A clinical guide to common drug-nutrient interactions

Note: The information provided in this chart is based on a review of literature available at the time of publication. While the content is considered to be accurate at the time of publication, new or updated research released after the publication date may impact the accuracy of the information. Please use clinical discretion when using this resource.

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Some combinations of pharmaceutical medications, nutrients and botanical extracts may interact and could result in potential adverse effects. Understanding the interactions between pharmaceutical medications, nutrients and botanical extracts can help to prevent possible negative health outcomes in patients.

For example, when combined with certain pharmaceuticals, various nutrients or botanicals may:

- Increase the effects of a particular drug through inhibition of its metabolism
- Decrease the effects of a particular drug through potentiation of its metabolism
- Decrease the effects of a particular drug by decreasing absorption or increasing excretion
- Increase the effects of a particular drug by increasing absorption or decreasing excretion
- Cause additive or adverse effects

The following is a review of current evidence that substantiates and/or theoretically supports the existence of interactions between commonly prescribed pharmaceutical medications and various nutrients or botanical extracts. The level of evidence for each interaction or mechanism of action is provided to support practitioners so that they can make informed decisions within their practices. Please use clinical discretion when using this resource.

**Review process**

The Fullscript Integrative Medical Advisory Team (IMAT) conducted a review of existing literature to confirm the listed interactions. This preliminary review included over 130 studies, including human, randomized, double-blind, placebo controlled (RDBPC) trials, in-vivo animals studies, and in-vitro studies. Periodic review will take place to ensure the content is up-to-date.

**Rating Scales for Evidence Based Medicine**

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<td>B</td>
<td>RDBPC human trials</td>
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<td>G</td>
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The original content review included all literature posted/published via:

- Pubmed
- U.S. Food & Drug Administration
- American Academy of Family Physicians
- Journal of the American Medical Association
- Science Direct

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**Acetaminophen/Hydrocodone**  
*(Vicodin, Norco, Paracetamol)*

Research has demonstrated that acetaminophen interacts with alcohol and caffeine.

**Alcohol**

(B) Alcohol consumption has been associated with an increased risk of acetaminophen-induced hepatotoxicity.25, 12 Conversely, a study compared the clearance of acetaminophen in healthy subjects, alcoholic subjects without liver disease, and subjects with alcoholic cirrhosis abstaining from alcohol. Results demonstrated increased clearance in healthy subjects.26 A second study of healthy individuals examined the effects of ethanol consumption on serum miR-122, a biomarker for liver injury. Increases (2.2-fold) in serum miR-122 were reported after moderate ethanol intake.27 Furthermore, a study conducted from 2002–2014 found that 35 patients were admitted to the hospital as a result of acute acetaminophen poisoning. They found that 20% of these cases resulted from ingestion of acetaminophen and alcohol resulting in a potentially fatal interaction.13

(C) Several studies have demonstrated that alcohol enhances the metabolism of acetaminophen by CYP2E1 into N-acetyl-p-benzoquinone imine (NAPQI), a toxic metabolite of acetaminophen, leading to increased risk of hepatotoxicity.25 A study with 10 healthy volunteers tested the effects of alcohol intake on the formation of NAPQI when acetaminophen was ingested just after alcohol was cleared from the body. Results demonstrated a 22% increase in NAPQI formation after the alcohol infusion was consumed compared to a 5% increase in subjects given dextrose in water.12

(D/E) Additionally, regular alcohol consumption may inhibit the breakdown of certain drugs metabolized by CYP2E1, prolonging the half-life of these drugs. This is because alcohol is also metabolized by CYP2E1 and could, therefore, compete with these drugs for metabolism by CYP2E1.14 A 2005 study examining the role cytochromes P450 in toxicity using CYP2E1-null mice found that high concentrations of acetaminophen may result in toxicity when CYP2E1 is absent.15 An in-vitro study also found that higher levels of acetaminophen may significantly inhibit alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) pathways and, therefore, hepatic and gastrointestinal first-pass metabolism of alcohol.54 However, it was also noted that alcohol consumption may increase the metabolism and decrease the half-life of drugs that are also substrates of CYP2E1 as chronic alcohol consumption induces CYP2E1.14

**Caffeine**

(A) Research has shown that, when used in combination, caffeine increases the analgesic effects of acetaminophen. A review of randomised, double-blind studies examining the effects of caffeine when consumed with common analgesics, including acetaminophen, found that caffeine intake (≥100 mg) resulted in a small but significant increase in pain relief.20

(B) This pain relieving effect has been attributed to increased absorption and prolonged half-life of acetaminophen with caffeine intake. A study investigating the effects of liver dysfunction on the pharmacokinetics of paracetamol, compared patients receiving paracetamol alone or with caffeine. Patients with hepatitis C (HCV) receiving paracetamol demonstrated earlier effective concentrations and decreased clearance of paracetamol compared to healthy subjects. The rapid absorption and prolonged half-life of paracetamol were even greater in patients who received both paracetamol and caffeine.25 Furthermore, a clinical trial with healthy Mexican volunteers was conducted to examine the effects of oral administration of 65 mg of caffeine in conjunction with 650 mg of acetaminophen. Acetaminophen absorption in the group receiving caffeine was slightly faster compared to the control group.32

(C) Conversely, one study found that caffeine accelerated the elimination of acetaminophen. An experimental assessment on mice, as well as an analysis of pharmacokinetics in men, determined the effects of caffeine on paracetamol-induced toxicity. The study found that co-administration of caffeine with paracetamol may decrease potential toxicity from paracetamol treatment. In men, when caffeine was administered, a decrease in plasma paracetamol levels was observed, indicating that caffeine may accelerate elimination of the drug.84

(D) While an interaction between caffeine and acetaminophen has been observed, it is unclear whether caffeine inhibits or stimulates acetaminophen-induced hepatotoxicity. An analysis of the interaction between acetaminophen and caffeine found that, with co-administration, caffeine both inhibits and stimulates acetaminophen-induced hepatotoxicity. Caffeine intake may reduce acetaminophen-induced hepatotoxicity through reduction of NAPQI, a toxic metabolite of acetaminophen, and through the regulation of genes that positively affects development of toxicity. However, there is also evidence that caffeine may potentiate acetaminophen-induced hepatotoxicity by affecting genes involved in cell death.34

Green Tea Extract

(D) A complex relationship exists between green tea extract and acetaminophen. Results of studies are conflicting; however, it appears that the timing of green tea extract intake may determine whether it has a protective or potentiating effect on hepatotoxicity induced by acetaminophen treatment. A study exploring the effects of green tea extract on acetaminophen-induced hepatotoxicity in rats supported this relationship. When green tea extract was administered before acetaminophen, it resulted in a protective effect, while the opposite effect was observed when administered after acetaminophen.10

(D) Similarly, when administered before acetaminophen, green tea extract resulted in a decrease in reactive metabolites, protecting against acetaminophen-induced hepatotoxicity.65 Another study examined the effects of EGCG, an active constituent of green tea, on acetaminophen treatment in rats. For one week, the rats received a diet with or without EGCG. They then received an intra-peritoneal injection of acetaminophen. Results showed that EGCG may reduce metabolism and toxicity of the drug. This was indicated by lower morphological damage, plasma alanine aminotransferase and aspartate aminotransferase, as well as reduced hepatic activities of midazolam 1-hydroxyluration (CYP3A), nitrophenol 6-hydroxylase (CYP2E1), UDP-glucuronosyltransferase, and sulfotransferase.13
(D) In contrast, when green tea extract is taken after the administration of acetaminophen, a decrease in glutathione is observed. As glutathione is needed to neutralize NAPQI, a decrease in levels of glutathione may increase the risk of hepatotoxicity. When administered after acetaminophen, green tea extract intake led to a significant depletion of glutathione and potentiated acetaminophen-induced hepatotoxicity in mice. In addition, a study examining the effects of green tea extract on acetaminophen-induced hepatotoxicity in male albino rats found that administration of green tea extract induces hepatotoxicity and may potentiate acetaminophen-induced hepatotoxicity in cases of acetaminophen overdose.

Amlodipine (Norvasc)

Research has demonstrated an interaction between the calcium channel blocker amlodipine and grapefruit juice. Potential interactions may also exist between amlodipine and St. John's Wort and Coleus forskohlii.

