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Review

Polyphenols-absorption and occurrence in the body system

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Polyphenols are commonly present in natural plants and serve as health benefiting food compounds. The health benefits and the metabolites of polyphenols have not yet been fully investigated because of lack of information about their bioavailability. This review was based on the previously reported literature focusing on the absorption and tissue accumulation of polyphenols. Furthermore, the physiological roles and the influx/efflux route(s) of non-absorbable polyphenols in the intestinal membrane were discussed.

Keywords: polyphenol, bioavailability, absorption, metabolism, accumulation

Introduction

Polyphenols are commonly present as secondary metabolic phytochemicals that naturally occur in plant components, including herbs, fruits, and vegetables. Although they were initially known to be natural pigments in plants, their predominant function is to protect the plant against environmental stresses, including light oxidation, pathogens, and predators (Bravo, 1998). Polyphenols are made of two or more benzene rings, each having at least one hydroxyl group. More than 8 000 polyphenols have been identified (Tsao, 2010) and are commonly present in human plant-based foods consumed daily worldwide (Bravo, 1998; Scalbert and Williamson, 2000).

The scientific interests in polyphenols appear to be because of their physiological potentials in maintaining human health or homeostasis, because the “French paradox”, a reduced incidence of cardiovascular disease (CVD), is associated with healthy “Mediterranean diet” characterized by low consumption of butter and high consumption of vegetables, fruits, cheese, and red wine (or wine polyphenols, like resveratrol) (Renaud and de Lorgeril, 1992; Catalgol *et al*., 2012). Moreover, epidemiological studies have shown the beneficial effects of polyphenols on human health (Medina-Remon *et al*., 2017; Tresserra-Rimbau *et al*., 2014). Clinical trials showed that an increased intake of dietary flavonoids, particularly flavanones, was associated with a significant decrease in postprandial lipid response (triglycerides and cholesterol) in the circulating bloodstream (Vetrani *et al*., 2018). A clinical report by Vabeiryureilai and Lalrinzuali (2015) indicated the protective effect of polyphenols against vessel dysfunction by a daily intake of hesperidin (500 mg/day) for 3 weeks, in which an increase in nitrogen monoxide (NO) production and a decrease in circulating inflammatory biomarkers was observed. Moreover, it is well

Abbreviations: ABC, ATP binding cassette; ADME, absorption/distribution/metabolism/excretion; AMPK, AMP-activated protein kinase; ASBT, apical sodium dependent-bile acid transporter; AUC, area under the curve; BCRP, breast cancer resistance protein; CaMKK, calmodulin-dependent protein kinase kinase; CVD, cardiovascular disease; ECG, epicatechin-3-*O*-gallate; EGCG, epigallocatechin-3-*O*-gallate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; LKB1, liver kinase B1; MALDI, matrix-assisted laser desorption/ionization; MCTs, monocarboxylate transporters; MRP, multidrug resistance protein; MS, mass spectrometry; NO, nitrogen monoxide; NTs, nucleoside transporters; OATP, organic anion transporting polypeptides; PepT1, peptide transporter 1; P-gp, P-glycoprotein; PKC, protein kinase C; SGLT-1, sodium-dependent glucose transporter; TAK-1, transforming growth factor-ß-activated kinase-1; TJ, tight junction; ZO-1, zonula occluden-1

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established that polyphenols (in particular, flavonoids) exhibit beneficial effects against the development of chronic degenerative diseases, such as diabetes, hypertension, and lipidemia in human studies (Table 1). For every bioactive compound listed in Table 1, the efficiency of its physiological functions must be determined by the bioavailability of polyphenols (Scalbert and Williamson, 2000; Wang, *et al*., 2017), but the understanding of their fate after intake is still insufficient and needs to be further investigated. Furthermore, while the functions of absorbed substances primarily depend on their bioavailability, their metabolism during absorption process is also crucial for the compound's physiological activity (Williamson *et al*., 2018). Indeed, the number and specific positions of the hydroxyl groups on the flavanones' aromatic rings have a great influence on their physiological effects (Barreca *et al*., 2017). However, further inquiries regarding the metabolites of polyphenols as well as their bioavailability are needed. Although mono-phenolic acids, such as chlorogenic acid and ferulic acid, are out of the category of polyphenols, we will also discuss their bioavailability because of common naturally occurring phenols.

Absorption of polyphenols in the circulatory bloodstream

Intestinal transport routes of polyphenols. Nutrients are incorporated into our body system mainly by crossing the intestinal membrane. Except for minerals and hydrophobic compounds (vitamin E, drugs, etc.) transported via the passive paracellular or transcellular (epithelial tight junction, TJ) transport system, most nutrients (monosaccharides, amino acids, di-/tripeptides, organic acids, fatty acids, and sterols) are recognized by intestinal transporters located at the brush border membrane of the apical side of the enterocytes, and are absorbed during the first and second phases (I/II) metabolism (Shimizu, 2010). These intestinal transporters include sodium-dependent glucose transporter 1 (SGLT1) (Turk *et al*., 1994) for glucose, peptide transporter 1 (PepT1) for di/tripeptides (Meredith and Price, 2006), apical sodium dependent-bile acid transporter (ASBT) (Claro *et al*., 2013), nucleoside transporters (NTs) (Baldwin *et al*., 2004), organic anion transporting polypeptides (OATP) (Yu *et al*., 2017), and monocarboxylate transporters (MCTs) for organic acids (Halestrap and Wilson, 2012). Once the nutrients are incorporated into the intracellular intestinal membrane via the influx transporters, they are either pumped out to the gut via the efflux ATP binding cassette (ABC) family transporters, including breast cancer resistance protein (BCRP), multidrug resistance protein 2 (MRP2), and P-glycoprotein (P-gp) (Chen *et al*., 2016), or are subjected to degradation via processes, such as phase I hydrolysis, demethylation (Booth *et al*., 1958; Nielsen *et al*., 1998), and methylation (Miyake et al., 2000). Subsequently, in phase II, the incorporated compounds are also susceptible to sulfation and glucuronidation, and their combination reactions at the position of hydroxyl group (Bravo *et al*., 1998). Mass spectrometry (MS), in particular, matrix-assisted laser desorption/ionization (MALDI)-MS in combination with imaging techniques, is a powerful tool to comprehensively analyze such metabolites, as imaging can provide visual evidence about the location and production of

