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by Afriza Yelnetty 04

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Evaluation of the Potential for Immunomodulatory and Anti-inflammatory Properties of Phytoconstituents Derived from Pineapple [*Ananas comosus* (L.) Merr.] Peel Extract Using an *In Silico* Approach

Trina Ekawati Tallei[1,8]*, Fatimawali[2,8], Afriza Yelnetty[3], Siti Marfuah[1], Adinda Dwi Tania[1], Marko Jeremia Kalalo[2], Billy Johnson Kepel[4], Nurdjannah Jane Niode[5], Diah Kusumawaty[6], and Rinaldi Idroes[7]

[1]Department of Biology, Faculty of Mathematics and Natural Sciences
Sam Ratulangi University, Manado 95115 North Sulawesi, Indonesia
[2]Pharmacy Study Program, Faculty of Mathematics and Natural Sciences
Sam Ratulangi University, Manado 95115 North Sulawesi, Indonesia
[3]Animal Products Technology Study Program, Faculty of Animal Husbandry
Sam Ratulangi University, Manado 95115 North Sulawesi, Indonesia
[4]Department of Chemistry, Faculty of Medicine
Sam Ratulangi University, Manado, North Sulawesi 95115 Indonesia
[5]Department of Dermatology and Venereology, Faculty of Medicine
University of Sam Ratulangi, RD Kandou Hospital
Manado 95163 North Sulawesi, Indonesia
[6]Department of Biology Education, Faculty of Mathematics and Science Education
Universitas Pendidikan Indonesia, Bandung 40154 Jawa Barat, Indonesia
[7]Department of Pharmacy, Faculty of Mathematics and Natural Sciences
Universitas Syiah Kuala, Kopelma Darussalam, Banda Aceh 23111 Indonesia
[8]The University Center of Excellence for Biotechnology and Conservation of Wallacea
Sam Ratulangi University, Manado 95115 North Sulawesi, Indonesia

Pineapple [*Ananas comosus* (L.) Merr.] has long been recognized as a source of bioactive compounds that are frequently used in health and wellness products. The benefits of pineapple, among others, include immunomodulatory and anti-inflammatory properties. This study aimed at evaluating the potential of phytochemical compounds in pineapple peel as immunomodulators and anti-inflammatory agents using an *in silico* approach. The phytochemical of the pineapple peel's n-hexane extract was analyzed using GC-MS (gas chromatography–mass spectrometry). The analysis of biological activities of the phytochemicals was performed using the PASS Online webserver. Computational toxicity estimation was performed using the ProTox II webserver. The drug-likeness of the compounds was analyzed using Lipinski's rule of five. Additionally, molecular docking of selected phytochemicals against the NLRP3 inflammasome was performed. The results suggested the presence of phytochemicals with immunomodulatory and anti-inflammatory properties in the n-hexane extract of pineapple peel. This information can be used as a starting point in the search for natural-based drugs that are effective at alleviating inflammatory symptoms, as well as in immunomodulatory aspects.

Keywords: anti-inflammatory, GC-MS, immunomodulator, *in silico*, inflammasome, pineapple peel

*Corresponding Author: trina_tallei@unsrat.ac.id

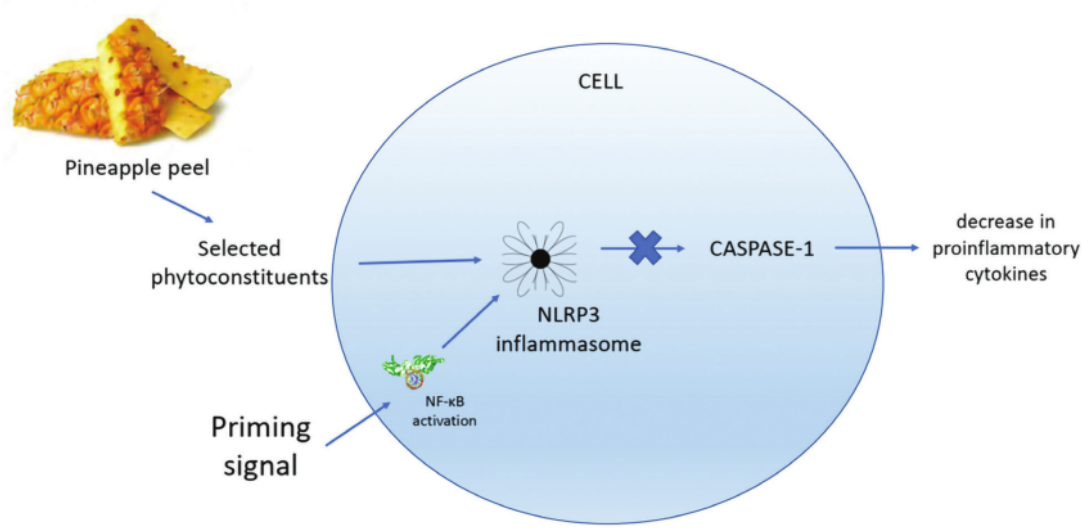


Figure I. Graphical abstract.

