

REVIEW

Cinnamic Acid Derivatives as α -Glucosidase Inhibitor AgentsTeni Ernawati^{1,2,*}, Maksun Radji¹, Muhammad Hanafi², Abdul Mun'im¹, and Arry Yanuar¹¹Faculty of Pharmacy, Universitas Indonesia, Depok 16242, Indonesia²Research Center for Chemistry – Indonesian Institute of Sciences (LIPI), Kawasan Puspiptek, Serpong Tangerang Selatan, Banten 15314, Indonesia

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ABSTRACT

This paper reviews biological activity of some cinnamic acid derivative compounds which are isolated from natural materials and synthesized from the chemical compounds as an agent of α -glucosidase inhibitors for the antidiabetic drug. Aegeline, anhydroaegeline and aeglinoside B are natural products isolated compounds that have potential as an α -glucosidase inhibitor. Meanwhile, α -glucosidase inhibitor class of derivatives of cinnamic acid synthesized compounds are *p*-methoxy cinnamic acid and *p*-methoxyethyl cinnamate. Chemically, cinnamic acid has three main functional groups: first is the substitution of the phenyl group, second is the additive reaction into the α - β unsaturated, and third is the chemical reaction with carboxylic acid functional groups. The synthesis and modification of the structure of cinnamic acid are very influential in inhibitory activity against α -glucosidase.

Keywords: cinnamic acid derivative; α -glucosidase inhibitor; antidiabetic; synthesis; natural products

ABSTRAK

Artikel ini mengulas aktivitas biologi beberapa senyawa turunan asam sinamat hasil isolasi bahan alam dan hasil sintesis yang berfungsi sebagai agen penghambat enzim α -glukosidase untuk obat diabetes. Aegeline, anhydroaegeline dan aeglinoside B adalah senyawa alam hasil isolasi yang memiliki potensi sebagai inhibitor α -glukosidase. Sementara itu, golongan inhibitor α -glukosidase kelas senyawa turunan sinamat sintesis adalah *p*-metoksi asam sinamat dan *p*-metoksi etil sinamat. Secara kimia, asam sinamat memiliki tiga gugus fungsi utama; pertama adalah substitusi pada gugus fenil, kedua reaksi adisi pada α - β tak jenuh dan ketiga adalah reaksi dengan gugus fungsi asam karboksilat. Sintesis dan modifikasi struktur senyawa asam sinamat sangat berpengaruh terhadap aktivitas inhibisi enzim α -glukosidase. Kami berharap ulasan artikel ini dapat memberikan kontribusi dalam penyebaran informasi ilmiah terkait kimia medisinal khususnya tentang senyawa turunan asam sinamat sebagai inhibitor α -glukosidase.

Kata Kunci: turunan asam sinamat; inhibitor α -glukosidase; diabetes; sintesis; senyawa alam

INTRODUCTION

Cinnamic acid, originally isolated from plant [1], has been widely reported to have a wide range of bioactivity such as anticancer [2], antitumor [3], anti-inflammatory [4], antioxidant [5], antimalarial, antituberculosis [6-7], antimicrobial [8], tyrosinase inhibitor [9], and antidiabetic [10]. For example, *trans*-cinnamic acid induces cytostasis and reversal of malignant properties of human tumor cells in vitro. Furthermore, molecular analysis has shown that the anti-tumor activity of cinnamic acid may be due in part to the inhibition of isoprenylation protein in transduction of mitogenic signal. Cinnamic acid and some of its compounds have been examined as a good inhibitor of the activity of AKR1C3 which is the cancer cells formed in the presence of hormones such as prostate cancer, breast cancer, and endometrial cancer.

Cinnamic acid and 3,4,5-trimethoxycinnamic acid (IC₅₀ = 50 mM) are quite good as AKR1C3 inhibitor (IC₅₀ = 50 mM). In addition, caffeic acid has low cytotoxic potential in vitro against leukemia myeloid cells (HL-60) and also has potential as a chemopreventive agent against skin cancer [11]. Combinations of cinnamic acid and guanylhydrazone compounds that have also been synthesized have high activity against Mycobacterium active tuberculosis H37Rv which is the causative agent of tuberculosis (TB) [7]. Bairwa et al. [6] reported that the synthesis of cinnamic acid with thionyl chloride to produce halides acid. Halides can also be reacted with the alcohol to become cinnamic ester (cinnamoyl ester). A cinnamic ester is a group of anti-cancer agents. Some cinnamic esters isolated from propolis Netherlands, benzyl caffeate, phenethyl caffeate, and cinnamoyl caffeate,

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have potential as an antiproliferative agent against carcinoma of the colon 26-L5 with EC_{50} values respectively of 0.288, 1.76, and 0.114 mg/mL.

Adisakwattana et al. [12] reported antidiabetic activity of the compounds and derivatives of cinnamic acid. They also studied the relationship between the substitution on the benzene ring of cinnamic acid and the activity of the α -glucosidase enzyme inhibition. This paper is a review of the literature on both cinnamic acid derivative compounds derived from isolating natural materials and synthesizing chemical compounds in the laboratory that have biological activity in inhibiting the α -glucosidase enzyme.

