Journal of Natural Medicines (2021) 75:449–466
https://doi.org/10.1007/s11418-021-01522-0

REVIEW

A review of antidiabetic active thiosugar sulfoniums, salacinol and neokotalanol, from plants of the genus *Salacia*

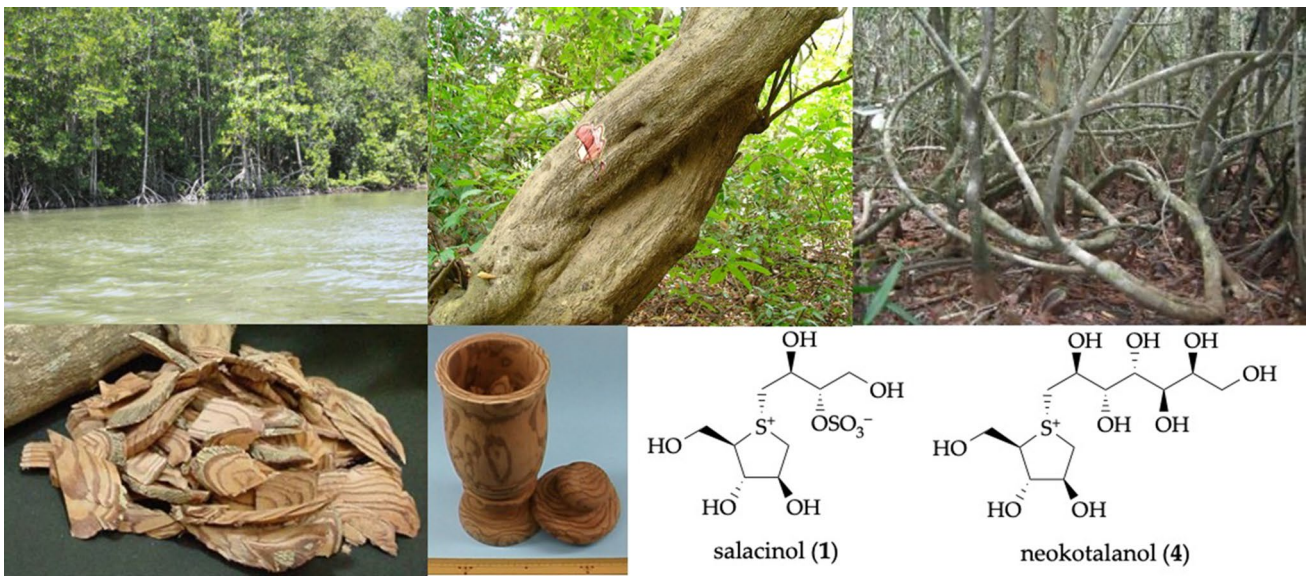
Toshio Morikawa[1,2] · Kiyofumi Ninomiya[1,2,5] · Genzoh Tanabe[1,3] · Hisashi Matsuda[4] · Masayuki Yoshikawa[1,4] · Osamu Muraoka[1,2,3]

Received: 20 March 2021 / Accepted: 20 April 2021 / Published online: 26 April 2021

Abstract

During our studies characterizing functional substances from food resources for the prevention and treatment of lifestyle-related diseases, we isolated the active constituents, salacinol (**1**) and neokotalanol (**4**), and related thiosugar sulfoniums, from the roots and stems of the genus *Salacia* plants [Celastraceae (Hippocrateaceae)] such as *Salacia reticulata* Wight, *S. oblonga* Wall., and *S. chinensis* L., and observed their antidiabetic effects. These plant materials have been used traditionally in Ayurvedic medicine as a specific remedy at the early stage of diabetes, and have been extensively consumed in Japan, the United States, and other countries as a food supplement for the prevention of obesity and diabetes. Here, we review our studies on the antidiabetic effects of plants from the genus *Salacia*, from basic chemical and pharmacological research to their application and development as new functional food ingredients.

Graphic abstract



Keywords *Salacia* · Salacinol · Neokotalanol · α-glucosidase inhibitor · Diabetes · Functional food

✉ Toshio Morikawa
morikawa@kindai.ac.jp

Extended author information available on the last page of the article

Introduction

Plants of the genus *Salacia,* classified as the Celastraceae (Hippocrateaceae) family [1], are widely distributed in Sri Lanka, India, Southeast Asia (*e.g.,* Thailand and Indonesia), and in torrid zone areas, such as Brazil [2–6]. According to The Plant List (www.theplantlist.org, accessed on March 16, 2021), 481 plants from *Salacia* genus, including *S. reticulata* Wight (an unresolved name), *S. oblonga* Wall. (an unresolved name, synonym of *Comocladia serrata* Blanco), and *S. chinensis* L. (an accepted name, synonyms of *S. prinoides* Willd. DC. and *Tontelea prinoides* Willd.), are recorded [1]. These *Salacia* plants are termed locally as "Kotala himbutu" in Singhalese for *S. reticulata*; "Chundan" in Tamil and "Ponkoranti" in Malayalam for *S. oblonga*; and "Kam Phaeng Chetchan" in Thai for *S. chinensis* [2, 7]. Their roots and stems have been used extensively for thousands of years in traditional medicines for the treatment of rheumatism, gonorrhea, and skin diseases. In the Ayurvedic system [8–10] and in Thai traditional medicine [11], they have also been used as a remedy at the early stage of diabetes. Traditionally, in Sri Lanka, aqueous extract was prepared by storing water overnight in mugs made from the root and stem parts of *S. reticulata* (Fig. 1). Throughout the course of our studies characterizing functional substances from food resources for the prevention and treatment of lifestyle-related diseases, our research group has focused on the antidiabetic effects of plants from the genus *Salacia* since the mid-1990s. Before we began our research, data on the in vivo hypoglycemic activities of extracts from *S. reticulata* [12, 13], *S. oblonga* [14], and *S. chinensis* [15] had been reported. However, at that time, the active constituents, and the mechanisms underlying the antidiabetic effects of plants from the genus *Salacia* had not yet been characterized. Here, we review our studies on the antidiabetic effects of plants from the genus *Salacia*, from basic chemical and pharmacological research to their application and development as new functional food ingredients. Particularly, we focus on and describe active constituents with antidiabetic activity, including salacinol (**1**), neosalacinol (**2**), kotalanol (**3**), neokotalanol (**4**), and related analogs (**5**–**8**), which are unique thiosugar sulfonium constituents with a novel class of α-glucosidase inhibitors from plants of the *Salacia* genus (Fig. 2).

Fig. 1 A mug made from the roots and stems of *Salacia reticulata* in Sri Lanka

Search for active antidiabetic constituents

Suppressive effects of the methanol extract from the roots and stems of *S. reticulata* on postprandial blood glucose elevation in sugar-loaded rats

According to "9th Edition of The International Diabetes Federation (IDF) Atlas", diabetes is one of the fastest growing global health emergencies of the twenty-first century. In 2019, an estimated 463 million individuals had diabetes, and this number is projected to reach 578 million by 2030, and 700 million by 2045 [16]. Type 2 diabetes mellitus, or non-insulin-dependent diabetes mellitus, is a chronic metabolic disorder characterized by symptoms such as hyperglycemia, insulin resistance, and relative insulin deficiency [17]. Chronic hyperglycemia can lead to long-term complications, such as cardiovascular and renal disorders, retinopathy, and poor blood flow. The development of type 2 diabetes mellitus can be prevented or delayed in individuals with impaired glucose tolerance by implementing lifestyle changes or through the use of therapeutic agents [18]. Through wide in vivo screening trials, we have identified extracts and their constituents isolated from several natural resources, including *Kochia scoparia* [19], *Borassus flabellifer* [20], *Solanum lycocarpum* [21], *Sinocrassula indica* [22], *Shorea roxburghii* [23], *Cistanche tubulosa* [24, 25], and *Helichrysum arenarium* [26], which could suppress elevated blood glucose levels in sugar-loaded rats and/or mice models. Our search for antidiabetic principles from plants of the genus *Salacia* began following the discovery of the suppressive effects of a methanol extract prepared from the roots and stems of *S. reticulata* (collected in Sri Lanka) on elevated blood glucose levels in maltose- and sucrose-loaded rats at a dose of 50 mg/kg (*p.o.*); the extract did not affect glucose-loaded rats up to 200 mg/kg (*p.o.*) [2, 28]. In addition, the extract did not exhibit hypoglycemic activity in alloxan-induced insulin-dependent diabetic mice following a single

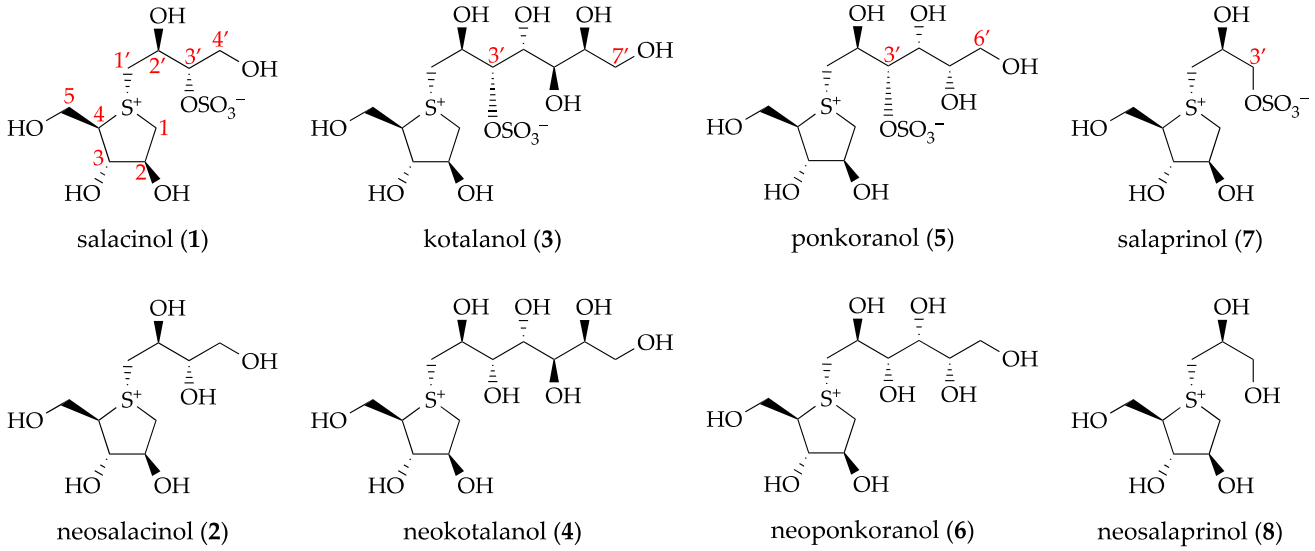


Fig. 2 Structures of salacinol (**1**), neosalacinol (**2**), kotalanol (**3**), neokotalanol (**4**), and related constituents (**5**–**8**)

administration of 3000 mg/kg (*p.o.*) [2, 28]. To characterize the mechanism underlying the suppression of postprandial glucose activity, the inhibitory effects on small intestinal *a*-glucosidases, such as maltase and sucrase, were evaluated using rat small intestinal brush border membrane vesicles as an enzymatic mixture. Consequently, the extract inhibited the enzymatic activity of both maltase (IC_{50} = 42 μg/mL) and sucrase (IC_{50} = 32 μg/mL). Thus, the *S. reticulata* extract was characterized as having *α*-glucosidase inhibitory activity, which inhibited the hydrolysis of oligosaccharides, such as maltose and sucrose, to glucose [2, 27, 28].

Unique thiosugar sulfonium sulfates, salacinol (1) and kotalanol (3), were isolated as the active principles by bioassay-guided separation using the maltase and sucrase inhibitory activities

Our first experiments evaluated the fractionation and isolation of the antidiabetic principles from extracts, including solvent distribution and filtration, column chromatography, and preparative HPLC; these procedures are summarized in Fig. 3. Thus, the active MeOH-soluble fraction (IC_{50} = 30 μg/mL for maltase and 18 μg/mL for sucrase) was subjected to normal-phase silica gel column chromatography to obtain eight fractions. Among these, fractions 3–6 presented maltase inhibitory activity (IC_{50} = 35–72 μg/mL), while fractions 2–5 presented sucrase inhibitory activity (IC_{50} = 6.7–60 μg/mL). Further separation and purification procedures using ODS and NH column chromatography, and finally preparative HPLC, isolated the active constituents salacinol (**1**) [27, 28] and kotalanol (**3**) [29] (Fig. 2), along with several sugars and sugar alcohols, including D-glucose, D-fructose, dulcitol, glycerol, sucrose, 3-*O*-*α*-D-galactopyranosyl(1 → 6)-*O*-*β*-galactopyranosyl-*sy*-glycerol, galactinol, and stachyose. Because the oligosaccharides as substrate for the enzymatic activities and D-glucose were obtained from the active fractions such as fractions 2–6, the condensation of the maltase and sucrase inhibitory activities of those fractions were not observed as much as the condensation of the active isolates (**1** and **3**). The structure of salacinol (**1**) was elucidated based on physicochemical evidence, including the NMR assignments, using several spectroscopy measurements and application of the deuterium shift rule to facilitate the locations of free hydroxy groups. Alkaline treatment of salacinol (**1**) with sodium methoxide gave 1-deoxy-4-thio-D-arabinofuranose (**1a**), which was identical to the synthesis from D-xylose. Finally, the absolute stereostructure was elucidated by X-ray crystallographic analysis, which showed that the unique spiro-like configuration of the inner salt was comprised of 1-deoxy-4-thio-D-arabinofuranosyl sulfonium cation and 1′-deoxy-D-erythrosyl-3′-sulfate anion [27, 28]. The stereostructure of kotalanol (**3**) was also characterized [29, 30]. To our knowledge, 5-thio-D-mannose was hitherto isolated from a marine sponge as the only naturally occurring thiosugar [31], and these compounds (**1** and **3**) are the first examples of sulfonium-type thiosugars in nature.