Table 1. Health benefits of polyphenols in humans

Family	Class	Compound	Health benefit	Reference
Flavonoids				
	Flavonols	Quercetin	Anti-hypertensive	Zahedi *et al*., 2013
			Cardio protective	Egert *et al*., 2009
	Flavanones	Naringenin	Anti-hypertensive	Habauzit *et al*., 2015
		Hesperidin	Anti-hypertensive	Morand *et al*., 2011
			Anti-inflammatory	Homayouni *et al*., 2018
		Naringin	Anti-hypertensive	Reshef *et al*., 2005
			Lipid-lowering	Toth *et al*., 2016
			Lipid & cholesterol-lowering	Jung *et al*., 2003
	Isoflavones	Genistein	Cholesterol-lowering	Lazarevic *et al*., 2011
	Catechins	Green tea extract	Anti-hypertensive	Islam, 2012
			Anti-hyperlipidemia	
Others		Resveratrol	Anti-diabetes	Brasnyó *et al*., 2011
			Anti-inflammatory	Espinoza *et al*., 2017
		Curcumin	Anti-inflammatory	Ganjali *et al*., 2014
			Lipid-lowering	Yang *et al*., 2014
			Anti-diabetes	Chuengsamarn *et al*., 2012

metabolites by non-targeted MS (Nguyen *et al*., 2016; 2019). As shown in Fig. 1, the transport behavior of epicatechin-3-*O*-gallate (ECG) through rat's jejunum membrane as well as the preferable metabolism of ECG to sulfated and methyl/sulfated conjugates at the microvillus region of intestinal membrane is successfully visualized by imaging (Nguyen *et al*., 2019). The visualized metabolic behavior of ECG at rat's jejunum membrane also revealed the preferable (or rapid) conversion of intact ECG to sulfated ECG rather than glucuronidation (Fig. 1). The phase II metabolic behavior is in line with the preferable methylation and sulfation metabolism of catechins reported previously (Donovan *et al*., 2001; Actis-Goretta *et al*., 2013). For macromolecules, microfold (M) cells in the follicle-associated envelope of Peyer's patches or endocytosis route may be involved in the absorption. However, polyphenols have no specific transporter route; for example, catechins were reported to cross via passive TJ and/or active carrier-mediated transporter routes, which were different from types of catechins (Konishi *et al*., 2003). Therefore, it appears that the transport routes of polyphenols are not restrictive and vary based on their structural and molecular characteristics. Thus, the characteristics (hydrophobicity, molecular size, functional group, etc.) of polyphenols regulating their intestinal transport routes remain unclear and further studies based on in silico and molecular targeting analyses are required.

Absorption of polyphenols in animal bloodstream. The extent of absorption, metabolism, and/or organ distribution may determine the reported physiological functions of polyphenols (Scalbert and Williamson, 2000; Scalbert *et al*., 2011). Table 2 summarizes the absorption properties of polyphenols in animal and human bloodstreams reported so far. As mentioned above, since some polyphenols are metabolized to form sulfated/glucuronided conjugates during intestinal transport, it should be noted whether intact or conjugated forms of polyphenols are used to evaluate the absorption amount in literature. Some studies reported absorption as the amount of intact form in the circulating bloodstream, whereas others reported a total of intact and conjugated forms (by deconjugation treatment with sulfatase/β-glucuronidase). However, considering that the definition of bioavailability or absorption / distribution / metabolism / excretion (ADME) denotes the absorbability of "physiologically active" forms,

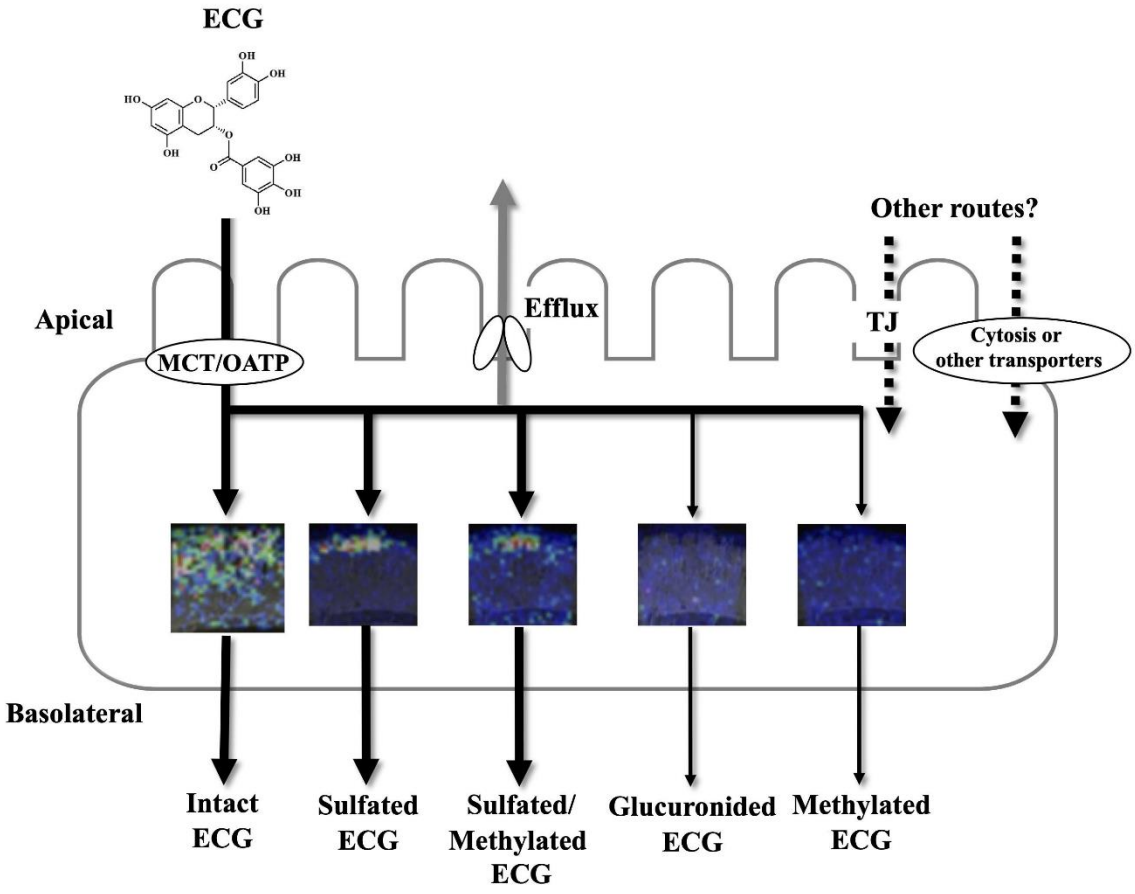

Fig. 1. Visualized absorption behavior of epicatechin-3-*O*-gallate (ECG) across rat intestinal membrane through matrix-assisted laser desorption/ionization-mass spectrometry (MALDI-MS) imaging

polyphenols showing less bioactivity must be excluded from the evaluation of absorption kinetics; therefore, analysis of the physiological functions of intact and/or conjugated polyphenols should be done together with the kinetic studies. As summarized in Table 2, the absorption of polyphenols in the bloodstream varies from C_{max} of 0.0005 μmol/L for puerarin to 10,378 μmol/L for quercetin-3-*O*-glucuronide. Within the limited data included in this review, the magnitude of C_{max} for most polyphenols in the bloodstream may lie in sub-micromolar to sub-millimolar ranges. The T_{max} of most polyphenols is < 3 h, indicating that polyphenols are rapidly absorbed into the circulatory bloodstream after their intake. It appears that higher doses result in higher absorption of epigallocatechin-3-*O*-gallate (EGCG, 200–800 mg in human), naringin (10.5–168 mg/kg in Sprague-Dawley rats), and resveratrol (20–150 mg in human). Notably, the molecular size of polyphenols may not be a determining factor for their absorption. In contrast, the hydrophobicity or log *P* of polyphenols partly regulate intestinal absorption, as reported in literature (Sugawara *et al*., 2001; Murota *et al*., 2002) and in Table 2 for glyceollins (glyceollin I: area under the curve for 8 h, $AUC_{0-8\ h}$, 8.5 μmol·h/L; log *P*, 3.91 > glyceollin III: 1.0 μmol·h/L; log *P*, 3.60 > daidzein: 0.6 μmol·h/L; log *P*, 2.63). However, a comparative evaluation of absorption of various polyphenols (e.g., naringin, lutein, and quercetin in Table 2) cannot be done since the results were obtained from different scenarios, including dose, targeting analyte (intact, conjugates, or individual conjugate), and animal species. Furthermore, a quantitative assay method for polyphenol-administered blood using HPLC, LC-MS, or LC-tandem MS, with the aid of internal standard, like taxifolin (Zhang *et al*., 2020), is needed to determine reliable absorption profiles.

