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Bioactive Glycosides in Citrus Fruit Peels[1)]

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Synopsis

Since 1980's we have been investigating bioactive compounds in citrus fruit peels. We have successfully isolated seventy-three glycosides including thirty-four new compounds. They were flavonoid glycosides, phenylpropanoid glycosides, terpenoid glycosides, limonoid glycosides, and alkyl glycosides. The biological activities of the compounds were studied for the utilization as hypotensive and hypertensive drugs. In this manuscript, recent works are briefly reviewed focussing on the isolation and mutual relationships between the structures of the compounds and their biological activities.

Introduction

The citrus fruit peels in general have been used as food with or without processing so far, and also extremely small amount of essential oils of the peels have been utilized as flavors, fragrances, or synthetic starting materials such as pharmaceutical and agricultural chemicals and other chemical products. However, a large parts of them have been wasted even now. Therefore, it is very important to find an efficient way to utilize of citrus fruit peels as one of the valuable organic chemical resources.

Citrus fruits is used for aromatic stomachic, diaphoresis, expectorans, a bath charges as crude drug and folk medicine from ancient times in China and Japan. Agents with biological activities such as inhibitory action of intestine exercise and antiallergic action may be involved.

Since 1980's we have been investigating[2-28)] bioactive compounds in citrus fruit peels. We have chosen eleven kinds of citrus fruit peels: namely lemon (*Citrus limon*), grapefruit (*Citrus paradishi*) and orange (*Citrus sinensis*) which are imported from the United States, unshiu (*Citrus unshiu*), hassaku (*Citrus hassaku*), zabon (*Citrus gradis*), iyo-kan (*Citrus iyo*) and amanatsu (*Citrus natsudaidai*) produced abundantly in Japan, and kinkan (*Fortunella japonica*), sudachi (*Citrus sudachi*) and yuzu (*Citrus junos*), part of the peels of which are edible. We have successfully isolated seventy-three glycosides including thirty-four new compounds. They were flavonoid glycosides, phenylpropanoid glycosides, terpenoid glycosides, limonoid glycosides, and alkyl glycosides. The biological activities of these compounds were studied for the utilization as hypotensive and hypertensive drugs.

In this manuscript, recent works are briefly reviewed focussing on the isolation and mutual relationships between the structures of the compounds and their biological activities.

Isolation and Purification

Method A The fresh peel of each citrus fruit was kept in hot H_2O at 96° for 20 min, chopped using a commercial blender, and homogenized after making up the total volume to 3 l with hot H_2O. Cold EtOH (7 l) was added to the hot H_2O solution, and the mixture was allowed to stand overnight in the dark. Then the hot H_2O extract was treated with *n*-hexane and *n*-BuOH, successively. A saturated

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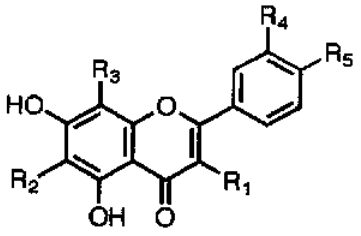
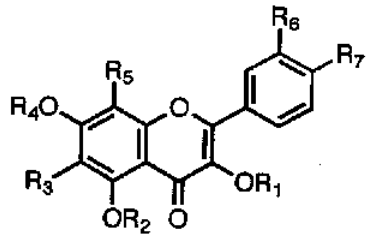
aqueous solution of lead subacetate was added to the *n*-BuOH extract, and the resulting precipitates were removed by filtration.

Flavonoid glycosides[4-14] were obtained by the following procedures. The precipitates were treated with a saturated aqueous solution of sodium carbonate. After stirring for 1 hr, a white precipitate of lead carbonate was removed by filtration, and the filtrate adjusted to pH 5.3 with 6M HCl was extracted with *n*-BuOH to afford a mixture of crude flavonoid glycosides from the *n*-BuOH solution. Flavonoid glycosides (1 - **51**, Fig.1 and Table 1) were purified by gel filtration on HW-40F TSK gel and by column chromatography on silica gel.