Grapefruit Juice

Research has shown that grapefruit juice may interact with amlodipine via inhibition of the cytochrome responsible for the metabolism of the drug, CYP3A4.

(C) In a two-phase, randomized, placebo-controlled crossover study, it was determined that prolonged exposure to grapefruit juice inhibits intestinal and hepatic CYP3A4. This indicates that an interaction may exist between grapefruit and medications that are CYP3A4 substrates. Furthermore, a review examining the effects of grapefruit juice intake on the metabolism of certain drugs noted a weak interaction between amlodipine and grapefruit juice. As the ingestion of grapefruit inhibits enteric CYP3A, this interaction would be limited to grapefruit administered orally. The review also notes that an interaction may also occur with prior intake of grapefruit juice, even when it is not physically present in the gastrointestinal tract.

(C) In addition to the interaction between grapefruit intake and CYP3A4, some evidence has been found demonstrating an interaction between grapefruit and amlodipine specifically. A study examined the effects of short-term exposure to grapefruit juice on the metabolism of amlodipine in 12 healthy males. Although only a small increase in amlodipine plasma concentration occurred as a result of grapefruit intake, researchers state that variation between individuals should be considered and a greater intake of grapefruit may impact results. In contrast, another study found that 240 ml of grapefruit juice taken at the same time as the amlodipine had no significant effects on the bioavailability of the drug in 20 healthy subjects.

St. John's Wort

Theoretically, St. John's Wort may interact with amlodipine through the induction of CYP3A4 and modulation of P-glycoprotein.

(F) Research has shown that St. John's Wort induces CYP3A4. While no studies were found examining the direct interaction between St. John's Wort and amlodipine, a potential interaction could exist between St. John's Wort and amlodipine as amlodipine is a CYP3A4 substrate. A study of eight healthy male volunteers examining the effects of St. John's Wort on calcium channel blockers, R- and S-verapamil, found that the bioavailability of both drugs decreased following repeated oral administration of St. John's Wort. This is thought to be the result of induction of first-pass CYP3A4 metabolism, most likely in the gastrointestinal tract. Further, a systematic review of 31 studies suggests that high-doses of hyperforin (greater than 10 mg per day), a primary constituent of St. John's Wort, induces CYP3A. This statistically-significant relationship was not present with low hyperforin doses (less than 4 mg per day).

(F) Theoretically, the mechanism of drug interaction with St. John's Wort may be a result of cytochrome P450 3A4 (CYP3A4) induction. However, it has also been suggested that St. John's Wort may be involved in the modulation of P-glycoprotein expression and function. In a single blind, randomized placebo controlled trial, healthy subjects were given three 600 mg doses of St. John's Wort daily or a placebo. While there were no changes observed in individuals given the placebo, the group taking St. John's Wort demonstrated increases in P-glycoprotein expression and enhanced drug efflux function. These findings suggest that drugs that modulate P-glycoprotein efflux may be inhibited by St. John's Wort. Another study, examining the effects of amlodipine on doxorubicin, noted a concentration-dependent modulatory effect of amlodipine on P-glycoprotein efflux. Theoretically, this may indicate an interaction between St. John's Wort and amlodipine as they may both be substrates of P-glycoprotein with the ability to modulate its function.

Coleus forskohlii

(F) Theoretically, an interaction between Coleus forskohlii and pharmaceuticals metabolized by CYP3A4, such as amlodipine, may exist. However, the evidence is mixed. An in-vitro study examining the metabolism of forskolin, an active constituent of C. forskohlii, found that concentrations between 0.1 ng x mL(-1) and 5 microg x mL(-1) of forskolin inhibited CYP3A4. However, another study on the effects of Coleus forskohlii on rat hepatocytes found no significant effect on cytochrome P450 (CYP3A, CYP2B, and CYP2C) mRNA expression. This indicates that C. forskohlii may not be involved in CYP450 induction-based drug interactions and may be safe to consume.
**Atorvastatin (Lipitor)**

Research has demonstrated interaction potential between atorvastatin and two plants: grapefruit and St. John’s Wort. Interaction may also exist with sweet orange and green tea, however, in vivo human clinical trials are needed for stronger evidence.

**Grapefruit**

Grapefruit (*Citrus paradisi*) juice is suggested to play a role in many drug-nutrient interactions through the inhibitory effects of its constituents on the CYP3A4 cytochrome.\(^6\) The inhibition of the cytochrome that metabolizes atorvastatin, CYP3A4, may lead to a more pronounced effect on lipid profile due to greater bioavailability of the drug, though there is conflicting evidence for this outcome. There is also evidence of an interaction between grapefruit and the organic anion transporter, OATP2B1, though this has only been demonstrated in vitro. Theoretically, this could offer further evidence of an interaction between atorvastatin and grapefruit juice, as atorvastatin is a substrate of OATP2B1.\(^3\)

**(B)** The co-administration of grapefruit juice and atorvastatin may alter bioavailability and effectiveness of the drug. One study demonstrated differences in serum drug and lipid profiles when comparing the effects of grapefruit juice consumption in two groups. Group A, 60 hyperlipidemic patients who received various doses of atorvastatin, experienced significant increases in serum atorvastatin (19-26%) with no clinical change in lipid profile.

Group B, 70 hyperlipidemic patients who reduced their normal dosing of atorvastatin by 50%, had slight decreases in serum atorvastatin (12-25%) with a small but significant increase in serum cholesterol, triglycerides and LDL:HDL ratio.\(^2\) In comparison, a randomized, two-phase crossover study with 12 healthy subjects, found that grapefruit juice increased the concentrations of serum atorvastatin acid and lactone metabolites, as well as active and total HMG-CoA reductase inhibitors.\(^8\)

**(C)** Tere is also evidence that grapefruit juice can induce CYP3A4, thereby increasing plasma concentrations of the atorvastatin acid and lactone metabolites. In a randomized, two-way crossover study with 20 healthy subjects, plasma concentrations of atorvastatin acid and atorvastatin lactone increased significantly following 10 mg of atorvastatin with 250ml of grapefruit juice three times per day for two days. It was suggested that metabolism of the drug was mainly induced by CYP3A4 in the small intestine.\(^6\)

**(E)** Grapefruit flavonoids are also suggested to inhibit the organic anion transporter, OATP2B1, a transporter of atorvastatin. An in vitro study using xenopus oocytes showed that OATP2B1 transport was mainly inhibited by naringin, a flavonoid in grapefruit, through decreased uptake of an OATP2B1 substrate, estrone-3–sulfate.\(^2\)

**St. John’s Wort**

Research has shown that St. John’s Wort (*Hypericum perforatum*) may interact with atorvastatin, causing an increase in LDL and total cholesterol. It is hypothesized that there is induction interaction potential between St. John’s Wort and cytochromes of the P450 system, as well as inhibition of the OATP2B1 transporter. However, no human clinical trials demonstrating these direct relationships were found.

