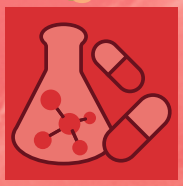

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by **Marina P. Savic**, **Ivana Z. Kuzminac** and **Andrea R. Nikolic**

Drug. Drug Candidates **2023**, *2*(1), 69-94; https://doi.org/10.3390/ddc2010005 (registering DOI) - 04 Feb 2023

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Article

Indonesian Vegetables: Searching for Antioxidant and Antidiabetic Therapeutic Agents

Dinar Mutia Rani [1], Nur Hanafi [2], Sudarko [2], Dessy Rachmawati [3,4], Tri Agus Siswoyo [5], Fransiska Maria Christianty [1], Ika Puspita Dewi [1] and Ari Satia Nugraha [1,4,5,6,*]

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Abstract: Diabetes mellitus prevalence in Indonesia reached 19.5 million cases, which has affected the productive age population. The indigenous people of Indonesia are blessed with the second largest biodiversity in the world, including vegetables, which are also prepared as medicaments. Vegetables are well-known as natural antioxidants which evolved in metabolic disease prevention, including diabetes mellitus. One of the Government of Indonesia's strategic plans in health is to develop new antidiabetic from nature. In this study, nineteen vegetable species were collected and evaluated for their antioxidant activity followed by computational-based bioprospecting. The study indicated *Ipomoea aquatica*, *Paederia foetida*, *Plumbago zeylanica*, *Nauclea pallida*, *Sauropus androgynus*, *Wrightia pubescens*, and *Psophocarpus tetragonolobus* to contain high antioxidant components. Computational experiments on chemical constituents previously reported from the same species showed potent compounds with high affinity against α-glucosidase (3a4a). 7-O-β-D-glucopyranosyl-dihydroquercetin-3-*O*-α-D-glucopyranoside **1**, stigmasterol **7**, and chitanone **12** are the most potent compounds from *Ipomoea aquatica*, *Paederia foetida*, and *Plumbago zeylanica*, respectively, which are superior to a standard drug, acarbose. The four vegetable species are feasible for conventional drug sources or developed as botanical dosage according to the Indonesian government's strategic plan. Further studies are necessary to ensure adequate preclinical and clinical data to meet the requirement of safe and potent medicine. Nevertheless, *Nauclea pallida* and *Psophocarpus tetragonolobus* are valuable species with potent yet understudied antioxidant sources.

Keywords: Indonesian vegetable; antioxidant; anti-diabetes; α-glucosidase inhibitory; docking; *Ipomoea aquatica*; *Paederia foetida*; *Plumbago zeylanica*; *Nauclea pallida*; *Sauropus androgynus*; *Wrightia pubescens*; *Psophocarpus tetragonolobus*

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1. Introduction

Diabetes mellitus (DM) is a complex and multifactorial metabolic disorder with the main pathologic condition presented by chronic hyperglycemia. The disease is associated with the impairment of insulin production due to pancreatic β-cells damage and/or peripheral insulin resistance [1]. According to the data released by the International Diabetes Federation (IDF), the global prevalence of diabetes in 2019 was 463 million people and will reach 578 million by 2030. There will be at least 700 million people living with diabetes by 2045 if there is no epidemiological intervention [2]. Additionally, the

Indonesian Basic Health Research conducted by the Indonesian Ministry of Health in 2018 reported an increase in Indonesian diabetes cases by 2% compared with data in 2013 [3]. The burden of diabetes mellitus is largely due to a wide range of risk factors including obesity, physical inactivity, oxidative stress, and an unhealthy diet low in whole grains, and vegetables [4,5]. Untreated diabetes may result in long-term damage to several organs such as kidneys, nerves, and eyes, leading to diabetic nephropathy, neuropathy, and retinopathy [6].

The etiology of DM are genetic factors, environmental factors, circumstances that burden insulin secretion, metabolic abnormalities, mitochondrial abnormalities, and several other conditions that interfere with glucose tolerance. DM can also be caused by pancreatic exocrine disease and disruption of hormones that work as insulin antagonists [7]. DM can be classified into four types. Type 1 is a DM condition caused by autoimmune β-cell damage leading to an absolute insulin deficiency. DM type 2 is caused by the progressive loss of β-cell insulin secretion. DM type 3, Gestational diabetes mellitus (GDM) is diabetes during pregnancy and often recovered after delivery. Type 4 is specific diabetes due to other causes, including a monogenic diabetes syndrome (such as neonatal diabetes and diabetes at a young age), an exocrine pancreatic disease (such as *cystic* fibrosis and pancreatitis), and a drug-induced or chemically induced diabetes (such as glucocorticoids-induced diabetes, in the treatment of HIV/AIDS, or after transplantation organ) [8].

Several glucose-lowering agents have been prepared to manage glucose levels in diabetes. The α-glucosidase inhibitor is one of the therapeutic agents to modulate the digestion rate of complex carbohydrates and disaccharides by competitively and reversibly inhibiting enzymes present in enterocytes membrane [9]. However, several adverse effects were reported due to the prolonged use of these conventional drugs, which led to the need for alternative options [10]. Natural products have become a reliable source of phytochemical components used as anti-diabetic agents to prevent and manage hyperglycemia [5,11]. Healthy diets containing vegetables rich in naturally occurring phenolics and flavonoids are associated with a lower risk of diabetes [12]. Vegetables constitute antioxidants for maintaining the biological functions of cells such as reducing insulin resistance [12]. Insulin resistance in diabetic complications has been associated with oxidative stress due to overproduction of free radicals and reactive oxygen species (ROS) [13]. ROS have been reported to activate five major pathologic mechanisms, including an increase in protein kinase C isoforms, flux in glucose, expression of advanced glycation end products (AGEs), formation of AGEs in intracellular, and overactivity of hexosamine pathways [13]. Furthermore, the bond between AGE and endothelial cells causes vascular lesions, vasoconstrictors, and thrombosis in people with DM. AGEs that bind to monocytes will later increase chemotaxis and monocyte activation. This event will simultaneously occur with an increase in the number of pro-inflammatory cytokines released, such as TNF-α, IL-1, and IL-6 [14,15]. Thus, one of the defense mechanisms for alleviating diabetes complications is through increasing activities and levels of antioxidants in the body. In addition, a meta-analysis study reported consuming 2–3 servings per day of vegetables conferred a lower diabetes mellitus risk [16]. This finding is consistent with most nutritional and global dietary recommendations to consume at least three servings of vegetables per day [17]. In addition, poor daily intake of vegetables is strongly linked to diabetes progression. The majority of evidence reported that vegetables provide an array of healthful phytonutrients in diabetes prevention [11,17]. In Indonesia, an array of vegetable varieties are collected from farms or the wild, in which the indigenous people of Indonesia have used several vegetables as traditional medicaments to cure and prevent diseases including diabetes [18].

The Indonesian government's master plan for modern medicine development sourced from medicinal plants is to employ adequate pre-clinic and clinic experiments ensuring safe and potent medicine prescribed in the modern health services (Figure 1) [19].

This is including supporting research funds and facilities in discovering new compounds or botanical-based medicine against diabetes mellitus. This study aimed to subject nineteen Indonesian commonly served vegetables to investigate the in vitro antioxidant activity of their ethanolic extract along with an in silico evaluation of their potential antidiabetic activity.

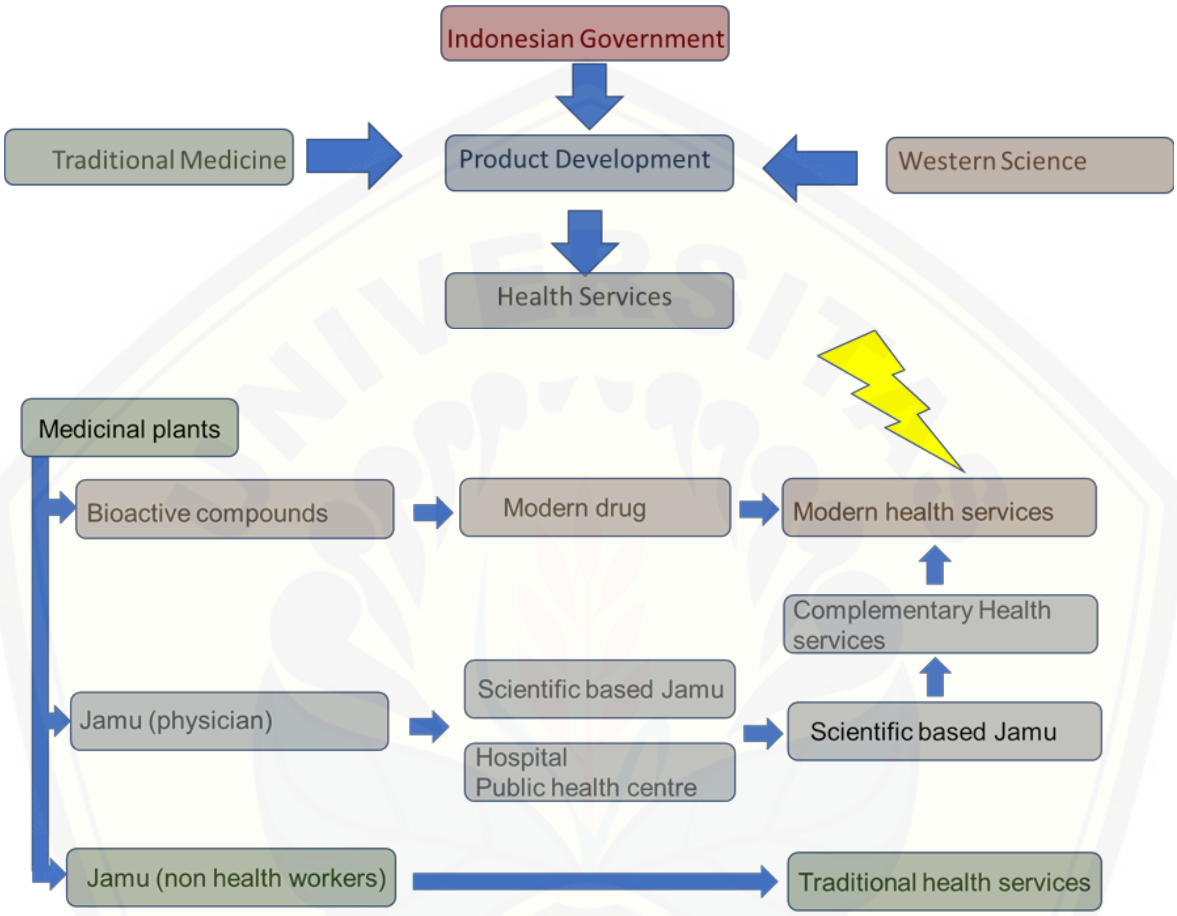

Figure 1. Indonesian government's strategy in developing modern medicine sourced from Indonesian medicinal plants.