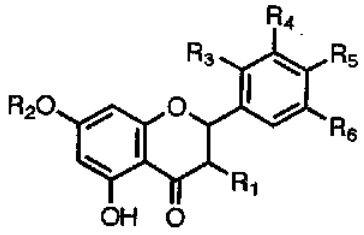
Phenylpropanoid glycosides[15-24], terpenoid glycosides[16-20], and alkyl glycosides[22] were obtained by the following procedures. The filtrate was adjusted to pH 9.0 and then extracted with *n*-BuOH to obtain a mixture of crude phenylpropanoid glycosides, terpenoid glycosides, and alkyl glycosides from the *n*-BuOH solution. Phenylpropanoid glycosides (**52, 53, 54, 58, 59, 60,** Fig. **2** and Table 2), terpenoid glycosides (**61** - **67**, Table 3), and alkyl glycosides (**70** - **73**, Fig. 3 and Table 4) were purified by gel filtration on HW-40F TSK gel and by column chromatography on silica gel.



di-*C*-glucosyl flavones (**1** - **6**)
mono-*C*-glucosyl flavones (**7** - **12**)
C-xyloglucosyl flavone (**13**)
C-rhamnoglucosyl flavones (**14** -**18**)
flavone glycosides (**33** - **38**)

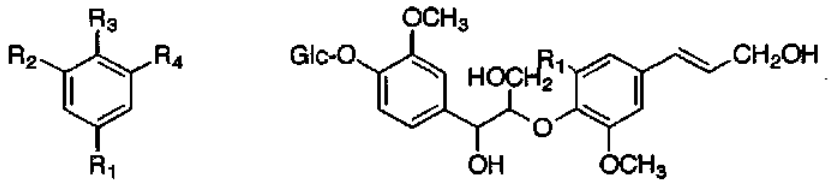


flavonol glycosides (**19** - **32**)



flavanone glycosides (**39** - **51**)

Fig. 1. Structures of flavonoid glycosides isolated from citrus fruit peels.



(52 - 57) (58, 59)

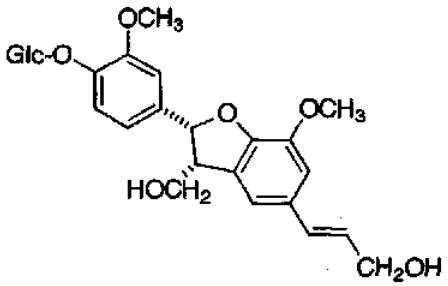


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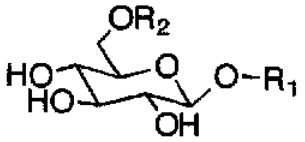
Fig. 2. Structures of phenylpropanoid glycosides isolated from citrus fruit peels.



(70 - 73)

Fig. 3. Structures of alkyl glycosides isolated from citrus fruit peels.

Method B The peel obtained from each citrus fruit was air-dried, chopped by a commercial blender, and homogenized after adding hot H_2O. The mixture was kept at 96° for 30 min and then filtered. The filtrate was deposited on an Amberlite XAD-2 column, washed with H_2O, and fractionated by successive elution with 20% MeOH-H_2O, 50% MeOH-H_2O, and MeOH. The 50% MeOH-H_2O eluate was concentrated *in vacuo*, dissolved in MeOH, charged on a neutral Al_2O_3 column, and chromatographed with 50% MeOH-H_2O. The eluate was concentrated *in vacuo*, giving a mixture of crude phenylpropanoid glycosides and limonoid glycosides. Phenylpropanoid glycosides (**52**, **53**, **55**, Fig. 2 and Table 2)[24] and limonoid glycosides (**68**, **69**, Table 3)[25] were purified by column chromatography on silica gel and by gel filtration on HW-60F TSK gel.

Method C The peel obtained from each citrus fruit was chopped and extracted with cold MeOH in darkness for three days. The MeOH extract was successively treated with *n*-hexane, EtOAc and *n*-BuOH. The *n*-BuOH extract was chromatographed over a Diaion HP 20 column. The column was

washed with H_2O, and successively eluted with 20% MeOH-H_2O, 60% MeOH-H_2O and MeOH. The 20% MeOH-H_2O eluate was concentrated *in vacuo*, giving a mixture of crude phenylpropanoid glycosides. Phenylpropanoid glycosides (**52, 53, 54, 56, 57**, Fig. 2 and Table 2)[26] were purified by column chromatography on silica gel and by gel filtration on HW-40F TSK gel.