Cinnamic Acid

Cinnamic acid (**1**) has long been used by humans for flavoring and fragrance needs. It is widely used as fragrance ingredients in cosmetics, shampoo, soap, and other toiletries as well as non-cosmetic products such as household cleaners and detergents. It is also used in food products as fruits flavor or flavorants. It has several synonyms names such as benzylidene acetic acid, cinnamic acid, 3-phenylacrylic acid, 3-phenylpropenoic acid, and 3-phenyl-2-propenoic acid. It has a chemical formula of $C_6H_5CH=CHCOOH$ or $C_9H_8O_2$. It has form as tangible crystals that are slightly soluble in water. It has a melting point of 134 °C and a molecular weight of 148.16 g/mol [13]. It is a phenolic acid compound which is contained in a lot of fruits and vegetables. It is also contained especially in the plant of *Rheum tanguticum Maxim.ex Balf* [14] and *Spiraea thunbergii Sieb* [15].

Toxicology and dermatology of cinnamic esters, cinnamic alcohol, and cinnamyl alcohol have been carried out and reported in [16]. Chemical aspects of cinnamic acid derivative compounds have received much attention in the research and development of drugs especially its derivative compounds. In recent

years, cinnamic acid and its derivatives are widely studied and researched as an anti-cancer agent, anti-proliferative, anti-angiogenesis, anti-leukemia, anti-hyperglycemia, antituberculosis, anti-bacterial, and anti-inflammatory. Moreover, a lot of research has been done in finding varieties of inhibiting enzymes such as transglutaminase, aminopeptidase N, histone deacetylase, etc [11,17].

NATURAL PRODUCTS

Aegeline (**2**) anti-hyperglycemia compound is isolated from the leaves of *Aegle Marmelos*. This compound is a form of the cinnamic acid amide. Therapy with natural aegeline can lower blood glucose levels down to 12.9% after 5 h and down to 16.9% with a span of 24 h at a dose of 100 mg/kg body weight while commercial drug with the same dose of metformin can reduce blood glucose levels by 23.5% after 5 hours and by 26.5% after 24 h [18]. Narender et al. have shown that (-)- aegeline (**3**) is associated with aegelinoside compound A (**9**). Aegelinoside B (**10**) has the potential to improve diabetes mellitus by pressing the blood glucose and plasma triglyceride levels. Therefore, compounds tend to be developed further to find a new antidiabetic drug that has dual functions. The phenyl ethyl cinnamate compound isolated from the leaves of *Aegle Marmelos* is a α -glucosidase inhibitor compound. The most potential compound as α -glucosidase inhibitors among phenyl ethyl cinnamate

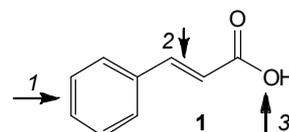


Fig 1. Structure of Cinnamic acid (**1**) and its three main of functional groups