2. Results

Indonesia has abundant vegetable species and is widely consumed as a nutritional source. However, the antioxidant and antidiabetic potential of Indonesian vegetables are not yet fully explored. Around 29 species of vegetables are consumed by the indigenous people of Indonesia, with some species being well distributed across the archipelago (Figure 2). Despite being commonly taken as nutritious diets, the majority of the vegetables are also prepared in traditional medicament to cure several ailments (Table 1). From 24 commonly used vegetables, nineteen species were freshly collected from the traditional market around Jember, Lumajang, Bondowoso, Banyuwangi, and Situbondo Districts in East Java Province, Indonesia. Antioxidant evaluations are summarized in Table 2 where vitamin C, a naturally occurring antioxidant present in vegetables and fruits was used as a standard.

Figure 2. Vegetables are commonly used and traded by the indigenous people of Indonesia in the traditional market (*Amaranthus spinosus* L. (1), *Artocarpus Altilis* (Park.) FSB. (2), *Artocarpus heterophyllus* Lam. (3), *Cajanus cajan* Millspaugh (4), *Carica papaya* L. (5), *Clitoria ternatea* L. (6), *Crassocephalum crepidioides* (Benth.) S.Moore (7), *Diplazium esculentum* Swartz. (8), *Etlingera elatior* (Jack) R.M.Sm. (9), *Ipomoea aquatica* Forssk. (10), *Limnocharis flava* (L.) Buch (11), *Luffa acutangular* (L.) Roxb. (12), *Marsilea minuta* L. (13), *Moringa oleifera* L. (14), *Musa paradisiaca* L. (15), *Nasturtium officinale* W.T. Aiton (16), *Nauclea pallida* Reinw (17), *Nothopanax scutellarium* Merr. (18), *Paederia foetida* L. (19), *Pluchea indica* L. (20), *Plumbago zeylanica* L. (21), *Portulaca oleracea* L. (22), *Psophocarpus tetragonolobus* (L.) D.C. (23), *Sauropus Androgynus* (L.) Merr. (24), *Sechium Edule* (Jacq.) Sw. (25), *Sesbania grandiflora* Pers. (26), *Tagetes erecta* L. (27), *Vigna cylindrica* (L.) Walp. (28), *Wrightia pubescens* R.Br. (29)).

Table 1. Indonesian vegetable species commonly used by the indigenous people of Indonesia.

No	Local Name	Part Used	Species Name	Family	Distribution in Indonesia	Ethnopharmacology Indication	Ref.
1	Bayam duri	Whole plant (young)	*Amaranthus spinosus* L.	*Amaranthaceae*	Sumatra, Jawa, Madura, Bali, Sulawesi, Maluku, Halmahera, Tidore	Blister, asthma, fever	[20]
2	Kluwih	Young fruit	*Artocarpus Altilis* (Park.) FSB.	*Moraceae*	Sumatera, Jawa, Madura, Bali, Nusa Tenggara, Timor, Sulawesi, Selayar, Maluku, Seram, Halmahera	Toothache, skin infection	[21]
3	Nangka	Young fruit	*Artocarpus heterophyllus* Lam.	Moraceae	Sulawesi, Jawa	Diarrhea	[22,23]
4	Gude	Seeds	*Cajanus cajan* Millspaugh	*Leguminosae*	Sumatera, Jawa, Madura, Bali, Nusa Tenggara, Timor, Sulawesi, Maluku, Halmahera, Ternate, Tidore	Scabies, cough, blood cleansing	[20]
5	Pepaya	Flower	*Carica papaya* L.	caricaceae	Sumatera, Kalimantan, Nusa Tenggara, Jawa, Sulawesi, maluku, Papua	Malaria, anthelmintic, stomachache,	[24]
6	Telang	Flower	*Clitoria ternatea* L.	Papilonaceae	Sumatra, Jawa, Sulawesi, Maluku, Halmahera, Ternate	Blister, eye irritation	[25]
7	Sintrong	Whole plant (young)	*Crassocephalum crepidioides* (Benth.) S.Moore	*Asteraceae*	Sumatera, Jawa	Stomachache, headache, blister	[26,27]
8	Pakis	Whole plant (young)	*Diplazium esculentum* Swartz.	*Polypodiaceae*	Sumatra, Jawa, Bali, Sulawesi, Maluku, Ambon	Rub	[28]
9	Kecombrang	Flower	*Etlingera elatior* (Jack) R.M.Sm.	Zingiberaceae	Jawa	Vitality	[29]
10	Kangkung	Whole plant (young)	*Ipomoea aquatica* Forssk.	Convolvulaceae	Sumatera, Jawa, Nusa Tenggara, Sulawesi, Gorontalo, Maluku, Halmahera, Tidore, Buru	Sedative agent	[20]
11	Genjer	Whole plant (young)	*Limnocharis flava* (L.) Buch	*Butomaceae*	Sumatera, Jawa, Madura	Food	[30]
12	Gambas	Young Fruit	*Luffa acutangular* (L.) Roxb.	Cucurbitaceae	Sumatera, Jawa, Madura, Maluku, Ternate	Fever, nausea, stomachache, toothache	[29]
13	Semanggi	Whole plant (young)	*Marsilea minuta* L.	Marsilaceae	Jawa	diuretic agents	[28]
14	Kelor	Young Leaves Fruit, seeds	*Moringa oleifera* L.	Moringaceae	Sumatera, Jawa, Madura, Bali, Nusa Tenggara, Maluku, Buru, Ternate, Tidore	Gum bleeding, period, headache, asthma, rheumatism, anti-emetic, spasm	[20]

Table 1. *Cont.*

No	Local Name	Part Used	Species Name	Family	Distribution in Indonesia	Ethnopharmacology Indication	Ref.
15	Pisang	Stem	*Musa paradisiaca* L.	*Musaceae*	Sumatera, Jawa, Ambon	Tonsil and gastro inflammation, anemia, trachoma inflammation, diarrhea, fever, food poisoning	[30]
16	Selada Air	Whole plant (young)	*Nasturtium officinale* W.T. Aiton		Sumatera	Excema	[31]
17	Kolpo	Young Leaves	*Nauclea pallida* Reinw	*Rubiaceae*	Jawa	Diuretic	[30]
18	Mangkokan	Young Leaves	*Nothopanax scutellarium* Merr.	Araliaceae	Jawa, Sulawesi, Mena, Maluku, Ambon, Roti, Halmahera, Ternate	Hari tonic, anti-inflammation (edema), diuretic agents	[20]
19	Sembukan	Leaves	*Paederia foetida* L.	Rubiaceae	Sumatera, Jawa, Madura, Maluku, Ternate	Sore	[32]
20	Beluntas	Young Leaves	*Pluchea indica* L.	Asteraceae	Sumatera, Jawa, Madura, Sulawesi, Nusa, Tenggara Timor	Fever, cough, body odor	[20]
21	Kareka	Young Leaves	*Plumbago zeylanica* L.	*Plumbaginaceae*	Sumatera, Jawa, Bali, Timor	Rheumatism, headache	[24]
22	Krokot	Whole plant (young)	*Portulaca oleracea* L.	*Portulaceae*	Sumatera, Jawa, Madura, Maluku, Ternate	Diarrhea, fever, stomachache	[20]
23	Kecipir	Fruit and seeds	*Psophocarpus tetragonolobus* (L.) D.C.	Fabaceae	Sumatera, Jawa, Bali, Maluku, Ternate	Ear inflammation	[20]
24	Katuk	Young Leaves	*Sauropus Androgynus* (L.) Merr.	Euphorbiaceae	Sumatera, Jawa, Madura	Breas milk stimulant, acne, fever, blister, eczema	[20]
25	Labu Siam	Fruit (young)	*Sechium Edule* (Jacq.) Sw.	Cucurbitaceae	Sumatera, Jawa, Madura	Food	
26	Turi	Flower	*Sesbania grandiflora* Pers.	*Leguminosae*	Sumatera, Jawa, Madura, Bali, Sulawesi, Nusa tenggara, Timor, Ternate, Tidore	Gastro-inflammation, mouth blister, scabies	[20]
27	Kenikir	Young leaves	*Tagetes erecta* L.	*Compositae*	Jawa	Insect repellant	[20]
28	Kacang panjang	Young Fruit	*Vigna cylindrica* (L.) Walp.	Fabaceae	Jawa	Diuretic	[28]
29	Bintaos	Young Leaves	*Wrightia pubescens* R.Br.	*Apocynaceae*	Sumatera, Jawa, Madura, Nusa Tenggara, Bali, Timor	Eye irritation	[30]

In this study, ethanolic extracts of vegetables were measured for antioxidant activity using several methods including DPPH, superoxide (SO) anion, and hydroxyl free radicals scavenging assay. Among 20 samples of 19 species, the inhibition percentages are shown in Table 2, ranging from 1.32–97.63%. Significant antioxidant activities were found in ethanolic extracts of I. aquatica, closely followed by several species including *P. foetida*, *P. zeylanica*, *N. pallida*, *W. pubescens*, *S. androgynus*, and *P. tetragonolobus*. However, several extracts including *M. oleifera*, *D. esculentum* and *P. indica* showed antioxidant activity variation within three different methods.

