Chapter

# Flavonoid-Mediated Modulation of CYP3A Enzyme and P-Glycoprotein Transporter: Potential Effects on Bioavailability and Disposition of Tyrosine Kinase Inhibitors

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## Abstract

The consumption of herbal products and dietary supplements along with conventional medicines has raised concerns regarding herb-drug interactions. The available literature from experimental and clinical studies suggested that the consumption of herbs or dietary supplements that modulate efflux proteins, especially P-glycoprotein (P-gp) and metabolic enzyme CYP3A, may cause clinically relevant herb-drug interactions by alteration of bioavailability and disposition profiles of targeted drug. It has been also hypothesized that both CYP3A and P-gp work synergistically to limit systemic exposure of orally administered substrate drugs. Many *in vitro* and *in vivo* studies suggested that co-administration of flavonoids significantly enhances the bioavailability of orally administered drugs, which may be due to inhibition of the CYP3A enzyme and P-gp transporter. Recently, a large number of orally administered tyrosine kinase inhibitors (TKIs) have been clinically approved for cancer chemotherapy, and many are currently estimated to be under development. TKIs are all primarily metabolized by CYP3A, and most of them are also substrates of P-gp. Numerous studies have suggested that the plasma exposure of orally administered TKIs increases when co-administered with other drugs due to their dual inhibitory activities against P-gp and CYP3A. However, limited data are available regarding the interaction between flavonoids and TKIs. The objective of this article is to review the potential role of flavonoids in modulation of CYP3A enzyme and P-gp transporter and their influence on bioavailability and disposition of TKIs.

**Keywords:** flavonoids, tyrosine kinase inhibitors, CYP3A4, P-glycoprotein, bioavailability, disposition

## 1. Introduction

Due to common belief that natural medicines are much safer than synthetic one, the use of complementary and alternative medical therapies (CAMs) has become a

common trend around the world. It can be used either alone or in combination with prescription medicines [1]. According to an estimate of World Health Organization (WHO), approximately 80% of the developing countries' population relies on CAMs for their primary healthcare needs [2, 3]. CAMs have been also become popular around the developed countries, and this has led to a tremendous growth in international herbal drug market for the last 15 years [4–6]. Consumption of CAMs is more pronounced in patients diagnosed with cancer or human immune virus (HIV) infection, especially with regard to various antidepressant and energy treatments to cope with their mental and physiological instability [7]. The bioavailability and the distribution characteristics are the key factor for the therapeutic effects of pharmaceuticals at their site(s) of action in the tissue [8]. Due to higher consumption of CAMs (herbal extracts and dietary supplements) with prescription medicines, there is a growing awareness that herbal remedies and/or phytoconstituents may affect the bioavailability and disposition characteristics of conventional pharmaceuticals [9]. The medical and scientific literature supported by *in vitro* and *in vivo* laboratory studies including preclinical and clinical trials suggested that the co-administration of natural products or its phytoconstituents may affect the metabolism and bioavailability of prescription drugs, which significantly increasing the risk of serious (clinical) adverse reactions or therapeutic failure. The primary mechanisms underlying the herb-drug interactions involve either the induction or the inhibition of intestinal drug efflux pumps (including efflux proteins, such as P-gp and MRPs) and the intestinal and hepatic metabolism mediated by cytochrome P450 enzymes (CYP3A) [10–12]. Hence, the consumption of herbs that can modulate efflux proteins and/or CYP3A may cause clinically relevant herb-drug interactions and alter drug bioavailability [13, 14]. Any inhibitory effect of herbal extracts/constituents on efflux proteins and/or CYP3A may result in high exposure of substrate drugs in plasma and tissue and lead to toxicity, whereas any inductive effect may cause low exposure, leading to a decrease in efficacy and treatment failure.

The biological effects produced by CAMs are due to the presence of various classes of phytochemicals present there, that is, alkaloids, flavonoids, terpenoids, carotenoids, polyketides, and phenylpropanoids. Among them, flavonoids have attracted much interest due to their numerous pharmacological activities and health benefit in the form of their antioxidant, anti-inflammatory, antimutagenic, antibacterial, antiangiogenic and enzyme modulatory, antiallergic, and anticancer activities [15, 16] and become the main components of herbal products where it presents in the form of quercetin, genistein, hypericin, kaempferol, and silibinin. There is accumulated evidence in the literature, which confirms that flavonoids modulate drug metabolism. Modulation may happen by either (1) altering the expression and/or activity of P450 enzymes, (2) affecting the P-gp-mediated cellular efflux of drugs, and/or (3) inhibiting the intestinal glucuronidation of the drug. This evidence confirms that the consumption of flavonoids or flavonoid-containing dietary supplements with conventional pharmacotherapeutic regimens should need to be examined to avoid drug-flavonoid interactions [17–21].

Among the novel classes of anticancer drug development, small molecule tyrosine kinase inhibitors (TKIs) currently represent one of the most promising and rapidly expanding groups. Almost 25 TKIs (mostly in oral dosage form) have been already approved by international drug agencies, >130 are being evaluated in different phases of clinical trials, and many more are in various stages of development [22, 23]. Most of TKIs are primarily metabolized by CYP3A4 and also interact with P-gp and/or Breast Cancer Resistance Protein (BCRP) where it serves as both substrates and inhibitors. Considering the dual roles of TKIs on both CYP3A4 and drug transporters (P-gp, BCRP) and its influence in drug disposition, the potential