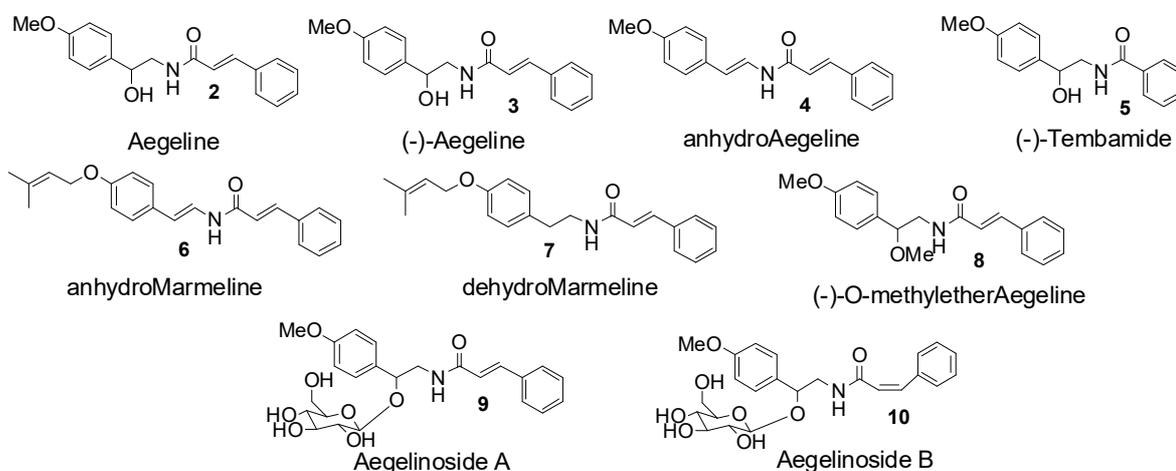


Fig 2. α -Glucosidase active inhibitors compounds from *Aegle marmelos*

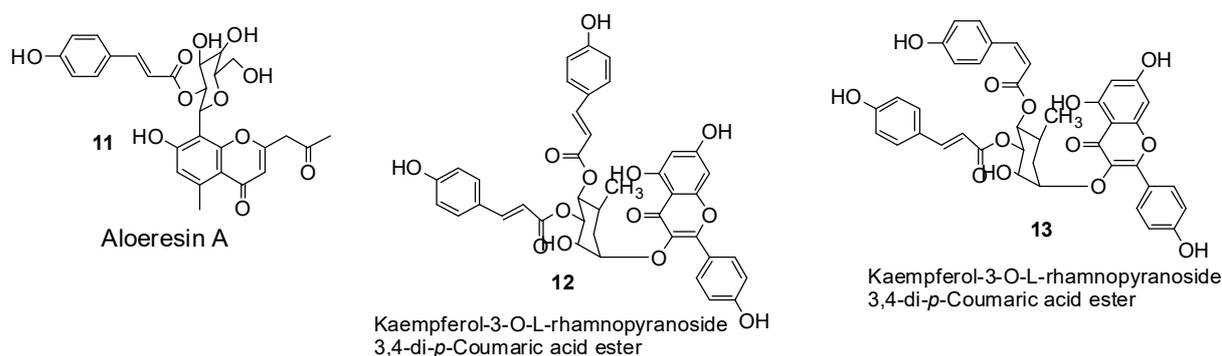


Fig 3. α -Glucosidase inhibitors active compounds from *Aloe ferox* and *Machilus philippinense* Merr.

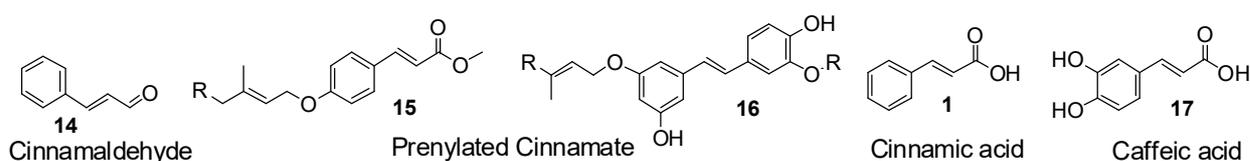


Fig 4. α -Glucosidase inhibitors active compounds from *Cinnamomum zeylanicum*; cinnamaldehyde (14), Propolis (15,16) and caffeic acid (17)

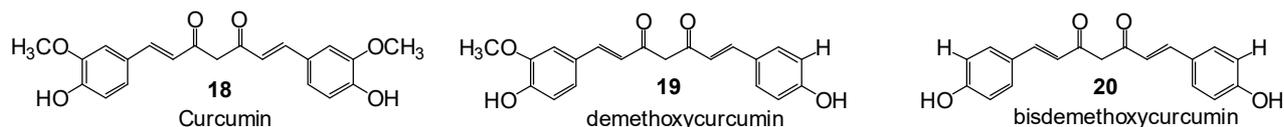


Fig 5. α -Glucosidase inhibitors active compounds from *Curcuma longa*; curcumin (18), demethoxycurcumin (19), bisdemethoxycurcumin (20)

compounds is a compound that has an anhydroaegeline (4) value of $IC_{50} = 35.8$ mM [19].

Aloe ferox aloe resin contains compound A (11) which has activity in inhibiting intestinal sucrose and maltose in mice with $IC_{50} = 11.94$ mM and $IC_{50} = 2.16$ mM. This compound is reported to reduce blood glucose levels in diabetics [20]. *Machilus philippinense* Merr. flavonol glycosides contain cinnamic compounds that have been evaluated and have activities of α -glucosidase inhibitors of type IV from *Bacillus stearothermophilus* with $IC_{50} = 6.10$ μ m for compounds (12) and $IC_{50} = 1.00$ μ m for compound (13) [21].

Cinnamaldehyde compound (14) which is the main component in *Cinnamomum zeylanicum* (cinnamon) is a plant that has been commonly used as a traditional medicine in India as an anti-diabetic. Cinnamaldehyde LD_{50} value is 1850 ± 37 mg/kg body weight. The effective dose of cinnamaldehyde as anti-diabetic is either 5, 10, or 20 mg/kg bw for 45 days against streptozotocin (STZ) (60 mg/kg bw) induced diabetic Wistar male rats. Plasma glucose concentration was reported to decrease significantly ($p < 0.05$) at a dose of 63.29% compared to control [21]. Prenylated cinnamic acid is contained in propolis [23]. Caffeic acid (17) and cinnamic acid are phenolic acid compounds which are stored up in a lot of fruits, vegetables, and coffee. Both

of these compounds are reported to have anti-hyperglycemic activity by stimulating the mechanism of action of insulin secretion from β -cells of the pancreas. Research results show that both of these phenolic acid compounds can raise insulin receptor tyrosine phosphorylation, regulate the expression of proteins associated with insulin signaling, including the insulin receptor, phosphatidylinositol-3 kinase, glycogen synthase, transporter-2 glucose, raising the glucose absorption and reducing insulin resistance in cells as consequences [8].

The compounds of curcumin (18), demethoxycurcumin (19), and bisdemethoxycurcumin (20), isolated from *Curcuma longa* (turmeric), have been evaluated in vitro for α -glucosidase inhibitory activity through UV circular dichroism spectroscopy (CD). The results showed that the natural compound bisdemethoxycurcumin showed the remarkable effect of inhibition with IC_{50} of 23.0 mM [24]. Kinetic studies for the above study showed that α -glucosidase inhibitory mechanism against bisdemethoxycurcumin compound was non-competitive.

