



Review Article

Polyphenols: The interactions with CYP₄₅₀ isoenzymes and effect on pharmacokinetics of drugs

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ABSTRACT

Recent clinical studies demonstrated that certain natural polyphenols like flavonoids present in dietary supplements modify the pharmacokinetics of some co-administered drugs. Number of herbal remedies interact selectively with different CYP₄₅₀ isoenzymes and hence alter CYP-mediated drug metabolism and pharmacokinetics. Drug-polyphenol interaction may alter drug bio availability through altered absorption, distribution and metabolism. There is need to collect clinical evidences to support whether the effect of drugs and polyphenols co-administration rather than relying on in-vitro experiments or animal studies. Herbal drugs containing variety of polyphenols interact with CYP₄₅₀ enzymes leading to either induction or inhibition of CYPs which alters the pharmacokinetic parameters of their respective substrate drugs. This information will be helpful for physicians and pharmacists to alleviate risks associated with polyphenolic remedies as well as to realize the benefits of alternative medicine.

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1. Introduction

More than 8000 polyphenolic compounds have been identified in various plant species, having several important functions. The phenolic groups in polyphenols can accept an electron to form relatively stable phenoxyl radicals, thereby disrupting chain oxidation reactions in cellular components.¹ In addition to fruits and vegetables, leaves, nuts, seeds, barks and flowers are also rich sources of polyphenols.² On the basis of in vivo or in vitro evidence, inhibition of the CYP forms responsible for the metabolism of co-administered drugs has been proposed as the mechanism responsible for the pharmacokinetic interactions caused by flavonoids.³ Flavonoids have high potencies and selectivities for inhibition of CYP

isoenzymes.⁴ Polyphenols may be classified into different groups as a function of the number of phenol rings that they contain and of the structural elements that bind these rings to one another. The main classes include phenolic acids, diferuloylmethanes, flavonoids, stilbenes and lignans. Phenolic acids are further classified as hydroxycinnamic acids (e.g. Caffeic acid, Caftaric acids) and hydroxybenzoic acids (e.g. Ellagic acid, Gallic acid, Corilagin). Diferuloylmethanes are phenolic compounds with two aromatic rings substituted with hydroxyls, and linked by aliphatic chain containing carbonyl groups (e.g. Curcumin).

The major and most abundant class within the dietary polyphenols is flavonoids and is further classified as: Anthocyanidins (e.g. Cyanidin, Delphinidin, Pelargonidin) and different Anthoxanthins including Flavonols (e.g. Myricetin, Quercetin, Kaempferol), Flavanones (e.g.

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Table 1: Sources of polyphenols with their interaction with different CYP subfamilies