INTRODUCTION

Medicinal plants have long been used by the community as a source of natural medicines to treat various diseases (Fernández *et al.* 2021; Martínez *et al.* 2020). One of the medicinal plants that have numerous health benefits is pineapple [*Ananas comosus* (L.) Merr.] (Tallei *et al.* 2021a). Pineapple peel is a potential drug discovery source that has received little attention to date. Pineapple peel is generally only used as animal feed, organic fertilizer, a reducing agent, a substrate for bioethanol production (Chávez-García *et al.* 2020; Itelima *et al.* 2013; Kyawt *et al.* 2020; Li *et al.* 2014). However, pineapple contains a variety of metabolites and enzymes with antioxidant, anti-inflammatory, and immunomodulatory properties (Cervo *et al.* 2014; Chakraborty *et al.* 2021; Hartati *et al.* 2020; Li *et al.* 2014; Saptarini *et al.* 2019).

A strong immune system is critical during a pandemic, such as the one the world is currently experiencing. However, the immune system's readiness to fight infectious diseases is not always sufficient. The risk and severity of infections vary with age – as determined by the immune system's development, maturation, and decline (Maggini *et al.* 2018). This lays the groundwork for future research to focus on compounds that may act as immunomodulators, as well as anti-inflammatory agents.

Immunomodulatory drugs alter the immune system's response by increasing or decreasing the production of serum antibodies (Avorn 2011). The immune modulation effect of anti-inflammatory agents includes modulating cytokine production and pro-inflammatory gene expression (Yahfoufi *et al.* 2018). The production of free radicals by various biological and environmental sources is caused by an imbalance of naturally occurring antioxidants, which further contributes to the development of a variety of inflammatory-associated diseases (Arulselvan *et al.* 2016). Given the critical nature of protecting oneself from free radicals that can cause inflammation and also maintaining the balance of the immune system, the search for natural alternatives is critical. In the current drug discovery process, *in silico* methods are indispensable (Agamah *et al.* 2020; Bristy *et al.* 2020; Khan *et al.* 2020; Rahman *et al.* 2020). Numerous computational methods are used to discover novel and highly effective drug candidates, as well as promising targets in a variety of diseases (Katsila *et al.* 2016; Lin *et al.* 2020; Rakib *et al.* 2020; Mousavi *et al.* 2021; Atanasov *et al.* 2021). Therefore, this study was conducted to evaluate the potential of the compounds contained in pineapple peel as immunomodulatory and anti-inflammatory agents using an *in silico* approach.

MATERIALS AND METHODS

Sample Preparation

Pineapple peel's extract was made by maceration. In a microtube, 1.5 mL of n-hexane solution was mixed with 0.5 g of pineapple peel powder. The microtube was subsequently vortexed for 3 min and allowed to stand

for 24 h. It was further vortexed for another minute before being centrifuged for three minutes at 9000 rpm. The supernatant was collected and subjected to GC-MS analysis.

GC-MS

GC-MS is a hybrid instrument that combines GC (gas chromatography) and MS (mass spectrometry) capabilities. This means that the sample being examined was identified beforehand with the GC instrument. The GC instrument used in this present study was Thermo Scientific Trace 1310 Gas Chromatograph. Following that, the compounds were identified using mass spectrometry (Thermo Scientific ISQ LT Single Quadrupole Mass Spectrometer). The supernatant produced in the extraction process was put into a vial for further derivatization and set for 60 min at a temperature of 260 °C. The HP-5MS UI column (30 m x 0.25 mm x 0.25 µm) was used at a flow rate of 1 mL/min using helium as the carrier gas. The temperature of the GC oven was initially set to 50 °C (hold for 2 min) and then increased to 240 °C (hold for 20 min) at a rate of 5 °C/min for a retention time of 60 min. The column heater was set to 250 °C in split-low mode with a flow rate of 50 mL/min. Mass spectrometry was performed in the electron impact mode (EI) at 70eV. Electronic integration measurements with a flame ionization detector set to 250 °C were used to determine the percentage compositions. The identification procedure carried out with the GC-MS instrument resulted in a list of compounds presented in the form of a chromatogram.

Bioactivity Analysis

The compounds identified as a result of the GC-MS analysis were both primary and secondary metabolites. In the present study, secondary metabolites were separated from primary metabolites manually. PASSonline (http://way2drug.com/PassOnline/) (Filimonov *et al.* 2014) was used to assess the bioactivities of these secondary metabolites – which included antioxidants, anti-inflammatory, immunomodulators, immunostimulants, and immunosuppressant activities. Compounds with a probability activity (Pa) value larger than 0.3 indicate that the potential is less plausible because it is only computationally evaluated, but this level is adequate for screening. Pa > 0.7, on the other hand, represents a positive prediction, indicating that the possible substances have been demonstrated by the study that has been carried out (Prasanth *et al.* 2020).

Prediction of Potential Toxicity

The potential hepatoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity activities of the selected phytoconstituents were analyzed using the ProTox-II webserver (https://tox-new.charite.de/protox_II/) (Banerjee *et al.* 2018). Toxicity classes are defined following the globally harmonized system of chemical classification and labeling. The LD_{50} values are given in mg/kg with the following description: Class V indicates the compound may be harmful if swallowed ($2000 < LD50 \leq 5000$), and Class VI indicates that the compound is non-toxic ($LD50 > 5000$).

Analysis of Lipinski's Rule of Five

Pharmacokinetic profiles were used to investigate ligands extracted from pineapple peel – which include absorption, distribution, metabolism, excretion, and toxicity or ADMET – all of which are important when developing orally active drugs. The Supercomputing Facility for Bioinformatics and Computational Biology or SCFBio webserver (https://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) (Jayaram *et al.* 2012) was employed for drug-likeness of the compounds based on the analysis of Lipinski's rule of five (Lipinski 2004).

