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Phyto-anesthetics: A mini-review on herb–anesthesia drug interactions

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ABSTRACT

Over the years studies have shown the high prevalence rate in the use of herbal drugs among patients, doctors and health workers as such there is a need to take care of any health consequences associated with herbal drugs administrations. Herbal drugs are made of pharmacologically effective constituents, that can interact with anesthesia drugs that risk the life of the patients in question. In addition, pharmacokinetics and pharmacodynamics of herbal drugs are yet to be fully understood thus still needs more study. In view of this anesthesiologist should take a thorough history of the patient in question, taking into full consideration earlier use of herbal medicine/drugs by the patient. The aim of this article is to provide a mini-review on herb–anesthesia drug interactions.

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1. Introduction

The formulation of effective and potent therapeutic agents has been improved by harnessing the natural capabilities of medicinal herbs and plants. Studies reveal that about 80% of citizens of most developing countries still believes in the use of traditional alternative medicine as their primary health care. Any plants

source administered either completely or partially with the aim to treat an injury can be referred to as an herbal drugs [1]. Simon and colleague corroborated this fact that herbal drugs are administered to treat diseases and injuries and are the most ancient form of health care available to man [2]. Over the years the World Health Organization (WHO) also has specific herbal drugs as complete, branded medicinal products made up of potent ingredients, however, WHO have stipulated and strict rules and guidelines setting the perimeters for the assessment of the safety, efficacy, and quality of herbal medicines [3].

Several medicine systems including homeopathic and ayurvedic and traditional medicine have their constituents fully grounded

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Table 1
Merits and demerits of herbal drugs.

Merits	Demerits
Less expensive compared to conventional drugs.	Not completely efficient for some diseases and accidents
Complete and easily accessible	Complexity in standardizations
Increased health protection	Risk with self-dosing
Potency and efficiency are very high.	Pharmacokinetics and pharmacodynamics still poorly understood.
Fewer side-effects have been reported as the case maybe	
Easily tolerable.	

in herbal drugs. Finally, past decades have witnessed an increase in the consumption of herbal drugs with no prescription from a qualified health worker. In this article, we will make a mini-review on the available interactions between anesthetic drugs and administered herbal drugs. See Table 1 for merits and demerits of herbal drugs.

1.1. Toxicity and safety classification for herbal drugs

In order to be sure of the safety and potency of various herbal drugs, the American Herbal Products Association has developed a safety classification in relation to their toxicity level [4–8]. In addition, these classifications only include herbs with detailed and reported traditional use. There are four identified safety classes for herbs (Fig. 1) [9]; Class 1: Safe herbs; Class 2: Herbs with specific restricted use; Class 3: Herbs to be administered or prescribed by a qualified and registered physician and finally Class 4: Herbs without enough safety data for classification.

Furthermore, the toxicity of herbal drugs can result from differences in cultivation and processing of different herbal drugs [10–13]. Toxicity related herbal therapy could be divided into four groups namely: Class 1: Herbal drugs/plants with unknown toxicity; Class 2: Mistakenly known herbal drugs/plants with toxic activity; Class 3: Contamination of herbal drugs/plant with pesticides, heavy metals and other chemical materials; Class 4: Toxic Interaction of herbal drug/plants with conventional drugs.

1.2. Mechanisms of herb–anesthesia drug interactions

The overlapping substrate specificity in the biotransformational pathways of the physiologic systems is seen as the major reason for drug–drug, food–drug, and herbal drug interaction (HDI) [14]. The two main mechanisms of herb–drug interaction are the induction or inhibition of intestinal and hepatic metabolic enzymes particularly the CYP enzyme family. In addition, the similar effect on drug transporters and efflux proteins particularly the *p*-glycoproteins in the intestines is responsible in most other cases [15]. The pre-systemic activity of CYP and efflux proteins often influence oral bioavailability, thus the modulating activity of co-administered herbal products has been shown to result in pronounced reduction or increase in the blood levels of the affected drugs [16]. Majorly the interaction of herbal products with hepatic enzymes has been reported to cause pharmacodynamic effects [17,18]. Mechanism of liver injury may include bioactivation of CYP, oxidative stress, mitochondrial injury, and apoptosis [19]