Fruits/ Herbs	Polyphenols	Interaction with CYP450 isoforms
Apple juice	Quercetin, Phloretin, Rutin, Phlorizin, Phloretin, (-)-Epicatechin, (+)-Catechin, Chlorogenic acid ⁵	Quercetin and phloretin inhibit CYP1A ⁶
Beet juice	Betacyanin ⁷	—
Black pepper	Piperine, Alkamides, Wisanine, Dipiperamide D, Dipiperamide E, Piptigrine ⁸	CYP3A4/5, Piperine, dipiperamides D and E inhibit CYP2D6 ^{9,10}
Blackberries	Ellagic acid, Tannins, Ellagitannins, Quercetin, Gallic acid, Anthocyanins, Cyanidins ^{11,12}	—
Blackcurrant	Delphinidin-3-O-Glucoside, Delphinidin-3-O-Rutinoside, Cyanidin-3-O-Glucoside, Cyanidin-3-O-Rutinoside ¹³	Inhibits CYP1A1 ¹⁴
Broccoli	<i>B</i> -Carotene, Lutein ¹⁵	Induces CYP1A2 and CYP2A6 ¹⁶
Cocoa	Catechin, Epicatechin, Caffeine, Theobromine, Theophylline ¹⁷	Crude cocoa inhibits CYP1A ¹⁸
Cranberries	Cyanidin, Peonidin, Quercetin ^{19,20}	Inhibits CYP2C9 ²¹
Turmeric	Curcumin	Inhibit CYP1A2, Induce CYP2A6 ²²
Green tea	Epigallocatechin-3-Gallate (EGCG), Epigallocatechin (EGC), Epicatechin-3-Gallate (ECG), Epicatechin, Caffeine	Caffeine induces CYP1A2 ²³
Ginkgo biloba extract	Terpenoids, Flavonoids, Amentoflavone	Inhibit CYP2C9, CYP1A2, CYP2E1, CYP3A4 ²⁴
Grape juice	Catechins, Ellagic acid, Myricetin, Quercetin, Kaempferol, Trans-Resveratrol, Syringetin, Syringetin 3-O-Galactoside, Laricitrin, Laricitrin 3-O-Galactoside, Delphinidin, Cyanidin, Petunidin, Peonidin, Malvidin ^{25–27}	Quercetin inhibits CYP 1A2, trans-resveratrol inhibits CYP1A1, CYP1A2, CYP1B1, CYP2E1 ^{28,29}
Grapefruit	Naringin, Bergamottin, Dihydroxybergamottin	Naringin inhibits CYP3A4 ³⁰
Lettuce	Mono-Caffeoyl Tartaric acid, Chicoric acid, 5-Caffeoylquinic acid (Chlorogenic acid), 3,5-Di-O-Caffeoylquinic acid (Isochlorogenic acid), Quercetin 3-O-(6-O-Malonylglucoside)-7-O-Glucoside, Quercetin 3-O-Glucuronide, Quercetin 3-O-Glucoside, Luteolin ^{31,32}	—