Cinnamic derivatives active compounds contained in the plant of *Tussilago farfara* L such as 3,4-dicaffeoylquinic acid (21), 3,5-dicaffeoylquinic acid (22), and 4,5-dicaffeoyl quinic acid (23), compounds showed

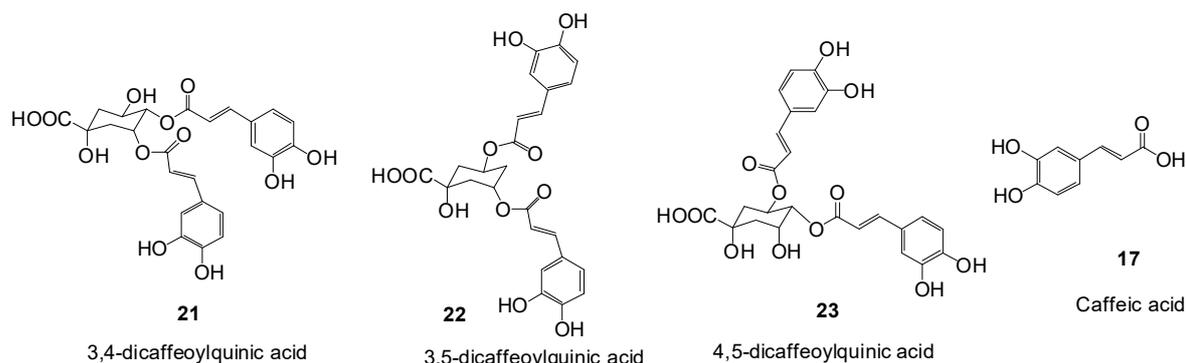


Fig 6. α -Glucosidase Inhibitors Active Compounds from *Tussilago farfara* L; 3,4-Dicafeoylquinic acid (21), 3,5-dicafeoylquinic acid (22), 4,5-dicafeoylquinic acid (23), and caffeic acid (17)

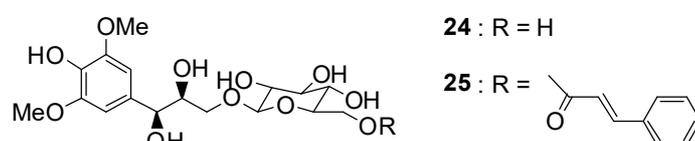


Fig 7. α -Glucosidase inhibitors active compounds from *Hyssopus officinalis*; (7S, 8S)-syringoyl glycerol-9-O-(6'-O-cinnamoyl)- β -D-glucopyranoside compound (24) and (7S, 8S)-syringoyl glycerol 9-O- β -D-glucopyranoside compound (25)

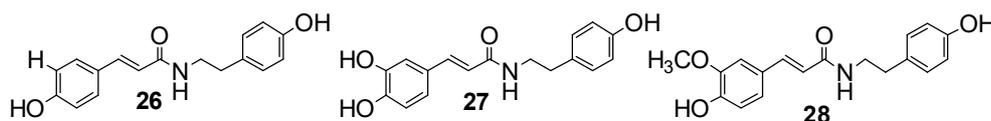


Fig 8. α -Glucosidase Inhibitors Active Compounds from *Tribulus terrestris* extracts *N-trans*-coumaroyltyramine (26),(27) and (28)

inhibitory activity against maltase with IC_{50} = 0.91, 0.90 and 0.89 mM, respectively [25].

Active compounds of α -glucosidase inhibitors contained in the methanol extract of leaves of *Hyssopus officinalis* were (7S, 8S)-syringoylglycerol-9-O-(6'-O-cinnamoyl)- β -D-glucopyranoside (24) and (7S, 8S)-syringoyl glycerol 9-O- β -D-glucopyranoside (25). Inhibitory activity against α -glucosidase enzyme by the above two compounds have resulted in 53 and 54% inhibition at a concentration of 3×10^{-3} M to the benchmark 1-deoxynojirimycin which had inhibitory activity of 58% at a concentration of 3×10^{-7} M. Compounds isolated from the leaves of *Hyssopus* have still relatively low inhibitory activity compared to the inhibitory activity of 1-deoxynojirimycin however *Hyssopus* has been consumed as a food ingredient for a long time hence it has a proven safety record [26].

Crude extracts and their corresponding fractions of flowers, fruits, stems, leaves, roots of the endemic North African plant, *Scabiosa arenaria* Forssk, were screened for their ability of α -glucosidase inhibition. It was found that the fruits ethyl acetate (EtOAc), the fruits butanol (*n*-BuOH), and the flowers ethyl acetate (EtOAc) fractions inhibited α -glucosidase in a noncompetitive manner with IC_{50} values of 0.11 ± 0.09 , 0.28 ± 0.04 and 0.221 ± 0.01

mg/mL respectively. The result of the RP-HPLC analysis indicated that the major components of these active fractions were flavonoid aglycone, cinnamic acid, and its derivatives [27].

Song et al. [28] reported the α -glucosidase inhibitory potential of *Tribulus terrestris* extracts. Fractionating *T. terrestris* extracts, three cinnamic acid amide derivatives (26), (27), and (28) were ascertained to be active components against α -glucosidase. The structure of *N-trans*-coumaroyl tyramine (26),(27), and (28) showed significant inhibition of α -glucosidase (IC_{50} =0.42, 1.86 and 10.62 μ M, respectively).