Table 2. Radical scavenging activity of commonly used Indonesian vegetables.

No	Sample	Plant Parts	Inhibition Percentage (%)		
			DPPH	SO	Hydroxyl
1	*Carica papaya*	Flos	47.2 ± 0.2	60.3 ± 1.0	59.3 ± 0.1
2	*Clitoria ternatea*	Flos	87.5 ± 0.2	53.7 ± 1.8	73.2 ± 0.1
3	*Etlingera elatior*	Flos	66.2 ± 0.2	93.6 ± 1.2	80.4 ± 0.1
4	*Ipomoea aquatica*	All parts	92.6 ± 0.2	97.6 ± 1.0	80.2 ± 0.1
5	*Limnocharis Flava*	All parts	27.7 ± 0.3	83.4 ± 1.0	79.2 ± 0.1
6	*Luffa acutangular*	Fructus	12.6 ± 0.2	72.7 ± 1.0	80.2 ± 0.1
7	*Marsilea minuta*	All parts	72.2 ± 0.1	74.5 ± 2.7	86.0 ± 0.1
8	*Moringa Oleifera*	All parts	5.3 ± 0.4	66.8 ± 2.1	78.6 ± 0.2
9	*Moringa Oleifera*	Flos	24.4 ± 0.2	95.1 ± 0.8	73.9 ± 0.1
10	*Nasturtium officinale*	All parts	36.3 ± 0.2	88.1 ± 0.8	86.3 ± 0.1
11	*Nauclea pallida Reinw.*	All parts	89.1 ± 0.1	72.3 ± 2.2	86.1 ± 0.1
12	*Nothopanax scutellarium*	All parts	1.1 ± 0.2	79.7 ± 0.6	84.2 ± 0.1
13	*Paederia foetida*	All parts	90.3 ± 0.2	93.5 ± 2.1	85.7 ± 0.1
14	*Pluchea indica*	All parts	86.4 ± 0.2	95.3 ± 2.1	57.9 ± 0.1
15	*Plumbago zeylanica*	All parts	90.0 ± 0.6	84.6 ± 2.1	89.2 ± 0.1
16	*Psophocarpus tetragonolobus*	Fructus	83.8 ± 0.2	87.5 ± 1.8	90.0 ± 0.1
17	*Sauropus Androgynus*	All parts	20.3 ± 0.2	34.5 ± 1.9	91.1 ± 0.1
18	*Vigna cylindrica*	All parts	22.0 ± 0.2	82.2 ± 1.8	82.9 ± 0.1
19	*Wrightia pubescens*	All parts	72.8 ± 0.1	96.5 ± 0.5	90.0 ± 0.1
20	*Diplazium esculentum*	All parts	25.0 ± 0.2	77.5 ± 2.1	90.2 ± 0.1
21	Vitamin C (standard)	-	88.8 ± 0.1	79.9 ± 2.6	38.1 ± 0.5

Molecular data mining revealed at least several constituents reported from *I. aquatica* [33–36], *P. foetida* [37], *P. zeylanica* [38–41], *S. androgynus* [42,43], and *W. pubescens* [44–46], in which no secondary metabolite isolation was previously reported from *N. pallida* and *P. tetragonolobus*. The majority of chemical components were phenolic, flavonoid, and terpenes derivatives with limited alkaloid present. Docking protocols were successfully employed with notable hits of compound, indicating profound interaction compared with the acarbose (Table 3).

Table 3. Secondary metabolites of the same species reported from different origins across the globe and their affinity against α-glucosidase (3a4a).

Name of Structure	Affinity (kcal/mol)
Ipomoea aquatica	
7-O-β-D-Glucopyranosyl-dihydroquercetin-3-O-α-D-glucopyranoside	−11.98
3,5-di-*O*-Caffeolyquinic acid	−10.75
Luteolin-7-glucoside	−10.31
4,5-Di-*O*-caffeolyquinic acid	−9.67
Quercetin-3,7-di-*O*-glucoside	−9.45
Astragalin	−9.06
Quercetin-3-*O*-*β*-*D*-glucoside	−8.71
Rutin	−8.34

Table 3. *Cont.*

Name of Structure	Affinity (kcal/mol)
Isoquercetin	−8.24
Dihydroxybenzoic acid di-pentoside	−8.23
Nicotiflorin	−7.52
Isorhamnetin-3-*O*-rutinoside	−7.40
Nomilinic acid glucoside	−6.97
Quercetin-3-*O*-sophoroside	−6.93
Dihydroxybenzoic acid pentoside	−6.65
Paederia foetida	
Stigmasterol	−10.18
(+)-α-Tocopherol	−9.94
γ-Sitosterol	−9.81
(−)-β-Sitosterol	−9.53
Asperuloside	−9.20
Benzbromarone	−8.88
Kaempferol 3-*O* -rutinoside	−8.68
Quercetin 3-glucoside	−8.63
Caffeic acid 4-*O*-β-D-glucopyranoside	−8.50
Deacetylasperuloside	−8.48
Scandoside	−8.44
2-Anthraquinonecarboxylic acid	−8.39
Rutin	−8.35
2-Hydroxy-3-methylanthraquinone	−8.12
Anthra [1,2-d]-1,3-dioxole-6,11-dione	−8.10
Rubiadin	−8.09
2-(Hydroxymethyl)anthraquinone	−8.00
Geniposide	−7.99
3-Hydroxy-2-(hydroxymethyl)anthraquinone	−7.98
2-Hydroxy-1,3,4-trimethoxy-9,10-anthracenedione	−7.96
1,4-Dihydroxy-2-(hydroxymethyl)-9,10-anthracenedione	−7.88
N-(4-Methylphenyl) benzenepropanamide	−7.86
6α-Hydroxygeniposide	−7.80
1-Hydroxy-2-(hydroxymethyl)-9,10-anthracenedione	−7.79
2-(Ethoxymethyl)-3-hydroxy-1-methoxy-9,10-anthracenedione	−7.71
1,3-Dihydroxy-2-methoxyanthraquinone	−7.69
Alizarin	−7.69
Capsaicin	−7.38
Friedelin	−7.01
Glutathione	−6.82
β-Carotene	−6.64
2,6-Di-tert-butyl-4-methylphenol	−6.58
Fraxidin	−6.48
Ethyl (*E*)-4-methoxycinnamate	−6.45
(±)-Pentobarbital	−6.39
Plumbago zeylanica L.	
Chitanone	−12.19
Zeylanone	−10.38
Isozeylanone	−10.38
Campesterol	−9.70
Plumbagoside D	−9.70
Stigmasterol	−9.50
Sitosterol	−9.42
Heneicosane	−9.41
Plumbagin C	−9.39

Table 3. *Cont.*

Name of Structure	Affinity (kcal/mol)
2-(3,4-Dihydroxyphenyl)-3,5,6-trihydroxychromen-4-one	−9.11
Droserone	−9.05
2-(2,4-Dihydroxy-phenyl)-3,6,8-trihydroxy-chromen-4-one	−8.54
Plumbagoside C	−8.13
Plumbagoside B	−7.95
3-(2,5-Dimethylphenyl)-1-(2-hydroxyphenyl)-propenone	−7.75
Plumbagin F	−7.68
Plumbagoside A	−7.51
Plumbagin D	−7.26
Plumbagin B	−7.16
Plumbagin G	−7.16
Plumbagin E	−7.11
2,5-Dimethyl-7-hydroxychromone	−6.98
Plumbagic acid	−6.84
Isoshinanolone	−6.75
Indole-3-carboxaldehyde	−5.83
Plumbagin A	−5.78
Vanilic acid	−5.78
trans-cinnamic acid	−5.76
4-Hydroxybenzaldehyde	−5.03
Acarbose (standard drug)	−7.80

3. Discussion

In biological systems, the imbalance of free radicals and antioxidant defense systems promotes oxidative stress, leading to oxidative cell damage [47]. To date, vegetables have been identified as a good source of phytochemicals that are able to downregulate free radical-associated mechanisms of diabetes complications, including diabetic neuropathy, retinopathy, and nephropathy [48]. The elevation amounts of glucose diverted into the polyol pathway accelerate the formation and interaction of glycation end products (AGEs) with their receptors, generating reactive oxygen species (ROS) [49]. ROS can disrupt histones (base) and single- or double-strand of nucleic acid, leading to DNA damage. In consequence, an excess in oxidant species production affects all the layers of the glomerular filtration barrier caused by diabetic kidneys, characterized by the presence of albuminuria [49]. Moreover, in the development of diabetic retinopathy, animal studies demonstrated that excessive levels of superoxide and hydrogen peroxide were reported in the retina of diabetic rats. Further, oxidative damage of DNA occurred and elevated as a consequence of ROS-induced injury [50]. Other than that, glucose metabolic impairment in diabetic nephropathy also causes activation in the polyol pathway, hexosamine pathway, and AGE pathway, which are theorized to generate DNA modification and nerve dysfunction [51]. Therefore, antioxidants are the appropriate strategy aiming to combat the progression of diabetic complications by reducing the oxidant species production.