Pineapple	Bromelain ³³	Inhibits CYP2C9 ³⁴
Onion	Spiraeoside (Quercetin-4'-O- <i>B</i> -D-Glucoside), Rutin, Quercetin ⁵	Induces CYP 1A, CYP 2B, Inhibits CYP 2E1 ^{35,36}
Licorice root	Tannic acid, Glycyrrhizin ⁵	Glycyrrhizin induces CYP3A, CYP1A2 ³⁷
Wanmi peach	Chlorogenic acid, Keracyanin, Quercetin-3-Rutinoside ³⁸	—
Persimmon	Astragaln, Hyperin, Quercetin, Isoquercetin, Myricetin, Kaempferol, Scopoletin, Rutin	Myricetin inhibits CYP3A4, CYP2C9 ³⁹
Plums	Gallic acid, Tannins ⁴⁰	Inhibits CYP1A1 ⁴¹
Pomegranates	Catechins, Gallocatechins, Ellagitannins, Punicalagins, Prodelphinidins, Delphinidin, Cyanidin, Pelargonidin ^{42,43}	Inhibits CYP3A4 ⁴⁴
Raspberry	Quercetin, Gallic acid, Anthocyanins, Cyanidins, Pelargonidins, Catechins, Kaempferol, Ellagitannin ⁴⁵	—
Soybean	Genistein, Daidzein, Phytic acid ^{46,47}	Induces CYP1A1, CYP2D1, Inhibits CYP3A1, CYP2D2 ⁴⁸
Spinach	Lutein, Zeaxanthin ⁴⁹	—
St. John's wart	Rutin, Hyperoside, Isoquercetin, Quercitrin, Quercetin, I3,II8-Biapigenin, Amentoflavone, Astilbin, Miquelianin, Chlorogenic acid, 3-O-Coumaroylquinic acid, Hypericin, Pseudohypericin, Protohypericin, Hyperforin, Protopseudohypericin, Adhyperforin ^{50,51}	Induces CYP3A4, CYP2C9 ⁵²
Tangerines	Nobiletin, Limonene, Myrcene ⁵³	Induces CYP3A4 ⁵⁴
Tomatoes	Lutein, Lycopene ^{55,56}	Induces CYP1A1, CYP1A2, CYP2B1, CYP2B2, CYP3A ⁵⁷
Orange	Hesperidin ⁵⁸	Inhibits CYP3A4 ⁵⁹
Strawberries	Cyanidins, Pelargonidins, Procyandins, Catechins, Gallocatechins, Epicatechins, Kaempferol, Quercetin, Ellagic acid, Gallic acid, Cinnamic acid, Coumaric acid, Caffeic acid, Ferulic acid, Ellagitannins, Gallotannins, Resveratrol ⁶⁰	—
Milk thistle	Silybin, Silymarin ⁶¹	Silybin Inhibits CYP2D6, CYP 2C9, Silymarin inhibits CYP3A4 ⁶²

Table 2: Different herbal drugs and their effect on pharmacokinetics of some drugs