A series of other thiosugar sulfonium constituents, neosalacinol (2), neokotalanol (4), and related isolates (5–8) from plans of the genus *Salacia*

As described above, a unique thiosugar sulfonium sulfate salacinol (**1**), which had a sulfated C4 polyol side chain connected at the sulfonium moiety, was first isolated from the methanol extract of *S. reticulata* and subject to structure

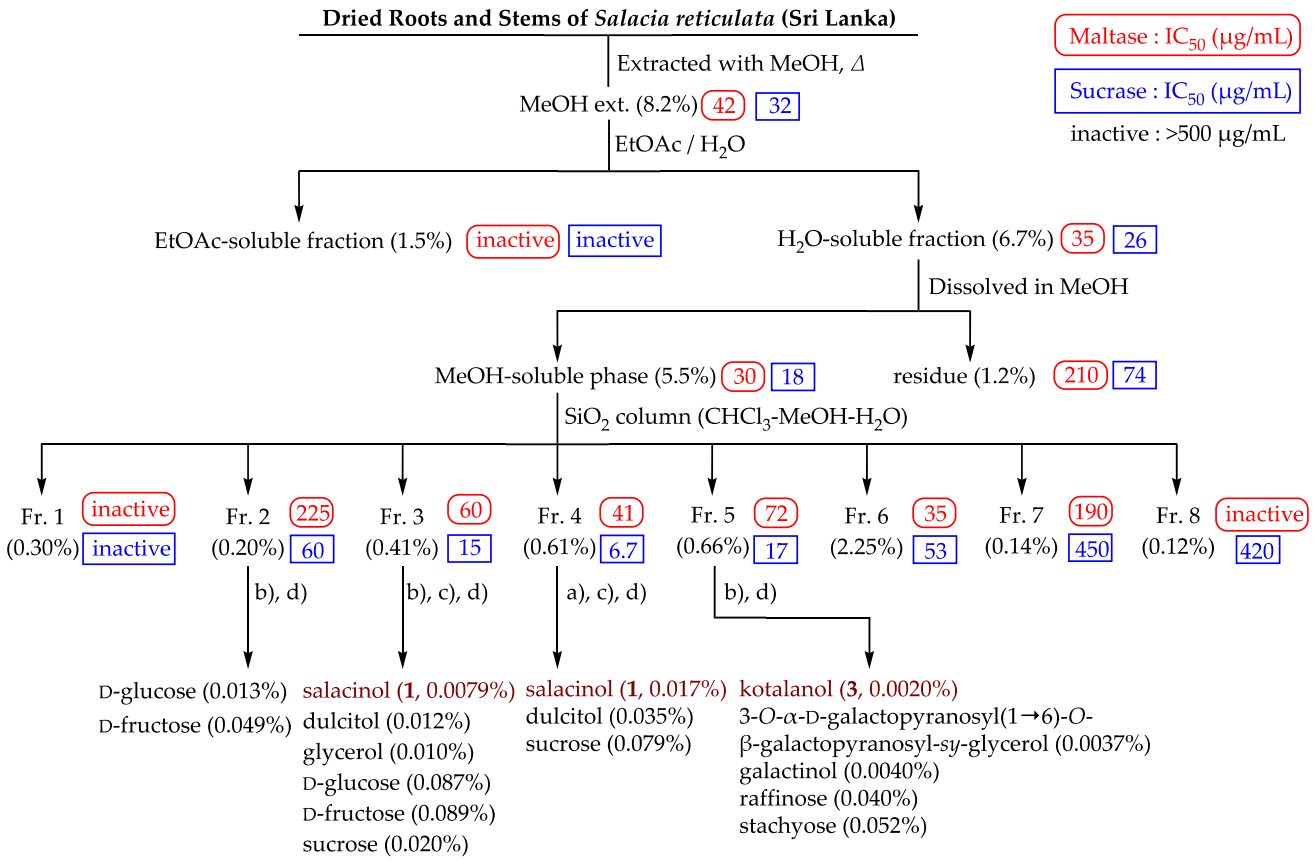


Fig. 3 Bioassay-guided separation from *S. reticulata* using the maltase and sucrase inhibitory activities. *conditions:* **a** ODS column (MeOH–H_2O); **b** NH column (CH_3CN–H_2O); **c** HPLC [detection: refractive index, column: Shodex SUGAR SC1011 (Ca^{2+}) and SUGAR SP0810 (Pb^{2+}) for ligand-exchange chromatography, mobile phase: H_2O, column temperature: 80 °C]; **d** HPLC [detection: refractive index, column: YMC-Pack Polyamine II, mobile phase: CH_3CN–H_2O solvent system]. Reproduced in part with permission from *Bioorg. Med. Chem.*, **10**, 1547–1554. Copyright [2002] Elsevier

determination, in 1997 [27, 28]. The related analog of **1** elongated the polyol side chain to C7, kotanlanol (**3**), and was isolated from the same plant resource in 1998 [29, 30]. Subsequently, **1** and **3** were isolated from the 80% aqueous methanol extract of *S. oblonga* in 1999 [32] and from the methanol extract of *S. chinensis* (*syn. S. pronoides*) in 2008 [33]. From *S. chinensis*, other related thiosugar sulfonium sulfates, ponkoranol (**5**) and salaprinol (**7**), were obtained, which have a sulfated C6, and C3 polyol side chains connected at the sulfonium moiety, respectively [33]. In addition, the desulfonated analogs of these sulfate ester constituents (**1**, **3**, **5**, and **7**), named neosalacinol (**2**) [35], neokotalanol (**4**) [35], neoponkoranol (**6**) [36, 37], and neosalaprinol (**8**) [36, 37], which presented higher polarity than each corresponding 3′-*O*-sulfate ester, were also obtained from the hot water extracts of genus *Salacia* plants. Thus, we optimized the practical isolation protocol by using the stems of *S. chinensis* originating in Thailand, and performing hot water extraction. The results demonstrated that we have established practical isolation procedures for **1**–**4**, as shown in Fig. 4 [34].

Thiosugar sulfoniums (1–6) as a novel class of *α*-glucosidase inhibitors

As shown in Table 1, salacinol (**1**) and kotalanol (**3**) were found to inhibit maltase, sucrase, and isomaltase inhibitory activities against rat small intestinal *α*-glucosidase (IC_{50} = 6.0, 1.3, and 1.3 μM for **1**; 2.0, 0.43, and 1.8 μM for **3**, respectively) [37]. The maltase inhibitory activities of **1** were weaker than those of acarbose and voglibose (1.7 and 1.3 μM, respectively) and equivalent to that of miglitol (8.2 μM). Regarding sucrase inhibitory activity, **1** (1.3 μM) demonstrated equivalence to acarbose (1.5 μM), whereas the isomaltase inhibitory activity was more potent than those of acarbose, voglibose, and miglitol (1.5, 0.22, and 0.43 μM, respectively). However, the common thiosugar moiety 1-deoxy-4-thio-D-arabinofuranose (**1a**) did

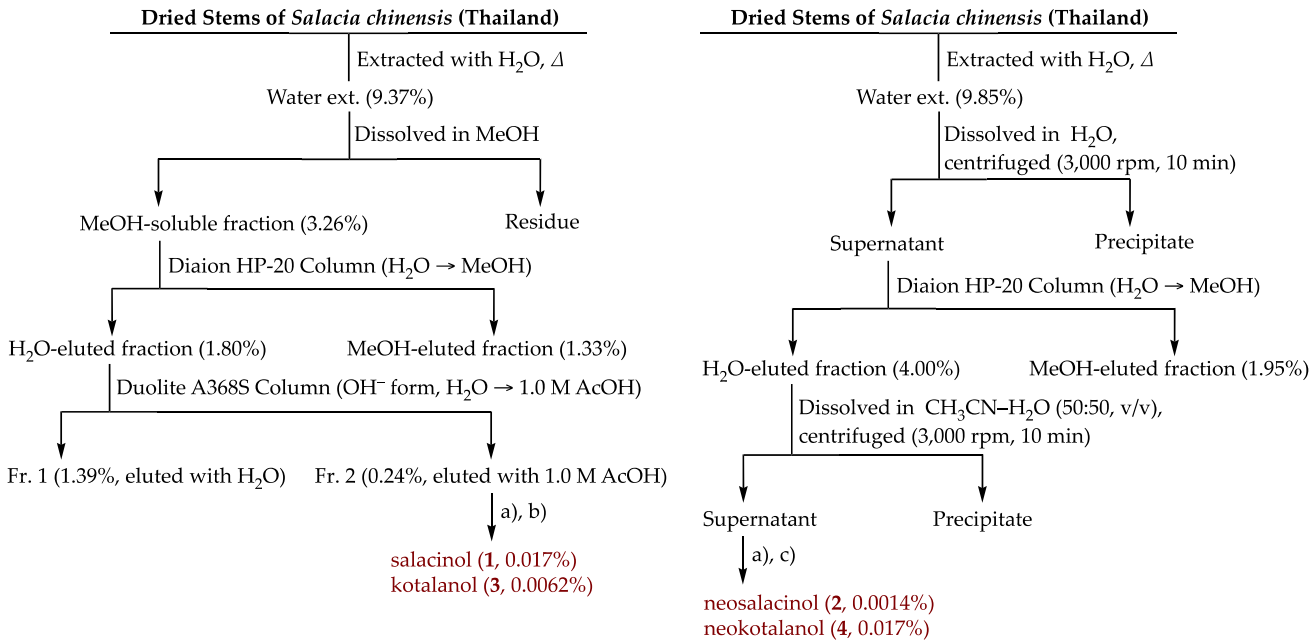


Fig. 4 Practical isolation protocols of the principal thiosugar sulfoniums (**1**–**4**) from the stems of *S. chinensis*. *conditions:* **a** NH column (CH_3CN–H_2O), **b** HPLC [detection: refractive index, column: Cosmosil Sugar-D, mobile phase: CH_3CN–H_2O solvent system], and **c** HPLC [detection: refractive index, column: Daisopak-SP-120-5-ODS-BP, mobile phase: H_2O and/or 0.1% (v/v) aqueous AcOH]. Reproduced in part with permission from *J. Pharm. Biomed. Anal.*, **52**, 770–773. Copyright [2010] Elsevier and *J. Nat. Med.*, **65**, 142–148. Copyright [2011] Springer Nature

Table 1 IC_{50} values of thiosugar sulfoniums (**1**–**8** and **1a**), acarbose, voglibose, miglitol, and 1-deoxynojirimycin against α-glucosideses from rat small intestine, *Saccharomyces cerevisiae*, and *Bacillus stearothermophilus*

	IC_{50} (μM) [(μg/mL)]						
	Rat[a]			*Saccharomyces cerevisiae*[b]		*Bacillus stearothermophilus*[c)]	
	Maltase	Sucrase	Isomaltase	Maltase	Sucrase	Maltase	Sucrase
Salacinol (**1**)	6.0 [2.0]	1.3 [0.42]	1.3 [0.44]	> 100	> 100	> 100	> 100
Neosalacinol (**2**)	22.2 [5.7]	2.5 [0.65]	0.68 [0.17]	> 100		> 100	
Kotalanol (**3**)	2.0 [0.86]	0.43 [0.18]	1.8 [0.78]	> 100		> 100	
Neokotalanol (**4**)	1.6 [0.54]	1.5 [0.53]	0.46 [0.16]	> 100	> 100	> 100	> 100
Ponkoranol (**5**)	5.6 [2.2]	0.41 [0.16]	4.6 [1.8]	> 100		> 100	
Neoponkoranol (**6**)	5.1 [1.6]	1.0 [0.32]	1.4 [0.43]	> 100		> 100	
Salaprinol (**7**)	> 329 [> 100]	> 329 [> 100]	14 [4.4]				
Neosalaprinol (**8**)	> 444 [> 100]	90 [20]	6.5 [1.5]				
1a	[> 400]	[> 400]					
Acarbose	1.7 [1.1]	1.5 [1.0]	645 [417]	> 100	> 100	0.20 [0.13]	0.021 [0.014]
Voglibose	1.3 [0.34]	0.22 [0.060]	2.2 [0.58]	> 100	> 100	> 100	> 100
Miglitol	8.2 [1.7]	0.43 [0.090]	4.6 [0.96]	> 100	> 100	> 100	> 100
1-Deoxynojirimycin	0.67 [0.11]	0.12 [0.020]	0.26 [0.042]	> 100	> 100	84.3 [13.8]	2.4 [0.39]

