REVIEW

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Tacrolimus and herbs interactions: a review

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The calcineurin inhibitor tacrolimus (TAC) shows inter-and intra-individual variability in blood levels and has a narrow therapeutic index. To reduce the chance of fluctuations in immunosuppressive activity and potential drug interactions, it is critical to keep track of drug concentrations. Cytochrome-P450 (CYP) isoenzymes CYP3A4 and CYP3A5, as well P-glycoprotein (P-gp) are involved in TAC bioavailability. TAC's interactions with herbal extracts are reviewed here, because with more people using TAC, it is becoming crucial to know which extracts, which are often part of self-medication, can alter TAC blood concentrations. TAC bioavailability was decreased when co-administered with St John's wort (SJW), cranberry, rooibos tea, and boldo in human models by induction of the CYP450 system and/or P-gp efflux pump, meanwhile, the TAC bioavailability was increased when co-administered with grapefruit juice (GFJ), schisandra, berberine, turmeric, pomegranate juice, pomelo, and ginger in human and or animal models by inhibition effect on CYP450 system and/or P-gp efflux pump. Thus, physicians and pharmacists should thoroughly educate their patients regarding the use of supplemental herbs before administering TAC. Furthermore, patients who are already undergoing TAC treatment should be informed about the possibility of dangerous interactions between herbal remedies and TAC.

1. Introduction

Tacrolimus (TAC) is a macrolide immunosuppressive drug used to prevent organ rejection in recipients of transplanted organs or tissues (Velickovic-Radovanovic et al. 2015). TAC has a restricted therapeutic index as well as inter-and intra-individual variability. Therefore, monitoring drug concentrations is mandatory to reduce the embarrassment of variations in immunosuppressive activity, and potential drug interactions or toxicity (Christians et al. 2002; van-Gelder 2002). Consequently, the transplanted patients who used TAC as a prophylactic agent against organ rejection perform a regular measurement of TAC concentration values in their blood. TAC has a low (about 20%) bioavailability due to its extensive pre-systemic metabolism (Iwasaki 2007; Wallemacq and Verbeeck 2001). It is a substrate of the P-glycoprotein (P-gp) efflux pump. Because TAC has a limited therapeutic range, it is important to estimate its levels in the blood carefully and to assess the effect of interacting medications. In addition, TAC is a substrate of CYP3A4 and CYP3A5, while it is mainly metabolized through CYP3A4 enzyme. TAC is highly lipophilic and is excreted from the body after excessive metabolism (Finch and Pillans 2014). The main metabolic pathways are hydroxylation and demethylation, where the predominant metabolite is 13-O-demethyl-tacrolimus (Iwasaki et al. 1995).

Abbreviations
Tacrolimus (TAC); Cytochrome-P450 (CYP); P-glycoprotein (P-gp); St John's wort (SJW); Grapefruit juice (GFJ); *Schisandra sphenanthera* (SchE); Epigallocatechin gallate (EGCG); Maximum blood concentration (C_{max}); Area under plasma concentration time curve (AUC_{0-t}); Apparent volume of distribution (V/F); Apparent clearance (CL/F); Wuzhi tablet (*Schisandra sphenanthera* extract) ; Pharmacokinetic (PK); Cyclosporine (CYC).

Herbal treatments are occasionally taken in combination with conventional medications, which increases the likelihood of adverse herb-drug interactions. Herbs are sometimes used in combination with medicinal drugs, increasing risky PK and/or pharmacodynamic interactions. Taking herbs and medicines concomitantly can cause clinically critical side effects by simulating, increasing, or decreasing the actions of any component (Chen et al. 2012; Hu et al. 2005). Synergistic or additive therapeutic effects may cause undesirable consequences and complicate long-term dose regimens, whereas antagonistic interactions will lead to decreased efficacy and therapeutic failure. The possibility for herbal extracts to interact with medications is a major safety concern, especially for treatments with limited therapeutic indices, which could contribute to life-threatening events. Drug absorption, metabolism, distribution, and excretion are all influenced by PK herb-drug interactions. The mechanisms that govern the changed drug concentrations induced by simultaneous natural medicines need to be identified, however, activation or inhibition of hepatic and intestinal drug-metabolizing enzymes e.g. cytochrome P450 (CYP) and/or drug transporters such as P-glycoprotein (P-gp) have been suggested (Bushra et al. 2011; Milić et al. 2014; Meng and Liu 2014; Wanwimolruk and Prachayasittikul 2014).