Fruit Juices/ Herbal Extracts	Interacting drug	Pharmacokinetic alterations
Apple Juice	Fexofenadine	A significant decrease in the fexofenadine AUC was observed compared with water (1342±519 vs. 284±79.2 ng·h/ml, P<0.05). ⁶³
Cranberry Juice (CJ)	Nifedipine	AUC of Nifedipine was approximately 1.6-fold higher when CJ injected intraduodenally. ⁶⁴
Grapefruit Juice (GFJ)	1.Talinolol	1. GFJ decreased the talinolol serum AUC and C _{max} , and urinary excretion values to 56% (P < .001), 57% (P < .001), and 56% (P < .001), respectively, of those with water. No effect on renal clearance, elimination half-life, or T _{max} . ⁶⁵
	2.Nilotinib	2. Concurrent intake of GFJ increased the nilotinib C _{max} by 60% and serum AUC _{0-∞} by 29% but did not affect T _{max} or t _{1/2} of nilotinib. ⁶⁶
	3.Tramadol	3. Tramadol T _{max} was increased from 1.33 to 1.70 h after GFJ treatment, plasma C _{max} decreased from 490 to 270 ng/ml and AUC decreased from 11,610 to 5,890 h·ng/ml with GFJ treatment. ⁶⁷
	4.Nisoldipine	4. C _{max} of nisoldipine was significantly increased after GFJ intake. ⁶⁸
Orange Juice (OJ)	1.Levofloxacin	1. Plasma C _{max} of Levofloxacin decreased from 3.49 ± 0.75 μg/ml to 2.57 ± 0.46 μg/ml when taken with OJ. Serum AUC _{0-∞} value was also reduced by 17.33%; AUC ₀₋₂₄ was decreased by 14.98%. ⁶⁹
	2.Fexofenadine	2. OJ decreased the oral exposure of fexofenadine by 31% in rats. ⁷⁰
	3.Indinavir	3. Coadministration of Seville OJ and indinavir resulted in significant increase in indinavir T _{max} from 1.25 to 1.87h; p < 0.05. ⁷¹
	4.Itraconazole	4. C _{max} and AUC ₀₋₄₈ of itraconazole were 1.1-fold to 1.3-fold higher when co-administered with OJ, than that with water. ⁷²
	5.Cyclosporine A	5.OJ significantly increased the AUC and C _{max} , and decreased the T _{max} of cyclosporine A. ⁷³
	6.Atenolol	6. OJ decreased plasma C _{max} of atenolol by 49% (range 16-59%, P<0.01), and plasma atenolol AUC ₀₋₃₃ by 40% (range 25-55%, P<0.01). The amount of atenolol excreted into urine was decreased by 38% (range 17-60%, P<0.01). ⁷⁴
	7.Celiprolol	7. OJ reduced plasma C _{max} of celiprolol by 89% (P< .01) and plasma AUC by 83% (P< .01). T _{max} increased from 4 to 6 h (P< .05), t _{1/2} was prolonged from 4.6 to 10.8 h (P = .05). Urinary excretion of celiprolol was reduced by 77% (P < .01). ⁷⁵
	8.Ethionamide	8.C _{max} was increased by OJ (9%), T _{max} delayed by (12%). ⁷⁶
Pomegranate Juice (PJ)	Tolbutamide	PJ significantly increased the AUC of tolbutamide by 22%. ⁷⁷
St John's Wort	1.Fexofenadine	1. A single dose of St John's wort increased plasma C _{max} of fexofenadine by 45% (P< .05) and decreased the oral clearance by 20% (P< .05). Compared with the single-dose treatment phase, long-term St John's wort caused 35% (P< .05) decrease in C _{max} and 47% (P< .05) increase in fexofenadine oral clearance. ⁷⁸
	2.Warfarin	2. Apparent clearances of S-warfarin after warfarin alone or with St John's wort 198 ± 38 ml/h, and 270 ± 44 ml/h. ⁷⁹
	3.Imatinib Mesylate	3.Reductions of 32% (p=0.0001) in the median AUC _{0-∞} , 29% (p=0.005) in C _{max} and 21% (p=0.0001) in t _{1/2} of Imatinib Mesylate. ⁸⁰
Ginseng	Warfarin	Apparent clearances of S-warfarin after warfarin alone or with ginseng 198 ± 38 ml/h and 220 ± 29 ml/h ⁷⁹
Tangerine Juice	Midazolam	Reduced the AUC _{0-1.5} of midazolam by 39% and prolonged the T _{max} (P < .05) without affecting the total AUC values, t _{1/2} values. ⁸¹
Green Tea Extract (GTE)	Clozapine	T _{max} was significantly increased by GTE. The mean total AUC _{0-∞} and C _{max} in GTE group were significantly lower than those of controls. Induced a about 2-fold increase in hepatic CYP1A2 levels. ⁸²