The development of computational chemistry has significantly provided a range of tools in medicinal chemistry research related to drug discovery and evaluation. Molecular calculation is able to resemble the interaction between enzyme and ligand in vacuo experiments prior to in vitro and/or in vivo evaluation. This application benefits drug discovery by reducing cost and time compared with those of conventional screening, especially in evaluating natural constituents in which compound access is limited naturally [52]. In this study, α-glucosidase inhibitory activity was indirectly explored through a docking protocol against 79 chemotypes based on metabolites from anti-oxidant-rich vegetables (*I. aquatica*, *P. foetida*, *P. zeylanica*, and *N. pallida*).

3.1. Ipomoea aquatica

I. aquatica, or water spinach, is a common green vegetable widely known by the people of Indonesia as kangkong. This perennial herb belongs to the Convolvulaceae family and is traditionally used to treat constipation and relieve sleep disturbances [53]. As daily consumed vegetables, *I. aquatica* is habitually growing wild or widely farmed across the archipelago of Indonesia. The antioxidant evaluation showed the ethanolic extract of *I. aquatica* to have the highest value of antioxidant activity. *I. aquatica* contains several phenolic compounds such as astragalin **6**, 3,5-di-caffeoylquinic acid **2**, and 4,5-di-*O*-caffeoylquinic acid **4**, which might be responsible for antioxidant activity [34,35,54]. Phenolic compounds are known to have one or more hydroxyl substituents linked to their antioxidant ability as hydrogen- or electron-donating groups and to suppress metal-catalyzed free radical formation [55]. A previous study reported astragalin **6** isolated from *Morus alba* L. to possess potent antioxidant activity by suppressing 2,2′-azobis(amidinopropane) dihydrochloride (AAPH)-induced hemolysis in red blood cells and protecting vascular endothelium dysfunction [56,57]. This finding is consistent with an antioxidant ability to prevent microvascular damage linked to diabetic complications. In addition, 3,5-di-caffeoylquinic acid **2** and 4,5-di-*O*-caffeoylquinic acid **4** were also reported as remarkable constituents present in *Dipsacus asper* Wall. These compounds possessed higher antioxidant activity with IC_{50} values of 18.2 ± 0.5 and 10.4 ± 0.5 μM compared with caffeic acid as the standard (IC_{50} = 31.1 ± 1.9 μM) [58].

The computational protocol performed on previously reported secondary metabolites of *I. aquatica* revealed their antidiabetic activity was superior to the positive control (vitamin C) and the rest of the vegetables. The affinity scores revealed six compounds (7-*O*-*β*-D-glucopyranosyl-dihydroquercetin-3-*O*-*α*-D-glucopyranoside **1**, 3,5-di-*O*-caffeolyquinic acid **2**, luteolin-7-glucoside **3**, 4,5-di-*O*-caffeolyquinic acid **4**, quercetin-3,7-di-O-glucoside **5**, and astragalin **6**, Figure 3) to have sounder exothermic polar correlation (<−9.0 kcal) with alpha-glucosidase enzyme than the standard drug ligand, acarbose (−7.8 kcal). Dehydrogenated quercetin, 7-*O*-*β*-D-glucopyranosyl-dihydroquercetin-3-*O*-*α*-D-glucopyranoside, has a higher affinity than its saturated aglycon version, Quercetin-3,7-di-*O*-glucoside. This might be due to sp3 at C2 providing a flexible bond that benefits its interaction with the enzyme. In addition, the quercetin derivative molecular size is comparable to the acarbose structure with an equal number of hydrogen bonding and extra interactions due to pi-pi orbital interaction (Figure 4).

Overall, flavonoid and phenolic compounds in general synergistically act to produce a strong antidiabetic effect. Diabetes is a metabolic disorder that can cause vascular and nonvascular complications due to oxidative stress. The formation of oxidative stress in diabetes occurs through three main pathways, i.e., non-enzymatic protein glycation, sorbitol polyol pathway, and glucose auto-oxidation. The antioxidant source of the plants is believed to be able to inhibit all three pathways. Flavonoids are secondary metabolites that have the potential to be antioxidants and have a positive correlation with diabetes therapy [59].

3.2. Paederia foetida

P. foetida is locally known in Indonesia as daun sembukan. This vegetable belongs to the family Rubiaceae and is traditionally used to treat blisters and stomach aches. Our investigation revealed that *P. foetida* presented potential antioxidant activity against DPPH radical formation. Steroids and monoterpenoids such as stigmasterol **7**, α-tocopherol **8**, β-sitosterol **10**, and asperuloside **11** were reported as several compounds abundant in *P. foetida* [60]. Stigmasterol **7** isolated from *Spondias mombin* was previously reported to possess antioxidant properties in Wistar rat experiments, in

which the phytosterol decreased production of ROS and oxidoreductase enzymes, including glutathione reductase (GR), glutathione peroxidase (GPX), catalase (CAT), and 6-phosphatase dehydrogenase [61]. Stigmasterol **7** was also reported to possess neuroprotective effects by modulating GABA receptors and suppressing the progression of cell apoptosis via mitogen-activated protein kinase (MAPK) proteins cyclin D1, p53, and p38 reduction [62]. On the other hand, Takayama and Fujihara in 2017 investigated whether asperuloside **11** isolated from *Eucommia ulmoides* could alleviate ROS production in choline-deficient, high fat and fructose-enriched (CDHFF)-diet rats [63]. Thereby, these provide evidence that stigmasterol **7** and asperuloside **11** possess promising constituents for the management of diabetic neuropathy associated with neurological damage due to oxidative stress.

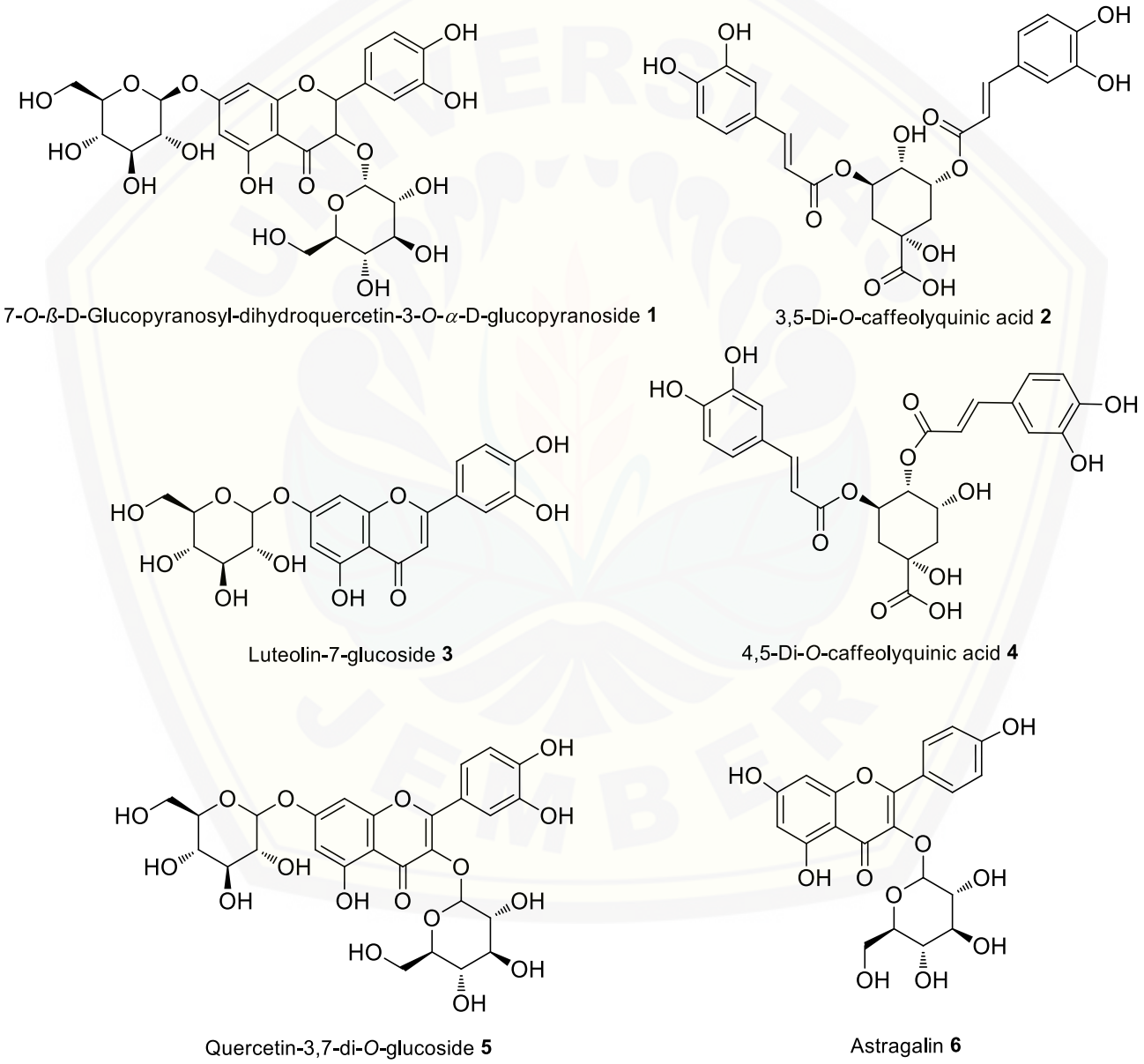

Figure 3. Secondary metabolites of *Ipomoea aquatica* with high affinity against α-glucosidase (3a4a).

