

Article Integrated UPLC/Q-TOF-MS/MS Analysis and Network Pharmacology to Reveal the Neuroprotective Mechanisms and Potential Pharmacological Ingredients of Aurantii Fructus Immaturus and Aurantii Fructus

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Abstract: Aurantii Fructus (AF) and Aurantii Fructus Immaturus (AFI) have been used for thousands of years as traditional Chinese medicine (TCM) with sedative effects. Modern studies have shown that Citrus plants also have protective effects on the nervous system. However, the effective substances and mechanisms of action in Citrus TCMs still remain unclear. In order to explore the pharmacodynamic profiles of identified substances and the action mechanism of these herbs, a comprehensive approach combining ultra-high-performance liquid chromatography with quadrupole time-of-flight mass spectrometry (UPLC/Q-TOF-MS/MS) analysis and network pharmacology was employed. Firstly, UNIFI 2.1.1 software was used to identify the chemical characteristics of AF and AFI. Secondly, the SwissTargetPrediction database was used to predict the targets of chemical components in AF and AFI. Targets for neuroprotection were also collected from GeneCards: The Human Gene Database (GeneCards-Human Genes | Gene Database | Gene Search). The networks between targets and compounds or diseases were then constructed using Cytoscape 3.9.1. Finally, the Annotation, Visualization and Integrated Discovery Database (DAVID) (DAVID Functional Annotation Bioinformatics Microarray Analysis) was used for GO and pathway enrichment analysis. The results showed that 50 of 188 compounds in AF and AFI may have neuroprotective biological activities. These activities are associated with the regulatory effects of related components on 146 important signaling pathways, derived from the KEGG (KEGG: Kyoto Encyclopedia of Genes and Genomes), such as neurodegeneration (hsa05022), the Alzheimer's disease pathway (hsa05010), the NF-kappa B signaling pathway (hsa04064), the hypoxia-inducible factor (HIF)-1 signaling pathway (hsa04066), apoptosis (hsa04210), the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor resistance signaling pathway (hsa01521), and others, by targeting 108 proteins, including xanthine dehydrogenase (XDH), glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B), and glucose-6-phosphate dehydrogenase (G6PD), among others. These targets are thought to be related to inflammation, neural function and cell growth.

Keywords: UPLC/Q-TOF-MS/MS; Aurantii Fructus Immaturus; Aurantii Fructus; network pharmacology; neuroprotection

1. Introduction

Aurantii Fructus (AF) and Aurantii Fructus Immaturus (AFI) have been used in traditional Chinese medicine (TCM) for thousands of years [1]. AF and AFI are the fruits of *Citrus aurantium* L. (CA) (bitter orange) and their cultivated varieties [2]. And *Citrus aurantium* L. Cv. *daidai* (CAD) is the most commonly used cultivated variety of *Citrus aurantium* L. and is widely grown as a medicinal plant [3]. AF and AFI are collected at



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Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). different stages of fruit growth with diverse clinical efficacy; the effect of AFI on promoting qi is obviously better than that of AF, and they are thus are recorded in the Chinese Pharmacopoeia as two distinct medicinal materials [4]. According to TCM theory, AF and AFI each have their own unique clinical applications [5]. Although AF and AFI have common effects of regulating visceral functions [6], AF is always used to alleviate chest pain and improve gastrointestinal functions, such as alleviating dyspepsia in a gentle yet efficient manner [7]. AFI, compared to AF, expresses a more rapid and robust method of action and is often employed to disperse severe abdominal distention and to eliminate phlegm [8]. We found that Citrus plants, including Citrus aurantium L., have beneficial effects on those with neurodegenerative diseases [9], suggesting AF and AFI to have potential protective effects on the nervous system. Therefore, it is reasonable to explore the protective effects of AF and AFI on nervous system. Currently, excitotoxicity and oxidative stress are recognized as two important aspects of nervous system damage [10]. Hence, we believe that it is meaningful to study the chemical components related to excitotoxicity and oxidative stress in AF and AFI. At present, chemical analysis methods, including chromatography [11], nuclear magnetic resonance (NMR) spectroscopy [12], and mass spectrometry (MS) [13], are usually used to study the chemical constituents of plant drugs. Among them, ultra-highperformance liquid chromatography (UPLC) alongside high-resolution mass spectrometry (HR-MS) can simultaneously detect a variety of chemical components in plant drugs [14]; however, to obtain accurate identification results, the UPLC-HR-MS detection results must be compared with the standard chromatogram of chemical components or the mass spectrometry database [15]. As an auxiliary mass spectrum analysis software, UNIFI supports multi-user, server-based workgroups to complete liquid chromatography (LC), LC/MS, and LC/MS/MS data collection, storage, management, mining, and sharing, which can greatly improve collaboration efficiency [16,17].

In this study, the chemical compositions of AF and AFI derived from *Citrus aurantium* L. and *Citrus aurantium* L. Cv. *daidai* were systematically evaluated with UNIFI software with UPLC/quadrupole time-of-flight (Q-TOF)-MS/MS. The chemical similarities and differences between AF and AFI were summarized. Furthermore, the target of compounds and the target of neuroprotection were predicted using the method of network pharmacology [18]. Finally, identifying bioactive compounds, potential targets, and signaling pathways relevant to the neuroprotection with AF and AFI was realized using an integrative network analysis [19].

The results indicated that 50 of the 188 compounds in AF and AFI may be bioactive, which may be related to their targeting of 108 targets such as XDH, GRIN2B, AKT1, PRKCG, CAPN1, CSNK2A1, G6PD, etc. One hundred and forty-six important signaling pathways were identified, including neurodegeneration (hsa05022), the Alzheimer's disease pathway (hsa05010), the NF-kappa B signaling pathway (hsa04064), the HIF-1 signaling pathway (hsa04066), apoptosis (hsa04210), and the EGFR tyrosine kinase inhibitor resistance signaling pathway (hsa01521), etc.

2. Results and Discussion

2.1. Identification of Compounds in AF and AFI

The total ion chromatograms of AF and AFI in both positive and negative ion modes are presented in Figure 1A–F. The process of identifying compounds via UNIFI software is shown in Figure 1G. The retention times and the MS data of the characterized compounds are summarized in Table 1. A total of 188 compounds were identified by UNIFI software based on the self-built database. Among these compounds, compounds (46, 47, 92, 106, 119, 130, 154) were unambiguously identified by comparison with reference compounds.



Figure 1. Identification of compounds in AF and AFI. (**A**) AF-CA; (**B**) AFI-CA; (**C**) AF-CAD; (**D**) AFI-CAD; (**E**) total ion chromatography of samples in positive ion mode; (**F**) total ion chromatography of samples in negative ion mode; (**G**) the identification process of compounds in UNIFI software: No. 142 compound identified as Gardenin A.

Table 1. Compounds identified in AF and AFI by UNIFI software.

No.	Compound Name	Observed m/z	Mass Error (mDa)	Observed RT (min)	Adducts	AFI-CAD	AF-CAD	AFI-CA	AF-CA
1	7-Hydroxycoumarin	167.0119	1.5	1.01	-H ₂ O+Na	1	1	1	1
2	Arginine	175.118	-1.0	1.05	+H	1	1	1	1
3	Isopimpinellin	251.0299	-1.6	1.09	-H ₂ O+Na	1			
4	Isoprenol	104.1062	-0.8	1.09	$+NH_4$	✓	1	1	1
5	Isomaltose	341.1088	-0.1	1.11	-H		1		1
6	Limonin	475.1763	3.6	1.12	-H ₂ O+Na, +H	1	1	1	1
7	Farnesyl Acetate	287.196	-2.2	1.17	+Na	1	1	1	1
8	Heterodendrin	262.1276	-0.9	1.18	+H	✓		1	
9	N-Methyl Proline	130.0852	-1.0	1.23	+H	✓	1	1	1
10	Betonicine	160.096	-0.8	1.24	+H	✓	1	1	1
11	Citric Acid	215.0155	-0.7	1.35	+Na	✓	1	1	1
12	5-Hydroxymethyl Furaldehyde	127.0383	-0.7	1.35	+H	1	1	1	1

No.	Compound Name	Observed m/z	Mass Error (mDa)	Observed RT (min)	Adducts	AFI-CAD	AF-CAD	AFI-CA	AF-CA
13	5-(Hydroxymethyl)Furan-3- Carbaldehyde	287.979	-0.7	1.36	-H ₂ O+Na				1
14	7-Hydroxy-6-Methoxy-	193.0481	-1.4	1.39	+H	1	1	1	
15	Coumarin L-Synophring Acotato	150 0913	0.0	1.42	H.O.H				1
15	Dopamine	136.0746	-11	1.42	-H ₂ O+H	1	· ·	<i>,</i>	•
17	L-Tyrosine	182.0808	-0.4	1.43	+H	1	·	<i>.</i>	1
18	N-Methyltyramine	152.1065	-0.5	1.45	+H	1	1	1	
19	Tyrosol	121.064	-0.8	1.45	-H ₂ O+H	1	1	1	<i>.</i>
20	Dimethyl Anthranilate	166.0856	-0.7	1.55	+H		/		1
21	Citronellyl Acetate	203.1389	-0.0 -1.7	1.62	$-H_2O+Na$	v	v	v	<i>,</i>
23	Salicylic Acid	137.024	-0.4	1.69	-H		1		•
24	Dehydrodieugenol	349.138	-3.1	1.73	+Na	1	1	1	1
25	Vanillin	153.0531	-1.5	1.74	+H	1		1	1
26	Epigallocatechin	324.1077	0.0	1.76	$+NH_4$	/	/	1	/
27	Isocoumarin	147 0428	-1.2	1.79	+11 +H	v	, ,	, ,	•
29	Subaphylline	265.1542	-0.4	1.94	+H		·	1	1
30	Tryptophan	205.097	-0.1	2.00	+H	1	1	1	1
31	Geniposide	389.1408	-3.4	2.05	+H			1	
32	Palmidin A	493.1303	2.1	2.05	$-H_2O+H$				
33	4-nyaroxy-3- Methoxystrychnine	195.0659	-0.4	2.06	+HCOO			1	
34	Caffetannic Acid	355.1007	-1.6	2.10	+H, +Na	1	1		
35	Ayapanin	177.0538	-0.8	2.12	+H				1
36	Scolymoside	595.1667	1.0	2.20	+H	1		1	
37	Vicenin 5 7 Dibydroyachromono	595.1665	0.8	2.23	+H, -H ₂ O+H	1	~	1	<i>,</i>
38	7-rutinoside	487.1441	-0.5	2.24	+H	1	1	1	
39	Ferulic Acid	177.0537	-0.9	2.27	-H ₂ O+H	1	1	1	1
40	Hyperoside	465.1027	0.0	2.31	- +H	1		1	
41	Chrysophanol-1-O-β-	623.1598	-1.9	2.35	+HCOO, -H				1
42	gentiobioside	105 0225	1.0	2 20	но,н	/	/	1	
42	Isorhamnetin-3-Rutinoside	625 1767	-1.0	2.39	-n ₂ 0+n +H	1	· ·	<i>.</i>	1
44	Phenethylamine	144.079	0.7	2.55	+Na	·	1	•	•
45	Naringenin-4'-Glucoside-7-	765 2212	0.0	2 78	+No	1	1		1
+U	Rutinoside	703.2212	0.0	2.70	TT	•	•	•	•
46	(+/-)-Naringenin	273.0752	-0.6	2.78	+H		~		1
48	Phenylacetic acid	135 0446	-0.5	2.80	-H	1		, ,	•
49	Salipurposide	435.1273	-1.3	2.82	+H	1	1	1	1
50	Methyl Chlorogenate	391.0965	-3.5	2.82	+Na	1	1	1	1
51	Eufin	123.0428	1.2	2.94	-H ₂ O+Na	,		1	
52	Cinaroside	449.1068	-1.0	2.94	$+H, -H_2O+H$	~		/	/
53 54	Naringenin-7-O-Glucuronide	431.0937	-2.8	2.94	$-H_2O+H_1$		1	v	•
	2-Hydroxy-6-	151 0270	1.1	2.10		,		,	,
55	Methoxybenzoic Acid	151.0379	-1.1	3.10	-н ₂ О+н, +н	~	~	<i>v</i>	<i>v</i>
56	Eriodictyol-7-Glucoside	473.1056	0.2	3.27	+Na		1	1	1
57	Coumarin Vitamin B	191.0345	-0.5	3.49	+HCOO				
59	5.7-Dihydroxychromone	179 0328	-11	3.75	+11 +H	1		1	1
60	Butylidenephthalide	189.0897	-1.3	3.79	+H	1	1	1	•
61	Helenalin	263.1256	-2.2	3.88	+H	1	1	1	1
62	Emodin 8-glucoside	433.1119	-1.0	3.90	+H	1	1		
63	Kaempferol Conjoisidia Acid	287.0545	-0.5	4.15	+H H.O.Na	~	/		
64 65	Friedictual	289.0688	-1.8	4.23	$-\Pi_2 O + INa$ +H	1	·	1	1
66	Ombuin	331.0805	-0.8	4.24	+H, -H ₂ O+H	1	·	•	•
67	Chrysophanein	417.1178	-0.2	4.24	+Ĥ	1	1	1	1
68	Lonicerin	595.1643	-1.4	4.28	+H	1	1	<i>✓</i>	<i>✓</i>
69 70	natsudaidain	419.131	-2.6	4.53	+H				
70	Caffeic Acid Olouropoin	163.0376	-1.4	4.62	-H ₂ O+H	~			
71	Hesperetin-7-O-B-D-	323.1773	-5.5	4.00	-1120+11		v	v	v
72	Glucoside	487.1202	-0.9	4.82	+Na	1	1	1	1
73	Hesperidin Methyl Chalcone	625.2081	-4.6	4.85	+H		1	1	1
74	3,4,7-Trimethoxycoumarin	237.0745	-1.3	4.94	+H	1		1	1
75	Narirutin-isomer	581.1862	-0.3	5.02	+H, +Na	1		1	1
70 77	Homoeriodictvol	303.0846	-1.3 -1.7	5.20	-п ₂ 0+п +Н	, ,	· ·	, ,	, ,
78	Chryso-Obtusin Glucoside	565.1554	-0.9	5.24	+HCOO	1		, ,	✓
79	Rhoifolin	579.1714	0.5	5.34	+H, +Na	1	1	1	1
80	Eriocitrin	579.1701	-0.8	5.39	-H ₂ O+H	1	1	✓	✓
81	Meranzin Hydrate	261.1109	-1.2	5.50 5.52	-H ₂ O+H			<i>,</i>	1
02	1 ac011101101111	403.1300	-3.2	5.32	-112U+П	v	v	~	~