Biological Activity

Flavonoid Glycosides

Flavonoids have already been well documented for numerous biological activities such as effect which increase hip systole and decrease heart rate[29,30], and catharsis effect[31,32], effect for the core which coronary vessel is widened and improve recycle in myocardium[33], and a component, vitamin P (hesperidin)[34,35] exhibits complete response in scorbutus with vitamin C or capillary bursting prevention effect declining capillary permeability. Recently, antioxidative activity was reported on flavonoids. For example, it is known that flavonols such as quercetin restrains decoloration of pigmentary carotenoids caused by $^1O_2$[36], and also exhibited radical scavenging ability on non-enzymatic generation of $O_2^{-\bullet}$. Although rutin (**25**) which is a glycoside of quercetin exhibited such an antioxidative activity, it is weak compared with quercetin[37].

We have been investigating hypotensive substances in food which have no need of concern about drug side reactions, contrary to the usual hypotensive agent. The hot H_2O extract of citrus fruits was examined with intravenous administration for SHR (spontaneously hypertensive rats) and SHR-SP (stroke-prone spontaneously hypertensive rats). As a result, we confirmed that flavonoid glycosides have conspicuous hypotensive effect[27,28]. We also found that many components among flavonoid glycosides in citrus fruits exhibits a strong hypotensive effect. Thus, we confirmed one of major components of hypotensive effect in citrus fruit peels to be a flavonoid glycoside. In the study of the peels of nine citrus fruit, we have successfully isolated fifty-one flavonoid glycosides (**1** - **51**) including twenty-two new compounds. Then, we have studied the mutual relationship between their structures and hypotensive activity by injecting those flavonoid glycosides intravenously into SHR-SP.

Di-C-glucosyl flavones Strong depressive effects were found for the following four compounds: namely apigenin (**1**) and diosmetin (**2**) having C-C bound glucose at C-6 and C-8 of the flavonoid nucleus, apigenin (**3**) and acacetin (**4**) having C-C bound glucose at C-3 and C-6. The strongest hypotensive effects are found in 6,8-di-C-glucosylapigenin (**1**) and 3,6-di-C-glucosylapigenin (**3**) after stomachic administration. In such case C-glucosyl flavonoids are considered to be not hydrolyzed by the digestion enzyme and hydrochloric acid in the stomach. Apigenin (**5**) and diosmetin (**6**) having C-C bound glucose at C-3 and C-8 do not exhibit any hypotensive effect.

Mono-C-glucosyl flavones Diosmetin (**7** or **8**) having the glucosyl group at C-6 or C-8 exhibits a moderate hypotensive effect, whereas isovitexin (**9**) shows only a weak hypotensive effect.

C-Rhamnoglucosyl flavones (C-xyloglucosyl flavones) Apigenin (**14**) and luteorin (**15**) having C-C bound neohesperidose at C-8 exhibit moderate hypotensive effects, whereas 2″-*O*-xylosylvitexin (**13**) exhibited a weak hypotensive effect. However, acacetin (**18**) and diosmetin (**17**) having C-C bound neohesperidose at C-6 and C-8, respectively, exhibit virtually no hypotensive effect.

Flavonol glycosides Compounds **19** and **21** having fully substituted A-ring exhibit strong hypotensive effects. Compound **20** exhibits a moderate hypotensive effect. Also limocitrin (**22**) and isolimocitrin (**23**) containing C-O bound glucose at C-3 exhibit weak hypotensive effects, but limocitrin (**24**) having C-O bound rhamnose does not exhibit any hypotensive effect. Rutin (**25**) exhibits a strong hypotensive effect, whereas limocitrins having C-O bound rutinose (**26**) and 3-hydroxy-3-methylglutaric acid (**28**), respectively, at C-3 exhibit weak hypotensive effects. Also compounds (**29**,

30, and **31**) having 3-hydroxy-3-methylglutaric acid at C-3 exhibit weak hypotensive effects. Narcissin (**32**), however, does not exhibit any hypotensive effect.