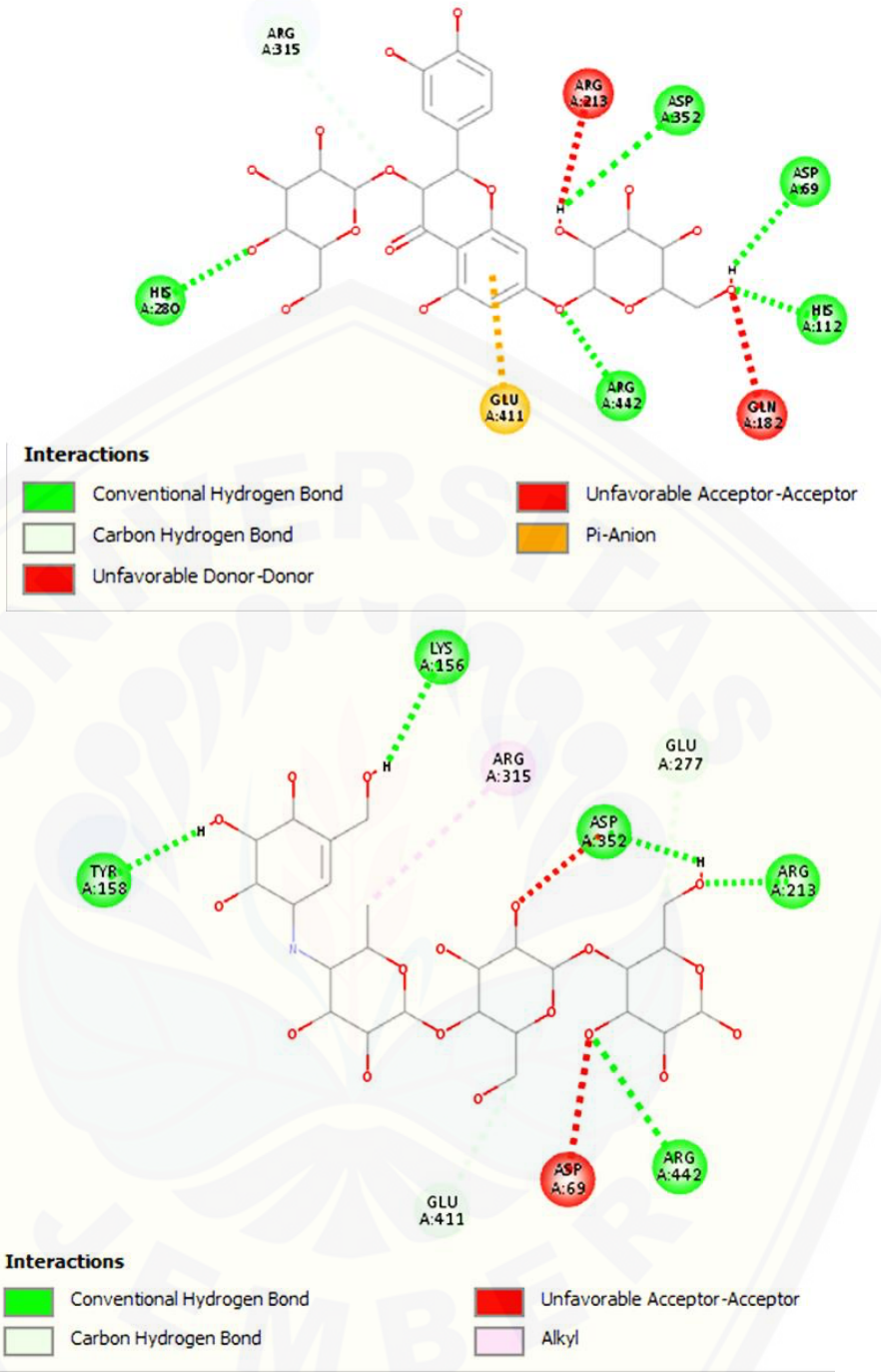

Figure 4. Molecular interaction between (**top**) 7-*O*-*β*-D-glucopyranosyl-dihydroquercetin-3-*O*-*α*-D-glucopyranoside **1** and amino acids residues of *α*-glucosidase (3a4a) and (**bottom**) acarbose and amino acids residues of *α*-glucosidase.

In a computational study of *Paederia foetida*, Linn revealed five potent compounds (stigmasterol **7**, (+)-*α*-tocopherol **8**, *γ*-Sitosterol **9**, (−)-*β*-sitosterol **10**, and asperuloside **11**) to possess high affinity against α-glucosidase enzyme, which indicate their effectiveness in inhibiting the enzyme reaction upon saccharide (Figure 5). Interestingly, the major compounds were terpenes, in which their interaction relied on van-der walls interaction compared with hydrogen bonding formed by acarbose, standard drugs (Figure 6). Nevertheless, phytosterol is infamous for its potent anti-diabetic activity.

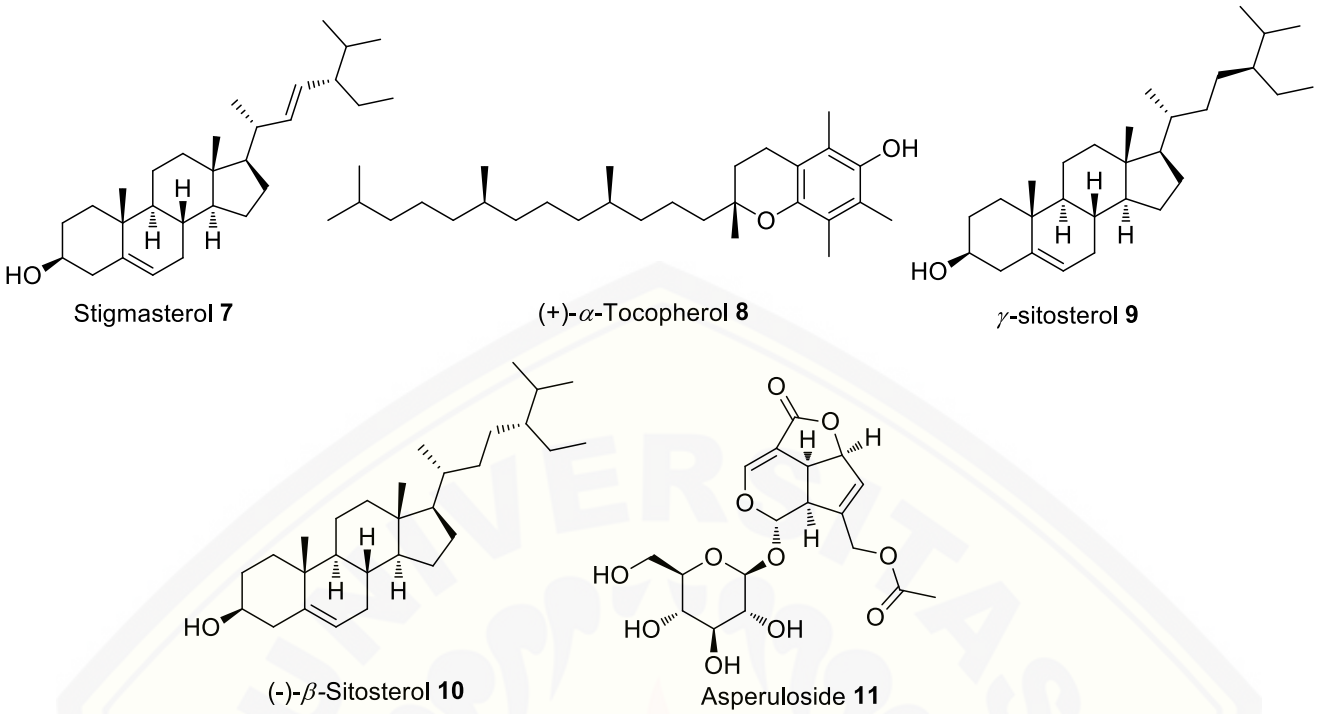

Figure 5. Secondary metabolites of *Paederia foetida* with high affinity against α-glucosidase (3a4a).