Tissue accumulation of polyphenols

Polyphenol-induced health benefits, such as improved insulin sensitivity (Park *et al*., 2012), vasorelaxation (Lorenz *et al*., 2009), and anti-atherosclerosis (Loke *et al*., 2010) indicate their local action or accumulation in the organs. However, studies that report tissue accumulation of polyphenols in the circulatory system are rare. Table 3 summarizes the amount of tissue accumulation of polyphenols in organs, including the liver, the kidneys, the heart, the lung, and the muscle. Although the available data on the tissue accumulation kinetics of polyphenols in literature were limited, it appears that they can be distributed and can accumulate in the organs rapidly (< 1 h) after absorption into the bloodstream. The accumulation of the four polyphenols in different organs listed in Table 3 occurs preferably in the following order: the kidney > the liver > the lung > the heart > the muscle. However, further accumulation studies are needed to clarify the pharmacokinetics of polyphenol accumulation in relation to polyphenol structure and to obtain insights on the absorbability by considering the total amount of absorption in the blood and the organs. In our unpublished study, > 80% of hydrophobic isoflavone metabolites are preferentially distributed into the organs, while > 80 % of the parent isoflavones are still present in the blood. Table 3 also shows the effect of tissue accumulation of conjugated polyphenols. The possible tissue accumulation of conjugated polyphenols has also been reported by other researchers (Chang *et al*., 2000; Soucy *et al*., 2006; Urpi-Sarda *et al*., 2008), in which glucuronided and sulfated conjugates of genistein were detected in the placenta of female rats (Soucy *et al*., 2006).

Organic anion transporters (MCT, OAT1, and OATP1B1) may be involved in the intracellular incorporation of intact and conjugated polyphenols, but their tissue incorporation routes and physiological action(s) in the accumulated organs are not well understood. Thus far, reports have shown that the sulfation of polyphenols induces glucose transporter 4 (GLUT4) translocation (Houghton *et al*., 2019) and anti-hypertensive effect (Van Rymenant *et al*., 2017), whereas glucuronided forms of polyphenols promote NO production (Serreli *et al*., 2021) and reduce hepatocyte fat accumulation (Trepiana *et al*., 2020). These findings allow us to investigate the physiological functions of conjugated polyphenols as their underlying inter-/intracellular mechanisms remain unexplored.

Non-absorbable polyphenols

Spinosin, a flavonoid glycoside that performs sedation and hypnosis actions, was incorporated mainly via MCT and partly SGLT1, together with recognition by P-gp-efflux route (Meng *et al*., 2016). In contrast, tomatoside A, a steroidal saponin from tomato seed (Li *et al*., 2018), as well as condensed catechins, theaflavins (Takeda *et al*., 2013), could not cross the intestinal membrane (Fig. 2). However, the saponin could reduce glucose transport by suppressing the expression of GLUT2. In *in vitro* transport experiments using Caco-2 cells, which are derived from human colon carcinoma, the saponin could be incorporated into cells via ASBT and then pumped out to the apical side through the MRP2 efflux route. During the influx/efflux transportation process, intracellular protein kinase C (PKC) was activated to inhibit GLUT2 expression (Li *et al*., 2018). For the intestinal transportation of theaflavins as non-absorbable compounds, like tomato saponin, more evidence on transportation behavior was visually obtained using MALDI-MS imaging technique, which suggested that theaflavins were incorporated into rat intestinal cells through both MCT and OATP transporters (Fig. 2) (Nguyen *et al*., 2019). Non-targeted MALDI-MS analysis also revealed that there was an efflux of non-absorbable theaflavins back to the gut via the ABC transporters, like other polyphenols (Chan *et al*., 2007), without any MS detection of metabolites,

Table 2. Pharmacokinetics of polyphenols in the bloodstream after oral administration.

Polyphenols	Sub-category	Compound	Dose	Metabolite(s) monitored	AUC (µmol/L·h) 0→t	0→t (h)	AUC (µmol/L·h) 0→∞	C_{max} (µmol/L)	T_{max} (h)	$T_{1/2}$ (h)	Reference
Flavonoids											
	Anthocyanin										
		Delphinidin-3-rutinoside	489 mg/kg (Wistar rats n=3)	Intact	1.33	4	*n.a.*	0.58 ± 0.41	2	0.8	Matsumoto *et al* ., 2001
		Cyanidin-3-rutinoside	476 mg/kg (Wistar rats n=3)	Intact	2.54	4	*n.a.*	0.85 ± 0.12	0.5	1.4	*ibid.*
		Cyanidin-3-glucoside	359 mg/kg (Wistar rats n=3)	Intact	1.51	4	*n.a.*	0.84 ± 0.19	0.5	2.1	*ibid.*
		Delphinidin-3-rutinoside	1.68 mg/kg (human n=8)	Intact	0.288 ± 0.110	8	*n.a.*	0.073 ± 0.035	1.8	3.2	*ibid.*
		Cyanidin-3-rutinoside	1.24 mg/kg (human n=8)	Intact	0.168 ± 0.075	8	*n.a.*	0.046 ± 0.023	1.5	3.5	*ibid.*
		Delphinidin-3-glucoside	0.488 mg/kg (human n=8)	Intact	0.069 ± 0.027	8	*n.a.*	0.023 ± 0.012	1.5	4.2	*ibid.*
		Cyanidin-3-glucoside	0.165 mg/kg (human n=8)	Intact	0.009 ± 0.007	8	*n.a.*	0.005 ± 0.004	1.3	1.3	*ibid.*
		Cyanidin-3-glucoside	500 mg/kg (human n=8)	Intact	0.28 ± 0.17 (SE)	48	*n.a.*	0.14 ± 0.07 (SE)	1.8	0.4	de Ferrars *et al* ., 2014
	Flavanol										
		Epicatechin	2.9 mg (Wistar rats n=5)	Intact + conjugates	83.6 ± 39.8	24	*n.a.*	6.4±5.1	0.7	2.4	Abrahamse et al., 2005
		Epigallocatechin-3-*O*-gallate	200 mg (human n=5)	Intact	0.81 ± 0.27 (SE)	24	*n.a.*	0.16 ± 0.06 (SE)	2.1	2	Chow *et al* ., 2001
		Epigallocatechin-3-*O*-gallate	400 mg (human n=5)	Intact	1.29 ± 0.78 (SE)	24	*n.a.*	0.24 ± 0.22 (SE)	1.8	2.7	*ibid.*
		Epigallocatechin-3-*O*-gallate	600 mg (human n=5)	Intact	3.71 ± 3.63 (SE)	24	*n.a.*	0.37 ± 0.31 (SE)	3	3.1	*ibid.*
		Epigallocatechin-3-*O*-gallate	800 mg (human n=5)	Intact	6.08 ± 2.07 (SE)	24	*n.a.*	0.96 ± 0.62 (SE)	4	1.9	*ibid.*
	Flavanone										
		Hesperidin	10 mg/kg (SD rats n=3)	Intact + conjugates	6.4 ± 0.9 (SE)	24	*n.a.*	0.49 ± 0.10 (SE)	16	*n.a.*	Nectoux *et al* ., 2019
		Hesperetin	135 mg (human n=6)	Intact + conjugates	14.23 ± 5.62	12	16.03 ± 5.54	2.73 ± 1.36	3.7	3.1	Kanaze *et al* ., 2007
		Naringin	42 mg/kg (SD rats n=12)	Intact	0.79 ± 0.19 (SE)	36	1.04 ± 0.23	0.31 ± 0.11 (SE)	0.5	9.5	Zeng *et al* ., 2019
		Naringin	42 mg/kg (SD rats n=12)	Metabolites (Naringenin + glucuronide)	121.6 ± 17.8 (SE)	36	122.8 ± 17.7	12.9 ± 1.6 (SE)	8.8	3.2	*ibid.*
		Naringin	10.5 mg/kg (SD rats n=10)	Intact + glucuronide	0.056 ± 0.048	24	0.061 ± 0.050	0.055 ±0.023	1.5	0.3	Bai *et al* ., 2020