SYNTHESIS OF CINNAMIC ACID DERIVATIVES

4-Hydroxy *trans*-cinnamic acid (32) has good activity against α -glucosidase enzyme inhibition (IC_{50} = 0.20 mM) whereas 4-methoxy *trans*-cinnamic acid (35) and 4-methoxy *trans*-cinnamic acid ethyl ester (36) were reported to have the most potential inhibitory activity both in inhibiting the enzyme α -glucosidase with values of IC_{50} = 0.04 mM and IC_{50} = 0.05 mM respectively compared to the reference compound 1-deoxynojirimycin which has IC_{50} = 5.60 mM. These

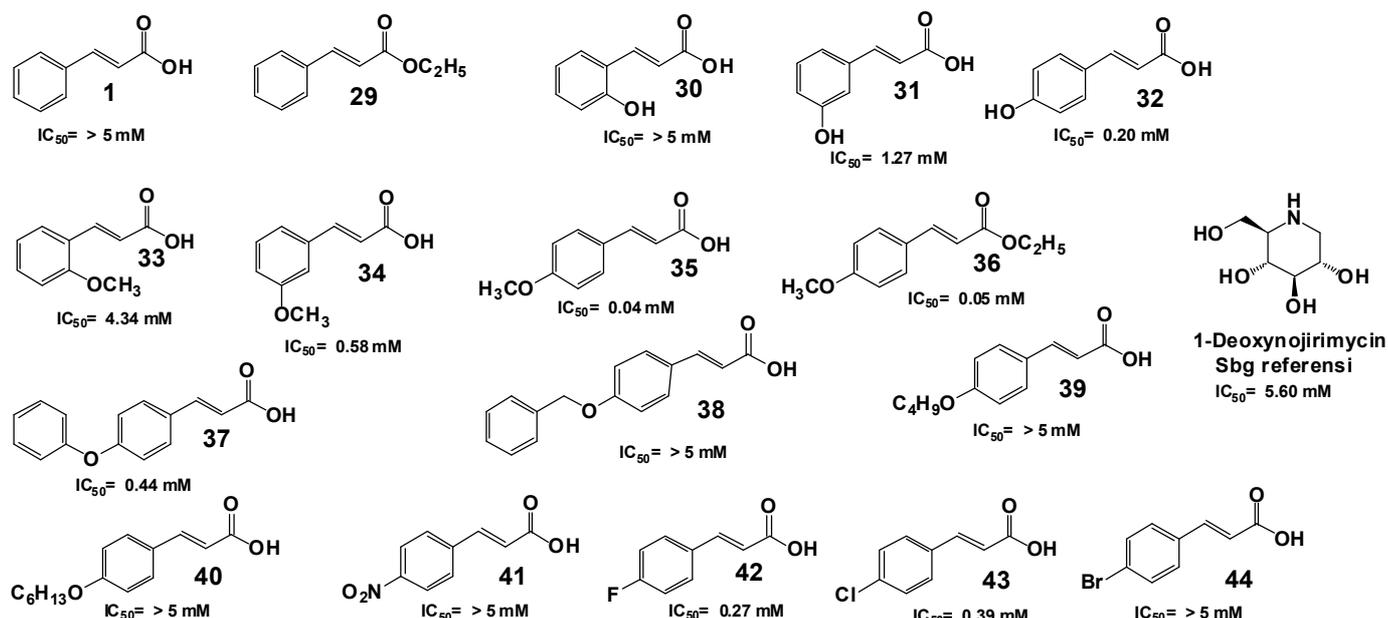


Fig 9. The structure-activity relationship of cinnamic acid derivative compounds to the Inhibition of α -glucosidase

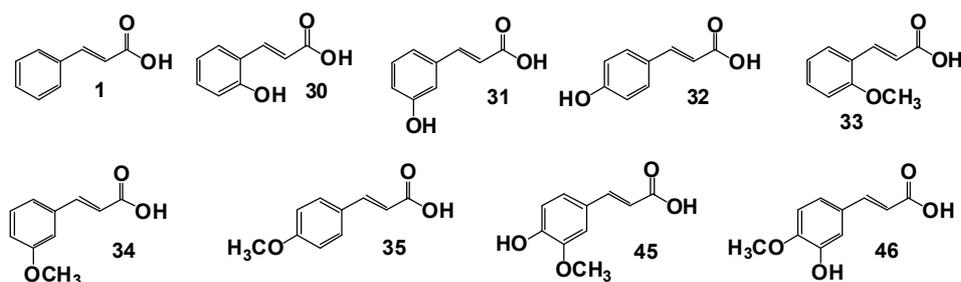


Fig 10. Cinnamic acid derivative compounds were evaluated for their activity in secretin in perfused rat pancreas insulin and pancreatic β -cells (INS-1) as well as the increase $[Ca^{2+}]_i$ in vitro

results indicate that the presence of a hydroxy or methoxy substituent at position 4 in the *trans*-cinnamic acid can increase the activity of the enzyme α -glucosidase inhibition. In this study, it is also indicated that the replacement of 4-hydroxy *trans*-cinnamic acid structures with methoxy functional groups can increase the activity of α -glucosidase inhibitors by 10 times. Likewise, with the addition of the carboxylic group ethyl ester group of cinnamic acid plays an important role in the inhibition of α -glucosidase. Increased of bulkiness and long-chain of 4-alkoxy substituent along with increased of the electron-withdrawing group has been shown to decrease the inhibitory activity. 4-methoxy-*trans*-cinnamic acid is a noncompetitive inhibitor of α -glucosidase while 4-methoxy-*trans*-cinnamic ethyl ester is a competitive inhibitor [11].

