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Potency of Genus *Cinnamomum* in Addressing Type 2 Diabetes: A Review

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Abstract: Nowadays, type 2 Diabetes Mellitus (T2DM) is denoted as prominent metabolic disorders worldwide and rank 6th of disease-associated death in Indonesia. Current T2DM medications are vary with their own benefits and drawbacks. The use of medicinal plants have their corridor in the treatment of diabetes because of significant results with less side effects compared to other medication. Among many herbs, genus *Cinnamomum* from Lauraceae family has broadly used as folklore medicine against chronic ailment like diabetes. This paper will review scientific finding related to potency of genus *Cinnamomum* as anti-T2DM. All data are obtained from ScienceDirect, Springer, PubMed, ResearchGate and Google Scholar that published in the last 20 years. At the beginning, the paper will indicate species of *Cinnamomum* which often studied for antidiabetic. Subsequently, each species will be identified phytochemistry which is bioactive compound that responsible for antidiabetic. Pharmacological properties comprising bioassay design and elaboration of molecular pathway will be discussed in the last part. This paper is expected to provide a reference for pharmaceutical research and clinical application of this genus in against T2DM.

Keywords: Antidiabetic, *Cinnamomum,* T2DM.

Introduction

Diabetes is a disease that requires special attention. Based on data from the Centers for Disease Control and Prevention (CDC), it is estimated that there are more than 463 million people with diabetes worldwide throughout 2022. In Indonesia, this case is also starting to receive special attention, where there are ± 20 million cases (Fatimah et al., 2020). There are two types of diabetes, but type-2 diabetes mellitus (T2DM) is the most common case. The T2DM is closely related to lifestyle, physical inactivity, aging, obesity and modernization (Galicia-Garcia et al., 2020; Wu et al., 2014).

Generally, T2DM is a metabolic disorder disease caused by imperfect insulin secretion from pancreatic islet β-cells, tissue insulin resistance and inadequate compensatory insulin secretory response (Galicia et al., 2020). Pathologically, insulin resistance refers to a decrease in biological regulation of insulin. This is manifested in a decrease in insulin and glucose sensitivity in peripheral tissues (Hao et al., 2020). The main manifestation in cases of insulin resistance refers to the mechanism of down-regulation, deficiency or genetic polymorphism of insulin receptor phosphorylation and IRS/PIP-3 kinase protein; moreover, it may also involve abnormal function of GLUT4 (Fargion et al., 2005). Counterregulatory hormones such as glucagon and catecholamines can contribute to insulin resistance if their secretory activity is too excessive (Masharani & German, 2017). In the case of insulin secretion, TNF-α plays an important role in inhibiting or disrupting signaling to insulin receptors (Abu Salem et al., 2020). TNF-α promotes an increase in pro-inflammatory cytokines so that the disruption of the expression of the type 4 glucose transporter (GLUT4) and also the induction of sirine phosphorylation on insulin receptor 1 substrates can act as a peripheral insulin inhibitor which leads to insulin resistance (Alzamil, 2020).

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There have been many drugs designed to medicate this T2DM (Chowdhury & Chakraborty, 2017); however, there are still side effect appearing. Tirzepatide is one of the new medicine treatment for diabetes and obesity, but its drug reaction profile has adverse effects. The most common side effects are like nausea, vomiting and diarrhea (Chavda et al., 2022). In order to support and avoid diabetes, using herbs and spices is the promising medical, specifically if it is integrated as culinary food (Ang, 2019).

Traditional medicine using plants is believed to provide therapeutic effects and improve health (Tan et al., 2018). Kayu manis (*Cinnamomum)* is one of those. The secondary metabolites produced by this plant have effects that can fight and increase insulin sensitivity (Kusumaningtyas et al., 2014). There are only 5 species from the genus *Cinnamomum* which can be classified as source of spices namely: *Cinnamomum burmannii, Cinnamomum cullilawan, Cinnamomum ceylon/zeylanicum/verum, Cinnamomum loureiroi/cassia/ Saigon* and *Cinnamomum cebuense*. The scientific literature search was perform from books and some database including ScienceDirect, Springer, PubMed, ResearchGate or Google Scholar. This paper was primarily expected to provide the main bioactive compounds and the pharmacological benefits of the genus Cinnamomum as anti-type 2 diabetes.