Flavone glycosides Apigenins (**34, 35**) containing C-O bound neohesperidose and rutinose at C-7 exhibit moderate hypotensive effects, whereas luteorin 7-*O*-rutinose (**36**) does not exhibit any hypotensive effect. The compound (**38**) having C-O bound glucose at C-4' and the flavonoid glycoside (**37**) having the fully substituted A-ring exhibit weak hypotensive effects.

Flavanone glycosides Naringenin (**39**) containing C-O bound glucose at C-4' and rutinose at C-7 exhibits strong hypotensive effect. Also compounds **40** and **41** exhibit weak hypotensive effects, but poncirin (**42**) and eriocitrin (**43**) exhibit almost no hypotensive effect, other components (**44 - 47**) do not exhibit hypotensive effect at all. The hypotensive effects of **48 - 51** have not been determined, because of their poor solubility in water.

A mutual relationship between the structures of flavonoid glycosides and their physiological activity As we have shown so far, fifty-one kinds of flavonoid and flavanoid glycosides have now been separated, and their structures and physiological activity have been investigated. As a result, we have found that the kinds and the position of the substituents and the sugar moieties strongly effect the physiological activity, as shown in Table 1. In particular, components having fully substituted A-ring or components having C-C bound glucose at C-6 of the flavonoid nucleus tend to show strong activity, as shown in Fig. 4. We have also found that the kind of the sugar moieties at C-3 of the flavonol nucleus strongly effects the physiological activity[2, 3, 14].

Table 1. Hypotentive effects of flavonoid glycosides isolated citrus fruit peels

Compounds	Maximal decrase of blood pressure (mmHg)	Citrus fruit peels
di-C-glucosy flavones		
6,8-di-C-glucosylapigenin **(1)**	-86(0.5mg/b.w.,i.v.)	lemon, kinkan**, zabon**
	-30(1.0mg/b.w.,i.p.)	grapefruit**, unripe unshiu**
6,8-di-C-glucosyldiosmetin **(2)**	-53(1.0mg/b.w.,i.v.)	lemon
3,6-di-C-glucosylapigenin **(3)***	-50(1.0mg/b.w.,i.v.)	unshiu, sudachi
	-20(1.5mg/b.w.,i.p.)	
3,6-di-C-glucosylacacetin **(4)***	-35(0.5mg/b.w.,i.v.)	kinkan
3,8-di-C-glucosylapigenin **(5)***	0(1.0mg/b.w.,i.v.)	sudachi, yuzu, zabon, hassaku, orange, unripe unshiu
3,8-di-C-glucosyldiosmetin **(6)***	0(1.0mg/b.w.,i.v.)	sudachi, orange
mono-C-glucosyl flavones		
6-C-glucosyldiosmetin **(7)**	-33(1.0mg/b.w.,i.v.)	lemon
8-C-glucosydiosmetin **(8)**	-30(1.0mg/b.w.,i.v.)	lemon
isovitexin (6-C-glucosylapigenin) **(9)**	-12(1.0mg/b.w.,i.v.)	lemon
vitexin (8-C-glucosylapigenin) **(10)**		kinkan
8-C-glucosylacacetin **(11)**		kinkan
6-C-glucosylacacetin **(12)**		kinkan
C-rhamnoglucosyl flavones (C-xyloglucosyl fravone)		
2"-*O*-xylosylvitexin (8-C-xyloglucosylapigenin) **(13)**	-18(1.0mg/b.w.,i.v.)	orange
2"-*O*- α-rhamnosylvitexin(8-C-rhamnoglucosylapigenin) **(14)**	-28(0.5mg/b.w.,i.v.)	kinkan**
2"-*O*- α-rhamnosylorientin(8-C-rhamnoglucosylluteorin) **(15)***	-25(0.5mg/b.w.,i.v.)	kinkan
2"-*O*- α-rhamnosyl-4'-*O*-methylvitexin(8-C-rhamnoglucosylacacetin) **(16)***	-4(0.5mg/b.w.,i.v.)	kinkan
2"-*O*- α-rhamnosyl-4'-*O*-methylorientin(8-C-rhamnoglucosyldiosmetin) **(17)***	0(0.5mg/b.w.,i.v.)	kinkan
2"-*O*- α-rhamnosyl-4'-*O*-methylisovitexin(6-C-rhamnoglucosylacacetin) **(18)***	0(0.5mg/b.w.,i.v.)	kinkan
flavonol glycosides		
limocitrol 3-β-D-glucopyranoside **(19)**	-63(1.0mg/b.w.,i.v.)	lemon
3,7,4'-trihydroxy-5,8,3'-tetramethoxyflavone-3-β-D-glucopyranoside **(20)***	-28(1.0mg/b.w.,i.v.)	unripe unshiu
3-hydroxy-5,6,7,8,3',4'-hexamethoxyflavone 3-β-D-glucopyranoide **(21)***	-12(0.3mg/b.w.,i.v.)	unshiu, orange, unripe unshiu
limocitrin3-β-D-glucopyranoside **(22)**	-12(1.0mg/b.w.,i.v.)	lemon, unshiu**, unripe unshiu
isolimoitrine3-β-D-glucopyranoside **(23)**	-11(0.5mg/b.w.,i.v.)	unshiu**
limocitrine3-*O*-rhamnopyranoside **(24)***	0(1.0mg/b.w.,i.v.)	unshiu
rutin **(25)**	-45(0.015mg/b.w.,i.v.)	unshiu, unripe unshiu
limocitrin 3-*O*-rutinose **(26)***	-10(1.0mg/b.w.,i.v.)	lemon
limocitrin 3-*O*-{[3-hydroxy-3-methylglutaryl (1→2)]-β-D-glucopyranoside} **(27)***		lemon

