Review Article

A Review on Influence of Herbal Products on CYP3A4 and CYP2D6 Isoenzyme Inhibition

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Received: 15-09-2022; **Revised:** 23-11-2022; **Accepted:** 30-11-2022; **Published on:** 15-12-2022.

ABSTRACT

Cytochrome P450 (CYP) enzymes belong to the superfamily of haem proteins, which plays a major role in metabolism of both exogenous as well as endogenous compounds. Drug metabolism takes place at different locations like liver, lungs, kidneys, intestine and plasma. The major site for drug metabolism is liver. Drugs are metabolized mainly by phase-I and phase-II reactions, and finally they can convert the compounds from lipophilic form to hydrophilic form to enhance its excretion. Not only in metabolism but also play a major role in systemic regulation of concentrations of progesterone and corticosteroids, which take part in mood swings and sleep- wake cycles. Cytochrome enzymes are mainly involved in phase-I metabolic reactions like oxidation, reduction or hydrolysis. The concurrent use of herbal products and synthetic drugs are more prevalent in this present era, this particularly leads to drug-herb interactions. Cytochrome enzymes are more vulnerable to multiple active constituents that are present in these herbal products. The net effect is either induction or inhibition of microsomal enzymes. Which may lead to pharmacokinetic or pharmacodynamic interactions. Cytochrome enzymes are classified into several subclasses, among which CYP3A4, CYP 2D6 will play a major role in metabolizing most of the drugs and other xenobiotics. Inhibition of these isozymes leads to drug toxicity in the body. Thus, the present study summarizes and gives knowledge about some herbal drugs and their inhibitory effect on Cytochrome isozymes like CYP3A4, CYP2D6. This review mainly focuses on giving awareness to the practitioners as well as people regarding dose adjustment of particular synthetic drugs when they are administered concurrently with herbal products.

Keywords: CYP P450, CYP3A4, CYP2D6, Metabolism, Herbal products, Drug- herb interactions, Therapeutic index.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2022.v77i02.017

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v77i02.017

INTRODUCTION

As most of the drugs are metabolized in the liver by enzymes, Cytochrome P450 (CYP) is one of the major liver enzymes responsible for many reactions like phase-I and phase-II, these enzymes are membrane-bound consisting of heme protein which functions as mono-oxygenase, where it actions by detoxification.[1] The CYP system present in the liver has a chief role in various medical disorders, dietary advantages and xenobiotic toxic effects; it is helpful to understand and treat many pathological processes linked with liver infection. Also, in the fetus, the CYP subfamily has its activity represented in the liver and brain which impacts drug metabolism in the fetus.[2] Moreover, studies in recent times have found the new effective property of CYP not just in drug metabolism as well as in some infections such as inflammation and illness which is complementary to the hepatic and extrahepatic conversion of drugs also with which various iso-forms are useful in systemic regulation on the concentration of progesterone and corticosteroids, that take part in mood swings and sleep- wake cycles.[3]

The isoforms of CPY are classified into different families which exert specific action depending on the binding activity of distinct chemical compounds. In humans, the number of CYP families are 18 with 43 subfamilies. Among these, on the basis of their activity, 5 CYP enzymes were known to have extensive action. Those are CYP1A (Subfamilies-CYP1A1 and CYP1A2), CYP2A(subfamily-CYP2A6), CYP2C (subfamilies-CYP2C8, CYP2C9, CYP2C18 and CYP2C19), CYP3A (Subfamilies-CYP3A4, CYP3A5 and CYP3A7), CYP2D (Subfamily-CYP2D6) and CYP2E1.[1] The functions of each isoform can vary from each other as, in aged individuals, the production of estrogens is said to be primarily done by CYP2C19. However, the majority of the chemical compounds are specific to CYP3A4 and CYP2D6, due to their abundance and specificity to a more chemical entity, inhibition of this isozyme is medically used for most disorders in order to increases the plasma concentration of a particular drug which eventually increases the half-life and helps in dose reduction.

Thus, depending on the binding substrate to CYP, its activity can be altered either by inducing or inhibiting. Inducer increases the activity of CYP which will eventually speed up the oxidation and elimination of that specific drug, wherein the Inhibitors retards the activity of CYP on its inter-action with the binding sites of CYP. The inhibitory

action corresponds with half-life of certain drugs by increasing the presence of drugs in the plasma for a longer time.

