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A REVIEW OF THEOPHYLLINE'S PHARMACOLOGICAL INTERACTIONS WITH MEDICINAL HERBS

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Theophylline (TPH) is a bronchodilator with a limited therapeutic index and high inter-individual pharmacokinetic (PK) variability. In this paper, the interactions between TPH and medicinal herbs recorded in the literature were summarized. The collected references in the analyzed literature were investigated. A decrease in TPH bioavailability by induction mechanism on CYP1A2 was reported during co-administration of herbs or herbal extracts as (Andrographis paniculata, Commiphora myrrha, Ephedra species, Evodia rutaecarpa, Lepidium sativum, Sophora flavescens, Salvia miltiorrhiza, and Trigonella foenum-graecum). TPH bioavailability was increased by inhibition mechanism on CYP1A2 when co-administered with herbs (Acacia catechu, Angelica species, Astragalus species, Cassia auriculata, Cardiospermum halicacabum and Scutellariae baicalensis. Meanwhile, concomitant use of TPH with (Cassia occidentalis, Glycyrrhiza glabra, Ginkgo biloba, Hypericum perforatum, Nigella sativa, Punica granatum and Rhodiola rosea) was reported to be insignificant. In this review, we focus on the interactions between TPH and medicinal herbs that haven't been covered in prior studies. To reduce the patients' health risks, health professionals involved in their treatment are expected to be thoroughly educated about the interactions between TPH and medicinal plants.

Keywords: *Theophylline, Herb-Drug Interaction, CYP1A2, Pharmacology, Bioavailability.*

INTRODUCTION

TPH has been one of the most prescribed drugs for the treatment of asthma and chronic obstructive pulmonary disease for more than 70 years. TPH is a bronchodilator with a limited therapeutic index, ranging from 5 to 20 µg/mL[1&2]. Because of its restricted therapeutic range and high inter-individual PK variability, therapeutic monitoring of TPH serum levels is essential[3]. The hepatic microsomal mono-oxygenase system's cytochrome P450 (CYP) 1A and, to a lesser extent, CYP2E oxidize TPH via N-demethylation and 8-hydroxylation pathways, respectively[4]. The enzymes CYPs play a crucial role in drug metabolism[5]. Approximately 90% of all marketed drugs are metabolized by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Medicine interactions and safety issues can be caused by substantial inhibition or induction of CYP isoenzymes[6]. Concerns about herb–drug interactions have risen as natural treatments, also known as phytotherapy or phytomedicine, have grown globally for therapeutic purposes. These interactions, which might be pharmacodynamic or PK, are especially significant for treatments with limited therapeutic thresholds[7-9]. As a result, it is probable that pretreatment with prescriptions or herbal remedies that modify CYP1A activities will affect the PK parameters of TPH. As a result, drug-drug or herb-drug interactions could influence TPH's treatment.

Therefore, these interactions may affect therapeutic dose, effectiveness, and toxicity of TPH[10]. In a several of laboratories, animal, and human research, potential herbal medicine-drug interactions have been reported. Herbal medicines have also been demonstrated to

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interact clinically with a variety of conventional medications[8]. Inhibition of CYPlA2 activity may increase plasma TPH concentration by inhibiting hepatic clearance and may contribute to the emergence of adverse effects. In contrast, induction of CYP1A2 may reduce plasma TPH to sub-therapeutic concentrations. The most of hazardous drug interactions are caused by another co-administered drug, food, or natural substance that interferes with the metabolic clearance of one drug. An extensive review of published studies in the PubMed database, Research gate, Google Scholar, Science Direct, and recent conference papers was performed to attain comprehensive publications. "Tables (1-3) show an overview of commonly used herbs", the results of herb-TPH interactions, and the associated mechanisms.

