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Hypothetical Review

Herbs affect anesthesia by the pharmacokinetic and pharmacodynamic interactions of herbal phytochemical components with anesthetic agents

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ABSTRACT

Herbal medicines and supplements have been increasingly used by people all over the world, who include patients undergoing surgery. While herbs are known to exhibit adverse coagulopathy, hepatotoxicity and sympathomimetic activity by interacting with perioperatively-used drugs, they may also influence the intrinsic effects of anesthetic agents. Phytochemicals contained in herbs act on the same metabolic enzymes and pharmacological targets as those for general anesthetics, sedatives, analgesics and local anesthetics. Phytochemicals have the properties to inhibit or induce cytochrome P450 enzymes, modulate γ-aminobutyric acid type A receptors positively or negatively, antagonize *N*-methyl-D-aspartate receptor responses and block voltage-gated Na^+ channels. Therefore, it is hypothesized that herbs affect anesthesia through the pharmacokinetic and pharmacodynamic interactions of their phytochemical components with anesthetics and anesthetic adjuncts. We review different classes of phytochemicals that possibly interact with anesthetic agents. The most popular herbs such as St. John's wort, ginkgo, chamomile, valerian, ginseng, kava, garlic, aloe, chili pepper, ginger, Echinacea, spearmint and green tea contain phytochemical flavonoids, terpenoids, ginsenosides, phloroglucinols, naphthodianthrones, kavalactones, capsaicinoids, organosulfur compounds, anthraquinonoids, alkylamides and vanillyl ketones, which would increase or decrease anesthetic, sedative and analgesic effects pharmacokinetically and pharmacodynamically. The hypothetical interactions have clinical implications that the use of herbs should be discontinued for a fixed period of time before surgery so that anesthesia is not affected by herbal phytochemical components.

Key words: Herb; Anesthetic agent; Interaction; Pharmacokinetic; Pharmacodynamic.

Abbreviations: CYP: cytochrome P450; $GABA_A$: γ-aminobutyric acid type A; NMDA: *N*-methyl-D-aspartate; TRPV1: transient receptor potential vanilloid type-1.

INTRODUCTION

The potential connection between plants and health has generated plant medication alternative or supplementary to standard and prescription medication. Such medication widely utilizes herbs, which are taken for the purpose of alleviating symptoms, maintaining health, preventing illness and improving the quality of life. Herbal medicines and supplements have been steadily gaining popularity worldwide. More than thousands of herbs are available over the counter without a prescription.

When herbal medicines and supplements are used by patients undergoing surgery, phytochemical components in them not only exert toxic or side effects directly but also interact with perioperatively-used drugs. Herb and drug interactions have been known to exhibit adverse coagu-

lopathy, hepatotoxicity and sympathomimetic activity.[1,2] Garlic, ginger, ginkgo and ginseng interact with antiplatelet drugs like aspirin and anticoagulant drugs like warfarin to elevate the risk of abnormal bleeding. Acetaminophen-induced liver damage is potentiated when concomitantly used with kava and Echinacea.The combined use of ginseng and sympathomimetic drugs causes arrhythmia, hypertension and hyperthermia. However, the influence of herbs on the intrinsic effects of anesthetics and anesthetic adjuncts has been overlooked.

HYPOTHESIS

St. John's wort, ginkgo, chamomile, valerian, ginseng, kava, garlic, aloe, chili pepper, ginger, Echinacea, spearmint and green tea have been most frequently used as medicinal herbs. These representative herbs contain different classes of phytochemicals that act on drug-metabolizing enzymes and pharmacological targets common to general anesthetics, sedatives, analgesics and local anesthetics. Such herbal components have the properties to inhibit or induce cytochrome P450 (CYP) enzymes, modulate γ-aminobutyric acid type A ($GABA_A$) receptors positively or negatively, antagonize *N*-methyl-D-aspartate (NMDA) receptor responses, and block or inhibit voltage-gated Na^+ channels. Therefore, it is hypothesized that herbal medicines and supplements affect anesthesia, sedation and analgesia by their enzyme-acting and neuro-active components that interact with anesthetics and anesthetic adjuncts pharmacokinetically and pharmacodynamically.