**(C)** An interaction has been demonstrated between St. John’s Wort and atorvastatin leading to decreased effectiveness of the drug. Co-treatment of atorvastatin with 300 mg of St. John’s Wort two times per day was shown to increase LDL and total cholesterol over the course of four weeks in 16 patients with hypercholesterolemia.\(^1\)

**(E)** It is believed that the mechanism of action explaining the interaction between atorvastatin and St. John’s Wort may be related to its induction effects on the cytochrome P450 family, which would increase the metabolism of pharmaceuticals.\(^2\) It has been shown that hyperforin, one of the main phytochemicals found in St. John’s Wort, may play a large role in the induction of the CYP3A pathway, indicating a potential interaction with atorvastatin.\(^2\) A systematic review showed that major interactions between drugs that are CYP3A4 substrates, such as atorvastatin, and St. John’s Wort may be dependent on hyperforin content. Researchers found that products that contained less than 1 mg of hyperforin were less likely to be associated with major interactions.\(^8\) Similarly, a study showed that administration of St. John’s Wort with low hyperforin content resulted in a mild induction of CYP3A4 cytochromes, though this induction was not considered as clinically relevant.\(^7\) Another systematic review showed that hyperforin interacts with CYP3A in a dose-dependant manner where high concentrations (greater than 10 mg per day) have induction outcomes, whereas low-doses (less than 4 mg per day) have no significant effect.\(^6\)

Hyperforin has also been shown to play an important role in the activation of the Pregnane X Receptor, which ultimately upregulates the CYP3A pathway in response to the exposure to foreign substances.\(^5\) Ten healthy subjects carrying varying combinations of the H1 and H2 haplotypes that regulate the Pregnane X Receptor gene were given 300 mg of St. John’s Wort three times per day. Administration of St. John’s Wort-induced transcriptional activity of CYP3A4 was greatest in the haplotype that initially had the weakest basal transcriptional activity.\(^2\)

**(E)** In contrast to the above studies that suggest that hyperforin induces the CYP3A cytochromes, one in vitro study using human liver microsomes was suggested that hyperforin may cause cytochrome inhibition. Researchers indicated that hyperforin was both metabolized by the CYP2D6 and CYP3A4 cytochromes, and that it inhibited them potently.\(^7\)

**(E)** Hyperforin and to a lesser extent, hypericin, may also play a role in hepaticacellular uptake, intestinal absorption of atorvastatin and upregulation of the CYP3A4 cytochrome. In an in vitro study using 11 St. John’s Wort formulations, it was shown that hyperforin increased the efflux ratio of atorvastatin from human epithelial cells. Hyperforin acted as an inhibitory substrate for OATP2B1, leading to activation of the CYP3A4 pathway through increased activation of the Pregnane X Receptor. It was, therefore, suggested that hyperforin may be a competitive inhibitor of OATP2B1. However, it was also noted that atorvastatin is not specific to OATP2B1 and other transporters can modulate its bioavailability.\(^3\)

**Sweet Orange**

No direct evidence was found supporting an interaction between atorvastatin and sweet orange (*Citrus sinensis*). However, theoretically, sweet orange may interact with atorvastatin as constituents of orange juice may have inhibitory effects on OATP2B1 in the small intestine.

**(E)** In vitro studies have demonstrated a theoretical relationship between atorvastatin and the OATP2B1 transporter, as well as between the transporter and sweet orange. One study showed...
that OATP2B1-mediated transport is significant for atorvastatin at a neutral pH, and that substrate specificity and OATP2B1 activity increased in a more acidic pH. It was also indicated that OATP2B1 inhibition was unattainable at a pH of 6.0. Other substrates of the OATP2B1 were primarily modulated by the presence of a proton ionophore. Decreased uptake of glibenclamide (an OATP2B1 substrate) in human intestinal epithelial cells has also been shown following exposure to orange and grapefruit juices with a pH of 7.4. In a 2010 review, researchers concluded that orange juice may have clinically relevant inhibition of OATP2B1. However, it was also stated that inhibition of OATP1B1 with orange and other juices is improbable.

Green Tea

Similarly to sweet orange, there is some evidence to suggest an inhibitory interaction potential between atorvastatin and green tea (Camellia sinensis), as well as with epigallocatechin gallate (EGCG) and epicatechin gallate (ECG), two of the most abundant constituents in green tea. However, no in vivo humans studies were found demonstrating this relationship directly. This interaction potential appears to be related to the inhibition of organic anion transporters involved in the transport of atorvastatin.

(E) In vitro, it has been shown that green tea inhibited transport of atorvastatin via OATP1B1 and OATP1B3 in a concentration dependent relationship. Independently, ECG also demonstrated inhibitory effects on these transporters in human embryonic kidney cells. Additionally, ECG and EGCG have been shown to be substrates of OATP1A2 and OATP1B3, but are not transported by OATP1B1 or OATP2B1 in human enterocytes and hepatocytes. OATP1B3-mediated transport of ECG and EGCG was found to be substrate-dependent and could cause noncompetitive inhibition or stimulation of transport activity. It was postulated, however, that one to two cups (250 ml) of green tea would contain adequate concentrations of ECG and EGCG to alter OATP mediated transport of their substrates.

Gabapentin (Neurontin, Neuraptine)

Research has demonstrated interaction potential between gabapentin and alcohol, caffeine and cannabis. Theoretical interactions may also exist between gabapentin and l-tryptophan, as well as gabapentin and kava.

Alcohol

Multiple randomized, placebo-controlled human studies have demonstrated interaction potential between gabapentin and alcohol. Evidence shows that the use of gabapentin in the treatment of alcohol dependency is effective, safe and well-tolerated by patients.

(A) The concurrent use of gabapentin has been demonstrated as an effective means of treating alcohol dependency, as well as in decreasing alcohol-withdrawal symptoms. In a single-site, clinical trial, 150 men and women seeking alcohol dependence treatment received placebo, 900 mg of gabapentin or 1800 mg of gabapentin per day in conjunction with guided counselling. Gabapentin significantly reduced the rates of heavy drinking and improved abstinence rates, while similar dose–response relationships were found in measures of mood, sleep and cravings, especially at the 1800 mg dose. A proof-of-concept study with 33 subjects found that titration up to a 1200 mg dose of gabapentin was significantly associated with reductions in alcohol cravings, as well as significant improvements in measures of sleep. Similarly, in another study with 21 subjects, titration up to a 1500 mg dose of gabapentin significantly delayed relapse to heavy drinking following both six and twelve weeks. While there were no differential effects on sleep between treatment groups, both gabapentin and the placebo improved insomnia. Finally, a recent review concluded that five of six studies reviewed using randomized, double blind, placebo-controlled methodologies supported the efficacy of gabapentin in alcohol use disorder. When used in conjunction with behavioural support, results showed that higher doses of gabapentin, greater than 1200 mg per day, were more effective than lower doses, less than 900 mg per day, in producing positive outcomes related to managing alcohol use disorder. Alcohol-related sleep issues were also improved with administration of gabapentin in six of eight studies.

(A) In addition to measuring the efficacy of treating alcohol dependency, multiple randomized placebo controlled studies also show that concurrent use of gabapentin with alcohol is safe. The aforementioned review showed that there were no significant differences in adverse effects between gabapentin and alcohol groups compared to control groups, indicating that gabapentin may be a novel way to safely treat alcohol use disorder. In a study with 17 participants, the acute provision of control, 1000 mg or 2000 mg of gabapentin did not alter the effects of alcohol on the body, as indicated by physiological and performance measures. While gabapentin did impair balance, co-administration was generally well tolerated. Similarly, in an eight day study with 35 participants, either 1200 mg of gabapentin or placebo was provided to patients not seeking alcohol-related treatment (ie. freely drinking alcohol). For the first five days, participants were monitored in their regular settings. On day seven, they had access to a free-choice but limited access “bar-lab”. Safety and tolerability were monitored throughout the protocol. It was determined that there were no differences in the subjective high or intoxication between subjects with or without gabapentin, and that the drug was safe to use with alcohol.
Cannabis: CBD and THC

Tetrahydrocannabinol (THC) and Cannabidiol (CBD) are the two main cannabinoids found in the Cannabis sativa plant. Similarly to gabapentin, CBD has been studied for its use as an anticonvulsant and research has demonstrated its effectiveness in treating epilepsy. CBD is metabolized by cytochromes of the P450 system in the liver, while gabapentin is not, indicating that interaction potential between the two may stem from other mechanisms of action. There is some evidence to suggest that cannabis may interact with gabapentin, however, studies primarily focus on specific cannabinoids.

(B) Gabapentin may also be beneficial in the treatment of cannabis withdrawal and dependence. In a 12-week, randomized, double-blind, clinical trial with 50 patients regularly smoking cannabis, subjects were titrated up to a 1200 mg dose of gabapentin or given a placebo. Measures of urine toxicology and cannabis use by self-report were conducted on a weekly basis. It was determined that cannabis use and symptoms of withdrawal were both significantly reduced with co-administration of gabapentin and had an acceptable safety profile. In contrast, a recent review indicated that, based on the available evidence, the co-administration of gabapentin may only have a weak effect on reducing the quantity of cannabis used, as well as on achieving abstinence.