Table 3: Brief summary of effect of different polyphenols on pharmacokinetics of some drugs

Polyphenol	Interacting drug	Pharmacokinetic alterations
Apigenin	Raloxifene	Apigenin with raloxifene in a 1:2 ratio by weight resulted in 55% and 37% increase in the C _{max} and AUC of raloxifene, respectively. When the ratio of 1:1 was administered, the C _{max} and AUC of intact raloxifene were increased by 173% and 97% respectively. ⁸³
Baicalin and Baicalein	1.Cyclosporine 2.Doxorubicin (DOX)	1. Baicalin and baicalein elevated C _{max} of cyclosporine by 408.1 % and 87.5 % and increased the AUC ₀₋₅₄₀ by 685.3 % and 150.2 %, respectively. ⁸⁴ 2. AUC _{0-∞} and C _{max} of DOX were significantly higher when given with baicalein. ⁸⁵
Caffeic Acid	L-Dopa, 3-O-Methyldopa (3-OMD)	Decreased about 22% of the peripheral formation of 3-OMD and about 31% of the C _{max} of 3-OMD, caffeic acid improves the bioavailability of L-dopa in rabbit plasma. ⁸⁶
(+)-Catechin	Carbamazepine	(+)-Catechin caused a delayed absorption of carbamazepine, as evidenced by shift of T _{max} from 2 h to 6 h. ⁸⁷
Hesperidin	1.Montelukast 2.Diltiazem 3.Verapamil	1.Reduction in the AUC _{0-∞} of montelukast (P = 0.032). ⁸⁸ 2. AUC _{0-∞} was significantly (5 mg/kg, P < 0.05; 15 mg/kg, P < 0.01) increased by 48.9-65.3% and C _{max} was significantly (P < 0.05) increased by 46.7-62.4% in the presence of hesperidin (5 or 15 mg/kg). The absolute bioavailability (F) of diltiazem with hesperidin was significantly (5 mg/kg, P < 0.05; 15 mg/kg, P < 0.01) higher than that in the control group. ⁸⁹ 3. Hesperidin significantly (p<0.01) increased plasma AUC of verapamil by 71.1-96.8% and C _{max} by 98.3-105.2%. Hesperidin significantly (p<0.01) decreased its total plasma clearance (CL/F) by 41.6-49.2% in rats. ⁹⁰
Curcumin	1.Talinolol 2.Celiprolol 3.Midazolam 4.Etoposide	1. Reduced AUC _{0-∞} of talinolol from 1860.0 ± 377.9 to 1246.0 ± 328.2 ng.h/mL, the C _{max} were significantly decreased from 147.8 ± 63.8 to 106.4 ± 39.9 ng/mL, and the CL/F was increased from 27.9 ± 5.5 to 43.1 ± 13.4 L/h (p < 0.05). ⁹¹ 2. The C _{max} , AUC ₀₋₈ , and total AUC of celiprolol were, respectively, 1.9- (p 0.01), 1.6- (p 0.01), and 1.3-fold (p 0.02) greater for rats in the treated group. CL _{oral} was decreased by 22% (p 0.01). ⁹² 3. Rats in the treatment group showed higher AUC ₀₋₄ (2.6-fold, p 0.04) and total AUC (3.8-fold, p 0.03) values, as well as lower CL _{oral} (75% lower, p 0.02) values, compared with control. ⁹² 4. Curcumin (2 or 8 mg/kg) increased significantly the oral bioavailability, AUC and C _{max} of etoposide. ⁹³
Daidzein	Theophylline	Comparing the kinetics parameters of theophylline alone of day 1 with those of 10-day daidzein treatment, the AUC ₀₋₄₈ , AUC _{0-∞} , C _{max} and t _{1/2} were significantly increased by 33.57 ± 21.75% (P< 0.05), 33.77 ± 21.45% (P<0.05), 23.54 ± 16.93% (P< 0.05) and 41.39 ± 45.92% (P=0.011), respectively. ⁹⁴
Diosmetin	Diclofenac	Diosmetin increased markedly the K _m (substrate concentration yielding 50% of V _{max}) of the reaction without affecting the V _{max} of reaction. ³
Diosmin	Metronidazole	Metronidazole plasma AUC _{0-X} and C _{max} were significantly higher after diosmin pretreatment by (mean) 27% and 24%, respectively. ⁹⁵
Epigallocatechin Gallate (EGCG)	1.Verapamil 2.Tamoxifen	1. Compared with the controls, both the AUC and the relative bioavailability of verapamil were significantly (p 0.01) increased by 74.3- 111% in the presence of EGCG. ⁹⁶ 2. Compared with the oral control group plasma AUC and the C _{max} of tamoxifen significantly (P<0.05 for 3 mg/kg of EGCG, P<0.01 for 10 mg/kg of EGCG) increased 48.4-77.0 and 57.1-89.7%, respectively. The relative bioavailability of tamoxifen was 1.48-1.77-fold greater than that of the control group. ⁹⁷
Genistein	1.Paclitaxel 2.Carbamazepine 3.Omeprazole	1. Genistein significantly (p<0.05) increased the AUC (54.7% greater) of orally administered paclitaxel, which was due to the significantly (p<0.05) decreased CL/F value of paclitaxel (35.2% lower). Genistein also increased the C _{max} of paclitaxel significantly (p<0.05 by 3.3mg/kg, 66.8% higher; p<0.01 by 10mg/kg, 91.8% higher). The absolute bioavailability (F) of paclitaxel elevated from 0.016 to 0.020-0.025 in the presence of genistein and the relative bioavailability (Fr) of orally administered paclitaxel was increased from 1.26- to 1.55-fold. ⁹⁸ 2. Bioavailability reduced, AUC _{0-t} , C _{max} , T _{max} reduced, Plasma CL increased, due to induction of CYP3A4. ⁹⁹ 3. Bioavailability increased, AUC _{0-t} , C _{max} , increased, Plasma CL reduced, due to inhibition of CYP2C9. ⁹⁹