Herbs with inductive effect on tph metabolism

Andrographis paniculata

Andrographis paniculata, also known as kalmegh or chuanxinlian, is a herb used to cure common colds, diarrhea, and fever caused by infectious diseases in Asia[11]. The major bioactive components of *A. paniculata* are andrographolide (ANGD) and neoandrographolide. These compounds exhibit anti-inflammatory, anticancer, anti-platelet aggregation, antiviral, and hepatoprotective activities[12-17]. The CYP450 family, CYP1A1 and CYP1A2 mRNAs were significantly induced by ANGD[18&19] but, the entire extract of the herb suppressed the activities of CYP1A2, CYP2C in rat and human liver microsomes[20]. In a recent in vitro investigation, it was discovered that ANGD inhibited the NF kappa B pathway, which could have a therapeutic effect in the treatment of asthma[21]. According to the results from an animal study, the clearance (CL) of TPH was dramatically raised and the area under the curve (AUC) was reduced in both pretreatment groups with ANGD and *A. paniculata* extract at low-dose administered TPH (1 mg/kg). When high-dose TPH (5 mg/kg) was given to the ANGD pretreatment group, the elimination half-life ($t_{1/2}$) and mean residence time (MRT) of TPH were decreased by 14% and 17%, respectively. This phenomenon found that other additional herbal components present in *A. paniculata* may interact with CYP1A2 substrate drugs like TPH, slowing its clearance mainly when TPH is given at large doses[22].

Commiphora myrrha

Briefly, myrrh is a dried oleo-gum resin of *Commiphora myrrha* (Burseraceae). Myrrh contains volatile oil (1.5–17%) composed of limonene, dipentene, pinene, eugenol, cinnamaldehyde and others, as well as up to 40% resins consisting of α-, β-, and γ-commiphoric acids[23]. Myrrh oil is used as a flavor ingredient or fixative in soaps, detergents, creams, lotions, and scents. It can be used as a flavoring agent in food[24]. In Ayurveda medicine, it has rejuvenating properties. It also has a historic place in traditional Chinese medicine (TCM). It is used to treat sinusitis, pharyngitis and bronchial complaints such as asthma[25]. It was observed in an animal study that significant differences were present in maximum blood concentration (C_{max}), area under moment curve (AUMC), AUC, $t_{1/2}$ and MRT of TPH when co-administered with *C. myrrha*, which affected metabolism and elimination of TPH. The markedly decreased C_{max} and AUC_{0-t} of TPH caused by co-administration with *C. myrrha* indicated that oral bioavailability of TPH was significantly reduced. This study has demonstrated that *C. myrrha* interferes with the PK of TPH at varying degrees in rabbits[26]. Clinical investigations are advised for the safe use of C. myrrha with CYP1A substrates.

Ephedra species

In asthma therapy, health professionals commonly prescribed herbal drugs containing *Ephedra*, alone or in a combination with Liquorice which may be prescribed by physicians with TPH, a commonly anti-asthmatic drug and a typical CYP1A2 substrate.

In a PK experiment, the rats were given oral TPH (10 mg/kg/day) pretreated with EWD (18 g/kg) and MXCT (0.2 g/kg) for 14 days. When compared to the control groups, the AUC_{0-24} hr and C_{max} of TPH were markedly lowered. The authors demonstrated that pretreatment with EWD or MXCT increased CYP1A2 activity, which sped up the metabolism of TPH. The administration of

EWD or MXCT with TPH at the same time may decrease the effect of TPH in rats[27].

Evodia rutaecarpa

Many studies have indicated that traditional Chinese herbs are beneficial in the prevention and treatment of a variety of diseases. *Evodia rutaecarpa* (Wu-Chu-Yu) is still China's most popular and multi-purpose herb for treating headaches, abdominal pains, postpartum bleeding, diarrhea, and amenorrhea. One of the interesting alkaloids isolated from *E. rutaecarpa* is rutaecarpine. It has a broad range of biological actions, including vasodilator, inotropic, platelet aggregation inhibitor, and anti-inflammatory properties[28].