Results and Discussion

Bioactive compounds of *Cinnamomum*

It was reported that there were 20 terpenoids found (Figure 1). A study by Liu et al. (2021) reported caryophyllene [1] was found in the bark extract of *C. burmannii*. Constituent (+)-abscisic acid [2], β-sitostenone [3] and β-sitosterol [4] were successfully isolated by Li et al. (2012) from *C. burmannii* leaf extract. Meanwhile the same compound, caryophyllene [1] and another compound namely α-muurolene [5], ɣ-muurolene [6], α-terpineol [7], isoledene [8], and eucalyptol [9] were identified within *C. burmannii* bark extract (Budiastuti et al., 2021). Bark extract of *C. zeylanicum* (Alizadeh Behbahani et al., 2020), *C. loureiroi* (Qiao et al., 2021), and *C. cebuense* (Ragasa et al., 2013) contained β-caryophyllene [10]. Souza et al. (2021) isolated oleanolic acid [11] from *C. zeylanicum* bark extract. In addition, delta-cadinene [12] was isolated from both *C. verum* (Khanjari et al., 2023) dan *C. cassia* (Xu et al., 2022). Beside that, α-copaene [13] was isolated from *C. loureiroi* bark extract while α-terpineol [15] and humulene [14] was identified in *C. cebuense* bark extract. Moreover, β-caryophyllene [10], α-amyrin [16] and bauerenol [17] were confirmed in *C. cebuense* leaf extract (Liang et al., 2019).

Conclusions

The understanding of literacy as a dynamic social practice allows teachers and librarians to develop literacy programs that are more diverse, contextual and always seek to involve all stakeholders, both inside and outside the school. ICT literacy aims to introduce and provide skills to students in understanding and applying ICT in everyday life. The role of teachers and libraries in the development of students' ICT literacy is very influential on maximizing students' ICT literacy skills, this is especially important so that students are able and ready to face the challenges of an ever-evolving era.

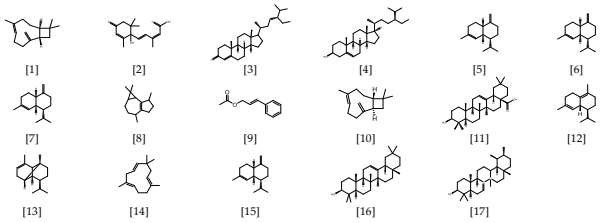

Figure 1. Terpenoid derivates isolated from the genus *Cinnamomum*

From 12 Phenylpropanoid derivatives, cinnamaldehyde [18] is the most frequently encountered compound, this compound was isolated by Souza et al. (2021), Nunes et al. (2022) and Khanjari et al. (2023) from the barks of *C. zeylanicum*, *C. cassia*, and *C. verum*. In addition, the isomer of cinnamaldehyde, namely (E)-Cinnamaldehyde [19] was also found in the bark extract of *C. zeylanicum* by (Benmoussa et al., 2023). Linalool [20] was synthesized from *C. zeylanicum.* Farag et al. (2018) managed to isolate several compounds from *C. verum* namely (E)-Cinnamaldehyde dimethylacetal [21] and (E)-o-Hydroxy-cinnamaldehyde [22]. Kim (2017) synthesized 2-hydroxycinnamaldehyde [23] from *C. cassia* barks. Espineli et al. (2014) isolated 4-hydroxy-3-methoxycinnamaldehyde [24] from the

bark of *C. cebuense*. Ragasa et al. (2013) isolated 4-hydroxy-3- methoxycinnamalde [25] from the bark of *C. cebuense*. Ramon (2012) isolated 5-(2-Propenyl)-1,3-benzodioxole [26] from the bark of *C. cebuense*. The chemical structure of this derivative can be seen in Figure 2.