Table 3 Cont....

Kaempferol	1.Etoposide	1. The presence of kaempferol significantly (4 mg/kg, $P < 0.05$; 12 mg/kg, $P < 0.01$) increased the plasma AUC and C_{max} of the oral etoposide. Kaempferol decreased significantly (4 or 12 mg/kg, $P < 0.05$) the CL/F value of oral etoposide. ¹⁰⁰
	2.Nifedipine	2. Plasma C_{max} of the three treated groups were 0.51, 0.70 and 0.81 $\mu\text{g/ml}$, respectively. The AUC ₀₋₈ values were 1.81, 2.83 and 3.63 $\mu\text{g/h/ml}$, respectively. The C_{max} , AUC ₀₋₈ and the mean retention time MRT ₀₋₈ of Nifedipine were significantly increased by oral treatment with kaempferol($P < 0.01$). ¹⁰¹
	3.Tamoxifen	3. In the presence of kaempferol, plasma AUC _{0-∞} of tamoxifen was significantly greater; C_{max} and F were greater than those without kaempferol. ¹⁰²
Luteolin	γ -Hydroxybutyrate (GHB)	Compared with the GHB alone, the AUC of GHB was significantly decreased from 170±40 mg/ml.min in the control rats to 113±21 mg/ml.min ($p < 0.05$) for luteolin 10 mg/kg group. In contrast, the total clearance of GHB was significantly increased from 6.19±1.59 ml/min/kg to 9.05±1.43 ml/min/kg($p < 0.05$) in the luteolin 10 mg/kg group. ¹⁰³
Morin	1.Diltiazem	1. Compared with the control group, pretreatment of morin significantly increased the absorption rate constant (K_a) and C_{max} of diltiazem ($p < 0.05$, $p < 0.01$). Plasma AUC in morin treated rats were significantly higher than that in the control group ($p < 0.05$, $p < 0.01$). Relative bioavailability (RB%) in rats pretreated with morin was increased by 1.36- to 2.03-fold. ¹⁰⁴
	2.Etoposide	2. Orally morin (15 mg/kg) significantly increased the AUC (45.8%), C_{max} (32.0%) and the absolute bioavailability (35.9%) of oral etoposide compared with the control. ¹⁰⁵
	3.Nicardipine	3. Morin significantly increased ($P < 0.01$, 67.8–112%) the plasma AUC and C_{max} ($P < 0.01$, 53.5–93.1%) of oral nicardipine. Morin (7.5 and 15 mg/kg) significantly decreased ($P < 0.01$, 40.4–52.8%) the CL/F of nicardipine compared with the control group. ¹⁰⁶
	4.Paclitaxel	4. Compared to the control, pretreatment with morin increased C_{max} and AUC of paclitaxel by 70–90% and 30–70%, respectively. ¹⁰⁷
	5.Tamoxifen	5. Morin significantly ($p < 0.05$) increased the K_a of tamoxifen compared to the control group, and the plasma AUC and C_{max} were significantly ($p < 0.05$) higher, especially by 1.5 and 7.5 mg/kg of morin coadministration ($p < 0.01$). The absolute bioavailability (AB %) were from 26.4% to 45.4% in the presence of morin, much higher than the control, 16.3%. The relative bioavailability (RB%) was 1.62- to 2.79-times higher than the control group. ¹⁰⁸
Myricetin	1.Doxorubicin (DOX)	1. Compared to the control group, myricetin significantly ($p < 0.05$, 2 mg/kg; $p < 0.01$, 10 mg/kg) increased the plasma AUC (51-117% greater) of oral DOX. Myricetin also significantly ($p < 0.05$, 2 mg/kg; $p < 0.01$, 10 mg/kg) increased C_{max} of DOX. The relative bioavailability of oral DOX was increased by 1.51- to 2.17-fold. ¹⁰⁹ 2. Myricetin (2 or 8 mg/kg) increased the plasma AUC of losartan by 31.4-61.1% and C_{max} by 31.8-50.2%. ¹¹⁰
	2.Losartan	
	3.Tamoxifen	3. Compared with the oral control group, the plasma AUC _{0-∞} and the C_{max} of tamoxifen were significantly ($P < 0.05$, 2 mg/kg; $P < 0.01$, 8 mg/kg) increased by 41.8–74.4 and 48.4–81.7%, respectively. The relative bioavailability (RB) was 1.14- to 1.74-fold greater than that of the control group. ¹¹¹
Naringin	1.Paclitaxel	1. Compared to the control, naringin increased the C_{max} of paclitaxel significantly ($p < 0.01$). The plasma AUC and C_{max} of paclitaxel with naringin significantly higher ($p < 0.01$) than the control. The half-life $t_{1/2}$ was significantly ($p < 0.05$) longer than the control. The absolute bioavailability (AB, of paclitaxel with naringin was significantly higher (3.5-6.8%, $p < 0.01$) than the control (2.2%). ¹¹²
	2.Tamoxifen	2. Naringin pretreated animals showed significantly ($p < 0.01$) increased plasma AUC and C_{max} . The absolute bioavailabilities (AB%) of tamoxifen in naringin pretreated animals were enhanced versus control (from 32.8% to 47.1%), and the relative bioavailabilities (RB%) of tamoxifen in the naringin pretreated groups were 2.02-2.88 times higher than that in the control. ¹¹³

Table 3 Cont....

