

Phenytoin's pharmacological interactions with medicinal herbs: a review

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Physiologic changes due to aging, pregnancy, nutritional status, drug interactions, and can affect pharmacokinetics and pharmacodynamics of antiepileptic drugs. In this review article, the interactions between phenytoin and herbs recorded in the literature were summarized according to the Medline database (via PubMed). Our results revealed that, changes in phenytoin's bioavailability were reported for co-administration of herbs or herbal extracts. An increase in phenytoin blood levels was established with *Piper nigrum*, Mentat, and *Lipidum sativum* in *in vitro* and/or *in vivo* studies. In contrast, herb-phenytoin interactions led to sub-therapeutic levels of phenytoin in other cases with herbs such as Cannabis, *Ginkgo biloba*, *Morinda citrifolia*, *Nigella sativa*, and *Trigonella foenum graecum*. In addition, the findings of other pharmacodynamic experiments showed that various herbs, including *Zizyphus jujube*, *Terminalia chebula*, *Curcuma longa* L, and *Centella asiatica*, improved the pharmacological impact of phenytoin. To reduce the patients' health risks, health professionals involved in their treatment are expected to be thoroughly educated about the interactions between phenytoin and medicinal plants.

1. Introduction

Epilepsy is a severe neurological disorder that involves abnormal electrical activity in the brain, which can affect the central nervous system or other unusual behavior, emotions, and even consciousness loss (Abu Dayyih et al. 2023). It is a neurological disorder distinguished by recurrent seizures caused by neuronal hyperexcitability (Vezzani and Friedman 2013). Phenytoin (PHT) is an antiepileptic drug (AED) that relieves epileptic symptoms by blocking open voltage-gated sodium channels (Lipkind and Fozzard 2010). PHT is a commonly prescribed antiepileptic medication used to treat both generalized and partial seizures (Ahmed 2006; Chua et al. 2000).

PHT's therapeutic range is only 10–20 µg/ml, and it has a poor solubility in water and a slightly acidic nature (pK_a of about 8.31). In order to boost PHT water solubility and reduce irregular oral absorption, many PHT prodrugs were developed like fosphenytoin solution. The main problem with PHT, however, is the extremely low aqueous solubility and the tendency to crystallize leading to precipitation in biological milieu. PHT precipitation in stomach medium causes slow and variable absorption (Burstein et

al. 1999; Fink et al. 2020; Yousfan et al. 2020). PHT therapeutic dose for patients ranges from 400 to 600 mg per day. The half-life ($t_{1/2}$) of PHT is prolonged and ranges from 12 to 36 hours. Inter-patient variability is seen by this $t_{1/2}$. Most patients can take PHT once daily, and the period to attain the steady state may take 1–4 weeks, according to the extended elimination ($t_{1/2}$) (Muchohi et al. 2002; Ahn et al. 2008). Because of PHT's narrow therapeutic index, therapeutic drug monitoring is necessary to ensure therapeutic and nontoxic levels of PHT, so that a balance can be found between efficacy and dose-related side effects (Winckelmann et al. 2008). Physiologic changes due to aging, pregnancy, nutritional status, drug interactions, and can affect pharmacokinetics (PK) and Pharmacodynamics (PD) of antiepileptic drugs (AEDs; Marvanova 2016).

Herbal remedies are containing more than one active constituent such as alkaloids, flavonoids, glycosides, anthraquinones, saponins and others, which have the potential to interact with conventional drugs through different mechanisms. It has also been demonstrated that many herbal products undergo metabolism catalyzed by Cytochrome P450 (CYP) and to elicit different effects on CYP-mediated pathways including induction and inhibition (Fang et al. 2011; Han et al. 2011; Ho et al. 2011; Doehmer and Eisenbraun 2011; Abushammala 2021). Herb–drug interactions (HDIs) are drug-related problems in therapy because they can cause therapeutic failures that are difficult to identify. The lack of reports on patients using drugs concurrently with herbal medicines and the inability of health workers to identify the emergence of potential and clinically relevant HDIs contribute to these problems (Sundhani et al. 2022). Thus, herb–drug interactions (HDI) are an important clinical concern, which may arise during the concomitant administration of herbs and conventional drugs. Currently, numerous researchers are working on the evaluation of HDI of the commonly used herbal preparations and extracts when used simultaneously with drugs (Asha et al. 2021).