In recent years, herbs or phytomedicines have become commonly used due to their global acceptance as complementary and alternative remedies. While modern medications are only accessible for purchase after laboratory testing, clinical studies, and approval from drug regulatory agencies. The bulk of herbal products on the market are devoid of such scientific evidence of efficacious and safe profile. This would lead to adverse clinical outcomes due to herb-drug interactions that are undocumented in terms of their temporal relationships and concurrent use (Parvez and Rishi 2019). TAC blood concentration is carefully monitored, and accordingly, the dose must be adjusted. Possible interactions of TAC with supplemental herbal extracts should be overcome at all costs. This paper aimed to introduce updated data about recent publications and case reports over the last two decades regarding TAC and herbs interactions. An extensive review of published studies in PubMed

database, Research gate, Google Scholar, Science Direct, and recent conference papers was performed to attain comprehensive publications. The Table shows an overview of commonly used herbs, the results of herb-TAC interactions, and the associated mechanisms.

Table: Herbs, the effect of herb-tacrolimus (TAC) interaction, and the mechanisms

Herbal supplement or extract	Effect of interaction on TAC bioavailability	Mechanism of interaction	Studies
St John's wort	Decreased	Induces intestinal and hepatic CYP3A4, CYP2B6 and P-gp	Human
Grapefruit juice	Increased	Inhibits intestinal CYP3A4	Human
Schisandra	Increased	Inhibits CYP3A mediated metabolism and P-gp	Human
Tea	Decreased	Inhibits P-gp and CYP1A2,CYP3A4	Animal
Berberine	Increased	Inhibits CYP3A4 and intestinal P-gp	Human (case report)
Turmeric	Increased	Inhibits intestinal CYP3A and P-gp	Human
Pomegranate juice	Increased	Inhibits intestinal CYP3A4	Human (case report)
Pomelo	Increased	Inhibits both CYP3A4 and P-gp	Human
Ginger	Increased	Inhibits intestinal CYP3A and P-gp	Animal
Cranberry	Decreased	Possible induction of CYP	Human (case report)
Rooibos tea	Decreased	Induces CYP3A4 and intestinal P-gp	Human
Boldo	Decreased	Possible induction of CYP	Human (case report)

The reported studies of the potential interactions for different herbs on TAC including *in vitro* and *in vivo* approaches will be summarized in the following sections.

2. St John's Wort

St John's wort (SJW), scientifically known as *Hypericum perforatum*, which is a medicinal herb that possesses antidepressant activity. Hyperforin and hypericin are the two major phytochemicals (Di et al. 2008). Hypericin can regulate P-gp, while hyperforin can induce CYP3A4, CYP2B6, and P-gp. Therefore SJW has been implicated in numerous clinical interactions with conventional drugs and has therefore been extensively studied (Wentworth et al. 2000). In *in vitro* experiments, whole-blood microparticle enzyme analysis of TAC levels were not affected by the addition of SJW (Dasgupta et al. 2006). A clinical study was conducted with ten healthy subjects, who were given a single 100 µg/kg dose of TAC alone, or after they took SJW 300 mg three times daily for 14 days. On average SJW decreased the C_{max} of TAC by 65% and its AUC_{0-t} by 32% (Hebert et al. 2004). Similar results have been found in a study on ten kidney transplanted recipients given SJW 600 mg daily for two weeks. To achieve target levels, the TAC daily dose was increased in all patients, from 4.5 mg daily to 8 mg. Two weeks after stopping SJW administration, TAC doses were reduced to 6.5 mg daily, and then to the original dose of 4.5 mg daily after about 4 weeks (Mai et al. 2003). In a case report, an interaction between SJW and TAC was proposed in a patient after kidney transplantation. Stable whole-blood TAC concentrations ranged from 6 to 10 µg/L before SJW initiation fell to 1.6 µg/L when SJW was administered (Bolley et al. 2002).