Piperine	1. Carbamazepine	1. Piperine increased AUC ₀₋₁₂ ($p < 0.001$), average C _{ss} ($p < 0.001$), t _{1/2el} ($p < 0.05$) and a decreased K _{el} ($p < 0.05$). C _{max} ($p < 0.01$) and T _{max} ($p < 0.01$) were increased significantly. ¹¹⁴
	2. Fexofenadine	2. Piperine increased AUC of fexofenadine by 180% to 190% in rats. The bioavailability of fexofenadine was increased by approximately 2-folds via the concomitant use of piperine. ¹¹⁵
	3. Phenytoin	3. Significant increase in AUC ₀₋₁₂ ($p < 0.01$), C _{max} ($p < 0.001$) and K _a ($p < 0.05$). Piperine enhanced the bioavailability of phenytoin significantly by increasing the absorption. ¹¹⁶
	4. Propranolol	4. Earlier T _{max} and a higher C _{max} and AUC were observed when co-administered with piperine. ¹¹⁷
Quercetin	1. Cyclosporine (CSP)	1. Quercetin significantly decreased the C _{max} of CSP by 67.8% and reduced the AUC ₀₋₅₄₀ by 43.3%. ¹¹⁸
	2. Fexofenadine	2. The plasma AUC of fexofenadine was increased by 55% by quercetin (2,005.3 versus 3,098.6 ng.h/ml, $P < 0.001$) and C _{max} during the quercetin phase was elevated by 68% compared to that of the placebo phase (295.3 versus 480.3 ng/ml, $P = 0.006$). The CL _{oral} of fexofenadine was decreased significantly by 37% after quercetin treatment (61.4 versus 38.7 L/h, $P < 0.001$). ¹¹⁹
	3. Tamoxifen	3. Coadministration of quercetin (2.5 and 7.5 mg/kg) significantly ($p < 0.05$) increased the K _a , C _{max} and plasma AUC of tamoxifen. The absolute bioavailability (AB%) of tamoxifen with 2.5 and 7.5 mg/kg quercetin ranged from 18.0% to 24.1%, which was significantly higher than the control group, 15.0% ($p < 0.05$). The relative bioavailability (RB%) of tamoxifen coadministered with quercetin was 1.20-1.61 times higher than the control group. ¹²⁰
Resveratrol	1. Diltiazem	1. Resveratrol (2.5 and 10 mg/kg) significantly ($P < 0.05$) increased the AUC of diltiazem by 47.7–59.9%, and C _{max} of diltiazem by 46.1–57.0% in rats. Resveratrol (2.5 and 10 mg/kg) increased the RB of diltiazem by 1.48- to 1.60-fold. ¹²¹
	2. Nicardipine	2. Resveratrol significantly increased both plasma AUC ($P < 0.01$, 111-126%) and C _{max} ($P < 0.01$, 105-121%), and significantly decreased CL/F ($P < 0.01$, 52.8-55.8%) of oral nicardipine. ¹²²
Rutin	1. Warfarin	1. Treatment with rutin significantly decreased the elimination t _{1/2} of S-warfarin by 37%. ¹²³
	2. Cyclosporine (CSP)	2. Rutin significantly decreased the C _{max} of CSP by 63.2% and reduced the AUC ₀₋₅₄₀ by 57.2%. ¹¹⁸
Silibinin	1. Paclitaxel	1. Silibinin significantly ($p < 0.05$ by 2.5 mg/kg, $p < 0.01$ by 10 mg/kg) increased the plasma AUC (65.8-101.7% higher) of oral paclitaxel. Silibinin significantly increased ($p < 0.05$ by 2.5 mg/kg, 31.0% higher; $p < 0.01$ by 10 mg/kg, 52.9% higher) the C _{max} of paclitaxel. The relative bioavailability of oral paclitaxel was increased 1.15 to 2.02 fold. ¹²⁴
	2. Pyrazinamide	2. Long-Term silibinin decreases AUC of Pyrazinamide from 19,300 ± 3800 to 18,200 ± 4500 (min/μg/ml), CL from 2.52 ± 0.8 to 2.30 ± 0.29 (ml/kg/min), t _{1/2} from 204 ± 33 to 189 ± 14 (min), and C _{max} increases from 119 ± 31 to 145 ± 46 (μg/ml). ¹²⁵
	3. Loratadine	3. The plasma AUC and C _{max} of loratadine were increased significantly ($P < 0.05$ for 1.5 mg/kg, $P < 0.01$ for 6 mg/kg) by 50.0-76.7% and 65.4-90.1%, respectively, by silibinin. The relative bioavailability of loratadine was 1.50 to 1.77 fold greater than that in the control group. ¹²⁶
	4. Tamoxifen	4. The plasma AUC _{0-∞} and C _{max} of tamoxifen were significantly ($p < 0.05$ for 2.5 mg/kg, $p < 0.01$ for 10 mg/kg) increased by 40.2-71.3% and 45.2-78.6%, respectively, with silibinin. The relative bioavailability (RB) was 1.40 to 1.72 fold greater than that in the control group. ¹²⁷
	5. Nifedipine	5. Nifedipine AUC was 1.13-fold higher in the silymarin period, C _{max} values were 0.70-fold of those of the reference period. ¹²⁸
	6. Talinolol	6. The C _{max} of talinolol was significantly higher after silymarin administration compared to the placebo. Plasma AUC ₀₋₃₆ and AUC _{0-∞} of talinolol was increased by 36.2±33.2 and 36.5±37.9%, respectively, by silymarin. The CL/F of talinolol was decreased by 23.1±16.6% during the silymarin-treated phase. ¹²⁹