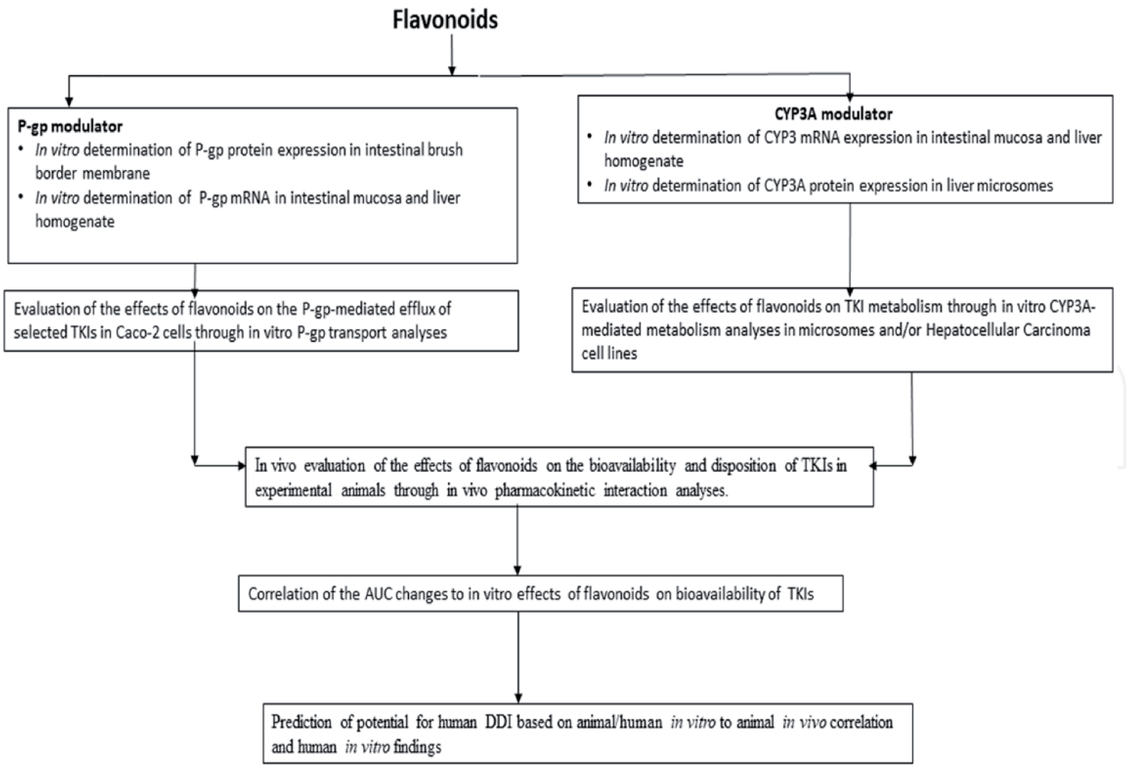


**Figure 1.**
*Schematic layout for prediction of flavonoids in modulation of CYP3A enzyme and P-gp transporter and its influence on disposition of TKIs.*

of TKI-drug interactions is an important consideration [24, 25]. In addition, most TKIs are being used orally and prescribed for long duration along with other medications, which may result in significant drug-drug interactions (DDI). This review provides a comprehensive overview of the potential role of flavonoids in modulation of CYP3A enzyme and P-gp transporter and their possible influence on bioavailability and disposition of tyrosine kinase inhibitors (**Figure 1**).

## 2. CYP3A

Cytochrome P450 enzymes (CYP) are the most versatile enzyme system involved in detoxification and oxidative metabolism of various endogenous substrates (steroid hormones, lipids, and bile acids) and xenobiotics (drugs, environmental pollutants, and dietary products) [26, 27]. It consists of over 400 isoforms, and their activities can be increased or decreased by many drugs either by inducing the biosynthesis or by directly inhibiting its activity, which is a major source for drug-induced toxicity via DDI. CYP3A enzymes, which constitute the predominant phase I drug-metabolizing enzymes, are estimated to metabolize between 50 and 70% of currently administered drugs [28]. Alone CYP3A4, which is the most abundant congener of the CYP3A family contributes approximately 30% of hepatic CYP activity and more than 70% of intestinal CYP activity [29]. Many drugs used in different types of therapies are substrates for CYP3A4, and it is presented at high levels in both liver and intestine [30, 31]. Reports from *in vitro* and *in vivo* studies have already established that naturally occurring dietary supplements and phytoconstituents can modulate hepatic and enterocytic CYP activity.

CYP inhibition-mediated DDI is widely recognized, and the necessity of the enzyme inhibition studies is included in the guidance from the USFDA [32]. Usually, two types of CYP inhibition occur: (1) reversible inhibition represented

by competitive inhibition, which is concentration-dependent inhibition and (2) irreversible inhibition, also called mechanism-based inhibition (MBI), where during inhibition process enzyme is inactivated by stable complex formation with a metabolite. In MBI, enzyme reduction activity continues until the inactivated CYP is replaced by a newly synthesized CYP, the duration of the elevated blood concentration of a drug coadministered with a mechanism-based inhibitor is longer. Therefore, MBI requires more attention because they have been reported to cause unanticipated adverse effects [33, 34].

## 3. P-gp

P-gp is an adenosine triphosphatase (ATPase) energy-dependent, membrane-bound protein that belongs to the ABC efflux transporter family [35]. The ABCB1 gene, which is also known as the multidrug resistance 1 (MDR1), encodes P-gp and is responsible for cellular efflux of numerous drugs [36]. It is more prominent in various resistant human tumors, where it is believed to be the major factors responsible for multidrug resistant (MDR). P-gp-mediated transport of drugs is saturable, ATP-dependent, osmotically sensitive mechanism that generates a concentration gradient. In intestines, P-gp expressed in apical side of the epithelial cells where it pumps the drug back into the GI lumen resulting in fecal excretion. In liver, it presents in canalicular surface of hepatocytes to remove drug and metabolites from the interior of the cell. In brain, it is expressed in endothelial cells of blood brain barrier and prevented the entry of xenobiotics into brain. In kidney, it is expressed in proximal tubes of kidney to efflux drug into urine and in certain hematological cells to put drug back into circulation [37–40]. Higher expression of P-gp in excretory organs (liver and kidney) facilitates metabolism of substrate drugs via biliary excretion and renal elimination. As an efflux transporter, ABCB1 prevents intestinal absorption of orally administered drugs and limits its oral bioavailability. A broad range of clinically used drugs are substrate of P-gp, including anticancer agents (anthracyclines, vinca alkaloids, epipodophyllotoxins, methotrexate, and taxol) [41], cardiac drugs (digoxin and quinidine) [42], protease inhibitors (saquinavir, indinavir, and ritonavir) [43], immunosuppressants (cyclosporine) [44], and antibiotics (actinomycin D) [45].

