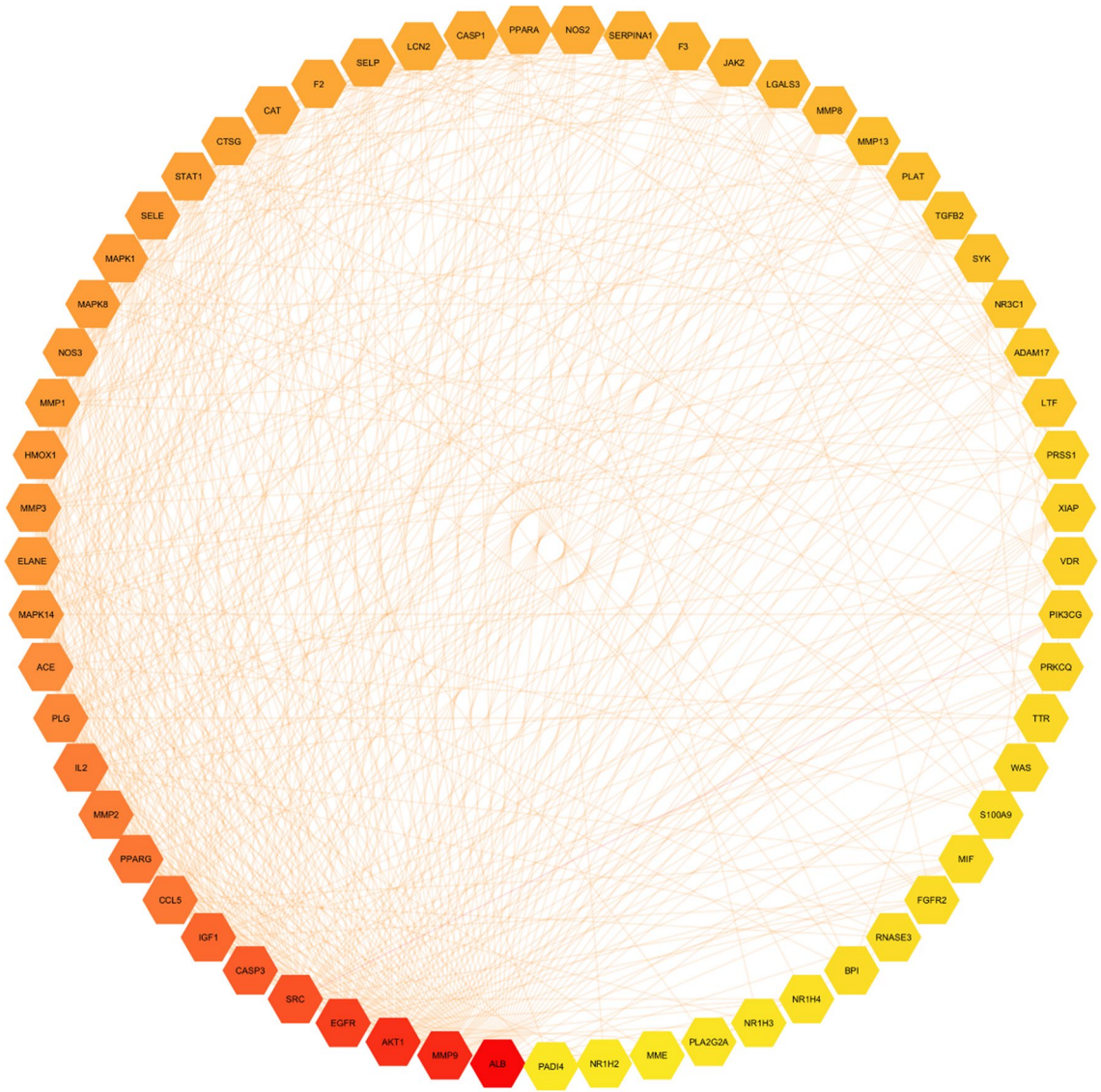


Fig. 2 Protein–protein interaction network of the 61 core targets of *A. cepa* in inflammation

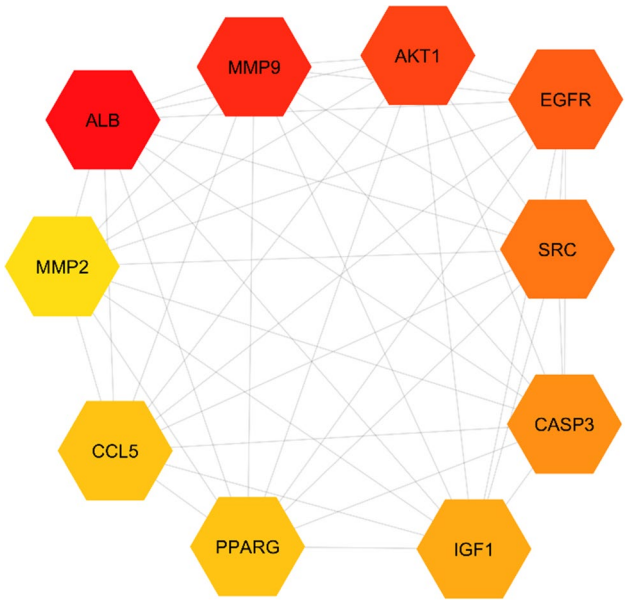


Fig. 3 The top ten targets of the PPI network based on degree of interactions

mechanism of *A. cepa* bioactive compounds and to establish a hypothesis for their further exploration in anti-inflammatory drug design and discovery.

One hundred and eighty-seven bioactive components of *A. cepa* were retrieved from the database. Pharmacokinetics screening plays an important role in drug discovery as it helps to identify compounds with desirable ADME profiles. Following pharmacokinetics screening of *A. cepa* bioactive compounds, sixty-nine drug-like compounds with desirable pharmacokinetics properties were identified. These include compounds such as phlorogenic acid, sinapic acid, stigmasterol, diosgenin, and oleanolic acid. Noteworthy, several studies have demonstrated that many of the identified compounds possess anti-inflammatory properties. For example, a study by Kang *et al*. revealed that oleanolic acid inhibited the expression of proinflammatory cytokines including tumor necrosis factor-α, interleukin (IL)-1β, and IL-17 while it increased the expression of anti-inflammatory cytokine IL-10 [26]. Also, Sun *et al*. reported that beta-sitosterol reduced the expression of IL-6, cyclooxygenase-2 (COX-2) and tumor necrosis factor-α [27]. Furthermore, stigmasterol, campesterol, and beta-sitosterol inhibited phosphorylated extracellular signal-regulated protein kinase (pERK), nitric oxide synthase (iNOS), and COX-2 [27, 28].