Cytochrome P450 activity is also modulated by several herbal drugs. Some of the plant constituents are considered to modulate xenobiotic metabolism and transport systems which play a crucial role in the absorption and deposition of API (active pharmaceutical ingredient).

Physiological improvement in both healthy and ill-conditioned individuals have seen to be effective by FOSHU (Food for Specified Health Uses) foods which have nutritive value, yet these foods have not been effectively chosen by the consumers as of less satisfaction even on the advertisement (in some cases). Apart from this, there are some reports on the adverse effects of these foods depending on person to person.[4,5] After all the researchers have noted that the alteration of hepatic function is not just due to conventional drugs but also from herbal supplements that have the potential to interact with specific enzymes to reframe it from its action. Example: The hepatic cells containing microsomes on binding with green tea (widely used beverage) inhibits the specific isozyme of CYP that is CYP2C9, CYP2D6, CYP3A4.[6] An herb-drug interaction can exhibit devastating effects on the body commonly when the drug is of low Therapeutic index. If the herb strongly shows inhibitory action on the CYP enzyme, even though the pharmacological effect will be enhanced but consequences in the retainment of the drug in the body for a longer period of time can be toxic if not eliminated therefore it is very essential to have adequate knowledge before co-administering herb and drug together.

Some of the conventional drugs that are showing cytochrome enzyme inhibition are cimetidine, isoniazid, erythromycin etc. Inhibition of these enzymes when co-administration of conventional drugs is appreciable for drugs having higher therapeutic index because the availability of the drug at the receptor site increases thereby prolonged pharmacological action exhibited. But this effect is not appreciable in the case of lower therapeutic index drugs, because transcription of new enzyme proteins (CYP) can take longer time thus accumulation of unmetabolized (parent) drugs will lead to adverse effects for the patients. Thus, some herbal products are useful in reducing the risk factor caused by the co-administration of conventional drugs. The importance of herbal products is to essentially have quick reversible activity from the cytochrome enzyme binding site. However, there are chances of drug interactions on herbal drugs with conventional drugs, and the appropriate knowledge of the pharmacokinetics of drug-drug interactions can be a useful tool.[7]

Thus, in this review article, mainly concentrated on the plants with its chemical constituents that are responsible for inhibition of the CYP3A4 and CYP2D6 isoenzymes which will lead to herb-drug interaction and hence leads to alterations in the therapy.

INHIBITORY EFFECTS OF HERBAL PRODUCTS ON CYP 3A4

The abundant number among all CYP's said to be the CYP3A family, consisting of 5 major subfamilies- 3A3, 3A4, 3A5, 3A43, 3A7.[7] Among which CYP3A4 is predominant and chiefly located on the liver cells and small intestine (in the duodenum). These enzymes are encoded with protein sequence which is represented on chromosome 7 as a cluster to form the CYP3A4 gene with more than 30 alleles of which some are functional and some are non-functional. CYP3A4 is known to have a principal role in the conversion of drugs from lipophilic to hydrophilic form which helps in the effective excretion of drugs. About 50% of modern drugs are metabolized by CYP3A4.[1]

Herbal medicine that possesses inhibitory action on CYP3A4 was studied for a quite long time and some research works have shown positive results which include

Grapefruit

Grapefruit Juice is a very useful herbal remedy for various treatments like skin disease, high cholesterol, and cancer. The juice contains constituents like flavonoids, carotenoids and coumarins which are responsible for these pharmacological actions. The constituents of grapefruit responsible for CYP3A4 inhibition are coumarins (furanocoumarins) and 5 key substituents of coumarin in grapefruit are umbelliferone, bergapten, bergamottin, 6',7'-dihydroxybergamottin (DHB) and Epoxy-bergamottin. Among these only epoxy-bergamottin showed potent inhibition, while bergamottin and DHB were the main compounds for the grapefruit effect and bergapten and umbelliferone had very weak effects on inhibition. Furanocoumarin (FC) has inhibitory actions at high levels and gives additive effects to other compounds. The studies of new grapefruit cultivars exhibiting low CYP3A4 - Inhibition activity reported that fresh grape juice on rat liver microsomes had significant CYP3A4 inhibitory action, specifically on Fluorogenic substrate binding site due to furanocoumarins. Moreover, new low - Furanocoumarin grapefruit cultivars were safe and didn't exhibit herb-drug interaction.[8,9]