3. Grapefruit juice

Grapefruit juice (GFJ), which is rich in naringin, pectin, flavonoids, furanocoumarins, among other compounds, has been recorded to interact with numerous drugs, including CYC (Bailey et al. 1991, 1998). The interaction mechanism is considered to occur through inhibition of the enzyme activity and the downregulation of intestinal wall CYP3A4 protein expression by active ingredients of GFJ (Dresser and Bailey 2003). TAC, like cyclosporine (CYC), is metabolized highly by CYP34A in enterocytes, and its bioavailability may be enhanced by GFJ (Staatz and Tett 2004). In one liver organ recipient, GFJ slowed the PK and pharmacodynamics of TAC (Fukatsu et al. 2006).

In a prospective clinical study, the co-administration of GFJ with TAC in liver transplant patients increased the bioavailability of TAC. However, the concentration level of TAC should be continuously checked and the dose must be adjusted to the therapeutic window (Liu et al. 2009). A case of TAC toxicity has been seen when a man with liver transplant ate more than 1.5 kg of grapefruit marmalade for one week. His TAC whole blood level was found to be markedly raised to 55.4 µg/L from a previous therapeutic level (between 8 and 13 µg/L), and renal impairment was detected (serum creatinine of 174 µmol/L) (Peynaud et al. 2007).

Another case report described a marked change of approximately 2-fold increase in blood TAC concentration levels caused by consumption of GFJ in kidney transplant recipient and led to an increase trend of renal function test values during hospitalization (Zhai et al. 2019).

4. Schisandra

Schisandra sphenanthera (SchE) is a very important herb in Chinese medicine. It is used as a tonic and has cardiotonic, hepatoprotective, immunomodulatory, and sedative effects. The major active components are dibenzocyclooctene lignans. The main groups are schizandrins and gomisins. The gomisins B, C, and N are inhibitors of CYP3A4 *in vitro* (Iwata et al. 2004). In contrast, schizandrin A and B induced CYP3A4 in another *in vitro* study (Mu et al. 2006).

In China SchE and TAC are often co-administered for the treatment of drug-induced hepatitis in renal or liver transplantation. In a PK study, twelve healthy subjects received an extract of SchE (containing 33.75 mg schizandrin) twice daily for two weeks, with a single 2 mg oral dose of TAC on day 14. SchE greatly increased AUC_{0-t}, and C_{max} of TAC by 164% and 227% but, the half-life was not altered (Xin et al. 2007). An *in vitro* study using schizandrins A and B, gomisins A and C suggested that these constituents are inhibitors of P-gp, other components had only weak effects (Pan et al. 2006).

A study found that SchE suppressed P-gp-mediated efflux and CYP3A metabolism of TAC which supposed that reduction of intestinal first-pass effect by SchE was the primary cause for improvement of oral TAC bioavailability (Qin et al. 2010). In another investigation, Wuzhi tablet (*Schisandra sphenanthera* extract) was found to increase TAC systemic exposure in rats (Qin et al. 2013). A recent study on animals found that PK of TAC was significantly affected by the pretreatment time as well as the dose of Wuzhi tablet (Xiao-ling et al. 2020).

5. Tea

Green tea (*Camellia sinensis*) is the most widely consumed beverage besides water in Asia and is gaining popularity worldwide. Catechins are flavanols which play an important role in the pharmacological activity of green tea (Butt et al. 2014). Epigallocatechin gallate (EGCG) could inhibit multiple CYP450 isoforms including CYP1A2, and CYP3A4 (Misaka et al. 2013; Satoh et al. 2016). In addition, an inhibitory effect of EGCG on P-gp has been observed in human Caco-cells (Jodoin et al. 2002). Green tea catechins appear to not affect CYC levels and may protect against CYC and TAC's detrimental renal effects. According to a study on rats found that EGCG did not affect CYC levels, while simultaneously appearing to protect against CYC-induced kidney injury (Mun 2004).

Pretreatment with green tea polyphenolic extract, followed by the administration of CYC or TAC, mitigated the decrease in glomerular filtration rate was reported with these medicines in another animal model. Supplements of green tea are expected to interact negatively with CYC or TAC, by these data on animals, it may even be useful (Zhong et al. 2006). However, it could be unfavorable for transplant recipients to take these immunosuppressants with tea supplements but, the usual consumption of tea beverages does not concern to be an issue until clinical data is available (Shi et al. 2003).