The purpose of this review article is to provide an overview of the clinical data on herbs-PHT PK and PD interactions. Herbs-PHT interactions are reviewed, with concrete examples and other clinical observations. To generate a comprehensive summary of

Abbreviations

Phenytoin (PHT), Antiepileptic drugs (AEDs), Therapeutic drug monitoring (TDM), Pharmacokinetics (PK), Pharmacodynamics (PD), Maximum concentration (C_{max}), Time to reach maximum concentration (T_{max}), Area under the curve from zero to time (AUC_{0-t}), Area under the curve from zero to infinity ($AUC_{0-\infty}$), Half-life ($t_{1/2}$), Volume of distribution at steady state (V_{ss}), Herb–drug interactions (HDIs), Cytochrome P450 (CYP450), Cannabis sativa (CS), Delta (9)-tetrahydrocannabinol (Δ^9 -THC), *Ginkgo biloba* (GB), Human immunodeficiency virus (HIV), *Ginkgo biloba* extract (GBE), P-glycoprotein (P-gp), *Zizyphus jujuba* (Z. jujuba), Hydroalcoholic extract of Z. jujube (HEZJ), Gamma-aminobutyric acid (GABA), *Terminalia chebula* (TC), *Terminalia chebula* hydroalcoholic fruit extract (HETC), *Centella asiatica* (CA).

reported herbs-PHT interactions an extensive review of published articles were collected from international databases such as the PubMed database, Research gate, Google Scholar, Science Direct, and Springer Link and Scopus was performed to attain comprehensive publications were undertaken. Table 1 shows an overview of commonly used herbs and the effects of herbs-PHT interactions. The overall purpose of this review article is to increase pharmacists' and physicians' understanding of this concern and thereby protect patients' health.

Previous studies (Jiang et al. 2011, 2013), Δ^9 -THC demonstrated reversible inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP2D6 activity; CBD demonstrated reversible inhibition of CYP1A2, CYP3A4, CYP2B6, CYP2C9, CYP2C19, and CYP2D6 (Jiang et al. 2013, 2011).

According to *in vitro* findings, the cytochrome P450 isoenzyme CYP2C9 is induced by Δ^9 -THC. This is suggesting the possibility of a synergistic effect between Δ^9 -THC and PHT administration, which could lead to lower PHT concentrations *in vivo* by increasing

Table: Herbs with PK and PD effects on AED phenytoin

Herb	Synonym	Outcome measures	Effect	Model	References
<i>Cannabis</i>	Marijuana	-	Decreases PHT concentrations	<i>In vitro</i>	Bland et al. 2005
<i>Ginkgo biloba</i>	Ginkgo	PK	Decreases PHT concentrations	Human	Kupiec et al. 2005
<i>Piper nigrum</i>	Black pepper	PK	Enhances PHT oral bioavailability	Human	Velpandian 2001; Bano et al. 1987, Pattanaik et al. 2006
Mentat	Mentat	PK	Increases PHT bioavailability	Animal	Tripathi et al. 2000
<i>Morinda citrifolia</i>	Noni plant	PK	Decreases PHT concentrations	Human	Kang et al. 2015
<i>Lepidium sativum</i>	Garden cress	PK	Increases PHT bioavailability	Animal	Ikharfy et al. 2013
<i>Nigella sativa</i>	Black seed	PK	Decreases PHT concentrations	Animal	Ikharfy et al. 2013
<i>Trigonella foenum-graceum</i>	Fenugreek	PK	Decreases PHT concentrations	Animal	Ikharfy et al. 2013
<i>Zizyphus jujuba</i>	Red date	PD	Enhancing the antiepileptic effectiveness of PHT	Animal	Pahuja 2012
<i>Terminalia chebula</i>	Retz	PD	Showed considerable anticonvulsant efficacy.	Animal	Kumar et al. 2018
<i>Curcuma longa</i>	Curcumin	PK & PD	Decrease the PHT dose and increase efficacy and reduce the side effect of PHT	Animal	Reeta et al. 2009, Reeta et al. 2011
<i>Centella asiatica</i>	Gotu kola	PK & PD	Alteration in PK-parameters and Enhancement of antiseizure effect	Animal	Kumar et al. 2021