α-Glucosidase inhibitory activity: [a]Rat small intestinal brush border membrane vesicles, [b]*Saccharomyces cerevisiae* (purchased from Sigma-Aldrich Co., LLC, St. Louis, USA), or [c]*Bacillus stearothermophilus* (purchased from Sigma-Aldrich) in 0.1 M maleate buffer (pH 6.0) was prepared as an enzyme solution, respectively. A substrate solution in the maleate buffer (maltose or sucrose: 74 mM; isomaltose: 7.4 mM, 50 µL), the test sample solution (25 µL), and the enzyme solution (25 µL) were mixed at 37 °C for 30 min and then immediately heated in boiling water for 2 min to stop the reaction. The glucose concentrations were determined using the glucose-oxidase method. The IC_{50} value was determined graphically by plotting the percent inhibition *vs*. log of the test compound. Each value represents the mean of two–four experiments. Commercial acarbose, voglibose, miglitol, and 1-deoxynojirimycin were purchased from FUJIFILM Wako Pure Chemicals Co. (Osaka, Japan)

Reproduced in part with permission from *Phytochem. Anal.*, **25**, 544–550. Copyright [2014] Jhon Wiley & Sons, Ltd

not present this activity (each IC_{50} value > 400 μg/mL for maltase, sucrase, and isomaltase). These data indicated that the sugar alcohol side chain connecting the sulfonium parts was essential for the activity. To examine how **1** and **3** inhibited maltase, sucrase, and isomaltase, small intestinal brush border membrane vesicles were incubated with increasing concentration of maltose (3.1–37 mM, K_m = 2.7 mM), sucrose (4.6–37 mM, K_m = 20 mM), and isomaltose (0.46–3.7 mM, K_m = 4.5 mM). The results plotted according to the Lineweaver–Burk revealed fully competitive inhibition on each α-glucosidase, and the K_i values were 0.31, 0.32, and 0.47 μg/mL for **1**; and 0.23, 0.18, and 1.8 μg/mL for **3**, respectively [28, 29].

Furthermore, we have also evaluated the inhibitory activities of the active sulfoniums (**1**–**6**) against human intestinal maltase [38]. As shown in Table 2, **1** (IC_{50} = 4.9 μM), **2** (9.0 μM), **3** (3.9 μM), **4** (3.9 μM), **5** (5.0 μM), and **6** (4.0 μM) inhibited the enzymatic activities of maltase, with almost equivalent activity to miglitol (3.7 μM) and greater potency than acarbose (15.2 μM). According to the Lineweaver–Burk plot, inhibition was characterized as being fully competitive,

Table 2 IC_{50} and K_i values of principal thiosugar sulfoniums (**1**–**6**), acarbose, voglibose, miglitol, and 1-deoxynojirimycin against human small intestinal maltase

	IC_{50} (μM)	K_i (μM)
Salacinol (**1**)	4.9	0.44
Neosalacinol (**2**)	9.0	1.2
Kotalanol (**3**)	3.9	0.32
Neokotalanol (**4**)	3.9	0.33
Ponkoranol (**5**)	5.0	0.32
Neoponkoranol (**6**)	4.0	0.70
Acarbose	15.2	2.6
Voglibose	1.3	0.17
Miglitol	3.7	0.57
1-Deoxynojirimycin	0.96	0.071

Maltase inhibitory activity: Human small intestinal microsome (batch MIC318017, purchased from BIOPREDIC International, Rennes, France) in 0.1 M maleate buffer (pH 6.0) was prepared as an enzyme solution. A substrate solution in the maleate buffer (maltose: 74 mM, 50 μL), the test sample solution (25 μL), and the enzyme solution (25 μL) were mixed at 37 °C for 30 min and then immediately heated in boiling water for 2 min to stop the reaction. The glucose concentrations were determined using the glucose-oxidase method. The IC_{50} value was determined graphically by plotting the percent inhibition *vs*. log of the test compound. Each value represents the mean of four experiments. Commercial acarbose, voglibose, miglitol, and 1-deoxynojirimycin were purchased from FUJIFILM Wako Pure Chemicals Co. (Osaka, Japan)

Kinetic analysis: The enzyme and test samples (1.0–4.0 μM: acarbose; **1** and **3**: 0.5–2.0 μM; **2**–**6** and miglitol: 0.25–1.0 μM; 0.10–0.40 μM: voglibose) were incubated with increasing concentrations of maltose (3.0–10.6 mM)

Reproduced in part with permission from *Nutrients*, **7**, 1480–1493. Copyright [2015] MDPI

and the K_i values of **1**–**6** were 0.44, 1.2, 0.32, 0.33, 0.32, and 0.70 μM, respectively.

To date, several research groups have performed synthetic and structure–activity relationship (SAR) studies of salacinol (**1**) and related analogues regarding α-glucosidase inhibitory activity [39–55]. We are also performing subsequent studies on the total syntheses of these sulfonium constituents (**1–8**) and their highly active analogues, as well as more detailed SAR studies [38, 56–62]; those data will be summarized separately.

Terpenoid and polyphenol constituents with aldose reductase inhibitory activity

Aldose reductase is a key enzyme that catalyzes the reduction of glucose to sorbitol in the polyol processing pathway. In normal tissue, aldose reductase has low substrate affinity to glucose, such that the conversion of glucose to sorbitol is little catalyzed. However, in diabetes mellitus, the increased availability of glucose in insulin-insensitive tissues (*e.g.*, lens, nerve, and retina) enhances the formation of sorbitol through the polyol pathway. Sorbitol dose not readily diffuse across cell membranes and thus accumulate intracellularly. The intracellular accumulation of sorbitol has been implicated in the chronic complications of diabetes, including cataracts, neuropathy, and retinopathy. These findings suggest that aldose reductase inhibitors have the capacity to prevent and treat such diabetic complications. Previously, we reported several aldose reductase inhibitors obtained from natural resources, such as flavonoids [63–69], stilbenoids [23, 65], quinic acid derivatives [68], and phenylthanoids [24]. As a continuation of the above study, several polyphenol constituents with aldose reductase inhibitory activity from *S. reticulata* [70], *S. oblonga* [32], and *S. chinensis* [71, 72] were further explored. We also investigated the inhibitory effect of the 80% aqueous methanol extracts of *S. oblonga* and *S. chinensis* against aldose reductase (IC_{50} = 3.4 and 3.6 μg/mL, respectively) [32, 71]. As shown in Fig. 5, several terpenoids including 14 friedelane-type (**9**–**22**), five oleanane-type (**23**–**27**), two ursane-type (**28** and **29**), and six nor-friedelane-type triterpenes (**30**–**35**) and squalene, two abietane-type diterpenes (**36**, **37**), and three acylated eudesmane-type sesquiterpenes (**38**–**40**), polyphenols including an xanthone, mangiferin (**41**), three lignans (**42**–**44**), two flavones (**45** and **46**), and six flavan-3-ols (**47**–**52**), 13 sugar derivatives, and a cyclitol, *myo*-inositol, were isolated from genus *Salacia* plants [28, 32, 33, 70–73]. Oleanane-type triterpenes, feidelane-3-one-29-ol (**17**, IC_{50} = 98 μM), maytenfolic acid (**23**, 72 μM), and 3*β*,22*β*-dihydroxyolean-12-en-29-oic acid (**24**, 26 μM), norfriedelane-type tritepenes, tingrnine B (**32**, 7.0 μM), tingenone (**33**, 13 μM), regeol A (**34**, 30 μM), and triptocalline A (**35**, 14 μM), an acylated eudesmane sesquiterpene celahin C (**38**, 95 μM), and a

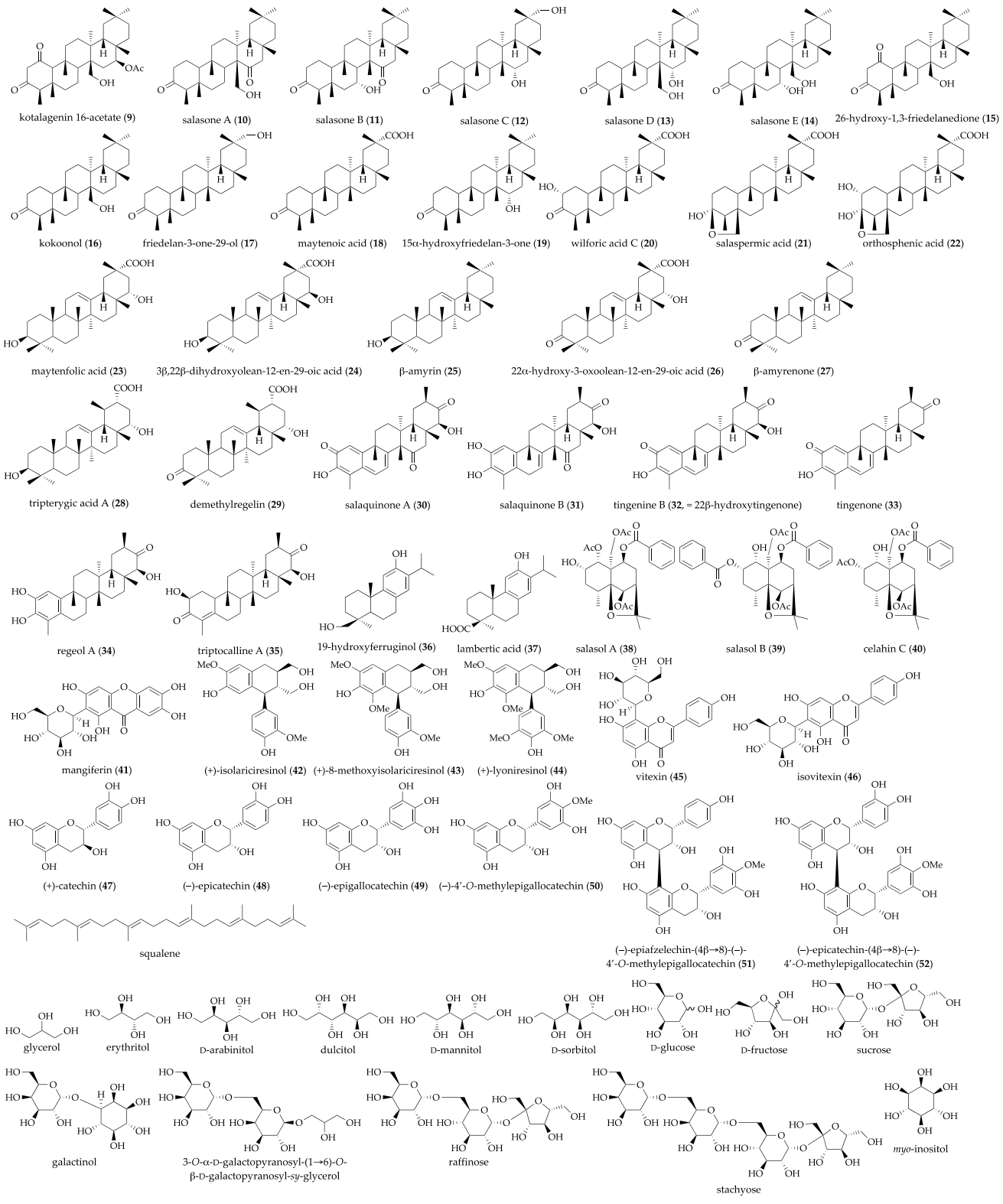


Fig. 5 Terpenoid, polyphenol, and polyol constituents isolated from plants of the genus *Salacia*

xanthone mangiferin (**41**, 3.2 μM), were found to exhibit the inhibitory effects of the constituents on aldose reductase (Table 3) [72]. Among those, mangiferin (**41**) was suggested to be the most active constituent in the extract of plants from the genus *Salacia* against aldose reductase [70]. However, the inhibitory activity was moderate compared with that of a clinically used aldose reductase inhibitor epalrestat (0.0072 μM); therefore, the contribution of aldose reductase inhibitory activity on the antidiabetic effect of plants from the genus *Salacia* is limited.