Black cohosh

Scientifically called *Cimicifuga racemosa* is a dietary supplement which was used in Chinese medicine to treat menstrual problems mainly during menopause. The rhizome of this plant contains 3 main Phytochemicals- Fukinokic acid, Cimicifuga acid and triterpene glycosides recorded to have altered CYP3A4 activity by retarding metabolic activity at that site. The paperwork "Fukinolic acid derivative and triterpene glycosides from black cohosh inhibit CYP isozymes, but are not cytotoxic to Hep-2 cells invitro". In this work, the ethanolic extract of black cohosh rhizome has reported a concentration-dependent inhibitory effect of the extract on CYP3A4, where Fukinokic acid and cimicifugic acid were the vital phytochemical

constituents responsible for enzyme inhibitory action and triterpene glycosides have proven for weak enzyme inhibitory action.[10,11]

Green tea

It is a traditional Japanese beverage enjoyed by many for a long time, consumption of green tea has increased recently due to its various benefits. Catechin, a polyphenol derivative of flavonoids, is a major constituent in green tea and responsible for many pharmacological activities like antioxidant, and anti-microbial. Catechins are gallate and non-gallate. The four main catechins in green tea are epicatechin, epicatechin-3-gallate, epigallocatechin and epigallocatechin-3-gallate, where gallate Catechin like Epigallocatechin-3-gallate has a significant inhibitory effect on CYP3A4 and non-gallate catechin have no such inhibitory effect on the enzyme.[12,13,14,15]

Ginseng

The Chinese traditional medicine scientifically known as *Panax ginseng*, is used in several ailments and has an effect on immunity improvement and lowering blood sugar levels. When experimentation of "*Panax ginseng* inhibits metabolism of diester alkaloids by downregulating CYP3A4 enzyme activity via the pregnane X receptor" was conducted, the results revealed the inhibitory action of *ginseng* on CYP3A4 due to reduced metabolism and elimination of diester alkaloids like aconitine, mesaconitine and hypaconitine as well as decreased gene expression of CYP3A4.[16,17]

Horse chestnut

Scientifically named *Aesculus hippocastanum* is a very well-known herbal plant which is used to treat inflammation, edema and chronic venous insufficiency conditions. The major phytochemical constituents present in plants are Aescin (a mixture of triterpene saponin) and Aesculetin. These constituents are present in leaves and seeds have antipyretic, and analgesic effects and treat haemorrhoids. The research paper "Effect of Aescin on CYP450 enzyme in rats'' studied on the interaction of cocktail probe and Aescin *in-vivo* and results suggest that the Asecin constituent of horse chestnut has an inhibitory action on CYP3A4, causing drug-herb interaction with CYP3A4 substrate. Whereas, other article "*In-vitro* inhibition of CYP3A4 and CYP2D6 activity by horse chestnut constituent Aescin and Aesculetin" reported that Aesculetin is a more potent inhibitor than Asecin.[18,19]

Fennel

Fennel is a treasured herb which can cure numerous disease conditions like anti-inflammatory, antiviral, antispasmodic, cytotoxic anti-allergic, anti-microbial and many more. It is broadly used in culinary spice and in various traditional medications like Siddha, Unani, and Ayurvedic. There are 13 compounds isolated from fennel which had individually different pharmacological actions, of which 5-methoxy psoralen had a prime inhibitory action on CYP3A4. The report "Inhibition on Human Liver Cytochrome P450 3A4 by Constituents of Fennel (*Foeniculum vulgare*): Identification and Characterization of a Mechanism-Based Inactivator" stated that the methanolic extract of fennel inhibited the action of CYP3A4 which mechanized based on inactivation of erythromycin-N-methylation. Later, further research documented that fennel has a time-dependent effect needs NADPH and restores enzyme activity by competitive inhibitors.[20,21]