PHYTOCHEMICALS IN HERBS

Flavonoids: St. John's wort contains quercetin, kaempferol, apigenin and luteolin, and ginkgo, quercetin and myricetin. Both herbs also contain a characteristic flavonoid amentoflavone. Chamomile contains chrysin, apigenin, luteolin, quercetin and kaempferol, and valerian, 6-methylapigenin and hesperidin. The major flavonoid components responsible for various bioactivities of green tea are (+)-catechin, (–)-epicatechin, (–)-epigallocatechin and (–)-epigallocatechin-3-gallate.

Terpenoids: With respect to bioactive herbal terpenoids, carvone, carveol, carvacrol and menthol are contained in spearmint, valerenic acid in valerian, and borneol in ginger. Bilobalide, ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J and ginkgolide M are present in ginkgo.

Phloroglucinols and naphthodianthrones: In addition to flavonoids, St. John's wort contains phloroglucinol hyperforin and adhyperforin, and naphthodianthrone hypericin and pseudohypericin, which are closely related to the medicinal utility of this herb.

Ginsenosides: Broad pharmacological spectra of ginseng are attributable to its component ginsenoside Rb, ginsenoside Rd, ginsenoside Rg and other ginsenosides.

Kavalactones: The bioactive substances in kava and its preparations are referred to as a series of kavalactones such as kavain, 7,8-dihydrokavain, yangonin, desmethoxyyangonin, methysticin and 7,8-dihydromethysticin.

Capsaicinoids: Capsaicin, a typical phytochemical belonging to capsaicinoids, is the pungent component in chili pepper that exhibits different bioactivities.

Organosulfur compounds: Pharmacological effects of garlic are derived from two major components, flavonoids and organosulfur compounds. The latter includes allicin, diallyl monosulfide, diallyl disulfide, diallyl trisulfide and ajoene, which provide garlic with not only a characteristic odor but also various effects as a medicinal herb.

Anthraquinonoids: The primary bioactive components in aloe are anthraquinonoids such as aloin (or barbaloin), aloe-emodin, aloesin, rhein, emodin, chrysophanol and danthron. These phytochemicals contribute to a wide range of useful effects of aloe.

Vanillyl ketones: Ginger is characterized to contain pungent vanillyl ketones with varying chain lengths (n6 to n10) such as 6-gingerol, 6-shogaol and 6-paradol. Terpenoid borneol is also present in ginger.

Alkylamides: Echinacea contains bioactive alkylamides such as dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamide, dodeca-2*E*,4*E*-dienoic acid isobutylamide, undeca-2*E*,4*E*/*Z*-diene-8,10-diynoic acid isobutylamide and dodeca-2-ene-8,10-diynoic acid isobutylamide.

METABOLISM OF ANESTHETIC AGENTS

CYP is a family of isozymes associated with the biotransformation of drugs. CYP3A4 isozymes expressed in liver and gastrointestinal tract play the most important role in drug metabolism, followed by other subtypes of CYP enzymes. CYP2B6, CYP2C9 and CYP3A4 isozymes are responsible for the metabolism of propofol; CYP2E1 exclusively for halothane, isoflurane, sevoflurane and enflurane; CYP2A6 and CYP3A4 to a lesser extent for these inhalational anesthetics; CYP3A4 and CYP2C19 for benzodiazepines (diazepam and midazolam); CYP2A6, CYP2B6, CYP2C9, CYP2C19 and CYP3A4 for ketamine; and CYP2B6, CYP2C9, CYP2C19 and CYP2D6 for barbiturates (thiopental, pentobarbital and phenobarbital).[3] CYP1A2 and CYP3A4 isozymes primarily regulate the metabolism of amide-type local anesthetics such as lidocaine, bupivacaine, mepivacaine, ropivacaine and etidocaine.[4]

