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Current Trends in Pharmacy and Pharmaceutical Chemistry

Journal homepage: https://www.ctppc.org/

Review Article

Polyphenols: The interactions with CYP $_{450}$ isoenzymes and effect on pharmacokinetics of drugs

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ARTICLE INFO

Article history:
Received 05-12-2021
Accepted 20-01-2022
Available online 17-02-2022

Keywords:
Polyphenols
CYP 450 isoenzymes
Pharmacokinetics

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 CYP_{450} 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 CYP_{450} 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 CYPlA 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 substitued 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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https://doi.org/10.18231/j.ctppc.2022.004
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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]	CYP3A415, 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	*B*-Carotene, Lutein [15]	Induces CYP1A2 and CYP2A6 [16]
Cocoa	Catechin, Epicatechin, Caffeine, Theobromine, Theophylline [17]	Crude cocao 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, Caffine	Caffine induces CYP1A2 [23]
Gingko 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]	Quircetin 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-*B*-D-Glucoside), Rutin, Quercetin5	Induces CYP 1A, CYP 2B, Inhibits CYP 2E1 [35,36]
Licorice root	Tannic acid, Glycyrrhizin5	Glycyrrhizin induces CYP3A, CYP1A2 [37]
Wanmi peach	Chlorogenic acid, Keracyanin, Quercetin-3-Rutinoside [38]	—
Persimmon	Astragalin, Hyperin, Quercetin, Isoquercitin, 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, Procyanidins, 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 Cmax, 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 Tmax.[65]
	2.Nilotinib	2. Concurrent intake of GFJ increased the nilotinib Cmax by 60% and serum AUC0-∞ by 29% but did not affect Tmax or t1/2 of nilotinib.[66]
	3.Tramadol	3. Tramadol Tmax was increased from 1.33 to 1.70 h after GFJ treatment, plasma Cmax 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. Cmax of nisoldipine was significantly increased after GFJ intake.[68]
Orange Juice (OJ)	1.Levofloxacin	1. Plasma Cmax of Levofloxacin decreased from 3.49 ± 0.75μg/ml to 2.57± 0.46μg/ml when taken with OJ. Serum AUC0-∞ value was also reduced by 17.33%; AUC0-24 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 Tmax from 1.25 to 1.87h; p < 0.05.[71]
	4.Itraconazole	4. Cmax and AUC0-48 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 Cmax, and decreased the Tmax of cyclosporine A.[73]
	6.Atenolol	6. OJ decreased plasma Cmax of atenolol by 49% (range 16-59%, P<0.01), and plasma atenolol AUC0-33 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 Cmax of celiprolol by 89% (P< .01) and plasma AUC by 83% (P< .01). Tmax increased from 4 to 6 h (P< .05), t1/2 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.Cmax was increased by OJ (9%), Tmax 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 Cmax 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 Cmax 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 AUC0-∞, 29% (p=0.005) in Cmax and 21% (p=0.0001) in t1/2 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 AUC0-1.5 of midazolam by 39% and prolonged the Tmax (P < .05) without affecting the total AUC values, t1/2 values.[81]
Green Tea Extract (GTE)	Clozapine	Tmax was significantly increased by GTE. The mean total AUC0-∞ and Cmax 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 Cmax and AUC of raloxifene, respectively. When the ratio of 1:1 was administered, the Cmax and AUC of intact raloxifene were increased by 173% and 97% respectively.[83]
Baicalin and Baicalein	1.Cyclosporine	1. Baicalin and baicalein elevated Cmax of cyclosporine by 408.1 % and 87.5 % and increased the AUC0 - 540 by 685.3 % and 150.2 %, respectively.[84]
	2.Doxorubicin (DOX)	2. AUC0-∞ and Cmax 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 Cmax 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 Tmax from 2 h to 6 h.[87]
Hesperidin	1.Montelukast	1.Reduction in the AUC0-∞ of montelukast (P = 0.032).[88]
	2.Diltiazem	2. AUC0-∞ was significantly (5 mg/kg, P < 0.05; 15 mg/kg, P < 0.01) increased by 48.9-65.3% and Cmax 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.Verapamil	3. Hesperidin significantly (p<0.01) increased plasma AUC of verapamil by 71.1-96.8% and Cmax 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	1. Reduced AUC0- ∞ of talinolol from 1860.0 ±377.9 to 1246.0 ±328.2 ng.h/mL, the Cmax 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.Celiprolol	2. The Cmax, AUC0–8, 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. CLoral was decreased by 22% (p 0.01).[92]
	3.Midazolam	3. Rats in the treatment group showed higher AUC0–4 (2.6-fold, p 0.04) and total AUC (3.8-fold, p 0.03) values, as well as lower CLoral (75% lower, p 0.02) values, compared with control.[92]
	4.Etoposide	4. Curcumin (2 or 8 mg/kg) increased significantly the oral bioavailability, AUC and Cmax of etoposide.[93]
Daidzein	Theophylline	Comparing the kinetics parameters of theophylline alone of day 1 with those of 10-day daidzein treatment, the AUC0-48, AUC0- ∞ , Cmax and t1/2 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 Km (substrate concentration yielding 50% of Vmax) of the reaction without affecting the Vmax of reaction.3