Similar to CYP3A4, CYP2D6 is the most vital and efficient group of isoenzymes from the cytochrome family. Among these two enzymes, CYP2D6 is an enzyme that is encoded via the CYP2D6 gene that contributes to about 30% metabolism of all drugs.[1] CYP2D6 is mainly expressed in the liver and is also largely located in the areas of CNS including substantia nigra. These enzymes are involved in the alteration of the pharmacokinetic profile of some drugs which includes antidepressants, antipsychotics, analgesics, antiarrhythmic agents and beta receptors antagonists and most of these have a narrow therapeutic index. Thus, it can affect the individuals having simultaneous herbal and conventional drug therapy, as some individuals will metabolize drugs in a fraction of minute and are called ultra-rapid metabolizers, while others metabolize slowly termed poor metabolizers.[22] Therefore, the dose of drugs plays a vital role. Even alteration in the smallest amount of dose can cause unfavourable conditions. It becomes very important to check meal conditions before making any recommendations because there are few natural sources which may have either inhibiting or inducing effects on CYP2D6 as it may lead to either dumping of the drug and thereby toxicity or enhancing metabolism, resulting in altered therapeutic effect.

INHIBITORY EFFECTS OF HERBAL PRODUCTS ON CYP2D6

1. Goldenseal

Scientifically known as *Hydrastis Canadensis* It is a medicinal plant widely used in the traditional system of medicine and as a food supplement. It is widely used in native America as a colouring agent and a medicinal remedy for common conditions like wounds and digestive disorders. Goldenseal contains berberine as the main constituent which is effective against many bacteria and fungi. Berberine can also regulate–blood pressure and helps in treating irregular heartbeat. People also used goldenseal for the common cold and other respiratory tract infections. It is known to be a potent inhibitor of CYP2D6 in in- Vivo and may give rise to various pharmacokinetic herb-drug interactions. Therefore, patients should be discouraged from taking goldenseal supplements. Reduced CYP2D6 activity can increase the risk of toxicity for certain classes of drugs including anti-arrhythmic, antipsychotic and beta blockers.[23,24]

As some drugs such as codeine and tamoxifen are administered as prodrugs, CYP2D6 is required for their activation, thus goldenseal reducing the efficacy of such

medications. The effect of goldenseal when combined with other classes of drugs may raise the level of digoxin in the blood hence used to treat heart diseases, may cause the level of unmetabolized cyclosporine in the body too high which leads to undesirable effects and increase the risk of bleeding with simultaneous consumption of blood thinners like warfarin and aspirin.[25]

2. Kava-Kava

Scientifically called Piper *methysticum forst*. It is a popular and favourable edible medicinal herb traditionally used to prepare non-fermented beverages. Numerous studies conducted on kava confirmed the presence of kavalactones and flavokawains. Extract of kava shows significant inhibition of CYP2D6. An active constituent present in kava is kavalactone which is used widely to treat anxiety and insomnia. It is very important to spread awareness among kava users, who also consume other drugs along with kava, which can be life-threatening. The cases were also found of hepatotoxicity. Cardiotoxicity cases were also reported due to kava inhibition of CYP2D6 which is the main enzyme behind the metabolism of haloperidol.[26]

Kava is a popular herbal remedy which is widely used in Hawaii and obtained from roots and rhizomes of the shrub Piper methysticum. It has been used for ages by native pacific Islanders for its sedative effect and also used for religious purposes.

Case Reports:

Case 1- One male Pacific Islander suffering from bipolar affective disorder was admitted to the emergency department due to worsening manic conditions. From his medication report and history, it was reported that he was having kava juice for ritualistic purposes. The Islander has given intravenous haloperidol 5mg and lorazepam 2 mg, within a few minutes of administration, he was obtunded with atrial flutter and hypoxia for that intravenous flumazenil was given. From his past history records, it was confirmed that he had been previously admitted due to some psychiatric problem, and the same treatment was provided but there were no life-threatening side effects as he had no access to kava.

