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〈Review〉

Herbal Medicines Are Activated by Intestinal Microflora

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Abstract – Glycosides of herbal medicines, such as glycyrrhizin, ginsenosides, kalopanaxsaponins, rutin and ponicirin, were studied regarding their metabolic fates and pharmacological actions in relation to intestinal bacteria using germ-free, gnotobiotic and conventional animals. When glycyrrhizin (GL) was orally administered, 18β-glycyrrhetinic acid (GA), not GL, was detected in plasma and intestinal contents of gnotobiotic and conventional rats. However, GA could not be detected in germ-free rats. When GL was incubated with human intestinal bacteria, it was directly metabolized to GA (>95%) or via 18β-glycyrrhetinic acid-3-β-D-glucuronide (<5%). Orally administered GL was effective in gnotobiotic and conventional rats for liver injury induced by carbon tetrachloride, but was not effective in germ-free rats. When ginseng saponins were orally administered to human beings, compound K in the plasma was detected, but the other protopanxadiol saponins were not detected. The compound K was active for tumor metastasis and allergy. When kalopanaxsaponins were incubated with human intestinal microflora, they were metabolized to kalopanaxsaponin A, kalopanaxsaponin I and hederagenin. These metabolites were active for rheumatoid arthritis and diabetic mellitus while the other kalopanxsaponins were not. When flavonoid glycosides were orally administered to animals, aglycones and/or phenolic acids were detected in the urine. The metabolic pathways proceeded by intestinal bacteria rather than by liver or blood enzymes. These metabolites, aglycones and phenolic acids, showed antitumor, antiinflammatory and antiplatelet aggregation activities. These findings suggest that glycosides of herbal medicines are prodrugs.

Keywords – herbal medicine, intestinal bacteria, glycyrrhizin, ginsenoside, kalopanaxsaponin, flavonoid

Introduction

The herbal medicines are used as ingredients of herbal formulae, which are composed of more than two kinds of herbal medicines, and orally administered. These herbal medicines contain many kinds of glycosides as main and/or active constituents, but the mechanism of pharmacological actions has not been clarified.

When herbal medicines are administered to human, their components should be metabolized in intestinal tract by intestinal microflora before their absorptions. Glycosides containing hydrophilic sugars are generally difficult to be absorbed from the gastrointestinal tract. Therefore, orally administered glycosides can be transformed by intestinal microflora and their hydrophobic metabolites can be absorbed into the blood and the biotransformants seem to exhibit the pharmacological actions. This review is intended to focus on the recent advances of the relation of intestinal microflora to pharmacological actions of natural glycosides, such as glycycrrhizin, ginsenosides, kalopanaxsaponins and flavonoids.

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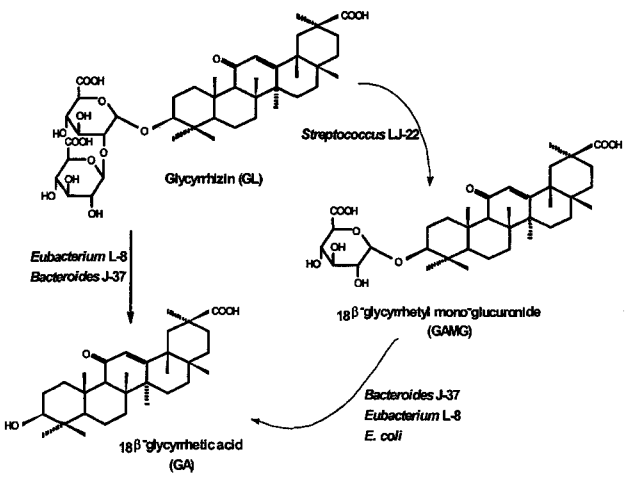
Glycyrrhizin – Glycyrrhizin (18β-glycyrrhetinic acid-3-O-(β-D-glucuronopyranosyl-(12)-β-D-glucuronopyranoside, GL), which is a main component of licorice extract (*Glycyrrhiza glabra*), is ingested orally as a sweetener as well as being a component in Oriental medicine. GL shows various pharmacological actions including steroid-like, antiviral and antiinflammatory activities (Kumagai *et al.*, 1957; Pompeo *et al.*, 1979; Abe *et al.*, 1982; Finney *et al.*, 1958; Tangri et al., 1965; Conn *et al.*, 1968). By the oral administration of GL to human, 18b-glycyrrhetinic acid (GA) was detected in the sera, but GL was not (Nakano *et al.*, 1980). Hattori *et al.* (1983) reported that GL is transformed to GA by human intestinal bacteria.