Table 1. Cont.

	No.	Compound Name	Observed m/z	Mass Error (mDa)	Observed RT (min)	Adducts	AFI-CAD	AF-CAD	AFI-CA	AF-CA
8 Procession 609.138 0.4 5.20 HI \prime \prime 8 Descension 609.138 0.4 5.81 HI \prime \prime 8 Noohogendoada 633.1791 -0.9 6.02 +Na \prime \prime 9 Noohogendoada 633.1791 -0.9 6.02 +Na \prime \prime 9 Phonesmine Dimetry Biber 403.054 -1.4 6.11 +H \prime \prime 9 Phonesmine Dimetry Biber 403.054 -0.6 6.31 HI \prime \prime 9 Obtasin 33.08 0.4 7.83 +Ho \prime \prime 9 Obtasin 33.0984 0.4 7.83 +HO \prime \prime 9 Obtasin 33.0984 0.4 7.83 +HO \prime \prime 9 Obtasin 33.1990 -1.0 7.76 +HO \prime \prime \prime 9	83	Gallic Acid	153.0171	-1.1	5.60	-H ₂ O+H	1	1	1	1
8 Dissum 60 3138 0.4 5.81 $+H$ r r 8 Hesperturbale 633173 -0.9 6.02 $+Na$ r 9 Dobaspeinda 631173 -0.9 6.02 $+Na$ r 9 Disancia 3011307 -1.0 6.11 $+H$ r r 9 Proveshin 3011607 -1.0 6.11 $+H$ r r 9 Proveshin 901107070 -1.0 6.11 $+H$ r r r 9 Proveshin 901107070 -1.0 6.13 $+H$ r r r 9 State St	84	Physcion-8-O-Beta-D-	609.1801	-1.3	5.79	+H	1		1	1
Integers in 2-0. integers in 2-0. <thintegers 2-0.<="" in="" th=""> <thintegers 2-0.<="" <="" in="" td=""><td>85</td><td>Diosmin</td><td>609.1818</td><td>0.4</td><td>5.81</td><td>+H</td><td>1</td><td>1</td><td>1</td><td></td></thintegers></thintegers>	85	Diosmin	609.1818	0.4	5.81	+H	1	1	1	
Northesperiture	86	Hesperetin-7-O-	633.1781	-0.9	6.02	+Na	·	1	·	
8 Tonadrysone 44.1.197 2.3 6.03 +NA \prime \prime \prime 9 Decometric ()meetric 301.097 -1.0 6.11 +H \prime \prime 90 Plorestric 633.18 1.0 6.63 +NA \prime \prime 91 Plorestric 633.18 1.0 6.65 +NA \prime \prime 92 Cubrain () mic Add 440.148 -0.6 7.22 +H \prime \prime 93 Cohumian () mic Add 7.27 1.4 7.23 +H \prime \prime 94 Cohumian () mic Add 7.27 1.4 7.23 +H \prime \prime 95 Dacatrybronin () 180.442 -0.4 7.23 +H \prime \prime \prime 90 5.7.1/Timethoxyformarch 180.0769 -1.6 7.21 +HON \prime \prime \prime 100 Dis-she () for () fo	97	Neohesperidoside	622 1781	0.0	6.02	. No	/			
99 Disservein 00007 -1.0 6.11 $+11$ 2 2 90 Processing Dimetely Life 00005 0.61 0.61 0.61 0.61 91 Reperturing 0.31 10.0 6.55 $+Nh$ 2 2 91 Coptisine 33.0894 0.4 0.28 $+10.041$ 2 2 92 Coptisine 30.0894 0.4 0.28 $+10.041$ 2 2 93 Coptisine 30.0892 -0.6 72.76 $+14.07Na$ 2 2 94 Nondinia cold Cucodal 72.202 -0.8 72.8 $+10.0Na$ 2	88	Torachrysone	431.1337	2.5	6.03	+Na	1	1	1	1
9 Phononsimol Dimension Letter 4 6.12 + NH, \checkmark \checkmark 9 Redrocation Letter 593.16.6 -0.6 6.53 +H \checkmark 9 Redrocation Letter 593.16.6 -0.6 6.53 +H \checkmark \checkmark 9 Chronian 345.096.0 -0.6 6.775 +H \checkmark \checkmark 9 Chronian Line LA 440.144 -0.6 7.22 +H.000.N \checkmark \checkmark 9 Descriptoronian 472.162 -0.4 7.23 +H \checkmark \checkmark 9 Descriptoronian 189.042 -0.4 7.23 +H \checkmark \checkmark 10 DS-Jmensity Lacter Acad 189.055 1.3 7.33 +H \checkmark \checkmark \checkmark 10 DS-Mensity Lacter Acad 189.0155 1.3 7.34 +H \checkmark \checkmark 10 Marrian 20.0111 1.0 8.23 +H \leftarrow \checkmark \checkmark <	89	Diosmetin	301.0697	-1.0	6.11	+H	1	1	1	
9 Robustonic biologic Spite 100 Control biologic Spite 100	90	Pinoresinol Dimethyl Ether	404.2054	-1.4	6.12	$+NH_4$	1	1	1	1
92 Hesperialins 633 18 1.0 6.65 +Na / 92 Ottosins 343,0004 0.4 2.08 -H_COHI / 94 Coppissine 343,0004 0.4 2.08 -H_COHN / / 94 Commitmic and Cacoside 777,2709 -2.0 7.6 -H_CONN / / 95 Desceptonomlin 473,2709 -2.0 7.6 -H_CONN / / 95 Discreptonomlin 473,2709 -1.6 7.91 +H_CONN / / / 90 5.7.4. Timethoxy Gaurani 189,052 -0.4 7.92 +H / / / 101 D3.4. Thenkbary Courani 189,052 -1.8 7.93 +H /	91	Rubrofusarin-6-B- Gentiobioside	595.1663	-0.6	6.31	-H			1	1
99 Obtain 335,0863 -0.6 6.79 $+11$ \prime \prime 91 Coprimiting $303,084$ 0.4 708 $116,0-Na$ \prime \prime 92 Coprimiting $403,1400$ -10 726 $+16,0-Na$ \prime \prime 93 Decceptinomilie $473,2162$ -0.8 728 $+16$ \prime \prime 90 Syst.Finethoxyfavore $317,0709$ -1.6 723 $+16,0+Na$ \prime \prime 100 Syst.Finethoxyfavore $317,0709$ -0.7 734 $+16$ \prime \prime 1010 Bessecatrol $222,0707$ -0.7 734 $+16$ \prime \prime 102 Resonantin $281,027$ -1.0 8.23 $+116$ \prime \prime 103 Meranzin $281,1277$ -0.7 9.54 $+Cl$ \prime \prime \prime 103 Meranzin $281,227$ -1.4 9.54 $+Cl$ \prime \prime \prime 104 Maresona	92	Hesperidins	633.18	1.0	6.65	+Na			1	
94 Coptisine 330.0894 0.4 7.08 -14.00.14 \prime \prime \prime 95 Curronit nipric, vici 407.120 -2.0 7.06 +14.00.Na \prime \prime 97 Normbritz, end Curcosite 97.172.09 -2.0 7.06 +14.00.Na \prime \prime 98 Deacetynomilin 473.202 -0.8 7.28 +14 \prime \prime 90 57.0Hentowy Countain 189.053.2 -1.3 7.03 +Na \prime \prime 101 D13.3Penyllactic Acid 189.053.7 -1.3 7.03 +Na \prime \prime 103 Bescentrol 222.0707 -0.8 8.20 +HCOO \prime \prime 104 Satimposide 451.1231 -1.5 8.20 +HCOO \prime \prime 105 Maranza 261.111 -1.1 8.23 +HCOO \prime \prime 104 Maranza 261.1127 -1.2 9.79 +HOHH	93	Obtusin	345.0963	-0.6	6.79	+H	1	1	1	1
29 Currentian 477 Han -1.0 2.46 $+HO-Na$ \checkmark 90 Nomitine add Checolic 777 279 12.00 7.6 H_1O-Na \checkmark \checkmark 90 Descriptionnin 4732162 -0.8 7.78 H_1O-Na \checkmark \checkmark 91 $5.74.$ Timethoyflauce $3170,070$ -1.6 792 $+H_1O+Na$ \checkmark \checkmark 100 $5.74.$ Timethoyflauce $4180,053$ 1.3 733 $+Na$ \checkmark \checkmark 101 Dis-Prepulatic Acid 189.0542 -0.4 722 34.4 41.7 \checkmark \checkmark 102 Stangoval 451.123 -1.5 82.0 $HICOO$ \checkmark \checkmark \checkmark 103 Merancin 251.137 -7.5 84.0 $+HICOO$ \checkmark \checkmark \checkmark 104 Reacomisside 351.1372 0.7 9.44 $+I_{CO}$ \checkmark $<$ \checkmark \checkmark <td>94</td> <td>Coptisine</td> <td>303.0894</td> <td>0.4</td> <td>7.08</td> <td>-H₂O+H</td> <td></td> <td>,</td> <td>1</td> <td></td>	94	Coptisine	303.0894	0.4	7.08	-H ₂ O+H		,	1	
9 Nomitine and Calconside 77,72709 -2.0 7.76 H_1ONS \checkmark 9 Descriptionniin 433,122 -0.8 7.78 H_1ONS \checkmark \checkmark 9 Descriptionniin 183,0253 1.3 7.93 $4H_1$ \checkmark \checkmark 10 D1-3 Pheryllacic Acid 189,0253 1.3 7.93 $4H_1$ \checkmark \checkmark 10 Baseria 227,070 -0.8 7.94 H_1 \checkmark \checkmark 10 Baseria 221,070 -0.8 7.93 $4H_1$ \checkmark \checkmark 10 Nammaria 241,1141 -0.6 8.48 $+H$ \checkmark \checkmark 10 Naringin 351,177 -1.2 9.79 $4I_0OH$ \checkmark \checkmark \checkmark 10 Cobscurone 453,1747 -1.2 9.79 $4I_0OH$ \checkmark \checkmark \checkmark 110 Cobscurone 453,075 -0.4 10.39 $+H$ \checkmark \checkmark \checkmark 110 Lucolin 253,0	95 96	3-Tert-Butyladinic Acid	449.1448 207.1001	-0.6	7.12	-H2O+N2	~	4		
98 Desceptionmin 4732162 -0.8 7.78 1.44 1.04 7.74 100 57.0 Innerboxy Counarin 189.0542 -0.4 7.92 $44_{1.04}$ 1.04 7.74 101 $Ds.3$ Physephilatic Acid 189.0531 1.3 7.92 $44_{1.04}$ 1.04 7.74 102 Sessein 22.000 -0.37 7.93 4.14 7.74 103 Saleposide 451.121 -1.08 8.23 HH 7.74 105 Meranzin 251.111 -1.08 8.23 HH 7.74 7.84 106 Narringin 551.372 0.7 9.54 $-4C$ 7.76 107 Teppinyl Acetale 231.1341 -0.5 8.80 $+HCOO$ 7.76 108 Excommoside 351.203 -1.4 9.94 $+1.074$ 7.76 108 Excommoside 351.203 -0.11 10.94 H_1O+H 7.76 113 Xamborato	97	Nomilinic acid Glucoside	717.2709	-2.0	7.76	-H ₂ O+Na	1	1		1
99 57,4 ⁺ Timethoxyfarone 370769 -1.6 7.91 H ₂ O-Na \prime \prime \prime 101 D1-3-Pheryllactic Acid 1890535 1.3 733 +Na \prime \prime 101 D1-3-Pheryllactic Acid 1890535 1.3 733 +Na \prime \prime 101 D1-3-Pheryllactic Acid 1890535 1.3 733 +Na \prime \prime 103 Session 2611111 -1.5 8.20 +HCOO \prime \prime 104 Session 261111 -1.5 8.20 +H \prime \prime \prime 105 Meranzia 261111 -1.0 8.23 +H \prime \prime \prime 106 Generoine 281127 0.7 9.54 +H \prime \prime \prime 110 Generoine 2010183 -1.0 10.57 +H \prime \prime \prime 111 Kasamperol-3- 2010183 -1.0 10.66 +H_O-Na \prime \prime \prime \prime 11	98	Deacetylnomilin	473.2162	-0.8	7.78	+H	1	1		•