2. Cannabis sativa

Cannabis sativa (CS) known as Marijuana, (*Cannabaceae*), is one of the most commonly mentioned illegal narcotics that is self-administered both orally as well as through smoking. The main psychotropic component in marijuana plants is delta (9)-tetrahydrocannabinol (Δ^9 -THC) (Sharma et al. 2012). CS has been used to cure a number of illnesses including rheumatism, epilepsy, asthma, skin burns, discomfort, difficulty during child labor, postpartum hemorrhage, and gastrointestinal disturbances. However, the use of CS is still limited, and it is illegal in most countries (Odieka et al. 2022). Due to the legalization of marijuana in many regions of the United States and other countries, there is a demand for a study sought to achieve of cannabis constituents and their potential for drug-drug interactions (Nasrin et al. 2021).

Serious adverse events can result from drug-drug interactions, specifically those affecting CYP-mediated drug metabolism. Δ^9 -THC is the major constituent of cannabis, potentially inhibiting CYPs. As cannabis has become more widely legalized worldwide, its medicinal use has also increased. Numerous medical diseases are treated with cannabis-based medicines, usually in combination with prescribed drugs (Doohan et al. 2021).

the rate of PHT hydroxylation in human liver microsomes and the expression of the CYP2C9 enzyme (Bland et al. 2005). This appears to be the only *in vitro* evidence that cannabis can alter PHT levels. As a consequence, any recommendations must be confirmed before they may be published.

3. Ginkgo biloba

Ginkgo biloba (GB) (*Ginkgoaceae*) is one of the most popular herbal medicines in the world, due to its purported pharmacological effects, including memory-enhancing, cognition-improving, and antiplatelet effects (Deng et al. 2008). *Ginkgo biloba* extract (GBE) is an herbal supplement that contains numerous constituents, namely flavonoids (quercetin, kaempferol, and isorhamnetin) and terpenoids (bilobalide and ginkgolides) (Naccarato et al. 2012).

Animal and *in vitro* data suggest that GBE may modulate CYP3A4 activity. As such, GBE may alter the exposure of human immunodeficiency virus (HIV) protease inhibitors metabolized by CYP3A4. It's also conceivable that GBE could alter the PK of protease inhibitors as a result of changing P-glycoprotein (P-gp) (Robertson et al. 2008). Various CYP enzymes' activity and concentration in the

liver increased in a dose- and time-dependent manner. On day 1 of feeding a 0.5% GBE diet and after receiving 10 mg GBE/kg body weight for 5 days by intragastric gavage, significant increases in the concentration and activity of CYP enzymes were found. Pentoxylresorufin O-dealkylase (PROD), a CYP2B enzyme, seemed to have the highest activity levels among some of the CYP enzymes (Umegaki et al. 2002).

A 55-year-old man with seizure disorders is receiving valproate and PHT, as reported in a case study. According to his medical history, he displayed unexplainable subtherapeutic serum levels of valproate and PHT three times while GBE was also administered. The patient had been taking a variety of vitamins, supplements, and herbal remedies without his doctor's knowledge, with GBE being the most prevalent component, it was eventually revealed (Kupiec and Rag 2005).

4. Piper nigrum

Piper nigrum (Piperaceae), known as black pepper, is one of the most widely used spices. It is valued for its distinct biting quality attributed to the alkaloid, piperine. Dietary piperine, by favorably stimulating the digestive enzymes of pancreas, enhances the digestive capacity and significantly reduces the gastrointestinal food transit time. Black pepper has important medicinal and preservative properties including fundamental effects on P-gp and many enzyme systems, leading to bio-transformative effects such as chemoprevention, detoxification, and enhancement of the absorption and bioavailability of herbal and conventional drugs. Based on modern cell, animal, and human studies, piperine has been found to have immunomodulatory, anti-oxidant, anti-asthmatic, anti-carcinogenic, anti-inflammatory, anti-ulcer, and anti-amoebic properties (Meghwal and Goswami 2013). Pepper or its active alkaloid piperine have been reported to enhance the oral bioavailability of PHT in three clinical studies.