Akao *et al.* (1987) reported that GL was directly metabolized to GA by the β-glucuronidase of *Eubacterium* GLH, a human intestinal bacterium. Kim *et al.* (1996; 1997) also isolated *Eubacterium* L-8 and *Streptococcus* LJ-22, two human intestinal bacteria metabolizing GL. The former directly transformed GL to GA like the previous report (Akao *et al.*, 1987). However, the latter did not transform GL to GA, but transformed GL to 18β-glycyrrhetinic acid-3-β-D-glucuronide (GAMG) (Kim *et al.*, 1999). This metabolic pathway of GL to GAMG in fecal suspension



Scheme 1. Proposed metabolic pathway of glycyrrhizin by human intestinal bacteria.

was too weak (<5%) compared to the other pathway, which directly transforms GL to GA. On the other hand, if GL was intravenously administered, it is metabolized to GA *via* GAMG by liver β-glucuronidase (Akao *et al.*, 1991). However, this enzyme did not directly hydrolyzed GL to GA (Scheme 1).

Kobashi and Akao (1997) reported the metabolism and pharmacological action of GL in germ-free and *Eubacterium* GLH-infected gnotobiotic rats. The fecal and caecal enzyme activities, β-glucuronidase and glycyrrhizin-hydrolyzing activities, of these rats were significantly different: these enzyme activities in germ-free rats were not detected, but in gnotobiotic and conventional rats, they were potent (Table 1). When GL (100 mg/kg) was orally administered to these rats, GA was not detected at all for 17 h in feces and caecal contents of germ-free rats, but GA was detected for 17 h in cumulative feces and caecal contents of gnotobiotic rats. GL was not detected in plasma of these rats by RIA and HPLC assays. However, GA was detected

Table 1. Activities of β-glucuronidase and glycyrrhizin-hydrolase of faeces and caecal contents in conventional, gnotobiotic and germ-free rats

	β-Glucuronidase (nmol min mg^{-1})		Glycyrrhizin-hydrolase (pmol min mg^{-1})	
	Feces	Cecum	Feces	Cecum
Conventional	10.8±1.2	7.39±0.94	81.0±12.3	39.3±17.9
Gnotobiotic	1.68±0.28	2.40±0.41	31.7± 3.7	31.3±11.8
Germ-free	ND	ND	ND	ND

ND : not detected.
Values represent mean±SE (n=6 except for seven gnotobiotic rats).

Table 2. Plasma glycyrrhetic acid in conventional, gnotobiotic and germ-free rats 17 hr after oral administration of glycyrrhizin

	18β-Glycyrrhetic acid (nmol/ml)		Glycyrrhizin (nmol/ml)	
	RIA	HPLC	RIA	HPLC
Conventional	0.767±0.237	0.600±0.240	ND	ND
Gnotobiotic	1.24±0.53	1.70±0.72	ND	ND
Germ-free	ND	ND	ND	ND

ND, not detected.

in plasma of gnotobiotic and conventional rats, not germ-free rats (Table 2).

The hepatoprotective activity of GL at a daily dose of 100 mg/kg for 3 days was observed in gnotobiotic hepatotoxic rats induced by carbon tetrachloride, however no activity was shown in germ-free group (Fujita *et al.*, 1978). Shim *et al.* (2000) also measured the hepatoprotective activity of GL and GA on carbon tetrachloride-induced liver-damaged rats (Table 3). Oral administration of GL and intraperitoneal administration of GA showed the protection for hepatotoxicity of rats. However, intraperitoneal administration of GL did not show the activity. Antiviral activity of GA was more potent than GL in *in vitro* assay system (Kim *et al.*, 2000). These results suggest that if GL is orally administered to human, it is converted to GA by human intestinal bacteria

Table 3. The preventive effect of glycyrrhizin and 18β-glycyrrhetinic acid on CCl_4-induced hepatotoxicity in rats

Group	CCl_4	Dose (mg/kg)	Adm. Route	AST (Karmen unit)	ALT (Karmen unit)
Normal control	−	0		432.0±91.2[a)]	351.0±59.2
CCl_4 control	+	0		3110.3±668.4[#]	2052.3±495.4[#]
GL	+	100	*p.o.*	1560.8±665.7*	738.8±170.4*
GL	+	50	*i.p.*	2784.6±676.5	1802.5±855.1
GL	+	100	*i.p.*	2653.2±465.2	1928.2±1212.2
GA	+	50	*i.p.*	2446.4±20.7*	1796.8±231.6
GA	+	100	*i.p.*	2155.8±98.1**	1120.8±473.3**
Silymarin	+	100	*i.p.*	2141.0±56.7**	1276.0±797.7*

[a)] Mean±S.D.
GL, glycyrrhizin; GA, 18-glycyrrhetinic acid.
[#]Statistically significant compared to normal control data ($p<0.001$).
Statistically significant compared to CCl_4 control data (, $p<0.05$; **, $p<0.01$).

before GL is absorbed into the body and GA exhibit the pharmacological actions.

