ejpmr, 2018,5(4), 270-272

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

HERBAL DRUG INTERACTIONS MEDIATED BY P-GLYCOPROTEIN – AN OVERVIEW

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Article Received on 12/02/2018 **Article Revised on 04/03/2018** **Article Accepted on 25/03/2018**

ABSTRACT

Herbal medicines are widely used for treating various ailments. Many herbs have shown to alter the pharmacological activity of co-administered allopathic medicines thus adversely affecting the clinical efficacy of these drugs. Concurrent use of drugs and herbal products can modulate p-glycoprotein drug transporter either by induction or inhibition of p-glycoprotein pump. P-glycoprotein is a member of the ATP-binding cassette super family of membrane transporters. The review provides an overview of commonly used medicinal and/or dietary herbs which taken part in interaction of the drugs which is mediated by p-glycoprotein.

KEYWORDS: Herbs, drug efflux, p-glycoprotein.

INTRODUCTION

Herbs have been used for medicinal purposes since time immemorial. Almost one third of most potent drugs such as digitalis, morphine, atropine and several chemotherapeutic agents were developed from plants. Herbs can affect body functions; hence, when herbs are taken concurrently with drugs, interactions are possible.[1] Due to high prices and potential side effects of synthetic drugs, people rely more on herbal. The irony is that herbal preparation contains several components of different biological activities and hence mimic, increase, or reduce the effects of co-administered drugs.[2]

P-glycoprotein (P-gp) is also known as multi-drug resistance protein 1 (MDR 1). P-gp functions as a transmembrane efflux pump, pumping its substrates from inside to outside the cell. Drugs which induce or inhibit P-gp can interact with other drugs handled by the pump.[3] Thus it plays an important role in regulating the absorption, distribution and elimination/ reabsorption and therapeutic efficacy of many clinically important therapeutic substances. Modulation of P-gp by herbal constituents may involve in direct interaction with one or more binding sites on the P-gp molecule through competitive or non-competitive inhibition or induction of the efflux of drugs. Phytochemicals may also inhibit ATP binding, hydrolysis or coupling of ATP-hydrolysed molecules, therefore, depleting the energy which drives the translocation of P-gp bound substrate drugs.[2]

Induction of P-gp will reduces the bioavailability of drugs which lead to therapeutic failure and inhibition of P-gp will produce toxicity by increasing the bioavailability of drugs. The relevant herbal interactions mediated by P-gp are summarized in table 1. Therefore, the inhibition or induction of P-gp by concurrent herbs may result in interactions potentially leading to therapeutic failure. On the other hand, the herbal modulation of their expression and/or activity could be a useful strategy to improve the efficacy and safety of P-gp substrate drugs.[4] This paper reviews some of the commonly used medicinal and/or dietary herbs which taken part in interaction of the drugs which is mediated by P-gp.

Table 1: Herbal drug interaction mediated by p-glycoprotein.

S. No.	Botanical name	Common name	Interacting drug	Effect
1.	*Ginkgo biloba*	Ginkgo	Talinolol	Inhibit P-gp efflux, increase talinolol bioavailability[5,6]
2.	*Allium sativum*	Garlic	Saquinavir	Induction of P-gp, decrease saquinavir bioavailability[6]
3.	*Allium cepa*	Onion	Ritonavir	Inhibit P-gp efflux, lead to intracellular accumulation of ritonavir[4]
4.	*Camellia sinensis*	Green tea	Doxorubicin, vinblastine	Inhibit transport activity of P-gp in various cancer cell, lead to intracellular accumulation of doxorubicin[7]