## 4. Interplay between CYP3A and P-gp

Various preclinical and clinical studies have postulated that both CYP3A enzyme and P-gp transporter display strong effects in modulation of oral drug bioavailability and elimination of numerous drugs. Both CYP3A and P-gp act in functional collaboration during the first-pass elimination of drug [46]. Extensive overlap exists between the substrate specificities and the tissue-specific expression patterns of P-gp and CYP3A, especially in the liver (hepatocytes) and intestine (enterocytes) [47, 48]. It has also been predicted that the orally administered drugs, which are dual substrates of P-gp and CYP3A, the back-transportation mechanism by P-gp in intestinal epithelial cells, are available for further CYP3A4-mediated metabolism within these cells resulting in massive first-pass effects in intestine [49]. The combined action of these two pathways was expected to be more efficient than the sum of their individual activities, resulting in synergistic effects of P-gp and CYP3A.

Two mechanistic frameworks have been suggested to support the possible synergistic action of P-gp and CYP3A in intestine. Under the first mechanism, P-gp acts to decrease the level of intracellular concentration of a substrate drug in

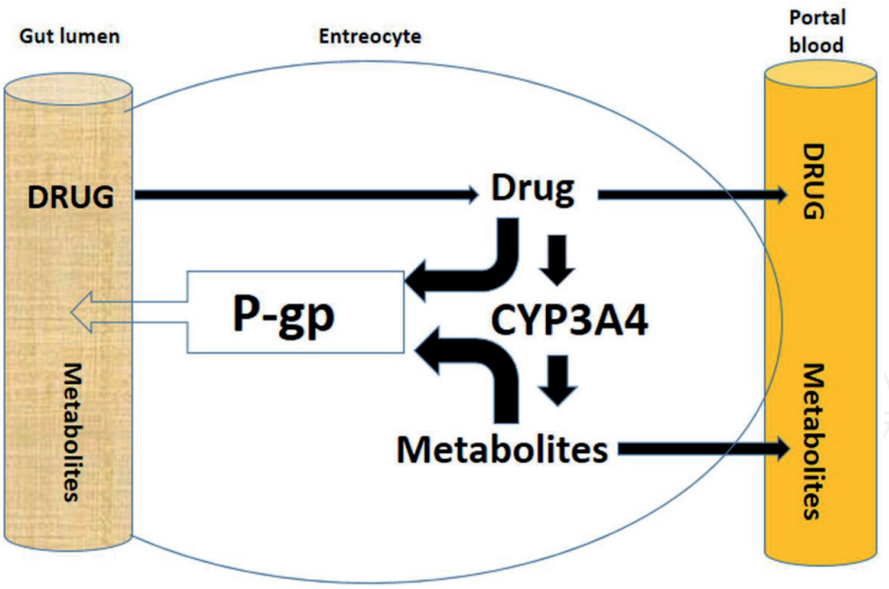


**Figure 2.**
*Potential functional relationships between P-gp and CYP3A4 in enterocytes.*

enterocytes, thus preventing possible saturation of the CYP3A enzyme by maintaining the drug within the linear range for metabolic activity. Under the second mechanism, the functional effects of P-gp, together with subsequent drug reuptake, allow the repetition of drug substrate, and therefore, probability of the drug to be metabolized increases by prolonged access to enterocyte CYP3A. The above cyclic repetition of drugs *per se* would itself increase the drug metabolism, even without considering saturating or nonsaturating conditions for CYP3A [50]. Based on above evidence, it is concluded that induction and inhibition of (intestinal) P-gp and CYP3A4 are important mechanisms underlying DDIs [51].

The hypothesis of synergistic collaboration between CYP3A and P-gp was clarified in a study that showed a dramatic increase in the systemic exposure of docetaxel and the risk of intestinal toxicity in P-gp$^{-/-}$CYP3A$^{-/-}$ double knockout mice. After oral administration of docetaxel, 3-fold and 12-fold increases in bioavailability were observed in P-gp$^{-/-}$ and CYP3A$^{-/-}$ mice, respectively, in comparison with wild-type mice. However, when both of the primary detoxification systems were missing, that is, in P-gp$^{-/-}$CYP3A$^{-/-}$ double knockout mice, bioavailability showed a disproportionate increase in >70-fold in comparison with wild-type mice [48].

Within the context described above, it is clear that drugs that are dual substrates for P-gp and CYP3A are highly susceptible to herb-drug interactions. Therefore, the consumption of herbs that modulate efflux transporters and CYP3A may cause clinically significant drug-herb interactions and alter drug bioavailability [13, 14]. The inhibitory effect of herbs on P-gp and CYP3A may result in increasing the drug concentration level in the plasma and tissues, leading to toxicity, whereas any inductive effect may result in lowering the concentration level, leading to loss of efficacy and/or treatment failure (**Figure 2**).

## 5. Regulation of CYP3A and P-gp expression

Pregnane X receptor (PXR) is a highly promiscuous nuclear hormone receptor, generally expressed on sites that are important to drug dispositions (e.g., small intestine, liver, and kidney). The human orthologue of PXR is also known as steroid

and xenobiotics receptor (SXR) and is coded by NR 112. It has been reported that PXR regulates the expression of CYP3A and several other genes encoding protein and other enzymes, which involves in drug disposition including P-gp [52, 53]. Based on this evidence, Maglich et al. hypothesized that PXR plays a more important role in the regulation of drug metabolizing enzymes and drug transporters in the small intestines [54]. The observation that PXR regulates both CYP3A and P-gp provides further evidence for the argument that these proteins coordinately mediate detoxification of many xenobiotics during oral absorptions [46]. Synold et al. were the first to describe coregulation of drug metabolism and efflux via CYP3A and P-gp in liver and intestine by the human receptor PXR/SXR. Their results indicate that paclitaxel reduces its own oral bioavailability by activating the PXR and induces its own metabolism and biliary elimination [55].