Case 2- An 80-year-old female pacific islander was admitted due to a medical emergency of acute psychosis. Her medical history report indicated that she was suffering from restless leg syndrome therefore she was consuming kava to get sleep as recommended by her friend. Eventually, she started drinking kava juice regularly followed by consuming more concentrated pills. The condition became worse when she started consuming old stock ropinirole (0.25-0.50mg daily) without consulting her physician. Later on, she started experiencing zoopsic visual hallucinations and paranoid delusions. Female Islander got cured quickly on the administration of low doses of quetiapine (25mg at bedtime daily). Further history revealed that she had taken ropinirole in the past also without concurrent kava use and developed no adverse effect.[27]

3. Turmeric

Scientifically known as *Curcuma longa*, extremely cultivated for rhizomes. Curcumin, dimethoxy curcumin, bisdemethoxy curcumin collectively known as curcuminoids are the major polyphenolic compounds found in turmeric rhizomes. The activity of Rhizome powder and ethanolic extract of *curcuma longa* on CYP2D6 was carried out *in-vitro* using human liver microsomes. The human subject was administered with a single dose of dextromethorphan syrup and in the second phase of studies, the syrup was administered with Turmeric powder. Turmeric extract showed convincing inhibitory action on CYP2D6, which is the main enzyme responsible for converting dextromethorphan to dextrorphan through CYP2D6 and 3-methoxymorphinan through CYP3A4. This study proved that *curcuma longa* potentially inhibits CYP2D6 in *in-vitro* as well as *in-vivo*.[28]

Curcumin is a chemical compound that is found in *curcuma longa* species, potentially inhibits CYP2D6, resulting in the increased exposure of the drug by affecting its metabolism, and rise the plasma concentrations of drugs like calcium channel blockers and Angiotensin receptor 2 antagonists. This is because turmeric lowers the activity of the enzyme CYP3A4 in the liver.[29]

4. Ginseng

Ginseng is one of the widely used herbal medicines in many countries, especially in the United States and Europe as a dietary supplement. The two main categories of ginseng are Asian ginseng and American ginseng which are widely identified and used. Nearly 200 substances have been isolated from ginseng. The constituents include ginsenosides (Saponin), polysaccharides, amino acids, volatile oil and polyacetylenes. *Panax ginseng* has shown mild inhibition of CYP2D6 activity when administered to the population. There is a wide range of drugs which are metabolized by the liver and *panax ginseng* might change the duration at which the liver breaks down the medication, and as a result, change in therapeutic effect and side effects of the medication.[17]

5. Horse Chestnut

Scientifically known as *Aesculus hippocastanum*. Seeds of the horse chestnut contain 65% to 70% of oleic acid, protein, ash, 75% of carbohydrates and triterpene oligoglycosides. The main active constituents isolated were aescin, prosapogenic, quercetin, kaempferol, proanthocyanin and coumarins are used to prepare an extract from Aesculus hippocastanum and it is used for the chronic disease of various kind of insufficiencies, haemorrhoids and postoperative edema. Aescin (triterpene saponin) being one of its important components of it, has anti-inflammatory and veno-tonic properties. The research work on "*In-vitro* inhibition of CYP3A4 and CYP2D6 activity by horse chestnut constituent

Aescin and Aesculetin'' claimed that, Horse chestnut shows *in-vitro* inhibitory effect on metabolizing enzyme on CYP2D6. An antitussive dextromethorphan is a breakdown in humans by o-demethylation to form dextrorphan through CYP2D6 and by N-demethylation to form 3-methoxy morphinan through CYP3A4.[18,19]

6. John's Wort

Scientifically known as *Hypericum perforatum*. Extract from aerial parts of the plant is used for the treatment of depression. John's wort when administered with antidepressants leads to a high level of serotonin in the body resulting in severe side effects such as muscle rigidity and seizures.[30,31] Pharmacologically active ingredients of the plant are naphthodianthrones, hypericin and its derivatives. Other constituents of the plant are hyperforin, hypericin and adhyperforin are responsible for its medical benefits among these hypericin is a potent inhibitor of CYP2D6.[32]

CYP2D6 LEVEL IN ALCOHOLICS

According to one affirmation, people who are consuming alcohol and tobacco have higher levels of CYP2D6 in their brains, a higher metabolic ratio was found in such people and a low metabolic ratio was detected for non-drinkers / smokers.[33,34]

ETHNIC GENOTYPIC FACTORS

There will be a lack of liver cytochrome CYP2D6 enzyme in 7-10% of white people and its amount is least in other groups such as Asians and Americans.[35] The reports from "CYP2D6 phenotype explains reported yohimbine concentration in four severe acute intoxications" by Anna Mueller-schoell *et al*, state that CYP2D6 acts as a major contributor to the clearance of yohimbine. It is known that CYP2D6 activity distribution is different in Caucasians and Chinese individuals, while east Asians show a lower frequency of individuals with no enzymatic activity, the frequency of decreased enzyme activity is much higher compared to Caucasians. The reduced metabolic activity could have resulted in the highly toxic yohimbine concentration.[22]