The putative targets of the compounds and inflammation were identified and the common targets were selected. PPI network analysis revealed the top 10 targets via which *A. cepa* exert its anti-inflammatory effect. These proteins include ALB, MMP9, AKT1, EGFR, SRC, CASP3, IGF1, CCL5, PPARG, and MMP2. Interestingly, ALB acts as an antioxidative agent and extracellular scavenger in the interstitium and its concentration is affected by inflammation by reducing its rate of synthesis [29, 30]. Matrix metalloproteinases (MMPs) including MMP2 and MMP9 play

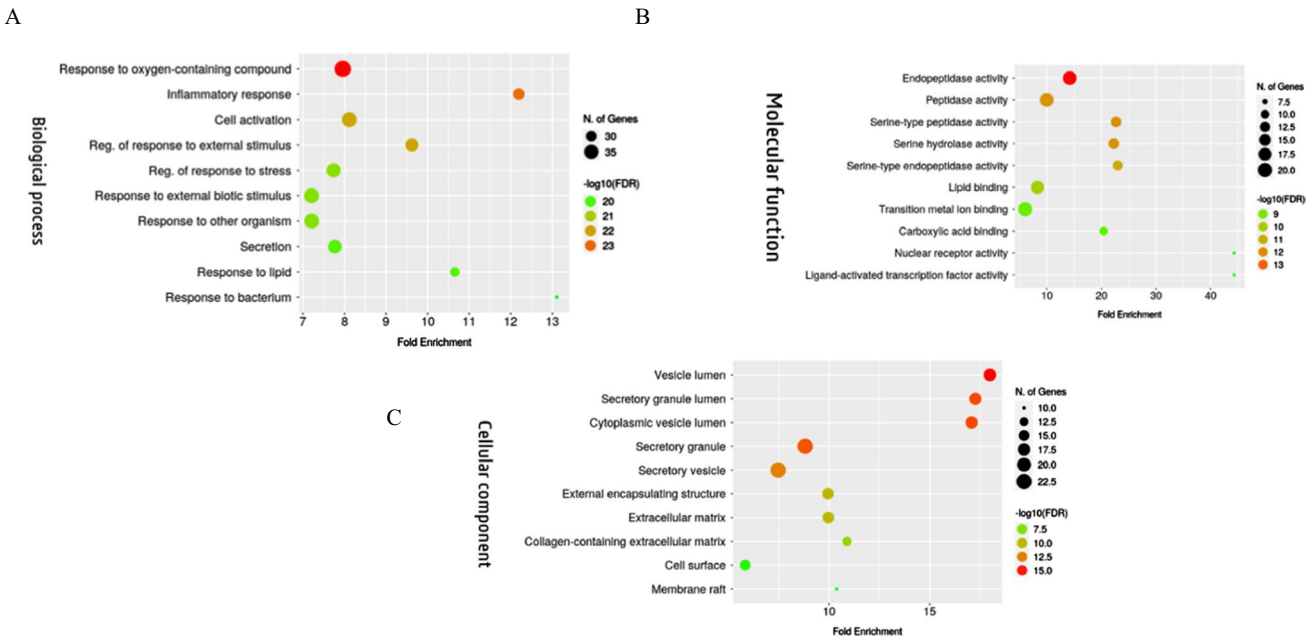


Fig. 4 The Gene ontology functional annotation analysis of the potential targets of *A. cepa* compounds in inflammation. **A** Biological process of *A. cepa* in anti-inflammatory response. **B** Molecular function of *A. cepa* in anti-inflammatory response. **C** Cellular components of *A. cepa* in anti-inflammatory response

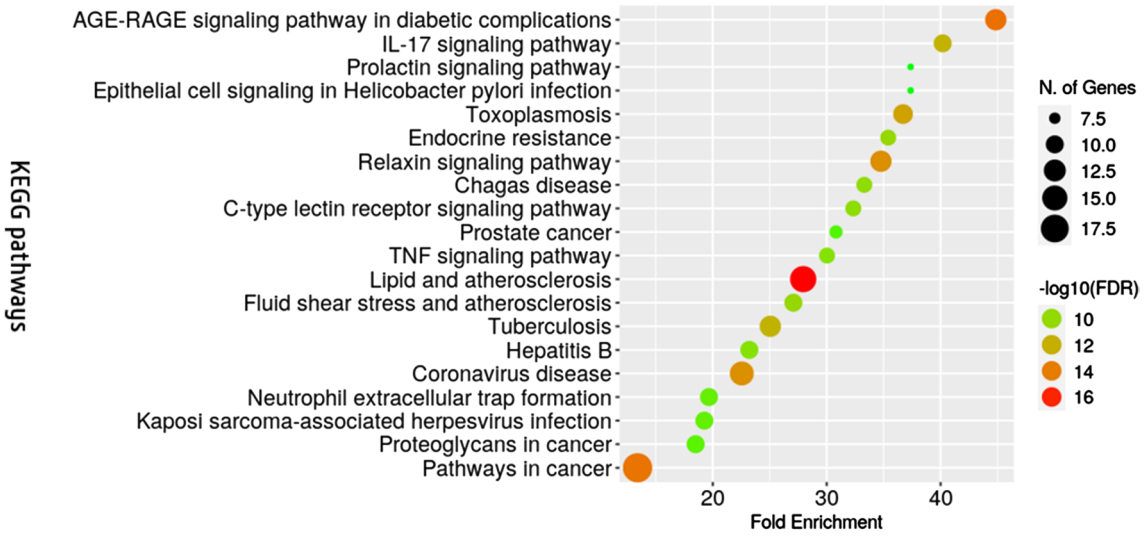


Fig. 5 KEGG pathway enrichment analysis of the top 20 signaling pathways of *A. cepa* in anti-inflammatory response

several roles in inflammation [31]. In a study by Zhang *et al*., they reported that MMP9 inhibited the upregulation of IL-1β induced by LPS in MC3T3-E1 cells. They also reported that the overexpression of MMP9 led to a decrease in the expression of TNF-α [32]. Furthermore, MMP2 and MMP9 function in the recruitment of immune cells and possess both pro- and anti-inflammatory effects through the generation of chemokine gradient [33]. Tang *et al*. also reported that AKT accelerates inflammatory response via increased expression of cytokines and TNF-α by phosphorylating and activating IκB kinase IKK-α, a process which leads to the degradation of IκB and nuclear translocation of NF-κB [34].