A new animal study showed that C_{max} and AUC_{0-t} of TAC were reduced, and V/F and CL/F of TAC were enhanced after co-administration of EGCG. These results revealed consumption of high dose EGCG may cause significant changes in the PK of TAC, distribution, and elimination profile through the regulation of drug metabolic enzymes (Huang et al. 2021).

6. Berberine

Berberine is a major isoquinoline alkaloid in herbs such as goldenseal, berberis, and *Coptis chinensis* and has been traditionally used to treat diarrea (Vuddanda et al. 2010). A well-documented interaction between TAC and berberine was published in a case report for a child with idiopathic nephrotic syndrome. TAC dose adjustment was based on therapeutic drug monitoring to maintain it at a therapeutic level of 5–15 ng/mL. As the child developed diarrhea, berberine (0.2 g three times daily) was started. TAC blood concentration level increased from 8 to 22 ng/mL and serum creatinine increased from 62 to 109 µmol/L. This may demonstrate that berberine strongly affects the disposition of TAC, with a clinically relevant increase in TAC concentrations and renal toxicity. In addition, pharmacogenotyping results indicated that the patient was deficient for CYP3A5 genes, and the CYP3A4 pathway became predominant (Wallemacq et al. 2009). Berberine is an inhibitor of CYP3A4. It has been documented to increase CYC concentration in renal transplant adults and midazolam concentrations in adult healthy volunteers (Guo et al. 2012; Wu et al. 2005).

7. Turmeric

Turmeric is a rhizomatous herb (*Curcuma longa*) of the ginger family. Curcumin is the main natural polyphenol found in turmeric (Priyadarsini 2014). *Curcuma longa* has been traditionally used in Asian countries as antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties (Aggarwal 2003; Lestari and Indrayanto 2014). Curcumin interacts with some beta-blockers, increases the absorption of midazolam, but does not affect the absorption of iron (Zhang et al. 2007; Tuntipopipat et al. 2006). Curcumin has been shown to change both functions and expression of the P-gp and the CYP3A enzymes (Anuchapreeda et al. 2002; Zhang and Lim 2008).

In 2012, a study of turmeric-TAC interactions demonstrated that the AUC_{0-t} values of TAC in rats pre-treated with turmeric juice were significantly higher than those pre-treated with water (Egashira et al. 2012). An old man with a history of liver transplantation presented with acute TAC nephrotoxicity after he added significant amounts of turmeric to his food (Nayeri et al. 2017).

8. Pomegranate juice

Intake of pomegranate supplements has increased recently due to reports of a wide range of health benefits. Information regarding drug interactions with pomegranate juice is limited in experimental and animal data. Animal studies suggested that carbamazepine concentrations were increased, but elimination half-life was not, perhaps pomegranate extract only inhibited gastrointestinal CYP3A4, not hepatic CYP3A4 (Farkas et al. 2007). The first case report of heart transplanted recipients with elevated TAC concentrations after consuming concentrated pomegranate juice popsicles was documented in the literature. Erratic pomegranate juice may lead to significant changes in TAC concentration levels (Scheffert and Raza 2014).

9. Pomelo

Citrus grandis, or pummelo is a well-known food, and the peel is used as a beverage ingredient and also a medicinal herb (Chinese Pharmacopoeia Committee 2000). Pomelo is closely related to grapefruit and contains furanocoumarins, which have been identified as inhibitors of both CYP3A4 and P-gp (Guo et al. 2000). A case of pomelo intake led to a more than 2-fold increase in the blood level of TAC in kidney transplanted patients (Egashira et al. 2003). An *in vitro* study confirmed that pomelo was as potent as grapefruit and its constituents inhibited both CYP3A4 and P-gp and produced an increase in the blood concentration of TAC (Egashira et al. 2004).