## 6. Experimental models for P-gp and CYP3A-mediated DDI studies

### 6.1 *In vitro* model for CYP3A and P-gp studies

The *in vitro* CYP inhibition study is usually performed in human liver microsomes (HLMs) or human liver hepatocytes (HLHs), Caco-2 cell lines, or recombinant CYP (rCYP) enzymes [56]. The technology used for CYP inhibition includes luminescence, florescence, radiometric, and HPLC or LC-MS/MS assay. In florescence and luminescence assays, the metabolism of profluorescent or proluminescent substrate by CYP enzyme to give their fluorescent or luminescent product, respectively, is measured in rCYP enzyme. In radiometric method, the release of radiolabel on metabolism of substrate is measured in HLM. In HPLC or LC-MS/MS assay, the concentration of substrate/probe drugs is measured in HLM, HLH, and rCYP enzymes [57].

The *in vitro* analyses used for P-gp-mediated efflux studies include cytotoxicity assay, accumulation/efflux assays, transport assays, and ATPase assays. In cytotoxicity assays, the $IC_{50}$ end point (concentration of P-gp substrates or inhibitors) that inhibits the growth of P-gp expressing cells is measured. In accumulation/efflux assay, the accumulation of drugs in P-gp expressing cells is measured. In transport assays, the permeation of drugs from apical-to-basolateral and basolateral-to-apical compartment in polarized epithelial cells is measured, whereas in ATPase assay, the stimulation or inhibition of P-gp ATPase enzyme activity in membranes of P-gp expressed cells is measured [58, 59].

### 6.2 *In vivo* models for CYP3A and P-gp-mediated DDI studies

Various strains of mice (including transgenic and knockout), rats, and nonhuman primate (monkey) have been used for CYP3A, P-gp, and dual CYP3A/P-gp-mediated DDI studies [60].

Since midazolam and triazolam are specifically extensively metabolized by CYP3A4 and ketoconazole is a potent inhibitor of CYP3A4, several groups of studies used as model for experimental CYP3A-mediated DDI studies. Moreover, midazolam is not a substrate for P-gp, whereas the ketoconazole can effectively inhibit both CYP3A and P-gp, which can confirm that the interaction between them can be sole attributed to effects on CYP3A. CYP gene knockout and humanized mice have been established for CYP3A-mediated drug interaction using midazolam as substrate [61]. Several strains of rats are most commonly used for CYP3A-mediated drug interaction using midazolam, diltiazem, nifedipine, and doxorubicin as substrates [62, 63]. In addition, cynomolgus monkey was also used as model for

| Flavonoids | Dose-dependent ($IC_{50}$) inhibition of CYP3A4 activity | ↑ Cellular accumulation of rhodamine (MCF-7/ADR cell) | References |
|---|---|---|---|
| Quercetin | 1.97 μM | 3–10 μM | [83] |
| Myricetin | 7.8 μM | 10–30 μM | [84] |
| Baicalein | 9.2 μM | 1–10 μM | [85] |
| Baicalein | 9.2 mM | 10–30 μM | [86] |
| Silibinin | 1.8 μM | — | [87] |

**Table 1.**
In vitro *effects of some common flavonoids on CYP3A4 and P-gp activity.*

CYP3A-mediated DDIs; however, its choice is limited due to its high cost, handling, and ethical concerns [64].

Valspodar, elacridar, and zosuquidar are more selective P-gp inhibitors and thought to be low affinity for CYP enzymes, and other drug transporter proteins are commonly used for *in vivo* DDI studies in mice and rats. The drugs such as paclitaxel, cyclosporine, and digoxin are most commonly used as substrates for P-gp-mediated inhibition. Moreover, Rho123 is attractive probe and has been widely used as marker to evaluate P-gp functions because it is not a substrate for CYP3A enzyme [65–67]. The cynomolgus monkey has been also used as model to evaluate effect of P-gp-mediated DDI using erythromycin and fexofenadine as substrate [64, 68].

The evaluation of flavonoid-mediated DDI by using dual substrates of CYP3A and P-gp, inhibitors, and species has been discussed in detail in Section 9 and summarized in **Table 1**.

## 7. Flavonoids as P-gp and CYP3A modulators

Flavonoids (a group of polyphenolic compounds) are mainly abundant in vegetables and fruits and routinely consume through our common diet and in the form of beverages (plant-derived), for example, wine and tea [37]. In addition, they are the main constituents of many herbal products/formulations. Structurally, these compounds possess a framework consisting of a chromane ring together with an aromatic ring that is attached at different positions. Based on various substitutions and the oxidation status of the ring C atoms, flavonoids can be categorized into various subclasses, including flavones, flavonols, flavonones, flavanols, isoflavones, and chalcones. Since the last decade, there has been a drastically increase in scientific work on flavonoids, with >2000 publications/year containing "flavonoids" as a keyword found in different literature sources. Flavonoids display antioxidant, anticarcinogenic, antiviral, anti-inflammatory, and antiesterogenic properties, and high intake of flavonoids has been linked with a reduced risk of cancer, cardiovascular disease, osteoporosis, and other age-related degenerative diseases [37, 69].

Due to the wide range of health benefits of flavonoids and their remarkable safety record, numerous herbal preparations containing these compounds are marketed in various formulations as dietary supplements. The total daily intake of flavonoids in the average US diet has been estimated to be more than 1 g [37]. Therefore, the concentration of flavonoid expected to be present is sufficient after the ingestion of flavonoids and/or flavonoid-containing supplements, suggesting a potential herb-drug interaction.