EGFR has been implicated in ultraviolet (UV) induced inflammation. El-Abaseri *et al*. showed that EGFR signaling increased COX-2 levels and the expression of pro-inflammatory cytokines following acute exposure to UV [35]. In another study, it was reported that the hyperactivation of SRC promoted the overexpression of proinflammatory transcription factors such as STAT3, NF-κB, and activator protein 1 (AP1) [36]. Notably, CASP3 is an important protein in the mediation of programmed cell death through the apoptotic and pyroptotic pathways. During apoptosis, the cleavage of Gasdermin E by CASP3 mediates the progression of apoptosis into pyroptosis [37].

Witkowska-Sędek *et al*. revealed that the action of IGF1 could be inhibited by IL-6, IL-1β, and TNF-α via the dysregulation of its intracellular mediators in the chondrocytes [38]. CCL5 plays a crucial role in inflammatory response by recruiting T-cells and other cells of the innate immune system to the sites of inflammation [39]. In a study by Choo and colleagues, it was shown that increased transcriptional activity of PPARG led to decreased pro-inflammation cytokine production and increased the production of anti-inflammatory cytokines [40]. From the above evidence, it can be inferred that the anti-inflammatory activities of *A. cepa* bioactive compounds might be by acting on one or more of these targets.

GO functional annotation analysis of the common targets revealed that the targets were primarily involved in biological processes which include response to oxygen-containing compounds, inflammatory response, cell activation, regulation of response to external stimulus, and regulation of response to stress among others. These processes could be considered the key processes by which *A. cepa* exerts its anti-inflammatory effects.

The KEGG pathway analysis of the targets of *A. cepa* bioactive components revealed that the targets were primarily enriched in pathways including the AGE-RAGE signaling pathway, IL-17 signaling pathway, prolactin signaling pathway, TNF signaling pathway, pathways in cancer, and relaxin signaling pathway. Advanced glycation end products (AGEs) play an important role in the pathogenesis of diseases such as rheumatoid arthritis, diabetes, and cancer via the AGE-RAGE signaling pathway [41]. This pathway enhances oxidative stress and contributes to the activation of the NF-κB signaling pathway, JAK-STAT signaling pathway, PI3K-Akt and MAPK signaling pathway, which ultimately results in the disruption of the normal physiological process of the cell [42]. Other pathways listed above are also involved in the triggering of proinflammatory and anti-inflammatory responses, and activation of other pathways associated with inflammation and apoptosis [43–46].

The interaction of the 66 bioactive components with the top ten targets was analyzed by molecular docking. The compounds 1-O-(4-Coumaroyl)-beta-D-glucose, stigmasterol, campesterol, and diosgenin showed better binding

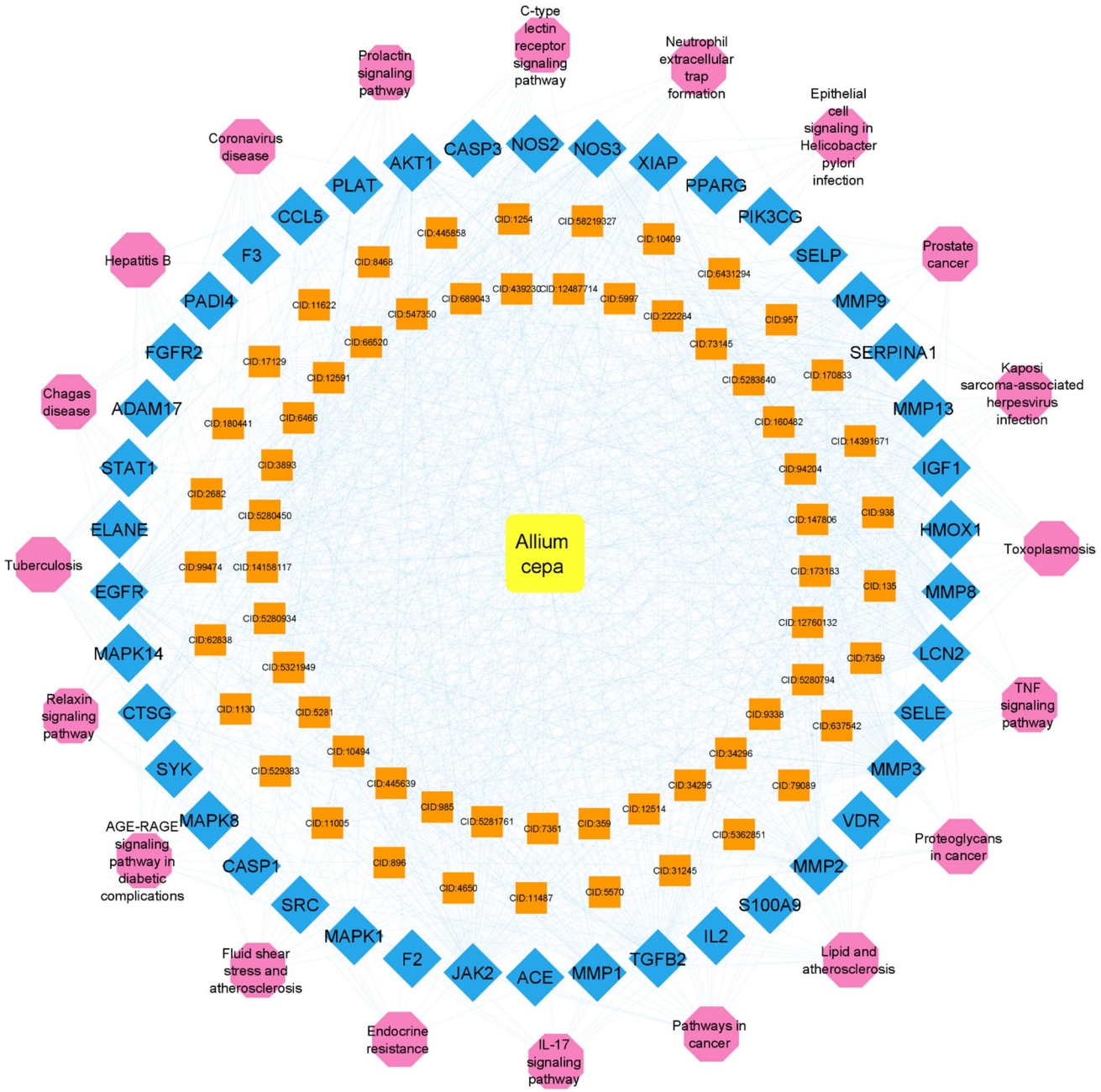


Fig. 6 Compound-target-pathway network *A. cepa* anti-inflammatory effect. *A. cepa* is represented by the yellow circle, the orange squares represent the active compounds of *A. cepa*, the blue triangles are the targets modulated by active compounds of *A. cepa,* while the pink octagons are the significantly enriched pathways for *A. cepa* anti-inflammatory effect. The connecting lines represent the interaction between the compounds, targets, and the enriched pathways