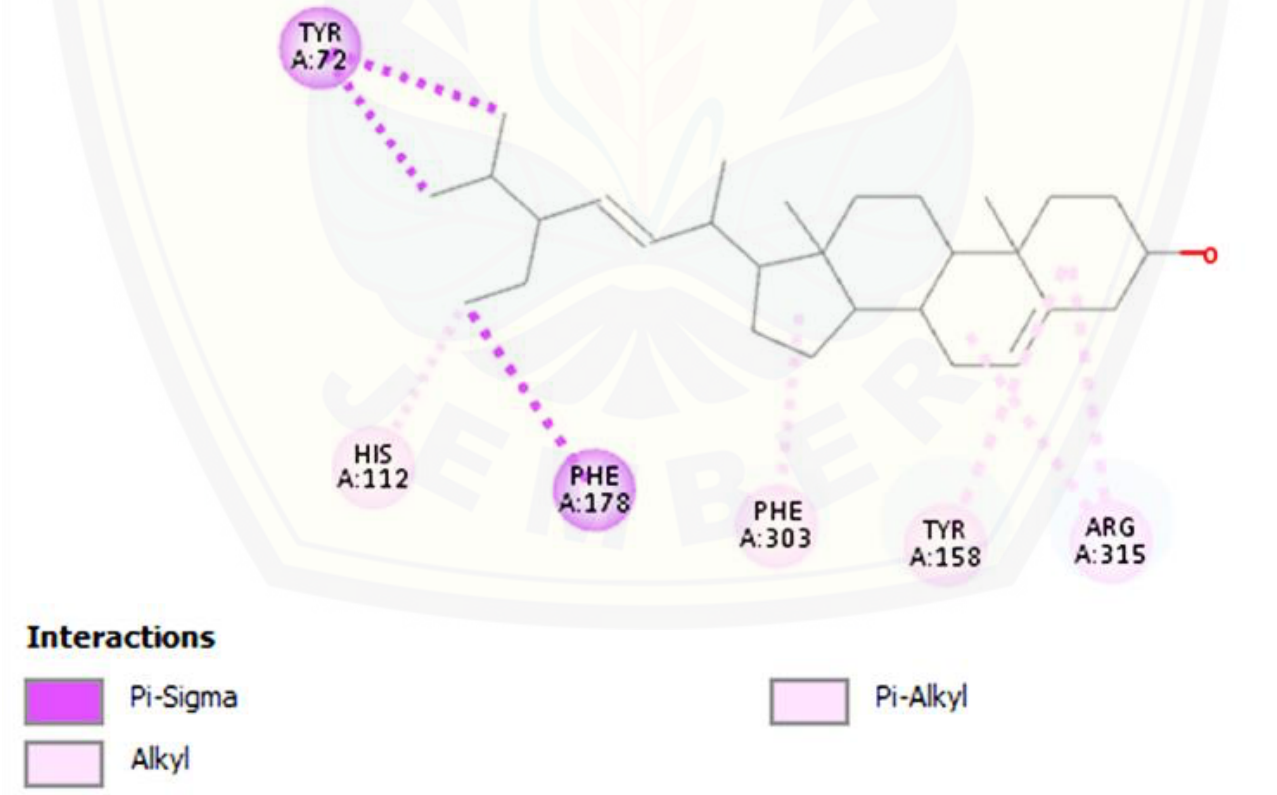

Figure 6. Molecular interaction between stigmasterol and amino acids residues of α-glucosidase (3a4a).

3.3. Plumbago zeylanica

Quinones are a class of natural constituents that have several beneficial mechanisms in biological systems. The compounds possess antioxidant activity due to their ability to undergo one or two electron reductions by cellular reductases [64]. Among bioactive compounds presented in *P. zeylanica*, quinones including chitanone **12**, zeylanone **13**, isozeylanone **14**, droserone **22**, and plumbagin **20** become important active compounds that might be associated with the plant's antioxidant activities [41]. As the bio-marker compound of Plumbago species, plumbagin **20** isolated from *Plumbago indica* was previously reported to possess potent antioxidant activity by reducing the levels of lipid peroxide in diabetic rats [65]. Plumbagin **20** was able to lower lipid peroxides levels, leading to the improvement of antioxidant defense systems [65]. In addition, some phytosterols such as stigmasterol **7**, sitosterol **17**, and campesterol **15** also appear in *P. zeylanica*. It has been reported that phytosterol was shown to have the most effective antioxidant activity among the sterols. Despite their potential activity as modest radical scavengers, phytosterols such as β-sitosterol and campesterol reduced membrane oxidation and stabilized lipid membranes [66].

A similar protocol performed on *Plumbago zeylanica* constitutes derived from literature studies showed compounds with significantly higher affinity than acarbose were Chitanone **12**, Zeylanone **13**, Isozeylanone **14**, Campesterol **15**, Plumbagoside D **16**, Stigmasterol **7**, Sitosterol **17**, Heneicosane **18**, Plumbagin C **19**, 2-(3,4-Dihydroxyphenyl)-3,5,6-trihydroxychromen-4-one **20**, and Droserone **21** (Figure 7). Interestingly, atropisomer chitanone generates the highest affinity due to its pi–pi interaction with amino acids PE303, TYR158, and ARG315, which is absent in acarbose interaction (Figure 8).

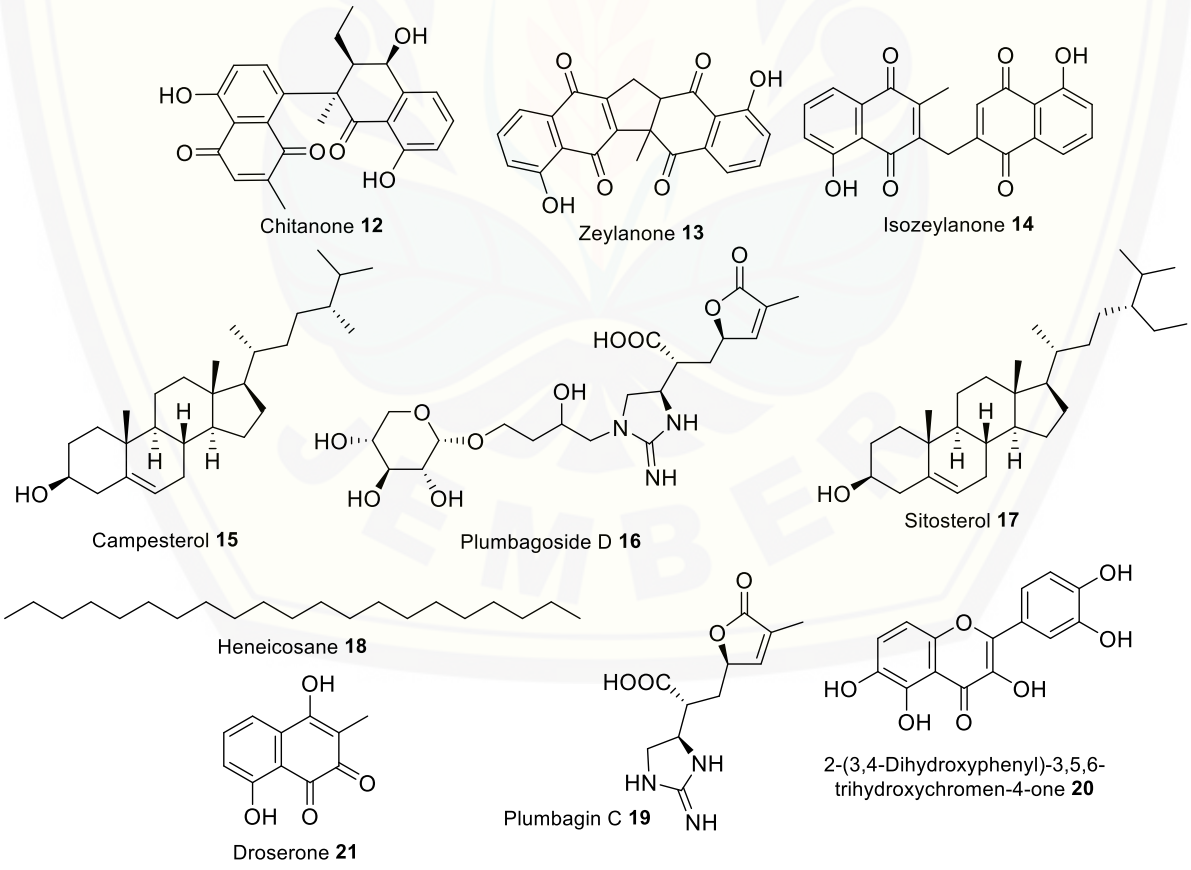

Figure 7. Secondary metabolites of *Plumbago zeylanica* with high affinity against α-glucosidase (3a4a).

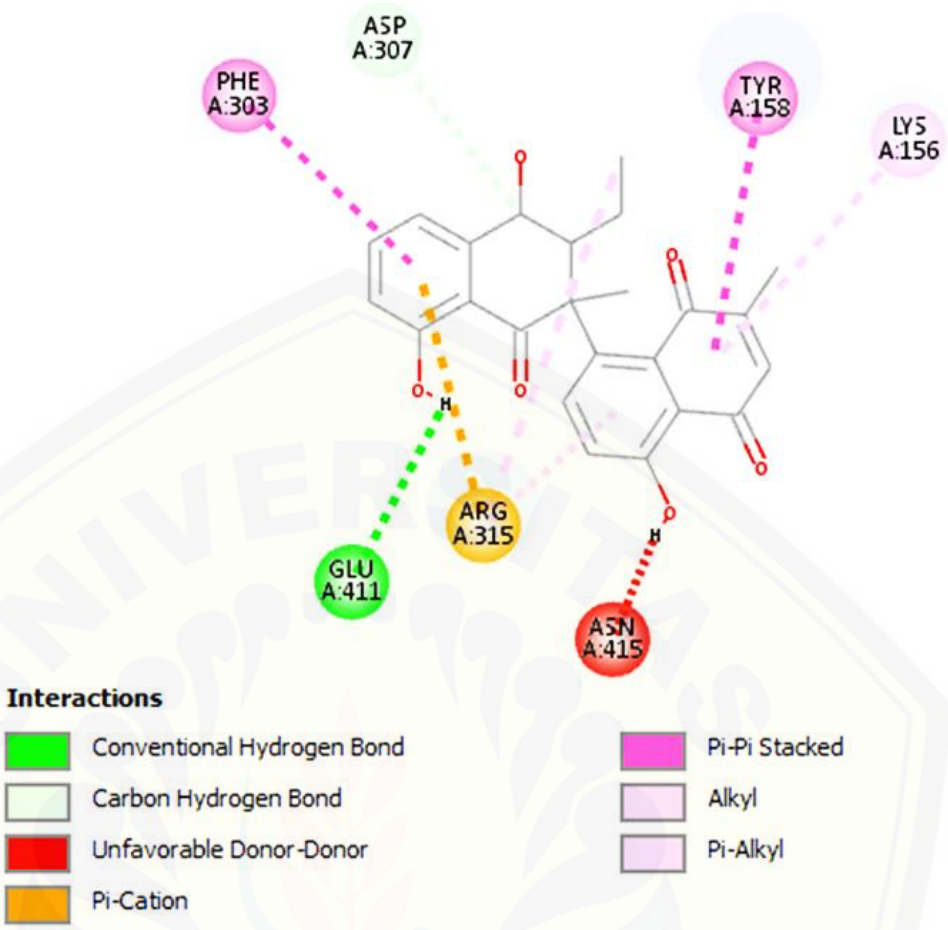

Figure 8. Molecular interaction between chitanone and amino acids residues of α-glucosidase (3a4a).