Cinnamic acid with some substitutions is evaluated for their activity in secreting insulin at the perfused pancreas in mice and pancreatic β -cells (INS-1) as well as the increase in $[Ca^{2+}]_i$ in vitro. The existence of *m*-hydroxy (31) or *p*-methoxy (32) on a cinnamic acid

substitution is significant and important and it is also effective as an agent in the release of insulin. The presence of *p*-hydroxy (45) and *m*-methoxy (46) in the structure of cinnamic acid turns cinnamic acid into ferulic acid which is widely reported as the best agent to secrete insulin. In this study, it shows that the *p*-methoxy cinnamic acid and ferulic acid can be beneficial for the treatment of diabetes mellitus because the blood glucose levels are regulated by stimulating insulin secretion from pancreatic β -cells [29].

Cinnamide derivatives compounds have been reported to have anti-hyperglycemic activity of such compounds *N*-acyl-2-arylethyl-amines (47) and *N*-acyl-3-coumaroyl amines (48) which can lower blood glucose levels up to 30.7% and 23.3% in the SLM (sucrose Loaded) and up to 25.6% and 25.4% in the model of STZ (Streptozotocin-induced diabetic mice models). In comparison, metformin and glibenclamide can lower blood glucose levels up to 12.9% and 33.7%

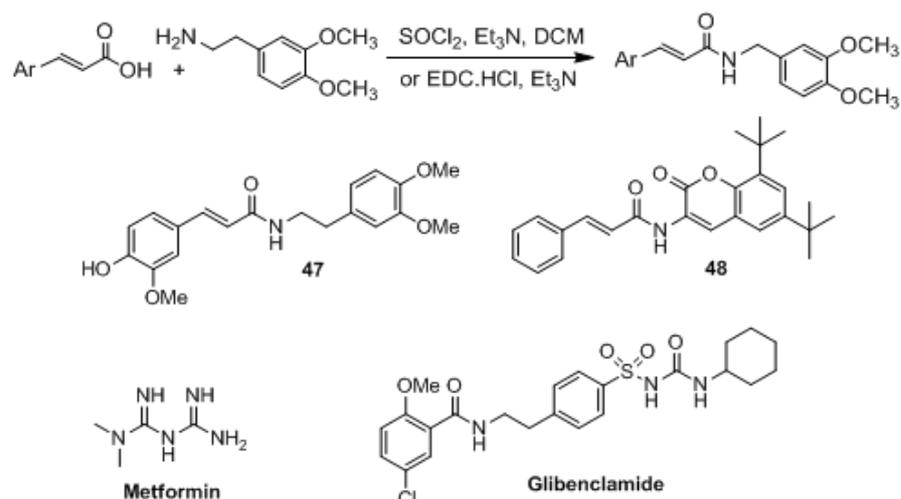


Fig 11. Cinnamic acid derivatives (*N*-acyl-2-arylethyl-amines (**47**) and *N*-acyl-3-Coumarylamines (**48**) were evaluated antihyperglycemic activity in SLM and STZ model

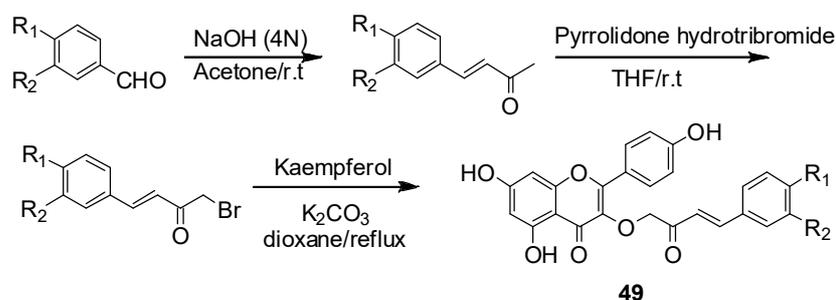


Fig 12. Synthesis of Tiliroside derivatives

Table 1. Synthesis of Tiliroside derivatives and glucose consumption effect of compound 49 in IR HepG2 cell

Compound	R ₁	R ₂	EC ₅₀ (mM)	R ₁	R ₂	EC ₅₀ (mM)
49 a	OH	H	0.368	49 m	CF ₃	>20
49 b	OBn	H	0.658	49 n	F	0.669
49 c	OMe	H	0.149	49 o	Cl	1.075
49 d	OCH ₂ CH ₃	H	0.042	49 p	Br	0.393
49 e	O(CH ₂) ₃ CH ₃	H	>20	49 q	SMe	>20
49 f	O(CH ₂) ₅ CH ₃	H	>20	49 r	OMe	5.070
49 g	O(CH ₂) ₇ CH ₃	H	>20	49 s	OH	6.190
49 h	H	H	0.473	49 t	OBn	>20
49 i	CH ₃	H	0.010	49 u	OH	3.555
49 j	<i>i</i> -Pr	H	0.015	49 v	Cl	2.587
49 k	<i>t</i> -Bu	H	0.013	49 w	OMe	>20
49 l	CN	H	0.003	Metformin		0.270
				Tiliroside		0.155

in the SLM and up to 20.5% and 25.5% in the model of STZ [30].