In the rat model, the ethanolic extract of *E. rutaecarpa* fruit (1 and 2 g/kg/day) was given orally to rats for three consecutive days and on the fourth day TPH was administered (2 mg/kg, IV). PK data were calculated by a non-compartmental model. The results elucidated that the TPH level was significantly decreased by concomitant administration with the extract in a dose-related manner. *E. rutaecarpa* may be a selective and potent inducer of the CYP1A enzymes which are responsible for oxidative biotransformation of drugs such as TPH[10].

Fenugreek and garden cress

Fenugreek is the dried ripe seeds of *Trigonella foenum-graecum* (Fabaceae). Simple alkaloids such as trigonelline, gentianine, and saponin account for the majority of fenugreek's components. It has long been utilized in nutrition and in the treatment of kidney problems, diabetes mellitus, cellulitis, and tuberculosis. Fenugreek has also been used in hypercholesterolemia, coagulation diseases, enhancement of breast milk production, and increasing male sexual desire[29-31].

Garden cress is the dried ripe seeds of *Lepidium sativum* (Cruciferae). Glucosinolates are the primary constituents of *Lepidium sativum*. Ascorbic acid, cucurbitacins, and cardenolides are some of the other compounds. It can be beneficial for respiratory disorders, vitamin C deficiency, constipation, poor immunity, and as a diuretic. Its seeds are used by Indian medicine practitioners to treat dysentery, as well as fever and catarrhal infections[32].

A study investigated the influence of fenugreek and garden cress on the PK of TPH in beagle dogs. Results showed that treatment with *fenugreek* led to a decrease in C_{max} and AUC_{0-t} of TPH of about 28% and 22%, respectively. Garden cress produced a smaller decrease in C_{max} and delayed time of peak concentration (t_{max}) of TPH, while AUC_{0-t} increased by about 37.44%[33]. The concurrent use of TPH with *fenugreek* or *garden cress* can make changes in the PKs of TPH in an animal model.

Sophora flavescens

Sophora flavescens, (Fabaceae), also known as Kushen, is still an important herb in TCM. *S. flavescens* has been extensively used, mainly as an adjuvant with other medicinal herbs to treat fever, dysentery, jaundice, oliguria, asthma, and inflammatory disorders. A large number of compounds have been isolated from *S. flavescens*. The major components that have been identified are flavonoids and alkaloids. At least 50 pure chemicals from *S. flavescens* have been found to have anticancer, antibacterial, antipyretic, anti-nociceptive, and anti-inflammatory properties in many in vitro and in vivo studies[34]. Effects of *S. flavescens* extract on TPH-metabolizing CYPs and the PK profile of TPH were tested in rats to evaluate this suggested interaction.

TPH-8-oxidation and N-demethylation activities were stimulated after *S. flavescens* extract was administered. The rise in oxidative activities corresponded to an increase in the protein levels of CYP1A2, CYP2B1/2, CYP2C11, and CYP3A. Both AUC and AUMC were reduced after the extract administration. These results demonstrated that *S. flavescens* decreased TPH blood concentration by accelerating the elimination process[35].

Salvia miltiorrhiza

Danshen, the common name of the dried root of *Salvia miltiorrhiza*, is used in TCM to promote circulation and blood stasis. It also treats and prevents coronary artery diseases, hyperlipidemia, and cerebrovascular illnesses. The amount of tanshinones (diterpene quinones), salvianolic acid and polyphenolic acids in the extract can be identified to standardize the danshen products[36&37].

According to limited in vitro and animal research, danshen extracts tend to modulate the activities of several CYP450 isoenzymes. However, these effects did not appear to be clinically relevant except a study published by Kuo and collaborators in 2006 in mice demonstrated that extract of danshen in ethyl acetate, which is not used in pharmaceutical preparations, induced the activity of the CYP1A2 isoenzyme by about 60%[38]. In a separate crossover designed study, 12 healthy volunteers were given a single 100 mg dose of TPH alone, followed by 14 days of taking 4 tablets, each containing 1 g of *danshen* extract, thrice a day. Danshen slightly reduced the duration to maximal TPH levels, but this was not expected to have any clinical implications, and no other PK parameters were changed[39]. The inductive effect of Danshan on isoenzyme CYP1A2 is likely due to Danshan's alcoholic extracts rather than aqueous extracts.