3.4. Nauclea pallida Reinw

Nauclea sp. belongs to the largest family of woody plants, Rubiaceae, which is traditionally used to manage several illnesses including malaria, diarrhea, viral, and non-viral infections [67]. The phytochemical constituents of *Nauclea* species have been reported since 1953, revealing steroids and saponins as the first identified metabolites [68]. Further, chemical investigations of *Nauclea* sp. generated a number of alkaloids such as naucledine **22**, strictosidine **23**, and several derivatives of angustine (Figure 9) [67]. Phenolic compounds including antiarol **24**, *p*-coumaric acid **25**, resveratrol **26**, and scopoletin **27** were also isolated from the three main *Nauclea* species (*Nauclea diderrichii*, *Nauclea pobeguinii*, and *Nauclea latifolia*) [69–71]. In addition, some pharmacological investigations on *Nauclea latifolia* species revealed antioxidant and antidiabetic activities. A previous study demonstrated *N. latifolia* to possess antioxidant activity by reducing CAT and GSH levels in liver tissues as well as inhibiting lipid peroxidation [72,73]. Furthermore, the aqueous leaf extract of *N. latifolia* was also found to alleviate glucose levels in a diabetic rats model by 45% [74]. However, there was no availability of *N. pallida* pharmacological evaluation reports and limited information regarding their constituents, which constrained the docking experiment. Nevertheless, a full study of this species is necessary to reveal its antimetabolic disease potency, and anti-diabetic, through in vitro or in vivo evaluations.

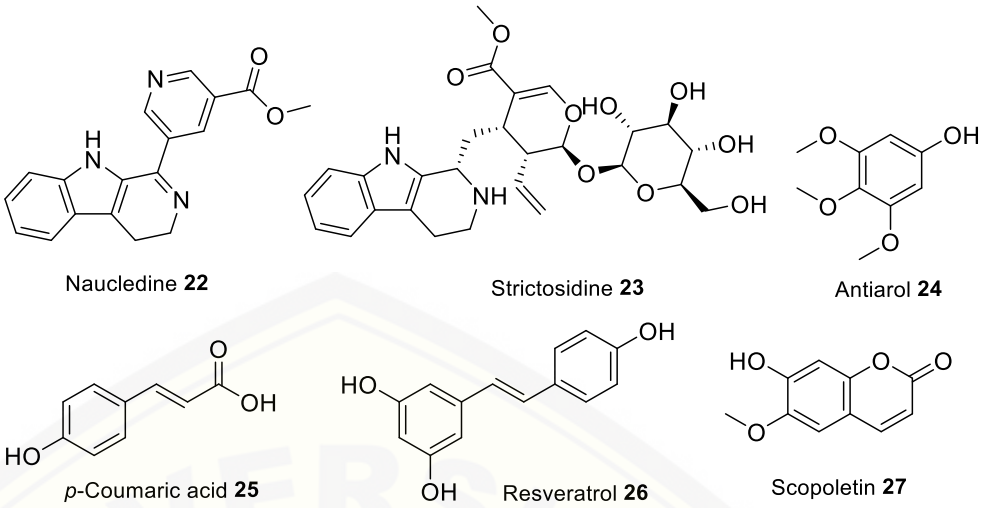

Figure 9. Several secondary metabolites of *Nauclea* sp.

3.5. Sauropus androgynus

S. androgynus, which belongs to Phyllanthaceae, is a tropical shrub commonly grown in South Asia and Southeast Asia. In Indonesia, it is known as 'katuk' and widely prepared as a clear soup [75]. Apart from its high-value vegetables, *S. androgynus* has gained broad attention due to its medicinal uses. It contains various classes of plant chemicals with various biological activities, in which research investigations mostly used leaves, followed by roots and seeds. It has led to the isolation and identification of several types of compounds, including lignans, steroids, flavonoids, terpenoids, and nucleosides [75]. Two flavonoids, apigenin **28** and luteolin **29,** were identified from *S. androgynus* (Figure 10) [42,43]. Previous research clarified the neuroprotective effect of apigenin **28** related to its antioxidant mechanism against APP/PS1 in mice models. It increased the brain's antioxidative capacity, indicated by a decline in the superoxide anion level of the cerebral cortex along with oxidative markers such as GSH and superoxide dismutase (SOD) [76]. Furthermore, the antioxidant capacities of luteolin **29** isolated from *Euterpe oleracea* Mart. was also reported to be significant, shown by an IC50 value of 6.35 µg/mL, and was measured using a cell-based anti-oxidant protection (CAP-e) assay [77]. The docking protocol revealed that apigenin **28** and luteolin **29** had docking energies of −8.517 and 8.52 kcal/mol, respectively, which are comparable to acarbose.

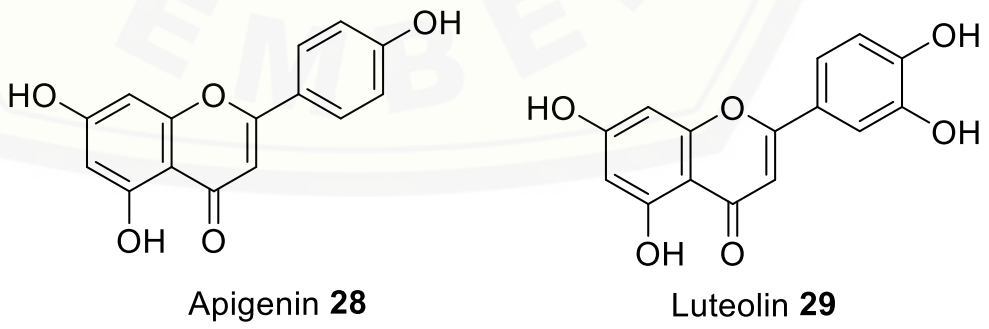

Figure 10. Secondary metabolites of *S. androgynus*.

3.6. Wrightia pubescens

Locally known as 'Bintaos', *W. pubescens* can grow up to 35 m tall and is widely distributed in deciduous lowland thickets and woodland. The ethnopharmacological uses include malaria and eye disease [30,78]. In an earlier study, isolation and identification of *W. pubescens* yielded several compounds including wrightiadione **30**, ursolic acid **31**, oleanolic acid **32**, squalene **33**, and tryptanthrin **34** (Figure 11) [44–46]. Interestingly, tryptanthrin **34** has been shown to have antioxidant properties against *tert*-butyl hydroperoxide-induced human hepatocyte-derived HepG2 cells through reactive oxygen species inhibition and GSH depletion. Moreover, this compound was also found to increase the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), which is associated with tryptanthrin-mediated cytoprotection [79]. Among compounds **30–34**, molecular docking protocol resulted in binding energy values of −8.472, −5.556, −6.838, −7.796, and −8.269 kcal/mol, respectively.

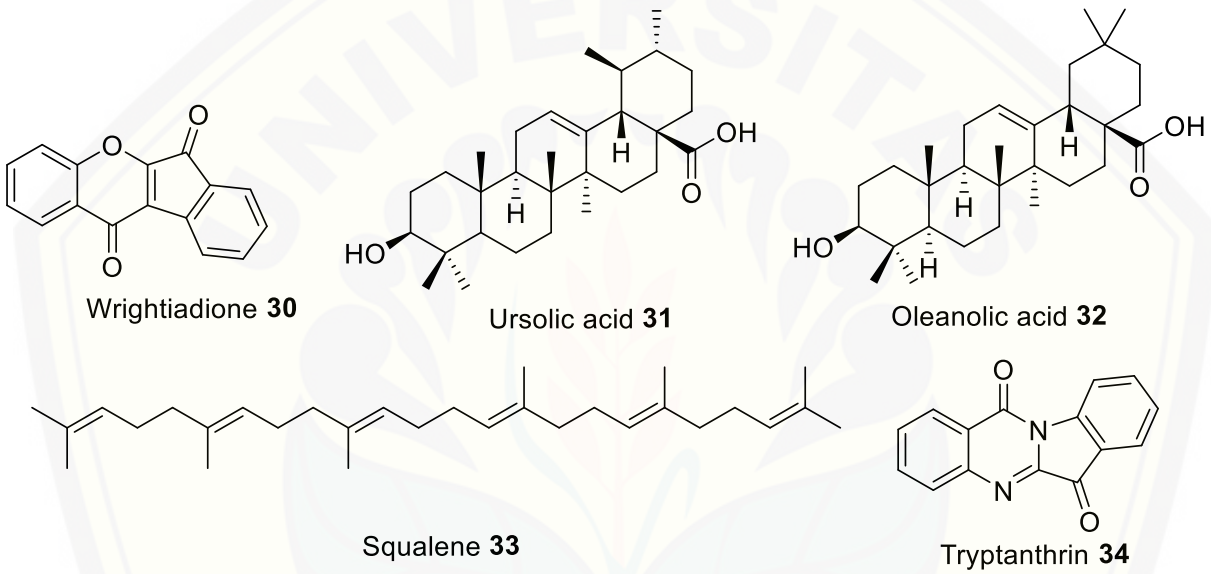

Figure 11. Secondary metabolites of *W. pubescens*.