5.	*Zingiber officinale*	Ginger	Vinblastine	Inhibit P-gp efflux, lead to intracellular accumulation of vinblastine produce toxicity[7]
6.	*Piper nigrum*	Black pepper	Digoxin	Inhibit P-gp efflux, lead to intracellular accumulation of digoxin[8]
7.	*Piper nigrum*	Pepper	Fexofenadine	Inhibit P-gp efflux, increase the bioavailability of fexofenadine thus lead to toxicity[18]
8.	*Capsicum frutescens*	chili pepper	Cyclosporine A	Inhibit P-gp efflux, increase Cyclosporine A bioavailability[23]
9.	*Rosmarinus officinalis*	Rosemary	Doxorubicin and vinblastine	Increase the accumulation of chemotherapeutic agents by inhibiting the binding to P-gp[9]
10.	*Curcuma longa*	Turmeric	Digoxin	By Inhibiting P-gp and MDR1 mRNA expression levels, lead to intracellular accumulation of drugs[10]
11.	*Panax ginseng*	Red ginseng	Fexofenadine	Inhibition of P-gp, fexofenadine bioavailability increases[11]
12.	*Hypericum perforatum*	St John's wort	Sulphonylureas	Induction of P-gp, decrease the efficacy of Sulphonylureas[12]
13.	*Hypericum perforatum*	St John's wort	Digoxin	Induction of P-gp, decrease digoxin blood concentration[19]
14.	*Hypericum perforatum*	St John's wort	Cyclosporine	Induction of P-gp, decrease blood concentration of cyclosporine[15,6]
15.	*Hypericum perforatum*	St John's wort	Tacrolimus	Induction of P-gp, decrease tacrolimus bioavailability[21]
16.	*Carica papaya*	Pawpaw	Digoxin, amiodarone	Increase drug bioavailability of digoxin, amiodarone by inhibiting P-gp[13]
17.	*Acacia nilotica*	Gum Arabic	Cyclosporine A	Increase drug bioavailability of Cyclosporine A by inhibiting P-gp[13]
18.	*Citrus aurantium L*	Sour orange	Felodipine, vinblastine	Inhibit P-gp efflux, increase the bioavailability of drugs and thus lead to toxicity[13, 14]
19.	*Ipomea batatas*	Sweet potato	Rhodamine 123	Inhibit P-gp efflux, increase the bioavailability of drugs and thus lead to toxicity [13]
20.	*Citrus paradise*	Grapefruit juice	Felodipine, nicardipine, nifedipine, nimodipine, isaradipine, verapamil	Inhibit P-gp efflux, increase the bioavailability of drugs and thus lead to toxicity[14, 17]
21.	*Citrus reticulate*	Tangerine juice	Digoxin, nifedipine	Increase the absorption of digoxin and nifidipine by inhibiting P-gp efflux[14]
22.	*Morinda lucida* Benth	Brimstone tree	Digoxin	Increase the bioavailability of digoxin by inhibiting P-gp efflux[13]
23.	*Sesamum indicum*	Sesame	Daunorubicin	Increase the bioavailability of daunorubicin by inhibiting P-gp efflux [13]
24.	*Colchicum autumnale*	Colchicine	Diltiazem	P-gp inhibition, lead to increase bioavailability[16]
25.	*Mangifera indica*	Mango juice	Diclofenac, midazolam, chlorzoxazone, verapamil, warfarin	Inhibit the P-gp drug efflux pump, lead to intracellular accumulation of drug, toxicity occur[14]
26.	*Morus nigra*	Mulberry juice	Midazolam, Cyclosporine	Activate the P-gp, decrease intracellular accumulation, decrease efficacy[14]
27.	*Psidium guajava*	Guava juice	Midazolam	Accumulation of P-gp substrates by inhibiting the drug efflux, weak P-gp inhibitor[14]
28.	*Glycyrrhiza glabra*	Liquorice	Cyclosporine A	Induction of P-gp, decrease cyclosporine blood concentration[20]
29.	*Momordica charantia*	Bitter melon	Vinblastine	Inhibit P-gp efflux, increase vinblastine bioavailability [22]

CONCLUSION

There is a continued global increase in the use of herbal products and supplements which increase the incidence of herbal drug interactions. Any new drugs that are substrates for CYP3A4 and/or P-gp have a potential to cause herbal drug interactions. Herbal medicines are found to be higher among patients; physicians should have a better knowledge on herbal drug interactions and adopt proper strategies to minimize harmful herbal drug interactions. Identifying the mechanism of drugs that

interact with herbal medicines is important. When drugs have to be used in combination with the herbs, dose adjustment may be needed and discontinuation of therapy is necessary when toxic drug-herb interactions occur.

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