1.3. Induction and inhibition of metabolic enzymes

Herbal drug interaction with conventional drugs may result in toxic reactions. There are few available fundamental proposed pathways but the basic molecular mode of action of this interaction is yet to be explained [20–22]. There are have been three proposed pathways responsible for herbal drug–anesthesia drug interaction: Firstly, variation in metabolic Phase I–III system by herbal drugs causing alterations in drug concentrations has been proposed as a pathway for herb–anesthesia drug interaction.

Phase I: The oxidative action of cytochrome P450(CYP) mono-oxygenase on xenobiotics. Herbal drugs have been identified to stimulate or suppress the activities of this enzymes thereby leading to altered metabolism of conventional drugs [23–25]. The CYP superfamily is generally involved in the oxidative, peroxidative, and reductive biotransformation of xenobiotics and endogenous compounds [26]. It is conventionally divided into families and subfamilies based on nucleotide sequence homology [27]. The most important CYP subfamilies responsible for drug metabolism in humans are 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5 [28]. Induction is the increase in intestinal and hepatic enzyme activity as a result of increased mRNA transcription leading to protein levels higher than normal physiologic values. Certain herbal products have been shown to be capable of inducing CYP. Concomitant administration of enzyme-inducing herbal products and prescription drugs can, therefore, result in sub-therapeutic plasma levels of the latter with therapeutic failure as a possible clinical consequence. Apart from enzyme induction, herbal products can also inhibit enzyme activities. The inhibition of CYP and other metabolic enzymes is usually competitive with instantaneous and inhibitor concentration-dependent effects [29].

Phase II: Besides their influence on the enzymatic activities of CYP, herbal medications can alter the absorption of concomitantly administered medicines through a number of mechanisms. Changes in the gastrointestinal pH and other biochemical factors can alter dissolution properties and the absorption of pH-dependent drugs such as ketoconazole and itraconazole. Complexation and chelation, leading to the formation of insoluble complexes and competition at the sites of absorption especially with site-specific formulations can greatly affect the absorption of medicines. Anthranoid-containing plants – cassia, Cascara, rhubarb and soluble fibers including guar gum and psyllium can decrease drug absorption by decreasing GI transit time. They are known to increase GIT motility. On concomitant use with prescribed medication, significant alteration in the absorption of the latter has been reported due to decreased GI transit time [30].

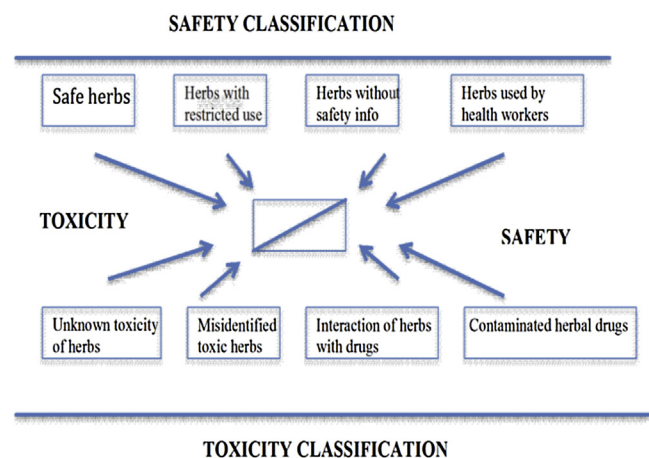


Fig. 1. Classification of toxicities related to herbal drugs and safety classification of herbal drugs. This figure was reproduced from [9].