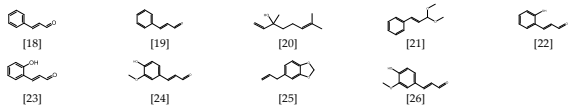

Figure 2. Components of phenylpropanoid derivatives isolated from the genus *Cinnamomum*

Phenolic were reported as the most isolated bioactive compounds then followed by terpenoids, phenylpropanoid, coumarin and other compounds. From the table there were 28 phenolic derivatives reported. Eugenol [27] was isolated by Liang et al. (2019) from *C. burmannii* barks, from *C. zeylanicum* barks by Mahomoodally et al. (2019), and from *C. cebuense* barks by Ramon (2012). Muhammad et al. (2021) isolated protocatechuic acid [28] from the bark extract of *C. burmannii*. Endo-borneol [29] and bornyl acetate [30] were found in the barks of *C. burmannii* by Liu et al. (2021). Astuti et al. (2022) isolated 1-(5-hydroxyisoquinoline-1- yl) ethanol [31] from the bark of *C. burmannii*. Li et al. (2012) synthesized p-hydroxybenzoic acid [32], syringic acid [33], vanillic acid [34], methyl vanillate [35] and kaempferol-3-O-rhamnoside [36] from the leaves of *C. burmannii*. Cinnamic acid [37] was isolated from *C. zeylanicum* barks (Muhammad et al., 2021), *C. zeylanicum* barks (de Souza et al., 2021), *C. verum* barks (Ibrahim Al Ahadeb, 2022), and *C. cassia* (Redondo et al., 2022). Sohilait (2016) synthesized methyl eugenol [38] and safrole [39] from *C. cullilawan* bark extract. In addition, safrole [39] was also found in the barks of *C. cebuense* by Ramon (2012). In the bark extract of *C. cullilawan*, 3,4-Methylenedioxybenzaldehyde (piperonal) was also found [40] which was isolated by Ngadiwiyana, (2013). Shahid et al. (2018) isolated gallic acid [41] from the bark of *C. zeylanicum*. de Souza et al. (2021) isolated proanthocyanidins [42] from the bark of *C. zeylanicum*. Phenethyl ester [43] was isolated by Ahadeb (2022) from the bark of *C. verum*. Ramon (2012) synthesized 4-allyl-2-methoxyphenol [44] from the bark of *C. cebuense*. The chemical structure of this derivative can be seen in Figure 3.

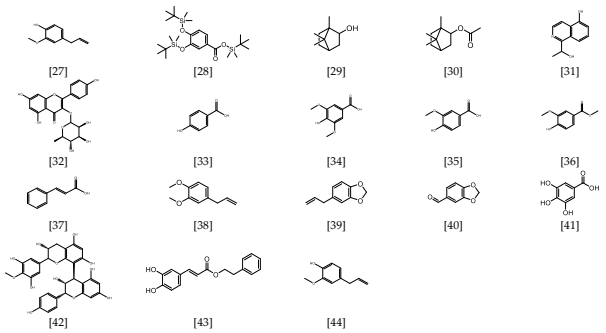

Figure 3. Components of phenolic derivatives isolated from the genus *Cinnamomum*

There were some other compounds found. Coumarins [45] were found in almost all Cinnamomum species, namely in *C. burmannii* barks extracted with n-butane, *C. verum* barks, *C. loureiroi* barks, and *C. cassia* barks, each synthesized by Liang et al. (2019), Redondo et al. (2022), (Ballin & Sørensen (2014), and Shinjyo et al. (2020). In addition, there is also p-coumaric acid [46] which was isolated by (Sharma et al., 2022) from the bark of *C. verum*. Lin et al. (2020) synthesized a new compound namely apocarotenoids 3-hydroxy-β-end [47] from the roots of *C. burmannii*. In the barks of *C. verum*, α-cubebene was found [48] by Khanjari et al. (2023), then myoinositol [49] by Sharma et al. (2022), Benzyl benzoate [50] by Qiao et al. (2021), and α -pinene [51] by (Monteiro et al., 2017). Y. Li et al. (2021) isolated α-copaene [52] and copaene [53] from *C. loureiroi* bark extract. α-guaiene [54] was isolated from the bark of *C. loureiroi* by Seshadri et al. (2020). Delta-terpinyl acetate [55] and camphene [56] were isolated from *C. cassia* barks by Benmoussa et al. (2023). Ramon (2012) synthesized trilinolein [57] from the roots of *C. cebuense*. Ragasa et al. (2013) isolated Squalene [58] from *C. cebuense* leaves. The chemical structure of this derivative can be seen in Figure 4.