(D) The use of THC has demonstrated potential use in the treatment of neuropathic pain. The concurrent use of gabapentin with THC may synergistically improve these outcomes. A 2019 study in mice showed that the co-administration of THC and gabapentin resulted in a greater reduction in pain associated with allodynia compared to THC alone. It was also noted that motor incoordination associated with the use of THC increased in the combination group, indicating the possibility of interaction-induced side effects.

Caffeine

There is interaction potential between gabapentin and caffeine, though this is based on evidence from animal studies. There is also evidence for theoretical interaction potential based on animal studies that have evaluated the prevalence of seizures with the administration of caffeine along with anticonvulsant drugs.

(D) Studies using mice have been conducted in order to detect the mechanism through which caffeine may diminish the effects of gabapentin. In a 2016 review, it was indicated that caffeine may play a role in reducing the anticonvulsant effects of gabapentin. With the administration of acute or chronic caffeine (0.12 - 0.24 mmol/kg), the anticonvulsant effects of gabapentin were reduced. When rats were administered with 200 mg/kg of gabapentin, provision of caffeine negated any further rise in the electroconvulsive threshold created by gabapentin, indicating that caffeine may decrease the threshold at which convulsions may occur. Furthermore, greater motor coordination impairment was noted with co-administration of gabapentin during acute or chronic caffeine intake. Another study of antiepileptic drugs determined that the increased electroconvulsive threshold normally established with gabapentin treatment was significantly reduced with both acute and chronic administration of caffeine. The co-administration of caffeine has also been found to significantly reduce gabapentin’s antihyperalgesic effects in a dose-dependent manner in mice. The researchers suggested that the activation of the adenosine A1 subtype receptor, responsible for the antihyperalgesic effects of gabapentin, may have inhibitory interaction potential with caffeine, reducing gabapentin’s effectiveness in pain relief.

(F) Reviews based on animal studies have suggested that the use of caffeine may increase the prevalence of seizures. A 2011 review indicated that data from experimental studies in animal models suggest that there may be a higher frequency of seizures if caffeine is ingested in large quantities. Additionally, caffeine may either decrease the electroconvulsive threshold by reducing the protective effects of certain antiepileptic drugs or reduce seizures at doses of 400 mg/kg of bodyweight in rodents. Another review of animal studies from 2018 suggested similar conclusions where the prevalence of seizures can either be increased or be protected against in the presence of caffeine. However, this depends on the timing, strength and duration of caffeine administration in relation to the stage of the seizure. In theory, increased susceptibility of seizures may be indicative of a reduction in the effectiveness of gabapentin, though human trials would need to be conducted to validate this potential interaction.

L-Tryptophan

Theoretically, an interaction may exist between L-tryptophan and gabapentin. L-Tryptophan is an amino acid that has sedative properties and that plays a role in neurotransmitter release, specifically serotonin. Gabapentin is absorbed by the L-amino acid transport system and can also induce sedative effects. Based on these similar effects, the co-administration of L-tryptophan with gabapentin may result in an additive effect. However, no evidence has been found supporting this theory or the mechanism of interaction specifically between L-tryptophan and gabapentin.

Some studies have shown that, similarly to gabapentin, L-tryptophan has an effect on sleep. A 1970 study examined the effects of L-tryptophan over ten consecutive nights in five healthy subjects and seven patients with insomnia. In the healthy subjects, L-tryptophan administration increased non-R.E.M. and delta wave sleep, while it decreased R.E.M. sleep. In comparison, total sleep and non-R.E.M. sleep increased in the group with insomnia. Another double-blind, crossover study conducted in 1985 tested mood and performance in 20 subjects receiving single oral doses of tryptophan, tyrosine, or a placebo. Tryptophan produced significant sedative effects. Subjects receiving tryptophan also reported decreased vigor and alertness, though it did not impair performance tests.
Kava

A theoretical interaction may exist between gabapentin and kava (Piper methysticum). Similarly to L-tryptophan, the interaction of kava with gabapentin may be a result of kava’s sedative properties and depressive effects in the central nervous system. Meta-analyses and randomized, double-blind, placebo controlled studies have also highlighted the use of kava in the treatment of anxiety.79, 93, 94, 129

While a theoretical relationship exists, there are currently no studies directly linking the mechanism of interaction between gabapentin and kava. However, caution has been recommended for the co-administration of kava and depressants of the central nervous system. A 2017 review of herbal supplements and drug interactions recommended caution when using kava with drugs that depress the CNS due to possible increased drowsiness and reduced motor-reflex.3 A study examining the effects of kava on driving found that the use of kava has been associated with a four-fold increased risk for serious injury in driving-related crashes.27 The World Health Organization (WHO) has also indicated that kava may have an effect on motor reflexes and the ability to drive and operate heavy machinery. They recommend that kava should not be taken for more than three months (even within recommended dosage ranges) without intermittent medical consultation.27

Insulin Glargine Injection (Lantus Solostar)

Research has demonstrated the possibility of a theoretical interaction between insulin glargine (Lantus Solostar) and berberine, as well as between insulin glargine and ethylenediaminetetraacetic acid (EDTA).

Berberine

While berberine can be used to reduce blood glucose, current evidence has only noted the possibility of a theoretical interaction between insulin glargine and hypoglycemic agents, such as berberine. However, as the occurrence of additive effects with insulin and hypoglycemic agents could be harmful and dangerous, extreme caution should be exercised, especially in the presence of type 1 diabetes.

(F) Clinical research suggests that berberine can lower blood glucose levels and plasma lipid profiles. While there are no human studies directly examining an interaction between the two, the hypoglycemic effects of berberine suggests that an interaction with insulin glargine could occur. To determine the potential mechanism and role of berberine in hepatic gluconeogenesis regulation, a study using mice was conducted. Reduction in fatty acid oxidation, inhibition of SIRT3 and degradation of MPC1 protein were observed following the administration of berberine, interfering with the supply of mitochondrial pyruvate needed for gluconeogenesis.55 A systematic review and meta-analysis demonstrated that berberine may be an effective therapy in the treatment of hyperglycemia associated with type 2 diabetes. It was also demonstrated that co-administration of berberine with oral medications used to lower blood glucose exhibited better glycemic control than the medications alone.22 Another study of 36 adults recently diagnosed with type 2 diabetes found that the administration of berberine lowered blood glucose levels similarly to metformin. A second trial of 48 adults with type 2 diabetes found that berberine administered for three months resulted in decreased HbA1c, fasting plasma insulin, HOMA-IR, LDL and total cholesterol when used in combination with other diabetic therapies such as sulfonylureas, metformin, acarbose or insulin therapy.134 Similarly, berberine has been shown to reduce glycemia and plasma cholesterol in patients with diabetes and metabolic syndrome. Decreases in BMI and waist circumference were also observed in patients with metabolic syndrome.127

Again, it is important to note, that though it has not been directly shown in the above literature, berberine and insulin may have potentially harmful additive hypoglycemic effects when used in combination. Extreme caution should be exercised when using insulin glargine with any hypoglycemic agents, especially in type 1 diabetes.

Ethylenediaminetetraacetic acid (EDTA)

A theoretical interaction may exist between EDTA and insulin glargine as EDTA binds to metals, which can increase the urinary excretion of zinc, a nutrient necessary for the production of insulin.9

(F) It has been theorized that intake of EDTA may lead to inadequate levels of zinc for insulin production. In a study with 16 patients, urinary excretion of metals was measured before and after an infusion of EDTA. Excretion of lead, zinc, cadmium, and calcium significantly increased as a result of the infusion.124 Similarly, a study recorded changes in the excretion of heavy metals in 18 male metal foundry workers following the administration of calcium disodium ethylenediamine tetraacetate (CaEDTA). Excretion of chromium, manganese, lead, and zinc were highest one to two hours after administration.92 Finally, it has been shown that EDTA binds to and increases the urinary excretion of metals. Excretion of iron and zinc increased most significantly.60
Levothyroxine (Levothroid, Synthroid)

In a 2017 review, authors listed a number of natural ingredients that may interact with levothyroxine, primarily through the modulation of its absorption. These include calcium, vitamin C, soy, coffee and iron.\(^{52}\) Grapefruit juice may also interact with levothyroxine.

Calcium

The interaction between levothyroxine and calcium has been well-documented. Multiple human studies in populations with hypothyroidism and euthyroidism have confirmed that administration of calcium can reduce the effects of levothyroxine due to decreased absorption, leading to decreased serum T3 and T4, increased TSH and increased thyrotropin.