Continued

Table 1. (*Continued*)

limocitrin 3-*O*- {[3-hydroxy-3-methylglutaryl(1→6)]- β-D-glucopyranoside} (28)*	-20(1.0mg/b.w.,i.v.)	unripe unshiu
3,7,4'-trihydroxy-5,6,8,3'-tetramethoxyflavone 3-*O*- {[3-hydroxy-3-methylglutaryl (1→6)]- β-D-glucopyranoside} (29)*	-15(1.0mg/b.w.,i.v.)	unripe unshiu
limocitrol 3-*O*- {[5-α-glucopyranosyl-3-hydroxy-3-methylglutaryl (1→2)]- β-D-glucopyranoside} (30)*	-15(1.0mg/b.w.,i.v.)	lemon
limocitrol 3-*O*- {[5-α-glucopyranosyl-3-hydroxy-3-methylglutaryl (1→2)]- β-D-glucopyranoside} (31)*	-13(1.0mg/b.w.,i.v.)	lemon, unshiu, hassaku
narcissin (32)	0(1.0mg/b.w.,i.v.)	unshiu**, unripe unshiu
flavone glycosides		
acacetin 7-*O*-neohesperidose (33)	-35(1.0mg/b.w.,i.v.)	kinkan
apigenin 7-*O*-neohesperodose (34)	-25(1.0mg/b.w.,i.v.)	lemon**, hassaku
apigenin 7-*O*-rutinose (35)	-22(1.0mg/b.w.,i.v.)	lemon**
luteorin 7-*O*-rutinose (36)	0(1.0mg/b.w.,i.v.)	lemon**
sudachiin A (37)	-12(1.0mg/b.w.,i.v.)	sudachi
sudachiin B (38)*	-13(1.0mg/b.w.,i.v.)	sudachi
flavanone glycosides		
naringenin 4'-*O*-glucopyranosy-7-*O*-rutinose	-47(1.0mg/b.w.,i.v.)	unripe unshiu
naringenin 7-*O*- [[α-rhamnopyranosyl(1→2)] - [α-rhamnopyranosyl (1→6)] - β-D-glucopyranoside] (40)*	-12(1.0mg/b.w.,i.v.)	yuzu
5,7,2',3',5'-pentahydroxyflavanone 7-*O*-rutinose (41)*	-18(1.0mg/b.w.,i.v.)	lemon
poncirin (42)	-7(0.5mg/b.w.,i.v.)	grapefruit, kinkan
eriocitrin (43)	-5(1.0mg/b.w.,i.v.)	lemon
hesperetin 7-*O*- [[α-rhamnopyranosyl (1→2)] - [α-rhamnopyranosyl (1→6)] - β-D-glucopyranoside] (44)*	0(1.0mg/b.w.,i.v.)	sudachi, yuzu
3,5,7-trihydroxy-3'-methoxyflavanone 7-*O*-neohesperidose(45)*	0(1.0mg/b.w.,i.v.)	yuzu
naringin (46)	0(1.0mg/b.w.,i.v.)	grapefruit, yuzu, hassaku, zabon
narirutin (47)	0(1.0mg/b.w.,i.v.)	unshiu, yuzu, orange, grapefrut, unripe unshiu
prunin (48)		zabon
hesperidin (49)		lemon, unshiu, yuzu, sudachi, hassaku, unripe unshiu
neohesperidin (50)		sudachi
homoeriodictiol 7-*O*-neohesperidose (51)		yuzu**