Preparation of Ligands and Receptor

The preparation of ligands and receptor followed the protocol provided by Sailah *et al.* (2021). The ligands used in the present study were secondary metabolites that showed anti-inflammatory activity with Pa > 0.5. The three-dimensional structures of the ligands were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and saved in .sdf format. Then using Open Babel (O'Boyle *et al.* 2011), the ligands were converted to a .pdb format. AutodockTools (Morris *et al.* 1996) was used to further optimize the ligands by adjusting torsions' number. The final output file was saved in the pdbqt format. The NLRP3 Inflammasome receptor macromolecule (PDB ID: 2NAQ) was downloaded and saved in the.pdb format from the Protein Data Bank website (http://www.rscb.org/pdb/). The receptor was separated from non-standard residues and native ligand using Discovery Studio Visualizer 2020 (BIOVIA, Dassault Systèmes), and then saved in a .pdb format. Subsequently, the receptors were optimized with AutodockTools, which included the addition of hydrogen atoms and the creation of grid boxes, and saved in pdbqt format. The grid box was adjusted with the receptor's active site as specified by the Computed Atlas of Surface Topography of proteins or CASTp webserver http://sts.bioe.uic.edu/castp/index.html?3igg (Binkowski *et al.* 2003).

Molecular Docking and Visualization of Receptor-Ligand Interactions

The molecular docking followed the protocol provided by Tumilaar *et al.* (2020), while the visualization of the docking results followed the protocol provided by Tallei *et al.* (2020). The ligands and receptor were prepared in

AutodockTools v1.3.6 (Morris *et al.* 2009) and saved in the .pdbqt format. Autodock Vina v1.1.2 (Trott and Olson 2009) was used as a docking engine. The Vina configurations were saved as conf.txt. The molecular docking process was executed *via* the command prompt. After the molecular docking process was completed, the files ligand.pdbqt and log.txt appeared. The binding free energy value was presented in the log.txt file. The molecular docking results were visualized using the Discovery Studio Visualizer 2021 (Dassault Systèmes) to determine the ligand's position and orientation relative to the receptor, as well as the interacting amino acids with the ligands.

RESULTS AND DISCUSSION

Phytoconstituents derived from pineapple peel are understudied for therapeutic purposes – in particular, during the course of the development of new anti-free radical, anti-inflammatory, and immunomodulatory agents. In the present study, phytoconstituents from n-hexane from pineapple peel were analyzed using GC-MS. Subsequently, the identified compounds were used as ligands in the search for candidates for active compounds with anti-inflammatory, immunomodulatory, and antioxidant properties.

The GC-MS total ion chromatogram (TIC) profile and identification data of each phytoconstituent are provided in Figure 1. These compounds were screened for secondary metabolites that will be used in further analysis. The screening revealed 74 secondary metabolites in the n-hexane extract of pineapple peel. The compounds were analyzed for their bioactivity as antioxidants, anti-inflammatory, immunomodulators, immunostimulants, and immunosuppressants using the PASS Online webserver, as shown in Table 1. These activities are inextricably linked to the immune response elicited by pathogens and viruses (Tay *et al.* 2020). Pa values greater than 0.7 are highlighted in bold, while Pa values greater than 0.3 but less than 0.7 are underlined. Almost all of these compounds exhibit immunomodulatory, immunostimulant, immunosuppressive, antioxidant, and anti-inflammatory activity – with values greater than 0.3 but less than 0.7. There are several compounds with a Pa value greater than 0.7 for anti-inflammatory activity, indicating a positive prediction that the potential has been demonstrated through research. These compounds are 1,2-propanediol, 3-(octadecyloxy)-, diacetate; 2-trifluoroacetoxydodecane; 2-trifluoroacetoxypentadecane; 2-trifluoroacetoxytridecane; 1-eicosene, (E); and 4-hydroxy-4-methylhex-5-enoic. 1,2-propanediol, 3-(octadecyloxy)-, diacetate can also be found in African black pepper (*Piper guineense*) (Sulaimon *et al.* 2020) and papaya (*Carica papaya*) pulp and seed (Amin *et al.* 2019). They discussed the anti-inflammatory properties of these plants' extract.

Predicting the toxicity of drug candidates is a critical aspect of modern drug development (Pu *et al.* 2019). Another important reason for the failure of otherwise promising drug candidates and the withdrawal of marketed drugs is unexpected drug toxicity. As a result, several secondary metabolites with anti-inflammatory, immunomodulatory, and antioxidant properties were chosen for toxicity assessment, as shown in Table 2. These compounds are classified as toxic class V (possibly harmful if swallowed) and VI (non-toxic). These compounds, on the other hand, are classified as carcinogens, with probabilities ranging from 0.50–0.69. With a probability value of 0.63, the compound 1,2-propanediol, 3-(octadecyloxy)-, diacetate is found to be mutagenic.