(B) In a prospective cohort design, 20 patients using at least 1 μg/kg of levothyroxine for hypothyroidism were provided with 1200 mg of calcium (as calcium carbonate). Average T4 and total T4 levels were significantly reduced during co-administration and significantly increased after discontinuation. Average thyrotropin significantly increased during calcium administration and significantly decreased after discontinuation. There were no changes in average T3 levels. In their follow up in vitro study, the researchers suggested that calcium carbonate reduces the absorption of T4 in the acidic gastric environments and that this may reduce the bioavailability of levothyroxine.\(^{58}\) In another cohort study, 50 postmenopausal hypothyroid women being treated with levothyroxine received 600-1000 mg per day of calcium. TSH was significantly higher when calcium was ingested within two hours of levothyroxine administration compared to levothyroxine alone, or after delayed calcium intake.\(^{70}\)

(B) Co-ingestion of calcium also shows interaction potential with levothyroxine in relation to the absorption and bioavailability of thyroid hormones in healthy subjects. Eight healthy, euthyroid subjects participated in a study to determine the effects of three different forms of calcium on the absorption of 1 mg of levothyroxine. In independent and randomized trials, the absorption of levothyroxine decreased by 20–25% following co-administration with 500 mg of elemental calcium in the forms of calcium carbonate, calcium citrate, and calcium acetate. The magnitude of the effect was similar for each of the forms of calcium.\(^{135}\) In a study with seven subjects without thyroid disease, it was shown that the co-administration of 2 g of calcium carbonate with 1000 μg of levothyroxine significantly decreased total serum T4, free T4 and total T3 levels compared to administration of levothyroxine alone. The researchers found that the maximum average absorption of T4 was significantly reduced from 83.7% to 57.9% following calcium co-administration.\(^{29}\)

(D) A retrospective population analysis with 10,999 patients using levothyroxine over a six-month period found that the co-administration of calcium, significantly increased serum TSH concentration.\(^{61}\)

Vitamin C

Interaction potential exists between levothyroxine and vitamin C. Co-administration can increase the circulating blood concentrations of T4 and T3 and decrease TSH, possibly through the increased absorption of levothyroxine.

(B) In a study of 31 patients with hypothyroidism and a history of gastritis receiving levothyroxine (median dose of 100 μg), serum TSH, T4 and T3 were measured at the end of two-month intervals. After administration of 500 mg vitamin C, TSH significantly decreased in all patients (average decrease of 69%), T4 significantly increased in thirty patients, and T3 increased in all sixteen subjects for which it was measured. Serum TSH and T4 did not return to baseline after discontinuation of the treatment with vitamin C. The authors hypothesized that these effects were due to an improvement in levothyroxine solubility.\(^{46}\) Similarly, in a study with eleven subjects using levothyroxine (average dose of 2.24 μg/kg), serum TSH decreased significantly (average of 68.6%) after six weeks of receiving 1000 mg of vitamin C daily. The authors concluded that administration of vitamin C increased absorption of levothyroxine.\(^{46}\)

Soy

While there is some evidence to suggest that soy and its isoflavones do not appear to interact with levothyroxine directly, other studies show that soy isoflavones may increase TSH and decrease T4 levels. This would suggest a theoretical interaction potential between soy isoflavones and levothyroxine whereby the drug’s effects may be reduced.

(C) In a study examining the direct pharmacokinetics between soy isoflavones and levothyroxine absorption, it was determined that soy isoflavones do not appear to cause an interaction or impair absorption of levothyroxine. In a randomized, open label, crossover study with 12 healthy postmenopausal subjects already receiving levothyroxine treatment for hypothyroidism, participants were provided with a single 60 mg dose of soy isoflavones with their dose of levothyroxine. Soy isoflavone consumption was repeated again six hours after the initial levothyroxine administration. It was determined that the absorption of levothyroxine was not altered following the co-administration of soy isoflavones.\(^{19}\)

(F) Recent studies from 2017 using randomized, double blind, parallel designs show that there is also theoretical oppositional interaction potential with soy isoflavones as soy increases TSH and decreases free T4 (the opposite effect of levothyroxine). As these studies do not use levothyroxine in their design, interaction potential remains theoretical. In a study with 200 type 2 diabetic male participants, snack bars were provided containing either 15 g of soy protein with 66 mg of soy isoflavones, or 15 g of soy protein without soy isoflavones for three months. There was a significant increase in TSH and significant reduction in free T4 levels in the soy isoflavone group.\(^{90}\) In another study with a similar methodological design, 200 menopausal women consumed either 15 g of soy protein with 66 mg of soy isoflavones, or 15 g of soy protein without soy isoflavones for six months. It was determined that soy isoflavones caused a significant increase in TSH and significant reduction in free T4 levels in the soy isoflavone group.\(^{91}\)

Coffee

There is potential for interaction between coffee and levothyroxine, though randomized control trials need to be conducted for improved evidence. A theoretical interaction may also exist between constituents of coffee and thyroid hormones, though this evidence is both scarce and conflicting. Based on available evidence, coffee may reduce intestinal absorption of thyroxine (T4) and increase TSH when levothyroxine is ingested in tablet form. Research suggests that soft gel forms may be an alternative solution to maintain bioavailability if patients do not wish to abstain from taking levothyroxine with coffee.
Studies suggest that there may be interaction potential between levothyroxine and coffee, limiting drug absorption when ingested simultaneously, especially when levothyroxine is in tablet form. A review of *in vitro* and *in vivo* studies examined the potential interaction between coffee and ingested thyroxine (T4). *In vivo* human studies demonstrated that coffee lowered average and peak incremental rise of serum T4 and delayed time of maximal incremental rise of serum T4 compared to water after ingestion of T4. This indicates that coffee interferes with the intestinal absorption.

Another study, with eight patients who had been using levothyroxine in tablet form was conducted to determine whether switching to a softgel would alter malabsorption associated with coffee. TSH levels were significantly higher in the tablet trials when ingesting coffee right away compared to one hour later, but there were no significant differences in TSH within the softgel trials. Also, TSH levels were significantly higher when ingesting levothyroxine with coffee in the tablet trials compared to softgel trials. The researchers suggest that softgel forms of levothyroxine may be preferable if patients do not wish to avoid consuming coffee.

Another study was conducted using a liquid form of levothyroxine. With 54 patients, it was shown that there were no significant differences in TSH, T3 or T4 concentrations when it was consumed at breakfast with coffee or when it was consumed without coffee before breakfast over both three and six month durations. The researchers thus suggest that liquid administration may reduce coffee’s effect on the malabsorption of levothyroxine.

**Iron**

An interaction potential between iron and levothyroxine has been demonstrated where co-administration may decrease the bioavailability of levothyroxine and may increase serum TSH. Randomized clinical trials need to be conducted in order to further validate this interaction potential.

The co-administration of iron can significantly increase the plasma concentrations of TSH, suggesting that iron may decrease the bioavailability of levothyroxine. In an uncontrolled clinical trial, 14 subjects began ingesting 300 mg of ferrous sulfate along with their normal daily dose of thyroxine for 12 weeks. Serum TSH levels rose significantly, while free thyroxine index did not change. In a follow up *in vitro* study, it was determined that iron and thyroxine bind together when co-administered. The researchers ultimately suggested that the efficacy of thyroxine decreased due to the binding of iron to the drug, resulting in a less soluble complex.

Furthermore, a retrospective population analysis study that included 10,999 patients using levothyroxine over a six month period found that the co-administration of iron significantly increased serum TSH concentration in subjects using levothyroxine.

**Grapefruit Juice**

Grapefruit juice (Citrus paradisi) has been shown to have a small but significant effect on the absorption of levothyroxine, though studies on the direct interaction between grapefruit juice and levothyroxine are limited.