Table 2. continued.

Flavanone	Naringin	21 mg/kg (SD rats n=10)	Intact + glucuronide	0.059 ± 0.035	24	0.066 ± 0.037	0.053 ± 0.028	1.5	0.5	*ibid.*
	Naringin	42 mg/kg (SD rats n=10)	Intact + glucuronide	0.070 ± 0.088	24	0.078 ± 0.095	0.091 ± 0.136	1.2	0.5	*ibid.*
	Naringin	168 mg/kg (SD rats n=10)	Intact + glucuronide	0.24 ± 0.11	24	0.25 ± 0.11	0.18 ± 0.13	2.9	0.7	*ibid.*
	Naringin	3.1 mg/kg (Beagle dogs n=6)	Intact + glucuronide	0.19 ± 0.10	12	0.22 ± 0.13	0.069 ± 0.018	1.3	1.8	*ibid.*
	Naringin	12.4 mg/kg (Beagle dogs n=6)	Intact + glucuronide	0.21 ± 0.56	12	0.23 ± 0.06	0.12 ± 0.03	1	1.3	*ibid.*
	Naringin	49.6 mg/kg (Beagle dogs n=6)	Intact + glucuronide	0.36 ± 0.16	12	0.39 ± 0.18	0.18 ± 0.13	1	1.3	*ibid.*
	Naringin	40 mg (human n=10)	Intact + glucuronide	0.013 ± 0.006	10	0.017 ± 0.007	0.004 ± 0.001	2	2.5	*ibid.*
	Naringin	80 mg (human n=10)	Intact + glucuronide	0.016 ± 0.006	36	0.021 ± 0.005	0.005 ± 0.002	2.1	1.9	*ibid.*
	Naringin	160 mg (human n=10)	Intact + glucuronide	0.027 ± 0.013	36	0.039 ± 0.016	0.007 ± 0.005	2.5	3.6	*ibid.*
	Naringin	320 mg (human n=10)	Intact + glucuronide	0.065 ± 0.055	36	0.069 ± 0.055	0.019 ± 0.021	1.7	2.5	*ibid.*
	Naringin	480 mg (human n=10)	Intact + glucuronide	0.033 ± 0.014	36	0.037 ± 0.014	0.010 ± 0.005	1.7	2	*ibid.*
	Naringenin	30 mg/kg (SD rats n=6)	Intact	1.87 ± 1.78	24	2.09 ± 2.22	0.44 ± 0.35	0.5	5.4	Xu *et al*., 2020
	Naringenin	30 mg/kg (Wistar rats n=10)	Intact	3.5	48	3.5	10.7	0.1	*n.a.*	Ma *et al*., 2006
	Naringenin	30 mg/kg (Wistar rats n=10)	Intact + glucuronide	113	48	113	62	0.5	*n.a.*	*ibid.*
	Naringenin	90 mg/kg (Wistar rats n=10)	Intact	66.3	48	66.3	13.7	0.3	*n.a.*	*ibid.*
	Naringenin	90 mg/kg (Wistar rats n=10)	Intact + glucuronide	488	48	488	102	2	*n.a.*	*ibid.*
	Naringenin	270 mg/kg (Wistar rats n=10)	Intact	80.4	48	80.4	16.2	0.1	*n.a.*	*ibid.*
	Naringenin	270 mg/kg (Wistar rats n=10)	Intact + glucuronide	1701	48	1664	161	2	*n.a.*	*ibid.*
	Naringenin	135 mg (human n=6)	Intact + conjugates	32.48 ± 10.02	12	34.62 ± 10.87	7.38 ± 2.83	3.7	2.3	Kanaze *et al*., 2007
Flavone										
	Apigenin	10 mg/kg (Wistar rats n=5)	Intact	542 ± 231	24	*n.a.*	79.1 ± 23.8	3.6	7.8	Alshehri *et al*., 2019
	Apigenin	50 mg/kg (Wistar rats n = *n.a.*)	Intact	0.54 ± 0.23 (SE)	24	*n.a.*	0.08 ± 0.02 (SE)	3.6	7.8	Altamimi *et al*., 2018

Table 2. continued.