100 52-Dimethoxy Countarin 189.0542 -0.4 722 +H,O+H ✓ ✓ 100 D3-Phenyllactic Acid 129.035 1.3 733 +Na ✓ ✓ 101 D3-Phenyllactic Acid 129.035 1.3 733 +Na ✓ ✓ 101 Bisimposida 211.031 -1.5 8.20 +H ✓ ✓ 103 Marman 261.1111 -1.0 8.23 +H ✓ ✓ ✓ 104 Balimposida 351.1217 0.7 9.54 +Cl ✓ ✓ ✓ 107 Decommissida 351.1747 -1.4 9.34 +H ✓ ✓ ✓ 108 Acanzoryholorgidoside B 551.1747 -1.4 9.34 +H ✓ ✓ ✓ 111 Kanhotoxol 320.1083 -1.0 10.35 +Na ✓ ✓ ✓ 111 Chorosyholorizationsida 639.1923 -0.1 10.05 +Na ✓ ✓ ✓ 1114 Lutoolin 259.205<	99	5,7,4'-Trimethoxyflavone	317.0769	-1.6	7.91	-H ₂ O+Na	1	1	1	1
111 D1-2-Pherpijate Acad 1880.55 1.3 235 +Na V V V 103 Seedinal 227.079 -0.67 7.93 +H V V 104 Seedinal 261.113 -1.5 8.20 +HCOO V V 105 Meranzin 261.111 -1.5 8.20 +H V V 105 Meranzin 261.111 -1.5 8.48 +H V V 106 Commisside 381.189 -0.6 8.48 +H V V 106 Co-Barcopholorigiosde 551.177 -1.2 9.79 +H_0CHC V V 110 Mathotosol 20.0183 -1.0 10.37 +H V V V 111 Kacompferol-3- 441.0769 -2.3 10.56 +Na V V V 113 Arabouranoside 39125 0.0 1066 +H_ONNa V V V 113 Arabouranoside 391925 0.1 11.1 11.33 +H_+N	100	5,7-Dimethoxy Coumarin	189.0542	-0.4	7.92	-H ₂ O+H				1
103 Essentiation 222.0707 -0.7 7.94 -14 \prime 104 Salireposide 451.1231 -1.5 8.20 $+HCOO$ \prime 105 Maringin 581.1859 -1.6 8.43 $+H$ \prime \prime 107 Terpinyl Acetate 381.1747 -12.8 8.80 $+HCOO$ \prime 108 6-O-Barzoypholorigidoside B 551.1747 -12.4 9.24 $-CI$ \prime 109 Obacrone 453.205 -1.4 9.24 $+H$ \prime \prime 110 Obacrone 453.205 -1.4 9.24 $+H$ \prime \prime 121 Anaborizonosia 441.0769 -2.3 10.56 $+Na$ \prime \prime 113 Kampionol.3. 201.0183 -1.1 10.94 $+H_O-Na$ \prime \prime 113 Kampionol.3. 291.051 0.1 11.303 $+Na$ \prime \prime 113 Intropioninologide 573.1932 -1.1 10.94 $+H_O-$	101	DI-3-Phenyllactic Acid	189.0535	1.3	7.93	+Na -H	1		1	1
104 Shiropoide 45.1221 -1.5 8.20 +HCOO 105 Merazian 26.1111 -1.0 8.23 +H 106 Merazian 26.1111 -1.0 8.23 +H 107 Terpinyl Acetate 28.1189 -0.6 8.48 +H 106 Descarolphologidide 35.1174 -1.2 9.79 +HCOV 100 Obacunone 20.10183 -1.0 10.37 +H 118 Karthotoxol 20.10183 -1.0 10.80 +Na 113 Norobicin 69.1925 0 10.66 +H ₅ O+Na <td< td=""><td>102</td><td>Resveratrol</td><td>227.0703</td><td>-0.7</td><td>7.94</td><td>-11 -H</td><td>1</td><td>v</td><td></td><td></td></td<>	102	Resveratrol	227.0703	-0.7	7.94	-11 -H	1	v		
105 Maringin 581.111 -10 8.23 +H	104	Salireposide	451.1231	-1.5	8.20	+HCOO	·	1		1
100 Naringin 581.1859 -0.6 8.48 $+H$ \prime \prime 101 Terpinyl Acetta 235.1277 0.7 9.54 $+Cl$ \prime 108 Eucommisside 385.1277 0.7 9.54 $+Cl$ \prime 100 $00-Bernoylphlorigideside B51.1747 -1.2 9.79 +L_0O+H \prime 110 Mathotoxol 20.1083 -1.0 0.37 +H \prime \prime 112 Karmofrend-3- 41.0769 -2.3 10.56 +Na \prime \prime 113 Norobiocin 893.04 -0.4 10.080 -H \prime \prime 114 Lateomin A 297.392.8 -0.4 10.080 -H_0 \prime \prime 115 Eucomin A 297.392.8 -0.4 10.080 -H_1 \prime \prime \prime 114 Eucomin A 573.192.2 -1.11 10.34 +H_0 \wedge Na \prime \prime 115 Eucomin A 597.095.056 1.4 11.36$	105	Meranzin	261.1111	-1.0	8.23	+H	1	1	1	
	106	Naringin	581.1859	-0.6	8.48	+H	1	1	1	1
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	107	Terpinyl Acetate	241.1441	-0.5	8.80	+HCOO		1		1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	108	Eucommioside 6-O-Bonzovlphlorigidosido B	385.1277 551 1747	0.7	9.54	+CI	1		~	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	110	Obacunone	455.205	-1.2 -1.4	9.84	+H	1		1	
112 Kaempferol-3- Arabo transoite 441.0769 -2.3 10.56 +Na ✓ ✓ ✓ 113 Novobiocin 639.1925 0.0 10.66 -H ₂ O-Na ✓ ✓ 115 Eucommin A 573.1938 -0.4 10.93 +Na ✓ ✓ 116 Cirusin B 573.1938 -0.4 10.93 +Na ✓ ✓ 117 (+)Threo-Gualacylglycerol 219.0644 1.7 11.23 +H ₂ O-Na ✓ ✓ 118 Genjingentiubioisde 585.1047 1.5 11.30 +H ✓ ✓ ✓ 112 Incoin Anthrone 257.097 -0.1 11.40 +H ✓ ✓ ✓ 121 Dectoinarin 632.197 -0.1 11.40 +H ✓ ✓ ✓ ✓ 122 Encolin Anthrone 237.0797 -1.1 11.54 +H ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ <t< td=""><td>111</td><td>Xanthotoxol</td><td>201.0183</td><td>-1.0</td><td>10.37</td><td>-H</td><td>1</td><td>1</td><td>1</td><td>1</td></t<>	111	Xanthotoxol	201.0183	-1.0	10.37	-H	1	1	1	1
Arabofuranoside Hastor Los Hastor C C 113 Novobiccin 63) 1925 0.0 10.66 -HgO+Na C 114 Luteolin 285.04 -0.4 10.80 -H C 115 Eucommin A 573.1932 -1.1 10.94 -HgO+Na C 116 Citrusin B 573.1932 -1.1 10.94 -HgO+Na C C 118 Genipingentiobioside 585.1607 1.5 11.30 +Cl C C 120 Isosakuranetin 287.0975 0.1 11.36 +H C C C 121 Pectoinarin 283.098 -1.4 12.41 -H C C C 122 Eignans 243.1491 -0.2 11.80 +H C C C 123 Isignans 413.1491 -0.2 11.80 +H C C C 122 Eignans 283.0598 -1.4 12.41 -H C C C 123	112	Kaempferol-3-	441 0769	-23	10.56	+Na	1	1	1	
113 Novobiocn 6/9/1925 0.0 10.66 -H / 114 Lutoolin 285.04 -0.4 10.93 +Na / / 115 Eucommin A 573.1938 -0.4 10.93 +Na / / 116 Citrusin B 573.1932 -1.1 10.94 +H_ONNA / / 117 (+) Threo-Guaiacylglycerol 219.0644 1.7 11.23 +H_ONNA / / 118 Genipingentiobioside 585.1607 1.5 11.30 +H, +Na / / / 120 Isosakuranetin 257.0797 -0.1 11.40 +H / / / 121 Petolinarin 623.197 -0.1 11.40 +H / / / / 123 Lignans 415.1381 -0.6 11.79 +H / / / / 124 Apigenin 269.0445 -0.5 12.81 +H / / / / 125 Physcion 283.0586	112	Arabofuranoside	111.07.07	2.0	10.50	II O M	·	•	•	
114 Lucoun 20.04 -0.4 10.00 $+1$ \checkmark 115 Eucommin A 573.1938 -0.4 10.93 $+R_0O+R_0$ \checkmark \checkmark 116 Citrusin B 573.1938 -0.1 10.94 $+R_0O+R_0$ \checkmark \checkmark 118 Gentpingentiobioside 585.1067 1.5 11.30 $+Cl$ \checkmark \checkmark 120 Isosakuranetin 287.0915 0.1 11.36 $+H$ \checkmark \checkmark \checkmark 121 pectolinarin 287.0797 -1.1 11.54 $+H$ \checkmark \checkmark \checkmark 122 Encodin Anthrone 257.0797 -1.1 11.54 $+H$ \checkmark \checkmark \checkmark 124 hopstanethoxyflavone 283.0998 -1.4 12.21 $+H$ \checkmark \checkmark \checkmark 125 Physcion 283.0998 -1.4 12.21 $+H$ \checkmark \checkmark \checkmark 126 Apigenin 269.045 -1.6 13.17 $+R_2O+H_1+H_1$ \star \checkmark <td>113</td> <td>Novobiocin</td> <td>639.1925</td> <td>0.0</td> <td>10.66</td> <td>-H₂O+Na</td> <td>/</td> <td></td> <td>1</td> <td>1</td>	113	Novobiocin	639.1925	0.0	10.66	-H ₂ O+Na	/		1	1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	114	Fucommin A	203.04 573 1938	-0.4 -0.4	10.80	-п +Na	1	1	1	1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	115	Citrusin B	573.1932	-1.1	10.95	-H ₂ O+Na	1	•	1	•
118 Genipingentiobioside 585 1067 1.5 11.30 +Cl ✓ 120 Josakuranetin 257 0915 0.1 11.36 +H ✓ ✓ ✓ 120 Josakuranetin 257 0915 0.1 11.36 +H ✓ ✓ ✓ 121 Pectolinarin 623.197 -0.1 11.40 +H ✓ ✓ ✓ 121 Endoin Anthrone 257,0797 -1.1 11.54 +H ✓ ✓ ✓ 123 Lignans 415.1381 -0.6 11.79 +H ✓ ✓ ✓ 124 Js 3/4 / 5.67.8- 433.1491 -0.2 11.80 +H ✓ ✓ ✓ 125 Physcion 283.0598 -1.4 12.81 +H ✓ ✓ ✓ 126 Apigenin 269.0445 -0.5 13.17 +H_20-H, H, H, ✓ ✓ ✓ 128 IsoMeranzin 23.1011 -0.5 13.17 +H_20-H, H, H, ✓ ✓ ✓ 130 Trager	117	(+)-Threo-Guaiacylglycerol	219.0644	1.7	11.23	-H ₂ O+Na				
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	118	Genipingentiobioside	585.1607	1.5	11.30	+Cl	1			
120 Isosakuranetin 287,0915 0.1 11.36 +H \checkmark \checkmark \checkmark 121 Pectolinarin 623,197 -0.1 11.40 +H \checkmark \checkmark \checkmark 122 Emodin Anthrone 257,0797 -1.1 11.54 +H \checkmark \checkmark \checkmark 121 Jeignans 415.1381 -0.6 11.79 +H \checkmark \checkmark 124 heptamethoxyflavone 433.1491 -0.2 11.80 +H \checkmark \checkmark 125 Physcion 283.0598 -1.4 12.41 -H \checkmark \checkmark 126 Apigenin 269.045 -0.5 12.81 -H \checkmark \checkmark 126 Radrazzian 243.1011 -0.5 13.17 -H ₂ O+H, +H \checkmark \checkmark 128 IsoMeranzin 329.0651 -1.6 13.22 -H \checkmark \checkmark 130 Tangeretin 373.1281 -0.1 14.19 +H, +Na \checkmark \checkmark 132 Gardenin B 359.11 -1.6	119	Didymin	595.2036	1.4	11.35	+H, +Na			1	1