affinity compared with our control drug (ketoprofen) for most of the targets. These compounds showed the best binding affinity with one target or more. Interestingly, Gabay *et al*. reported that stigmasterol through the inhibition of NF-κB signaling pathway, inhibited the secretion of proinflammatory cytokines [47]. This is further corroborated by a recent study by Jie *et al*., in which they reported that the activation of AMPK by stigmasterol protected BV2 cells against $A\beta_{42}$ oligomers induced inflammation via NF-κB and NLRP3 signaling pathways [48]. Noteworthy, 4 of the top ten targets (AKT1, CCL5, CASP3, MMP9) were involved in this pathway.

Similarly, Mohamadi-Zarch *et al*. reported that diosgenin reduced the hepatic levels of reactive oxygen species, IL-1β, IL-6, TNF-α and NF-κB in LPS/D-Gal model of acute liver failure [49]. Furthermore, campesterol

Table 2 The binding affinities of *A. cepa* compounds in Kcal mol^{-1} to the top ten targets of inflammation

Compounds	Targets									
	AKT1/3OCB	ALB/5YOQ	CASP3/1RE1	CCL5/6AEZ	EGFR/7LGS	IGF1/3LVP	MMP2/1HOV	MMP9/4XCT	PPARG/4HEE	SRC/2H8H
(−)-Isopulegol	−5.1	−6.1	−4.2	−4.7	−7.4	−6.3	−5.7	−5.7	−6.8	−6.9
1,4 − Benzoquinone	−4.6	−1.5	−5.7	−6.4	−9.3	−8.1	−7.5	−8	−7.7	−9.1
1-Caffeoyl-beta-D-glucose	−7.5	−6.1	−3.5	−3.6	−5.3	−5	−4.7	−6.3	−5.9	−5.9
1-Hexadecanol	−4.8	−4.8	−4.6	−4.9	−6.1	−5.7	−6.2	−7.4	−6.4	−6.6
1-O-(4-Coumaroyl)-beta-D-glucose	−7.4	−6.7	−4.2	−4.6	−6.5	−6.1	−6.4	−7.9	−7.1	−7
1-Octanol	−4.4	−5.9	−3.4	−3.6	−5.2	−4.5	−4.3	−5.9	−5.6	−5.6
2,3 Dihydroflavn-3-ol	−7.2	−3.9	−3.5	−3.3	−5.1	−4.5	−4.8	−4.8	−4.7	−5.1
2,3-Dimethylthiphene	−4.1	−4.4	−3.2	−3	−4	−3.6	−4.5	−5.1	−4.6	−4.5
2,4,6-Triethyl-1,3,5-dithiazinane	−4.8	−5.8	−4.5	−4	−5.7	−5.2	−5.7	−6.8	−6.3	−6.1
2,4,6-Triethyl-1,3,5-trithiazinane	−4.4	−5.6	−3.4	−3.1	−5.5	−4.5	−5.6	−6.4	−6.4	−6.2
2,4,6-Trihydroxybenzoic acid	−5.3	−4.7	−5.3	−5.6	−9.4	−7.8	−7.5	−8.1	−8.2	− 10.2
2,4-Dimethylthiophene	−4.1	−5.5	−4.8	−4.1	−5.3	−4.8	−5.7	−6.2	−5.3	−5.7
2,5-Dimethylthiophene	−4.1	−7.5	−6.1	−5.8	−7.5	−7.2	−7.3	−8.6	−7.3	−7.8
2,6-Dihydroxybenzoic acid	−5.3	−6.3	−3.5	−3.7	−6.3	−5.4	−5.2	−6.6	−6.2	−6.2
2-Ethylbutanal	−3.9	−7.4	−5.3	−5.4	−7.9	−7.4	−7.1	−9.5	−8.3	−9.1
2-Methylbutyl 2-methylbutyrate	−4.6	−6.9	−5.5	−5.8	−8.3	−7.1	−7.3	−9	−7.7	−8.4
2-Methylpent-2-en-1-ol	−4.1	−5.9	−5.1	−6	−9.5	−8.7	−7.9	−8.4	−8.7	−9.5
2-Methylpentanal	−4	−5.9	−4.6	−3.9	−5.6	−5.3	−6.1	−6.7	−6.2	−6.2
2-Tridecanone	−4.8	−5.9	−3.4	−3.4	−5	−4.8	−4.9	−5.9	−6.4	−6
5-Methyl-2-Octyl-3(2H)-Furanone	−5.2	−5.3	−5.4	−6	−9.1	−9	−7.4	−8.4	−8.5	−9.7
3,4-Dimethylthiophene	−4.1	−6.5	−3.8	−4	−6	−5.4	−5.3	−6.9	−6.2	−6.2
4-Hydroxybenzoic acid	−5.1	−6.1	−5.5	−6.1	−8.9	−8.5	−8.1	−8	−8.7	−9.5
4-Hydroxycinnamic acid	−5.9	−5.3	−4.3	−3.2	−5.1	−4.4	−5.2	−6	−5.7	−6
4-Octylcyclopentane-1,3-dione	−5.5	−5.1	−4.2	−4.6	−4.9	−4.4	−5.1	−5.9	−5	−4.9
24-Methylenecycloartanol	−8.1	−3.6	−3.1	−2.9	−3	−3.1	−3.4	−3.6	−3.3	−3.6
24-Methylenelophenol	−8	−4.2	−3.2	−2.9	−3.7	−3.5	−4	−4.5	−4.3	−4.2
beta-Amyrin	−8.2	−4.6	−3	−2.8	−4.1	−3.8	−4.1	−4.9	−4.1	−4.5
beta-Sitosterol	−8.2	−4.4	−3.2	−2.9	−4	−3.6	−4.5	−5.1	−4.6	−4.4
Caffeic acid	−6.1	−4.8	−3.7	−3.9	−4.8	−4.6	−5	−5.3	−4.4	−4.8
Campesterol	−8.2	−6.1	−3.8	−3.3	−5	−4.6	−4.6	−6.2	−5.5	−5.9
Catechol	−4.8	−5	−4.2	−3.4	−4.3	−4.1	−4.5	−5	−4.7	−4.8
Cholesterol	−7.7	−5.8	−4.7	−3.5	−5.5	−5.6	−5	−6.5	−6.4	−6.4
Choline	−3.4	−6.2	−5.1	−4.7	−6.1	−6.1	−6.5	−7	−6.2	−6.4
cis-3,5-diethyl-1,2,4-trithiolane	−3.5	−5.1	−3.4	−3.4	−4.9	−4.3	−4.5	−5.1	−4.6	−4.9
Cycloartanol	−7.6	−2.8	−2.6	−2.6	−2.8	−2.7	−3.4	−3	−3.1	−3.1
Cyclopentadecanone	−5.5	−5.7	−3.6	−3.5	−5.8	−5	−4.9	−6.6	−5.9	−6.1