The effect of pomelo on the PK of CYC and TAC were studied using a rat model. The outcomes showed that co-administration of pomelo markedly increased C_{max} and AUC_{0-t} of CYC and TAC, suggesting that oral bioavailabilities of CYC and TAC were significantly increased (Lin et al. 2011). TAC blood concentration in rats pre-treated with 100% pomelo juice was much higher than those in animals administered with water. On the other hand, the TAC blood concentration of the rats pre-treated with 50% pomelo juice was not significantly different from those with water. The pomelo-TAC interaction was concentration-dependent (Egashira et al. 2012).

10. Ginger

Ginger is a spice and herbal remedy made from the roots of *Zingiber officinale*. Ginger and turmeric are consumed widely in the world. The hidden risk of herb-drug interaction is often overlooked. Ginger was reported to change the activity of CYP3A4 and P-gp (Zhang and Lim 2008). *In vivo* studies established a clear interaction between ginger juice and TAC in rats. The AUC_{0-t} values of TAC in the rats given ginger juice were considerably greater than those receiving water (Egashira et al. 2012).

11. Cranberry

Cranberry extracts and juices show moderate efficacy in the prevention of recurrent urinary tract infections in women and children (De Souza and Olsburgh 2008). The immunosuppressive level may play a predominant role in the development of urinary tract infections of organ transplant recipients. Cranberry's protective properties are linked to its high proanthocyanidin concentration. Cranberry juices or extracts are widely used as a complementary medicine accompanied with antimicrobials or other therapies (Dason et al. 2011).

A case report documented that, cranberry extracts may alter the metabolism of TAC, and led to sub-therapeutic serum levels in kidney transplanted patients (Dave and Samuel 2016). There was no direct clinical reference to the *in vitro* or *in vivo* interaction of cranberry extracts with TAC in the literature. On the other hand, cranberry has been established to block the intestinal CYP3A enzymes, resulting in an increase in serum TAC levels (Paine and Oberlies 2007). Most of the reported cranberry interactions mediated by CYP3A inhibition were associated with an increase in serum levels of drugs, in contrast to the reported case. Such results can be explained by the unstable composition of herb extracts or other conditions.

12. Rooibos tea

Rooibos tea is one of several popular herbal teas prepared from the dried leaves of *Aspalathus linearis*, and is expected to suppress allergic reactions, such as pollen allergies or asthma (McKay and Blumberg 2007). Rooibos tea is rich in flavonoids such as quercetin or aspalathin. Quercetin has been documented to stimulate the activity of CYP3A, and thus it could be a major component of the drug herbal interaction of rooibos tea (Joubert 1996).

The first case of a clinically significant drug interaction between TAC and rooibos tea reported a patient after bone marrow transplantation, in which the interaction reduced the concentration of TAC and resulted in the development of graft-versus-host disease (Beppu et al. 2013).

13. Boldo

Boldo is an extract of Chilean tree leaves (*Peumus boldus* Molina) that have been traditionally used in folk medicine for gastrointestinal ailments (Brien et al. 2006). There is a scarcity of information about the interactions of boldo with pharmaceutical medications. A possible link between boldo-fenugreek and prolonged bleeding time in warfarin-treated individuals has been suggested (Lambert and Cormier 2001).

In 2010, the first report of boldo-TAC interaction, leading to a subtherapeutic level of TAC in an elderly kidney transplant patient, has been recognized. TAC levels returned to the intended target concentration after discontinuation of boldo (Mendoza et al. 2011).

14. Conclusions

Herbal supplements are commonly taken in combination with conventional medications, which raise the risk of undesirable herb-drug interactions. Herbs are frequently administered accompanied with therapeutic drugs, increasing the potential of PK and/or pharmacodynamic herb-drug interactions. Changes in TAC bioavailability were reported during co-administration of herbs or herbal extracts. An increase in TAC blood level was established with grapefruit juice, schisandra, berberine, turmeric, pomegranate juice, pomelo, and ginger in human and/or animal models. In contrast, herb-TAC interactions led to a sub-therapeutic level of TAC in other cases with herbs e.g. St John's wort, cranberry, rooibos tea, and boldo.

Accordingly, clinicians should be aware of the probability of herb-drug interactions and should have a guide when and how much to adjust the dose of therapeutic monitored drugs such as TAC.

Conflicts of interest: None to declare.

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