121 Fectomiant 02.17 -0.1 11.54 +11 V V V 122 Eignans 415.1381 -0.6 11.79 +H V V V 123 Lignans 415.1381 -0.6 11.79 +H V V V 124 Ja3.4'5.6.7.8- 43.1491 -0.2 11.80 +H V V V 125 Physcion 283.0598 -1.4 12.41 -H V V V 126 Apigenin 269.045 -0.5 12.81 -H V V V 128 IsoMeranzin 243.1011 -0.5 13.17 -H_2O+H, +H, +M V V V 126 Apigenin 329.0651 -1.6 13.22 -H V V V 130 Tangeretin 373.1281 -0.1 14.19 +H V V V 130 Chrysoobtusin 357.0971 -0.9 14.22 -H V V V 137 Pertysobtu	120	Isosakuranetin Postolinarin	287.0915	0.1	11.36	+H			1	1
123 Lignans 415.1381 -0.6 11.79 +H / / 124 hgspanethoxyflavone 433.1491 -0.2 11.80 +H / / 125 Physcion 283.0598 -1.4 12.41 -H / / 126 Apjgenin 269.045 -0.5 12.81 -H / / 127 Genistein 269.0445 -1.1 12.84 -H / / / 128 IsoMeranzin 243.1011 -0.5 13.17 -H_0+H, +H, +M / / / 129 Direthoxyflavone 329.0651 -1.6 13.22 -H / / / 130 Targeretin 373.1281 -0.0 14.27 -H / / / 132 Gardenin B 359.111 -1.6 14.29 +H / / / 133 Chrysoobtusin 355.158 -0.1 14.32 +H_0 / / / 133 Isolimonic Acid 489.2118 -0.1 </td <td>121</td> <td>Emodin Anthrone</td> <td>257 0797</td> <td>-0.1 -1.1</td> <td>11.40</td> <td>+11 +H</td> <td>1</td> <td>1</td> <td>, ,</td> <td>v</td>	121	Emodin Anthrone	257 0797	-0.1 -1.1	11.40	+11 +H	1	1	, ,	v
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	123	Lignans	415.1381	-0.6	11.79	+H	·	·	1	
124 heptamethoxyflavone 450.1491 -0.2 11.00 $+11$ \checkmark \checkmark \checkmark 125 Physcion 283.0598 -1.4 12.41 $+H$ \checkmark \checkmark 126 Apigenin 269.045 -0.5 12.81 $+H$ \checkmark \checkmark 127 Genistein 269.045 -1.1 12.84 $+H$ \checkmark \checkmark 128 IsoMeranzin 243.1011 -0.5 13.17 $+Na$ \checkmark \checkmark 129 52.76 ⁻ Trihydroxy-7.8- -0.1 14.19 $+H$, $+Na$ \checkmark \checkmark 130 Targeretin 373.1281 -0.1 14.19 $+H$, $+Na$ \checkmark \checkmark 130 Chryscobtusin 357.0971 -0.9 14.27 $+H$ \checkmark \checkmark 133 P-Cymene 135.158 -1.1 14.31 $+H$ \checkmark \checkmark 134 Coniferin 297.1477 -0.8 14.32 $+H_0O+H$ \checkmark \checkmark 135 Isolimonic Acid 489.2118 -0.1 <	124	3,3′,4′,5,6,7,8-	422 1401	0.2	11.80	, U	/	/	/	/
125 Physion 283.0598 -1.4 121 -H ✓ 126 Apigenin 269.045 -0.5 12.81 -H ✓ 127 Genistein 269.0445 -1.1 12.84 -H ✓ ✓ 128 IsoMeranzin 243.1011 -0.5 13.17 'H ₂ O+H, +H, +Na ✓ ✓ 129 Dimethoxyflavone 329.0651 -1.6 13.22 -H ✓ ✓ 130 Tangeretin 373.1281 -0.1 14.19 +H, +Na ✓ ✓ ✓ 130 Chrysoobtusin 357.0971 -0.9 14.27 -H ✓ ✓ ✓ 132 Gardenin B 359.117 -0.6 14.32 -H ₂ O+H ✓ ✓ ✓ 133 Bolimonic Acid 489.2118 -0.1 14.36 -H ₂ O+H ✓ ✓ ✓ 135 Isolimonic Acid 489.212 -0.9 14.60 +H ✓ ✓ ✓ 136 Witamin E 491.227 -0.9 14.60 +H <td>124</td> <td>heptamethoxyflavone</td> <td>455.1491</td> <td>-0.2</td> <td>11.00</td> <td>+11</td> <td>v</td> <td>v</td> <td>v</td> <td>v</td>	124	heptamethoxyflavone	455.1491	-0.2	11.00	+11	v	v	v	v
12b Apigenin 269.045 -0.5 1.281 -H \checkmark 127 Genistein 269.0455 -1.1 12.84 -H \checkmark \checkmark 128 IsoMeranzin 243.1011 -0.5 13.17 $^{-H_2O+H_1+H_1}$ \checkmark \checkmark 129 52',6'-Trihydroxy-7,8- 0 13.17 -H \checkmark \checkmark 130 Tangeretin 373.1281 -0.1 14.19 +H, +Na \checkmark \checkmark 130 Chrysoobtusin 357.0971 -0.9 14.27 -H \checkmark \checkmark 131 Chrysoobtusin 357.0971 -0.9 14.29 +H \checkmark \checkmark 133 P-Cymene 1351158 -1.1 14.31 +H \checkmark \checkmark 134 Coniferin 297.1477 -0.8 14.32 -H_2O+H \checkmark \checkmark 135 Isolimonic Acid 489.2118 -0.1 14.36 +H_O+H \checkmark \checkmark 136 Vitamin E 491.274 -4.9 14.39 +H \checkmark \checkmark	125	Physcion	283.0598	-1.4	12.41	-H			1	
12 Genesen 20.0440 -1.1 1.64 +1.4 \checkmark \checkmark 128 IsoMeranzin 243.1011 -0.5 13.17 $^{+}H_2O+H, +H, +N_4$ \checkmark \checkmark 129 $52', 6'$ -Trihydroxy-7,8- Dimethoxyflavone 329.0651 -1.6 13.22 -H \checkmark \checkmark 130 Tangeretin 373.1281 -0.1 14.19 +H, +Na \checkmark \checkmark 131 Chrysoobtusin 357.0971 -0.9 14.27 -H \checkmark \checkmark 132 Gardenin B 359.111 -1.6 14.29 +H \checkmark \checkmark 133 P-Cymene 135.1158 -1.1 14.31 +H \checkmark \checkmark 134 Coniferin 29.1477 -0.8 14.32 -H_2O+H \checkmark \checkmark 135 Isolimonic Acid 489.2118 -0.1 14.36 +H_2O+H \checkmark \checkmark 136 Vitamin E 491.2274 -4.9 14.39 +H \checkmark \checkmark \checkmark 138 Pentamethoxyflavone 389.1222 -	126	Apigenin Conistoin	269.045	-0.5	12.81	-H _H		1		
128 isoMeranzin 243.101 -0.5 13.17 $+Na$ \checkmark \checkmark 129 $52',6'-Trihydroxy-7,8-$ Dimethoxyflavone 329.0651 -1.6 13.22 $-H$ \checkmark \checkmark 130 Tangeretin 373.1281 -0.1 14.19 $+H, +Na$ \checkmark \checkmark 130 Chrysobtusin 357.0971 -0.9 14.27 $-H$ \checkmark \checkmark 131 Chrysobtusin 357.0971 -0.9 14.27 $-H$ \checkmark \checkmark 133 Cardenin B 359.111 -1.6 14.29 $+H$ \checkmark \checkmark 133 P-Cymene 135.158 -1.1 14.31 $+H$ \checkmark \checkmark 134 Coniferin 297.1477 -0.8 14.32 $+H_2O+H$ \checkmark \checkmark 135 Isolimonic Acid 489.2118 -0.1 14.39 $+H$ \checkmark \checkmark \checkmark 136 Vitamin E 491.2274 -4.9 14.39 $+H$ \checkmark \checkmark \checkmark <td< td=""><td>127</td><td>Genisten</td><td>209.0445</td><td>-1.1</td><td>12.04</td><td>-H2O+H, +H.</td><td>v</td><td>v</td><td></td><td></td></td<>	127	Genisten	209.0445	-1.1	12.04	-H2O+H, +H.	v	v		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	128	IsoMeranzin	243.1011	-0.5	13.17	+Na			1	1
130Tangeretin373.1281 -0.1 14.19 $+H, +Na$ \checkmark \checkmark \checkmark \checkmark 131Chrysoobtusin357.0971 -0.9 14.27 $-H$ \checkmark \checkmark \checkmark 132Gardenin B359.111 -1.6 14.29 $+H$ \checkmark \checkmark \checkmark 133P-Cymene135.1158 -1.1 14.31 $+H$ \checkmark \checkmark 134Coniferin297.1477 -0.8 14.32 $-H_2O+H$ \checkmark \checkmark 135Isolimonic Acid489.2118 -0.1 14.36 $-H_2O+H$ \checkmark \checkmark 136Vitamin E491.2274 -4.9 14.39 $+H$ \checkmark \checkmark 137Marmin355.151 -0.6 14.58 $+Na$ \checkmark \checkmark 138Pentamethoxyflavone389.1222 -0.9 14.60 $+H$ \checkmark \checkmark \checkmark 139Majudin217.0487 -0.8 14.64 $+H$ \checkmark \checkmark \checkmark 1407-Methoxy-5- Prenyloxycoumarin283.0932 -0.9 14.69 $+Na$ \checkmark \checkmark 141 $5_2', 5'-Trihydroxy-6, 7, 8-Prenyloxycoumarin359.07750.214.75-H\checkmark\checkmark142Cardenin A419.132-1.714.87+H\checkmark\checkmark\checkmark142Columbianadin329.1352-3.115.02+H\checkmark\checkmark143Columbianadin373.1262-2.015.25+H\checkmark\checkmark144$	129	5,2',6'-Irihydroxy-7,8- Dimethoxyflavone	329.0651	-1.6	13.22	-H	1		1	
131 Chrysoobtusin 357.0971 -0.9 14.27 $-H$ 132 Gardenin B 359.111 -1.6 14.29 $+H$ \checkmark 133 P-Cymene 135.1158 -1.1 14.31 $+H$ \checkmark 134 Coniferin 297.1477 -0.8 14.32 $-H_2O+H$ \checkmark 135 Isolimonic Acid 489.2118 -0.1 14.36 $-H_2O+H$ \checkmark 135 Vitamin E 491.2274 -4.9 14.39 $+H$ \checkmark \checkmark 137 Marmin 355.151 -0.6 14.58 $+Na$ \checkmark \checkmark 138 Pentamethoxyflavone 389.1222 -0.9 14.60 $+H$ \checkmark \checkmark 140 7 -Hethoxy-5- 283.0932 -0.9 14.69 $+Na$ \checkmark \checkmark 141 $52'_2/5'-Trihydroxy-6.7.8- 359.0775 0.2 14.75 -H \checkmark 142 Gardenin A 419.132 -1.7 14.87 +H \checkmark \checkmark <$	130	Tangeretin	373.1281	-0.1	14.19	+H, +Na	1	1	1	1
132 Gardenin B 399.111 -1.6 14.29 +H \checkmark 133 P-Cymene 135.1158 -1.1 14.31 +H \checkmark \checkmark 134 Coniferin 297.1477 -0.8 14.32 -H ₂ O+H \checkmark \checkmark 135 Isolimonic Acid 489.2118 -0.1 14.36 -H ₂ O+H \checkmark \checkmark 136 Vitamin E 491.2274 -4.9 14.39 +H \checkmark \checkmark \checkmark 137 Marmin 355.151 -0.6 14.58 +Na \checkmark \checkmark \checkmark 138 Pentamethoxyflavone 389.1222 -0.9 14.60 +H \checkmark \checkmark \checkmark 139 Majudin 217.0487 -0.8 14.64 +H \checkmark \checkmark \checkmark 140 7-Methoxy-5- 283.0932 -0.9 14.69 +Na \checkmark \checkmark 141 5,2',5'-Trihydroxy-6,7,8- 359.0775 0.2 14.75 -H \checkmark \checkmark 142 Gardenin A 419.132 -1.7 <td>131</td> <td>Chrysoobtusin</td> <td>357.0971</td> <td>-0.9</td> <td>14.27</td> <td>-H</td> <td>,</td> <td></td> <td></td> <td>1</td>	131	Chrysoobtusin	357.0971	-0.9	14.27	-H	,			1