In a randomized, two-phase, cross-over study, ten subjects were provided with grapefruit juice or water three times daily for two days. Levothyroxine (600 μg) was then provided with grapefruit juice or water on the third day. The maximal concentration and AUC (0, 6h) of T4 was slightly but significantly decreased by grapefruit juice. However, grapefruit juice had no effect on the decreased concentration of TSH, 24 hours after drug administration. Although the effect was small, the authors concluded that grapefruit juice may delay the absorption of levothyroxine.
**Metformin (Glucophage)**

Although the mechanisms are not fully understood, there is a potentiating interaction potential between metformin and berberine, which are both hypoglycemic agents. Additionally, a theoretical additive interaction potential exists between metformin and alcohol, especially in populations with diabetes, though controlled human studies have not been found to validate this relationship.

While metformin is not metabolized by the liver, transporters and other enzymes are involved in its absorption and excretion, as well as in exerting the drug’s effects on the body.

Upon ingestion, metformin is transported into the intestinal cells by Plasma Membrane Monoamine Transporters (PMAT) and Organic Cation Transporters (OCT) 3. From the intestinal cells, metformin is transported into the blood via OCT 1, where it then circulates throughout the body before absorption into the liver, kidney or muscle cells. OCT 1 and OCT 3 are the transporters involved in transporting metformin into the liver from the blood to inhibit gluconeogenesis. Within the liver, the drug may be eliminated from the body by the Multidrug And Toxin Extrusion (MATE) protein 1, though this does not appear to be in significant amounts. Metformin’s main route of excretion occurs after it is transported from the blood into the kidney via OCT 1 and OCT 2. Once metformin enters the kidney, MATE 1 and MATE 2 are responsible for transporting the drug into the urine for excretion, ultimately decreasing metformin’s systemic blood concentration over time.29

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Figure 1. Mechanism of metformin action in the body
**Berberine**

While the mechanism is not fully understood, a 2018 review suggests there is evidence of a potentiating interaction between berberine and metformin.\(^\text{10}\)

**B** A possible additive interaction between berberine and metformin has been demonstrated in human trials. The combination of 500 mg of berberine and metformin can lead to improved insulin sensitivity, and decreased HOMA-IR, total cholesterol and LDL cholesterol compared to either agent alone in patients with type II diabetes. In trial A of a pilot study, 36 subjects randomly received either 500 mg of berberine before each meal or 500 mg of metformin following each meal for 13 weeks. In trial B, 48 subjects already being treated with diet plus sulfonylureas, acarbose, insulin therapy or metformin were also then provided with 500 mg of berberine before each meal. When berberine caused heavy gastrointestinal distress, the dose was reduced to 300 mg. Groups in both of the trials experienced similar improvements in glycemic measures (HbA1c, fasting blood glucose, postprandial blood glucose), though combination therapy also improved insulin sensitivity with a 50% decrease in HOMA-IR. Berberine alone also reduced total cholesterol significantly, while combination therapies decreased both total cholesterol and LDL-C.\(^\text{14}\)

**D** Other studies have examined the mechanisms through which a possible potentiating interaction between metformin and berberine may occur. Evidence suggests that interactions may be through the modulation of the transporters involved in metformin and berberine uptake from the blood and in their excretion. In an in vitro and in vivo study using human kidney cells and rats, respectively, it was determined that co-administration of a single dose of berberine inhibited OCT1 and OCT2 uptake of metformin. In vitro, there was a concentration-dependent relationship between the inhibition of OCT1 and OCT2. In vivo, rats received intravenous co-administration of 2 mg/kg of metformin and 10 mg/kg of berberine. Results showed increased bioavailability, decreased systemic clearance and decreased volume of distribution of metformin. It was suggested that this was due to the interference of OCT1 and 2 in the kidney.\(^\text{52}\) A 2019 in vivo study with rats also found that the co-administration of berberine decreased maximum plasma concentration, AUC, kidney concentration, and urinary and biliary excretion of metformin. In the non-everted intestinal sac portion of the study, the absorption and transportation of metformin was inhibited by berberine in rat kidney OCT1, OCT2, and MATE1. In comparison, maximum plasma concentration and AUC of berberine was increased with the concurrent administration of metformin, but with no significant difference with the berberine-only group. Kidney and liver concentrations of berberine were increased with the co-administration of metformin while urinary and biliary excretion was decreased. In the non-everted intestinal sac study, metformin decreased berberine transport in OCT1, OCT2, and MATE1. However, metformin did not decrease berberine concentration in MATE1.\(^\text{16}\)

**E** Despite the mechanism of action of metformin with respect to AMPK,\(^\text{28}\) studies have also suggested that the interaction between metformin and berberine may be independent of AMPK. In an in vitro mechanistic study using human hepatoma cells and mouse myotubular cells, it was shown that berberine increased glucose consumption and lactate release significantly, with and without the presence of AMPK phosphorylation. Metformin similarly increased glucose metabolism. When AMPK was inhibited, other mechanisms still led to increased glucose consumption in the presence of berberine or metformin. The authors indicate that this may have been due to the inhibition of mitochondrial respiratory chain complex I, leading to the associated decrease in ATP synthesis and increase in lactate release.\(^\text{12}\) Another in vitro study using rat L6 Microtubules showed that administration of berberine increased uptake of 2-deoxyglucose (2DG) in a time- and concentration-dependent manner. Co-administration of berberine with metformin increased the maximal uptake 4.1 times the amount from baseline. It was also noted that administration of berberine increased expression of GLUT4 receptors and the PPAR-gamma gene.\(^\text{81}\)

**F** As metformin plays a role with AMPK,\(^\text{29}\) a theoretical interaction may also be suggested since evidence shows that berberine may induce an increase in AMPK modulated lipid metabolism, as well as glucose production, uptake and use. In an in vitro study using human hepatoma cells, as well as in an in vivo study with hyperlipidemic hamsters, it was determined that administration of berberine to human cells resulted in the inhibition of cholesterol and triglyceride synthesis. The study also noted significant increases in AMPK activity and phosphorylation. Similarly, administration of 100 mg of berberine per kg of body weight significantly reduced serum LDL-C, fat storage in the liver and free fatty acid levels in hamsters. This was correlated with the phosphorylation of acetyl-CoA carboxylase, a substrate of AMPK.\(^\text{11}\)

In contrast to aforementioned studies, other research may indicate that the theoretical interaction between metformin and berberine may be difficult to achieve with acute oral administration of berberine. It has been contended that acute administration of oral berberine may not increase bioavailability enough to stimulate an interaction with other drugs in vivo due to its inefficient absorption from the gastrointestinal tract. A dose of 500 mg of berberine can produce 0.07±0.01 nM in plasma berberine, whereas chronic administration of berberine at 15 mg/kg of body weight can result in measures of berberine as high as 4.0±2.0 nM, suggesting that it may have a potential accumulatory effect in vivo. However, the researchers question whether these low concentrations will have a clinically relevant effect.\(^\text{19}\)

In summary, it appears that berberine may have a synergistic effect with concurrent administration with metformin, and that 300 mg three times per day of berberine is well-tolerated. Additionally, metformin and berberine seem to play similar roles on glucose and lipid regulation, however, there is possible competitive inhibition for one another with respect to their transporters responsible for uptake from the blood. There may also be differences in transporter inhibition when co-administration occurs orally versus intravenously. The inhibition of uptake and excretory transporters may offset the associated increases or decreases in blood concentration of the drug if these transporters are simultaneously inhibited. It is postulated, however, that the combination of berberine and metformin may improve the oral bioavailability of berberine and possible side effects of metformin or berberine alone.\(^\text{19}\)
Alcohol

Although the exact mechanism(s) are not fully understood, alcohol is believed to interact with a variety of drugs. Researchers have started to investigate potential interactions with metformin, especially with regard to the risk involved with diabetes. Literature seems to be indicative of a theoretical interaction between metformin and alcohol, mainly through the possible induction of hypoglycemic effects, though some evidence may suggest otherwise.

(F) A number of studies have indicated that alcohol consumption induces hypoglycemia in both healthy subjects and in patients with type 1 diabetes. A review similarly suggested that the co-administration of alcohol with other agents that reduce blood sugar can increase the risk of hypoglycemia, and may have important implications especially in diabetic populations, while a cross-sectional stratified survey showed that 13.3% of respondents ‘at-risk’ (self-reported consumption of greater than seven drinks per week) of drug interactions reported using metformin. The authors discuss that metformin’s effects may be further induced by alcohol, which can lead to hypoglycemia in diabetic populations, as well as increase lactate metabolism and, in rare cases, lactic acidosis. Taken as a whole, the British and American Diabetes Associations have recommended that diabetic individuals abstain from any more than one alcoholic beverage per session.