Quantitative evaluation of principal sulfonium constituents as characteristic marker molecules

As discussed, we previously investigated the suppressive effects of the methanol extract from the roots and stems of *S. reticulata* on the elevated blood glucose levels in maltose- and sucrose-loaded rats [2, 28]. We have also demonstrated the antihyperglycemic effects of the 80% aqueous methanol extracts from *S. oblonga* and *S. chinensis,* as well as *S. reticulata* using the same sugar-loaded animal models [2, 71]. Based on these findings, interest in *Salacia* as a possible nutraceutical product for patients with diabetes and/or prediabetes is increasing. Thus, there has been a high demand for efficient quality control measures to ensure the authenticity and active contents of these products, and to verify the claims on product labels. Therefore, to evaluate the quality of *Salacia* extracts for antidiabetic effects, quantitative analyses of sulfonium constituents (**1**–**8**) have been developed as two separate protocols using LC–MS. The sulfonated derivatives (**1**, **3**, **5**, and **7**) were obtained using an Asahipak NH2P-50 column (Showa Denko K.K., Tokyo, Japan) with an acetonitrile–water solvent system (78:22, v/v) as a mobile phase, associated with negative-ion electrospray ionization mass (ESI–MS) sources (*m/z* 333, 423, 393, and 303 $[M - H]^-$, respectively) [34, 37]. The de-*O*-sulfonate derivatives (**2**, **4**, **6**, and **8**) were established by ion pair chromatography using an ODS column with 5 mM aqueous undecafluorohexanoic acid–MeOH (99:1, v/v) as the mobile phase and positive-ion ESI–MS measurement (*m/z* 255, 345, 319, and 225 $[M]^+$, respectively) [35, 37]. Using the established protocols, a variety of *Salacia* samples collected in different geographical regions (*e.g.,* Sri Lanka, India, and Thailand), as well as their distribution in each part of the plant, including the stems, roots, leaves, and fruit, were evaluated. The distribution of sulfoniums (**1**–**8**) in the stems and roots of these plants differed between the collection areas. Among these, neokotalanol (**4**) was the major compound in samples from Thailand, whereas salacinol (**1**) was the major compound in samples from Sri Lanka and India. Regarding differences in the characteristic distributions between plant parts, the sulfoniums were only present in trace amounts in the leaf and fruit parts. [34, 35, 37]. An effort was made to discriminate the *Salacia* plant species based on the DNA sequence of the internal transcribed spacer (ITS) region in the nuclear ribosomal RNA gene in an authentic specimen, and a genotype characteristic of *S. chinensis*, which is distinguishable from those of *S. reticulata* and *S. oblonga* was identified [74]. Correlations between the total content of four principal sulfoniums (**1**–**4**) and the maltase and sucrase inhibitory activities ($1/IC_{50}$) of the corresponding extracts from the stems of *S. chinensis* were plotted. Strong correlations were observed between the total content (%, reduced value to **4**) and inhibitory activity ($R = 0.959$ for maltase and 0.795 for sucrase) [35]. Furthermore, when ponkoranol (**5**) and neoponkoranol (**6**) were plotted in addition to total sulfonium (**1**–**6**), these correlations were found to be stronger and almost fully explained both the maltase ($R = 0.954$) and the sucrase ($R = 0.929$) inhibitory activities of the extract (Fig. 6). Thus, these practical LC–MS methods for the quantitative determination of sulfoniums with potent α-glucosidase inhibitory activity could be readily utilized for the evaluation of genus *Salacia* plants.

Table 3 Inhibitory effects of constituents from plants of the genus *Salacia* on rat lens aldose reductase

	IC_{50} (μM)
Friedelan-3-one-29-ol (**17**)	98
Maytenfolic acid (**23**)	72
3β,22 β-Dihydroxyolean-12-en-29-oic acid (**24**)	26
Tingenine B (**32**)	7.0
Tingenone (**33**)	13
Regeol A (**34**)	30
Triptocalline A (**35**)	14
Celahin C (**38**)	95
Mangiferin (**41**)	3.2
Epalrestat	0.0072

Aldose reductase inhibitory activity: The supernatant fluid of a rat lens homogenate was used as a crude enzyme. The incubation mixture contained 180 mM Na, K-phosphate buffer (pH 7.0), 100 mM Li_2SO_4, 0.03 mM NADPH, 1 mM DL-glyceraldehyde as a substrate, and 100 μL of enzyme fraction, with or without 25 μL of sample solution, in a total volume of 0.5 mL. The reaction was initiated by the addition of NADPH at 30 °C. After 30 min, the reaction was stopped by the addition of 150 μL of 0.5 M HCl. Then, 0.5 mL of 6 M NaOH containing 10 mM imidazole was added, and the solution was heated at 60 °C for 20 min to convert NADP to a fluorescent product. Fluorescence was measured using a fluorophotometer (luminescence spectrometer LS50B, Perkin-Elmer, UK) at an excitation wavelength of 360 nm and an emission wavelength of 460 nm. Each test sample was dissolved in DMSO. Measurements were made in duplicate, and the IC_{50} value was determined graphically by plotting the percent inhibition *versus* log of the test compound. An aldose reductase inhibitor epalrestat was used as a reference compound

Reproduced with permission from *J. Nat. Prod.*, **66**, 1191–1196. Copyright [2003] ACS

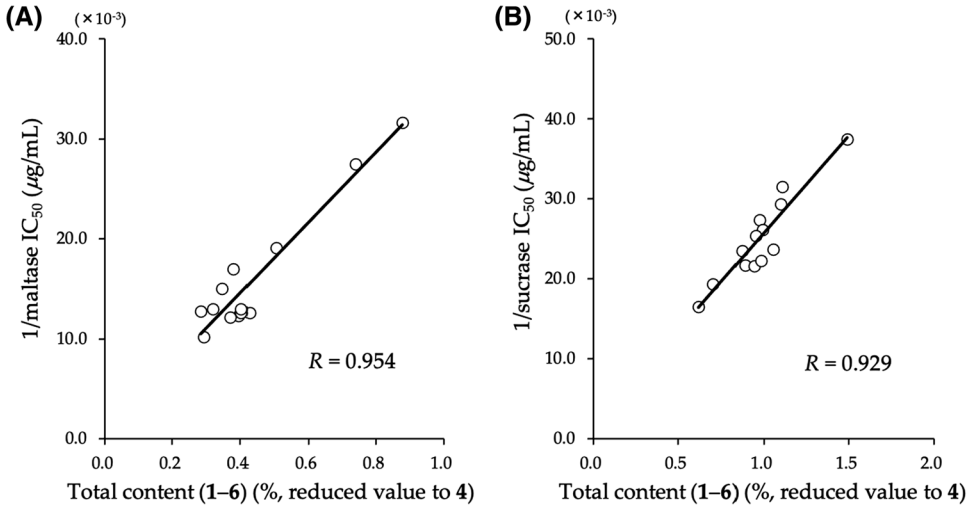


Fig. 6 Correlations between maltase and sucrase inhibitory activities and total content of six thiosugar sulfoniums (**1**–**6**). Total contents (%) of the six thiosugar sulfoniums (**1**–**6**) are presented in values reduced to the content of neokotalanol (**4**), calculated based on the ratio of IC_{50} values (μg/mL) of **1**–**6** against those of (**a**) maltase or (**b**) sucrase

Evaluation of hot water extract from the stems of *S. chinensis* (SCE) as a functional food material for improving the effects on blood glucose and HbA1c levels in animal models

In Japan, the government can label two types of food products with certain health claims: Foods for Specified Health Uses (FOSHU) and Foods with Function Claims (FFC) [75–81]. Due to the increasing interest in plants of the genus *Salacia* as a possible food product with health claim for individuals with prediabetes and/or those with high blood glucose levels, we examined the suppressive effects of the hot water extract from the stems of *S. chinensis* (SCE). Strong correlations have been observed between the total content of four principal thiosugar sulfoniums (**1**–**4**) and the *a*-glucosidase inhibitory activity (*vide supra*), on postprandial blood glucose levels in starch-loaded rats. As shown in Fig. 7, SCE significantly suppressed the increase in blood glucose levels in a dose-dependent manner (30–300 mg/kg, *p.o.*), with an ED_{50} value of 94.0 mg/kg. Among the sulfonium constituents, salacinol (**1**), kotalanol (**3**), and neokotalanol (**4**) were also evaluated using the in vivo assay, with ED_{50} values of > 2.06, 0.62, and 0.54 mg/kg, respectively [38].

Next, the effects of 3-weeks' administration of SCE on postprandial blood glucose and HbA1c levels were evaluated

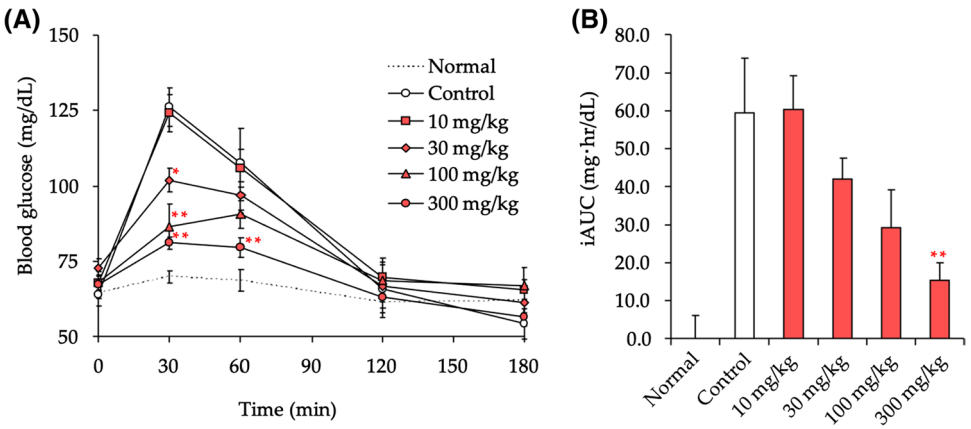


Fig. 7 Effect of SCE on blood glucose levels in starch-loaded rats. Male SD rats (5-week-old, Kiwa Laboratory Animals, Ltd., Wakayama, Japan) were housed for 1 week in meal cages. Animals were fasted overnight for 20 h, but allowed water ad libitum, and the rats were then administered a 5% (w/v) α-starch solution (1 g/kg) orally with or without a sample (SCE, 10–300 mg/kg) using a stomach tube. At 0, 30, 60, 120, and 180 min after the administration of α-starch, blood samples were taken from the tail vein and immediately used to measure blood glucose via the glucose-oxidase method. As a baseline, distilled water was administrated to rats in the Normal group. Median effective dose (ED_{50}) was determined by plotting the inhibition rate of incremental $AUC_{0\text{-}120\ min}$ (i $AUC_{0\text{-}120\ min}$; the AUC above baseline) *versus* corresponding inhibitor dosage. Each value represents the mean ± S.E.M. ($n = 8$). Significantly different from the control: $^{*}p < 0.05$, $^{**}p < 0.01$. Reproduced with permission from *Nutrients*, **7**, 1480–1493. Copyright [2015] MDPI

in a typical model of type 2 diabetes mellitus (KK-A^y mice). As shown in Fig. 8, feeding animals a CE-2 diet containing 0.25 and/or 0.50% (w/w) SCE significantly suppressed the increase in both blood glucose and HbA1c levels without significant changes in body weight and food intake. Furthermore, a glucose tolerance test (2 g/kg) was performed following continuous administration of an AIN93M purified diet containing 0.12% (w/w) SCE to glucose-loaded KK-A^y mice for 27 days. The results showed that SCE significantly suppresses the elevation in blood glucose. Thus, SCE exerted antidiabetic effects by both inhibiting the increase in postprandial blood glucose levels and improving glucose tolerance [38].

To verify whether the suppressive effects of SCE on HbA1c levels were due to the presence of α-glucosidase inhibitors, we performed similar chronic experiments using a customized diet, in which all the digestible glucides in AIN93M (AIN93M/Glc) were substituted by D-glucose. There were no significant differences in HbA1c levels in KK-A^y mice fed a customized (AIN93M/Glc) or standard (AIN93M purified) diet supplemented with 0.30% SCE for 14 days compared with the corresponding control group. These results indicate that the antidiabetic effect of SCE is due to the potent α-glucosidase inhibitory activity of its active constituents, which are characteristic sulfoniums, including salacinol (**1**), neokotalanol (**4**), and their related analogues isolated from genus *Salacia* plants [38].

In addition, we examined the antidiabetic effects of SCE and its principal thiosugar sulfonium, neokotalanol (**4**), using genetically hyperglycemic model *ob/ob* mice, which are grossly overweight, hyperphagic, obese, hyperinsulinemic, and hyperglycemic, and used as models of diabetes with obesity [82]. Thus, administration of a single-dose of SCE significantly suppressed the elevated blood glucose in enteral nutrient Ensure H® (10 mL/kg, Abbott Japan Co., Ltd., Tokyo, Japan)-loaded *ob/ob* mice in a dose-dependent manner (50–150 mg/kg *p.o.*) (Fig. 9). Thus, the suppressive curve of the blood glucose elevation of SCE was similar to that of a clinical α-glucosidase inhibitor voglibose, but dissimilar to that of a clinical dipeptidyl peptidase-4 (DPP-4) inhibitor, alogliptin. Furthermore, continuous administration of 0.20 and 0.50% (w/w) SCE in CE-2 diet-fed *ob/ob* mice for 23 days significantly suppressed the increase in both blood glucose and HbA1c levels in a dose-dependent manner (Fig. 10). Notably, the water intake of mice in the SCE-treated groups was lower than that of mice in the control group during the administration period [average intake per day: 0.20% SCE group (7.7 ± 1.2 g), 0.50% SCE group (6.2 ± 0.6 g), and Control group (11.5 ± 2.0 g)], which was similar to that of mice treated with 0.001% (w/w) voglibose (5.6 ± 0.5 g). These results suggest that SCE has a beneficial effect on polydipsia with diabetes mellitus.