The absorption of drugs such as phenoxymethylpenicillin, metformin, glibenclamide, and lovastatin may be reduced by high-fiber herbal products through the sequestration of bile acids [31]. Mochiki and his team also reported the ability of Kambo, a traditional Japanese medicine, to stimulate elevated intestinal blood flow, and to induce increased secretion of gastrointestinal hormones including motilin, vasoactive intestinal peptide, and calcitonin gene-related peptide [32]. **Phase III:** Transporter proteins are responsible for the dumping of xenobiotic compounds out of the cell, however, natural compounds like herbal drugs inhibit the actions of these transporter proteins most importantly, ATP-binding cassette (ABC) transporter and P-glycoprotein [33]. The ATP-binding cassette (ABC) family of drug transporters plays

significant roles in the absorption, distribution, and elimination of drugs. P-gp, the most studied member of this family is a 170-kDa-plasma glycoprotein encoded by the human MDRI gene. It is constitutively expressed in a number of body tissues and concentrated on the apical epithelial surfaces of the bile canaliculi of the liver, the proximal tubules of the kidneys, the pancreatic ductal cells, the columnar mucosal cells of the small intestine, colon, and the adrenal glands [34]. It is actively involved in drug absorption and elimination from the intestines of the liver, kidneys, and the brain. Specifically, these proteins are involved in the processes of hepatobiliary, direct intestinal, and urinary excretion of drugs and their metabolites [35]. Thus, the modulation of P-gp, or competitive affinity as substrates for its binding sites by co-

Table 2
Important Herbal-Drugs interactions from Anesthesia Perspective.

Herbal drugs	Common Use	Interacting Drugs	Effects	References
Garlic	Most commonly used by individuals with high cholesterol, heart disease, and high blood pressure	Warfarin General anesthetics	Alters bleeding time Antagonistic effect on immunosuppressing medications	[52] [53]
Ginkgo biloba	To improve memory and prevent or treat Alzheimer disease and other dementias	Warfarin, aspirin, ticlopidine, clopidogrel, dipyridamole Trazodone Levodopa	Increased bleeding risk Coma Increases "off" periods in Parkinson patients Bilateral subdural hematoma	[54] [53]
Ginger	Anti-inflammatory agent, analgesic, antioxidant, thermogenic, and antibiotic	Warfarin Chemotherapy	Alteration of bleeding time Reduces side effect of chemotherapy (nausea)	[55]
Ginseng	To increase a sense of well-being (physical, mental, and/or emotional)	Warfarin Chlorpropamide Phenelzine sulfate	Decreases blood concentration of warfarin Hypoglycemia Induction of mania	[56]
St. John's wort	Treatment of mild-to-moderate depression, anxiety, or sleep disorders	Cyclosporine, Midazolam, Tacrolimu Amitriptyline, Digoxin, Indinavir, Warfarin, Phenprocoumon, Theophylline, Irinotecan, Alprazolam, Dextromethorpha, Simvastatin Sertraline, paroxetine, and Nefazodone Antidepressant or serotonergic drugs	Decreases blood concentrations of these drugs Serotonin syndrome Gastrointestinal disorder, allergic reactions, fatigue, dizziness, confusion, dry mouth, photosensitivity	[57]
Flaxseed	To lower serum cholesterol levels and as a laxative	Laxatives	Flaxseed may cause diarrhea and should be taken with ample water to prevent constipation and intestinal obstruction These products should not be taken with other dietary supplements or medications because the high fiber content may lower the body's capacity for absorption	[58]
Aloe	Laxative	Digoxin Thiazide diuretic Laxatives Antidiabetic agents	Increases potential for potassium loss which may increase the risk of toxicity Increases laxative effect may cause excessive fluid/electrolyte loss May potentiate hypoglycemia Less glycosuria	[48]
Karela or bitter melon	Used as a folk remedy for a variety of ailments like stomach complaints	Chlorpropamide		[59]
Liquorice	To relieve a spasmodic cough and gastric ulcers	Pregnisolone Hydrocortisone Oral contraceptives	Decreases plasma clearance, and increases plasma concentrations prednisolone Potentiates of cutaneous vasoconstrictor response Hypertension, edema, hypokalemia Decreased lithium concentrations	[60]
Psyllium	Dietary fiber and lower serum cholesterol	Lithium		[30]
Shankhapushpi	To improve memory	Phenytoin	Decreased phenytoin concentration loss of control of seizures	[53]
Chilli pepper	General analgesic	ACE inhibitors Theophylline	Cough Increased absorption and bioavailability	[53]
Black cohosh	The herbal antidote for such menopausal symptoms as hot flashes.	Oral contraceptives Tamoxifen Warfarin	Contains coumarin constituents Increases potential for bleeding	[61]
Milk thistle	Treatment of liver, spleen and kidney diseases	Acetaminophen Cyclosporine Cisplatin	Reduce liver toxicity because of these drugs	[53]
Kava	Treatment of anxiety and depression	Anti-Parkinson drugs Hepatotoxic drugs	Possible additive effects May increase risk of developing liver Damage	[62]
Goldenseal	Treatment of gastrointestinal disturbances, urinary disorders, skin ailments, and various infections	Debrisoquine Midazolam	Decreases urinary recovery ratio Increases blood concentration	[62]