Naringenin, Hesperetin), Flavones (eg. Apigenin, Luteolin), Flavanols (e.g. (+)-Catechin, (-)-Epicatechin, (-)-Epicatechin 3-gallate, Morin, (-)-Epigallocatechin, (+)-Gallocatechin, Procyanidins), Isoflavones (eg. Daidzein, Genistein), and Flavonoid glycosides (eg. Rutin, Hesperidin, Naringin). Stilbenes are polyphenolics exist in the form of monomers or oligomers (eg. Trihydroxystilbenes like Resveratrol, Trans-resveratrol). Tannins are a group of water-soluble polyphenols which are subdivided into condensed and hydrolysable tannins (eg. Catechin polymers, Epicatechin polymers, Ellagitannins, Proanthocyanidins, Sanguin, Tannic acids).^{130–132}

Polyphenols causes induction or inhibition of CYP₄₅₀ enzymes by different mechanisms. Their mechanism of inhibition of CYP includes reversible inhibition, quasi-irreversible and irreversible inhibition. Reversible inhibition can be further divided, based on enzyme kinetics, into competitive, noncompetitive, and uncompetitive. In quasi-irreversible inhibition, inhibitor is metabolically activated by the CYP enzyme, and then this inhibitory metabolite forms a stable metabolic intermediate (MI) complex with the prosthetic heme of CYP, rendering the enzyme functionally inactive. Irreversible inhibition is also called mechanism-based or suicide inhibition.¹³³ CYP induction is mediated by specific nuclear receptors eg. CYP3A4 induction by pregnane X receptor (PXR), constitutive androstane receptor (CAR), and glucocorticoid receptor.¹³⁴ Induction of CYP1A enzymes mediated by formation of a dimer of the cytosolic aryl hydrocarbon receptor (AhR) and the AhR nuclear translocator protein (Arnt). There are also other mechanisms of CYP enzyme induction, for example ethanol induces CYP2E1 primarily by stabilizing the enzyme.¹³⁵ Interaction of herbal remedies with some drugs have been assessed in clinical trials showing changes in pharmacokinetic parameters like AUC, C_{max} , T_{max} , CL_{oral} , etc, possibly indicating that its polyphenols inhibit or induce CYP₄₅₀ enzymes.

The aim of this paper was to review the current literature on variety of polyphenols present in fruits and herbs, their interaction with different CYP isoenzymes, and their effect on pharmacokinetics of different drug molecules.

1.1. Polyphenols present in fruits and herbs and their interaction with different cyp₄₅₀ isoforms

It is now fairly established that naturally occurring dietary supplements can modulate hepatic and enterocytic CYP activity (Table 1). There is need to study the drug-polyphenol interactions to monitor and predict the possible positive or negative outcomes of their co-administration.

1.2. Effect of fruit juices and herbal extracts on pharmacokinetics of drugs

Use of herbal drugs has been increased enormously because of their efficacy coupled with decreased risk of side effects.

Ever-increasing use of herbs with western medicines raises the potential for drug–herbal interactions, which may alter drug bioavailability (Table 2) through altered absorption, distribution and metabolism.⁴⁰ Concomitant drug and food intake creates the opportunity for interactions that may change the oral bioavailability and resulting effectiveness or toxicity of a drug.¹³⁶

1.3. Effect of specific polyphenols on pharmacokinetics of drugs

It may be of interest to determine the identity of polyphenols in fruit juices that exhibits significant effect on disposition of prescription drugs (Table 3). Understanding the nature of these chemicals would enable health care professionals to avoid food-drug interactions.¹³⁷

2. Conclusion

Literature reveals that herbal drugs containing variety of polyphenols interact with CYP₄₅₀ enzymes leading to either induction or inhibition of CYPs. Majority of the drugs in market are metabolized by the CYP₄₅₀ isoenzymes present in liver and intestine. Induction or inhibition of these different CYP isoenzymes and other phase I, phase II enzymes alters the pharmacokinetic parameters of their respective substrate drugs. These pharmacokinetic alterations may lead to either beneficial or adverse effect on drug- action. In-vitro studies have demonstrated that several different types of fruit juices have the capacity to influence drug disposition, but many of these interactions are not clinically significant. This difference may be because of: a) the concentration of the inhibitors might not be high enough in the juice or b) there might be species difference in drug-metabolizing enzymes, in the case where the juices were shown to interact with drugs in animals.¹³⁸

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None.

4. Conflict of Interest

None.

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