PHARMACOLOGICAL MECHANISMS OF ANESTHETIC AGENTS

Intravenous and inhalational anesthetic agents are frequently accompanied by sedative benzodiazepines such as midazolam, diazepam and lorazepam. These anesthetics and anesthetic adjuncts act on inhibitory $GABA_A$ receptors that are ligand-gated Cl^- channels to allow the influx of Cl^- ions into postsynaptic neurons, inhibiting neuronal excitability through synaptic phase

currents in the central nervous system.[5] The $GABA_A$ receptor complex comprises a Cl^- channel and specific allosteric binding sites for inhibitory neurotransmitter GABA and different anesthetic agents. Intravenous agents: propofol, etomidate, barbiturates and benzodiazepines, and inhalational agents: sevoflurane, isoflurane and nitrous oxide positively allosterically modulate and directly activate $GABA_A$ receptors to enhance their inhibitory functions, thereby inducing general anesthesia, sedation, anxiolysis and convulsion cessation.[6]

Excitatory NMDA receptors, a specific type of ionotropic glutamate receptors, are activated by glutamate and glycine to open the channels non-selective to positively charged ions, inducing-neuronal excitation. Although the detailed mechanisms have not been well understood, ketamine and nitrous oxide are very likely to act on NMDA receptors as a non-competitive antagonist and a channel blocker, respectively, to exert analgesic, sedative and anesthesia-maintaining effects.[7]

Local anesthetics act on ion channels in the nervous and cardiovascular systems. Lidocaine, prilocaine, bupivacaine, mepivacaine, ropivacaine, etidocaine and other related drugs reversibly block voltage-gated (voltage-dependent or voltage-sensitive) Na^+ channels to inhibit sensory and motor functions.[8] Voltage-gated Na^+ channels, integral membrane proteins composed of a core α-subunit associated with one or more regulatory β-subunits, are responsible for the initiation and propagation of action potentials in excitable cells. The α-subunit not only forms a pore selectively permeable for Na^+ ions but also contains a binding or receptor site for local anesthetic and anti-arrhythmic drugs. Local anesthetics bind to such sites, causing occlusion of the pores with the resultant block of Na^+ channels.

DISCUSSION

PHARMACOKINETIC INTERACTIONS

Pharmacokinetic interactions occur when phytochemicals modify the absorption, distribution, metabolism and excretion of anesthetic agents. Drug concentrations in blood are significantly modulated by hepatic and intestinal drug-metabolizing enzymes. Since a variety of phytochemicals inhibit and induce CYP isozymes responsible for drug metabolism, they would increase and decrease in vivo concentrations of anesthetics and anesthetic adjuncts, thereby causing the pharmacokinetic interactions to enhance or reduce anesthetic, sedative and analgesic efficacy.

Herbs containing CYP inhibitors: Of phytochemical flavonoids, amentoflavone is the most potent inhibitor of CYP3A4 and CYP2C9 isozymes.[9] St. John's wort and ginkgo contain this flavone. Therefore, both herbs would interact with propofol, benzodiazepines, barbiturates and ketamine to potentiate anesthesia, sedation and analgesia or prolong their duration time. Green tea could also cause the pharmacokinetic interactions with intravenous and inhalational anesthetics, benzodiazepines, barbiturates and ketamine to increase their effects because its major component (–)-epigallocatechin-3-gallate has the property to inhibit CYP2B6, CYP2C19, CYP3A4 and CYP2E1 activity.[10] Chamomile contains quercetin, kaempferol, chrysin, apigenin, luteolin and morin that inhibit CYP3A4 and CYP2C9 activity.[11,12] These CYP-inhibitory flavonoids may interact with anesthetic agents to enhance their clinical efficacy.