	Apigenin	100 mg/kg (SD rats n=6)	Intact	20.5 ± 9.1	24	*n.a.*	2.48 ± 0.63	2.2	*n.a.*	Huang *et al* ., 2019
	Luteolin	5.72 mg/kg (SD rats n=6)	Intact	*n.a.*	*n.a.*	0.78 ± 0.09	0.65 ± 0.04	0.1	3.5	Deng *et al* ., 2017
	Luteolin	14.3 mg/kg (SD rats n=5)	Intact	*n.a.*	*n.a.*	373.8 ± 7.7	6.88 ± 0.52	1	4.9	Zhou, P. *et al* ., 2008
	Luteolin	30 mg/kg (Wistar rats n=50)	Intact	10.1 ± 2.4	10	12.0 ± 2.5	3.13 ± 0.78	0.5	3.7	Chen *et al* ., 2010
	Luteolin	100 mg/kg (SD rats n=6)	Intact	*n.a.*	*n.a.*	35.6 ± 5.2 (SE)	10.7 ± 2.5 (SE)	4.8	2.2	Lin *et al* ., 2015
	Luteolin	200 mg/kg (SD rats n=6)	Intact	109.7 ± 24.8	24	110.3 ± 25.0	22.3 ± 4.8	2	4.7	Shi *et al* ., 2018
	Luteolin-7-glucoside	1000 mg/kg (SD rats n=6)	Intact	*n.a.*	*n.a.*	78.4 ± 13.0 (SE)	6.78 ± 1.70 (SE)	4.8	11.4	Lin *et al* ., 2015
Flavonol										
	Morin	25 mg/kg (SD rats n=6)	Intact	2.80 ± 0.68 (SE)	24	*n.a.*	3.1 ± 0.8 (SE)	*n.a.*	*n.a.*	Hou *et al* ., 2010
	Morin	25 mg/kg (SD rats n=6)	Intact + conjugates	16.0 ± 6.8 (SE)	24	*n.a.*	18.5 ± 7.2 (SE)	*n.a.*	*n.a.*	*ibid*.
	Morin	50 mg/kg (SD rats n=6)	Intact	104.5 ± 22.7 (SE)	24	*n.a.*	84.9 ± 18.1 (SE)	*n.a.*	*n.a.*	*ibid*.
	Morin	50 mg/kg (SD rats n=6)	Intact + conjugates	47.5 ± 14.6 (SE)	24	*n.a.*	20.9 ± 6.2 (SE)	*n.a.*	*n.a.*	*ibid*.
	Rutin	75 mg/kg (Wistar rats n=5)	Intact + conjugates	*n.a.*	*n.a.*	13.55 ± 0.75	1.53 ± 0.16	6	3.3	Domínguez Moré *et al* ., 2021
	Rutin	100 mg/kg (Wistar rats n=5)	Intact + conjugates	*n.a.*	*n.a.*	17.30 ± 1.55	2.08 ± 0.32	6	3.1	*ibid*.
	Rutin	200 mg/kg (Wistar rats n=5)	Intact + conjugates	926 ± 515	48	*n.a.*	28.9 ± 18.7	20.8	*n.a.*	Nishijima *et al* ., 2009
	Rutin	16 mg (human n=12)	Intact + conjugates	0.79 ± 0.18	32	*n.a.*	0.04	6.5	*n.a.*	Erlund *et al.*, 2000
	Rutin	40 mg (human n=12)	Intact + conjugates	1.30 ± 0.22	32	*n.a.*	0.08	7.4	*n.a.*	*ibid*.
	Rutin	100 mg (human=12)	Intact + conjugates	1.97 ± 0.67	32	*n.a.*	0.15	7.5	*n.a.*	*ibid*.
	Rutin	108 mg (human n=12)	Intact + conjugates	4.10 ± 3.60	24	*n.a.*	0.52 ± 0.56	7	11.8	Graefe *et al.*, 2001
	Isoquercetin	50 mg/kg (SD rats n=5)	Intact	0.06 ± 0.03	24	*n.a.*	0.0008 ± 0.0002	0.5	0.7	Yin *et al.*, 2019
	Quercetin	3 mg.kg (Wistar rats n=5)	Intact + conjugates	77.5 ± 35.8	24	*n.a.*	2.6 ± 1.3	1.3	9.5	Abrahamse *et al.*, 2005
	Quercetin	10 mg/kg (SD rats n=5)	Intact	34.4 ± 9.6	12	*n.a.*	9.63 ± 9.17	0.6	10	Abdelkawy *et al.*, 2017

Table 2. continued.

Quercetin	10 mg/kg (SD rats n=5)	Intact	*n.a.*	*n.a.*	0.199	0.662	0.1	*n.a.*	Chen *et al.*, 2005
Quercetin	10 mg/kg (SD rats n=5)	Conjugates	*n.a.*	*n.a.*	48.41	9.694	0.3	*n.a.*	*ibid.*
Quercetin	15 mg/kg (SD rats n=6)	Intact + conjugates	2.6 ± 0.7 (SE)	12	*n.a.*	0.26 ± 0.06 (SE)	*n.a.*	*n.a.*	Makino *et al.*, 2009
Quercetin	25 mg/kg (Wistar rats n=6)	Intact	1.82 ± 0.83	48	*n.a.*	1.22 ± 0.27	1	0.5	Peñalva *et al.*, 2019
Quercetin	50 mg/kg (Wistar rats n=5)	Intact	187 ± 31	48	*n.a.*	19.5 ± 4.1	5	5.8	Li *et al.*, 2009
Quercetin	50 mg/kg (Wistar rats n=5)	Intact + conjugates	25.3 ± 6.4	24	*n.a.*	3.48 ± 0.72	1.8	*n.a.*	Nishijima *et al.*, 2009
Quercetin	50 mg/kg (SD rats n=5)	Intact	151 ± 24	72	167 ± 23	6.65 ± 1.29	*n.a.*	35.5	Wang *et al.*, 2017
Quercetin	50 mg/kg (SD rats n=5)	Intact	143 ± 54	24	*n.a.*	0.025 ± 0.009	0.9	7.3	Yin *et al.*, 2019
Quercetin	50 mg/kg (SD rats n=6)	Intact + conjugates	48.4 ± 3.8 (SE)	24	*n.a.*	4.9 ± 1.0 (SE)	*n.a.*	*n.a.*	Hou *et al.*, 2010
Quercetin	100 mg/kg (SD rats n=6)	Intact + conjugates	80.3 ± 6.4 (SE)	24	*n.a.*	9.5 ± 1.6 (SE)	*n.a.*	*n.a.*	*ibid.*
Quercetin	100 mg/kg (SD rats n=6)	Intact	5241 ± 1930	24	5285 ± 1951	2786 ± 1682	0.3	0.8	Yang *et al.*, 2016
Quercetin	8 mg (human n=12)	Intact + conjugates	2.08 ± 0.15 (SE)	32	*n.a.*	0.14	1.9	17.1	Erlund *et al.*, 2000
Quercetin	20 mg (human n=12)	Intact + conjugates	3.50 ± 0.17 (SE)	32	*n.a.*	0.22	2.7	17.7	*ibid.*
Quercetin	50 mg (human n=12)	Intact + conjugates	4.38 ± 0.30 (SE)	32	*n.a.*	0.285	4.9	15.1	*ibid.*
Quercetin	1095 mg (human n=9)	Intact + conjugates	11.6 ± 1.0 (SE)	24	*n.a.*	1.10 ± 0.13 (SE)	5.7	8.9	Guo *et al.*, 2013
Quercetin-4′-*O*-glucoside	71 mg/kg (human n=12)	Intact + conjugates	18.13 ± 19.64	24	*n.a.*	4.58 ± 3.52	0.7	11.9	Graefe *et al.*, 2001
Quercetin-3-*O*-glucuronide	50 mg/kg (SD rats n=5)	Intact	33.5 ± 21.0	24	*n.a.*	4.26 ± 1.78	3.7	6.3	Yin *et al.*, 2019
Quercetin-3-*O*-glucuronide	100 mg/kg (SD rats n=5)	Intact	51474 ± 3269	24	65486 ± 22353	10378 ± 2289	3.1	2.6	Yang *et al.*, 2016
Kaempferol	25 mg/kg (SD rats n=6)	Intact	37.29	24	38.21	5.95	2	5.1	Zhang *et al.*, 2010
Kaempferol	25 mg/kg (SD rats n=6)	Glucuronide	78.34	24	81.57	7.34	9	4.1	*ibid.*
Kaempferol	50 mg/kg (SD rats n=6)	Intact	55.81	24	66.97	8.21	2	7.2	*ibid.*

Table 2. continued.