Table 3 summarizes the results of the drug-likeness analysis using Lipinski's rule of five. Lipinski's rule of five states that a compound must have five key physicochemical parameters (molecular weight, lipophilicity, polar surface area, hydrogen bonding, and charge) to cross the blood-brain barrier passively (Lipinski *et al.* 2001). These compounds exhibited an average of one violation, with the exception of propane, 1,3-bis(octadecyloxy)-, which exhibited two violations, and only methoxyacetic acid, 2-tetradecyl ester and methoxyacetic acid, 2-tridecyl ester

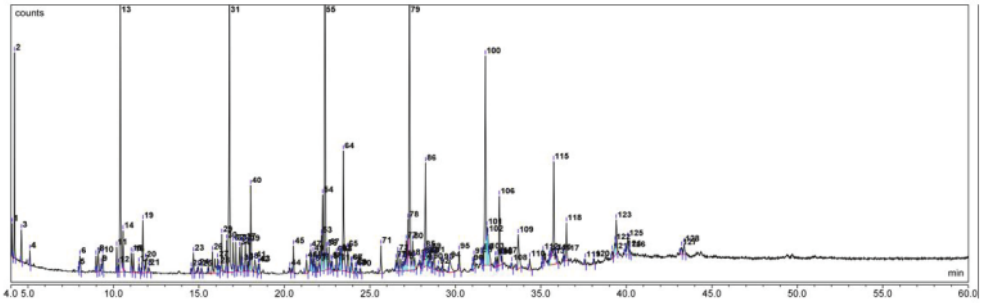


Figure 1. TIC of n-hexane extract of pineapple peel.

Table 1. Bioactivity analysis of the secondary metabolite in n-hexane extract of pineapple peel. Pa values greater than 0.7 are written in bolded, while Pa values less than 0.7 but greater than 0.3 are underlined.

PubChem CID	IUPAC name of the compounds	Bioactivities				
		Immunomodulator	Immunostimulant	Immunosuppressant	Antioxidant	Anti-inflammatory
628694	1 Spirost-8-en-11-one, 3-hydroxy-, (3ß,5a,14ß,20ß,22ß,25R)-	–	–	0.634	0.244	0.664
537324	1,2-Propanediol, 3-(octadecyloxy)-, diacetate	0.522	0.602	0.558	0.238	**0.719**
76492	1-Heptene, 2,6-dimethyl-	0.186	0.552	0.514	0.314	0.352
522551	1-Undecene, 4-methyl-	0.192	0.411	0.607	0.419	0.442
139395	2,6-Dimethyldecane	0.365	0.453	0.423	0.381	0.309
98299	2-Bromo dodecane	–	–	0.373	–	–
551194	2-Butene, 1-butoxy-3-m	0.315	0.326	0.455	0.348	0.495
536258	2-Trifluoroacetoxydodecane	0.394	0.289	0.228	–	**0.704**
534405	2-Trifluoroacetoxypentadecane	0.394	0.289	0.228	–	**0.704**
536345	2-Trifluoroacetoxytridecane	0.394	0.289	0.228	–	**0.704**
543279	3-(Prop-2-enoyloxy)dodecane	0.423	0.488	0.452	0.261	0.453
5365051	3-Eicosene, (E)	0.371	0.380	0.371	0.336	**0.802**
534403	3-Trifluoroacetoxytridecane	0.403	0.301	0.318	–	0.659
549495	4-Cyclopropylcarbonyloxytridecane	0.432	0.355	0.432	0.146	0.454
19882843	4-Hydroxy-4-methylhex-5-enoic	0.253	0.432	0.459	0.203	**0.727**
543571	4-Trifluoroacetoxyhexadecane	0.394	0.344	0.323	0.129	0.651
543277	4-Trifluoroacetoxypentadecane	0.394	0.344	0.323	0.129	0.651
543275	4-Trifluoroacetoxytridecane	0.394	0.344	0.323	0.129	0.651
5363222	7-Methyl-Z-tetradecen-1-ol acetate	0.422	0.463	0.637	0.257	0.649
91693137	Carbonic acid, eicosyl vinyl ester	0.264	0.360	0.297	–	0.628
15600	Decane	0.385	0.372	0.392	0.170	0.424
545611	Decane, 2,3,5,8-tetramethyl	0.289	0.308	0.315	0.254	–
537327	Decane, 2,4,6-trimethyl	0.357	0.399	0.435	0.316	0.331
43924	Decane, 2,6,7-trimethyl-	0.335	0.378	0.328	0.175	–
23415	Decane, 2-methyl-	0.385	0.429	0.394	0.21	0.27
17835	Decane, 4-methyl-	0.368	0.436	0.441	0.392	0.340
522798	Dichloroacetic acid, tetradecyl ester	–	0.204	0.323	–	0.451
8182	Dodecane	0.385	0.372	0.392	0.170	0.424
35768	Dodecane, 2,6,11-trimethyl-	0.333	0.418	0.412	0.428	0.275
93447	Dodecane, 2,7,10-trimethyl	0.350	0.445	0.413	0.371	0.272
545627	Dodecane, 4,6-dimethyl-	0.361	0.384	0.453	0.324	0.363
520105	Dodecane, 5,8-diethyl-	0.333	0.457	0.336	0.163	–
41208	Eicosane, 10-methyl-	0.368	0.436	0.441	0.392	0.340
519146	Eicosane, 2-methyl-	0.385	0.429	0.394	0.210	0.270