CYP2D6 AND PERSONALITY TRAITS

CYP2D6 plays a major role in the breakdown of serotonin and dopamine and on this basis, we can relate the activity of the mentioned enzyme with human personality, behaviour patterns and psychiatric disorders. CYP2D6 activity is used against the treatment of anxiety, and neurodegenerative and autoimmune diseases. CYP2D6-poor metabolizers are more exposed to anxiety and are less socialized. Many studies were performed on this and came to the conclusion that poor metabolizers may be at a higher risk of developing Parkinson's disease and Alzheimer's disease. Higher levels of the enzyme were also associated with eating disorders (ultra-rapid metabolizers). Poor metabolizers may do well in cognitive tasks. They may also have better-wrought memory, higher consciousness /responsibility, and orderliness.[36]

CONCLUSION

From the above study, we conclude that the herbal products that show inhibitory action on CYP3A4 and CYP2D6 (metabolizing enzymes that are solely responsible for more than 90% and 30% metabolizers of drugs respectively) can cause serious side effects when consumed with conventional drugs of low therapeutic index. As a result of enzyme inhibition, the concentration of these drugs may rise in the body leading to toxicity. At the same time, enzyme inhibition could be beneficial to sustain drug effects for a longer time and reduce the number of dosing when the high therapeutic index drugs are administered with herbal sources. Thus, it becomes very important to have adequate knowledge of herb-drug interactions before the administration of conventional drugs along with herbal products.

ACKNOWLEDGEMENTS: The authors are thankful to Karavali College of Pharmacy for carrying out the project in the college laboratory, and sincerely thank our management for approval to submit the paper to the journal.

REFERENCES

1. Fahad Khan, Pratibha Pandey, Tarun K. Upadhyay. Cytochrome P450 role in metabolism of drugs and chemicals. Publisher: Lambert Academic Publisher Germany. 2019; 978-620-0-22974-8.
2. Hakkola J, Raunio H, Purkunen R, Saarikoski S, Vahakangas K, Pelkonen O, Edwards RJ, Boobis AR, Pasanen M. Cytochrome P450 3A expression in the human fetal liver: evidence that CYP3A5 is expressed in only a limited number of fetal livers. Biology of the Neonate. 2001; 80(3):193-201. DOI: 10.1159/000047142; PMID: 11585982.
3. Choi SY, Koh KH, Jeong H. Isoform-specific regulation of cytochromes P450 expression by oestradiol and progesterone. Drug Metabolism and Disposition. 2013;41(2):263-269. DOI: 10.1124/dmd.112.046276; PMID: 22837389.
4. Bibi Z. Role of cytochrome P450 in drug interactions. Nutrition & metabolism. 2014 ;11(1):11. DOI: 10.1186/1743-7075-5-27; PMID: 18928560.
5. Sasaki T, Sato Y, Kumagai T, Yoshinari K, Nagata K. Effect of health foods on cytochrome P450-mediated drug metabolism. Journal of pharmaceutical health care and sciences. 2017; 3(1):1-1. DOI: 10.1186/s40780-017-0083-x; PMID: 28496987.
6. Wanwimolruk S, Phopin K, Prachayasittikul V. Cytochrome P450 enzyme mediated herbal drug interactions. Journal of Experimental and clinical sciences. 2014; 13:869. PMID: 26417265.
7. McDonnell AM, Dang CH. Basic review of the cytochrome p450 system. Journal of the advanced practitioner in oncology. 2013 ;4(4):263. DOI: 10.6004/jadpro.2013.4.4.7; PMID: 25032007.
8. Bailey DG, Dresser GK, Bend JR. Bergamottin, lime juice, and red wine as inhibitors of cytochrome P450 3A4 activity: comparison with grapefruit juice. Clinical Pharmacology &

Therapeutics. 2003; 73(6):529-537. DOI: 10.1016/S0009-9236(03)00051-1; PMID: 12811362.