	Kaempferol	50 mg/kg (SD rats n=6)	Glucuronide	225.55	24	237	21.15	9	4.3	*ibid*.
	Kaempferol	100 mg/kg (SD rats n=4)	Intact	3.11 ± 0.07	12	*n.a.*	0.63 ± 0.03	1.5	5.3	Zhou *et al.*, 2016
	Kaempferol	250 mg/kg (SD rats n=4)	Intact	5.28 ± 0.25	12	*n.a.*	1.61 ± 0.10	1	3.5	*ibid*.
	Kaempferol	1250 mg/kg (SD rats n=6)	Intact	*n.a.*	*n.a.*	2.55 ± 0.10	0.58 ± 0.01	1.1	3.3	Zhang *et al.*, 2009
	Kaempferol	2500 mg/kg (SD rats n=6)	Intact	*n.a.*	*n.a.*	6.04 ± 0.20	0.81 ± 0.02	1.2	9.3	*ibid*.
	Isorhamnetin	0.25 mg/kg (Wistar rats n=6)	Intact + conjugates	2.65 ± 0.56	60	2.73 ± 0.65	0.18 ± 0.06	8	8.4	Lan *et al.*, 2007
	Isorhamnetin	0.5 mg/kg (Wistar rats n=6)	Intact + conjugates	3.99 ± 1.09	60	4.19 ± 1.03	0.20 ± 0.05	6.4	11.4	*ibid*.
	Isorhamnetin	1 mg/kg (Wistar rats n=6)	Intact + conjugates	5.13 ± 1.47	60	5.48 ± 1.30	0.24 ± 0.02	7.2	11.2	*ibid*.
Isoflavone										
	Genistein	6.25 mg/kg (SD rats n=6)	Intact	1.45	36	1.67	0.39	0.2	3.2	Zhou, S. *et al.*, 2008
	Genistein	6.25 mg/kg (SD rats n=6)	Glucuronide	10.7	36	11	13.2	0.2	2.2	*ibid*.
	Genistein	12.5 mg/kg (SD rats n=6)	Intact	4.99	36	5.11	0.95	0.2	8.5	*ibid*.
	Genistein	12.5 mg/kg (SD rats n=6)	Glucuronide	29	36	30.2	18.3	0.2	6.3	*ibid*.
	Genistein	50 mg/kg (SD rats n=6)	Intact	11	36	11.3	2.77	0.2	8.4	*ibid*.
	Genistein	50 mg/kg (SD rats n=6)	Glucuronide	106	36	108	33.5	0.2	7.2	*ibid*.
	Genistein	30 mg/kg (human n=10)	Intact	9.59 ± 3.13	48	9.76 ± 3.25	0.89 ± 0.29	4	7.6	Ullmann *et al.*, 2005
	Genistein	60 mg/kg (human n=10)	Intact	23.9 ± 7.4	48	24.3 ± 17.8	2.04 ± 0.97	5	7.5	*ibid*.
	Genistein	150 mg/kg (human n=10)	Intact	71.6 ± 31.2	48	73.2 ± 32.4	5.49 ± 1.24	5	8	*ibid*.
	Genistein	300 mg/kg (human n=10)	Intact	96.7 ± 32.8	48	96.7 ± 39.7	6.56 ± 1.39	6	9.5	*ibid*.
	Daidzein	1.0 mg/kg (SD rats n=4)	Intact + conjugates	0.6 ± 0.1	8	*n.a.*	0.11 ± 0.03	8	*n.a.*	Zhang *et al.*, 2020
	Daidzein	10 mg/kg (SD rats n=3)	Intact	1.45 ± 0.40	12	*n.a.*	0.52 ± 0.12	0.4	*n.a.*	Shen *et al.*, 2011

Table 2. continued.

	Daidzein	10 mg/kg (Wistar rats n=6)	Intact + conjugates	36.0 ± 6.2	24	45.0 ± 8.7	2.78 ± 0.36	6.5	*n.a.*	Panizzon *et al.*, 2019
	Daidzein	15 mg/kg (SD rats m=6)	Intact	0.65± 0.12	24	0.72 ± 0.09	0.102 ± 0.008	2.7	6	Li, Y. *et al.*, 2021
	Daidzein (in 0.5 % CMC Na)	20 mg/kg (SD rats n=6)	Intact	6.33 ± 3.22	48	6.35 ± 3.26	0.50± 0.19	5	4.6	Qiu *et al.*, 2005
	Daidzein (in 0.5 % CMC Na)	20 mg/kg (SD rats n=6)	Glucuronide	10.4 ± 6.4	48	10.8 ± 6.8	0.76 ± 0.22	3.7	10.3	*ibid.*
	Daidzein (in 0.9 % NaCl solution)	20 mg/kg (SD rats n=6)	Intact	13.3 ± 11.7	48	13.3 ± 11.7	2.36 ± 1.19	0.5	3.4	*ibid.*
	Daidzein (in 0.9 % NaCl solution)	20 mg/kg (SD rats n=6)	Glucuronide	59.1 ± 52.4	48	60.3 ± 52.4	11.8 ± 9.7	0.4	10.8	*ibid.*
	Daidzein	100 mg/kg (SD rats n=6)	Intact	31.7 ± 14.0	24	*n.a.*	3.66 ± 8.77	1.5	*n.a.*	Huang *et al.*, 2019
	Puerarin	100 mg/kg (SD rats n=6)	Intact	0.0021 ± 0.0001	14	0.0027 ± 0.0002	0.0005 ± 0.0001	0.6	6	Ouyang *et al.*, 2012
	Isoformononetin	10 mg/kg (SD rats n=5)	Intact	2.98 ± 0.75	30	2.98 ± 0.75	1.00 ± 0.22	0.4	1.9	Raju *et al.*, 2019
	Equal-OH	1.0 mg/kg (SD rats n=4)	Intact + conjugates	0.2 ± 0.1	8	*n.a.*	0.05 ± 0.02	0.5	*n.a.*	Zhang *et al.*, 2020
	Glyceollin I	1.0 mg/kg (SD rats n=4)	Intact + conjugates	8.5 ± 0.7	8	*n.a.*	1.9 ± 0.6	0.5	3.1	*ibid.*
	Glyceollin III	1.0 mg/kg (SD rats n=4)	Intact + conjugates	1.0 ± 0.2	8	*n.a.*	0.25 ± 0.05	0.5	4.7	*ibid.*
Flavonolignan										
	Silybin stereoisomer 2R 3R 10R 11R	200 mg/kg (Wistar rats n=3)	Intact	0.97	6	*n.a.*	0.27	4.1	2	Marhol *et al.*, 2015
	Silybin stereoisomer 2R 3R 10R 11R	200 mg/kg (Wistar rats n=3)	Intact + conjugates	7.32	6	*n.a.*	2.18	3.9	2.2	*ibid.*
	Silybin stereoisomer 2R 3R 10S 11S	200 mg/kg (Wistar rats n=3)	Intact	2.09	6	*n.a.*	0.95	1	1.4	*ibid.*
	Silybin stereoisomer 2R 3R 10S 11S	200 mg/kg (Wistar rats n=3)	Intact + conjugates	134.6	6	*n.a.*	30	2.6	2.9	*ibid.*
Xanthones										
	Mangiferin	38 mg/kg (SD rats n=6)	Intact	*n.a.*	*n.a.*	1.65 ± 0.33	0.46 ± 0.18	2	1.4	Chang *et al.*, 2018
Stilbenes										
	Resveratrol	15 mg/kg (Wistar rats n=6)	Intact	1.23 ± 0.57	4	*n.a.*	0.88 ± 0.09	0.6	0.3	Peñalva *et al.*, 2018
	Resveratrol	40 mg/kg (SD rats n=5)	Intact	2.47 ± 0.36	12	*n.a.*	2.42 ± 0.24	0.3	*n.a.*	Siu *et al.*, 2018
	Resveratrol	50 mg/kg (SD rats n=6)	Intact	8.31 ± 2.39	24	*n.a.*	1.68 ± 0.54	1.2	3.6	Qiu *et al.*, 2017

Table 2. continued.