1301 Conferin103.1100-1.114.31+1.1+1.1134Conferin297.1477-0.814.32 $-H_2O+H$ ✓135Isolimonic Acid489.2118-0.114.36 $-H_2O+H$ ✓136Vitamin E491.2274-4.914.39+H✓137Marmin355.151-0.614.58+Na✓✓138Pentamethoxyflavone389.1222-0.914.60+H✓✓139Majudin217.0487-0.814.64+H✓✓1407-Methoxy-5- Prenyloxycoumarin283.0932-0.914.69+Na✓141 $5.2',5'-Trihydroxy-6.7.8-$ Prenyloxycoumarin359.07750.214.75-H✓142Gardenin A419.132-1.714.87+H✓✓143Columbianadin329.1352-3.115.02+H✓144Cucurbic Acid211.1332-0.715.04-H✓145Isosinensetin373.1267-1.515.26+H, +Na✓✓145Sinensetin373.1267-1.315.28+H✓✓147Obacunoic Acid473.2157-1.315.48-H2O+H✓14835.6-Trihydroxy-7.4'- 313.07-0.715.48-H2O+H✓	132	Gardenin B P-Cymono	359.111	-1.6 -1.1	14.29	+H +H	1		1	
135 Isolinonic Acid 489.2118 -0.1 14.36 $-H_2O+H$ \checkmark 136 Vitamin E 491.2274 -4.9 14.39 $+H$ \checkmark 137 Marmin 355.151 -0.6 14.58 $+Na$ \checkmark \checkmark 138 P-Hydroxyl-3,5,6,3',4'- 389.1222 -0.9 14.60 $+H$ \checkmark \checkmark 139 Majudin 217.0487 -0.8 14.64 $+H$ \checkmark \checkmark 140 7-Methoxy-5- 283.0932 -0.9 14.69 $+Na$ \checkmark \checkmark 141 $5.2', 5'$ -Trihydroxy-6,7,8- 359.0775 0.2 14.75 $-H$ \checkmark 142 Gardenin A 419.132 -1.7 14.87 $+H$ \checkmark \checkmark 143 Columbianadin 329.1352 -3.1 15.02 $+H$ \checkmark \checkmark 144 Cucurbic Acid 211.1332 -0.7 15.04 $-H$ \checkmark \checkmark 144 Sosinensetin 373.1267 -1.5 15.26 $+H$ \checkmark <td>133</td> <td>Coniferin</td> <td>297.1477</td> <td>-0.8</td> <td>14.32</td> <td>-H₂O+H</td> <td>1</td> <td></td> <td>1</td> <td>1</td>	133	Coniferin	297.1477	-0.8	14.32	-H ₂ O+H	1		1	1
136Vitamin E491.2274-4.914.39+H \checkmark \checkmark 137Marmin355.151-0.614.58+Na \checkmark \checkmark \checkmark 1387-Hydroxyl-3,5,6,3',4'- Pentamethoxyflavone389.1222-0.914.60+H \checkmark \checkmark \checkmark 139Majudin217.0487-0.814.64+H \checkmark \checkmark \checkmark \checkmark 1407-Methoxy-5- Prenyloxycoumarin283.0932-0.914.69+Na \checkmark \checkmark 1415.2',5'-Trihydroxy-6,7,8- Trimethoxyflavone359.07750.214.75-H \checkmark \checkmark 142Gardenin A419.132-1.714.87+H \checkmark \checkmark \checkmark 143Columbianadin329.1352-3.115.02+H \checkmark \checkmark 144Cucurbic Acid211.1332-0.715.04-H \checkmark \checkmark 145Isosinensetin373.1267-1.515.26+H, +Na \checkmark \checkmark 147Obacunoic Acid473.2157-1.315.28+H \checkmark \checkmark 1483.5,6-Trihydroxy-7,4'- 313.07-0.715.48-H2O+H \checkmark \checkmark	135	Isolimonic Acid	489.2118	-0.1	14.36	-H ₂ O+H	·		1	1
137 Marmin 355.151 -0.6 14.58 $+Na$ \checkmark \checkmark \checkmark 138 7-Hydroxyl-3,5,6,3',4'- Pentamethoxyllavone 389.1222 -0.9 14.60 $+H$ \checkmark \checkmark \checkmark 139 Majudin 217.0487 -0.8 14.64 $+H$ \checkmark \checkmark \checkmark 140 7-Methoxy-5- Prenyloxycoumarin 283.0932 -0.9 14.69 $+Na$ \checkmark \checkmark 141 5,2',5'-Trihydroxy-6,7,8- Trimethoxyflavone 359.0775 0.2 14.75 $-H$ \checkmark \checkmark 142 Gardenin A 419.132 -1.7 14.87 $+H$ \checkmark \checkmark \checkmark 143 Columbianadin 329.1352 -3.1 15.02 $+H$ \checkmark \checkmark 143 Columbianadin 329.1352 -0.7 15.04 $-H$ \checkmark \checkmark 144 Cucurbic Acid 211.1332 -0.7 15.04 $-H$ \checkmark \checkmark 1445 Isosinensetin 373.1267 -1.5 15.26 $+H$ \checkmark	136	Vitamin E	491.2274	-4.9	14.39	+H			1	
138 7 -Hydroxyl-35,6,3',4'- 389.1222 -0.9 14.60 $+H$ \checkmark \checkmark \checkmark 139 Majudin 217.0487 -0.8 14.64 $+H$ \checkmark \checkmark 140 7-Methoxy-5- 283.0932 -0.9 14.69 $+Na$ 141 $5,2',5'$ -Trihydroxy-6,7,8- 359.0775 0.2 14.75 $-H$ \checkmark 142 Gardenin A 419.132 -1.7 14.87 $+H$ \checkmark \checkmark 143 Columbianadin 329.1352 -3.1 15.02 $+H$ \checkmark \checkmark 144 Cucurbic Acid 211.1332 -0.7 15.04 $-H$ \checkmark 144 Sosienesetin 373.1262 -2.0 15.25 $+H$ \checkmark 145 Isosinensetin 373.1267 -1.5 15.26 $+H$, $+Na$ \checkmark \checkmark 147 Obacunoic Acid 473.2157 -1.3 15.28 $+H$ \checkmark \checkmark 148 3.5,6-Trihydroxy-7,4'- 313.07 -0.7 15.48 $-H_2O+H$ \checkmark	137	Marmin	355.151	-0.6	14.58	+Na	1	1	1	1
139 Majudin 217.0487 -0.8 14.64 +H ✓ ✓ 140 7-Methoxy-5- Prenyloxycoumarin 283.0932 -0.9 14.69 +Na 141 52',5'-Trihydroxy-6,7,8- Trimethoxyflavone 359.0775 0.2 14.75 -H ✓ 142 Gardenin A 419.132 -1.7 14.87 +H ✓ ✓ 143 Columbianadin 329.1352 -3.1 15.02 +H ✓ ✓ 144 Cucurbic Acid 211.1332 -0.7 15.04 -H ✓ ✓ 145 Isosinensetin 373.1262 -2.0 15.25 +H ✓ ✓ 146 Sinensetin 373.1267 -1.3 15.26 +H, +Na ✓ ✓ 147 Obacunoic Acid 473.2157 -1.3 15.28 +H ✓ ✓ 148 Direct/word/word/word 313.07 -0.7 15.48 -H2O+H ✓	138	7-Hydroxyl-3,5,6,3',4'-	389.1222	-0.9	14.60	+H	1	1	1	1
159 Mathematical Mathmatematical Mathematical Mathmatematical Mathematical	130	Majudin	217 0487	-0.8	14.64	тH	1	1		1
140 Prenyloxycoumarin 283.0932 -0.9 14.69 $+Na$ 141 $5,2',5'$ -Trihydroxy-6,7,8- 359.0775 0.2 14.75 $-H$ \checkmark 141 $5,2',5'$ -Trihydroxy-6,7,8- 359.0775 0.2 14.75 $-H$ \checkmark 142 Gardenin A 419.132 -1.7 14.87 $+H$ \checkmark \checkmark 143 Columbianadin 329.1352 -3.1 15.02 $+H$ \checkmark \checkmark 144 Cucurbic Acid 211.1332 -0.7 15.04 $-H$ \checkmark 145 Isosinensetin 373.1262 -2.0 15.25 $+H$ \checkmark 146 Sinensetin 373.1267 -1.5 15.26 $+H, +Na$ \checkmark \checkmark 147 Obacunoic Acid 473.2157 -1.3 15.28 $+H$ \checkmark \checkmark 148 35.6 -Frinhydroxy-7,4'- 313.07 -0.7 15.48 $-H_2O+H$ \checkmark	159	7-Methoxy-5-	217.0407	-0.0	14.04	711	v	v		•
141 $5/2$, $5'$ minutoxy- $5/7$, $5''$ 359.0775 0.2 14.75 $-H$ \checkmark 142 Gardenin A 419.132 -1.7 14.87 $+H$ \checkmark \checkmark 143 Columbianadin 329.1352 -3.1 15.02 $+H$ \checkmark \checkmark 144 Cucurbic Acid 211.1332 -0.7 15.04 $-H$ \checkmark 145 Isosinensetin 373.1262 -2.0 15.25 $+H$ \checkmark 146 Sinensetin 373.1267 -1.5 15.26 $+H, +Na$ \checkmark \checkmark 147 Obacunoic Acid 473.2157 -1.3 15.28 $+H$ \checkmark \checkmark 148 $\frac{3.5,6-Trihydroxy-7,4'-}{Direct furged urgen urgen 313.07 -0.7 15.48 -H_2O+H \checkmark $	140	Prenyloxycoumarin	283.0932	-0.9	14.69	+Na				1
142Gardenin A419.132 -1.7 14.87 $+H$ \checkmark \checkmark \checkmark \checkmark 143Columbianadin329.1352 -3.1 15.02 $+H$ \checkmark \checkmark 144Cucurbic Acid211.1332 -0.7 15.04 $+H$ \checkmark 145Isosinensetin373.1262 -2.0 15.25 $+H$ \checkmark 146Sinensetin373.1267 -1.5 15.26 $+H, +Na$ \checkmark \checkmark 147Obacunoic Acid473.2157 -1.3 15.28 $+H$ \checkmark \checkmark \checkmark 148Direct further fur	141	Trimethoxyflavone	359.0775	0.2	14.75	-H	1			
143 Columbianadin 329.1352 -3.1 15.02 $+H$ \checkmark 144 Cucurbic Acid 211.1332 -0.7 15.04 $-H$ \rightarrow 145 Isosinensetin 373.1262 -2.0 15.25 $+H$ \checkmark 146 Sinensetin 373.1267 -1.5 15.26 $+H, +Na$ \checkmark \checkmark 147 Obacunoic Acid 473.2157 -1.3 15.28 $+H$ \checkmark \checkmark 148 $\frac{3.5,6-Trihydroxy-7,4'-}{Dirent querger 313.07 -0.7 15.48 -H_2O+H \checkmark $	142	Gardenin A	419.132	-1.7	14.87	+H	1	1	1	1
144 Cucurbic Acid 211.1332 -0.7 15.04 $-H$ 145 Isosinensetin 373.1262 -2.0 15.25 $+H$ \checkmark 146 Sinensetin 373.1267 -1.5 15.26 $+H$, $+Na$ \checkmark \checkmark 147 Obacunoic Acid 473.2157 -1.3 15.28 $+H$ \checkmark \checkmark 148 Discription of user 313.07 -0.7 15.48 $-H_2O+H$ \checkmark	143	Columbianadin	329.1352	-3.1	15.02	+H			1	
140 Isosurensetin 57.3.1202 -2.0 15.25 $+H$ \checkmark 146 Sinensetin 373.1267 -1.5 15.26 $+H$, $+Na$ \checkmark \checkmark 147 Obacunic Acid 473.2157 -1.3 15.28 $+H$ \checkmark \checkmark 148 $3.5.6$ -Trihydroxy-7,4'- 313.07 -0.7 15.48 $-H_2O+H$ \checkmark	144	Cucurbic Acid	211.1332	-0.7	15.04	-H	/			1
147 Obacunic Acid 473.2157 -1.3 15.28 $+H$ \checkmark \checkmark 148 3,5,6-Trihydroxy-7,4'- 313.07 -0.7 15.48 $-H_2O+H$ \checkmark	145 146	Sinensetin	373.1262 373.1267	-2.0 -1.5	15.25	+H +H +N2	<i>v</i>	1	1	1
148 3,5,6-Trihydroxy-7,4'- Directly are 0 areas 313.07 −0.7 15.48 -H ₂ O+H	147	Obacunoic Acid	473.2157	-1.3	15.28	+H	1	1	1	1
Limetnoxynavone	148	3,5,6-Trihydroxy-7,4'- Dimethoxyflavone	313.07	-0.7	15.48	-H ₂ O+H			1	1