Thus, the consumption of higher doses of flavonoids is common in daily life, and it may increase the risk of pharmacokinetic interactions with clinically used

medicine. This concern is also confirmed by increasing evidence, which showed significant or even life-threatening interactions between flavonoids or flavonoid containing products and prescription drugs [70, 71].

Initial publications cite various examples of flavonoids as P-gp transport inhibitors, thereby affecting the bioavailability and cellular uptake of anticancer drugs. These experiments include *in vitro* analyses of the effects of flavonoids on the intracellular accumulation of P-gp substrates using P-gp-overexpressing cells and a variety of clinical and animal model studies, especially involving P-gp knockout animals [37]. For example, concomitant administration of quercetin increased moxidectin oral bioavailability in lambs [72]; oral bioavailability of quinine was increased by naringin [73]; cyclosporine by baicalein and its aglycone [74]; and paclitaxel by flavones in rats [75]. Similarly, quercetin increased the oral bioavailability of paclitaxel and tamoxifen in rats [76, 77] and digoxin in pigs, which results in high toxicity [78]. All of these studies indicate that flavonoid-P-gp interactions can occur *in vivo*, resulting in pharmacokinetic interactions. In contrast to the above results, several flavonoids appear to induce P-gp transport, resulting in a decrease in the bioavailability of substrate drugs. For instance, *in vitro* studies, kaempferol and quercetin, produced inductive effects on P-gp efflux [79, 80], and therefore, the consumption of pure herbal constituents, which contains hypericin, kaempferol, quercetin, and silibinin for 10 days, may produce a significant increase in the expression of P-gp mRNA [81]. *In vivo* studies have also indicated that long-term exposure (14 days) to St. John's wort (a flavonoid-containing herbal product) leads to higher expression of MDR1 in the rat intestine [82]. Based on these findings, it has been concluded that chronic exposure to some flavonoids induces intestinal expression of P-gp, resulting in reduced intestinal drug absorption, possibly due to enhanced drug efflux; however, the inhibitory effects on P-gp-mediated efflux are based on short-term exposure. Meanwhile, subsequent *in vitro* and *in vivo* studies indicate that the pharmacokinetic interactions of drugs with flavonoids may result in the modulation not only of drug transporters (P-gp) but also of metabolizing enzymes, especially CYP3A, that is, dual inhibition of P-gp and CYP 3A. *In vitro* studies confirmed that quercetin, myricetin, baicalein, and silibinin were found to produce dose-dependent inhibition of CYP 3A4 activity in CYP inhibition assay and increased the cellular accumulation of rhodamine (MCF-7/ADR cell) in P-gp transport studies [83–87]. However, in another study, quercetin and rutin were found to induce the function of CYP 3A4 and P-gp, which may lead to increase the bioavailability of substrate drugs [88]. *In vitro* effects of some common flavonoids on CYP3A4 and P-gp activity are summarized in **Table 1**. In *in vivo* studies, coadministration of quercetin, baicalein, silibinin, epigallocatechein, and kaempeferol increased the bioavailability of oral tamoxifen dose dependently through inhibition of P-gp efflux and reduction in the first-pass metabolism through inhibition of CYP3A metabolism in the small intestine and/or liver [78, 84, 89–91]. Similarly, quercetin, silibinin, naringin, flavone (2-phenyl-4H-1-benzopyran-4-one), genistein, and morin also increased the oral bioavailability of paclitaxel mainly through inhibition of CYP3A4-mediated metabolism in the small intestine and/or liver and inhibition of the P-gp efflux in the small intestine [75–77, 92–94]. Additionally, quercetin, myricetin, and baicalein also reduced the bioavailability of doxorubicin by similar mechanism [83, 84, 95]. Similar results were also produced by morin, quercetin, and niringin with diltiazem and baicalein with nimodipine [85, 96–98]. In contrast, reduced oral bioavailability of tamoxifen by biochanin A and cyclosporine by quercetin and rutin was also reported in rats [88, 99]. *In vivo* interaction of flavonoids with dual substrates of CYP3A4 and P-gp is summarized in **Table 2**.