	Resveratrol	50 mg/kg (SD rats n=6)	Intact	7 ± 2	12	7.1 ± 2.0	6.57 ± 1.55	0.3	1.5	Marier *et al.*, 2002
	Resveratrol	50 mg/kg (SD rats n=6)	Intact + glucuronide	322 ± 57	12	325 ± 58	105 ± 32	0.4	1.6	*ibid.*
	Resveratrol	60 mg/kg (SD rats n=6)	Intact	9.59 ± 1.88	8	*n.a.*	3.08 ± 0.74	0.5	5.2	Liu *et al.*, 2019
	Resveratrol	100 mg/kg (SD rats n=6)	Intact	*n.a.*	*n.a.*	23.4 ± 3.13	*n.a.*	0.17	1.97 ± 0.34	Liang *et al.*, 2013
	Resveratrol	150 mg/kg (Kunming mice n=5)	Intact	*n.a.*	*n.a.*	5.11 ± 4.53	9.91 ± 5.66	0.2	*n.a.*	Wang *et al.*, 2021
	Resveratrol	5.9 mg/kg (pigs n=4)	Intact	30.64 ± 0.03	5	35.76 ± 0.04	15.96 ± 0.08	1	1.2	Azorin-Ortuno *et al.*, 2010
	Resveratrol	0.5 mg (human n=10)	Intact	*n.a.*	*n.a.*	0.98	0.32 ± 0.16	0.8	2.9	Boocock *et al.*, 2007
	Resveratrol	1.0 mg (human n=10)	Intact	*n.a.*	*n.a.*	2.39 ± 1.37	0.51 ± 0.38	0.8	8.9	*ibid.*
	Resveratrol	2.5 mg (human n=10)	Intact	*n.a.*	*n.a.*	3.45 ± 1.25	1.17 ± 0.65	1.4	4.2	*ibid.*
	Resveratrol	5.0 mg (human n=10)	Intact	*n.a.*	*n.a.*	5.78 ± 3.42	2.36 ± 1.71	1.5	8.5	*ibid.*
	Resveratrol	1.36 mg (human n=10)	Intact + conjugates	3.326 ± 0.47	96	*n.a.*	0.473 ± 0.117	2.4 ± 0.9	*n.a.*	Tani *et al.*, 2014
	Resveratrol	25 mg (human n=8)	Intact + conjugates	27.3 ± 3.0 (SE)	72	*n.a.*	*n.a.*	*n.a.*	9.2	Walle *et al.*, 2004
	Resveratrol	25 mg (human n=8)	Intact	0.004 ± 0.002	3	*n.a.*	0.006 ± 0.003	1	2	Almeida *et al.*, 2009
	Resveratrol	50 mg (human n=8)	Intact	0.019 ± 0.012	3	*n.a.*	0.029 ± 0.025	0.9	1.8	*ibid.*
	Resveratrol	100 mg (human n=8)	Intact	0.085 ± 0.074	3	*n.a.*	0.094 ± 0.106	1.3	1.1	*ibid.*
	Resveratrol	150 mg (human n=8)	Intact	0.140 ± 0.086	3	*n.a.*	0.109 ± 0.086	1.3	1.9	*ibid.*
	Resveratrol	180 mg (human n=6)	Intact	4.14± 0.81 (SE)	3	*n.a.*	2.3 ± 0.5 (SE)	1.9	2.1	Ianitti *et al.*, 2020
	Resveratrol-3-*O*-glucoside	75 mg/kg (SD rats n=8)	Intact	*n.a.*	*n.a.*	3.20 ± 1.31	*n.a.*	*n.a.*	1.6	Su *et al.*, 2019
	Resveratrol-3-*O*-glucoside	150 mg/kg (SD rats n=8)	Intact	*n.a.*	*n.a.*	9.53 ± 3.66	*n.a.*	*n.a.*	1.3	*ibid.*
	Resveratrol-3-*O*-glucoside	300 mg/kg (SD rats n=8)	Intact	*n.a.*	*n.a.*	19.52 ± 5.71	*n.a.*	*n.a.*	1.3	*ibid.*
Curcuminoids										
	Curcumin	300 mg/kg (SD rats n=5)	Intact	1.26 ± 0.94	24	1.44 ± 1.26	0.36 ± 0.54	4.13 ± 4.97	6.38 ± 4.65	Yu *et al.*, 2019

Table 2. continued.

	Curcumin	340 mg/kg (Wistar rats n=3)	Intact	0.22	2	*n.a.*	0.0065 ± 0.0045	0.5	*n.a.*	Marczylo *et al.*, 2007
	Curcumin	340 mg/kg (Wistar rats n=3)	Glucuronide	9.08	2	*n.a.*	0.225 ± 0.0006	0.5	*n.a.*	*ibid.*
	Curcumin	340 mg/kg (Wistar rats n=3)	Sulfate	0.7	2	*n.a.*	0.007± 0.0115	1	*n.a.*	*ibid.*
Phenolic acids										
	Ferulic acid	50 mg/kg (SD rats n=6)	Intact	0.0053 ± 0.0013	6	0.0057 ± 0.0012	0.0038 ± 0.0007	0.2	3.8	Ouyang *et al.*, 2012
	Caffeic acid	10 mg/kg (SD rats n=6)	Intact	1.68 ± 0.14	12	1.97 ± 0.18	1.39 ± 0.21	0.3	2.1	Wang *et al.*, 2014
	Caffeic acid	17 mg/kg (SD rats n=6)	Intact	4.37 ± 0.45	12	4.56 ± 0.48	2.50 ± 0.08	0.3	1.3	Shi *et al.*, 2019
	Caffeic acid	20 mg/kg (SD rats n=6)	Intact	77.817 ± 42.481	12	77.88 ± 42.47	43.69 ± 13.77	0.3	1.3	Wang *et al.*, 2015
	Caffeic acid	18 mg/kg (Wistar rats)	Intact	1.82	1.5	*n.a.*	2.27 ± 0.16 (SE)	0.17	0.57	Konishi *et al.*, 2005
	Caffeic acid	18 mg/kg (Wistar rats)	Conjugates	26.9	1.5	*n.a.*	30.30 ± 2.48	0.3	*n.a.*	*ibid.*
	Syringic acid	30 mg/kg (SD rats n=3)	Intact	295.9 ± 121.8	8	298.4 ± 124.4	165.3 ± 36.4	0.7	1.2	Zhou *et al.*, 2012
	Salicylic acid	30 mg/kg (SD rats n=3)	Intact	1978.7 ± 173.8	8	4141.3 ± 614.5	439.3 ± 33.8	0.7	8.9	*ibid.*
	p-Coumaric acid	2.35 mg/kg (Wistar rats n=6)	Intact	13.95 ± 3.35	6	14.13 ± 3.47	19.19 ± 2.98	0.2	1.3	Cui *et al.*, 2010

Data represent the mean ± standard deviation (SD), except for the representation of SE (standard error); *n.a.*, not available

Table 3. Pharmacokinetics of polyphenols in different tissues after a single oral administration in Sprague-Dawley rats in literature