Table 2 (continued)

Compounds	Targets									
	AKT1/3OCB	ALB/5YOQ	CASP3/1RE1	CCL5/6AEZ	EGFR/7LGS	IGF1/3LVP	MMP2/1HOV	MMP9/4XCT	PPARG/4HEE	SRC/2H8H
Diosgenin	−8.2	−6.3	−5.3	−6.2	−9.4	−8.3	−7.5	−8.2	−9.1	−9.6
Diphenylamine	−5.7	−6.3	−3.4	−3.6	−6.1	−5.3	−5	−7	−6.2	−6.7
Ferulic acid	−6	−7.5	−6	−5.6	−7.7	−7.6	−7.6	−8.9	−7.1	−7.9
Flavylium	−7.3	−5.4	−3.3	−3.7	−5.6	−4.8	−4.3	−6.4	−6.2	−6.4
Furfuryl alcohol	−4	−5.6	−4.9	−6.2	−9.6	−8.3	−8.1	−8.3	−9.1	−9.9
Gibberellic acid	−7.6	−6.6	−3.7	−4	−5.9	−5	−5.1	−6.7	−6	−6.4
Lauric acid	−5	−6.1	−4.4	−4.5	−6.2	−5.1	−6.2	−6.8	−6.3	−6.9
Linoleic acid	−5.1	−4.3	−4	−3.3	−3.9	−4	−4.3	−4.8	−4.3	−4.5
Linolenic acid	−5.8	−4.3	−3.4	−3.5	−5.1	−4.5	−5.1	−5.1	−5	−5.1
Lophenol	−7.2	−5.1	−3.9	−3.8	−5	−4.5	−5.1	−5.7	−5	−5.4
Melatonin	−6.7	−4.6	−3.3	−3	−4.4	−3.6	−4.2	−4.8	−4.6	−4.7
Menthol	−5.2	−5.7	−5.5	−6	−8.8	−9	−7.6	−7.9	−8.3	−9.6
Mevalonic acid	−4.1	−6.2	−4.4	−3.9	−5.1	−4.6	−5	−6.1	−5.2	−5.8
Myristic acid	−5.3	−6.6	−5.1	−4.6	−6.1	−5.7	−6	−7.1	−6	−6.2
Neodecanoic acid	−4.9	−3.6	−2.7	−2.8	−4.2	−3.7	−4.3	−4.4	−4.5	−4.6
Nicotinic acid	−4.8	−5.7	−5.7	−5.7	−8.2	−7.4	−7	−6.9	−7.2	−8.2
Nonadecanoic acid	−4.8	−5.4	−5.1	−4.8	−5.5	−5.1	−5.9	−6.4	−5.3	−5.9
Oleanolic acid	−7.7	−6.5	−5.2	−4.7	−6.4	−5.8	−6.3	−7.4	−5.9	−6.4
Oleic acid	−5.7	−1.4	−5.7	−6.7	−10.1	−8.1	−7.9	−8.5	−7.7	−8.6
Palmitic acid	−4.9	−4.4	−3.2	−3	−3.8	−3.6	−4.2	−4.5	−4.4	−4.3
Phloroglucinol	−4.5	−4.2	−3.9	−3.5	−3.9	−3.8	−4.5	−4.8	−4.1	−4.5
Propionaldehyde	−2.8	−4.6	−3	−3.1	−4.1	−3.7	−4.1	−4.7	−4	−4.4
Stearic acid	−5.6	−5.9	−4.6	−4.2	−5.6	−5.1	−6	−6.4	−5.4	−5.8
Stigmasterol	−8.4	−6.7	−4.6	−4.9	−6.6	−6.3	−6.3	−7.8	−7.2	−7.3
Thiamine	−6	−5.8	−5	−4.7	−5.4	−5.1	−5.6	−6.2	−5.4	−6.2
Thiosulfinate	−4	−5.2	−4	−3.9	−4.9	−4.4	−5.2	−5.7	−5	−5.3
Tianshic acid	−5.8	−5.9	−5.5	−6.5	−8.4	−8.9	−8.4	−8.3	−8.6	−9.4
Trigonelline	−4.9	−4.7	−3.8	−3.5	−4.2	−3.9	−4.4	−5	−4.8	−4.9
Tsibulin 2	−5.6	−5.5	−3.4	−3.3	−5.5	−5	−5.6	−6.3	−6	−6.1
Vanillic acid	−5.4	−5.7	−5.6	−7.2	−10.7	−8.7	−9	−9.5	−9.1	−10.4

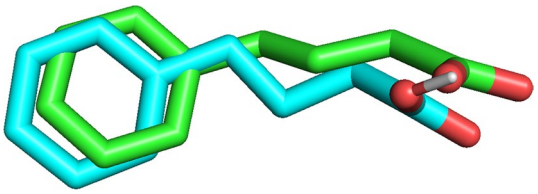


Fig. 7 The superimposition of the redocked cognate ligand of ALB with the cognate ligand

and 1-O-(4-Coumaroyl)-beta-D-glucose have also been reported to possess anti-inflammatory properties through the suppression of proinflammatory mediators [28, 50]. Ultimately, these compounds can be considered candidate drugs and could be further explored in the development of anti-inflammatory drugs. It is worth noting that the abundance and bioavailability of the compounds previously mentioned differs *in A. cepa* and these greatly influences their therapeutic effects. Diosgenin is mostly present in *A. cepa* bulbs at high levels and it is one of the most abundant spirostanol sapogenins identified in Allium plants [51]. However, it possesses low solubility and bioavailability which are been improved via the development of amphiphilic conjugates [52]. Conversely, *A. cepa* is a major source of phytosterols including campesterol and stigmasterol, with both compounds also possessing high bioavailability. Noteworthy, certain mutations in genes including ABCG5 and ABCG8 genes have been reported to modulate the bioavailability of both compounds [53]. Hence, this could influence their development into anti-inflammatory drug candidates. The bioavailability of 1-O-(4-Coumaroyl)-beta-D-glucose has not been well explored in studies, however, its predicted pharmacokinetics properties reveal the compounds as being water soluble and probably bioavailable [54]. The overall components of *A. cepa* explored in this study, their targets, and the pathways via which they mediate their anti-inflammatory drugs are visualized in Fig. 6. Notably, this provides a peek into the results of the whole study.