Similarly, the antidiabetic effects of neokotalanol (**4**), one of the highest contributing principles based on its potent α-glucosidase inhibitory activity and high content in SCE, were evaluated by evaluating the blood glucose and HbA1c levels of *ob/ob* mice following 20-day continuous administration. As show in Table 4, administration of the diet containing 0.0003% of neokotalanol (**4**) was found to significantly suppress the increase in HbA1c levels without causing changes in body weight. Consequently, the potent α-glucosidase inhibitor neokotalanol (**4**) was identified as

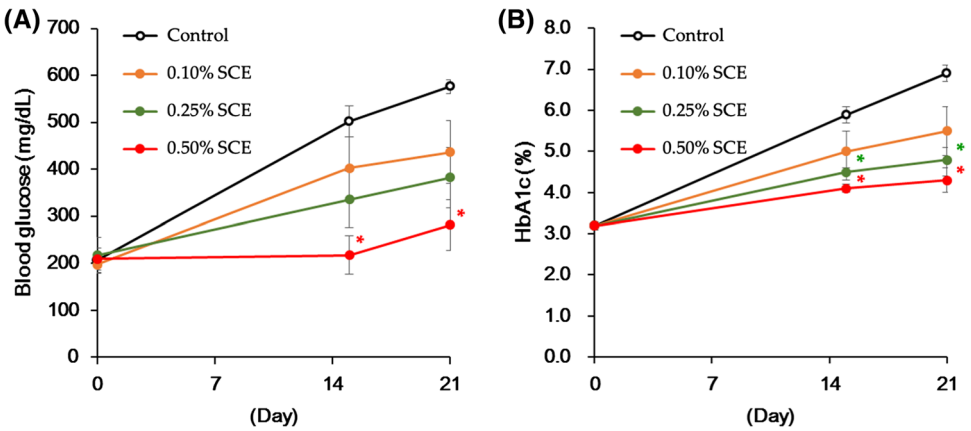


Fig. 8 Effect of chronic administration of SCE on blood glucose and HbA1c levels in CE-2 diet-fed KK-A^y mice. Male KK-A^y mice (5-week-old, CLEA Japan, Inc., Tokyo, Japan) were housed for 1 week in individual meal cages. These mice were divided into four groups based on body weight, blood glucose, and HbA1c levels. Mice in the control group were fed a standard diet (CE-2, CLEA Japan, Inc.) and those in the SCE-treated groups were fed diets supplemented with 0.10, 0.25, and 0.50% (w/w) SCE, respectively. On day 15 and at the end of the treatment period, blood samples were taken from the tail vein under non-fasting conditions. Blood glucose and HbA1c levels were measured using the glucose-oxidase method and a DCA Vantage Analyzer™ (Siemens, New York, USA), respectively. Each value represents the mean ± S.E.M. ($n = 6$). Significantly different from the control: $^{*}p < 0.05$, $^{**}p < 0.01$. Reproduced with permission from *Nutrients*, **7**, 1480–1493. Copyright [2015] MDPI

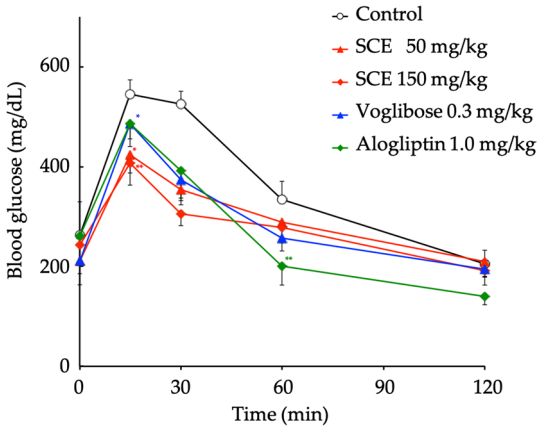


Fig. 9 Effects of SCE, voglibose, and alogliptin on blood glucose levels in Ensure H®-loaded *ob/ob* mice. Male B6.Cg-Lep^{ob}/J (*ob/ob*) mice (6-week-old, Charles River Laboratories Japan, Inc., Yokohama, Japan) were housed for 1 week in individual meal cages. Mice were fasted overnight for 20 h, but allowed water ad libitum. Then, the mice were orally administered an enteral nutrient Ensure H® [10 mL/kg (per 10 mL energy: 15 kcal; dextrin: 1668 mg; sucrose: 392 mg)] with or without a sample (SCE: 50 or 150 mg/kg) using a stomach tube. At 0, 15, 30, 60, and 120 min after administration, blood samples were taken from the tail vein and immediately used to measure blood glucose via the glucose-oxidase method. Each value represents the mean ± S.E.M. ($n = 6$). Significantly different from the control: $^{*}p < 0.05$, $^{**}p < 0.01$. Reproduced with permission from *J. Nat. Med.*, **73**, 584–588. Copyright [2019] Springer Nature

one of the active constituents hampering the progress of diabetes in obese-hyperglycemic *ob/ob* mice.

Mangiferin (41) is a promising marker molecule for the antidiabetic effect of plants in the genus *Salacia*

A xanthone *C*-glycoside mangiferin (**41**), originally obtained from the stem bark of mango tree (*Mangifera indica* L.) [83–85], was isolated from plants of the genus *Salacia* as a moderate aldose reductase inhibitor (*vide supra*) and reported to exert a hypoglycemic effect in KK-A^{y} mice [2, 86]. Thereafter, mangiferin (**41**) has attracted attention as a bio-functional molecule for its antidiabetic [83, 84, 87–89], antioxidant [83, 84, 90–92], antibacterial, antiviral [84], antiparasitic [84], antiinflammatory [83, 84, 90–94], and anticancer [83, 84, 95, 96] activities. These findings indicate that mangiferin (**41**) may be a possible marker molecule for the antidiabetic activity of plants from the genus *Salacia*. Therefore, simultaneous quantitative determination of polyphenol constituents, including mangiferin (**41**), by LC–MS was performed to further evaluated plants from the genus *Salacia* [97]. The results showed that the mangiferin (**41**) content in plants of the genus *Salacia,* such as *S. reticulata*, *S. oblonga*, and *S. chinensis,* from different regions were higher in the root part than in the corresponding stem part. Among the root part, the inner root bark was found to possess the richest content of mangiferin (**41**).

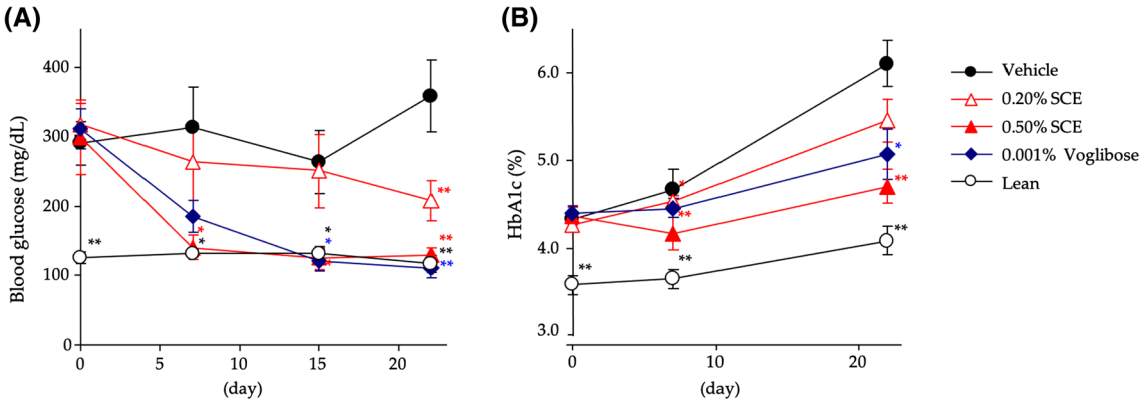


Fig. 10 Effect of SCE and voglibose on blood glucose and HbA1c levels after 23 days administration in CE-2 diet-fed *ob/ob* mice. Male B6.Cg-Lep^{ob}/J (*ob/ob*) mice (6-week-old, Charles River Laboratories Japan, Inc., Yokohama, Japan) were housed for 1 week in individual meal cages. These mice were divided into five groups based on body weight, blood glucose, and HbA1c levels. Mice in the control group were fed a standard diet of CE-2. Mice in the SCE-treated and positive control groups were fed the same diet supplemented with 0.20 and 0.50% (w/w) of SCE, respectively. Mice in the positive control group were fed the same diet supplemented with 0.001% of voglibose. On days 7, 15, and 22, blood glucose and HbA1c levels were measured using the glucose-oxidase method and a DCA Vantage Analyzer™ (Siemens, New York, USA), respectively. Each value represents the mean ± S.E.M. ($n = 6$). Significantly different from the control: $^{*}p < 0.05$, $^{**}p < 0.01$. Reproduced with permission from *J. Nat. Med.*, **73**, 584–588. Copyright [2019] Springer Nature

Table 4 Effects of SCE, neosalacinol (**4**), and voglibose on food and water intakes, body weight, and HbA1c levels after 20 days of administration in AIN-93 M purified diet-fed *ob/ob* mice

	Dose	Food intake	Water intake	Body weight (g)							
	(%)	(g/day, average)		Day 0	Day 3	Day 6	Day 9	Day 12	Day 15	Day 18	Day 20
Control	–	3.5 ± 0.1	4.0 ± 0.7	32.9 ± 0.6	35.6 ± 0.7	36.4 ± 0.4	36.9 ± 0.5	38.1 ± 0.4	39.2 ± 0.5	40.3 ± 0.4	41.0 ± 0.4
SCE	0.05	3.6 ± 0.1	2.5 ± 0.1**	33.4 ± 0.5	36.1 ± 0.3	36.8 ± 0.2	37.4 ± 0.2	38.6 ± 0.3	39.3 ± 0.2	40.8 ± 0.3	41.3 ± 0.3
Neokotalanol (4)	0.0003	3.5 ± 0.2	2.5 ± 0.2**	32.2 ± 0.5	35.1 ± 0.4	35.8 ± 0.4	36.0 ± 0.4	37.2 ± 0.4	37.8 ± 0.4	39.4 ± 0.4	40.1 ± 0.4
Voglibose	0.0001	4.5 ± 0.2	3.3 ± 0.2	33.0 ± 0.5	36.2 ± 0.4	36.3 ± 0.5	37.1 ± 0.3	38.0 ± 0.4	39.0 ± 0.2	40.2 ± 0.3	40.8 ± 0.4

	Dose	HbA1c (%)	
	(%)	Day 0	Day 20
Control	–	6.1 ± 0.0	6.5 ± 0.2
SCE	0.05	6.1 ± 0.1	6.0 ± 0.1*
Neokotalanol (**4**)	0.0003	5.9 ± 0.1	5.9 ± 0.1**
Voglibose	0.0001	5.9 ± 0.1	6.0 ± 0.1*

Effects on HbA1c levels of AIN-93 M purified diet-fed ob/ob mice following 20 days of administration: Male B6.Cg-Lep^{ob}/J (*ob/ob*) mice (6-week-old, Charles River Laboratories Japan, Inc., Yokohama, Japan) were housed for 1 week in individual meal cages. These mice were divided into four groups based on body weight, blood glucose, and HbA1c levels. Mice in the control group was fed a standard AIN-93 M purified diet. Mice in the SCE-, neokotalanol (**4**)-, and voglibose-treated groups were fed the same diet supplemented with 0.05, 0.0003, and 0.0001% (w/w) of the respective treatments. On days 0, 3, 6, 9, 12, 15, 18, and 20 (end of the treatment period), their body weights were measured. On days 0 and 20, the HbA1c levels were measured using Quo-Lab (Nipro, Osaka, Japan)

Each value represents the mean ± S.E.M. ($n = 6$)

Significantly different from the control: *$p < 0.05$, **$p < 0.01$

Safety profiles

Extracts from plants of the genus *Salacia* have been found to have good safety profiles in animal models, such as rats, mice, guinea pigs, and horses, and also in healthy adults, and in patients with borderline diabetes and type 2 diabetes [4, 98–106]. Thus, no serious oral toxicity of *Salacia* extracts, such as aqueous extracts from *S. reticulata* and *S. oblonga,* has been observed following single-dose treatment in sub-chronic administration tests [4, 98–105]. In addition, the extract from *S. reticulata* presented no mutagenicity [98], hepatotoxicity [103], antigenicity, or phototoxicity [104]. The *S. chinensis* extract was found to exert no reproductive toxicity in SD rats, even at a high dosage level [102]. In addition, Stohs and Ray (2015) stated that no adverse effects have been reported in studies evaluating the safety of *Salacia* extracts in humans [4]. We performed two randomized double-blind placebo-controlled trials to evaluate the safety of long-term and excessive intake of the hot water extract of *S. chinensis* [106]. The subjects were healthy or had borderline diabetes with fasted blood glucose levels of 100–125 mg/dL. For the long-term intake study, 42 subjects were divided into a test group and a placebo group, and administered three tablets [containing more than 0.221 mg of neokotalanol (**4**) per tablet] per day for 12 weeks. In the excess intake study, 41 subjects were given 15 tablets per day for 4 weeks under the same conditions. No adverse effects in terms of clinical parameters were observed in either trial, confirming the safety of long-term and excessive intake of *S. chinensis* extract [106].