Six healthy volunteers had a single 300 mg dose of PHT in a crossover study 30 minutes following either a soup with or without black pepper (1g per 200 mL). The AUC_{0-48} , $AUC_{0-\infty}$ and C_{max} of PHT increased by 49%, 133%, and 13%, respectively, in the presence of pepper, while the elimination half-life increased from 22.48 to 49.71 hours (Velpandian et al. 2001). In a further crossover trial, five healthy volunteers either received a single 300 mg dosage of PHT orally along with 20 mg of piperine per day for seven days as a pretreatment. The effects of piperine on PHT AUC and C_{max} levels were raised by 50% and 27%, respectively (Bano et al. 1987).

Individuals with epilepsy taking 150 mg or 200 mg of PHT twice per day (10 patients each) experienced a small rise in their PHT AUC and C_{max} when given a single 20 mg dosage of piperine in addition to their regular dose of PHT. PHT AUC and C_{max} increased by roughly 9% in the 150 mg and 17% and 22% in the 200 mg groups, respectively, while the elimination half-life remained unchanged (Pattanaik et al. 2006).

Piperine may improve gastrointestinal absorption and decrease excretion, increasing the bioavailability of PHT. When PHT was given to individuals who were already receiving it, the effects of piperine were far less apparent than they were in healthy individuals. This may be due to the fact that in the patient experiment, a single dose of piperine was administered simultaneously with the PHT rather than before to the PHT.

5. Mentat

Mentat (Mentat, Theaceae), is a herbal preparation containing extracts of twenty four herbs recommended to correct memory disturbances, learning and language disability, enuresis, anxiety, depression and neurosis (Garg et al. 1999). Mentat has shown synergistic activity in clinical trials with other AED such as sodium valproate, carbamazepine, and phenobarbitone by enhancing seizure control. When Mentat was used simultaneously with PHT, the plasma AUC of PHT increased substantially when compared to PHT alone. PHT's C_{max} and T_{max} were also evaluated. The findings suggest that because Mentat has a greater efficacy than

anti-epileptic drugs, co-administration of the latter may improve their efficacy. To prevent any toxic consequences, this must be done under close medical supervision, ideally with therapeutic drug monitoring (TDM), which could also aid in dose adjustment (Tripathi et al. 2000).

6. Morinda citrifolia

Morinda citrifolia (Rubiaceae) known as Noni, has a broad range of therapeutic effects including antibacterial, antiviral, antifungal, analgesic, anti-hypertensive, anti-inflammatory and immune enhancing properties. All parts of the plant and especially fruits are used in herbal medicine and known as Noni Juice (McClatchey 2002).

An observation of the herb-drug interactions between a commercially noni juice product and PHT in a human case was reported in a published study. A 49-year-old man has been receiving PHT for more than ten years to treat his epilepsy. Notwithstanding his adherence to his medication, chronic sub-therapeutic PHT levels, which occasionally varied from low to undetectable, were noted when the noni fruit juice was co-administered regularly, resulting to having poor seizure control. The possible mechanism is speculated to be due to noni juice induced cytochrome P-450 2C9 metabolism of PHT (Kang et al. 2015).

In conclusion, this report is significantly important for clinicians to be aware of the interaction between antiepileptic drugs and some herbs like noni juice.

7. *Lepidium sativum*, *Nigella sativa* and *Trigonella foenum-graceum*

Lepidium sativum (Brassicaceae), known as Garden cress, is a rapidly growing annual herb. The herb is used for different conditions such as cough, vitamin C deficiency, constipation, poor immunity and as a diuretic. It is useful as poultices for sprains and in leprosy, skin diseases, dysentery and diarrhea (Moser et al. 2009).

The seeds of *Nigella sativa* (Ranunculaceae) are known as Black seed. Their oil has been used as an Arab traditional medicine for the treatment of arthritis, lung diseases, and hypercholesterolemia (Khader et al. 2009). Recent studies also showed that the oil of black seed may be considered as a potential adjuvant for the therapy of rheumatoid arthritis (Gheita and Kenawy 2012). The active ingredients in the seeds include thymoquinone which has been reported to be an effective antimicrobial and anthelmintic agent. It may also play a role in women's health, stimulating menstruation and increasing milk flow (Ajayi et al. 2006).