Conclusion

Summarily, this is the first study systematically explore the anti-inflammatory mechanism of *A. cepa* using integrated computational approaches. Our study revealed that compounds 1-O-(4-Coumaroyl)-beta-D-glucose, stigmasterol, campesterol, and diosgenin might be the core bioactive components of *A. cepa* that exert its anti-inflammatory action. Furthermore, the anti-inflammatory action of *A. cepa* could be mediated via response to oxygen-containing compounds, response to inflammation, cell activation, regulation of response to external stimulus, and regulation of response to stress via various signaling pathways including AGE-Rage

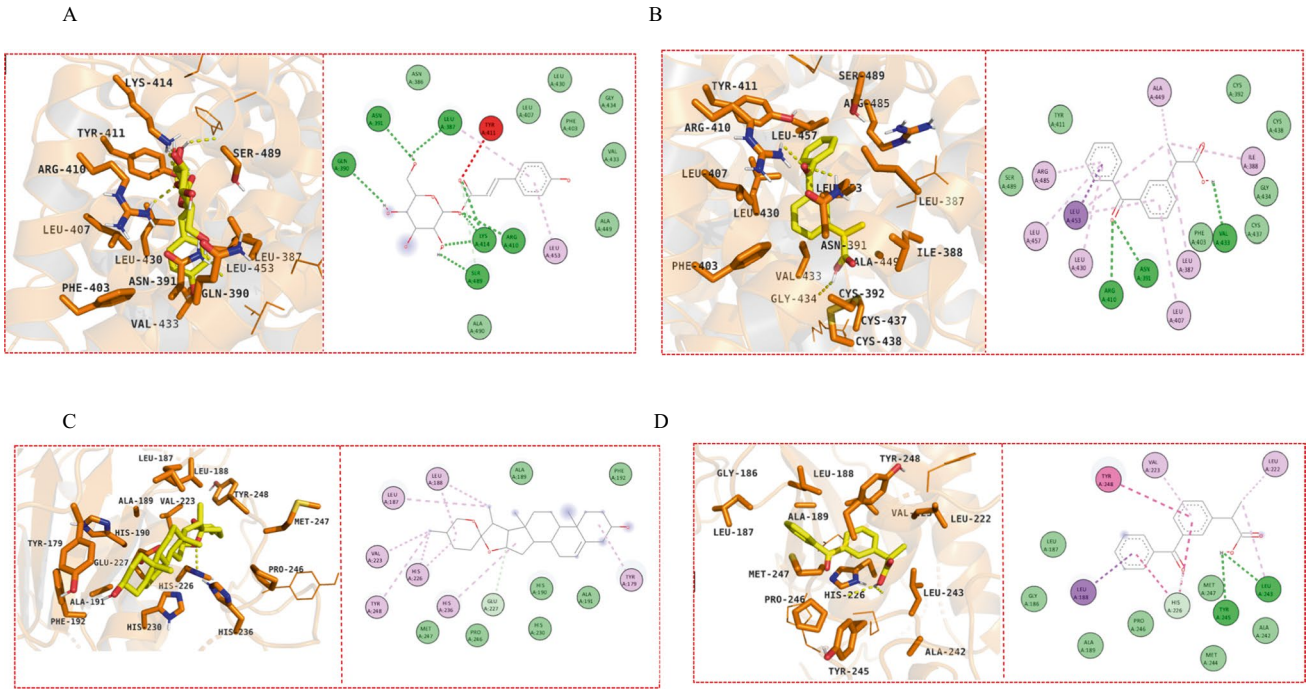


Fig. 8 Binding mode of 1-O-(4-Coumaroyl)-beta-D-glucose, diosgenin, and control inhibitor (Ketoprofen), in the binding site of ALB and MMP9 proteins. **A** ALB- 1-O-(4-Coumaroyl)-beta-D-glucose complex. **B** ALB-ketoprofen complex. **C** MMP9-diosgenin complex. **D** MMP9-ketoprofen complex

signaling pathway, IL-17 signaling pathway, prolactin signaling pathway, and TNF signaling pathway. Conclusively, this study further establishes a basis for the exploration of A. cepa and its bioactive components in inflammation and might facilitate the development of alternative anti-inflammatory drugs. However, further computational and experimental validation are needed to validate the results of this study.

Author contributions Conceptualization: VO, OSO; Investigation: VO, OSO, BO, GAO, AFF, RTA; Writing—original draft: VO, RTA, TAA, OI, TAA, TAO; Writing—review & editing: RTA, VO, GAO, BO, OSO.

Funding No funding was received for this research.

Declarations

Conflict of interest No potential conflict of interest was reported by the authors.

Ethical approval Not applicable.