Ginsenosides – Ginseng (the root of *Panax ginseng* C.A. Meyer, Araliaceae) is frequently used as a crude substance taken orally in Asian countries as a traditional medicine. The major components of ginseng are ginsenosides, which contain glycosides with a dammarane skeleton. These ginsenosides have been reported to show various biological activities including anti-inflammatory activity and anti-tumor effects (inhibition of tumor-induced angiogenesis and prevention of tumor invasion and metastasis) (Wu *et al.*, 1992; Sato *et al*, 1994; Mochizuki *et al.*, 1995; Wakabayashi *et al.*, 1998). However, the cytotoxic ginsenosides were not isolated from Ginseng. When ginseng was orally administered to human beings and rats, 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol (compound K) in the plasma was detected (Kanaoka *et al.*, 1998; Akao *et al.*, 1998). The other protopanaxadiol glycosides were not detected.

To solve this clue, many researchers studied the metabolism of ginseng saponins by intestinal bacteria. When protopanaxadiol ginsenosides were incubated with human intestinal microflora, the main metabolite was compound K (Kaneoka *et al.*, 1994; Hasegawa *et al.*, 1996; Bae *et al.*, 2000; Hasegawa *et al.*, 1997; Bae *et al.*, 2002). This metabolic pathway was catalyzed by *Provetella oris*, *Fusobacterium* K-60, *Bacteroides* JY-6, *Eubacterium* A-44 and *Bifidobacterium*

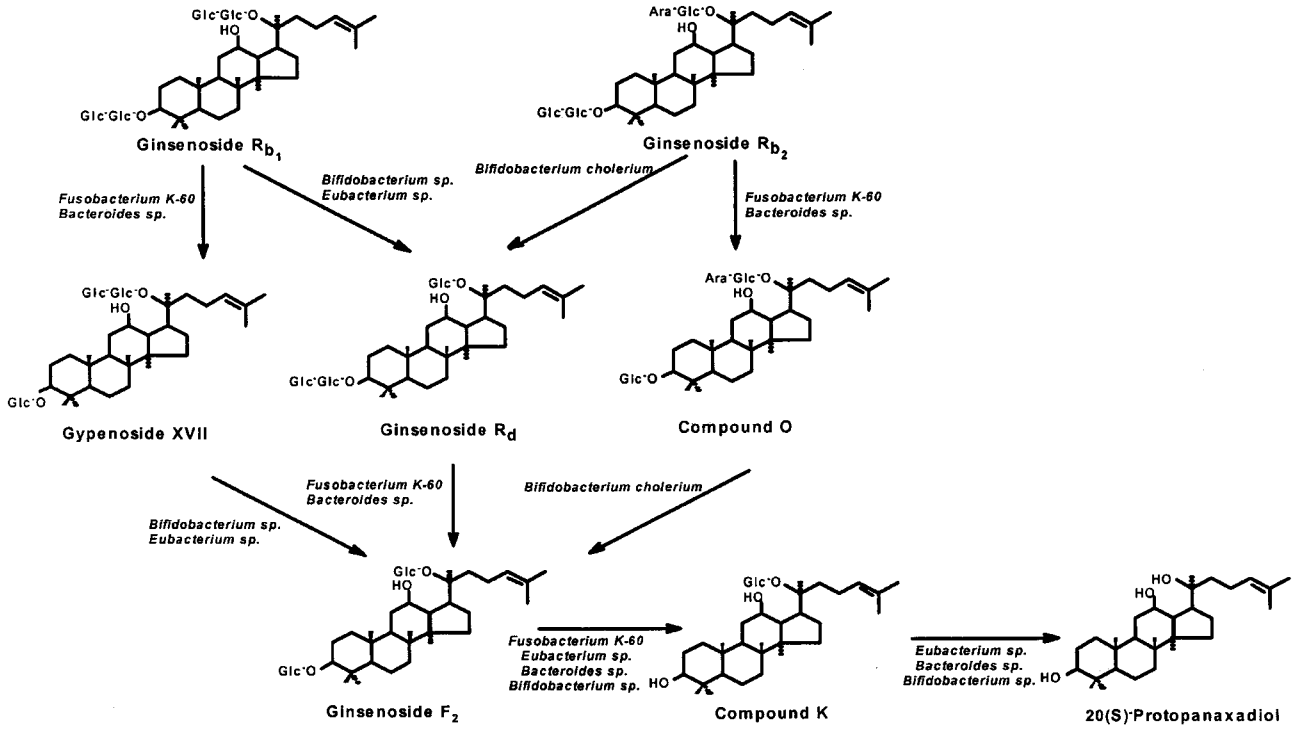
Table 4. Metabolic Activity of Ginsenoside Rc by Intestinal Bacteria Isolated from Human Feces