Compound	Dose (mg/kg)	Metabolite(s)	C_{max} (μmol/L or nmol/mL or nmol/g-tissue) (intact + conjugates)						Reference
			Plasma	Liver	Kidney	Heart	Lung	Muscle	
Ferulic acid	3.3	Intact	5.73 (T_{max}, 0.66 h)	1.62 (*n.a.*)	12.66 (*n.a.*)	0.21 (*n.a.*)	0.19 (*n.a.*)	*n.a.*	Chen *et al*., 2021
Naringin	42	Intact	0.309 (0.5 h)	12.2 (0.25 h)	13.2 (0.25 h)	0.363 (0.25 h)	188 (1 h)	0.618 (0.25 h)	Zeng *et al*., 2019
Naringin	42	Naringenin Naringenin-Glucuronide Naringenin-Sulfate Naringenin-Glucuronide/Sulfate	12.9 (0.25 h)	78.7 (6 h)	46.7 (6 h)	5.24 (6 h)	9.32 (1 h)	1.07 (6 h)	*ibid.*
Daidzein	1.64	Equol *cis*-4-OH-Equol Dihydrodaidzein Tetrahydrodaidzein	0.38 (0.89 h)	0.43 (*n.a.*)	0.25 (*n.a.*)	0.022 (*n.a.*)	0.18 (*n.a.*)	*n.a.*	Prasain *et al*., 2004; Chen *et al*., 2018
Resveratrol	50	Sulfate Glucuronide	7 (2 h)	1.1 (2 h)	4 (2 h)	0.1 (2 h)	0.4 (2 h)	*n.a.*	El-Moshen *et al*., 2006
Pelargonidin	50	Glucuronide Aglycone	*n.a.*	0.27	0.65	Not detected	0.24	*n.a.*	*ibid.*
Dihydrimyrcetin	100	Intact	*n.a.*	5.4 (0.25 h)	4.91 (0.25 h)	12 (0.25 h)	17.1 (0.25 h)	*n.a.*	Fan *et al*., 2017
Neochrogenic acid	5.09	Intact	*n.a.*	0.72 (0.25 h)	0.6 (0.22 h)	0.44 (0.22 h)	0.53 (0.25 h)	*n.a.*	Li, S. *et al*., 2021
Chlorogenic acid	6.88	Intact	*n.a.*	0.85 (0.25 h)	0.81 (0.25 h)	0.56 (0.21 h)	0.67 (0.25 h)	*n.a.*	*ibid.*
Cryptochlorogenic acid	3.24	Intact	*n.a.*	0.89 (0.24 h)	0.85 (0.25 h)	0.61 (0.25 h)	0.81 (0.25 h)	*n.a.*	*ibid.*
Caffeic acid	3.01	Intact	*n.a.*	1.93 (0.22 h)	1.85 (0.25 h)	1.48 (0.25 h)	1.67 (0.25 h)	*n.a.*	*ibid.*
Resveratrol	100	Intact	*n.a.*	3.14 (0.25 h)	2.53 (0.25 h)	2.25 (0.25 h)	1.66 (0.25 h)	*n.a.*	Liang *et al*., 2013
Catechin	543	Intact	11.8 (0.38 h)	59 (0.5 h)	*n.a.*	6.05	12.8	*n.a.*	Wang *et al*., 2019
Epicatechin	34	Intact	1.42 (0.46 h)	8.77 (0.25 h)	*n.a.*	2.48 (0.5 h)	1.67 (0.25 h)	*n.a.*	*ibid.*

n.a. indicates not available

indicating that the incorporated theaflavins are stable or less susceptible to phase I/II metabolism. Although the physiological roles of non-absorbable theaflavins are not fully understood, the influx/efflux transportation dynamics may result in the activation of AMP-activated protein kinase (AMPK), affecting the expression of intestinal absorption pathways, such as carrier-mediated and paracellular passive pathways (Peng *et al*., 2009; Pieri *et al*., 2010; Sopjani *et al*., 2010). Previous reports revealed that theaflavins caused the suppression of PepT1 expression (Takeda *et al*., 2013), enhancement of intestinal membrane barrier via the expression of TJ-related proteins, including occludin, claudin-1, and zonula occluden (ZO)-1 (Park *et al*., 2015), suppression of SGLT1 expression (Li *et al*., 2020), and stimulation of incretin (glucagon-like peptide-1, GLP-1, and glucose-dependent insulinotropic polypeptide, GIP) secretion (Li, B. *et al*., 2021). The activation of AMPK requires the phosphorylation of Thr-172 at the loops of α1 and α2 subunits through activation of upstream kinases, including liver kinase B1 (LKB1), Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK), or transforming growth factor-ß-activated kinase-1 (TAK-1) (Hardie, 2008; Kim and He, 2013). However, the upstream signaling mechanism(s) that are involved in AMPK activation during the influx/efflux transportation process of theaflavins remain unclear.

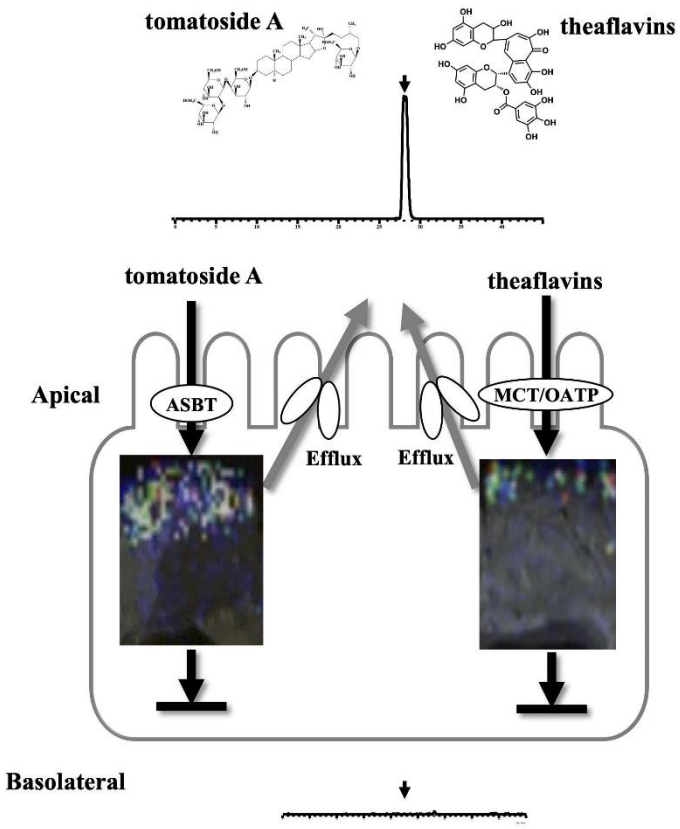

Fig. 2. Visualized absorption behavior of steroidal saponin (tomatoside A) and theaflavins across rat intestinal membrane through matrix-assisted laser desorption/ionization-mass spectrometry (MALDI-MS) imaging

Perspective

Polyphenols have diverse physiological potentials for maintaining homeostasis. However, these compounds are susceptible to metabolic phase I/II reactions during intestinal absorption and form a variety of conjugates. Although in this review, the bioavailability of major polyphenols was discussed, little is known about the absorbability of other naturally occurring polyphenols. Considering the *in vivo* findings that polyphenols can provide diverse health benefits, more research on tissue distribution is required to explore the effects of polyphenols. Furthermore, the combinatory effect of polyphenols on contaminated food compounds should also be taken into consideration while developing strategies for polyphenol-derived health promotion (Wendling *et al*., 2015).

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Conflict of interest There are no conflicts of interest to declare.

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