| Flavonoids (oral dose) | Dual substrate of CYP3A and P-gp (oral dose) | Aimals/ species | Effect on bioavailability parameters | | | References |
|---|---|---|---|---|---|---|
| | | | % change in $C_{max}$ | % change in AUC | Change in RBA* (fold) | |
| Quercetin (2.5 and 7.5 mg/kg) | Tamoxifen (10 mg/kg) | Rat | ↑23–35 | ↑ 34–60 | ↑1.35–1.61 | [78] |
| Baicalein (0.5, 3, and 10 mg/kg) | Tamoxifen (10 mg/kg) | Rat | ↑ 54.8–100 | ↑47.6–89.1 | ↑1.47–1.89 | [86] |
| Silibinin (0.5, 2.5, and 10 mg/kg) | Tamoxifen (10 mg/kg) | Rat | ↑45.2–78.6 | ↑40.2–71.3 | ↑1.40–1.72 | [87] |
| Epigallocatechein (0.5, 3, and 10 mg/kg) | Tamoxifen (10 mg/kg) | Rat | ↑57.1–89.7 | ↑48.4–77.0 | ↑1.48–1.77 | [90] |
| Kaempeferol (2.5 and 10 mg/kg) | Tamoxifen (10 mg/kg) | Rat | ↑48.9–47.7 | ↑39.8–47.7 | ↑1.40–1.48 | [91] |
| Biochanin A (100 mg/kg) | Tamoxifen (10 mg/kg) | Rat | ↓23.5 | ↓32.3 | ↓ 1.32 | [99] |
| Quercetin (2–20 mg/kg, p.o.) | Paclitaxel (40 mg/kg) | Rat | — | — | ↑ 1.76–3.29 | [76] |
| Silibinin (0.5, 2.5, and 10 mg/kg) | Paclitaxel (40 mg/kg) | Rat | ↑31.0–52.9 | ↑65.8–101.7 | ↑1.15–2.02 | [87] |
| Naringin (1, 3, 10, and 20 mg/kg) | Paclitaxel (40 mg/kg) | Rat | — | — | ↑1.35–1.69 | [92] |
| Flavone (2–20 mg/kg)** | Paclitaxel** (40 mg/kg) | Rat | — | — | ↑2.4–3.1 | [75] |
| Genistein (3.3 and 10 mg/kg) | Paclitaxel (30 mg/kg) | Rat | — | — | ↑1.26–1.55 | [93] |
| Morin (3.3–10 mg/kg) | Paclitaxel (30 mg/kg) | Rat | ↑ 70–90 | ↑30–70 | ↑1.32–1.68 | [95] |
| Quercetin (0.6, 3, and 15 mg/kg) | Doxorubicin (50 mg/kg) | Rat | ↑ 35.1–125.7 | ↑ 31.2–136 | ↑1.33–2.36 | [83] |
| Myricetin(0.4, 2, and 10 mg/kg) | Doxorubicin (40 mg/kg) | Rat | ↑45–105 | ↑51–117 | — | [84] |
| Baicalein (0.3, 1.5, and 6 mg/kg) | Doxorubicin (40 mg/kg) | Rat | — | — | ↑1.20–1.96 | [95] |
| Morin (1.5, 7.5, and 15 mg/kg) | Diltiazem (15 mg/kg) | Rat | ↑ 30–120 | — | 1.38–1.80 | [96] |
| Quercetin (2, 10, and 20 mg/kg) | Diltiazem (15 mg/kg) | Rabbit | — | — | 1.75–2.76 | [97] |
| Naringin (5 and 15 mg/kg) | Diltiazem (15 mg/kg) | Rat | — | — | ↑2.07–2.20 | [98] |
| Quercetin | Cyclosporine | Rat | ↓67.8 | ↓43.3 | — | [88] |
| Rutin | Cyclosporine | Rat | ↓63.2 | ↓57.2 | — | [88] |
| Baicalein (0.4, 2, and 8 mg/kg) | Nimodipine (12 mg/kg) | Rat | — | — | ↑1.39–1.58 | [85] |

**RBA, relative bioavailability.*
***Flavone, 2-phenyl-4H-1-benzopyran-4-one.*

**Table 2.**
In vivo *interaction of some common flavonoids with dual substrates of CYP3A and P-gp.*

## 8. Significance of flavonoids as P-gp and CYP3A inhibitors

Various experimental and clinical studies confirmed that flavonoids produce antioxidant, anti-inflammatory, and anticarcinogenic effects. Studies also confirmed that these effects were attributed due to their inhibitions of efflux transporter enzyme (P-gp) and/or drug metabolizing enzyme (CYP3A). Therefore, flavonoids as P-gp inhibitor may use with other chemotherapeutic drugs for cancer treatment [100]. Occurrence of P-gp protein in various body tissues affects the absorption, distribution, metabolism, and excretion of drugs. Therefore, the dual effect of anticarcinogenic and P-gp modulation may synergistically act for the treatment of cancer [101]. The chemotherapeutic treatment of metastatic brain tumors is limited due to its low distribution in brain tissue by blood brain barrier and blood-cerebrospinal fluid barrier. P-gp is presented in the apical membranes of these cells, and flavonoids can improve the permeation of chemotherapeutic drugs by inhibiting the P-gp-mediated efflux [102]. Flavonoids can be used as nontoxic P-gp and/or CYP3A inhibitors and by its coadministration could improve the bioavailability of poorly unavailable drugs, especially for anticancer drugs, by interfering its clearance or inhibiting its metabolism [103]. P-gp presents in bile canaliculi and kidney suggested that it can also play a role in biliary and renal elimination of drugs. Coadministration of flavonoids (as P-gp inhibitors) can reduce the clearance of anticancer drugs, for example, vinblastine, doxorubicin, and irinotecan [104, 105]. Flavonoids can also play an important role in reversal of MDR in cancer chemotherapy. P-gp-associated MDR is a serious concern for limitation of cancer treatment. P-gp occurrence in tumor cell has been extensively characterized, and its overexpression has been confirmed during relapse. Therefore, it can be concluding that P-gp inhibitors (flavonoids) can potentially reverse the MDR during cancer chemotherapy [106].

## 9. Tyrosine kinase inhibitors

The evidence of protein tyrosine kinase enzyme involvement in tumor development makes it novel targets for selective chemotherapy and thus target for rational design of drug development. Now protein kinases, especially tyrosine kinases, are being used as main targets for drug development related to malignancy, resulting in the high approval rate of various TKIs by the FDA [24, 107]. Imatinib was the first of its kind, which was introduced clinically, followed by various molecules such as gefitinib, erlotinib, sorafenib, afatinib, nilotinib, bosutinib, crizotinib, ponatinib, lapatinib, sunitinib, and dasatinib, and many more are in pipeline [108]. Although mechanism of action of these compounds is same, that is, competitive ATP inhibition at the catalytic binding site of tyrosine kinases, they differ from each other in the spectrum of targeted kinase activity, pharmacokinetic profile, and compound-specific adverse effects [109]. These TKIs have been developed in oral formulations, are administered on a daily basis, and usually prescribed at a fixed dose. Although oral administration may be convenient for patients as it can reduce health care costs, improve quality of life of patients, and avoid heavy burden of day-stay infusion units, this practice also displays a disadvantage, in that the oral bioavailability of most of TKIs is highly dependent on their absorption through gastrointestinal tract and first-pass hepatic metabolism [25, 107].