Microbe	Transformant[a] (μM)				
	R_d	M_b	F_2	M_c	CK
Human fecal microflora[b]	–	–	5.1	11.7	65.2
Bifidobacterium K-110	3.4	–	–	–	–
Bifidobacterium K-506	–	60.2	3.8	22.5	10.4
Bifidobacterium 3215	40.2	–	–	–	–
Lactobacillus II-46	1.2	–	–	–	–
Eubacterium A-44	66.5	–	–	–	5.3
Bacteroides HJ-15	–	80.6	9.1	2.7	0.9
Fusobacterium K-60	–	73.2	9.2	7.3	1.2

[a]Amounts of transformed metabolites after incubating 100 mM of ginsenoside Rc with intestinal bacteria (250 mg) cultured in TS or GAM broth for 24 h.
[b]Fecal microflora prepared from fresh human feces.

K-506 (Scheme 2). The protopanaxadiol saponins were easily transformed to ginsenoside Rg3 by the treatment of mild acids (Han *et al.*, 1982; Bae *et al.*, 2002). This ginsenoside Rg3 was transformed to ginsenoside Rh2 by human intestinal bacteria (Bae *et al.*, 2002) (Table 4). This result suggests that protopanaxadiol saponins can be metabolized to compound K in the intestine by intestinal micrflora and to ginsenoside Rh2 by acid and intestinal bacteria.

Therefore, to explain many kinds of pharmacological actions of ginseng in human beings, it is believed that



Scheme 2. Proposed metabolic pathway of ginsenoside Rb1 and Rb2 by human intestinal bacteria.

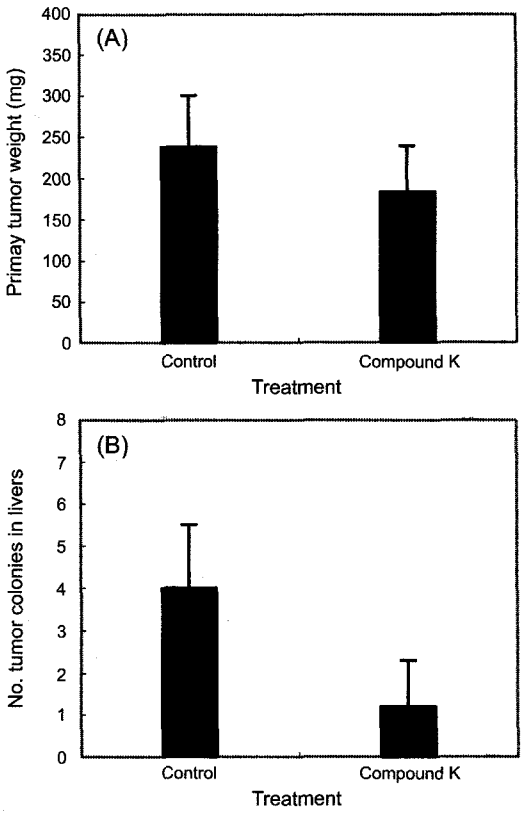


Fig. 1. Effect of compound K on growth and metastasis of tumors inoculated into the liver. A, tumor growth; B, metastasis (Wakabayashi *et al.*, 1998).

Table 5. Cytotoxicity of Ginsenosides and Their Metabolites against Tumor Cell Lines