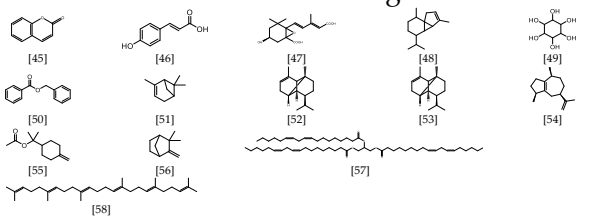

Figure 4. Other derived components isolated from the genus *Cinnamomum*

Table 1. Summary of isolated compounds from Genus *Cinnamomum*

Compound	Species	Reference	Compound	Species	Reference
Terpenoid					
Caryophyllene [1]	*C. burmannii*	(Liu et al., 2021),	Oleanolic [11]	*C. zeylanicum*	(Souza et al., 2021)
(+)-Abscisic acid [2]	*C. burmannii*	(Li et al., 2012)	Delta-cadinene [12]	*C. verum*	(Khanjari et al., 2023)
β-Sitostenone [3]	*C. burmannii*	(Li et al., 2012)	β -Caryophyllene [10]	*C. loureiroi*	(Qiao et al., 2021)
β-Sitosterol [4]	*C. burmannii*	(Li et al., 2012)	α-Copaene [13]	*C. loureiroi*	(Liang et al., 2019)
α-Muurolene [5]	*C. burmannii*	(Budiastuti et al., 2021)	Delta-cadinene [12]	*C. cassia*	(Xu et al., 2022)
γ-Muurolene [6]	*C. burmannii*	(Budiastuti et al., 2021)	Humulene [14]	*C. cebuense*	(Espineli et al., 2014), (Ragasa et al., 2013)
α-Terpineol [7]	*C. burmannii*	(Budiastuti et al., 2021)	α-Terpineol [15]	*C. cebuense*	(Ragasa et al., 2013)
Isoledene [8]	*C. burmannii*	(Budiastuti et al., 2021)	β-Caryophyllene [10]	*C. cebuense*	(Ragasa et al., 2013)
Eucalyptol [9]	*C. zeylanicum*	(Behbahani et al., 2020)	α-Amyrin [16]	*C. cebuense*	(Ragasa et al., 2013)
β-caryophyllene [10]	*C. zeylanicum*	(Behbahani et al., 2020)	Bauerenol [17]	*C. cebuense*	(Ragasa et al., 2013)
Phenylpropanoid					
Cinnamaldehyde [18]	*C. zeylanicum*	(de Souza et al., 2021)	(E)-O-Hydroxy-cinnamaldehyde [22]	*C. verum*	(Farag et al., 2018)
(E)-Cinnamaldehyde [19]	*C. zeylanicum*	(Benmoussa et al., 2023)	Cinnamaldehyde dimethyl acetate [21]	*C. loureiroi*	(Liang et al., 2019)
Linalool [20]	*C. zeylanicum*	(Kačániová et al., 2017)	2-Hydroxycinnamaldehyde [23]	*C. cassia*	(Kim, 2017)
Cinnamaldehyde [18]	*C. cassia*	(Nunes et al., 2022)	4-Hydroxy-3-methoxycinnamaldehyde [24]	*C. cebuense*	(Espineli et al., 2014)
Cinnamaldehyde [18]	*C. verum*	(Khanjari et al., 2023)	5-(2-Propenyl)-1,3-benzodioxole [25]	*C. cebuense*	(Ramon , 2012)
(E)-Cinnamaldehyde dimethyl acetate [21]	*C. verum*	(Farag et al., 2018)	4-Hydroxy-3- methoxy cinnamaldehyde [26]	*C. cebuense*	(Ragasa et al., 2013)
Phenolic					
Eugenol [27]	*C. burmannii*	(Liang et al., 2019)	Methyl eugenol [38]	*C. cullilawan*	(Sohilait, 2016)
Protocatechuic acid [28]	*C. burmannii*	(Muhammad et al., 2021)	Safrole [39]	*C. cullilawan*	(Sohilait, 2016)
Endo-borneol [29]	*C. burmannii*	(Liu et al., 2021)	3,4-Metilendioksibenzaldehid (piperonal) [40]	*C. cullilawan*	(Ngadiwiyana, 2013)
Bornyl acetate[30]	*C. burmannii*	(Liu et al., 2021)	Methyl eugenol [38]	*C. zeylanicum*	(Sedighi et al., 2018)
1-(5-Hydroxyisoquinoline-1- yl) ethanol [31]	*C. burmannii*	(Astuti et al., 2022)	Gallic acid [41]	*C. zeylanicum*	(Shahid et al., 2018)
Kaempferol-3-*O*-rhamnoside [32]	*C. burmannii*	(Li et al., 2012)	Proanthocyanidins [42]	*C. zeylanicum*	(de Souza et al., 2021)
p-Hydroxybenzoic acid [33]	*C. burmannii*	(Li et al., 2012)	Cinnamic acid [37]	*C. verum*	(Ahadeb, 2022)
Syringic acid [34]	*C. burmannii*	(Li et al., 2012)	Phenethyl ester [43]	*C. verum*	(Ahadeb, 2022)
Vanillic acid [35]	*C. burmannii*	(Li et al., 2012)	Cinnamic acid [37]	*C. cassia*	(Redondo et al., 2022)