(F) In comparison, there is a little evidence to suggest that a theoretical interaction between alcohol and metformin may not be of any significance, at least in populations with type 2 diabetes. The acute and chronic administration of wine in moderation did not lead to hypoglycemic outcomes. However, chronic alcohol consumption increased serum insulin levels in 18 patients with type 2 diabetes. From this study, the researchers concluded that using alcohol in moderation may be safe for people with type 2 diabetes.

(F) Two in vitro studies, using mouse myocytes and myoblasts, present some evidence of a possible theoretical interaction between alcohol and metformin through the modulation of the AMPK pathway responsible for protein synthesis. Researchers found that administration of ethanol increased AMPK activity and that this would ultimately contribute to a decrease in protein synthesis through greater phosphorylation of downstream enzymes (including them) involved in upregulating protein synthesis. As previously discussed, metformin phosphorylates and also activates AMPK, and thus a theoretical potentiating interaction may exist.

Omeprazole (Prilosec, Zegerid)

Current evidence demonstrates interactions between omeprazole and St. John’s Wort and between omeprazole and grapefruit juice. A theoretical interaction also exists between omeprazole and cannabis.

St. John’s Wort

St. John’s Wort (Hypericum perforatum), a well-studied botanical used in the treatment of depressive symptoms, has been used in conjunction with various pharmaceutical treatments to potentiate or reduce the effects of specific drugs.

(C) Evidence has shown that St. John’s Wort can reduce the effectiveness of omeprazole. In a two-phase, randomized crossover study, twelve healthy subjects were genotyped for CYP2C19, a cytochrome responsible for the metabolism of omeprazole. Participants were provided with either placebo or 300 mg of St. John’s Wort three times per day for 14 days. Participants then ingested a single 20 mg of omeprazole. Compared with control, the treatment with St. John’s Wort significantly reduced plasma concentrations of omeprazole and increased plasma concentrations of omeprazole metabolites through the CYP3A4-sulfoxidation and CYP2C19-hydroxylation of omeprazole. This demonstrates that St. John’s Wort can reduce the effectiveness of omeprazole. In a follow up study also using a two-phase, randomized, crossover design, six participants considered ‘extensive metabolizers’ of CYP2C19 and six ‘poor metabolizers’ all either received placebo or 300 mg of St. John’s Wort three times per day for 14 days. Cytochrome activity was measured using mephentoin and caffeine. It was determined that St. John’s Wort significantly increased CYP2C19 activity in the extensive metabolizers, while there was no significant change in metabolites with the poor metabolizers as seen through measures of metabolites in excreted in urine. The authors indicate that St. John’s Wort can decrease the effectiveness of drugs through the inducing interaction with CYP2C19.

(E) The interaction between St. John’s Wort and omeprazole may also be attributed to its effects on CYP3A4, a cytochrome involved in the metabolism of omeprazole. Hyperforin, one of the main phytochemicals found in St. John’s Wort, may play a large role in the induction of the CYP3A4 pathway, and may, therefore, interact with omeprazole. Evidence has shown that St. John’s Wort can reduce the effectiveness of omeprazole. In a two-phase, randomized crossover study, six participants considered ‘extensive metabolizers’ of CYP2C19 and six ‘poor metabolizers’ all either received placebo or 300 mg of St. John’s Wort three times per day for 14 days. Cytochrome activity was measured using mephentoin and caffeine. It was determined that St. John’s Wort significantly increased CYP2C19 activity in the extensive metabolizers, while there was no significant change in metabolites with the poor metabolizers as seen through measures of metabolites in excreted in urine. The authors indicate that St. John’s Wort can decrease the effectiveness of drugs through the inducing interaction with CYP2C19.

(E) The interaction between St. John’s Wort and omeprazole may also be attributed to its effects on CYP3A4, a cytochrome involved in the metabolism of omeprazole. Hyperforin, one of the main phytochemicals found in St. John’s Wort, may play a large role in the induction of the CYP3A4 pathway, and may, therefore, interact with omeprazole. Hyperforin has been shown to activate the Pregnane X Receptor in vitro, ultimately inducing the CYP3A pathway in response to exposure to foreign substances. This interaction may be dose-dependent as products that contain small dosages of hyperforin (less than <1 mg daily), are less likely to demonstrate major interactions with CYP3A4 substrates (i.e., omeprazole). Further supporting a dose-dependent relationship between hyperforin and CYP3A, a systematic review found that high concentrations of hyperforin (>10mg/day) resulted in induction of CYP3A4, whereas low-doses (<4mg/day) had no significant effect. In contrast, another in vitro model using human liver microsomes found CYP3A4 to be potently inhibited by hyperforin.

(E) Hypericin, another main phytochemical found in St. John’s Wort, is believed to increase p-glycoprotein (P-gp) expression, upregulating efflux function. In an in vitro study using human Caco-2 cells and L-MDRI cells, omeprazole showed specificity to the P-gp transporter. However, inhibition of P-gp did not significantly alter omeprazole transport, indicating that omeprazole is also transported by other proteins.
Grapefruit
Grapefruit (Citrus paradisi) juice is suggested to play a role in many drug interactions through the inhibitory effects of its constituents on the CYP3A4 cytochrome. An in vivo randomized crossover study was conducted with 13 healthy subjects that had fasted overnight to determine whether ingestion of grapefruit juice with orally administered omeprazole (20 mg) would have any effect on the drug’s metabolism. Blood samples were taken to measure omeprazole concentrations, as well as those of two of its major metabolites, 5-hydroxyomeprazole and omeprazole sulphone. Grapefruit juice caused a significant decrease in omeprazole sulphone, but not 5-hydroxyomeprazole, though the half-life for either metabolite was not affected. This suggests that grapefruit juice may inhibit intestinal CYP3A4, but not hepatic CYP2C19, as CYP2C19 primarily metabolizes omeprazole into 5-hydroxyomeprazole, while omeprazole sulphone is mainly yielded by CYP3A4. Additionally, it is suggested that grapefruit juice inhibits the metabolism of omeprazole rather than increases its excretion as the half-life of its metabolites did not change (i.e. there was no change in the rate of excretion).

In a review on a variety of drugs, including omeprazole, it was discussed that grapefruit juice interacts with the CYP3A family, where even prior exposure to grapefruit juice can be significant enough to cause a possible interaction. Enteric recovery half-life following the singular exposure to grapefruit juice is estimated to be 23 hours, whereas complete recovery may be achieved after three days. As grapefruit juice inhibits CYP3A at the enteric level, intravenous administration of drugs will not prolong the systemic exposure to a drug (i.e. the drug would need to be administered orally for any interaction to occur).

Cannabis: CBD and THC
Cannabidiol (CBD) and tetrahydrocannabinol (THC) are two of the main cannabinoids found in cannabis. Both CBD and THC are metabolized by cytochromes of the P450 family in the liver, and may, theoretically, result in an interaction between CBD/THC and omeprazole.

Although some studies have shown that CBD and THC are metabolized by CYP2C19 and CYP3A4, there is conflicting evidence. A 2017 review of cannabis highlighted that in vitro studies have shown that both CBD and THC are metabolized by the cytochrome P450 family, and can inhibit a number of liver cytochromes including CYP1A1, CYP1A2, and CYP1B1. CBD specifically can significantly inhibit CYP2C19 and CYP3A4, which as previously discussed, are primarily involved in the metabolism of omeprazole. Theoretically, as cannabinoids can be metabolised and can inhibit cytochromes that are involved with other drugs, potential interactions may occur.

In an in vitro study, it was indicated that CBD potently inhibited CYP2C19 activity and that a phenolic hydroxyl group and the pentyl side chain of CBD may be needed to inhibit the cytochrome. It was suggested that under these conditions, potential interactions between CBD and drugs that are metabolized by CYP2C19 may occur. Another review provides similar indication of the metabolic pathways of the hydroxylation of phytocannabinoids (via CYP2C9, CYP2C19 and CYP3A4), where CBD is the most potent inhibitor of these cytochromes. A possible mechanism in the alteration of cytochrome expression and activity may be due to the activation or inhibition of the nuclear receptors responsible for regulating CYP pathways in the liver. It is noted however, that the clinical relevance of this inhibition is unclear.