We then evaluated the duration of the α-glucosidase inhibitory effect of SCE in a starch-preloaded model. Thus, starch-loaded rats for 0–120 min were administered SCE (75 mg/kg, *p.o.*) orally, and suppression of elevated blood glucose levels was subsequently observed. In the group subjected to 30 min pre-starch-loading, the increase in blood glucose level was significantly suppressed. However, no effect was observed in the group that was loaded with starch for more than 60 min before treatment, as shown in Fig. 11. Therefore, the suppressive effect of SCE against the increase in blood glucose was estimated to last for approximately 30 min after administration and then weakened over time [38].

Next, we evaluated the kinetics of the principal sulfoniums (**1**–**4**) in SCE following oral administration by examining (i) stability in an artificial gastric juice and (ii) bioavailability through the intestine using an in situ rat ligated intestinal loop model. We found that more than 96% of each sulfonium (**1**–**4**) survived following treatment at 37 °C for 1.0 h. Even after 3.0 h of treatment under the experimental conditions, more than 90% of survived, and the stability of these sulfoniums (**1**–**4**) in the artificial gastric juice was high [38]. Furthermore, these sulfoniums (**1**–**4**) were minimally absorbed in the small intestine [38]. Thus, these data indicated that the sulfoniums reached the small intestine following oral administration without being degraded by gastric juice, where they exerted inhibitory activity against α-glucosidase. In addition, most sulfoniums remained in the intestinal tract without being absorbed. Furthermore, SCE has no effects on reproductive outcomes in rats, even at the high dosage level of 2,000 mg/kg/day [102].

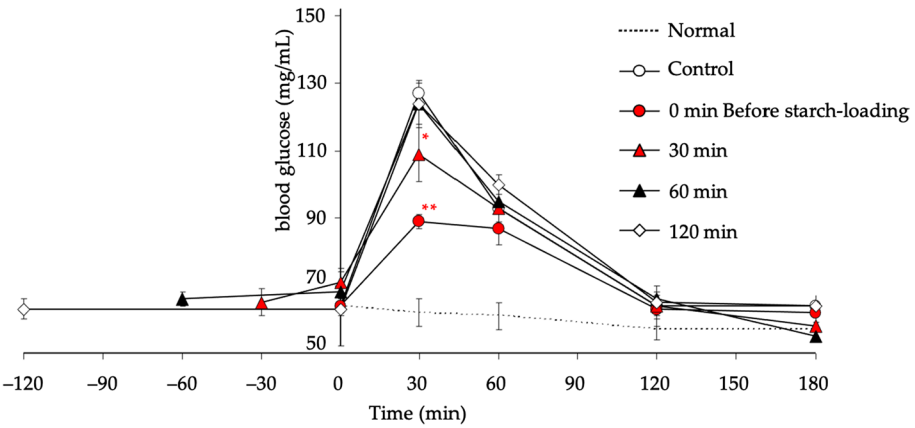


Fig. 11 Effect of SCE on blood glucose levels in SCE-pretreated starch-loaded rats. Male SD rats (5-week-old, Kiwa Laboratory Animals, Ltd., Wakayama, Japan) were housed for 1 week in meal cages. Rats were fasted overnight for 20 h, but allowed water ad libitum. Then, the rats were orally administered SCE (75 mg/mg) using a stomach tube at 0, 30, 60, and 120 min before loading of 5% (w/v) α-starch solution (1 g/kg). At 0, 30, 60, 120, and 180 min after the administration of α-starch, blood samples were taken from the tail vein and used immediately to measure blood glucose via the glucose-oxidase method. As a baseline, distilled water was administrated to rats in the Normal group. Each value represents the mean ± S.E.M. ($n = 8$). Significantly different from the control: $^{*}p < 0.05$, $^{**}p < 0.01$. Reproduced with permission from *Nutrients*, **7**, 1480–1493. Copyright [2015] MDPI

Clinical study

Clinical trials on the aqueous extract of *S. reticulata* have demonstrated that 5 min pre-treatment with the extract (200 mg) prior to sucrose (50 g) loading suppressed postprandial blood glucose elevation in human volunteers. [107]. Additionally, an extract-containing diet (240 mg/kg/day) fed to patients with mild type 2 diabetes for 6 weeks was found to exert inhibitory effects on fasting blood glucose levels, HbA1c, and BMI in a placebo-controlled and cross-over trial [108]. The aqueous extract was also found to be an effective and safe treatment for patients with type 2 diabetes in a double-blind randomized placebo-controlled cross-over study when administered as a herbal tea containing *S. reticulata* for 3 months [109]. Finally, the extract (500 mg/day for 6 weeks) was found to improve serum lipids and glycemic control in patients with prediabetes and mild-to-moderate hyperlipidemia in a double-blind placebo-controlled, randomized trial [110]. Clinical trials have also investigated the aqueous extract of *S. oblonga*, and found it to possess suppressive effects at 500–1000 mg on postprandial plasma glucose and insulin AUC values in healthy adults [111, 112]. In addition, at 240 and 480 mg, the extract was found to possess inhibitory effects on postprandial glycemia and insulinemia in patients with type 2 diabetes after ingestion of a high-carbohydrate meal [113]. To verify the clinical effectiveness of *S. chinensis*, we evaluated the suppressive effect of SCE on postprandial hyperglycemia in human subjects. This randomized double-blind and cross-over trial was performed in 32 human volunteers with borderline diabetes and fasting blood glucose levels between 100 and 125 mg/dL. Single-dose intake of a tablet containing 100 mg of SCE with 0.221 mg neokotalanol (**4**) followed by a rice diet (200 g: containing 69.4 g of carbohydrate, 302 kcal) significantly suppressed the increase in postprandial blood glucose levels 30 min after a meal compared with the placebo. In addition, the AUC for blood glucose and serum insulin levels up to 3 h in SCE treatment group were also significantly lower than those in the placebo group [114]. Furthermore, in a placebo-controlled, randomized, double-blind cross-over trial, we recently confirmed the dose-dependent suppression of postprandial hyperglycemia, and improvement of blood glucose parameters following a single-dose of SCE (150, 300, or 600 mg). Additionally, in a placebo-controlled, randomized double-blind trial, we demonstrated that 12-week ingestion of SCE (600 mg before each of three meals daily) improved parameters related to blood glucose, such as HbA1c, glycoalbumin, and 1,5-anhydro-D-glucitol levels, and glucose tolerance after a glucose challenge [115].

Conclusion

Since safety profiles and clinical findings associated with the antidiabetic effects of genus *Salacia* plants have been reported, several *Salacia*-containing products, which contribute to the regulation of postprandial blood glucose elevation, have been approved as FOSHU or notified as an FFC to the Consumer Affairs Agency in Japan. The evidence discussed above for the antidiabetic effects of plants from the genus *Salacia* may have contributed to the development of these functional foods. Furthermore, we hope that additional research on the genus *Salacia* as beneficial plant resources for the prevention and early treatment of diabetes, and also on their thiosugar sulfonium constituents, such as salacinol (**1**) and neokotalanol (**4**), will attract attention to these plants as promising candidates for a new class of antidiabetic agents in the future.

Acknowledgements This work was supported in part by the 'High-Tech Research Center' Project for Private Universities: a matching fund subsidy from MEXT (Ministry of Education, Culture, Sports, Science and Technology), 2007–2011 (T.M. and O.M.), an MEXT-Supported Program for the Strategic Research Foundation at Private Universities, 2014–2018, S1411037 (T.M.), and JSPS KAKENHI, Japan [Grant Numbers 16K08313 (O.M.), 18K06726 (T.M.)]. The authors thank the Division of Joint Research Center of Kindai University for performing the NMR and MS measurements. We would like to thank Editage (www.editage.com) for English language editing.

Declarations

Conflict of interest The authors declare no conflict of interest.

References

1. The Plant List: http://www.theplantlist.org/tpl1.1/search?q=Salacia. Accessed date 16 Mar 2021
2. Matsuda H, Yoshikawa M, Morikawa T, Tanabe G, Muraoka O (2005) Antidiabetogenic constituents from *Salacia* species. J Trad Med 22(Suppl. 1):145–153
3. Vyas N, Mehra R, Makhija R (2016) *Salacia*—the new multi-targeted approach in diabetics. AYU 37:92–97

4. Stohs SJ, Ray S (2015) Anti-diabetic and anti-hyperlipidemic effects and safety of *Salacia reticulata* and related species. Phytother Res 29:986–995
5. Musini A, Giri A (2015) *Salacia oblonga* wall: an endangered plant of immenses pharmaceutical value. J Chem Pharm Res 7:1125–1129
6. Kushwaha PS, Singh AK, Keshari AK, Maity S, Saha S (2016) An updated review on the phytochemistry, pharmacology, and clinical trials of *Salacia oblonga*. Pharmacogn Rev 10:109–114
7. Matsuda H, Morikawa T, Yoshikawa M (2002) Antidiabetogenic constituents from several natural medicines. Pure Appl Chem 74:1301–1308
8. Chandrasena JPC (1935) The chemistry and pharmacology of Ceylon and Indian medicinal plants. H&C Press, Colombo
9. Jayaweera DMA (1981) Medicinal plants used in ceylon part 1. National Science Council of Sri Lanka, Colombo, p 77
10. Vaidyaratnam PS (1996) Indian medicinal plants: a compendium of 500 species. In: Warrier PK, Nambiar VPK, Ramankutty C, (Eds.), Orient Longman, Madras, India, pp. 47–48
11. Chuakul W, Saralamp P, Paonil W, Temsiririkkul R, Clayton T (1997) Medicinal plants in Thailand (volume II). Department of Pharmaceutical Botany, Faculty of Pharmacy, Mahidol University, Bangkok, pp 192–193
12. Karunanayake EH, Welihinda J, Sirimanne SR, Sinnadorai G (1984) Oral hypoglycaemic activity of some medicinal plants of Sri Lanka. J Ethnopharmacol 11:223–231
13. Serasinghe S, Sirasinghe P, Yamazaki H, Nishiguchi K, Hombhanje F, Nakanishi S, Sewa K, Hattori M, Namba T (1990) Oral hypoglycemic effect of *Salacia reticulata* in the streptozotocin-induced diabetic rat. Phytother Res 4:205–206
14. Augusti KT, Joseph P, Babu TD (1995) Biologically active principles isolated from *Salacia oblonga* Wall. Indian J Physiol Pharmacol 39:415–417
15. Pillai NR, Seshadri C, Santhakumari C (1979) Hypoglycaemic activity of the root bark of *Salacia prinoides*. Indian J Exp Biol 17:1279–1280
16. International Diabetes Federation (IDF) Atlas 9th Edition 2019: https://www.diabetesatlas.org/en/
17. Dash RP, Babu RJ, Srinivas NR (2018) Reappraisal and perspectives of clinical drug-drug interaction potential of *a*-glucosidase inhibitors such as acarbose, voglibose and miglitol in the treatment of type 2 diabetes mellitus. Xenobiotica 48:89–108
18. Ríos JL, Francini F, Schinella GR (2015) Natural products for the treatment of type 2 diabetes mellitus. Plant Med 81:975–994
19. Yoshikawa M, Shimada H, Morikawa T, Yoshizumi S, Matsumura N, Murakami T, Matsuda H, Hori K, Yamahara J (1997) Medicinal foodstuffs. VII. On the saponin constituents with glucose and alcohol absorption-inhibitory activity from a food garnish "tonburi", the fruit of Japanese *Kochia scoparia* (L.) Schrad.: structures of scoparianosides A, B, and C. Chem Pharm Bull 45:1300–1305
20. Yoshikawa M, Xu F, Morikawa T, Pongpiriyadacha Y, Nakamura S, Asao Y, Kumahara A, Matsuda H (2007) Medicinal foodstuffs. XII. New spirostane-type steroid saponins with antidiabetogenic activity from *Borassus flabellifer*. Chem Pharm Bull 55:308–316
21. Yoshikawa M, Nakamura S, Ozaki K, Kumahara A, Morikawa T, Matsuda H (2007) Structures of steroid alkaloid oligoglycosides, robeneosides A and B, and antidiabetogenic constituents from the Brazilian medicinal plant *Solanum lycocarpum*. J Nat Prod 70:210–214
22. Yoshikawa M, Wang T, Morikawa T, Xie H, Matsuda H (2007) Bioactive constituents from Chinese natural medicines. XXIV. Hypoglycemic effects of *Sinocrassula indica* in sugar-loaded rats and genetically diabetic KK-A^y mice and structures of new acylated flavonol glycosides, sinocrassosides A_1, A_2, B_1, and B_2. Chem Pharm Bull 55:1308–1315
23. Morikawa T, Chaipech S, Matsuda H, Hamao M, Umeda Y, Sato H, Tamura H, Kon'i H, Ninomiya K, Yoshikawa M, Pongpiriyadacha Y, Hayakawa T, Muraoka O (2012) Antidiabetogenic oligstilbenoids and 3-ethyl-4-phynyl-3,4-dihydroisocoumarins from the bark of *Shorea roxburghii*. Bioorg Med Chem 20:832–840
24. Morikawa T, Ninomiya K, Imamura M, Akaki J, Fujikura S, Pan Y, Yuan D, Yoshikawa M, Jia X, Li Z, Muraoka O (2014) Acylated phenylethanoid glycosides, echinacoside and acteoside from *Cistanche tubulosa*, improve glucose tolerance in mice. J Nat Med 68:561–566
25. Morikawa T, Xie H, Pan Y, Ninomiya K, Yuan D, Jia X, Yoshikawa M, Nakamura S, Matsuda H, Muraoka O (2019) A review of biologically active natural products from a desert plant *Cistance tubulosa*. Chem Pharm Bull 67:675–689
26. Morikawa T, Ninomiya K, Akaki J, Kakihara N, Kuramoto H, Matsumoto Y, Hayakawa T, Muraoka O, Wang LB, Wu LJ, Nakamura S, Yoshikawa M, Matsuda H (2015) Dipeptidyl peptidase-IV inhibitory activity of dimeric dihydrichalcone glycosides from flowers of *Helichrysum arenarium*. J Nat Med 69:494–506
27. Yoshikawa M, Murakami T, Shimada H, Matsuda H, Yamahara J, Tanabe G, Muraoka O (1997) Salacinol, potent antidiabetic principle with unique thiosugar sulfonium sulfate structure from the Ayurvedic traditional medicine *Salacia reticulata* in Sri Lankan and India. Tetrahedron Lett 48:8367–8370
28. Yoshikawa M, Morikawa T, Matsuda H, Tanabe G, Muraoka O (2002) Absolute stereostructure of potent α-glucosidase inhibitor, salacinol, with unique thiosugar sulfonium sulfate inner salt structure from *Salacia reticulata*. Bioorg Med Chem 10:1547–1554
29. Yoshikawa M, Murakami T, Yashiro K, Matsuda H (1998) Kotalanol, a potent *a*-glucosidase inhibitor with thiosugar sulfonium sulfate structure, from antidiabetic Ayurvedic medicine *Salacia reticulata*. Chem Pharm Bull 46:1339–1340
30. Muraoka O, Xie W, Osaki S, Kagawa A, Tanabe G, Amer MFA, Minematsu T, Morikawa T, Yoshikawa M (2010) Characteristic alkaline catalyzed degradation of kotalanol, a potent α-glucosidase inhibitor isolated from Ayurvedic medicine *Salacia reticulata*, leading to anhydroheptitols: another structural proof. Thtrahedron 66:3717–3722
31. Capon RJ, MacLeod JK (1987) 5-Thio-D-mannose from the marine sponge *Clathria pyramida* (Lendenfeld). The first example of a naturally occurring 5-thiosugar. Chem Commun 1987:1200–1201
32. Matsuda H, Murakami T, Yashiro K, Yamahara J, Yoshikawa M (1999) Antidiabetic principles of natural medicines. IV. Aldose reductase and *a*-glucosidase inhibitors from the roots of *Salacia oblonga* Wall. (Celastraceae): structure of a new friedelane-type triterpene, kotalagenin 16-acetate. Chem Pharm Bull 47:1725–1729
33. Yoshikawa M, Xu F, Nakamura S, Wang T, Matsuda H, Tanabe G, Muraoka O (2008) Salaprinol and ponkoranol with thiosugar sulfate structure from *Salacia prinoides* and α-glucosidase inhibitory activity of ponkoranol and kotalanol desulfate. Heterocycles 75:1397–1405
34. Muraoka O, Morikawa T, Miyake S, Akaki J, Ninomiya K, Yoshikawa M (2010) Quantitative determination of potent α-glucosidase inhibitors, salacinol and kotalanol, in *Salacia* species using liquid chromatography-mass spectrometry. J Pharm Biomed Anal 52:770–773
35. Muraoka O, Morikawa T, Miyake S, Akaki J, Ninomiya K, Pongpiriyadacha Y, Yoshikawa M (2011) Quantitative analysis of neosalacinol and neokotalanol, another two potent α-glucosidase inhibitors from *Salacia* species, by LC-MS with ion pair chromatography. J Nat Med 65:142–148