Herbs with inhibitory effect on tph metabolism

Acacia catechu

The heartwood extract of *Acacia catechu*, has pharmacological actions such as immune-modulatory, antipyretic, hepatoprotective, and antioxidant activities. *Acacia catechu* is mostly used in traditional or folk medicine, mainly in Asia[40-43].

An animal study of pretreated rabbits with extract of heartwood resulted in highly elevation of TPH C_{max}, t_{max}, and AUC which was about 41.32%, 35.71% and 15.03%, respectively. TPH CL, the volume of distribution (Vd), and $t_{1/2}$ were decreased. These observations suggest that heartwood inhibits CYP1A enzymes and P-gp (P-glycoprotein) activity[4].

Angelica species

Angelica rhizome, (Umbelliferae), is promoted as a functional food supplement for women's health, a sedative, anodyne, and/or tonic agent in Asia. Three different *Angelica* species have been recorded to contain the most active principle, decursin[44]. Decursin, has various pharmacological properties, including anticancer, anti-bacterial, platelet aggregation inhibitor and anti-inflammatory effects[45]. A study has pointed out that decursin suppressed the activities of CYP1A2, CYP2D15, and CYP3A12 in canine liver microsomes[46]. A recent in vitro investigation revealed that decursin derivatives had a potential therapeutic benefit in the treatment of asthma[47].

A study investigated the impact of decursin on the PK of TPH, a typical substrate of CYP1A2 isoenzyme in rats. When TPH (10 mg/kg) was given, CL, elimination rate constant (Ke) of TPH were substantially reduced, whereas AUC, C_{max}, and $t_{1/2}$ were increased in decursin (25 mg/kg) pretreatment. Based on these results, pretreatment of decursin decreased the elimination of TPH. So, chronic use of decursin with TPH concomitantly could elevate the concentration of TPH in the blood. There are suggestions about the interaction of decursin with CYP1A2 substrates[45].

Astragalus species

Astragaloside IV (AGS-IV) is a triterpene glycoside derived from the radix of *Astragali* which has different pharmacological properties such as antihypertensive cardio-tonic, antioxidant, anti-inflammatory, and antiviral actions. The effect of AGS-IV on the CYP1A2 isoenzyme was studied in vitro with phenacetin and in vivo with TPH. AGS-IV inhibited the activity of CYP1A2 isoenzyme and influenced the PK parameters of TPH in rats[48].

Cassia auriculata and Cardiospermum halicacabum

Herbal teas made from dried flowers of *C. auriculata* (Leguminosae) and aerial portions of *C. halicacabum* (Sapindaceae) are most widely consumed in Sri Lanka. *C. auriculata* is considered to be beneficial for individuals suffering from diabetes mellitus, constipation, and diseases of the urinary tract, while *C. halicacabum* is reputed to be beneficial for rheumatism, nervous diseases, digestive, and pulmonary disorders. In the past, a study was established to determine the impact of co-administration of teas prepared from *C. auriculata* or *C. halicacabum* with TPH, on the steady-state serum levels of the prescribed TPH, using rats as an experimental model. When TPH was given concurrently with herbal tea made from either of the above herbs, the results showed a significant increase in steady-state levels of TPH. *C. auriculata* and *C. halicacabum* enhanced steady-state levels of TPH by 32.5% and 48.2%, respectively, when compared with the levels in animals receiving

TPH alone at the same time[49]. Herbal preparations from the aforementioned herbs should be avoided by patients treated with TPH as these two herbs have the potential to influence the bioavailability of TPH.