Almost all TKIs are rapidly absorbed, and their maximum plasma concentration ($C_{max}$) was achieved in 3–6 h after oral administration except sunitinib (6–12 h). Food intake has no significant effect on the absorption of imatinib, dasatinib, gefitinib, sorafenib, or sunitinib. However, the bioavailability of lapatinib and

| TKIS | CYP 3A4 | P-gp | References |
|---|---|---|---|
| Imatinib | √ | √ | [108, 110, 111] |
| Gefitinib | √ | √ | [24, 108, 115, 118] |
| Erlotinib | √ | √ | [24, 118] |
| Sorafenib | √ | X | [24, 108, 118] |
| Dasatinib | √ | √ | [24, 108, 118] |
| Sunitinib | √ | √ | [24, 108, 118] |
| Lapatinib | √ | √ | [24, 108, 118] |
| Nilotinib | √ | √ | [24, 108] |
| Crizotinib | √ | √ | [108, 111, 118] |
| Vandetanib | √ | X | [108, 111] |
| Vemurafenib | X | √ | [108, 112, 118] |
| Axitinib | √ | √ | [108, 111, 118] |
| Bosutinib | √ | X | [108, 111, 118] |
| Pazopanib | √ | √ | [108, 111, 118] |
| Ponatinib | √ | √ | [108, 111, 118] |
| Dabrafenib | √ | √ | [108, 111, 118] |
| Cediranib | √ | √ | [114, 118] |
| Tandutinib | NA | √ | [118] |
| Ibrutinib | √ | X | [116, 121] |
| Afatinib | X | √ | [108, 111] |
| Cabozantinib | √ | X | [108, 111] |
| Regorafenib | √ | X | [108, 111] |
| Ruxolitinib | √ | X | [108, 117] |
| Osimertinib | √ | √ | [120] |

**Table 3.**
*Substrate potential of TKIs with CYP3A4 and/or P-gp.*

nilotinib is increased pronouncedly with food intake. Almost all TKIs are high to plasma protein (>90%) and therefore extensively distribute into tissues resulting in large volume of distribution and prolong terminal half-life. Excretion of TKIs is predominantly through feces, and only a small fraction is eliminated with urine. Almost all TKIs are dual substrates of CYP3A4 (the most abundant CYP in the human liver and intestine) and P-gp efflux transporter, except sorafenib, vandetanib, bosutinib, ibrutinib, cabozantinib, regorafenib, and ruxolitinib, which are only substrate of CYP3A4, whereas vemurafenib and afatinib, which are effluxed by P-gp only [24, 108, 110–121]. **Table 3** summarizes the substrate potential of TKIs with CYP3A4 and/or P-gp.

## 10. Drug-drug interaction with TKI

DDIs represent a serious concern, especially for agents that influenced by efflux transporters and CYP3A4 enzyme, and can produce clinically relevant drug interactions by alteration of its bioavailability. Because the majority of TKIs

are substrate of CYP3A4 and/or P-gp, DDI with CYP3A4 and/or P-gp inhibitors and inducers must be taken into account, and they must be used with caution, as advised in the package insert. Recently, it has been reported that coprescription of those medicines, which may induce or inhibit the metabolic pathways used by TKIs, is very high. Overall coprescribing rates of drugs that induce metabolism of TKI and may lead to decrease the effectiveness of TKIs ranged from 23 to 57%, whereas coprescribing rates of drugs that inhibit metabolism of TKIs and may increase its toxicity ranged from 24 to 74% [122]. For example, coadministration of imatinib with dual inhibitors CYP3A4 and P-gp increases not only the plasma concentration but also the intracellular concentration of imatinib. Dual inhibitors CYP3A4 and P-gp, such as verapamil fluconazole, itraconazole [123], erythromycin, clarithromycin [124], cyclosporine [125], and ketoconazole [126], increased the intracellular concentration of imatinib by inhibiting both its CYP3A4-mediated metabolism and its efflux through P-gp, which might result in increasing its cellular toxicity. Moreover, P-gp-mediated efflux inhibition by proton pump inhibitors, such as pantoprazole, has reported to increase the brain concentration of imatinib [127]. In contrast, coadministration of CYP3A4 inducers, such as rifampicin or certain antiepileptics, may lead to a reduction in imatinib exposure of up to 74% [24, 110]. Similarly, inhibitors of both CYP3A4 and P-gp increase both the plasma and intracellular concentrations of dasatinib as well, which are also expected to occur for verapamil, erythromycin, clarithromycin, fluconazole, itraconazole [123], cyclosporine [125], and ketoconazole [123, 128]. Concomitant administration of the CYP3A4 inducer rifampicin leads to a reduction in dasatinib exposure of 80% [24, 129, 130]. The area under curve (AUC) of nilotinib is increased 3-fold in healthy subjects receiving ketoconazole [130], whereas coadministration of CYP3A4 inducers, such as rifampicin, leads to a 4.8-fold reduction in nilotinib exposure [24, 129, 130]. Administration of gefitinib in the presence of rifampicin reduces the AUC of gefitinib by 83%, while in the presence of itraconazole, the AUC of gefitinib is increased by 78% [24, 131]. Furthermore, coadministration of ketoconazole results in a 3.6-fold increase in lapatinib plasma exposure, whereas coadministration of carbamazepine results in a decrease in the AUC of lapatinib by 72% [24, 132]. Although the result of above studies confirmed the risk of frequent DDIs among TKIs, but did not addressed the clinical consequences of these, that is, increased toxicity or therapeutic failure. Moreover, in some cases, in spite of knowing, these potential interacting combinations could have been intentionally prescribed by physicians because they considered the potential benefits to outweigh the risks or because the patient had the ability to tolerate these combinations in the past [133]. Since most of these TKIs are relatively new, their scientific evidence that supports their DDIs is limited. Therefore, it is not unexpected to observe that medical oncologists are not able to report TKI DDI pairs, which might have a high probability of causing deleterious effects in the treatment of cancer patients [134].