36. Xie W, Tanabe G, Akaki J, Morikawa T, Ninomiya K, Minematsu T, Yoshikawa M, Wu X, Muraoka O (2011) Isolation, structure identification and SAR studies on thiosugar sulfonium salts, neosalaprinol and neoponkoranol, as potent α-glucosidase inhibitors. Bioorg Med Chem 19:2015–2022
37. Akaki J, Morikawa T, Miyake S, Ninomiya K, Okada M, Tanabe G, Pongpiriyadacha Y, Yoshikawa M, Muraoka O (2014) Evaluation of *Salacia* species as anti-diabetic natural resources based on quantitative analysis of eight sulphonium constituents: a new class of α-glucosidase inhibitors. Phytochem Anal 25:544–550
38. Morikawa T, Akaki J, Ninomiya K, Kinouchi E, Tanabe G, Pongpiriyadacha Y, Yoshikawa M, Muraoka O (2015) Salacinol and related analogs: new leads for type 2 diabetes therapeutic candidate from the Thai traditional natural medicine *Salacia chinensis*. Neutrients 7:1480–1493
39. Yuasa H, Takada J, Hashimoto H (2000) Synthesis of salacinol. Tetrahedron Lett 41:6615–6618
40. Ghavami A, Johnston BD, Pinto BM (2001) A new class of glycosidase inhibitor: synthesis of salacinol and its stereoisomers. J Org Chem 66:2312–2317
41. Johnston BD, Ghavami A, Jensen MT, Svensson B, Pinto BM (2002) Synthesis of selenium analogues of the naturally occurring glycosidase inhibitor salacinol and their evaluation as glycosidase inhibitors. J Am Chem Soc 124:8245–8250
42. Ghavami A, Sadalapure KS, Johnston BD, Lobera M, Snider BB, Pinto BM (2003) Improved syntheses of the naturally occurring glycosidase inhibitor salacinol. Synlett 9:1259–1262
43. Johnston BD, Jensen HH, Pinto BM (2006) Synthesis of sulfonium sulfate analogues of disaccharides and their conversion to chain-extended homologues of salacinol: new glycosidase inhibitors. J Org Chem 71:1111–1118
44. Ravindranath HL, Nasi R, Jayakanthan K, Kumarasamy N, Sim JL, Heipel H, Rose DR, Pinto BM (2007) New synthetic routes to chain-extended selenium, sulfer, and nitrogen analogues of the naturally occurring glucosidase inhibitor salacinol and their inhibitory activities against recombinant human maltase glucoamylase. J Org Chem 72:6562–6572
45. Mohan S, Pinto BM (2007) Zwitterionic glycosidase inhibitors: salacinol and related analogues. Carbohydr Res 342:1551–1580
46. Nasi R, Patrick BO, Sim L, Rose DR, Pinto BM (2008) Studies directed toward the stereochemical structure determination of the naturally occurring glucosidase inhibitor, kotalanol: synthesis and inhibitory activities against human maltase glucoamylase of seven-carbon, chain-extended homologues of salacinol. J Org Chem 73:6172–6181
47. Jayakanthan K, Mohan S, Pinto BM (2009) Structure proof and synthesis of kotalanol and de-*O*-sulfonated kotalanol, glycosidase inhibitors isolated from an herbal remedy for the treatment of type-2 diabetes. J Am Chem Soc 131:5621–5626
48. Mohan S, Pinto BM (2009) Sulfonium-ion glycosidase inhibitors isolated from *Salacia* species used in traditional medicine, and related compounds. Collect Czech Chem Commun 74:1117–1136
49. Mohan S, Pinto BM (2010) Towards the elusive structure of kotalanol, a naturally occurring glucosidase inhibitor. Nat Prod Rep 27:481–488
50. Sim L, Jayakanthan K, Mohan S, Nasi R, Johnston BD, Pinto BM, Rose DR (2010) New glucosidase inhibitors from an Ayurvedic herbal treatment for type-2 diabetes: structures and inhibition of human intestinal maltase-glucoamylase with compounds from *Salacia reticulata*. Biochemistry 49:443–451
51. Eskandari R, Jayakanthan K, Kuntz DA, Rose DR, Pinto BM (2010) Synthesis of a biologically active isomer of kotalanol, a naturally occurring glucosidase inhibitor. Bioorg Med Chem 18:2829–2835
52. Eskandari R, Kuntz DA, Rose DR, Pinto BM (2010) Potent glucosidase inhibitors: de-*O*-sulfonated ponkoranol and its stereoisomer. Org Lett 12:1632–1635
53. Eskandari R, Jones K, Rose DR, Pinto BM (2011) The effect of heteroatom substitution of sulfur for selenium in glucosidase inhibitors on intestinal α-glucosidase activities. Chem Commun 47:9134–9136
54. Mohan S, Eskandari R, Pinto BM (2014) Naturally occurring sulfonium-ion glucosidase inhibitors and their derivatives: a promising class of potential antidiabetic agents. Acc Chem Res 47:211–225
55. Bagri P, Chester K, Khan W, Ahmad S (2017) Aspects of extraction and biological evaluation of naturally occurring sugar-mimicking sulfonium-ion and their synthetic analogues as potent α-glucosidase inhibitors from *Salacia*: a review. RSC Adv 7:28152–28187
56. Xie W, Tanabe G, Xu J, Wu X, Morikawa T, Yoshikawa M, Muraoka O (2013) Research progress of synthesis and structure-activity relationship studies on sulfonium-type α-glucosidase inhibitors isolated from *Salacia* genus plants. Min Rev Org Chem 10:141–159
57. Nakamura S, Takahira K, Tanabe G, Morikawa T, Sakano M, Ninomiya K, Yoshikawa M, Muraoka O, Nakanishi I (2010) Docking and SAR studies of salacinol derivatives as α-glucosidase inhibitors. Bioorg Med Chem Lett 20:4420–4423
58. Tanabe G, Nakamura S, Tsutsui N, Balakishan G, Xie W, Tsuchiya S, Akaki J, Morikawa T, Ninomiya K, Nakanishi I, Yoshikawa M, Muraoka O (2012) *In silico* design, synthesis and evaluation of 3'-*O*-benzylated analogs of salacinol, a potent α-glucosidase inhibitor isolated from an Ayurvedic traditional medicine "*Salacia*". Chem Commun 48:8646–8648
59. Tanabe G, Xie W, Balakishan G, Amer MFA, Tsutsui N, Takemura H, Nakamura S, Akaki J, Ninomiya K, Morikawa T, Nakanishi I, Muraoka O (2016) Hydrophobic substituents increase the potency of salacinol, a potent α-glucosidase inhibitor from Ayurvedic traditional medicine '*Salacia*'. Bioorg Med Chem 24:3705–3715
60. Ishikawa F, Jinno K, Kinouchi E, Ninomiya K, Marumoto S, Xie W, Muraoka O, Morikawa T, Tanabe G (2018) Diastereoselective synthesis of salacinol-type α-glucosidase inhibitors. J Org Chem 83:185–193
61. Takashima K, Sakano M, Kinouchi E, Nakamura S, Marumoto S, Ishikawa F, Ninomiya K, Nakanishi I, Morikawa T, Tanabe G (2021) Elongation of the side chain by linear alkyl groups increases the potency of salacinol, a potent α-glucosidase inhibitor from the Ayurvedic traditional medicine "*Salacia*", against human intestinal maltase. Bioorg Med Chem Lett 33:127751
62. Ishikawa F, Hirano A, Yoshimori Y, Nishida K, Nakamura S, Takashima K, Marumoto S, Ninomiya K, Nakanishi I, Xie W, Morikawa T, Muraoka O, Tanabe G (2021) Ligand compatibility of salacinol-type α-glucosidase inhibitors toward the GH31 family. RSC Adv 11:3221–3225
63. Yoshikawa M, Morikawa T, Murakami T, Toguchida I, Harima S, Matsuda H (1999) Medicinal flowers. I. aldose reductase inhibitors and three new eudesmane-type sesquiterpenes, kikkanols A, B, and C, from the flowers of *Chrysanthemum indicum* L. Chem Pharm Bull 47:340–345
64. Matsuda H, Morikawa T, Ueda H, Yoshikawa M (2001) Medicinal foodstuffs. XXVI. Inhibitors of aldose reductase and new triterpene and its oligoglycoside, centellasapogenol A and centellasaponin A, from *Centella asiatica* (Gotu Kola). Heterocycles 55:1499–1504
65. Matsuda H, Morikawa T, Toguchida I, Yoshikawa M (2002) Structural requirements of flavonoids and related compounds