Trigonella foenum-graecum (Fabiaceae), known as Fenugreek has been traditionally used against respiratory infections (bronchitis and pneumonia), and since it nourishes the body during illness, the herb has also been used to reduce fever, when taken with lemon and honey. Fenugreek has been shown to possess hypoglycemic, antihypertensive, and hypolipidemic activities (Xue et al. 2007).

An *in vivo* PK interaction study was designed to evaluate the effect of various commonly used herbs, including fenugreek, black seed, and garden cress, on the disposition of PHT following oral administration in a dog model. PHT was given orally at a dose of 50 mg, and blood samples were obtained for the determination of drug's PK parameters. Animals were initiated on a particular herb treatment for one week after an appropriate washout period. Garden cress treatment caused a modest increase in maximum observed concentration (C_{max}) and terminal half-life ($t_{1/2}$) of PHT with a reduction in clearance by 33%. Black seed treatment had a more significant effect on drug excretion than on its volume of distribution at steady state (V_{ss}), which led to an 87% reduction in systemic exposure as assessed by area under the curve ($AUC_{0-\infty}$). The effect of Fenugreek therapy resembled, that of Black seed with a significant reduction in $AUC_{0-\infty}$ by ~72%. Furthermore, the V_{ss} improved by 73%. The findings suggest that the PHT disposition can be significantly altered by the concurrent consumption of tested herbal products (Ikharfi et al. 2013).

8. *Zizyphus jujuba*

Chinese jujube (*Zizyphus jujuba*, Ramniaceae), known as Red date, is a highly nutritious and functional fruit reported to have various health benefits, has been extensively planted worldwide, especially in China. Sedative, tranquilizing, hypnotic, and antiepileptic effects of *Z. jujuba* in experimental models in rats are known (Lu et al. 2021; Pahuja et al. 2011; Peng et al. 2000; Yuan et al. 2007). A protective effect of a hydroalcoholic extract of *Z. jujuba* fruits against pentylentetrazole and maximal electroshock-induced seizures, oxidative stress, and cognitive impairment in rats has been reported (Pahuja et al. 2011).

In another framework by using maximal electrical shock induced seizures, co-administration of a hydroalcoholic extract of *Z. jujuba* with sub-therapeutic doses of PHT, exhibited protection against tonic hind limb extension. A significant increase in glutathione levels and a decrease in malondialdehyde levels were found with pretreatment of *Z. jujuba* with the sub-therapeutic doses of PHT. In accordance with the report's findings, the antiepileptic effectiveness of PHT was enhanced in maximal electrical shock seizures when *Z. jujuba* and subtherapeutic doses of PHT were administered simultaneously. As HEZJ acts through both of these pathways, it can be hypothesized that GABA and voltage-gated channels are associated with the anticonvulsant activity of *Z. jujuba*. As a result, *Z. jujuba* enhanced the antiepileptic effect of PHT (Pahuja 2012).

9. *Terminalia chebula*

Chebulia terminalis (TC) (Combretaceae), known as Retz, has been utilized as a traditional medicine for a long time. It has been extensively exercised in various indigenous medicine practices like Unani, Tibb, Ayurveda, and Siddha to remedy human ailments such as bleeding, carminative, dysentery, liver tonic, digestive, antidiarrheal, analgesic, anthelmintic, antibacterial and was also be considered helpful in skin disorders, asthma, inflammation, dryness of throat, cough, nausea, diarrhea, pain, colic, hiccups, nervous disorders, kidney and urinary tract disorders, candidiasis, and wound infections (Sadgahnia et al. 2017; Hassan Bulbul et al. 2022).

The results of an PD experimental study that investigated the effect of *Terminalia chebula* hydroalcoholic fruit extract (HETC) on experimental models of seizures, seizure-induced cognitive impairment, and oxidative stress in rats as an animal model, propose that HETC exhibited significant anticonvulsant activity and also potentiated the subtherapeutic dose of PHT and valproate, revealing its usefulness as an adjuvant to antiepileptic drugs with the advantage of preventing cognitive impairment and oxidative stress (Kumar et al. 2018).