3.7. Psophocarpus tetragonolobus

P. tetragonolobus taxonomically belongs to the family of Fabaceae, which is listed as underutilized legumes, and is widely spread around South East Asia. This perennial plant is characterized by its winged pods and is commonly used as a food source which is mostly eaten raw or cooked [80,81]. Moreover, a previous study reported that *P. tetragonolobus* seeds and root constituents present several biological activities such as α-amylase inhibitor, hemagglutinin activity, and Kunitz-type trypsin inhibitor [81]. In the present study, *P. tetragonolobus* was shown to have promising antioxidant activities in three different methods. However, there was limited availability regarding the constituents of *P. tetragonolobus*, which constrained the docking assessment as well as their pharmacological evaluation. Therefore, it is necessary to study their potency in order to evaluate their anti-diabetes and antioxidant properties.

4. Materials and Methods

4.1. Plant Materials

Vegetables were collected from the traditional market Besuki Regions (Jember, Banyuwangi, Bondowoso, and Situbondo Districts) in Jawa Timur, Indonesia, and were transported to the Laboratory Drug Utilisation and Discovery Research Group for identification. Voucher samples were stored under the code described in Table 4.

Table 4. Indonesian vegetables sample.

No	Species	Local Name	Voucher Code
1	*Carica papaya*	Bunga papaya	CP
2	*Clitoria ternatea* L.	Bunga telang	CT
3	*Etlingera elatior*	Bunga kecombrang	EE
4	*Ipomoea aquatica*	Kangkung	IA
5	*Limnocharis Flava*	Genjer	LF
6	*Luffa acutangular*	Buah gambas	LA
7	*Marsilea minuta* L.	Semanggi	MM
8	*Moringa Oleifera*	Daun kelor	MO
9	*Nasturtium officinale*	Selada air	NO
10	*Nauclea pallida* Reinw.	Daun kolpo	NP
11	*Nothopanax scutellarium* Merr.	Daun mangkokan	NS
12	*Paederia foetida* Linn	Daun sembukan	PF
13	*Pluchea indica*	Daun beluntas	PI
14	*Plumbago zeylanica* L.	Daun encok	PZ
15	*Psophocarpus tetragonolobus*	Kecipir	PT
16	*Sauropus androgynus*	Daun katuk	SA
17	*Vigna cylindrica* (L.) Skeels	Kacang panjang	VC
18	*Wrightia pubescens* R.Br	Daun dan tangkai Bintaos	WP
19	*Diplazium esculentum*	Pakis	DE

4.2. Extract Preparation

Vegetable extracts were prepared using the ultrasonication and maceration method. The dried samples powder (0.5 g) was homogenized in an extraction vessel and then extracted with ethanol solvent in a ratio of 1:20. Samples were ultrasonicated in an ultrasonic bath for 30 min at a temperature of 35 °C. The sample was left in a macerator vessel for 6 h at room temperature. Extraction was carried out three times with different solvents. The resulting filtrate was evaporated to obtain a concentrated extract

4.3. Antioxidant Determination

4.3.1. 2-2-Diphenyl-1-picrylhydrazyl (DPPH) Assay

Sample solutions (2 GAE/mL, 200 µL) were loaded into 96-well plates (4 replicates) and serially diluted. Another set of wells was loaded with 200 µL of MeOH or vitamin C (1 mM, 50 µL) as negative and positive controls, respectively. DPPH (90 µM, 100 µL) was added to the first three rows of sample solution and mixed thoroughly, and the last row was used to correct for background absorbance (Abs blank). Plates were incubated in the absence of light for 30 min before measuring absorbance at 515 nm using a spectrophotometer UV-Vis microplate reader (U-2900, Hitachi, Japan). Low absorbance indicated high scavenging activity. Radical scavenging activity was determined using the formula below (Equation (1)).

$$\text{Percentage activity} = \text{A0} - \text{A1/A0} \times 100\% \quad (1)$$

4.3.2. Superoxide Anion Radical Scavenging Assay

Pirogalol was used in free radical scavenging evaluation based on an established method [82]. Ascorbic acid was used as a standard (1 mM, 50 µL). Each extract solution (2 µg GAE/mL, 200 µL) was incubated in tris-HCL buffer (pH 8.2, 50 mM, 1.7 mL). After 10 min, pirogalol (10 mM in HCl 10 mM, 100 µL) was added and the absorbance was measured at 320 nm using spectrophotometry UV-Vis. The inhibition percentage of the pirogalol radical by the test solution was determined using the Equation (1) formula.

4.3.3. Hydroxyl Radical Scavenging Assay

All vegetable extracts were evaluated for antioxidant potential essentially by established protocol [83]. Briefly, extracts solution (2 µg GAE/mL, 150 µL) and 2-deoxy-D-ribose (28 mM, 50 µL) dissolved in phosphate buffer (20 mM, pH 7.4), EDTA (1 mM, 100 µL), $FeCl_3$ (10 mM, 100 µL), H_2O_2 (11 mM, 50 µL) and ascorbic acid (1 mM, 50 µL) was added into an Eppendorf tube. Before incubating at 37 °C for 1 h, a solution of 2-tiobarbiturat (ATB) (1%, 500 µL) and ATC (2.8%, 500 µL) were loaded into the tube. Afterward, the solution was vortexed and re-incubated at 100 °C for 20 min. The resulting pink coloration solution was then cooled to room temperature followed by absorbance measurements using spectrophotometry UV-Vis at λ 532 nm. Radical scavenging activity was determined using the Equation (1) formula.

4.4. Molecular Docking

Secondary metabolites of vegetable medicinal plants were obtained through extensive searching using the SciFinder® database (https://scifinder.cas.org, accessed on 6 September 2022). Protein 3a4a was obtained from RCSB PDB (https://www.rcsb.org, accessed on 22 September 2022). 2D molecular structures were constructed using ChemDraw v20.0.0.41 (https://perkinelmerinformatics.com, accessed on 22 September 2022). Molecular energy minimization was performed using Avogadro v1.2.0 (https://avogadro.cc, accessed on 22 September 2022) into pdb, whereas molecules pdbqt format were generated using OpenBabel v3.1.1 (https://openbabel.org, accessed on 22 September 2022). Docking parameters were set using AutoDock Tools v1.5.7 (https://autodock.scripps.edu, accessed on 17 October 2022) while docking was performed using autodocking autodock vina v1.2.3 run in quad-core CPU composed of four sets of Intel(R) Core (TM) i3-6006U CPU @ 2.00GHz, 1690 MHz. Data visualization was undergone using BIOVIA Discovery Visualizer v21.1.0.20298 (https://discover.3ds.com, accessed on 17 October 2022).

The docking process was initiated by collecting and collating the secondary metabolite dataset from selected Indonesian vegetables with a potent antioxidant activity using the SciFinder database, which covers molecules isolated from the same species grown across the globes. The molecules were constructed in 2D form prior to 3D generation, which was followed by molecular mechanic calculation to produce the most stable conformation. These molecules (*.pdb) were then converted into *.pdbqt format. The enzyme was also prepared into *.pdbqt format, in which griding parameters for docking were measured and set. Molecular docking was then performed for ligands (secondary metabolites of potent vegetable species and acarbose as the standard). Data logs produced were evaluated into an ordered list revealing hits of molecules with better affinity than the standard drug (acarbose). Molecules with the highest interest were visualized to give an understanding of their interaction with the enzyme.

5. Conclusions

DM sufferers in developed countries have adhered to the treatment given because uncontrolled DM can subsequently cause various complications that involve various organ systems of the human body that can affect the quality of life and economy of the sufferer. Many Indonesian vegetables are prepared also as traditional medicine. The study on selected Indonesian vegetables revealed six species to possess high antioxidant content: *I. aquatica*, *P. foetida*, *P. zeylanica*, *N. pallida*, *S. androgynus*, *W. pubescens*, and *P. tetragonolobus*. Molecular modeling successfully revealed 7-*O*-*β*-D-glucopyranosyl-dihydroquercetin-3-*O*-*α*-D-glucopyranoside, stigmasterol, and chitanone were the potent secondary metabolites as anti-diabetic candidates (α-glucosidase inhibitory agent) from *I. aquatica*, *P. foetida*, and *P. zeylanica*, respectively. This left the *N. pallida* and *P. tetragonolobus* species to be understudied yet potent sources of antioxidant agents. Nevertheless, this finding supports the idea of developing the selected medicinal vegetables as a source of anti-diabetic agents and could be further developed in the form of conventional natural-based drugs or standardized

botanical dosage forms according to the Indonesian government's strategic development of medicinal plant-based medicine.

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