292289	Eicosane, 7-hexyl-	0.331	0.443	0.337	0.171	–
292291	Heneicosane, 11-(1-ethylpropyl)-	0.424	0.462	0.336	0.163	0.402
12398	Heptadecane	0.385	0.372	0.392	0.170	0.424
41209	Heptadecane, 2,6,10,15-tetramethyl	0.350	0.445	0.413	0.371	0.272
545603	Heptadecane, 2,6-dimethyl-	0.365	0.453	0.423	0.381	0.309
292286	Heptadecane, 9-octyl-	0.331	0.443	0.337	0.171	–
137658	Heptane, 2,4,6-trimethyl-	0.321	0.324	0.407	0.307	0.303
16656	Heptane, 2,4-dimethyl-	0.344	0.376	0.422	0.312	0.307
89304	Heptane, 3,4,5-trimethyl	0.262	0.273	0.251	–	–
11006	Hexadecane	0.385	0.372	0.392	0.170	0.424
136331	Hexadecane, 2,6,11,15-tetramethyl-	0.333	0.418	0.412	0.428	0.275
14045	Hexane, 2,3,5-trimethyl-	0.303	0.265	0.272	–	–
11511	Hexane, 2,4-dimethyl-	0.338	0.347	0.408	0.268	0.296
86067	Hexane, 3-ethyl-2-methyl	0.429	0.450	0.289	0.151	0.298
545729	Methoxyacetic acid, 2-tetradecyl ester	0.590	0.553	0.416	0.166	0.642
545728	Methoxyacetic acid, 2-tridecyl ester	0.590	0.553	0.416	0.166	0.642
137081	Nonadecane, 2-methyl-	0.385	0.429	0.394	0.210	0.270
38626	Nonahexacontanoic acid	0.419	0.504	0.451	0.222	0.515
8141	Nonane	0.385	0.372	0.392	0.17	0.424
624534	Octadecane, 1,1'-[1,3-propanediylbis(oxy)]bis	0.400	0.352	0.360	0.134	0.504
15264	Octadecane, 2-methyl-	0.385	0.429	0.394	0.210	0.270
292285	Octadecane, 3-ethyl-5-(2-ethylbutyl)-	0.324	0.403	0.344	0.130	–
520183	Octadecane, 5-methyl-	0.368	0.436	0.441	0.392	0.340
93065	Octadecane, 6-methyl-	0.368	0.436	0.441	0.392	0.340
545612	Octane, 2,4,6-trimethyl-	0.338	0.347	0.408	0.268	0.296
85925	Octane, 4-ethyl-	0.333	0.457	0.336	0.163	–
16665	Octane, 4-methyl	0.368	0.436	0.436	0.392	0.340
61823	Oxirane, [(hexadecyloxy)methyl]-	0.374	0.392	0.332	0.163	0.300
12391	Pentadecane	0.385	0.372	0.392	0.170	0.424
21205	Pentadecanoic acid, 14-methyl-, Methyl ester	0.421	0.456	0.482	0.243	0.392
551406	Stearic acid, 3-(octadecyloxy)propyl ester	0.437	0.455	0.448	0.178	0.641
6421051	Sulfurous acid, dodecyl pentyl ester	–	0.311	–	–	–
6421048	Sulfurous acid, nonyl pentyl ester	–	0.311	–	–	–
12389	Tetradecane	0.385	0.372	0.392	0.170	0.424
85785	Tetradecane, 2,6,10-trimethyl-	0.365	0.453	0.423	0.381	0.309
21206	Tetradecanoic acid, 12-methyl-, methyl ester	0.420	0.487	0.519	0.316	0.420
545963	Tetrapentacontane, 1,54-dibromo-	0.216	–	0.513	–	–
522536	Trichloroacetic acid, hexadecyl ester	0.384	0.455	0.398	–	0.530
522535	Trichloroacetic acid, pentadecyl ester	0.384	0.455	0.398	–	0.530
14257	Undecane	0.385	0.372	0.392	0.170	0.424
28453	Undecane, 2,6-dimethyl	0.365	0.453	0.423	0.381	0.309

Table 2. Computational toxicity estimations of selected phytoconstituents extracted from pineapple peel.

PubChem CID	LD_{50} mg/kg	Toxicity Class	Average Similarity (%)	Prediction Accuracy (%)	Hepatotoxicity		Carcinogenicity		Immunotoxicity		Mutagenicity		Cytotoxicity	
					Prediction	Probability	Prediction	Probability	Prediction	Probability	Prediction	Probability	Prediction	Probability
534403	6000	6	71.66	69.26	Inactive	0.69	Inactive	0.55	Active	0.83	Inactive	0.93	Inactive	0.87
628694	6000	6	71.66	69.26	Inactive	0.69	Inactive	0.55	Active	0.83	Inactive	0.93	Inactive	0.87
537324	10000	6	89.49	70.97	Inactive	0.90	Active	0.69	Inactive	0.80	Active	0.63	Inactive	0.85
543275	5000	5	75	69.26	Inactive	0.67	Inactive	0.54	Inactive	0.98	Inactive	0.86	Inactive	0.69
5363222	3460	5	100	100	Inactive	0.76	Active	0.50	Inactive	0.88	Inactive	0.98	Inactive	0.74
91693137	5000	5	75	69.26	Inactive	0.78	Active	0.57	Inactive	0.98	Inactive	0.98	Inactive	0.79
545729	3000	5	80.26	70.97	Inactive	0.84	Active	0.52	Inactive	0.92	Inactive	0.73	Inactive	0.79
545728	3000	5	80.26	70.97	Inactive	0.84	Active	0.52	Inactive	0.92	Inactive	0.73	Inactive	0.79
624534	3000	5	84.32	70.97	Inactive	0.90	Active	0.64	Inactive	0.83	Inactive	0.86	Inactive	0.87
522536	5000	5	75	69.26	Inactive	0.81	Active	0.57	Inactive	0.99	Inactive	0.78	Inactive	0.75
522535	5000	5	75	69.26	Inactive	0.81	Active	0.57	Inactive	0.99	Inactive	0.78	Inactive	0.75

Table 3. The results of Lipinski's rule of five analysis of the selected phytoconstituents.