References

1. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L (2018) Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 9:7204–7218. https://doi.org/10.1832/oncotarget.23208
2. Greten FR, Grivennikov SI (2019) Inflammation and cancer: triggers, mechanisms, and consequences. Immunity 51:27–41. https://doi.org/10.1016/j.immuni.2019.06.025
3. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB (2019) Inflammation and cancer. Ann Afr Med 18:121–126. https://doi.org/10.4103/aam.aam_56_18
4. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH, Mantovani A, Weyand CM, Barzilai N, Goronzy JJ, Rando TA, Effros RB, Lucia A, Kleinstreuer N, Slavich GM (2019) Chronic inflammation in the etiology of disease across the life span. Nat Med 25:1822–1832. https://doi.org/10.1038/s41591-019-0675-0
5. Haley RM, von Recum HA (2018) Localized and targeted delivery of NSAIDs for treatment of inflammation: a review. Exp Biol Med 244:433–444. https://doi.org/10.1177/1535370218787770
6. Kianian F, Marefati N, Boskabady M, Ghasemi SZ, Boskabady MH (2021) Pharmacological properties of *Allium cepa*, preclinical and clinical evidences; a review. Iran J Pharm Res. https://doi.org/10.2037/ijpr.2020.112781.13946
7. Marefati N, Ghorani V, Shakeri F, Boskabady M, Kianian F, Rezaee R, Boskabady MH (2021) A review of anti-inflammatory, antioxidant, and immunomodulatory effects of *Allium cepa* and its main constituents. Pharm Biol 59:287–302. https://doi.org/10.1080/13880209.2021.1874028
8. Yamaguchi M, Weitzmann MN (2011) Quercetin, a potent suppressor of NF-κB and Smad activation in osteoblasts. Int J Mol Med 28:521–525. https://doi.org/10.3892/ijmm.2011.749
9. Teshika JD, Zakariyyah AM, Zaynab T, Zengin G, Rengasamy KR, Pandian SK, Fawzi MM (2019) Traditional and modern uses of onion bulb (*Allium cepa* L.): a systematic review. Crit Rev Food Sci Nutr 59:39–70. https://doi.org/10.1080/10408398.2018.1499074
10. Chandran U, Mehendale N, Patil S, Chaguturu R, Patwardhan B (2017) Network pharmacology. Innov Approaches Drug Discov. https://doi.org/10.1016/B978-0-12-801814-9.00005-2
11. Mohanraj K, Karthikeyan B, Vivek-Ananth R, Chand R, Aparna S, Mangalapandi P, Samal A (2018) IMPPAT: a curated database of Indian medicinal plants, phytochemistry and therapeutics. Sci Rep 8:1–17. https://doi.org/10.1038/s41598-018-22631-z
12. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, Bolton EE (2021) PubChem in 2021 new data content and improved web interfaces. Nucleic Acids Res 49:D1388–D1395. https://doi.org/10.1093/nar/gkaa971
13. Yang H, Lou C, Sun L, Li J, Cai Y, Wang Z, Li W, Liu G, Tang Y (2019) admetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. Bioinformatics 35:1067–1069. https://doi.org/10.1093/bioinformatics/bty707
14. Chen X, Li H, Tian L, Li Q, Luo J, Zhang Y (2020) Analysisofthe physicochemical properties of acaricides based on Lipinski's rule of five. J Comput Biol 27:1397–1406. https://doi.org/10.1089/cmb.2019.0323
15. Liu X, Ouyang S, Yu B, Liu Y, Huang K, Gong J, Zheng S, Li Z, Li H, Jiang H (2010) PharnNapper server: a web server for potential drug target identification using pharmacophore mapping approach. Nucleic Acids Res 38:W609–W614. https://doi.org/10.1093/nar/gkq300
16. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, Stein T, Nudel R, Lieder I, Mazor Y, Kaplan S, Dahary D, Warshawsky D, Guan-Golan Y, Kohn A, Rappaport N, Safran M, D, (2016) Lancet, genecards suite: from gene data mining to disease genome sequence analyses. Curr Protoc Bioinform 54:1301–13033. https://doi.org/10.1002/cpbi.5
17. Szklarczyk D, Gable A, Lyon D, Junge A, Wyder S, Huerta-Cepas J, Simonovic M, Doncheva N, Morris J, Bork P, Jensen L, Mering C (2019) protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res 47:D607–D613. https://doi.org/10.1093/nar/gyk1131
18. Kohl M, Wiese S, Warscheid B (2011) Cytoscape: software for visualization and analysis of biological networks. Data Min Proteomics 96:291–303. https://doi.org/10.1007/978-1-60761-987-1_18
19. Ge S, Jung D, Yao R (2020) ShinyGO: a graphical gene-set enrichment tool for animals and plants. Bioinformatics 36:2628–2629. https://doi.org/10.1093/bioinformatics/btz931
20. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, Ferrin TE (2004) UCSF chimera-A visualization system for exploratory research and analysis. J Comput Chem 25:1605–1612. https://doi.org/10.1002/jcc.20084
21. Guex N, Peitsch M (1997) SWISS-MODEL and the Swiss-pdb viewer: an environment for comparative protein modeling. Electrophoresis 18:2714–2723. https://doi.org/10.1002/elps.1150181505
22. Dallakyan S, Olson AJ (2015) Small-molecule library screening by docking with PyRx. In: Hempel J, Williams C, Hong C (eds) Chemical biology. Humana Press, New York, NY, pp 243–250. https://doi.org/10.1007/978-1-4939-2269-7_19
23. Wallace AC, Laskowski RA, Thornton JM (1995) LIGPLOT: a program to generate schematic diagrams of protein-ligand interactions. Protein Eng Des Sel 8:127–134. https://doi.org/10.1093/protein/8.2.127
24. DeLano WL (2002) PyMOL: an open-source molecular graphics tool. CCP4 Newslett Protein Crystallograph 40:82–92