10. Curcumin

Curcuma longa L. (Zingiberaceae) is one of the most well studied functional foods. *Curcuma longa* and *Curcuma domestica*, both Zingiberaceae members, are widely cultivated in Asia's tropical regions. Curcumin has anti-inflammatory, anti-mutagenic, antibacterial, antioxidant and anticancer properties. Neuropathic pain associated with chronic alcohol intake is a bothersome problem that affects both the central and peripheral nerve systems and has no satisfactory treatment to date (Kim et al. 2001). Curcumin has been reported to cause a decrease in lipid peroxidation, mitochondrial dysfunction, and apoptotic indices in oxidative stress conditions (Wang et al. 2005). A study aimed to investigate the effect of chronic curcumin administration on PHT-induced cognitive impairment and oxidative stress in rats. It was demonstrated that curcumin is effective in preventing PHT-induced cognitive impairment and oxidative stress in rats without altering the serum PHT levels. This suggests the potential of adjuvant curcumin therapy in ameliorating cognitive impairment caused by chronic PHT therapy (Reeta et al. 2009), as oxidative stress is known to contribute to the deficits of cognitive function (Fukui et al. 2002; Keller et al. 2005). In another study the pharmacological interaction of curcumin with four antiepileptic drugs was investigated in male Wistar rats. The

percentage protection against seizures with sub-therapeutic doses of valproate, PHT, phenobarbitone and carbamazepine was also enhanced by concomitant curcumin administration. The results thus suggest the potential effect of curcumin as an adjunct to these antiepileptic drugs in epilepsy with the advantage of increasing the efficacy, reducing the dose and side effects of the antiepileptic drugs (Reeta et al. 2011).

11. *Centella asiatica*

Centella asiatica (CA, Apiaceae), known as Gotu kola, is used for the treatment of central nervous system (CNS) disorders include epilepsy, dementia, Alzheimer's disease, anxiety etc (Orhan 2012). CA shows considerable promise for development as a botanical drug for cognitive decline. Its primary bioactive components include triterpene glycosides asiaticoside and madecassoside and their corresponding aglycones asiatic acid and madecassic acid (Wright et al. 2020). CA is a commonly used herbal medicine for the treatment of epilepsy which has CYP2C9, CYP2D6 and CYP3A4 enzymes inhibition property and used as an adjuvant therapy with conventional antiepileptic drugs (AEDs), that may be responsible for HDI.

In a study planned to evaluate the pharmacological interaction profile of a hydroalcoholic *Centella asiatica* extract (HECA) with the antiepileptic drugs valproate and phenytoin (PHT) in experimental models in Wistar rats it was found that co-administration could alter the C_{max} and AUC_{0-24} and the clearance of AEDs and improve the therapeutic efficacy of VPA and PHT (Kumar et al. 2021).

Oxidative stress and glutamate excitotoxicity contribute in the acute conditions of neuronal degeneration such as epilepsy (Radi et al. 2014). The antiepileptic properties of HECA may be due to the asiaticoside and/or madecassoside. The enrichment with asiaticoside and madecassoside of CA may enhance anticonvulsant property. The PHT produced complete protection against seizures in their therapeutic doses. Co-administration of HECA with a sub-therapeutic dose of PHT enhanced the protection of seizures and significantly attenuated the seizure induced oxidative stress and cognitive impairment. (Kumar et al. 2021).

12. Conclusion

Utilizing herbal supplements with prescription medicines raises the likelihood of undesirable PK and/or PD herb-drug interactions. They may be beneficial by enhancing the efficacy and reducing the toxicities of the co-administered drugs. However, herb-drug interactions may increase toxicity or even be fatal. Thus, more studies are needed to confirm and assess the clinical significance of these potential herb-drug interactions. Herb-drug interactions are a reality and can present a serious threat to human health as shown in the Table. Healthcare professionals should be aware of this potential and researchers should strive to fill the numerous gaps in our present understanding of this problem. Accordingly, clinicians should be mindful of the potential of herb-drug interactions and establish a strategy for establishing dose adjustment of drugs with narrow therapeutic index like PHT.

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