administered herbs presents a potential for alteration in the pharmacokinetic profile of the drug. Pharmacokinetic interaction occurs when herbal drugs inhibit or decrease the normal activity level of drug transporters through a competitive or non-competitive mechanism. Interactions can also occur through the induction of transport proteins via the increase of the mRNA of the relevant protein. Studies have identified a number of clinically important P-gp inhibitors including phytochemicals – flavonoids, furanocoumarins, reserpine, quinidine, yohimbine, vincristine, vinblastine among others [36,37] reported that mobile ionophores such as valinomycin, nonactin, nigericin, monensin, calcimycin, and lasalocid inhibit the efflux of anthracycline by P-gp. The activation or suppression of signal transduction pathways might be another route for herb-anesthesia drug interaction. Fang and colleagues reported the importance and potency of technologies like transcriptomic and proteomic in detecting any modifications in signal transduction pathways resulting in herb-drug interactions [38].

1.4. Implications of herb–drug interaction

Several studies have reported the existences of pharmacological effects if herbal drugs that may lead to unhealthy and harmful herbal-drug interactions with prescribed with conventional medicines. Aged patients have been identified has the largest patronize of prescription medications and as such are more exposed to the risk of medication-related harmful events [39]. Antiplatelets and anticoagulants drugs are commonly prescribed for patients with cardiovascular and cerebrovascular diseases, however, [G1] patients with these diseases can also seek help in alternative medicine through the concomitant use of herbal medication [G2] with conventional medication to reduce their risk of developing arterial or venous thrombosis and stroke [40]. It should be noted that the number of these herbal drugs consumed actually increases the risk for drug interactions. Furthermore, patients do complicate issues by adding several over-the-counter medications/drugs with the already prescribed medication by a doctor thereby leading to poly-pharmacy in clinical practice [41,42]. Interactions between several administered herbs as reported by Raghuram and colleagues in the case of fenugreek (*Trigonella foenum-graecum* L., Fabaceae) responsible for lowering blood sugar levels, and when consumed with other herbs like *Momordica charantia* L. (Cucurbitaceae), necessary cares in the place of dose adjustments is required [43]. Basila and co-worker reported cases of coagulation and blood loss caused by the use of garlic, ginseng, and ginkgo during a surgical procedure [44]. The effect of general anesthesia can be potentiated by kava and valerian, which are known to possess sedative properties [45]. The hepatic microsomal enzyme cytochrome P450 3A4 is stimulated by St. John's wort and has been observed to alter the metabolism of an immunosuppressant and oncological chemotherapy [46]. Cheng and co-worker also reported the harmful interference of the use of herbal drugs with anesthesia drugs among pre-surgical patients without the knowledge of the anesthetists [47]. Any alteration in the diagnostic and therapeutic action of a drug caused by another administered specific exogenous drug or herbs is called drug interaction. The concept of drug interaction especially between herbal drugs and conventional drugs has been extensively studied [48]. See Table 2 for important herb–drug interactions. Several studies have reported Herbal–drug interactions including anesthesia drugs occurring in situations like the use of herbal drugs for weight reduction, performance and so on [13,49–51].