25. C.N. Serhan, P.A. Ward, D.W. Gilroy (2010) Fundamentals of inflammation. Yale Journal of Biology and Medicine, 2011
26. Kang G-D, Sumin L, Kim D-H (2015) Oleanolic acid ameliorates dextran sodium sulfate-induced colitis in mice by restoring the balance of Th17/Treg cells and inhibiting NF-κB signaling pathway, oleanolic acid ameliorates dextran sodium sulfate-induced colitis in mice by restoring the balance of Th17/Treg cells and inhibiting NF-KB signaling pathway. Int Immunopharmacol. https://doi.org/10.1016/j.intimp.2015.10.024
27. Sun Y, Gao L, Hou W, Wu J (2020) β-Sitosterol alleviates inflammatory response via inhibiting the activation of ERK/p38 and NF-κB pathways in LPS-exposed BV2 cells. Biomed Res Int. https://doi.org/10.1155/2020/7532306
28. Yuan, Zhang, Shen, Jia, Xie (2019) Phytosterols suppress phagocytosis and inhibit inflammatory mediators via ERK pathway on LPS-triggered inflammatory responses in RAW2647 macrophages and the correlation with their structure. Foods 8:582. https://doi.org/10.3390/foods8110582
29. Don BR, Kaysen G (2004) Poor nutritional status and inflammation: serum albumin: relationship to inflammation and nutrition. Semin Dial 17:432–437. https://doi.org/10.1111/j.0894-0959.2004.17603.x
30. Soeters PB, Wolfe RR, Shenkin A (2019) Hypoalbuminemia: pathogenesis and clinical significance. J Parenter Enter Nutr 43:181–193. https://doi.org/10.1002/jpen.1451
31. Fingleton B (2017) Matrix metalloproteinases as regulators of inflammatory processes. Biochim et Biophys Acta (BBA)—Mol Cell Res 1864:2036–2042. https://doi.org/10.1016/j.bbamcr.2017.05.010
32. Zhang H, Liu L, Jiang C, Pan K, Deng J, Wan C (2020) MMP9 protects against LPS-induced inflammation in osteoblasts. Innate Immun 26:259–269. https://doi.org/10.1177/1753425919887236
33. Loffek S, Schilling O, Franzke C-W (2011) Biological role of matrix metalloproteinases: a critical balance. Eur Respir J 38:191–208. https://doi.org/10.1183/09031936.00146510
34. Tang B, Tang F, Wang Z, Qi G, Liang X, Li B, Yuan S, Liu J, Yu S, He S (2016) Upregulation of Akt/NF-κB-regulated inflammation and Akt/Bad-related apoptosis signaling pathway involved in hepatic carcinoma process: suppression by carnosic acid nanoparticle. Int J Nanomed 11:6401–6420. https://doi.org/10.2147/IJN.S101285
35. El-Abaseri TB, Hammiller B, Repertinger SK, Hansen LA (2013) The Epidermal growth factor receptor increases cytokine production and cutaneous inflammation in response to ultraviolet irradiation. ISRN Dermatol 2013:1–11. https://doi.org/10.1155/2013/848705
36. Cirotti C, Contadini C, Barilà D (2020) SRC kinase in glioblastoma: news from an old acquaintance. Cancers (Basel) 12:1558. https://doi.org/10.3390/cancers12061558
37. Rogers C, Fernandes-Alnemri T, Mayes L, Alnemri D, Cingolani G, Alnemri ES (2017) Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death. Nat Commun 8:14128. https://doi.org/10.1038/ncomms14128
38. Witkowska-Sędek E, Pyrżak B (2020) Chronic inflammation and the growth hormone/insulin-like growth factor-1 axis. Cent Eur J Immunol 45:469–475. https://doi.org/10.5114/ceji.2020.103422
39. Liu H, Ning H, Men H, Hou R, Fu M, Zhang H, Liu J (2012) Regulation of CCL5 expression in smooth muscle cells following arterial injury. PLoS One 7:e30873. https://doi.org/10.1371/journal.pone.0030873
40. Choo J, Lee Y, Yan X, Noh TH, Kim SJ, Son S, Pothoulakis C, Moon HR, Jung JH, Im E (2015) A novel peroxisome proliferator-activated receptor (PPAR)γ agonist 2-hydroxyethyl 5-chloro-4,5-didehydrojasmonate exerts anti-inflammatory effects in colitis. J Biol Chem 290:25609–25619. https://doi.org/10.1074/jbc.M115.673046
41. Yue Q, Song Y, Liu Z, Zhang L, Yang L, Li J (2022) Receptor for advanced glycation end products (RAGE): a pivotal hub in immune diseases. Molecules 27:4922. https://doi.org/10.3390/molecules27154922
42. Singh VP, Bali A, Singh N, Jaggi AS (2014) Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol 18:1. https://doi.org/10.4196/kjpp.2014.18.1.1
43. Borba VV, Zandman-Goddard G, Shoenfeld Y (2018) Prolactin and autoimmunity. Front Immunol. https://doi.org/10.3389/fimmu.2018.00073
44. Liu T, Li S, Ying S, Tang S, Ding Y, Li Y, Qiao J, Fang H (2020) The IL-23/IL-17 pathway in inflammatory skin diseases: from bench to bedside. Front Immunol. https://doi.org/10.3389/fimmu.2020.594735
45. Alam MS, Otsuka S, Wong N, Abbasi A, Gaida MM, Fan Y, Meerzaman D, Ashwell JD (2021) TNF plays a crucial role in inflammation by signaling via T cell TNFR2. Pro Natl Acad Sci. https://doi.org/10.1073/pnas.2109972118
46. Martin B, Gabris-Weber BA, Reddy R, Romero G, Chattopadhyay A, Salama G (2018) Relaxin reverses inflammatory and immune signals in aged hearts. PLoS One 13:e0190935. https://doi.org/10.1371/journal.pone.0190935
47. Gabay O, Sanchez C, Salvat C, Chevy F, Breton M, Nourissat G, Wolf C, Jacques C, Berenbaum F (2010) Stigmasterol: a phytosterol with potential anti-osteoarthritic properties. Osteoarthr Cartil 18:106–116. https://doi.org/10.1016/j.joca.2009.08.019
48. Jie F, Yang X, Yang B, Liu Y, Wu L, Lu B (2022) Stigmasterol attenuates inflammatory response of microglia via NF-κB and NLRP3 signaling by AMPK activation. Biomed Pharmacother 153:113317. https://doi.org/10.1016/j.biopha.2022.113317
49. Mohamadi-Zarch S-M, Baluchnejadmojarad T, Nourabadi D, Khanizadeh AM, Roghani M (2020) Protective effect of diosgenin on LPS/D-Gal-induced acute liver failure in C57BL/6 mice. Microb Pathog 146:104243. https://doi.org/10.1016/j.micpath.2020.104243
50. Vo VA, Lee J-W, Kim J-Y, Park J-H, Lee HJ, Kim S-S, Kwon Y-S, Chun W (2014) Phosphorylation of Akt mediates anti-inflammatory activity of 1- p -coumaroyl β-D-glucoside against lipopolysaccharide-induced inflammation in RAW2647 cells. Kor J Physiol Pharmacol 18:79. https://doi.org/10.4196/kjpp.2014.18.1.79
51. Arshad MS, Sohaib M, Nadeem M, Saeed F, Imran A, Javed A, Amjad Z, Batool SM (2017) Status and trends of nutraceuticals from onion and onion by-products: a critical review. Cogent Food Agric 3:1280254. https://doi.org/10.1080/23311932.2017.1280254
52. Cai B, Zhang Y, Wang Z, Xu D, Jia Y, Guan Y, Liao A, Liu G, Chun C, Li J (2020) Therapeutic potential of diosgenin and its major derivatives against neurological diseases: recent advances. Oxid Med Cell Longev 2020:1–16. https://doi.org/10.1155/2020/3153082
53. Salehi B, Quispe C, Sharifi-Rad J, Cruz-Martins N, Nigam M, Mishra AP, Konovalov DA, Orobinskaya V, Abu-Reidah IM, Zam W, Sharopov F, Venneri T, Capasso R, Kukula-Koch W, Wawruszak A, Koch W (2021) Phytosterols: from preclinical evidence to potential clinical applications. Front Pharmacol. https://doi.org/10.3389/fphar.2020.599959

54. Showing Compound p-coumaroyl hexose (FDB093521) - FooDB, (n.d.). Accessed January 23, 2023 from https://foodb.ca/compounds/FDB093521.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.