Scutellariae baicalensis

Baicalin, a flavone glucoronide, is one of the major flavonoidal compounds of *Scutellariae* radix, the root of *Scutellariae baicalensis*. Baicalin has been used as a phytochemical marker for quality control in TCM. Also, baicalin has been reported to possess different pharmacological actions, including anti-allergic, anti-inflammatory and antioxidant properties[50]. The binding of baicalin to human plasma proteins was between 86% and 92%[51]. In a study that focused on plasma protein binding and the influence on CYP1A2, the effect of baicalin on the PK of TPH in rats was investigated. C_{max} was remarkably increased by 43% and Vd was decreased by 29% for unbound TPH in rats treated with different dosage regimens of baicalin. Baicalin resulted in alterations in C_{max}, $t_{1/2,}$ CL, and AUC of TPH by two mechanisms: plasma protein binding displacement and CYP1A2 activity suppression[52].

Herbs with insignificant effect on tph metabolism

Nigella sativa

Nigella sativa (Ranunculaceae) usually known as black seed, is an annual herb that grows in Mediterranean-coastal regions. Over a thousand years, the seeds have been recognized as a natural treatment to enhance health and treat ailments[53]. For example, the oil of *Nigella sativa* is used as a traditional medicine for the treatment of arthritis, lung diseases, and hypercholesterolemia[54&55]. Some important constituents of the seeds include thymoquinone, nigellone, and isoquinoline alkaloid. Thymoquinone is 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[56]. A study investigated the influence of *black seed* on the PK of TPH in beagle dogs. The black seed treatment group had no significant effect on TPH disposition as determined by C_{max}, t_{max}, AUC_{0-t}, and CL[33].

Cassia occidentalis

Cassia occidentalis, (Caesalpiniaceae), is an ayurvedic medicinal herb. It is also known by other names, e.g. *coffee senna*, *fetid cassia*, and *negro coffee*. It has been found to possess significant antibacterial, antifungal, analgesic, laxative, and diuretic features. The main phytochemicals present in *C. occidentalis* include achrosin, aloe-emodin, emodin, and anthraquinones[57]. When ethanolic extract of *C. occidentalis* was co-administered with TPH in rats, no differences in TPH bioavailability were identified when compared to methotrexate, methylprednisolone, and acetaminophen groups[58].

Pomegranate and Licourice

Pomegranate, Punica granatum has gained popularity as a natural antioxidant that may be taken as a fruit or juice[59&60]. However, it showed PK interactions with antiarrhythmics, calcium channel blockers, and statins[61]. Pomegranate juice has been proven to inhibit CYP3A and to interfere with the intestinal absorption of certain drugs, most likely due to the modulation of transporters involved in the absorption process[62&63]. *Licorice*, *Glycyrrhiza glabra*, is a famous well-known traditional drink, particularly in the Middle East. However, licorice was observed to interact with some drugs like digoxin, thiazides, and spironolactone[64]. *Licorice* was also found to impair cyclosporine bioavailability by interacting with P-gp and CYP3A4 enzyme[65].
A preliminary report showed that one-week administration of aqueous *licorice* extract did not affect the PK of midazolam, a CYP3A4 substrate[66]. However, both glycyrrhizin and glycyrrhetic acid have recently been proved to induce CYP3A4 in humans[67&68]. A study was performed to determine the impact of pomegranate and *licorice* on TPH in rats. Findings showed that there was no interaction between *pomegranate* or *licorice* and TPH in rats. This was expressed by statistically non-significant differences between (C_{max}, t_{max} and AUC_{0-24} hr) between groups of rats that received TPH alone and those which received TPH with pomegranate juice or *licorice* juice orally. If extended to humans, this might be important in terms of providing information about TPH administration and usage. So, consumption of *pomegranate* or *licorice* juice

before oral intake of TPH did not result in significant PK interaction[69].

Ginkgo biloba

The extract of Ginkgo biloba contains many compounds, including flavonoids such as ginkgetin and bilobetin, which account for 27% of the extract. Another phytochemical category is ginkgolides, such as A, B, and C bilobalide, which make up 22% of the standardized extract[70]. In vitro and in vivo, ginkgo has been shown to have some small effects on CYP1A2. Ginkgo has been found to affect CYP2C9, CYP2D6 and CYP1E2 in vitro and in rat, but studies employing the specific probe substrates have revealed no clinically important effect. However, the impact of ginkgo on CYP3A4 is unclear (induction and inhibition reported), but any effect appears to be minor at best[71-73].