* : new compounds
** : The compounds have not been previously found in those citrus fruits.

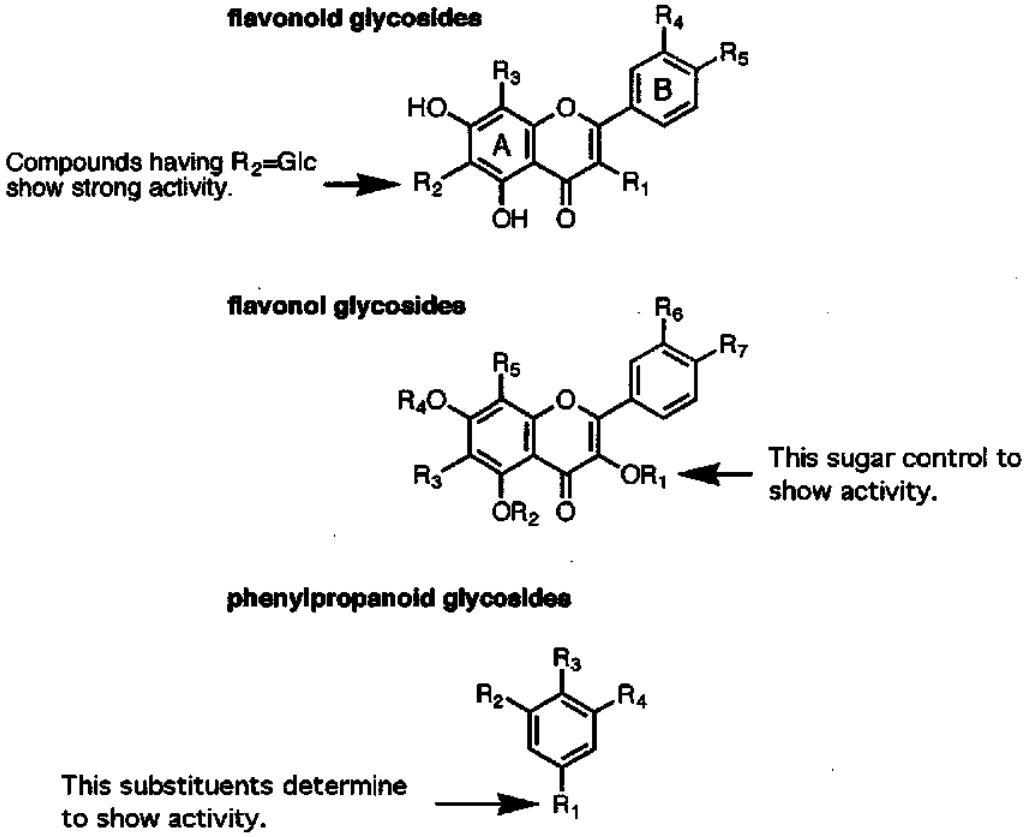


Fig. 4. A mutual relationship between the structures of the compounds and their biological activities.