Action mechanism of *Cinnamomum* as anti-T2DM

The potency of genus *Cinnamomum* to ameliorate type 2 diabetes mellitus (T2DM) has been assessed in silico, in vitro, in vivo and even clinical trial (Table 2). Molecular docking of epicatechin, *C. burmanii* main compound, showed strong (-6.2 Kcal/mol) molecular interactions with procaspase-9 compared to Saxaglipt (-5.6 Kcal/mol) as a control ligand. At in vivo study level, treatment of 10 µg/ml *C. burmanii* effectively reduced number of apoptotic cells in brain region (Kalsum et al., 2022). Water extract of *C. burmanii* exhibited inhibitory effect towards *α*-glucosidas with the best IC_{50} value 0.485 µg/mL which was very effective than standard drug acarbose with IC_{50} equaled to 103.35 µg/mL (Ervina et al., 2019). Meanwhile, two *Cinnamomum* bioactive compound namely cinnamaldehyde and eugenol regulated insulin signaling and glycogen synthesis. Eugenol promoted glycogen synthesis in primary astrocytes whereas the effect of cinnamaldehyde was attenuated. Treatment of cinnamon extract in ob/ob mice improved insulin action in the brain, enhance brain activity and locomotion as well as decrease liver fat and increase glucose homeostasis (Sartorius et al., 2014). Saifudin et al. (2013)reported that 5'-Hydroxy-5-hydroxymethyl-4″,5″-methylenedioxy-1,2,3,4-dibenzo-1,3,5-cycloheptatriene and trans-cinnamaldehyde inhibited protein tyrosine phosphatase 1B (PTP1B) with IC_{50} value 29.7 and 57.6 µM, respectively. PTP1B is a negative regulator of insulin signaling which is overexpressed in T2DM (Cho, 2013). Both constituents of *C. burmanii* may contribute to treat and/or prevent T2DM.

Alusinsing et al. (2014) assessed anti-hyperglichemia activity of *C. burmanii* in hyperglichemic mice-induced by sucrose. *C. burmanii* was able to reduce blood glucose level as well as inhibit *α*-glucosidase/amylase. This enzyme inhibition interfered carbohydrate hydrolysis into glucose (Poovitha & Parani, 2016). Treatment of *C. cassia* extract in T2DM animal model (C57BIKsj db/db) significantly decreased blood glucose level in dose dependent manner. Moreover, the same treatment increased serum insulin and HDL-cholesterol level but lowered concentration of triglyceride, total cholesterol and intestinal alpha-glycosidase activity (Kim et al., 2006). Study by Qin et al. (2003) proved that administration of 300 mg/kg BW cinnamon extract caused significantly higher glucose infusion rate (GIR) over control. However, no significant differences between treatment and control cohorts in the term of insulin receptor (IR)-beta, IR substrate (IRS)-1, and phosphatidylinositol (PI) 3-kinase protein content. Even though, insulin-signaling pathway in skeletal muscle was enhance in treatment group. Another study also support that 300 mg/kg/day of cinnamon extract prevent the development of insulin resistance (Qin et al., 2004).