149 Javanicin 313.0693 1.1 15.48 +Na \checkmark 150 4',5,7,8-Tetramethoxyflavone 343.1172 -0.5 15.55 +H, +Na \checkmark \checkmark 151 Elemicin 231.1007 1.6 15.75 +Na \checkmark \checkmark 152 Balanophonin 401.1233 -0.9 15.81 +HCOO \checkmark 153 Isolimonicacid 471.2008 -0.6 15.92 -H ₂ O+H, +H \checkmark \checkmark 154 Nobiletin 403.1412 2.5 16.40 +H \checkmark \checkmark 155 Thaliglucinone 388.136 -2.0 16.62 +Na \checkmark \checkmark 155 Thaliglucinone 388.136 -2.0 16.60 -H \checkmark \checkmark 155 Tealiglucinone 373.0931 0.2 16.60 -H \checkmark \checkmark 156 Eupatoretin 373.0931 0.2 16.60 -H \checkmark \checkmark 157 Cassiaside 403.1016 -1.8 16.65 -H \checkmark \checkmark	
149Javanicin313.06931.115.48+Na \checkmark 1504',5,7,8-Tetramethoxyflavone343.1172-0.515.55+H, +Na \checkmark \checkmark 151Elemicin231.10071.615.75+Na \checkmark \checkmark 152Balanophonin401.1233-0.915.81+HCOO153Isolimonicacid 16->17-Lactone471.2008-0.615.92-H ₂ O+H, +H \checkmark 154Nobiletin403.14122.516.40+H \checkmark \checkmark 155Thaliglucinone388.1136-2.016.42+Na \checkmark \checkmark 156Eupatoretin373.09310.216.60-H \checkmark \checkmark 157Cassiaside403.1016-1.816.65-H \checkmark \checkmark 158Nomilinicacid515.22770.216.96-H2O+H \checkmark \checkmark 159Nomilin515.22770.216.96+H2O+H \checkmark \checkmark 160Palmitic Acid274.2735-0.517.29+NH4 \checkmark \checkmark 161Caffeic Acid Dimethyl Ether191.0693-0.917.39-H2O+H \checkmark \checkmark 162 $^{3}_{5,6}$ -Tirthydroxy-7,3',4'- Trimethoxyflavone343.0804-0.817.70-H2O+H \checkmark \checkmark 163Vomifoliol247.13171.218.86+Na \checkmark \checkmark	
150 $4',5,7,8$ -Tetramethoxyflavone $343,1172$ -0.5 15.55 $+H, +Na$ \checkmark \checkmark 151 Elemicin 231,1007 1.6 15.75 $+Na$ \checkmark \checkmark 152 Balanophonin 401,1233 -0.9 15.81 $+HCOO$ 153 Isolimonicacid $401,1233$ -0.9 15.81 $+HCOO$ 153 Isolimonicacid $471,2008$ -0.6 15.92 $-H_2O+H, +H$ \checkmark \checkmark 154 Nobiletin 403.1412 2.5 16.40 $+H$ \checkmark \checkmark 155 Thaliglucinone 388.1136 -2.0 16.42 $+Na$ \checkmark \checkmark 156 Eupatoretin 373.0931 0.2 16.60 $-H$ \checkmark \checkmark 157 Cassiaside 403.1016 -1.8 16.65 $-H$ \checkmark \checkmark 158 Nomilinicacid 515.2277 0.2 16.96 $-H_2O+H$ \checkmark \checkmark 160 Palmitic Acid 274.2735 -0.5 17.29 <td></td>	
151 Elemicin 231.1007 1.6 15.75 $+$ Na \checkmark \checkmark 152 Balanophonin 401.1233 -0.9 15.81 $+$ HCOO 153 153 Isolimonicacid 401.1233 -0.9 15.81 $+$ HCOO \checkmark 153 Isolimonicacid 471.2008 -0.6 15.92 $-H_2O+H, +H$ \checkmark \checkmark 154 Nobiletin 403.1412 2.5 16.40 $+$ H \checkmark \checkmark 155 Thaliglucinone 388.1136 -2.0 16.42 $+$ Na \checkmark \checkmark 156 Eupatoretin 373.0931 0.2 16.60 $-$ H \checkmark \checkmark 157 Cassiaside 403.1016 -1.8 16.65 $-$ H \checkmark \checkmark 158 Nomilinicacid 515.2277 0.2 16.96 $-$ H2O+H \checkmark \checkmark 159 Nomilin 515.2261 -1.5 16.98 $+$ H \checkmark \checkmark 161 Caffeic Acid Dimethyl Ether 191.0693 -0.9 17.39 $-$ H2O+H </td <td></td>	
152 Balanophonin 401.1233 -0.9 15.81 $+HCOO$ 153 Isolimonicacid $16 > 17 - Lactome$ 471.2008 -0.6 15.92 $-H_2O+H, +H$ \checkmark \checkmark 154 Nobiletin 403.1412 2.5 16.40 $+H$ \checkmark \checkmark 155 Thaliglucinone 388.1136 -2.0 16.42 $+Na$ \checkmark \checkmark 156 Eupatoretin 373.0931 0.2 16.60 $-H$ \checkmark \checkmark 157 Cassiaside 403.1016 -1.8 16.65 $-H$ \checkmark \checkmark 158 Nomilinicacid 515.2277 0.2 16.96 $-H_2O+H$ \checkmark \checkmark 159 Nomilin 515.2261 -1.5 16.98 $+H$ \checkmark \checkmark 160 Palmitic Acid 274.2735 -0.5 17.29 $+NH4$ \checkmark \checkmark 161 Caffeic Acid Dimethyl Ether 191.0693 -0.9 17.39 $-H_2O+H$ \checkmark \checkmark 162 $3.5.6$ -Trihydroxy- $7.3'/4'$ - <b< td=""><td></td></b<>	
153Isolimonicacid $16>17-Lactome$ 471.2008 -0.6 15.92 $-H_2O+H, +H$ \checkmark \checkmark 154Nobiletin403.14122.516.40 $+H$ \checkmark \checkmark 155Thaliglucinone388.1136 -2.0 16.42 $+Na$ \checkmark \checkmark 156Eupatoretin373.09310.216.60 $-H$ \checkmark 157Cassiaside403.1016 -1.8 16.65 $-H$ \checkmark 158Nomilinicacid515.22770.216.96 $-H_2O+H$ \checkmark 159Nomilin515.2261 -1.5 16.98 $+H$ \checkmark 160Palmitic Acid274.2735 -0.5 17.29 $+NH4$ \checkmark 161Caffeic Acid Dimethyl Ether191.0693 -0.9 17.39 $-H_2O+H$ \checkmark 162 $3.5.6$ -Trihydroxy-7.3'.4'- Trimethoxyflavone343.0804 -0.8 17.70 $-H_2O+H$ \checkmark 163Vomifoliol247.13171.218.86 $+Na$ \checkmark	
154 Nobiletin 403.1412 2.5 16.40 +H ✓ ✓ 155 Thaliglucinone 388.1136 -2.0 16.42 +Na ✓ ✓ 156 Eupatoretin 373.0931 0.2 16.60 -H ✓ ✓ 157 Cassiaside 403.1016 -1.8 16.65 -H ✓ 158 Nomilinicacid 515.2277 0.2 16.96 -H_2O+H ✓ ✓ 159 Nomilin 515.2261 -1.5 16.98 +H ✓ ✓ 160 Palmitic Acid 274.2735 -0.5 17.29 +NH4 ✓ ✓ 161 Caffeic Acid Dimethyl Ether 191.0693 -0.9 17.39 -H_2O+H ✓ ✓ 162 $3,5,6$ -Trihydroxy-7,3',4'- 343.0804 -0.8 17.70 -H_2O+H ✓ ✓ 163 Vomifoliol 247.1317 1.2 18.86 +Na ✓ ✓ 164 $2,4,4$ -Trimethyl-3-(3- 209.152 -1.6 18.89 +H ✓ ✓	
155 Thaliglucinone 388.1136 -2.0 16.42 $+Na$ \checkmark \checkmark 156 Eupatoretin 373.0931 0.2 16.60 $-H$ \checkmark 157 Cassiaside 403.1016 -1.8 16.65 $-H$ \checkmark 158 Nomilinicacid 515.2277 0.2 16.96 $-H_2O+H$ \checkmark \checkmark 159 Nomilin 515.2261 -1.5 16.98 $+H$ \checkmark \checkmark 160 Palmitic Acid 274.2735 -0.5 17.29 $+NH4$ \checkmark \checkmark 161 Caffeic Acid Dimethyl Ether 191.0693 -0.9 17.39 $-H_2O+H$ \checkmark \checkmark 162 $3.5,6$ -Trihydroxy- $7.3'A'$ - 343.0804 -0.8 17.70 $-H_2O+H$ \checkmark \checkmark 163 Vomifoliol 247.1317 1.2 18.86 $+Na$ \checkmark 164 2.44 -Trimethyl-3-(3- 209.152 -1.6 18.89 $+H$ \checkmark \checkmark	J J J J
156 Eupatoretin 373.0931 0.2 16.60 -H \checkmark 157 Cassiaside 403.1016 -1.8 16.65 -H \checkmark 158 Nomilinicacid 515.2277 0.2 16.96 -H2Q+H \checkmark 159 Nomilin 515.2261 -1.5 16.98 +H \checkmark 160 Palmitic Acid 274.2735 -0.5 17.29 +NH4 \checkmark \checkmark 161 Caffeic Acid Dimethyl Ether 191.0693 -0.9 17.39 -H2Q+H \checkmark \checkmark 162 $3,5,6$ -Trihydroxy-7,3',4'- 343.0804 -0.8 17.70 -H2Q+H \checkmark \checkmark 163 Vomifoliol 247.1317 1.2 18.86 +Na \checkmark \checkmark 164 $2,4,4$ -Trimethyl-3-(3- 209.152 -1.6 18.89 +H \checkmark \checkmark	J J
157 Cassiaside 403.1016 -1.8 16.65 $-H$ \checkmark 158 Nomilinicacid 515.2277 0.2 16.96 $-H_2O+H$ \checkmark \checkmark 159 Nomilini 515.2261 -1.5 16.98 $+H$ \checkmark \checkmark 160 Palmitic Acid 274.2735 -0.5 17.29 $+NH4$ \checkmark \checkmark 161 Caffeic Acid Dimethyl Ether 191.0693 -0.9 17.39 $-H_2O+H$ \checkmark \checkmark 162 $3.5.6$ -Trihydroxy-7,3',4'- 343.0804 -0.8 17.70 $-H_2O+H$ \checkmark \checkmark 163 Vomifoliol 247.1317 1.2 18.86 $+Na$ \checkmark 164 $2.4.4$ -Trimethyl-3-(3- 209.152 -1.6 18.89 $+H$ \checkmark \checkmark	<i>✓ ✓</i>
158 Nomilinicacid 515.2277 0.2 16.96 $-H_2O+H$ \checkmark \checkmark 159 Nomilin 515.2261 -1.5 16.98 $+H$ \checkmark 160 Palmitic Acid 274.2735 -0.5 17.29 $+NH4$ \checkmark \checkmark 161 Caffeic Acid Dimetyl Ether 191.0693 -0.9 17.39 $-H_2O+H$ \checkmark 162 $3,5,6-Trihydroxy-7,3',4'-$ Trimethoxyflavone 343.0804 -0.8 17.70 $-H_2O+H$ \checkmark 163 Vomifoliol 247.1317 1.2 18.86 $+Na$ 164 $2,4,4-Trimethyl-3-(3-$ 209.152 -1.6 18.89 $+H$ \checkmark	✓ ✓
159 Nomilin 515.2261 -1.5 16.98 $+H$ \checkmark 160 Palmitic Acid 274.2735 -0.5 17.29 $+NH4$ \checkmark \checkmark 161 Caffeic Acid Dimethyl Ether 191.0693 -0.9 17.39 $-H_2O+H$ \checkmark 162 $3.5,6$ -Trihydroxy-7,3',4'- 343.0804 -0.8 17.70 $-H_2O+H$ \checkmark 163 Vomifoliol 247.1317 1.2 18.86 $+Na$ 164 2,4,4-Trimethyl-3-(3- 209.152 -1.6 18.89 $+H$ \checkmark	
160 Palmitic Acid 274.2735 -0.5 17.29 $+NH4$ \checkmark \checkmark 161 Caffeic Acid Dimethyl Ether 191.0693 -0.9 17.39 $-H_2O+H$ \checkmark 162 $3,5,6$ -Trihydroxy-7,3',4'- 343.0804 -0.8 17.70 $-H_2O+H$ \checkmark \checkmark 163 Vomifoliol 247.1317 1.2 18.86 $+Na$ 164 2,4,4-Trimethyl-3-(3- 209.152 -1.6 18.89 $+H$ \checkmark	1
161 Caffeic Acid Dimethyl Ether 191.0693 -0.9 17.39 $-H_2O+H$ 162 $3,5,6$ -Trihydroxy- $7,3',4'-$ 343.0804 -0.8 17.70 $-H_2O+H$ \checkmark 163 Vomifoliol 247.1317 1.2 18.86 $+Na$ 164 $2,4,4$ -Trimethyl-3-(3- 209.152 -1.6 18.89 $+H$ \checkmark	/ /
162 $3.5.6$ -Irthydroxy-7/3'.4'- Trimethoxyflavone 343.0804 -0.8 17.70 $-H_2O+H$ \checkmark 163 Vomifoliol 247.1317 1.2 18.86 +Na 164 2,4,4-Trimethyl-3-(3- 209.152 -1.6 18.89 +H \checkmark	1
163 Vomifoliol 247.1317 1.2 18.86 +Na 164 2,4,4-Trimethyl-3-(3- 209.152 -1.6 18.89 +H .///	✓ ✓
164 2,4,4-Trimethyl-3-(3- 209 152 -1.6 18.89 +H	\checkmark
Oxobutyl) Cyclohex-2-Enone	/ /
165 Tauremisin 265.1423 −1.1 18.90 +H, -H ₂ O+H ✓	/ /
166 Dodec-2-Enal 200.1996 −1.3 18.94 +NH₄ ✓ ✓	/ /
167 Phytosphingosine 318,2987 -1.6 20.36 +H	/ /
168 L-Leucine 130.0867 −0.6 20.57 -H ✓	/ /
169 Aurapten 297.1522 2.6 20.80 -H 🗸	/ /
170 Thalcimine 619.2839 3.7 21.01 -H ₂ O+H	1
171 Dodecanoic Acid 297.1523 0.4 21.04 +HCOO /	
172 Magnorandiolide 265147 2.5 21.24 -H /	• •
173 Isotetrandrine 640 3442 6.1 21.29 +NH4	1
174 Palmitolici Acid 277 215 12 21 38 +Na /	
175 Zoomaric Acid 277 2152 14 2142 +Na	
176 Mothyl Palmitato 3152523 -18 2145 \pm HCOO / /	
177 Civetone 2952277 -0.1 2351 +HCOO /	, , ,
1-Palmitovl-Sn-Glycero-3-	• •
178 Phosphocholine 496.3394 -0.3 24.01 +H 🗸	
179 Ochrolifuanine A 483.2731 −3.5 24.62 +HCOO ✓ ✓	
180 Phthalic acid 149.0222 −1.1 25.28 −H ₂ O+H ✓ ✓	/ /
181 Diisobutyl phthalate 279.1582 −0.9 25.28 +H ✓	/ /
182 Monopalmitin 353,2665 0.2 26,50 +Na /	, , , ,
183 Aplotaxene 277.2166 -0.7 27.71 +HCOO	1
184 Magnoflorine 377 1413 1.3 27 72 +Cl	•
185 B-Sitosterol 397 38230.6 28.02 -H-O+H	1
186 (3R)-3-Methylpentanal 123/078 0.0 28.81 + Na /	
187 Linoleic $263.2364 - 0.6$ 2919 $-H_2O+H + NH_4$	/ /
188 β-Ecdysterone 481.313 -3.0 29.64 +H	