Carveol and menthol inhibit rat hepatic microsomal CYP-dependent aminopyrine-*N*-demethylase responsible for the metabolic glucuronidation and ring hydroxylation of propofol.[13] Borneol is effective in inhibiting the activity of CYP2B6 isozymes in human hepatic microsomes at micromolar concentrations.[14] Spearmint and ginger containing these CYP-inhibitory terpenoids would increase in vivo concentrations of propofol, barbiturates and ketamine, possibly potentiating anesthesia, sedation and analgesia.

Ginsenoside Rd potently inhibits CYP2C9, CYP2C19, CYP2D6 and CYP3A4 activity, and ginsenoside Rb_2 moderately inhibits CYP1A2, CYP2D6 and CYP3A4 activity.[15] Ginsenoside Rg_3 and ginsenoside Rh_2 are also effective in inhibiting the activity of CYP2C9, CYP2C19 and CYP3C4 isozymes.[16] Ginseng containing these CYP-inhibitory ginsenosides would increase the effects of intravenous anesthetics, benzodiazepines, barbiturates and ketamine by the pharmacokinetic interactions to increase in vivo concentrations of these drugs.

Hyperforin and hypericin inhibit CYP3A4, CYP2C9, CYP2C19 and CYP2D6 activity at low micromolar concentrations as well as amentoflavone and quercetin.[17] Since St. John's wort contains these potent phytochemical CYP inhibitors, this herb would interact with propofol, benzodiazepines, barbiturates and ketamine to potentiate anesthesia, sedation and analgesia.

Methysticin, 7,8-dihydromethysticin, kavain and 7,8-dihydrokavain inhibit CYP2C9, CYP2C19, CYP2D6 and CYP3A4 activity.[17] Kava containing these CYP inhibitors would interact with propofol, benzodiazepines, barbiturates and ketamine, increasing their anesthesia-relevant effects. However, kavalactones were also suggested to have the property to induce different CYP isozymes.[18] Therefore, the pharmacokinetic interactions between kava and anesthetic agents can be complicated.

Capsaicin is effective in inhibiting CYP1A2, CYP2C9, and CYP3A4 activity.[19] Therefore, capsaicin possibly increases in vivo concentrations of propofol, benzodiazepines, barbiturates and ketamine by inhibiting their metabolism-relevant CYP enzymes. Chili pepper containing capsaicin would increase anesthetic and sedative effects.

Emodin, rhein, danthron and chrysophanol inhibit the activity of CYP1A2, CYP2C9, CYP2D6, CYP2E1 and CYP3A isozymes in rat hepatic microsomes.[20] Since aloe contains these CYP-inhibitory anthraquinonoids, this herb would increase the effects of intravenous and inhalational anesthetics, barbiturates, ketamine and local anesthetics.

Dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamide and dodeca-2*E*,4*E*-dienoic acid isobutylamide inhibit CYP2C19, CYP2D9 and CYP3A activity.[21] Echinacea containing these alkylamides would interact with intravenous anesthetics, benzodiazepines, barbiturates and ketamine to enhance anesthetic, sedative and analgesic efficacy.

6-Gingerol, 8-gingerol and 10-gingerol are able to inhibit the activity of CYP2C9, CYP2C19, CYP3A4 and CYP2D6 isozymes in human hepatic microsomes.[22] Ginger containing these vanillyl ketones would cause the pharmacokinetic interactions with propofol, benzodiazepines, barbiturates and ketamine to potentiate anesthesia, sedation and analgesia.

Herbs containing CYP inducers: Bilobalide, ginkgolide A and ginkgolide B induce CYP3A and CYP2E1 isozymes.[23] Ginkgo containing these CYP-inducible terpenoids would decrease in vivo concentrations of inhalational anesthetics, propofol, benzodiazepines, barbiturates and ketamine, thereby reducing anesthetic and sedative efficacy. Bilobalide with the property to induce hepatic CYP1A1 isoform may also influence the effects of local anesthetics.