At trial study, administration of 500 mg of *C. verum* capsules twice daily for 3 months in T2DM patients could improve anthropometric , glycemic, and lipids outcomes. Anthropometric comprising BMI, body fat, and visceral fat; glycemic comprising level of fasting plasma glucose (FPG), two hours postprandial glucose (2hpp), glycated

hemoglobin (Hb_{A1C}), fasting insulin, and insulin resistance; whereas lipid comprising total cholesterol, low density lipoprotein cholesterol (LDL-C) and low density lipoprotein cholesterol (HDL-C) (Zare et al., 2019). Treatment of cinnamon (*C. cassia*) water extract with the dose 250 mg/twice a day for 2 months also reduced fasting insulin, glucose, total cholesterol, and LDL cholesterol. Moreover, insulin sensitivity also enhanced in treatment group (Anderson et al., 2016). A mixture containing cinnamon, chromium and carnosine with the dose 1.2 g/day was proven to lower fasting plasma glucose in randomized, double-blind, placebo-controlled study (Liu et al., 2015). Both Vafa et al (2012) and Radhia et al (2010) reported supplementation of cinnamon could reduce blood glucose. In contrast, Mang et al. (2006) denoted that consuming cinnamon powder 3 g/day moderately reduce fasting plasma glucose concentrations. Even, no alteration of glucose level in diabetic patients after treated by cinnamon (*C. cassia*) reported by Hasanzade et al. (2013). Those different results of trial were due to different treatment respond in diverse population as indicated by Blevins et al. (2007).

Table 2. Bioactivity effect of *Cinnamomum* as anti-T2DM

Bioactivity Effect	Extract/ Compound		Dose/Affinity	Approach	Reference
Inhibit activity of phosphoenolpyruvate carboxy kinase (PEPCK)	*C. burmannii* bark		1.25 µg/mL	In vivo	(Kalsum et al., 2022)
			5 µg/mL		
			10 µg/mL		
	Saxagliptin (control)		-5.6 Kcal/mol	In silico	
	Epicatechin		-6.2 Kcal/mol		
	Caffeic Acid		-5.1 Kcal/mol		
	Cinnamaldehyde		-4.7 Kcal/mol		
	Trigonelline		-4.1 Kcal/mol		
Inhibit activity of α-glucosidase	*C. burmannii* bark	Extract 1	IC_{50} = 0.485 µg/mL	In vitro	(Ervina et al., 2019)
		Extract 2	IC_{50} = 0.632 µg/mL		
		Extract 3	IC_{50} = 0.608 µg/mL		
		Extract 4	IC_{50} = 0.705 µg/mL		
		Extract 5	IC_{50} = 0.760 µg/mL		
		Extract 6	IC_{50} = 0.822 µg/mL		
		Extract 7	IC_{50} = 0.900 µg/mL		
		Extract 8	IC_{50} = 1.044 µg/mL		
	Acarbose (control)		IC_{50} = 103.35 µg/mL		
Improvement of all anthropometric, glycemic, and lipids.	*C. verum* bark		500 mg/twice a day	Triple-blind placebo-controlled randomized clinical trial	(Zare et al., 2019)
Reduce fasting insulin, glucose, total cholesterol, and LDL cholesterol and enhance insulin sensitivity	Water extract of cinnamon (CinSulin®)		250 mg/twice a day	Placebo-controlled double-blind trial	(Anderson et al., 2016)
Decrease fasting plasma glucose	dietary supplement containing cinnamon, chromium and carnosine		1.2 g/day	Randomized, double-blind, placebo-controlled study	(Liu et al., 2015)
Reduce glycogen formation and diminish insulin-stimulated glycogen formation	Cinnamaldehyde		50 µM	In vitro	(Sartorius et al., 2014)
Enhance phosphorylation of GSK3 and ameliorate phosphorylation of AKT	Eugenol		500 µM		
Improve insulin sensitivity in the brain	*C. zeylanicum* bark		0.8 g/kg BW	In vivo	
Lower blood glucose level	*C. burmannii* bark		1.26/200g BW	In vivo	(Alusinsing et al., 2014)
			2.52/200 g BW		
			5.04/200g BW		
Inhibit protein tyrosine phosphatase 1B (PTP1B)	5'-Hydroxy-5-hydroxymethyl-4",5"-methylenedioxy-1,2,3,4-dibenzo-1,3,5 cycloheptatriene		IC_{50} = 29.7 µM	In vitro	(Saifudin et al., 2013)

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