Table 1. Cont.

2.2. Identification of the AFI- and AF-Associated Targets and Analysis of the "Compound–Target" Network

Using the SwissTargetPrediction databases, we obtained the 9021 target proteins of the 188 compounds in AFI and AF. The entire list of targets of each compound is provided in Supplementary Table S2. After removing redundancy, we identified 1052 AFI- or AF-associated targets (Supplementary Table S3). Compound–target networks were constructed on the basis of compounds 1 (7-Hydroxycoumarin), 6 (Limonin), 46 ((+/–)-Naringenin), 61 (Helenalin), and 63 (Kaempferol) and their corresponding targets, as shown in Figure 2. The round, yellow nodes and round, blue nodes represent the compounds and targets, respectively, and the edges represent the interactions between compounds and targets.

2.3. Identification of the Neuroprotective Targets and Analysis of the "Disease-Target" Network

By means of the available resource, namely, the GeneCards: The Human Gene Database. we obtained 151 excitotoxicity-associated targets (relevance > 1.0) and 187 antioxidant-associated targets (relevance > 1.0). And detailed information on the collected targets is provided in Supplementary Table S4 (excitotoxicity-associated targets) and Supplementary Table S5 (antioxidant-associated). Disease–target networks were constructed, as shown in Figure 3. The network consisted of two parts (A: an excitotoxicity-associated target network with 151 nodes; B: an antioxidation target network with 187 nodes). The round, blue nodes and round, yellow nodes represent the targets and diseases, respectively, and the edges represent the interactions between diseases and targets.



Figure 2. Compound–target networks for AFI and AF. (**A**) Compound **1** (7-Hydroxycoumarin) compound–target network; (**B**) Compound **6** (Limonin) compound–target network; (**C**) Compound **46** ((+/–)-Naringenin) compound–target network; (**D**) Compound **61** (Helenalin) compound–target network; (**E**) Compound **63** (Kaempferol) compound–target network.





2.4. Recognition of the Candidate Compounds and Potential Targets and Analysis of the "Compound–Disease–Target" Network

A total of 125 overlapping protein targets were recognized, and 50 candidate compounds were obtained, as described in Supplementary Table S6. Figure 4 shows the compound–disease–target network, which was composed of one hundred and seventyseven nodes (one hundred and twenty-five targets, fifty compounds, and two diseases) and two hundred and fifty edges. The round, yellow nodes, round, red nodes, and green nodes represent the compounds, targets, and diseases, respectively, and each node size is proportional to its degree. The edges represent the interactions between any two types of nodes. The results showed that the 50 compounds and 125 targets may be the candidate bio-active substances and the potential pharmacological targets for neuroprotection of AF and AFI. In particular, the neuroprotective candidate compounds are shown in Table 2 and Figure 5, and the potential pharmacological targets are shown in Table 3. There are significant differences in the chemical composition of AF and AFI [2], and we found that the neuroprotective effects of the compounds of AF and AFI are less different, as shown in Figure 5. Limonin in Table 2 is present in four samples, and studies have shown that it has a neuroprotective effect [20].



Figure 4. Compound–disease–target network. The yellow, red, and green nodes represent the compounds (the numbers represent the serial numbers of the compounds in Table 1), targets and diseases, respectively, and a node's size is proportional to its degree. The edges represent the interactions between any two nodes.

Table 2. Neuroprotective candidate compounds in AF and AFI.

No.	Compound Name	AFI-CAD	AF-CAD	AFI-CA	AF-CA	No. Compound Name	AFI-CAD	AF-CAD	AFI-CA	AF-CA
1	7-Hydroxycoumarin	1	1	1	1	60 Butylidenephthalide	1	1	1	
2	Arginine	1	1	1	1	63 Kaempferol	1			
3	Isopimpinellin	1				65 Eriodictuol	1	1	1	1
5	Isomaltose		1		1	67 Chrysophanein	1	1	~	1
6	Limonin	1	1	1	1	74 3,4,7- Trimethoxycoumarin	1	1	1	1
7	Farnesyl Acetate	1	1	1	1	82 Paeonioflorin	1	1	1	1
8	Heterodendrin	1		1		88 Torachrysone	1	1	1	1
9	N-Methyl Proline	1	1	1	1	98 Deacetylnomilin	1	1		
11	Citric Acid	1	1	1	1	100 5,7-Dimethoxy Coumarin	1	1	1	1
14	7-Hydroxy-6- Methoxy-Coumarin	1	1	1		101 Dl-3-Phenyllactic Acid	1	1	1	1
15	L-Synephrine Acetate	1	1	1	1	102 Seselin		1		
16	Dopamine	1	1	1		123 Lignans			1	
20	Dimethyl Anthranilate	1		1	1	125 Physcion	1		1	
22	Citronellyl Acetate				1	127 Genistein	1	1		
23	Salicylic Acid		1			130 Tangeretin	1	1	1	1
24	Dehydrodieugenol	1	1	1	1	140 7-Methoxy-5- Prenyloxycoumarin				1
29	Subaphylline			1	1	152 Balanophonin				1

No	. Compound Name	AFI-CAD	AF-CAD	AFI-CA	AF-CA	No. Compound Name	AFI-CAD	AF-CAD	AFI-CA	AF-CA
32	Palmidin A	1	1			155 Thaliglucinone	1	1	1	1
34	Caffetannic Acid	1	1			160 Palmitic Acid	1	1	1	1
35	Ayapanin				1	161 Caffeic Acid Dimethyl Ether				1
44	Phenethylamine		1			165 Tauremisin	1		1	1
	Naringenin-4'-									
45	Glucoside-7-	1	1	1	1	166 Dodec-2-Enal	1	1	1	1
	Rutinoside									
46	(+/-)-Naringenin	1	1	1	1	168 L-Leucine	1	1	1	1
53	Testosterone			1	1	169 Aurapten	1	1	1	1
55	2-Hydroxy-6- Methoxybenzoic Acid	1	1	1	1	176 Methyl Palmitate	1	1	1	





Figure 5. A Venn diagram of neuroprotective candidate compounds among AF-CA, AFI-CA, AF-CAD, and AFI-CAD.