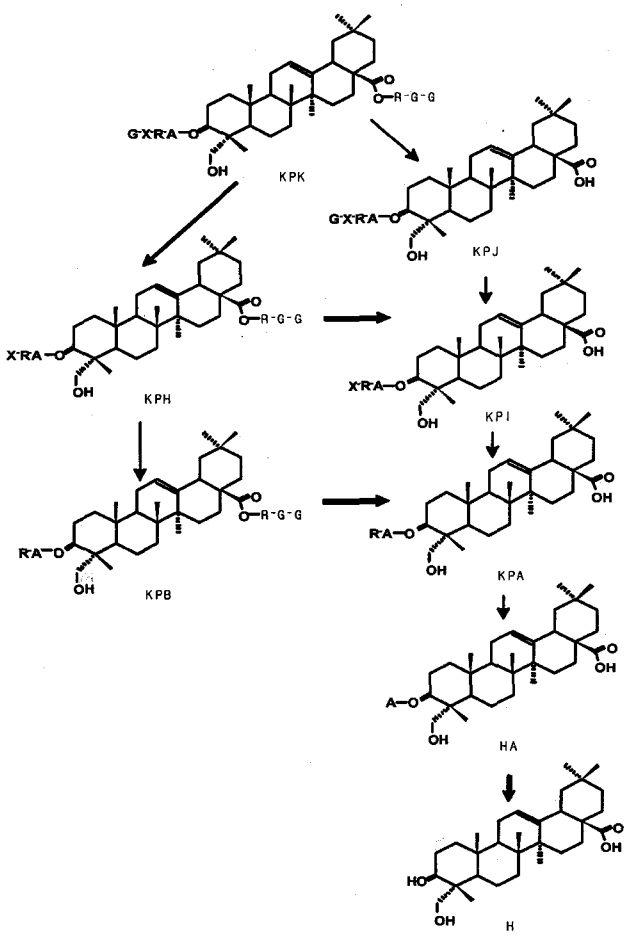
Compound	IC_{50} (μM)		
	L1210	P388	A549
Ginsenoside Rb1	>100	>100	>100
Ginsenoside Rb2	>100	>100	>100
Ginsenoside Rc	>100	>100	>100
Ginsenoside Rd	>100	>100	>100
Ginsenoside F2	>100	>100	>100
Compound K	24	33	33
Protopanaxadiol	18	32	28

ginseng saponins may be metabolized by human intestinal microflora after being taken orally and the metabolites exhibit many kinds of pharmacological actions. For example, protopanaxadiol ginsenosides are transformed to compound K by human intestinal bacteria. The transformed compound K shows an anti-metastatic or anti-carcinogenic effect by blocking tumor invasion or preventing chromosomal aberration and tumorigenesis (Wakabashi *et al.*, 1998; Lee *et al.*, 1999) (Fig. 1). Among the ginsenosides and their metabolites, compound K and 20(S)-protopanaxadiol showed potent cytotoxicity against tumor cell lines (Table 5). When the antiallergic activity of ginsenosides was evaluated by its

Table 6. Inhibitory Activity of Ginsenosides and their Metabolites on the Release of β-hexosaminidase and NO production

Compound	IC_{50} (μM)	
	β-hexosamindase release	NO production
Ginsenoside Rb1	>100	>100
Ginsenoside Rb2	>100	>100
Ginsenoside Rc	>100	>100
Ginsenoside F2	90	>100
Compound K	24	53
Protopanaxadiol	>100	67
Dexamethasone	–[a)]	60
Disodium cromoglycate	500	–

[a)]Not determined.



Scheme 3. Proposed metabolic pathway of kalopanaxsaponins by human intestinal bacteria G-X-L-A; β-D-Glc-(1→4)-β-D-Xyl-(1→3)-α-L-Rha-(1→2)-α-L-Ara-; R-G-G, α-L-Rha-(1→4)-β-D-Glc-(1→6)-β-D-Glc-.

inhibitory activity upon β-hexosaminidase release from RBL-2H3 cells, compound K showed the most potent inhibitory activity (Table 6). These results suggest that ginsenosides of ginseng are prodrugs, which can be transformed to active compounds by intestinal microflora.

Finally, we believe that compound K transformed from ginseng saponins can play an important role in antitumor and antiallergic activities.

Kalopanaxsaponins – The stem bark of *Kalopanax pictus* (Family *Araliacease*) has been used as tonic, analgesic and antidiabetic preparations in Korea. Its main components are hederagenin glycosides (kalopanaxsaponin A-J) (Sano *et al.*, 1991; Shao *et al.*, 1989; Lee and Han, 1991). These saponins are hydrophilic, because these compounds contain more than two sugars. These compounds could not be easily absorbed from intestinal tract to the blood when they were orally administered. Therefore, to absorb these compounds and show the pharmacological actions, they were metabolized by human intestinal bacteria. When kalopanaxsaponin K (KPK) was incubated with human intestinal bacteria, kalopanaxsaponin H (KPH), kalopanaxsaponin J (KPJ) and kalopanaxsaponin I (KPI) were quickly produced and then kalopanaxsaponin A (KPA) and hederagenin were slowly produced (Kim *et al.*, 2002) (Scheme 3). These metabolites were produced by *Bacteroides sp., Bifidobacterium sp. Lactobacillus sp., Streptococcus sp.* and *Fusobacterium sp.* (Table 7). When KPH was incubated with human intestinal bacteria, it was converted to KPI, and then to KPA, hederagenin arabinoside (HA) and hederagenin (Kim *et al.*, 1998). When KPB was incubated with human intestinal bacteria, KPB was converted to KPA, and then to HA and hederagenin (Kim *et al.*, 1998). The main metabolites of kalopanaxsaponins by human intestinal microflora are KPA, KPI and hederagenin. The metabolic pathway was catalyzed by *Bacteroides* JY-6, *Bifidobacterium breve* K-110. From these results, the proposed metabolic pathway of kalopanaxsaponins by human intestinal bacteria is shown in Scheme 3.