PubChem CID	Molecular weight	No. H-bond acceptors	No. H-bond donors	Log *P*	Molar refractivity	No. violation
534403	296	2	0	5.401	73.452	1
628694	428	4	1	5.037	118.160	1
537324	428	5	0	6.759	122.551	1
543275	296	2	0	5.401	73.452	1
5363222	268	2	0	5.272	82.163	1
91693137	368	3	0	8.324	111.409	1
545729	286	3	0	4.875	83.890	0
545728	272	3	0	4.485	79.273	0
624534	580	2	0	13.932	185.347	2
522536	387	2	0	5.761	93.432	1
522535	373	2	0	5.371	88.815	1

complied with the rule. The log P value is proportional to the molecule's hydrophobicity. Molecules that are excessively hydrophobic are more toxic because they stay longer in the lipid bilayer and are dispersed more widely throughout the body, lowering the selectivity of the target enzyme's binding. A negative log P value is also undesirable because it indicates that the molecule cannot pass through the lipid bilayer membrane. The number of hydrogen bond donors and acceptors indicates the hydrogen bonding capacity; the greater the hydrogen bonding capacity, the greater the energy required to initiate the absorption process. Lipinski's rule, in general, describes the solubility of certain compounds in order for them to pass through cell membranes *via* passive diffusion. When the molecular weight of the compound exceeds 500 Da, poor oral absorption is more likely (Alex *et al.* 2011).

The compounds with a strong anti-inflammatory tendency (Pa > 0.5) were used as ligands in a molecular docking analysis of the pyrin domain-containing 3

(NLRP3) inflammasome (PDB ID: 2NAQ). The NLRP3 inflammasome shows a significant role in innate immune system. This compound induces caspase-1 activation and the release of proinflammatory cytokines such as IL-1β/IL-18, which results in a response to microbial or viral infection, as well as cellular damage (Kelley *et al.* 2019; Rodrigues *et al.* 2020). Molecular docking analysis of the selected ligands is presented in Table 4. The visualization of the docking analysis of the binding of NLRP3 inflammasome with selected phytoconstituents of pineapple peel's n-hexane extract is displayed in Figure 2. The compound 3-trifluoroacetoxytridecane has the highest binding free energy value (–6.7 kcal/mol) and the next is 1 spirost-8-en-11-one, 3-hydroxy-, (3ß,5a,14ß,20ß,22ß,25R)- with a binding free energy value of –6.6 kcal/mol. Both compounds exhibit various interactions with the receptor – including van der Waals, alkyl, pi-alkyl, and unfavorable donors. The binding-free energy, hydrogen bonds, and other residual interactions are all parameters that affect how ligands and receptors interact (Tallei *et al.* 2021b).

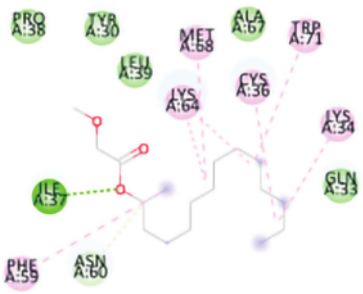
The compound 3-Trifluoroacetoxytridecane has been found in Aryuvedic formulations for the treatment of ailments – including diabetes, skin, and urinary tract disorders (Jessica *et al.* 2016). It was also reported to be present in *Kirganella reticulata* and to have anticancer and antimicrobial activities (Sudha *et al.* 2013). The compound 1 spirost-8-en-11-one, 3-hydroxy-, (3ß,5a,14ß,20ß,22ß,25R)- is also present in *Aremisia annua* (Hameed *et al.* 2016) and *Quercus infectoria* (Hussein *et al.* 2016). There is currently no information available regarding the anti-inflammatory or immunomodulatory properties of these two compounds.

Because it has not been tested in a clinical setting, the findings of this study cannot be considered clinically significant. However, although it has only been proven *in silico*, there are indications that some of the phytoconstituents present in pineapple peel have medicinal potential associated with immunomodulatory and anti-inflammatory properties. As a result, there is still a large enough opportunity to conduct further research into it.

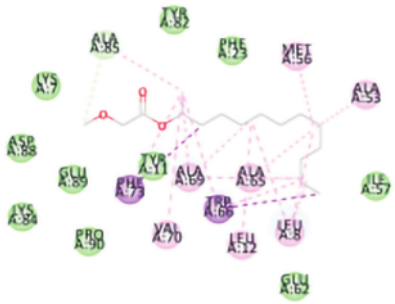
Table 4. Molecular docking analysis of the selected ligands on NLRP3 Inflammasome receptor.