Conversely, in an open-label, randomized, crossover design, 36 healthy subjects were divided evenly into three groups and given CYP3A and CYP2C19 inducer rifampicin (600 mg), the CYP3A inhibitor ketoconazole (400 mg) or the CYP2C19 inhibitor omeprazole (40 mg), along with four sprays of THC/CBD spray (10.8mg/10mg, respectively). Each group was treated with THC/CBD alone, followed by rifampicin, ketoconazole, or omeprazole alone, and then in combination (respective to their drug group) throughout the first trial. This sequence was then altered in the second trial where each group was treated with their respective drugs alone, then in combination with THC/CBD, and then with just THC/CBD alone. Blood samples were taken to measure concentrations of CBD, THC and the 11-hydroxy-THC metabolite. Unlike rifampicin and ketoconazole, omeprazole did not show any changes in blood concentration for CBD, THC or the THC metabolite when administered with the THC/CBD spray, though clearance of only the THC metabolite increased. These results suggest that CBD, THC and the THC metabolite are not substrates of the CYP2C19 cytochrome, but are for CYP3A4.
Rosuvastatin (Crestor)

Research has demonstrated interaction potential between rosuvastatin and grapefruit, and rosuvastatin and green tea. An interaction may also exist between rosuvastatin and St. John’s Wort, as well as between rosuvastatin and sweet orange.

Grapefruit

Grapefruit (Citrus paradisi) juice is suggested to play a role in many drug interactions, through the inhibitory effects of its constituents on the CYP3A4 cytochrome. Rosuvastatin is not metabolized by CYP3A4 to a significant extent, and its blood concentration does not increase significantly in response to CYP3A4 inhibition.

However, a theoretical interaction between grapefruit juice and rosuvastatin exists as grapefruit juice is also suggested to be a strong inhibitor of OATP2B1 and OATP1B1, and rosuvastatin has been shown to be a substrate for both OATP2B1 and OATP1B1.

(C) Grapefruit has been shown to inhibit OATP2B1 in vivo and in vitro. In a 2017 study, 23 healthy subjects received small doses of five drugs: rosuvastatin, sulfasalazine, glibenclamide, celiprolol, and sumatriptan, along with atorvastatin (10mg), water, or grapefruit juice (200ml, 3x/day after meals). Grapefruit juice exerted an inhibitory effect on OATP2B1 regardless of genotype and decreased the bioavailability of the five drugs, other than atorvastatin. These results have also been supported in vitro using xenopus oocytes, where OATP2B1 was shown to be mainly inhibited by naringin, a flavonoid in grapefruit, through decreased uptake of an OATP2B1 substrate, estrone-3-sulfate.

(F) Grapefruit has also been shown to play a role with OATP1B1 in the intestine, which can hypothetically exert an inhibitory effect on the uptake of rosuvastatin into hepatocytes. In an open-label, single dose, randomized, two-phase crossover clinical study, 12 healthy male subjects received 2 mg of pitavastatin orally with water or with grapefruit juice. Following the statin ingestion, there were differences in increases in blood concentration of the of pitavastatin acid and lactone metabolites between genotypes of OATP1B1. However, there were no differences in the small but significant increase in metabolite concentration between genotypes when grapefruit juice was administered.

While Rosuvastatin is a substrate of OATP1A2, a 2010 review indicated that at the time, there had been no report of studies indicated altered bioavailability of rosuvastatin with co-administration of grapefruit through OATP1A2 mediated transport.

Green Tea

Green Tea (Camellia sinensis) has two main constituents: epigallocatechin gallate (EGCG) and epicatechin gallate (ECG). EGCG has been shown to have interaction potential with rosuvastatin as it can significantly decrease the systemic exposure of the drug when it is co-administered in vivo. This effect may be attributed to the inhibition of OATP2B1 or OATP1A2. In vitro evidence also exists to support interaction potential through the inhibition of OATP1B1 and OATP1B3, as rosuvastatin is a substrate of OATP2B1, OATP1B1, OATP1B3 and OATP1A2.

(C) In a 2017 clinical trial investigating the interaction potential between EGCG and rosuvastatin, green tea extract decreased systemic exposure of rosuvastatin. In an open-label, three-treatment, fixed-sequence study, 11 female subjects were provided with 20 mg of rosuvastatin on day 1, both 300 mg of EGCG and 20 mg of rosuvastatin on day 4, only 300 mg of EGCG over the next nine days, and both EGCG and rosuvastatin on day 15. It was suggested that the 19% decrease in systemic exposure to rosuvastatin following co-administration was a result of the inhibition of OATP2B1 or OATP1A2 uptake in the intestine. There was no change in the degree of increased systemic exposure of rosuvastatin even with prolonged pretreatment. It was noted, however, that the concentration of the EGCG provided in this study is approximately double the concentration found in a cup of green tea and that the inhibitory effects of the pure extract may have different effects than green tea itself.

(E) EGCG and ECG have also been shown to inhibit OATP1B1 AND OATP1B3 transporters in vitro, allowing for interaction potential with rosuvastatin. In a study using human embryonic kidney cells, green tea inhibited transport of atorvastatin via OATP1B1 and OATP1B3 in a concentration dependant relationship by inhibiting the transporters. Another study showed that EGCG and ECG are substrates of OATP1A2 and OATP1B3, but are not transported by OATP1B1 or OATP2B1 in human enterocytes and hepatocytes. In this study, OATP1B3-mediated transport of ECG and EGCG was found to be substrate-dependent and could cause noncompetitive inhibition or stimulation of transport activity. It was postulated that consuming one to two cups of green tea on an empty stomach would contain adequate concentrations of ECG and EGCG to alter OATP mediated transport of their substrates.
St. John’s Wort

St. John’s Wort (Hypericum perforatum) has been used in conjunction with various pharmaceutical treatments to potentiate or reduce the effects of specific drugs. While there are no studies directly examining the interaction between St. John’s Wort and rosuvastatin, human studies have evaluated the effects of St. John’s Wort on CYP2C9. CYP2C9 has been shown to be the cytochrome responsible for rosuvastatin metabolism. Thus, theoretically, there is the possibility of a theoretical interaction, though based on current evidence, this does not appear to be the case. Based on two studies, it does not appear that there are any significant interactions between St. John’s Wort and the CYP2C9 cytochrome. In a fixed-schedule study of twelve healthy subjects, neither the initial administration of a 900 mg dose of St. John’s Wort, nor the longer term administration of St. John’s Wort (300 mg three times per day for two weeks), had any effect on CYP2C9 activity. In another study with nine healthy subjects with a genotype expressing active CYP2C9 and four subjects with a genotype expressing low activity for CYP2C9, patients were provided with Bosentan (a drug metabolised by CYP2C9) for 20 days along with St. John’s Wort (300 mg/day) for the final 10 days. CYP2C9 activity was not altered during or after exposure to St. John’s Wort in either group of subjects.

Sweet Orange

No evidence was found demonstrating a specific interaction potential between sweet orange with rosuvastatin in humans. However, constituents of orange juice have been theorized to have possible inhibitory effects with OATP2B1 in the small intestine. In vitro studies have demonstrated a theoretical relationship between rosuvastatin and the OATP2B1 transporter, as well as between sweet orange and OATP2B1. One study showed that while OATP2B1 mediated transport is significant for atorvastatin at a neutral pH, substrate specificity and OATP2B1 activity increased in a more acidic pH. OATP2B1 inhibition was unattainable at a pH of 6.0. Other substrates of the OATP2B1 were primarily modulated by the presence of a proton ionophore. In connection, it has also been shown that after exposure to orange and grapefruit juices with a pH of 7.4, there was decreased uptake of glibenclamide, another OATP2B1 substrate, in human intestinal epithelial cells. In a 2010 review, researchers concluded that orange juice may possibly have clinically relevant inhibition of OATP2B1. However, it was also stated that inhibition of OATP1B1 with orange and other juices is improbable.

References