for aldose reductase inhibitory activity. Chem Pharm Bull 50:788–795
66. Matsuda H, Morikawa T, Toguchida I, Harima S, Yoshikawa M (2002) Medicinal flowers. VI. Absolute stereostructures of two new flavanone glycosides and a phenylbutanoid glycosides from the flowers of *Chrysanthemum indicum* L.: their inhibitory activities of rat lens aldose reductase. Chem Pharm Bull 50:972–975
67. Yoshikawa M, Murakami T, Ishiwada T, Morikawa T, Kagawa M, Higashi Y, Matsuda H (2002) New flavonol oligoglycosides and polyacylated sucroses with inhibitory effects on aldose reductase and platelet aggregation from the flowers of *Prunus mume*. J Nat Prod 65:1151–1155
68. Xie H, Wang T, Matsuda H, Morikawa T, Yoshikawa M, Tani T (2005) Bioactive constituents from Chinese natural medicines. XV. Inhibitory effect on aldose reductase and structures of saussureosides A and B from *Saussurea medusa*. Chem Pharm Bull 53:1416–1422
69. Morikawa T, Xie H, Wang T, Matsuda H, Yoshikawa M (2008) Bioactive constituents from Chinese natural medicines. XXXII. Aminopeptidase N and aldose reductase inhibitors from *Sinocrassula indica*: structures of sinocrassosides B_4, B_5, C_1, and D_1–D_3. Chem Pharm Bull 56:1438–1444
70. Yoshikawa M, Nishida N, Shimoda H, Takada M, Kawahara Y, Matsuda H (2001) Polyphenol constituents from *Salacia* species: quantitative analysis of mangiferin with α-glucosidase and aldose reductase inhibitory activity. Yakugaku Zasshi 121:371–378
71. Yoshikawa M, Pongpiriyadacha Y, Kishi A, Kageura T, Wang T, Morikawa T, Matsuda H (2003) Biological activities of *Salacia chinensis* originating in Thailand: the quality evaluation guided by α-glucosidase inhibitory activity. Yakugaku Zasshi 123:871–880
72. Morikawa T, Kishi A, Pongpiriyadacha Y, Matsuda H, Yoshikawa M (2003) Structures of new friedelane-type triterpenes and eudesmane-type sesquiterpenes and aldose reductase inhibitors from *Salacia chinensis*. J Nat Prod 66:1191–1196
73. Kishi A, Morikawa T, Matsuda H, Yoshikawa M (2003) Structures of new friedelane- and norfriedelane-type triterpenes and polyacylated eudesmane-type sesquiterpene from *Salacia chinensis* Linn. (*S. prinoides* DC., Hippocrateaceae) and radical scavenging activities of principal constituents. Chem Pharm Bull 51:1051–1055
74. Nakamura K, Akaki J, Ishibushi F, Tani K, Morikawa T, Pongpiriyadacha Y, Muraoka O, Hayakawa T, Kakutani K (2015) Discrimination of *Salacia chinensis* based on the DNA sequence of the rDNA ITS region. Shoyakugaku Zasshi 69:53–58
75. Yamada K, Sato-Mito N, Nagata J, Umegaki K (2008) Health claim evidence requirements in Japan. J Nutr 138:1192S-1198S
76. Tsutani K, Takuma H (2008) Regulatory sciences in herbal medicines and dietary supplements. Yakugaku Zasshi 128:867–880
77. Nagata J, Yamada K (2008) Foods with health claims in Japan. Food Sci Technol Res 14:519–524
78. Shimizu M (2012) Functional food in Japan: current status and future of gut-modulating food. J Food Drug Anal 20(Suppl. 1):213–216
79. Kamioka H, Tsutani K, Origasa H, Yoshizaki T, Kitayuguchi J, Shimada M, Tang W, Takano-Ohmuro H (2017) Quality of systematic reviews of the foods with function claims registered at the consumer affairs agency Web site in Japan: a prospective systematic review. Nutr Res 40:21–31
80. Kamioka H, Tsutani K, Origasa H, Yoshizaki T, Kitayuguchi J, Shimada M, Wada Y, Takano-Ohmuro H (2019) Quality of systematic reviews of the foods with function claims in Japan: comparative before- and after-evaluation of verification reports by the consumer affairs agency. Nutrients 11:1583
81. Maeda-Yamamoto M, Ohtani T (2018) Development of functional agricultural products utilizing the new health claim labelling system in Japan. Biosci Boitechnol Biochem 82:554–563
82. Kobayashi M, Akaki J, Yamaguchi Y, Yamasaki H, Ninomiya K, Pongpiriyadacha Y, Yoshikawa M, Muraoka O, Morikawa T (2019) *Salacia chinensis* stem extract and its thiosugar sulfonium constituent, neokotalanol, improves HbA1c levels in *ob/ob* mice. J Nat Med 73:584–588
83. Vyas A, Syeda K, Ahmad A, Padhye S, Sarkar FH (2012) Perspectives on medicinal properties of mangiferin. Min Rev Med Chem 12:412–425
84. Matkowski A, Kus P, Góralska E, Wozniak D (2013) Mangiferin—a bioactive xanthanoid, not only from mango and not just antioxidant. Mini-Rev Med Chem 13:439–455
85. Ehianeta TS, Laval S, Yu B (2016) Bio- and chemical syntheses of mangiferin and congeners. BioFactors 42:445–458
86. Miura T, Ichiki H, Hashimoto I, Iwamoto N, Kato M, Kubo M, Ishihara E, Komatsu K, Okada M, Ishida T, Tanigawa K (2001) Antidiabetic activity of a xanthone compound, mangiferin. Phytomedicine 8:85–87
87. Telang M, Dhulap S, Mandhare A, Hirwani R (2013) Therapeutic and cosmetic application of mangiferin: a patent review. Expert Opin Ther Pat 23:1561–1580
88. Fomenko EV, Chi Y (2016) Mangiferin modulation of metabolism and metabolic syndrome. BioFactors 42:492–503
89. Singh AK, Raj V, Keshari AK, Rai A, Kumar P, Rawat A, Maity B, Kumar D, Prakash A, De A, Samanta A, Bhattacharya B, Saha S (2018) Isolated mangiferin and naringenin exert antidiabetic effect via PPARγ/GLUT4 dual agonistic action with strong metabolic regulation. Chem-Biol Int 280:33–44
90. Yoshikawa M, Ninomiya K, Shimoda H, Nishida N, Matsuda H (2002) Hepatoprotective and antioxidative properties of *Salacia reticulata*: preventive effects of phenolic constituents on CCl_4-induced liver injury in mice. Biol Pharm Bull 25:72–76
91. Saha S, Sadhukhan P, Sil PC (2016) Mangiferin: a xanthanoid with multiportent anti-inflammatory potential. BioFactors 42:459–474
92. Jyotshna KP, Shanker K (2016) Mangiferin: a review of sources and interventions for biological activeties. BioFactors 42:504–514
93. Luczkiewicz P, Kokotkiewicz A, Dampc A, Luczkiewicz M (2014) Mangiferin: a promising therapeutic agent for rheumatoid arthritis treatment. Med Hypoth 83:570–574
94. Sekiguchi Y, Mano H, Nakatani S, Shimizu J, Kataoka A, Ogura K, Kimira Y, Ebata M, Wada M (2017) Mangiferin positively regulates osteoblast differentiation and suppresses osteoclast differentiation. Mol Med Rep 16:1328–1332
95. Salles AJN, Daglia M, Rastrelli L (2016) The potential role of mangiferin in cancer treatment through its immunomodulatory, anti-angiogenic, apoptotic, and gene regulatory effects. BioFactors 42:475–491
96. Gold-Smith F, Fernandez A, Bishop K (2016) Mangiferin and cancer: mechanisms of action. Nutrients 8:396
97. Morikawa T, Akaki J, Pongpiriyadacha Y, Yoshikawa M, Ninomiya K, Muraoka O (2018) Simultaneous quantitative determination of polyphenol constituents in *Salacia* species from different regions by LC-MS. Jpn J Food Chem Saf 25:130–138
98. Shimoda H, Fujimura T, Makino K, Yoshijima K, Naitoh K, Ihota H, Miwa Y (1999) Safety profile of extractive from trunk of *Salacia reticulata* (Celastraceae). J Food Hyg Soc Jpn 40:198–205
99. Shimoda H, Furuhashi T, Naitou K, Nagase T, Okada M (2001) Thirteen-week repeat dose oral toxicity study of *Salacia reticulata* extract in rats. Jpn J Pharm Sci 46:527–540
100. Wolf BW, Weisbrode SE (2003) Safety evaluation of an extract from *Salacia oblonga*. Food Chem Toxicol 41:867–874

101. Oda Y, Yuasa A, Ueda F, Kakinuma C (2015) A subchronic oral toxicity study of *Salacia reticulata* extract powder in rats. Toxicol Rep 2:1136–1144
102. Jihong Y, Shaozhong L, Jingfeng S, Kobayashi M, Akaki J, Yamashita K, Tamesada M, Umemura T (2011) Effects of *Salacia chinensis* extract on reproductive outcome in rats. Food Chem Toxicol 49:57–60
103. Im R, Mano H, Nakatani S, Shimizu J, Wada M (2008) Safety evaluation of the aqueous extract Kothala Himbutu (*Salacia reticulata*) stem in the hepatic gene expression profile of normal mice using DNA microarrays. Biosci Biotechnol Biochem 72:3075–3083
104. Shimoda H, Asano I, Yamada Y (2001) Antigenicity and phototoxicity of water-soluble extract from *Salacia reticulata* (Celastraceae). J Food Hyg Soc Jpn 42:144–147
105. Ueda F, Iida A, Saito H, Seki S, Amao A, Yamate H (2019) Assessment of the effect and safety of salacinol in horses. J Equine Sci 30:105–111
106. Kobayashi M, Akaki J, Yamaguchi Y, Yamasaki H, Morikawa T, Ninomiya K, Yoshikawa M, Muraoka O (2016) Safety evaluation of long term and excess intake of the tablet containing hot water extract of *Salacia chinensis* –randomized double-blind placebo-controlled trials. Jpn Pharmacol Ther 44:399–408
107. Shimoda H, Kawamori S, Kawahara Y (1998) Effects of an aqueous extract of *Salacia reticulata*, a useful plant in Sri Lanka, on postprandial hyperglycemia in rats and humans. J Jpn Soc Nutr Food Sci 51:279–287
108. Kajimoto O, Kawamori S, Shimoda H, Kawahara Y, Hirata H, Takahashi T (2000) Effects of a diet containing *Salacia reticulata* on mild type 2 diabetes in humans—a placebo-controlled, crossover trial. J Jpn Soc Nutr Food Sci 53:199–205
109. Jayawardena MHS, de Alwis NMW, Hettigoda V, Fernando DJS (2005) A double blind randomized placebo controlled cross over study of a herbal preparation containing *Salacia reticulata* in the treatment of type 2 diabetes. J Ethnopharmacol 97:215–218
110. Shivaprasad HN, Bhanumathy M, Sushma G, Midhun T, Raveendra KR, Sushma KR, Venkateshwarlu K (2013) *Salacia reticulata* improves serum lipid profiles and glycemic control in patients with prediabetes and mild to moderate hyperlipidemia: a double-blind, placebo-controlled, randomized trial. J Med Food 16:564–568
111. Collene AL, Hertzler SR, Williams JA, Wolf BW (2005) Effects of a nutritional supplement containing *Salacia oblonga* extract and insulinogenic amino acids on postprandial glycemia, insulinemia, and breath hydrogen responses in healthy adults. Nutrition 21:848–854
112. Heacock PM, Hertzler SR, Williams JA, Wolf BW (2005) Effects of a medical food containing an herbal a-glucosidase inhibitor on postprandial glycemia and insulinemia in healthy adults. J Am Diet Assoc 105:66–71
113. Williams JA, Choe YS, Noss MJ, Baumgartner CJ, Mustad VA (2007) Extract of *Salacia oblonga* lowers acute glycemia in patients with type 2 diabetes. Am J Clin Nutr 86:124–130
114. Kobayashi M, Akaki J, Yamashita K, Morikawa T, Ninomiya K, Yoshikawa M, Muraoka O (2010) Suppressive effect of the tablet containing *Salacia chinensis* extract on postprandial blood glucose. Jpn Pharmacol Ther 38:545–550
115. Kobayashi M, Akaki J, Ninomiya K, Yoshikawa M, Muraoka O, Morikawa T, Odawara M (2021) Dose-dependent suppression of postprandial hyperglycemia and improvement of blood glucose parameters by *Salacia chinensis* extract: two randomized, double-blind, placebo-controlled studies. J Med Food 24:10–17

Authors and Affiliations

Toshio Morikawa[1,2] · Kiyofumi Ninomiya[1,2,5] · Genzoh Tanabe[1,3] · Hisashi Matsuda[4] · Masayuki Yoshikawa[1,4] · Osamu Muraoka[1,2,3]

1 Pharmaceutical Research and Technology Institute, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan

2 Antiaging Center, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan

3 Faculty of Pharmacy, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan

4 Kyoto Pharmaceutical University, 1 Shichono-cho, Misasagi, Yamashina-ku, Kyoto 607-8412, Japan

5 Present Address: School of Pharmacy, Shujitsu University, 1-6-1 Nishigawara, Naka-ku, Okayama, Okayama 703-8516, Japan