PubChem CID	Binding free energy (kcal/mol)	Type of interaction	Interacting residues
534403	–6.7	Alkyl	MET(A:56), 2LEU(A:12), LEU(A:81), 3ALA(A:69), 2ALA(A:85), 2VAL(A:70);
		Pi-alkyl	PHE(A:23), 2TRP(A:66), TYR(A:11), 3PHE(A:73), TYR(A:82)
		van der Walls	LEU(A:81), ARG(A:78), ALA(A:74), ALA(A:65), ILE(A:57), ALA(A:53), GLU(A:62), LEU(A:52), LEU(A:27)
628694	–6.6	Pi-Alkyl	TYR(A:30)
		Unfavorable donor-donor	HIS(A:26)
		van der Waals	ALA(A:75), ILE(A:72), MET(A:68), TRP(A:71), PRO(A:31), PRO(A:32), LYS(A:34), GLN(A:33)
537324	–4.8	Alkyl	2LEU(A:39), MET(A:68), ILE(A:37), 2CYS(A:36)
		Carbon H-bond	ILE(A:37);
		Pi-alkyl	TYR(A:30)
		van der Waals	PRO(A:32), PRO(A:38), PRO(A:31), GLU(A:28), ASP(A:29), ARG(A:31), LEU(A:27), GLN(A:33), GLY(A:35), ASN(A:60), PHE(A:59), LYS(A:64),
543275	–4.6	Alkyl	PRO(A:31), ALA(A:75)
		Pi-alkyl	HIS(A:26), 2TYR(A:30), 2TRP(A:71)
		Pi-sigma	TRP(A:71)
		Conventional H-bond	HIS(A:26)
		Halogen (fluorine)	TRP(A:71), MET(A:68)
		van der Waals	GLN(A:33), PRO(A:32), ILE(A:72), ALA(A:67), ALA(A:74)
5363222	–4.4	Alkyl	2LYS(A:64), 2CYS(A:36), 2ILE(A:37)
		Conventional H-bond	ASN(A:60)
		van der Waals	LEU(A:27), LEU(A:39), MET(A:68), ALA(A:67), TYR(A:30), MET(A:56), TRP(A:71), GLN(A:33), PHE(A:59), LYS(A:34), GLY(A:35)

91693137	–3.8	23 Alkyl	ALA(A:67), MET(A:68), 2LYS(A:64), CYS(A:36), ILE(A:37)
		Pi-alkyl	TRP(A:71), PHE(A:59)
		van der Waals	LEU(A:27), LEU(A:39), TYR(A:30), ASN(A:60), GLN(A:33), LYS(A:64)
545729	–4.0	22 Alkyl	LYS(A:34), 2LYS(A:64), CYS(A:36), MET(A:68);
		Pi-alkyl	PHE(A:59), TRP(A:71)
		Carbon H-bond	ASN(A:60)
		Conventional H-bond	ILE(A:37)
		der Waals	PRO(A:38), TYR(A:30), LUE(A:39), ALA(A:67), GLN(A:33)
545728	–4.7	22 Alkyl	ALA(A:85), VAL(A:70), 3ALA(A:69), LEU(A:12), 3LEU(A:8), ALA(A:53), 2ALA(A:65), MET(A:56)
		Pi-alkyl	PHE(A:73), 2TRP(A:66);
		Pi-sigma	PHE(A:73), TRP(A:66)
		Carbon H-bond	ALA(A:85)
		van der Walls	LYS(A:7), ASP(A:88), GLU(A:89), LYS(A:84), PRO(A:90), TYR(A:11), GLU(A:62), ILE(A:57), PHE(A:23), TYR(A:82)
624534	–4.6	23 Alkyl	2CYS(A:36), 3LYS(A:64), MET(A:68), ILE(A:37), PRO(A:32), 4PRO(A:38), ARG(A:41)
		Pi-alkyl	PHE(A:59)
		van der Waals	ALA(A:67), TRP(A:71), TYR(A:30), GLN(A:33), ASN(A:60), LYS(A:34), GLY(A:35), LEU(A:39), LEU(A:27), PRO(A:31), GLU(A:28), PRO(A:40), ASP(A:29)
522536	–4.5	23 Alkyl	CYS(A:36), MET(A:68), 3LYS(A:64), 4ALA(A:67)
		Pi-alkyl	3TRP(A:71)
		van der Waals	LEU(A:39), PHE(A:59), ASN(A:60), ILE(A:37), GLN(A:33), TYR(A:30), TRP(A:66), VAL(A:70), LYS(A:86), GLU(A:63)
522535	–5.2	Alkyl	LEU(A:12), MET(A:56), 5LEU(A:8), 3ALA(A:69), 2ALA(A:65), 2ILE(A:57), ALA(A:53)
		Pi-alkyl	TYR(A:11), PHE(A:73), 5TRP(A:66)
		van der Walls	THR(A:4), GLU(A:62), PHE(A:23), LEU(A:81), TYR(A:82), VAL(A:70), ALA(A:85)



Methoxyacetic acid, 2-tetradecyl ester



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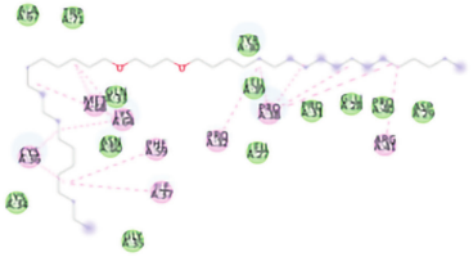
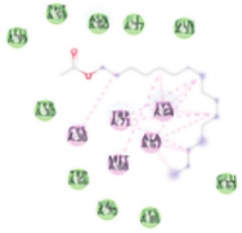
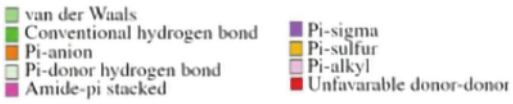