9. Chen M, Zhou SY, Fabriaga E, Zhang PH, Zhou Q. Food-drug interactions precipitated by fruit juices other than grapefruit juice: An update review. Journal of food and drug analysis. 2018; 26(2): S61-71. DOI: 10.1016/j.jfda.2018.01.009; PMID: 29703387.

10. Tsukamoto S, Aburatani M, Ohta T. Isolation of CYP3A4 inhibitors from the black cohosh (Cimicifuga racemosa). Evidence-based complementary and alternative medicine. 2005; 2(2):223-226. DOI: 10.1093/ecam/neh086; PMID: 15937564.

11. Huang Y, Jiang B, Nuntanakorn P, Kennelly EJ, Shord S, Lawal TO, Soni KK, Mahady GB. Fukinolic acid derivatives and triterpene glycosides from black cohosh inhibit CYP isozymes, but are not cytotoxic to Hep-G2 cells *in-vitro*. Current drug safety. 2010; 5(2):118-124. DOI: 10.2174/157488610790936150; PMID: 20406160.

12. Reygaert WC. Green tea catechins: Their use in treating and preventing infectious diseases. Bio Medical research international. 2018; 9105261. DOI: 10.1155/2018/910526; PMID: 30105263.

13. Mancuso C, Barone E. Therapeutic use of tea derivatives: all that glitters is not gold. Blood, The Journal of the American Society of Hematology. 2009; 114(11):2359-2360. DOI: 10.1182/blood-2009-07-231761.

14. Muto S, Fujita KI, Yamazaki Y, Kamataki T. Inhibition by green tea catechins of metabolic activation of procarcinogens by human cytochrome P450. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 2001; 479(1-2):197-206. DOI: 10.1016/S0027-5107(01)00204-4.

15. Satoh T, Fujisawa H, Nakamura A, Takahashi N, Watanabe K. Inhibitory effects of eight green tea catechins on cytochrome P450 1A2, 2C9, 2D6, and 3A4 activities. Journal of Pharmacy & Pharmaceutical Sciences. 2016; 19(2):188-197. DOI: 10.18433/j3ms5c; PMID: 27518169.

16. Malati CY, Robertson SM, Hunt JD, Chairez C, Alfaro RM, Kovacs JA, Penzak SR. Influence of Panax ginseng on cytochrome P450 (CYP) 3A and P-glycoprotein (P-gp) activity in healthy participants. The Journal of Clinical Pharmacology. 2012; 52(6):932-939. DOI: 10.1177/0091270011407194; PMID: 21646440.

17. Yang L, Wang Y, Xu H, Huang G, Zhang Z, Ma Z, Gao Y. Panax ginseng inhibits metabolism of diester alkaloids by downregulating CYP3A4 enzyme activity via the pregnane X receptor. Evidence-Based Complementary and Alternative Medicine. 2019; (3-4):1-13. DOI: 10.1155/2019/3508658; PMID: 31057647.

18. Huang Y, Zheng SL, Zhu HY, Xu ZS, Xu RA. Effects of aescin on cytochrome P450 enzymes in rats. Journal of Ethnopharmacology. 2014; 151(1):583-590. DOI: 10.1016/j.jep.2013.11.016.

19. Spanakis M, Vizirianakis IS, Mironidou-Tzouveleki M and Niopas I. In vitro inhibition of CYP3A4 and CYP2D6 activity by the horse chestnut constituents' aescin and aesculetin. Front. Pharmacol. Conference Abstract: 8th Southeast European Congress on Xenobiotic Metabolism and Toxicity - XEMET 2010. DOI: 10.3389/conf.fphar.2010.60.00199.

20. Badgujar SB, Patel VV, Bandivdekar AH. Foeniculum vulgare Mill: A review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. Bio Medical research international. 2014; 842674. DOI: 10.1155/2014/842674; PMID: 25162032.

21. Zaidi SF, Kadota S, Tezuka Y. Inhibition on human liver cytochrome P450 3A4 by constituents of fennel (Foeniculum vulgare): identification and characterization of a mechanism-based inactivator. Journal of Agricultural and Food Chemistry. 2007; 55(25):10162-10167. DOI: 10.1021/jf0713253; PMID: 17988092.