Diosmin	Metronicazole	Metronicazole plasma AUC0-X and Cmax were significantly higher after diosmin pretreatment by (mean) 27% and 24%, respectively.[95]
Epigallocatechin Gallate (EGCG)	1.Verapamil	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.Tamoxifen	2. Compared with the oral control group plasma AUC and the Cmax 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	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 Cmax 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.Carbamazepine	2. Bioavailability reduced, AUC0-t, Cmax, Tmax reduced, Plasma CL increased, due to induction of CYP3A4.[99]
	3.Omeprazole	3. Bioavailability increased, AUC0-t, Cmax, 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 Cmax 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 Cmax of the three treated groups were 0.51, 0.70 and 0.81 μg/ml, respectively. The AUC0-8 values were 1.81, 2.83 and 3.63 μg/h/ml, respectively. The Cmax, AUC0-8 and the mean retention time MRT0-8 of Nifedipine were significantly increased by oral treatment with kaempferol(P 0.01). [101]
	3.Tamoxifen	3. In the presence of kaempferol, plasma AUC0-∞ of tamoxifen was significantly greater; Cmax 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 (Ka) and Cmax 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%), Cmax (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 Cmax (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 Cmax and AUC of paclitaxel by 70–90% and 30–70%, respectively. [107]
	5.Tamoxifen	5. Morin significantly (p<0.05) increased the Ka of tamoxifen compared to the control group, and the plasma AUC and Cmax 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) 2.Losartan	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 Cmax 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 Cmax by 31.8-50.2%. [110]
	3.Tamoxifen	3. Compared with the oral control group, the plasma AUC0–∞ and the Cmax 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 Cmax of paclitaxel significantly (p<0.01). The plasma AUC and Cmax of paclitaxel with naringin significantly higher (p<0.01) than the control. The half-life t1/2 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 Cmax. 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 AUC0-12 ($p<0.001$), average Css ($p<0.001$), t1/2el ($p<0.05$) and a decreased Kel ($p<0.05$). Cmax ($p<0.01$) and Tmax ($p<0.01$) 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 AUC0-12 ($p < 0.01$), Cmax ($p < 0.001$) and Ka ($p < 0.05$). Piperine enhanced the bioavailability of phenytoin significantly by increasing the absorption.[116]
	4. Propranolol	4. Earlier Tmax and a higher Cmax and AUC were observed when co-administered with piperine.[117]
Quercetin	1.Cyclosporine (CSP)	1.Quercetin significantly decreased the Cmax of CSP by 67.8% and reduced the AUC0−540 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 Cmax 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 CLoral 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 Ka, Cmax 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 Cmax 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 Cmax ($P < 0.01$, 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 t1/2 of S-warfarin by 37%.[123]
	2.Cyclosporine (CSP)	2. Rutin significantly decreased the Cmax of CSP by 63.2% and reduced the AUC0−540 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 Cmax 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), t1/2 from 204 ± 33 to 189 ± 14 (min), and Cmax increases from 119 ± 31 to 145 ± 46 (μg/ml).[125]
	3.Loratadine	3. The plasma AUC and Cmax 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 silybinin. 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 AUC0–∞ and Cmax 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 silybinin. 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, Cmax values were 0.70-fold of those of the reference period.[128]
	6.Talinolol	6. The Cmax of talinolol was significantly higher after silymarin administration compared to the placebo. Plasma AUC0-36 and AUC0-∞ 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). Stibenes are polyphenolics exist in the form of monomers or oligomers (eg. Trihydroxy-stilbenes like Resveratrol, Trans-resveratrol). Tannins are a group of water-soluble polyphenols which are subdivided into condensed and hydrolisable tannins (eg. Catechin polymers, Epicatechin polymers, Ellagitannins, Proanthocyanidins, Sanguin, Tannic acids).[130–132]

Polyphenols causes induction or inhibition of CYP_{450} 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 inductionis 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 CYP_{450} 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 cyp$_{450}$ 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 CYP_{450} enzymes leading to either induction or inhibition of CYPs. Majority of the drugs in market are metabolized by the CYP_{450} 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]

3. Source of Funding

None.

4. Conflict of Interest

None.

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Cite this article: Bhamre Vaibhav G., Deore Pranjal D., Amrutkar Rakesh D, Patil Vinod R.. Polyphenols: The interactions with CYP $_{450}$ isoenzymes and effect on pharmacokinetics of drugs. *Curr Trends Pharm Pharm Chem* 2022;4(1):13-23.