Octadecane, 1,1'-[1,3-propanediylbis(oxy)]bis



Trichloroacetic acid, hexadecyl ester

Trichloroacetic acid, pentadecyl ester



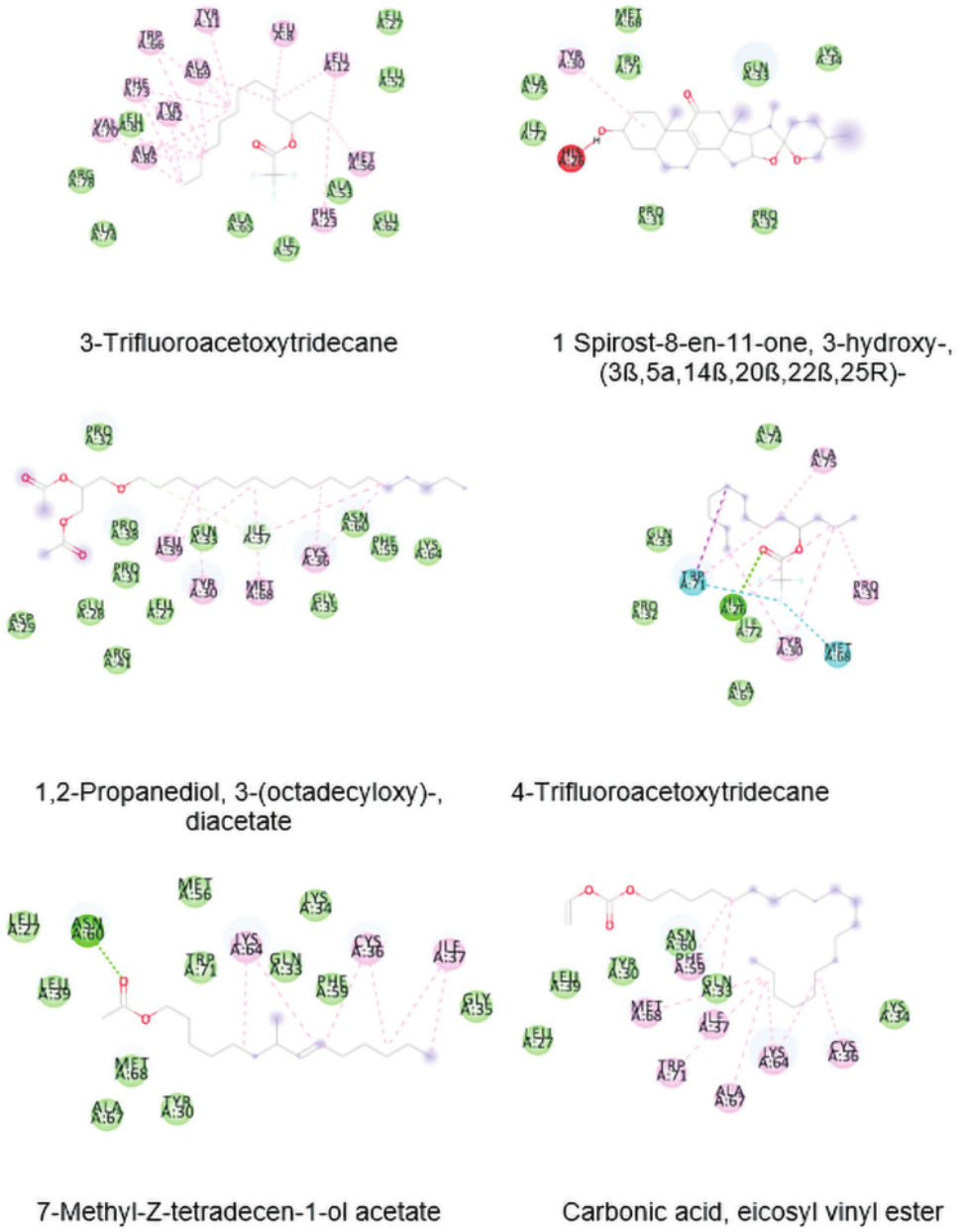


Figure 2. Docking visualization of the binding of NLRP3 inflammasome with selected phytoconstituents of pineapple peel's n-hexane extract.

CONCLUSION

The GC-MS analysis revealed that the n-hexane extract of pineapple peel contained 74 secondary metabolites. Almost all of these compounds have immunomodulatory, immunostimulant, immunosuppressive, antioxidant, and anti-inflammatory properties, with Pa values greater than 0.3 but less than 0.7. Certain compounds have a Pa value greater than 0.7 and exhibit anti-inflammatory activity, implying that their potential has been demonstrated through research. The compounds 3-trifluoroacetoxytridecane and 1-spirost-8-en-11-one, 3-hydroxy-, (3ß,5a,14ß,20ß,22ß,25R)- have binding free energies of –6.7 and 6.6 kcal/mol with NLRP3 inflammasome receptor, respectively. Additionally, these two compounds have a favorable pharmacokinetic profile, indicating that they have the potential to be investigated further *in vitro* and *in vivo* as inflammasome inhibitors.

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