22. Mueller-Schoell A, Michelet R, Weinelt F, Kloft C, Mikus G. CYP2D6 phenotype explains reported yohimbine concentrations in four severe acute intoxications. 2021; 95:2867–70. DOI: 10.1007/s00204-021-03082-4; PMID: 34027562.

23. Mandal SK, Maji AK, Mishra SK, Ishfaq PM, Devkota HP, Silva AS, Das N. Goldenseal (Hydrastis canadensis L.) and its active constituents: a critical review of their efficacy and toxicological issues. Pharmacological research. 2020; 160:105085. DOI: 10.1016/j.phrs.2020.105085; PMID: 32683037.

24. Mandal SK, Maji AK, Mishra SK, Ishfaq PM, Devkota HP, Silva AS, Das N. Goldenseal (Hydrastis canadensis L.) and its active constituents: a critical review of their efficacy and toxicological issues. Pharmacological research. 2020; 160:105085. DOI:10.1016/j.phrs.2021.105439.

25. Horn JR, Hansten PD. Goldenseal Drug Interactions. Pharmacy Times. 2012; 79(9).

26. Mathews JM, Etheridge AS, Black SR. Inhibition of human cytochrome P450 activities by kava extract and kavalactones. Drug Metabolism and Disposition. 2002; 30(11):1153-1157.

27. Toohey TP, Lu BY, Wada C. Toxic effects of psychotropics related to possible p450 enzyme inhibition by kava: report of 2 cases. The Primary Care Companion for CNS Disorders. 2013; 15(5):26940. DOI:10.1124/dmd.30.11.1153.

28. Al-Jenoobi FI, Al-Thukair AA, Alam MA, Abbas FA, Al-Mohizea AM, Alkharfy KM, Al-Suwayeh SA. Effect of Curcuma longa on CYP2D6-and CYP3A4-mediated metabolism of dextromethorphan in human liver microsomes and healthy human subjects. European journal of drug metabolism and pharmacokinetics. 2015; 40(1):61-66. DOI: 10.1007/s13318-014-0180-2; PMID: 24510399.

29. Kaminsky LS, Zhang ZY. Human P450 metabolism of warfarin. Pharmacology & therapeutics. 1997; 73(1):67-74. DOI: 10.1016/S0163-7258(96)00140-4.

30. Komoroski BJ, Zhang S, Cai H, Hutzler JM, Frye R, Tracy TS, Strom SC, Lehmann T, Ang CY, Cui YY, Venkataramanan R. Induction and inhibition of cytochromes P450 by the St. John's wort constituent hyperforin in human hepatocyte cultures. Drug Metabolism and Disposition. 2004; 32(5):512-8. DOI: 10.1124/dmd.32.5.512; PMID: 15100173.

31. Nilius B, Szallasi A. Are Brain TRPs Viable Targets for Curing Neurodegenerative Disorders and Improving Mental Health? In: TRP Channels as Therapeutic Targets: From

Basic Science to Clinical Use. Elsevier Inc. 2015; 419–456. DOI: 10.1016/B978-0-12-420024-1.00023-0.

32. Wang Z, Gorski JC, Hamman MA, Huang SM, Lesko LJ, Hall SD. The effects of St John's wort (Hypericum perforatum) on human cytochrome P450 activity. Clin Pharmacol Ther. 2022; 70(4):317–26. DOI: 10.5507/bp.2011.047; PMID: 22286810.

33. Wanwimolruk S, Prachayasittikul V. Cytochrome P450 enzyme mediated herbal drug interactions. Experimental and Clinical Sciences journal. 2014; 13:347-391. PMID: 26417265.

34. Vincent-Viry M, Fournier B, Galteau MM. The effects of drinking and smoking on the CYP2D6 metabolic capacity. Drug Metabolism and Disposition. 2000; 28(6): 617-619.

35. Bertilsson L, Dahl ML, Dalén P, Al-Shurbaji A. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. British journal of clinical pharmacology. 2002; 53(2):111-122. PMID: 10820131.

36. Penas-LLedo EM, Dorado P, Pacheco R, Gonzalez I, LLerena A. Relation between CYP2D6 genotype, personality, neurocognition and overall psychopathology in healthy volunteers. Pharmacogenomics. 2009; 10(7):1111-20. DOI: 10.2217/pgs.09.75; PMID: 19604084.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.