Phenylpropanoid Glycosides

Phenylpropanoids have been known for numerous biological activities such as alleviation of fever, relief, antioxidative activity, growth inhibitory activity for higher plant, insect attraction activity, and so on.

Nine phenylpropanoid glycosides (**52** - **60**) including six new compounds have been successfully isolated from ten kinds of citrus fruit peels. The effect of these phenylpropanoid glycosides on the blood pressure was examined by using SHR-SP. Compounds **52** and **53** exhibited hypertensive effects, whereas compounds **54**, **55**, **56**, **58** and **60** exhibited hypotensive effects, as shown in Table 2. The finding of the presence of components having a hypertensive effect is of particular importance in view of the other components with the same fundamental skeleton showing the opposite physiological effect. In particular, by comparing **52** with **55**, it was clear that **52** showed a hypertensive effect, while **55** showed a hypotensive effect by only a difference in the position of sugar moiety. Comparisons between **52** and **54**, and between **52** and **56** showed the opposite physiological effect is induced by a difference in the substituents of C-1. Therefore, we found that the substituents of C-1 (R_1) were critical in the physiological activity of the phenylpropanoid glycosides [2,3], as shown in Fig. 4.

Table 2. Hypertentive and hypotensive effects of phenyl propanoid glycosides isolated from citrus fruit peels

Compounds	Maximal increase and decrease of blood pressure (mmHg)	Citrus fruit peels
phenylpropanoid glycosides		
coniferin (**52**)	+10(1.0mg/b.w.,i.v.)	lemon, unshiu, kinkan, yuzu, sudachi, hassaku, zabon, iyo, orange, amanatsu
syringin (**53**)	+16(1.0mg/b.w.,i.v.)	lemon, unshiu, kinkan, yuzu, sudachi, hassaku, zabon, iyo, orange, amanatsu
citrusin C* (**54**, 1-(4-β-D-glucopyranosyl-3-methoxyphenyl)propane-2-en)	-20(1.0mg/b.w.,i.v.)	kinkan, hassaku, zabon, orange, amanatsu
citrusin D* (**55**, 3-(4-hydroxy-3-methoxyphenyl)-1-β-D-glucopyranosyl-2-propene)	-30(1.0mg/b.w.,i.v.)	unshiu
citrusin E* (**56**, methyl 3-[4-β-D-glucopyranosyl-3-methoxyphenyl)propionate)	-25(0.5mg/b.w.,i.v.)	lemon
citrusin F* (**57**, methyl 3-[4-(6-*O*-α-glucopyranosyl-β-glucopyranosyl)-3-hydroxyphenyl] propionate)		lemon
citrusin A* (**58**, 1-(4-β-D-glucopyranosyl-3-methoxyphenyl)-2-[2-methoxy-4-[1-(*E*)-propane-3-ol] phenoxy] propane-1,3-diol)	-11(1.0mg/b.w.,i.v.)	lemon, unshiu, kinkan, yuzu, sudachi, hassaku, zabon, iyo, orange, amanatsu
citrusin B* (**59**, 1-(4-β-D-glucopyranosyl-3-methoxyphenyl)-2-[2,6-dimethoxy-4-[1-(*E*)-propane-3-ol] phenoxy] propane-1,3-diol)		lemon, unshiu, kinkan, yuzu, sudachi, hassaku, zabon, iyo orange, amanatsu
dehyrodiconiferyl alcohol 4-β-D-glucopyranoside (**60**)	-14(1.0mg/b.w.,i.v.)	lemon, kinkan, yuzu, hassaku, orange, amanatsu