Qin et al. [31] reported that the tiliroside derived compounds (in Fig. 12, Table 1) have antidiabetic activity tested in vitro using HepG2 cells. Compounds of **49c**, **49d**, **49i**, **49j**, **49k**, and **49l** can cause an increase in the consumption of glucose by insulin-resistant HepG2 cells compared with control cells. This is done also to metformin (as antidiabetic drugs). The compound

of **49l** is more active significantly than that of adenosin-5'-monophosphate kinase protein and also reduces the activity of acetyl-CoA carboxylase. Tiliroside derivative compounds (especially compound of **49c**, **49d**, **49i**, **49j**, **49k**, and **49l**) have significantly better antidiabetic activities than that of commercial drug metformin. From the results of the study, it was suggested that the compound tiliroside derivatives could be developed into a type II antidiabetic drug candidate.

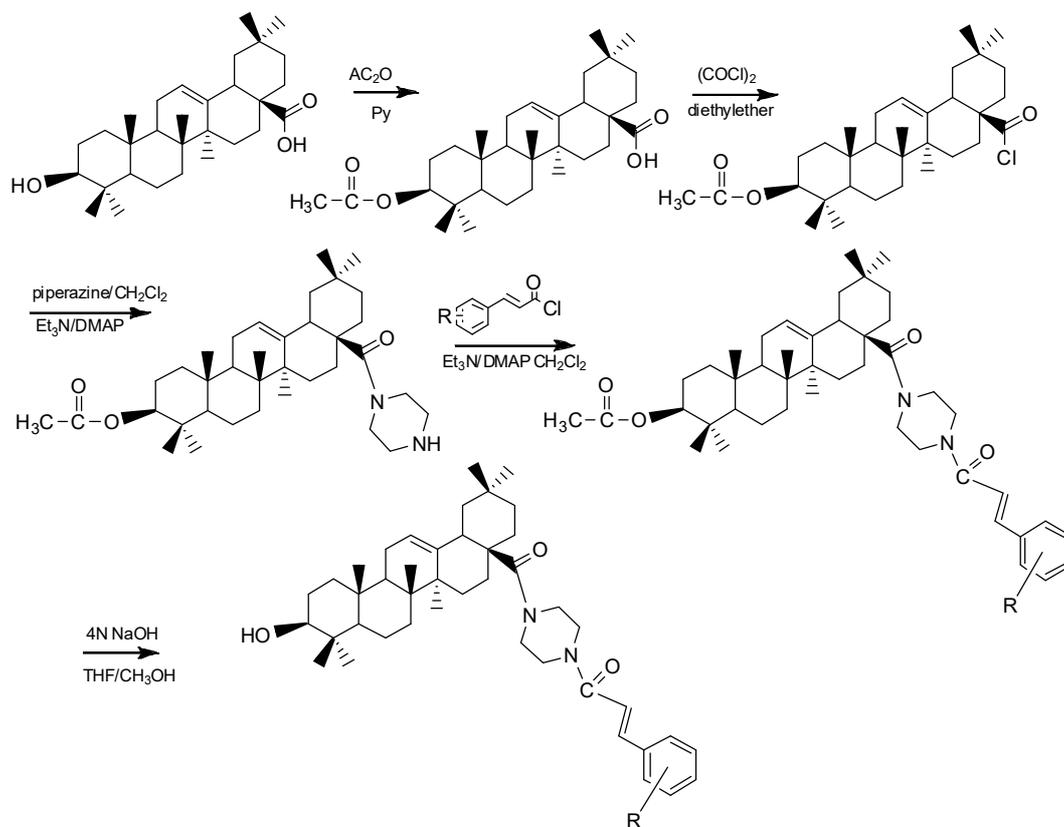
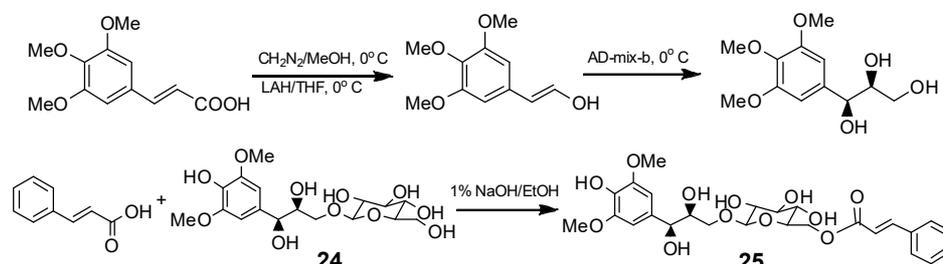


Fig 13. Synthesis of oleanolic acid derivatives

Fig 14. Synthesis of active compounds from *Hyssopus officinalis*; (7*S*, 8*S*)-syringoylglycerol-9-*O*-(6'-*O*-cinnamoyl)- β -D-glucopyranoside (**24**) and (7*S*, 8*S*) – syringoyl glycerol 9-*O*- β -D-glucopyranoside (**25**)

A series of α -glucosidase inhibitors with a core of oleanolic acid and with different ligands of cinnamic amide have been designed and synthesized. Nie et al. [32] reported that variations of cinnamic amide substitution significantly affect the α -glucosidase inhibitory activities. Most of the compound oleanolic acid derivatives show strong inhibitory activity against α -glucosidase.