In an experimental study in rats pretreated with oral Ginkgo extract 100 mg/kg for 5 days, the serum level and AUC of a single 10 mg/kg oral dose of TPH given on day 6 were reduced by about 20% and 40% respectively, and a 70% increase of the CL was documented[74]. Activation of CYP1A2 by ginkgo is thought to be the cause of this interaction. Increasing the activity of this isoenzyme allows TPH to be metabolized and eliminated more quickly. Only experimental evidence supports the interaction between ginkgo and TPH. However, a human study using caffeine as CYP1A2 probe substrate, found that ginkgo has not clinically relevant effect[75].

St. John's wort

Hypericum perforatum, sometimes known as *St. John's wort* (SJW), is an antidepressant herbal medication. The two main constituents are hyperforin and hypericin[76]. P-gp regulated by hypericin, and hyperforin can induce CYP3A4, CYP2B6, and P-gp. SJW has been thoroughly explored because it has been linked to several clinical interactions with standard medications[77].

The findings of two cases of herb-drug interaction in healthy subjects' study between SJW and TPH were different. In the first case, no PK interaction was found after two weeks of co-administration of SJW with TPH, whereas a patient required an increase in TPH dosage while he was taking SJW for two months. In the first case of a study in 12 healthy subjects, it has been found that a standardized preparation of SJW 300 mg (hypericin 0.27%) three times daily for 15 days had no significant effect on the plasma level of a single 400 mg daily oral dose of TPH[78]. In the second case of the same study, it has been reported that a woman who had previously been stable for several months taking TPH 300 mg twice daily, was found to need a marked increase in her TPH dosage to 800 mg twice daily to achieve a serum level of 9.2 mg/L. Two months previously, she had started to take 300 mg of a SJW supplement (hypericin 0.3%) each day and when she stopped taking SJW, her serum TPH levels were doubled within 14 days to 19.6 mg/L and her TPH dosage was consequently reduced in spite of she was a smoker and subjected to other treatment regimens[79].

The mechanism of interaction is uncertain, but it has been suggested that treatment with SJW for 15 days was unlikely to induce the isoenzymes sufficiently to cause changes in TPH levels. SJW is regarded to have a limited potential to stimulate CYP1A2, whereas the second case should explain the considerable interaction over a two-months period. Furthermore, most clinically significant interactions with SJW are mediated by CYP3A4. However, it would be prudent to be mindful of the possibility of an interaction until more information is available. Patients should be aware of possible adverse effects with concurrent use[80].

Rhodiola rosea

Rhodiola is a herb that is widely utilized all over the world. It is classified as an adaptogen, and it is used to cope with stress, improve mood, and alleviate depression. Rosavins are regarded to be the most active constituents in *Rhodiola.* They are a complex series of monoterpene alcohol and phenylpropanoid glycosides such as rosin and rosarin. *Rhodiola* also contains flavonoids, β-sitosterol, tannins, and rhodiolosides. An in vitro study found that *Rhodiola* root extract inhibited CYP3A4 isoenzyme, but the extent of the inhibition increased with high concentrations of rosarin content[81]. *Rhodiola* did not affect TPH, hence it appears unlikely to affect the metabolism of other drugs that are CYP1A2 substrates. Only experimental

evidence supports the interaction of rhodiola and TPH. Rats in a study were given a standardized *rhodiola* extract twice daily for 3 days with a single dose of aminophylline (an ethylenediamine salt of TPH), given one hour after the last dose of rhodiola. The PKs of TPH were slightly influenced by the rhodiola extract (less than 15% decrease in AUC)[82]. Data obtained from this single study appears to be limited, and cannot be directly applied to humans. However, the PK of TPH is unlikely to be affected by *rhodiola* extract in a clinically significant manner.