KPA showed more potent inhibitory effect on rheumatoid arthritis induced by FCA in rats than KPI (Kim *et al.*, 2002) (Table 8). Both KPA and KPI quickly showed significant effects when their doses were increased. The prolongation of KPA and KPI administration exhibited more potent antiedema effects. KPA and KPI reduced the vascular permeability and KPA was more effective than KPI. However, intraperitoneal administeration of KPK was not effective. Among KPB, KPH and their metabolites, KPA showed the most potent antidiabetic activity, followed by hederagenin (Park *et al.*, 1998; Kim *et al.*, 1998) (Table 9). However, the main components, KPB and KPH, in *K. pictus* were inactive. KPA was also found to be the most active compound for the inhibition of hyperglycemia (Park *et al.*, 1998; Kim *et al.*, 1998), cytotoxicity (Park *et al.*, 2001; Lee *et al.*, 2000), mutagenicity (Lee *et al.*, 2000) and fungal growth (Kim *et al.*, 1998). It is believed that KPA and hederagenin could improve diabetes mellitus and rheumatoid arthritis.

Flavonoids – Flavonoid glycosides are polyphenolic compounds produced by most fruits, vegetables and herbal

Table 7. KPK and KPJ Transforming Activity of Intestinal Bacteria Isolated from Human Feces

Microbe	Transformed product[a] (μM)										
	KPK							KPJ			
	KPH	KPB	KPJ	KPI	KPA	HA	H	KPI	KPA	HA	H
Bacteroides JY6	32.30	7.70	<0.05	25.31	7.39	0	6.16	78.58	8.70	0	6.16
Bifidobacterium K110	2.79	2.02	0.90	0.78	1.37	0	0	<0.05	0.81	0	0
Eubacterium A44	2.79	4.15	4.28	0	0.99	0	0.21	<0.05	5.78	0.93	4.46
Eubacterium L8	0	0	<0.05	2.29	1.24	0	3.33	<0.05	0	0	11.54
Fusobacterium K60	2.79	0.82	0.83	0	1.55	0.81	4.46	<0.05	0.99	0.75	4.74
Lactobacillus L2	0	0	<0.05	2.10	7.02	0.75	0	<0.05	2.42	1.12	0
Streptococcus S10	0	0	<0.05	1.61	2.80	0	0	<0.05	0.99	0	0

[a]To assay transformed products, the reaction mixture was incubated with a 25 mg pellet of each intestinal bacterium at 37°C for 20 h.

Table 8. Inhibitory Effect of KPA and KPI on Freunds Complete Adjuvant Reagent-Induced Rat Edema Model

Group	Dose (mg/kg)	Swelling (%)				
		0	3	5	7	10 (d)
Control		74.4±5.58	78.6±4.39	75.9±3.27	71.3±4.92	74.2±5.49
KPA	5		80.6±11.3	66.5±3.57	63.3±2.82*	61.8±1.44*
	10		73.7±3.44*	67.9±2.58	53.4±3.73*	50.6±2.45*
KPI	5		75.3±5,26*	75.3±2.41	73.9±4.59	72.4±2.80*
	10		76.2±4.40	71.5±2.00	62.1±2.50*	62.8±2.17*

KPA and KPI were intraperitoneally administered to rats once a day for 10 days.
Values represent means ± S.D. (n=10).
*Significantly different from the control ($p<0.05$).