* : new compounds

Table 3. Terpenoid glycosides isolated from citrus fruit peels

Compounds	Citrus fruit peels
terpenoid glycosides	
trans-carveol 6-β-D-glucopyranoside (**61**)*	unshiu, unripe unshiu, yuzu, hassaku, orange
α-terpineol 8-β-D-glucopyranoside (**62**)*	orange
(2E,6R)-2,6-dimethyl-2,7-octadien-6-ol-1-*O*-β-D-glucopyranoside (**63**)	unshiu, unripe unshiu, yuzu, hassaku, orange
(1S,4R,6S)-1,3,3-trimethyl-2-oxabicyclo [2.2.2] octan-6-*O*-β-D-glucopyranoside (**64**)*	unripe unshiu
(4S,6S)-6-*O*-β-D-glucopyranosyl-p-menth-1-en-3-one (**65**)*	sudachi
vomifoliol 9-*O*-β-D-glucopyranoside (**66**)	unshiu, unripe unshiu, yuzu, hassaku, orange
(6R,7E,9R)-9-hydroxymegastigma-4,7-dien-3-one-9-*O*-β-D-glucopyranoside (**67**)	unshiu, unripe unshiu, hassaku, orange
limonoid glycosides	
ichangin 4-β-D-glucopyranoside (**68**)*	lemon, unshiu
nomilinic acid 4-β-D-glucopyranoside (**69**)*	lemon, unshiu

* : new compounds

Terpenoid Glycosides

Since terpenes are well known to be one of the most widely distributed components in food and are utilized as industrial intermediates for perfumes, agricultural chemicals, and medicine, numerous

physiological activities of terpenes have already been well documented. However, very little is known so far about the activity of the glycosides of terpenoids. Therefore, the studies on their physiological activities are highly anticipated.

Seven terpenoid glycosides (**61** - **67**) including four new compounds have been successfully isolated from five kinds of citrus fruit peels. The effect of these terpenoid glycosides on seed germination was examined by using lettuce seeds. However, these terpenoid glycosides were found to have no effect on the germination of lettuce seed.

Limonoid Glycosides

Limonoids[38-42] are known as bitter taste components of Rutaceae and Meliaceae. Recently, Lam *et al.*[43-45] reported that limonoids have an antitumor activity.

Two new limonoid glycosides (**68**, **69**) have been successfully isolated from lemon and unshiu peels. The antitumor activity of these limonoid glycosides was examined by using P-388 leukemia mouse. However, these limonoid glycosides were found to have no activity.

Table 4. Hypertentive and hypotensive effects of alkyl glycosides isolated from citrus fruit peels

Compounds	Maximal increase and decrease of blood pressure (mmHg)	Citrus fruit peels
alkyl glycosides		
ethyl-1-*O*-*β*-D-glucopyranoside (**70**)	-25(1.0mg/b.w.,i.v.)	yuzu
propyl-1-*O*-*β*-D-glucopyranoside (**71**)		yuzu
hexyl-1-*O*-*β*-D-glucopyranoside (**72**)	+25(1.0mg/b.w.,i.v.)	iyo
hexyl-1-*O*-(6-*O*-apiosyl-*β*-D-glucopyranoside (**73**)	+28(1.0mg/b.w.,i.v.)	hassaku

Alkyl Glycosides

Four alkyl glycosides (**70** - **73**) were obtained from the hot water extract of citrus fruit peels. The effect of these alkyl glycosides on the blood pressure was examined by using SHR-SP. Compound **70** exhibited hypotensive effect, whereas compounds **72** and **73** exhibited hypertensive effects, as shown in Table 4. The finding of the components having a hypertensive effect (**72**, **73**) is of particular importance in view of the presence of the other components having the different carbon number of alkyl group which show the opposite physiological effect (**70**). Thus, we found that the carbon number of alkyl group was the most critical for the mutual relationship between the structure of the alkyl glycosides and their physiological activity.

Conclusions

During the course of our studies on physiologically active substances in citrus fruit peels for exploiting the most effective utilization of the peels, we have analyzed eleven kinds of citrus fruits. As a consequence, we have successfully isolated seventy-three glycosides including thirty-four new compounds. Among these compounds, we found a series of flavonoid glycosides having a hypotensive effect, and phenylpropanoid glycosides and alkyl glycosides having an interesting effect on the blood pressure of SHR-SP.

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柑橘類果皮中の生物活性配糖体

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摘　要

有用植物資源として、貴重な柑橘類果皮のより高度な利用開発の基礎研究として、著者らは11種の柑橘類果皮中から34種の新規化合物を含む73種の生物活性物質の分離に成功した。これらの化合物の構造と生物活性の相関性について考察した。