2.5. GO and Pathway Enrichment Analyses of Potential Targets

One of the functions of GO processes is to predict genes related to a disease [21]. GO and pathway enrichment analyses of the 108 potential targets for neuroprotection in AF and AFI were performed using the DAVID database to understand the relationships between functional units and their underlying significance in the biological system networks [22]. All of the biological processes and pathways were extracted ($p \le 0.05$). Figure 6 lists the top 30 most significantly enriched GOBP terms. Supplementary Tables S7 and S8 provide detailed information about the biological processes and signaling pathways. In total, 146 related pathways were identified, including pathways of neurodegeneration (hsa05022), the Alzheimer's disease pathway (hsa05010), the NF-kappa B signaling pathway (hsa04064), the HIF-1 signaling pathway (hsa04066), apoptosis (hsa04210), and the EGFR tyrosine kinase inhibitor resistance signaling pathway (hsa01521). And numerous targets were involved in the memory process, gene expression, the rhythmic process, the neuron apoptotic process, and the apoptotic process.

	Excito	Antiox	ridant		
XDH	GRIN2B	APP	IL1B	CSNK2A1	G6PD
AKT1	PRKCG	PRKCA	CAPN1	NFKB1	FABP1
DAO	GRM2	MAPK10	SLC8A1	STAT3	NR1I3
GSR	ADORA2A	TP53	SLC1A1	CASP3	NR1I2
PARP1	GAPDH	PPARG	GRIK1	MAPK14	PPARA
SNCA	HSPA8	PLA2G2A	GRIA2	VCP	IL6
ACHE	SLC1A2	GLUL	BIRC3	BCL2	ICAM1
NOS2	CHRNA7	MAPT	BIRC2	CTSB	VCAM1
NOS1	PTGS2	PIK3CG	GRIN2A	NR1H4	HMOX1
JAK2	SRC	CDK5		PTGS1	ODC1
VEGFA	GRIN1	TGFB1		ALB	CREBBP
FGF2	TH	GRK2		NQO1	PGD
DRD2	HTT	XIAP		EP300	SOAT1
FOLH1	GRM5	TGM2		NOX4	HDAC3
OPRM1	CYP19A1	NTRK3		MPO	PLA2G6
MAPK1	GRIA4	HDAC9		CSNK2A2	PON1
TNF	DAPK1	PLAT		NFE2L2	CXCR3
BCL2L1	RPS6KA5	SLC1A3		ABCC1	SIRT3
KCNJ5	MAPK8	NTRK2		CXCL8	NR0B2
CNR1	GRIA1	PSEN1			GSTA1

Table 3. The potential neuroprotective pharmacological targets of AF and AFI.



Figure 6. The top 30 enriched gene ontology terms for the biological processes of potential targets.

3. Materials and Methods

3.1. Experimental Compounds Discovery

3.1.1. Chemicals and Materials

AF-CA and AFI-CA (batch number: S202108-0932, S202101-0929) were collected from Xinyu County, Jiangxi Province, China. AF-CAD and AFI-CAD (batch number: S202108-0933, S202106-0930) were collected from Jinhua County, Zhejiang Province, China. And all samples were stored at room temperature until experimentation. All collected samples have accompanying voucher specimens held in the National Engineering Research Center of TCM Standardization Technology, Shanghai Institute of Materia Medica (Shanghai Institute

of Material Medical Chinese Academy of Sciences (cas.cn)) accessed on 6 February 2024), Chinese Academy of Sciences, Shanghai, China.

Seven compounds were used as reference standards (purity > 98%): namely, Hesperidins, Nobiletin, Tangeretin, Didymin, Naringin, Naringenin, and Narirutin, which were purchased from Shanghai Standard Technology Co. Ltd. (Shanghai, China) (nature-standard.com). Ultra-pure water was prepared by a Milli-Q water purification system (Millipore, Bedford, MA, USA). All other chemicals were of analytical grade and obtained commercially. All extractions used in UPLC-Q-TOF were carried out with high-performance liquid chromatography (HPLC)-grade solvents.

3.1.2. Sample Preparation

AF-CA, AFI-CA, AF-CAD, and AFI-CAD powder (100 mg) were extracted successively with 2 mL of 50% MeOH in an ultrasonic bath (40 kHz) for 30 min. After centrifuging at $15,890 \times g$ for 10 min, the supernatant was used for later analysis.

3.1.3. UPLC/Q-TOF-MS/MS Analysis

The equipment used was an ACQUITY UPLC I-Class System coupled to a Xevo G2-XS Q-TOF mass spectrometer (Waters, Milford, MA, USA). Each prepared sample was subjected to LC-MS/MS analysis with a scan event recording MS/MS spectrum in datadependent acquisition mode. An ACQUITY UPLC[®] BEH C18 ($1.7 \,\mu m \times 2.1 \times 100 \,mm$) column was used for the separation of analytes in the extracts with a flow rate of 0.2 mL/min at 30 °C. The injection volume was 2 µL. A linear gradient program with a mobile phase system including solvent A (0.1% formic acid in water, v/v) and solvent B (0.1% formic acid in acetonitrile, v/v) was performed as follows: solvent A at 85~79% for 0.01~3 min, 79% for 3~7 min, 79~65% for 7~12 min, 65~50% for 12~16 min, 50~40% for 16~22 min, 40~20% for 22~25 min, and 20~5% for 25~29 min, with isocratic elution performed at 5% for 4 min. The MS spectra were acquired in positive and negative ion modes to provide complementary information for structural identification. The scan range was from 100 to 1200 m/z. The acquisition parameters for Q-TOF mass spectra were as follows: cone voltage at 40 V for both electron spray ionization (ESI)+ and ESI– modes. The desolvation gas was set to 800 L/h at a temperature of 300 °C, the cone gas was set to 50 L/h, and the source temperature was set to $120 \degree$ C. The mass spectrometry was operated linearly in data-dependent acquisition mode at a low energy level of 25–35 eV and a high energy level of 40-50 eV. All analyses were acquired using the LockSpray to ensure accuracy and reproducibility. Leucine-enkephalin was used as the lock mass at a concentration of 300 ng/mL and flow rate of 20 μ L/min. Data were collected in continuum mode, the LockSpray interval was set at 10 s. The data acquisition rate was set to 1.5 s. All acquisition of data was controlled by Waters Masslynx v4.2 software (Waters, Manchester, UK).

3.1.4. UNIFI Data Processing Method

The chemical constituent library of AF and AFI was firstly established for component analysis [23]: The complete information on the compounds of AF and AFI was collected and obtained by searching the China National Knowledge Infrastructure (CNKI) (cnki.net, accessed on 31 January 2024), PubMed (PubMed (nih.gov) accessed on 31 January 2024), PubChem (PubChem (nih.gov) accessed on 6 February 2024), Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (tcmsp-e.com, accessed on 31 January 2024), ChemSpider (chemspider.com, accessed on 31 January 2024), and other databases. The self-built compound library, including compound name and chemical structure (saved in "mol" format), was imported into UNIFI. Among them, a total of 1190 compounds were listed (Supplement Table S1). We imported the original files on the samples solution and blank sample solution obtained by UPLC-Q-TOF-MS into the UNIFI software for sample comparison. Based on the automatic matching function of the UNIFI software, compounds can be quickly identified. The parameter settings were as follows: analysis time range, 1–36 min; quality allowable error range, ± 10 ppm; quality testing range, 100 m/z to 1200 m/z; positive adducts including H⁺, Na⁺, and K⁺; and negative adducts containing H⁻, HCOO⁻, and Cl⁻. Finally, using the MassLynx workstation, the above identification results were reviewed in combination with the precise mass of excimer ions, retention time, fragment ion information, and the literature [17].

3.2. *Target Prediction of the Compounds in AFI and AF and Neuroprotective Target Collection* 3.2.1. Predicting Targets of Compounds in AFI and AF

According to our study (Section 3.1), all of the compounds in AFI and AF were chosen to predict the biological targets. The canonical SMILES [24] of the compounds were uploaded into the SwissTargetPrediction database (http://www.swisstargetprediction.ch/accessed on 31 January 2024) to obtain the UniProt IDs for predicting targets [25].

3.2.2. Collecting Neuroprotective Targets

"Excitotoxicity" and "antioxidation" are considered to be the two key directions of neuroprotection [26]. The biological targets related to neuroprotection were selected from the GeneCards: The Human Gene Database [27] (https://www.genecards.org/, accessed on 6 February 2024, version 5.15.0, relevance > 1.0) using "excitotoxicity" and "antioxidation" as keywords [28].

3.3. Identification of Potential Targets for the Neuroprotection of AFI and AF

3.3.1. Screening Candidate Compounds and Potential Targets

We selected the overlapping targets of AF and AFI for neuroprotection and used the compounds corresponding to these targets as candidate compounds.

3.3.2. Gene Ontology (GO) and Pathway Enrichment of Potential Targets

The Gene Ontology (GO) biological process (BP) was analyzed to further validate whether the potential targets were indeed matched for neuroprotection [29]. GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) [30] signaling pathway analyses were carried out using the Database for Annotation, Visualization and Integrated Discovery (DAVID) (https://david.ncifcrf.gov/, accessed on 31 January 2024, version v2023q1). A *p*-value \leq 0.05 was considered significant.

3.3.3. Constructing the Network of Compounds, Diseases, and Targets

To comprehensively understand the neuroprotection of AF and AFI, the compoundtarget and disease-target networks were constructed using Cytoscape 3.9.1 (Bethesda, MD, USA) [31]. In these networks, the nodes represented the compounds, diseases, targets, or signaling pathways, and the edges represented their interactions [32].

4. Conclusions

In this study, a comprehensive method combining UPLC/Q-TOF-MS/MS analysis and network pharmacology was used to reveal the differences in the chemical components of AF and AFI that applied to their neuroprotective effects. The results indicated that 50 of the 188 compounds in AF and AFI may be bioactive, which may be related to their targeting of 108 targets such as XDH, GRIN2B, AKT1, PRKCG, CAPN1, CSNK2A1, G6PD. One hundred and forty-six important signaling pathways were implicated, including neurodegeneration (hsa05022), the Alzheimer's disease pathway (hsa05010), the NF-kappa B signaling pathway (hsa04064), the HIF-1 signaling pathway (hsa04066), apoptosis (hsa04210), and the EGFR tyrosine kinase inhibitor resistance signaling pathway (hsa01521). These findings fully reflect the multi-component, multi-target, and multi-approach characteristics of TCM in disease treatment. This study shows that AF and AFI have great potential in neuroprotection, and their neuroprotective effects deserve further study.

In some network pharmacological studies, compounds are collected indiscriminately from databases; however, this can produce false-positive results. The method we applied in this research was built on the basis of experimentally identified components and corresponding targets, which will greatly reduce the prediction range and improve the accuracy of the prediction results. However, further pharmacological experiments are needed to verify its main biological components and related targets, so as to deeply understand the neuroprotective mechanism of AF and AFI, which will be the direction of our further research.

Supplementary Materials: The following supporting information can be downloaded at: https: //www.mdpi.com/article/10.3390/ph17020239/s1, Table S1: Chemical compounds contained in citrus traditional Chinese medicine, Table S2: The entire list of targets of each compound, Table S3 1052 AFI- or AF-associated targets, Table S4: Excitotoxicity-associated targets, Table S5: Antioxidantassociated targets, Table S6: The Candidate Compounds and Potential Targets, Table S7: Information about the biological processes, Table S8: Information about the signaling pathways.

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