Conclusion

Asthmatic patients are increasingly turning to complementary and alternative therapies. Because TPH has a limited therapeutic index and high inter-individual PK variability, therapeutic monitoring of TPH serum levels is critical to avoid any unwanted events. When medicine with a limited therapeutic index (e.g., theophylline, warfarin, cyclosporine, tacrolimus, etc.) is involved, the interactions might have dangerous or perhaps even devastating consequences. Despite a rise in the amount of data available on medicinal herb interactions, there is still a scarcity of information on the pharmacodynamics and PKs of herb-drug interactions, as well as their complicated role. Enzyme induction is a process in which certain herbal medicines and/or medications cause an increase in biotransformation and, as a result, a decrease in efficacy due to rapid metabolism, while enzyme inhibition, on the other hand, can result in higher serum levels of the un-metabolized substance, increasing the risk of toxicity. This makes it challenging to characterize and forecast interactions, as well as gain knowledge about the mechanisms.

Changes in TPH bioavailability were reported by induction mechanism when it is used concomitantly with the following herbs: *Andrographis paniculata, Commiphora myrrha, Ephedra species, Evodia rutaecarpa, Lepidium sativum, Sophora flavescens, Salvia miltiorrhiza,* and *Trigonella foenum-graecum* as shown in Table 1. TPH bioavailability was increased by inhibition mechanism on CYP1A2 when co-administered with *Acacia catechu, Angelica species, Astragalus species, Cassia auriculata, Cardiospermum halicacabum* and *Scutellariae baicalensis* as shown in Table 2 meanwhile, concomitant use of TPH with *Cassia occidentalis, Glycyrrhiza glabra, Ginkgo biloba, Hypericum perforatum, Nigella sativa., Punica granatum* and *Rhodiola rosea* as illustrated in Table 3 were reported to be statistically insignificant.

Table 1: Herbs with inductive effect on TPH metabolism:

Herb	Synonym	Mechanism of interaction	Effect	Model	Reference
Andrographis paniculata	Kalmegh	Induced expression of CYP1A2	TPH clearance significantly increased	Rat	22
Commiphora myrrha	Myrrh	Induced CYP1A2	TPH blood level markedly decreased	Rabbit	26
Ephedra species	Ma huang	Potent inducer of CYP1A2	Metabolism highly increased, TPH serum level decreased	Rat	27
Evodia rutaecarpa	Wu-Chu-Yu	Potent inducer of CYP1A2	TPH level significantly decreased	Rat	10
Lepidium sativum	Garden cress	Induced CYP1A2	TPH serum level decreased	Beagle dogs	33
Sophora flavescens	Kushen	Induced CYP1A2 and accelerated elimination	TPH concentration decreased	Rat	35
Salvia miltiorrhiza	Danshen	Induced CYP1A2	Alcoholic extract highly induced CYP1A2 protein expression	Mice	38
Salvia miltiorrhiza	Danshen	Induced CYP1A2	Time to maximum TPH level slightly decreased, no changes in PK parameters	Human	39
Trigonella foenum-graecum.	Fenugreek	Induced CYP1A2	TPH serum level decreased	Beagle dogs	33

Table 2: Herbs with inhibitory effect on TPH metabolism:

Herb	Synonym	Mechanism of interaction	Effect	Model	Reference
Acacia catechu	Black cutch	Inhibited both CYP1A2 and P-gp	TPH serum level significantly increased	Rabbit	4
Angelica species	Dong quai	Inhibited CYP1A2	TPH blood serum levels increased	Rat	45
Astragalus species	Milkvetch	Inhibited CYP1A2	TPH blood serum levels increased	Rat	48
Cassia auriculata	Avaram senna	Inhibited CYP1A2	Enhanced TPH steady-state levels	Rat	49
Cardiospermum halicacabum	Balloon vine	Inhibited CYP1A2	Enhanced TPH steady-state levels	Rat	49
Scutellariae baicalensis	Baikal skullcap	Inhibited CYP1A2 Plasma protein binding displacement	TPH serum significantly increased	Rat	52