1.5. Mechanisms of herb–anesthesia drug interactions

Pharmacokinetics and pharmacodynamics are the two broad groups that mechanisms for herbal-anesthesia drug interaction

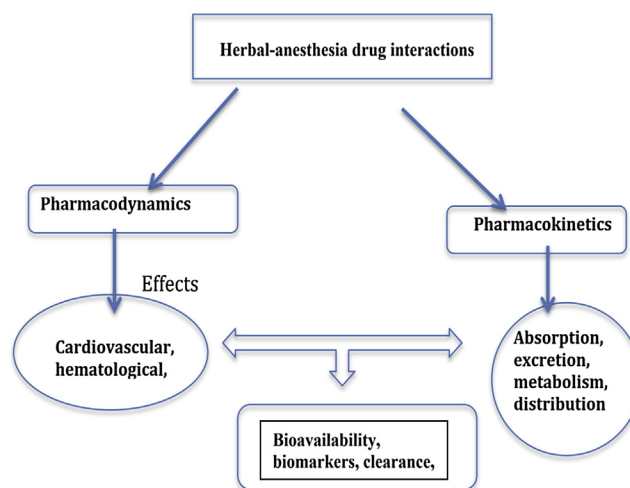


Fig. 2. Mechanisms of herb– anesthesia drug interactions. This figure was reproduced from [67].

can be divided [63–66]. When drugs either drug–drug or herbal–drug are co-administered resulting into one drug affecting the rate of metabolism of the other drug via induction of the drugs metabolizing enzymes is termed pharmacokinetic drug interaction (Fig. 2) [67].

Herbals like aloe gel, flaxseed, and psyllium that contain hydrocolloidal fibers, gums, and mucilage may experience abnormal absorption when administered together, they also have the ability to suppress other drugs absorption rate by binding to them thereby decreasing their systemic availability [68–70]. Furthermore, herbs like aloe latex, rhubarb, and senna have been reported by Kuhn and co-worker that they can cause loss of potassium ions and fluid that may result in toxicity when administered with digoxin [71]. Pharmacodynamic interactions are associated with any actions that can affect organ systems, receptor sites as a result of changes in the pharmacologic activity of the interacting agents. In addition, pharmacodynamic interactions have been found to be additive or synergetic as in the case of the increased hypnotic activity of benzodiazepines as a result of co-administration with valerian. In another case when lengthy doses of acetaminophen are concurrently administered with a hepatotoxic herbal drug it can result in increased risk of organ toxicity. However, no accurate or scientific, pharmacological and clinical based data are available for a vast majority of the herbal drugs as such the concepts of anesthesia drug–herbal drug interaction still remains unclear [64,68,72–78].

2. Conclusion

Though there have been several reported cases on herb–drug interactions but few reports have been made on herbal drug–anesthesia drug interaction [79–83]. In many of the reported cases of herbal–conventional drugs, no scientific basis have been provided for the mechanism as such extra care should be taken in administering herbal drugs with anesthesia drugs for pre-operative surgical patients [84–87]. However, if herbal drugs are to be continued to be administered for precise diagnose and treatment, qualified health workers will have to make an explicit assessment of the use of herbal drugs. Conclusively, more detailed and in-depth scientific research on the administration of herbal drugs and their co-administration with conventional drugs should be carried out rather than on the scantily reported data [88–91].

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SV and AE conceived of the study and participated in its design and coordination. SV supervised the whole study. All authors read and approved the final manuscript.

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