## 11. Flavonoids and TKI interaction

Compounds that are capable of inhibiting the activity of tyrosine kinase receptors (RTKs) are expected to display antiproliferative properties. Various *in vitro* and *in vivo* studies suggested that most of the flavonoids quercetin, genistein, hesperidin, and naringenin have TKI properties, which play a significant role in its anticancer effects [135–138]. Due to antiproliferative properties, flavonoids can be use along with conventional TKIs in clinical practice and therefore it definitely raise concern of pharmacokinetic interaction. So, it is understood that similar to

conventional medicines, flavonoids act as dual modulators of CYP3A4 and P-gp, which may produce significant effects on the disposition kinetics of TKIs. In spite of that, limited data are available relevant to interaction of flavonoids with TKIs in the literature. St. John's wort that contains numerous flavonoids was found to increase imatinib clearance by 43% and decrease its AUC and $C_{max}$ by 30 and 29%, respectively [139, 140] in human subjects. Similarly, St. John's wort may also decrease the plasma concentration of dasatinib, and its use is discouraged in patients receiving it [141]. Genistein (isoflavone) when administered for 15 days significantly decreased the $C_{max}$ and AUC of imatinib, whereas its single dose did not produce any effects in rats [142]. Silybin, a constituent of silymarin, also decreased the AUC of imatinib after multiple dose administration (15 days) in rats [143]. However, apigenin in single dose increased the AUC of imatinib but decreased it in multiple dose administration (15 days) in rats [144], which suggests that apigenin may act as enzyme inhibitor in single dose and become inducer after long-term administration. Epigallocatechin-3-gallate also decreased the $C_{max}$ and AUC of sunitinib after single dose administration in rats [145]. However, Bas 100, a novel mechanism-based CYP3A4 inhibitor, isolated from grapefruit juice increased 2.1-fold AUC of erlotinib after single dose administration [146]. Similar

| Flavonoids/constituents | TKI inhibitors | Model | Pharmacokinetic effects | References |
|---|---|---|---|---|
| St. John's wort (300 mg, p.o) | Imatinib (400 mg, p.o.) | Healthy volunteers | ↓AUC (30%)<br>↑ Oral clearance (43%) | [139] |
| St. John's wort (300 mg, p.o) | Imatinib (400 mg, p.o.) | Healthy volunteers | ↓AUC (30%)<br>↓ $C_{max}$ (29%) | [140] |
| Genistein (50, 100 mg/kg, p.o.) for 15 days | Imatinib (30 mg/kg, p.o.) | Rat | ↓AUC (27–28%)<br>↓ $C_{max}$ (23–25%) | [142] |
| Genistein (50, 100 mg/kg, p.o.) single dose | Imatinib (30 mg/kg, p.o.) | Rat | No effects | [142] |
| Apigenin (165 mg/kg, p.o) for 15 days | Imatinib (30 mg/kg, p.o.) | Rat | ↓AUC (25%) | [144] |
| Apigenin (165 and 252 mg/kg, p.o) single dose | Imatinib (30 mg/kg, p.o.) | Rat | ↑ AUC (25–40%) | [144] |
| Silybin (50 mg/kg, single and multiple for 15 days, p.o. | Imatinib (p.o.) | Rat | ↓ AUC significantly | [143] |
| BAS 100 (10 mg/kg, p.o.) | Erlotinib 10 mg/kg, p.o.) | Mice | ↑ AUC (2.1 fold) | [146] |
| Epigallocatechin-3-gallate (100 mg/kg, p.o.) | Sunitinib (30 mg/kg, p.o.) | Rats | ↓$C_{max}$ (47.7%)<br>↓AUC (51.5%) | [145] |
| Grapefruit juice (240 mL), p.o | Nilotinib (400 mg, p.o.) | Healthy volunteers | ↑ AUC (29%)<br>↑ $C_{max}$ (60%) | [147] |

**Table 4.**
In vivo *pharmacokinetic interaction of flavonoids or flavonoids containing herbal constituents with TKIs.*

effects were produced by the intake of 240 ml of grapefruit juice (an inhibitor of CYP3A4 and P-gp), which are shown to increase the nilotinib AUC by 60%, and thus, coadministration of nilotinib with grapefruit juice is not recommended [147]. Additionally, a case study showed that patients who had already developed resistance to gefitinib treatment become responsive after the withdrawal of all CAMs [148]. **Table 4** summarizes the pharmacokinetic interaction of flavonoids or flavonoids containing herbal constituents with TKIs in both experimental animals and clinical studies.

## 12. Conclusions

The CYP3A enzyme accounts approximately 30% of hepatic and more than 70% of intestinal CYP activity. P-gp efflux protein is encoded by ABCB1 gene (MDR1) and is responsible for cellular efflux of numerous drugs. PXR regulates both CYP3A and P-gp and coordinately mediates detoxification of many xenobiotics during oral absorptions. The flavonoid constituent-mediated modulation of CYP3A and P-gp is the main mechanism through which the bioavailability and disposition of conventional drugs are regulated. The synergistically modulation of CYP3A and P-gp by flavonoids may increase the potency of chemotherapeutic drugs. Moreover, it increases the permeability of drugs in brain and reduces the MDR in cancer chemotherapy. Most of the TKIs are oral dosage formulations and also dual substrates of CYP3A and P-gp, so the risk of pharmacokinetic interactions with flavonoids is expected on concurrent administration. Therefore, there is a compelling need to study the cellular and molecular mechanisms involved in the flavonoid-mediated modulation of CYP3A and P-gp and their expected impact on the exposure and disposition of TKIs. Results from some experimental and clinical studies have confirmed the interaction between TKIs and flavonoids, but these unwanted clinical consequences in cancer patients have not been elaborated. However, even small changes in drug metabolism and pharmacokinetics of TKIs may lead to therapeutic failure or toxicity in cancer patients. Nevertheless, it is a challenging task to determine the clinical effects of the DDI due to the large interpatient variability in the pharmacokinetics of the TKIs.

## Conflict of interest

The author declares that there is no conflict of interest.

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