Table 3: Herbs with insignificant effect on TPH metabolism:

Herb	Synonym	Mechanism of interaction	Effect	Model	Reference
Cassia occidentalis	Coffee senna	Not found	Not significant	Rat	58
Glycyrrhiza glabra	Licorice	No relevant interaction	Not significant	Rat	69
Ginkgo biloba	Ginkgo	Minor CYP1A2 induction	TPH serum level decreased	Rat	74
Ginkgo biloba	Ginkgo	Minor CYP1A2 induction	No effect	Human	75
Hypericum perforatum	St. John's wort	Uncertain	No significant outcomes, TPH serum level decreased in one case of clinical study	Human	78
Nigella sativa	Black seed	No relevant interaction	Not significant	Beagle dogs	33
Punica granatum	Pomegranate	No relevant interaction	Not significant	Rat	69
Rhodiola rosea	Rose root	Unlike to affect CYP1A2	Not significant, TPH level slightly decreased	Rat	82

In vitro research, animal studies, and individual case reports provide the majority of the scientific evidence regarding TPH's interactions with medicinal herbs, but clinical studies are rare and meta-analyses are not reported in the literature. New interactions between TPH and medicinal herbs are likely to emerge as a result of the widespread use of herbal supplement therapy with TPH, which must be within the therapeutic range.

Because the results of the in vitro and in vivo experiments can not be extrapolated to humans, there is no way to predict how TPH may interact with herbal supplements in humans. This approach can lead to additional studies of putative interactions between TPH and some bioactive components of medicinal herbs. When patients are treated with a TPH regimen in combination with other herbs, each case report must be accurately documented, carefully analyzed, and revised. Co-administration of herbal supplements should be closely monitored.

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دراسة استعراضية للتفاعلات الدوائية للثيوفيللين مع الأعشاب الطبية

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الثيوفيلين (TPH) هو موسع قصبي بمؤشر علاجي محدود ذو حركية دوائية متقلبة بين الأفراد. تعد التفاعلات المحتملة بين الأدوية والأعشاب مصدر قلق كبير للسلامة ، خاصة بالنسبة للأدوية ذات المؤشرات العلاجية المقيدة ، مثل TPH ، والتي يمكن أن تؤدي إلى آثار ضارة خطيرة تهدد الحياة. في هذه الورقة ، تم تلخيص التفاعلات بين TPH والأعشاب الطبية المسجلة في الأدبيات وتم التحقيق والبحث للمراجع التي تم تحليلها. تم الإبلاغ عن انخفاض في التوافر الحيوي لـ TPH أثناء اعطائه مع بعض الأعشاب أو المستخلصات العشبية (Andrographis paniculata، Commiphora myrrha ، أنواع الإيفيدرا ، Evodia rutaecarpa، Lepidium sativum، Sophora flavescens ، سالفيا ميلتيورون. – graecum) كما وتم زيادة التوافر الحيوي لـ TPH بواسطة آلية التثبيط على CYP1A2 عند تناوله بالاشتراك مع الأعشاب (أكاسيا كاتشو ، وأنجيليكا ، وأنواع استراغالوس ، وكاسيا أوريكولاتا ، و Cardiospermum halicacabum و Scutellariae baicalensis) وفي الوقت نفسه ، الاستخدام المتزامن لـ TPH مع (Cassialycyralis)، Ginkgo biloba، Hypericum perforatum، Nigella sativa، Punica granatum و Rhodiola rosea) تم الإبلاغ عنها بأنها احصائيا غير ذات أهمية. في هذه المراجعة ، ركزنا على التفاعلات بين TPH والأعشاب الطبية التي لم تتم تغطيتها في الدراسات السابقة. لتقليل المخاطر الصحية للمرضى والتى من المتوقع أن تخدم المتخصصين فى المجال الصحى .