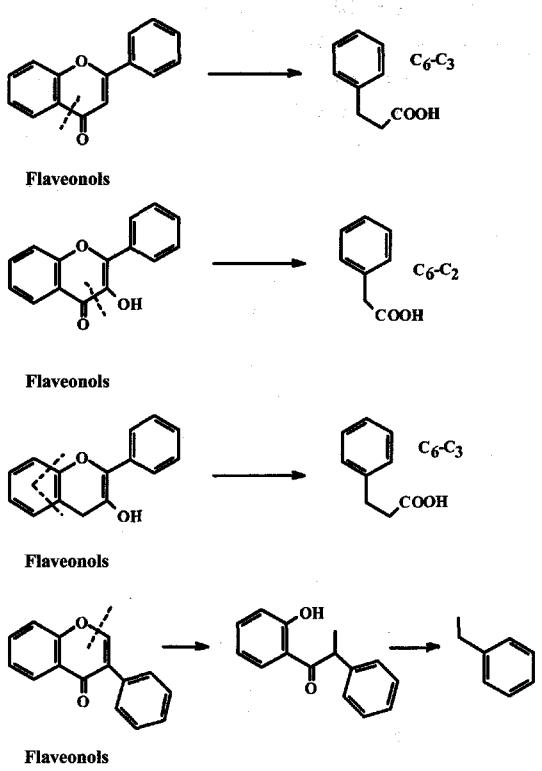
Table 9. Effect of the Constituents of the Stem Bark of *Kalopanax pictus* on the Serum Glucose Levels in Normal and Diabetic Rats

Group	Dose (mg/kg)	Glucose (mg/dl)
Normal		88.5±10.59[a)]
Streptozotocin		323.3±52.52[#]
Hederagenin	50	203.3±45.71*
Kalopanaxsaponin A	25	105.8±12.23*
Kalopanaxsaponin B	50	315.0±49.52*
Kalopanaxsaponin H	25	320.8±54.21*

[a)]Values are means±S.D. (n=8).
[#] Significantly different from normal group ($p<0.05$).
* Significantly different from streptozotocin group ($p<0.05$).

medicines. These compounds are ingested daily more than 1 g by human, but are resistant to boiling and fermentation. After ingestion of flavonoid glycosides, most of them are not easily absorbed in mammalian gut. These compounds can be transformed by intestinal bacteria. Evidence for the involvement of the intestinal microflora in the metabolism of flavonoid compounds *in vivo* has been presented by Griffiths group (Griffiths, 1964; Griffith and Barrow, 1972). Particularly, it was reported that the ring fissuring as well as glycosidation from orally administered flavonoids were significantly decreased by the coadministration of oral antibiotics. The metabolites from the urine of rats orally treated with flavonols, such as quercetin and kaemfpherol, were phenolic acids. When flavonoid glycosides, such as rutin, naringin, poncirin and hesperidin, were incubated with human intestinal microflora, they were transformed to their aglycones and then to phenolic acid (Kim *et al.*, 1994; Kim *et al.*, 1998; Booth *et al.*, 1956; Bokkenhweuser *et al.*, 1987). For example, rutin transformed to 3,4-dihyroxyphenylacetic acid, 3,4-dihydroxybenzoic acid and 4-hydroxybenzoic acid via quercetin by human intestinal microflora. The rutin glycosidating bacterium was *Bacteroides* JY-6, which potently produced α-rhamnosidase and β-glucosidase. Quercetin C-ring was fissured by *Pediococcus* Q-5, *Streptococcus* S-3, *Bacteroides* JY-6 and *Bifidobacterium* B-9 (Table 10).

Flavones and flavanones were metabolized to C6-C3



Scheme 4. Proposed metabolic pathway of flavonoids by human intestinal bacteria

phenolic acids by intestinal intestinal bacteria (Kim *et al.*, 1994; Kim *et al.*, 1998; Abe *et al.*, 1993; Booth *et al.*, 1958; Griffiths and Smith, 1972; Cheng *et al.*, 1971). For example, when apigenin was incubated with rat intestinal bacteria, p-hydroxyphenylpropionic acid was produced. Flavanols were metabolized to C6-C2 phenolic acid by intestinal bacteria (Booth *et al.*, 1956; Griffiths and Smith, 1972; Petrakis *et al.*, 1959; Nakayama *et al.*, 1965; Kim *et al.*, 1998). For example, when quercetin administered to rats, 3,4-dihyroxyphenylacetic acid was excreted in urine. Catechols were metabolized to phenyl-γ-valeric acid lactone C6-C3 m-hydroxypenylpropionic acid (Kim *et al.* 1998; Das, 1969). Isoflavones were metabolized to C6-C2 phenylacetic acid