Synthesis of the active α -glucosidase inhibitor compounds contained in the methanol extract of leaves of *Hyssopus officinalis*, which are (7*S*, 8*S*) –syringoyl glycerol-9-*O*-(6-*O*-cinnamoyl) - β -D-glucopyranoside (**24**) and (7*S*, 8*S*) –syringoyl glycerol 9-*O*- β -D-glucopyranoside (**25**) compounds, was carried out as in Fig. 14 [26].

Diabetes Mellitus

Diabetes mellitus is one of the metabolic disorder of carbohydrate metabolism, i.e. glucose conditions underutilized and causing hyperglycemia which is characterized by either insulin deficiency or insulin resistance, or both [33]. Type II diabetes is generally caused by obesity. Treatment of type II diabetes is done by prescribing diet and exercise, but it can also be treated with antidiabetic drugs [34].

Diabetes drugs are tailored to the causes of diabetes. There are several types of oral antidiabetic drugs that are commercially available. One of the antidiabetic drugs is used that has a function as a α -glucosidase inhibitor, as an example is an acarbose.

These drugs inhibit specific enzymes that decompose starch in the small intestine thereby delaying the absorption of glucose results in the breakdown of carbohydrates in the gut. α -Glucosidase is an inhibitor that reversibly binds to the α -glucosidase enzyme cells of the small intestine, an enzyme which is designed to divide disaccharides and oligosaccharides, thus preventing the digestion and absorption of carbohydrates, along with the small intestine [35].

α -Glucosidase Inhibitors

The α -glucosidase enzyme is a type of hydrolase enzyme that catalyzes the hydrolysis of the terminal non-reducing reaction of α -carbohydrates into glucose [36]. Carbohydrates are digested by enzymes in the mouth and intestines into simpler sugars are then absorbed into the body and increases blood sugar levels. With the denial of enzyme α -glucose, glucose levels in the blood can be returned within normal limits [37]. Inhibition of the α -glucosidase enzyme causes inhibition of glucose absorption. Compounds that can inhibit a α -glucosidase enzyme called α -glucosidase inhibitors (IAG). IAG compound is widely used for the treatment of type 2 diabetes patients [38]. These drugs work on a competitive basis in the digestive tract that can slow the absorption of glucose so it can reduce hyperglycemia. There are many α -glucosidase enzyme inhibitors that are effective such as acarbose, 1-deoxynorijimycin (consumed as herbal tea), miglitol, and voglibose resulting from microbial *Actinoplanes* strains SE 50 [39]. The α -glucosidase inhibitor is recommended as first-line therapy by The International Diabetes Federation (IDF) and the American Association of Clinical Endocrinologists (AACE). IAG's efficacy, safety, tolerability cardiovascular benefits, and lack of hypoglycemia makes them suitable for use for diabetics. IAG can be used as monotherapy, or part of combination therapy with other oral medications and insulin, as well as with the fixed-dose combination [40]. Some compounds of cinnamic acid derivatives which can be potential as α -glucosidase inhibitor are aegeline, aegelinoside A, aegelinoside B, anhydroaegeline, aloe resin, flavonol glycoside cinnamate, cinnamaldehyde, *p*-methoxy cinnamic acid, and *p*-methoxyethyl cinnamate.

CONCLUSION

Cinnamic acid, its derivatives, and analogs have potential as an antidiabetic drug candidate. Natural materials, such as aegeline, aloe resin A, and cinnamaldehyde, can inhibit the α -glucosidase enzyme. Tests carried out in vitro for inhibition of α -glucosidase using those natural materials produced better results

than that of existing commercial drug such as metformin and glibenclamide. The synthesis and modification of the structure of cinnamic acid are very influential in inhibitory activity against α -glucosidase. For example, the presence of a hydroxy or methoxy substitution at position 4 in the *trans*-cinnamic acid can increase the activity of the enzyme α -glucosidase inhibition. Replacement of 4-hydroxy cinnamic acid structures with methoxy functional groups can increase the activity of α -glucosidase inhibitors by 10 times. Likewise, the addition of the carboxylic group into ethyl ester group of cinnamic acid plays an important role in the inhibition of α -glucosidase.

Based on the articles summarized, many cinnamic acid derivatives have potential as antidiabetic agents but they are still not optimally utilized for the needs of antidiabetic drugs. Apart from all that, the necessary understanding of antidiabetic activity, especially the mechanism of action of compounds in inhibiting the enzyme α -glucosidase needs to be understood. Investigation more about cinnamic acid derivative compounds and techniques for modification of cinnamic acid compounds useful as inhibitors of α -glucosidase is important in the near future.

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CONFLICT OF INTEREST

We declare no conflict of interest.

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