Table 10. Flavonoid-transforming intestinal bacteria

Metabolic pathway	Intestinal bacteria
Baicalin → baicalein	*E. coli* HGU-3, *Bacteroides* J-37, *Eubacterium* A-44
Rutin → quercetin	*Bacteroides* JY-6, *Fusobacterium* K-60, *Eubacterium* YK-4
Hesperidin → hesperetin	*Fusobacterium* K-60, *Eubacterium* YK-4, *Bacteroides* JY-6
Poncirin → ponciretin	*Fusobacterium* K-60, *Eubacterium* YK-4, *Bacteroides* JY-6
Baicalein → phenolic acids	*Streptococcus* S-2, *Lactobacillus* L-2, *Bifidobacterium* B-9
Quercetin → phenolic acid	*Streptococcus* S-2, *Lactobacillus* L-2, *Bifidobacterium* B-9, *Bacteroides* JY-6
Quercetin → phenolic acid	*Streptococcus* S-2, *Lactobacillus* L-2, *Bifidobacterium* B-9, *Bacteroides* JY-6
Hesperetin → phenolic acid	*Streptococcus* S-2, *Lactobacillus* L-2, *Bifidobacterium* B-9, *Bacteroides* JY-6
Ponciretin → phenolic acid	*Streptococcus* S-2, *Lactobacillus* L-2, *Bifidobacterium* B-9, *Bacteroides* JY-6
Catechin → phenolic acids	*Lactobacillus* L-2, *Bifidobacterium* B-9, *Bacteroides* JY-6

Table 11. Cytotoxic effect of flavonoids and their metabolites

Flavonoid Glycoside	SNU-C4	SNU-1	P-388	HepG2
Rutin	>1	>1	0.3	>1
Hesperidin	>1	0.5	0.5	>1
Poncirin	>1	>1	>1	>1
Baicalin	0.5	0.05	0.05	0.8
Quercetin	0.05	0.04	0.05	>1
Hesperetin	>1	0.6	0.3	>1
Ponciretin	0.17	0.07	0.17	>1
Baicalein	0.1	0.04	0.05	0.5
Catechin	>1	>1	>1	>1
4-Hydroxyphenylacetic acid	>1	>1	>1	–[a]
3,4-Dihydroxyphenylacetic acid	0.5	0.03	0.1	–
4-Hydroxybenzoic acid	>1	>1	0.55	–
2,4-Dihydroxybenzoic acid	>1	>1	1	–
3,4-Dihydroxybenzaldehyde	0.25	0.045	0.1	–
2,4,6-Trihydroxybenzaldehyde	0.03	0.3	0.5	–
Adriamycin	0.05	0.001	0.003	>1

[a]not determined.

(Kim *et al.*, 1998) (Scheme 4).

MacDonald *et al.* (1983) and Tamura *et al.* (1980) reported that rutin could be metabolized to quercetin by intestinal bacteria and the transformed quercetin showed strong mutagenic activity by Ames test. However, many researchers (Bjeldans and Chang, 1997; Kim *et al.*, 1996; MacGregor, 1979; Stewsand *et al.*, 1984) believed that quercetin was not a carcinogen by *in vivo* experiment using mice and hamster, although Pamucku (1980) reported that quercetin caused intestinal and bladder cancers in rats. Kim *et al.* (1996) also reported that, after rutin was admininstered orally to rats, mutagenicity of its metabolites in the urine was measured by Ames test. The urine administrated less than 100 mg/kg rutin did not show mutagenicity. These results suggest that quercetin was metabolized to phenolic acid by intestinal bacteria. In addition, antiinflammatory activity of oral administeration of poncirin was more potent than that of intraperitoneal administeration of poncirin on carrageenanin-induced rats (Youn *et al.*, 1992). It was also reported that flavonoid metabolites 3,4-dihydroxyphenylacetic acid, 4-hydroxylphenylacetic acid, quercetin and ponciretin were more potent than those of flavonoid glycosides (Kim *et al.*, 1998). Generally, the phenolic acids showed the strongest activity of antiplatelet aggregation, followed by aglycones and glycosides. Among the metabolites, phenolic acids and algycones, against tumor cell lines were higher than those of glycosides (Table 11). On the preventive effect of flavonoid glycosides for chronic illness (stoke, tumor and inflammation), the biotransformation of flavonoid glycosides to their aglycones and phenolic acids by intestinal bacteria should be important.

Conclusion

Most herbal medicines are orally administered, digested by gastric and pancreatic juices, and then absorbed. However, most glycosides contained in herbal medicines are resistant to boiling, gastric acid and digestive enzymes. Therefore, these glycosides pass through the upper intestinal tract without their absorptions to the lower tract, in which numerous bacteria, particularly anaerobes, inhabit. Unabsorbed glycosides are metabolized to their aglycones by bacterial enzymes and further could be metabolized. Aglycones and metabolites are absorbed and show pharmacological or toxic effects. Sometimes, they seem to show mild effects, because they take time to reach the lower intestinal tract and transform into active components and their metabolites are continuously and slowly absorbed to the blood. Therefore, the glycosides of herbal medicines exhibiting pharmacological actions should be natural prodrugs.

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