St. John's wort extracts containing total hyperforins (hyperforin plus adhyperforin) and total hypericins (hypericin plus pseudohypericin) increase the activity of CYP3A and CYP2E1 isozymes in mouse hepatic microsomes after administration for three weeks.[24] St. John's wort supplements containing hypericin induce CYP3A4 and CYP2E isozymes in human volunteers who received them for 28 days.[25] In contrast, hyperforin and hypericin were suggested to inhibit CYP3A4, CYP2C9, CYP2C19 and CYP2D6 activity as well as amentoflavone and quercetin.[17] Whether St. John's wort decreases or increases anesthetic effects may depend on the dose of such CYP inducers and CYP inhibitors.[26]

Administration of diallyl monosulfide, diallyl disulfide and allyl methyl sulfide time-dependently increases CYP1A2, CYP2B1 and CYP3A protein levels in rat livers.[27] Garlic containing these CYP inducers may interact with anesthetic agents to reduce anesthetic and sedative efficacy, although other studies suggested that diallyl disulfide and allicin inhibit CYP enzymes.[28]

PHARMACODYNAMIC INTERACTIONS

When anesthetic agents and phytochemicals share the same pharmacological targets, their concomitant use possibly causes the pharmacodynamic interactions to show either cooperative, additive and synergistic effects or antagonistic and counteracting effects in anesthesia, sedation and analgesia. Many phytochemicals possess high affinity to the same receptors and ion channels as those for general anesthetics, local anesthetics and anesthetic adjuncts. The phytochemicals to modulate $GABA_A$ receptors and block voltage-gated Na^+ channels are likely to interact with anesthetic agents.

Herbs containing $GABA_A$ receptor modulators: Different flavonoids act as $GABA_A$ receptor partial and inverse agonists or antagonists, which potentially influence sedative, anxiolytic and anticonvulsant effects. Quercetin, apigenin, 6-methylapigenin and (–)-epigallocatechin-3-gallate positively allosterically modulate $GABA_A$ receptors.[29,30] Since St. John's wort, ginkgo, chamomile, valerian and green tea contain such $GABA_A$ receptor modulators, these herbs would interact with $GABA_A$ receptor-acting propofol, inhalational anesthetics, benzodiazepines and barbiturates, resulting in potentiation of anesthesia and sedation. Flavanone glycoside hesperidin has sedative and sleep-enhancing properties.[31] Valerian containing hesperidin may increase the effects of benzodiazepines by the synergistic interaction.

Menthol, carvacrol, carvone and borneol act as the positive modulators of $GABA_A$ receptors,[32] and menthol also increases GABA responses by acting on the same site of $GABA_A$ receptors as propofol.[33] Borneol and valerenic acid produce the positive $GABA_A$ receptor modulation equivalent to that of etomidate and much greater than that of diazepam.[34,35] Since spearmint, ginger and valerian contain such $GABA_A$ receptor-modulatory terpenoids, these herbs would interact with propofol, etomidate, isoflurane, sevoflurane, benzodiazepines and barbiturates, possibly increasing anesthetic and sedative effects.

Ginkgolide A, ginkgolide B and ginkgolide C negatively modulate $GABA_A$ receptors to inhibit GABA responses.[36] Ginkgo containing these negative modulators would interact with anesthetics and anesthetic adjuncts to decrease their effects. Ginkgo also contains CYP-inducible terpenoid bilobalide, ginkgolide A and ginkgolide B that decrease in vivo concentrations of anesthetic agents. This herb has the possibility to reduce anesthetic and sedative efficacy through both pharmacodynamic and pharmacokinetic interactions.

Herbs containing NMDA receptor antagonists: In contrast to phytochemical modulators of $GABA_A$ receptors, only a limited number of phytochemicals have been reported to modulate NMDA receptors. Hyperforin antagonizes NMDA receptors in rat brains at low micromolar concentrations.[37] Hypericin also has affinity to NMDA receptors of rat forebrain membranes.[38] Although hypericin and hyperforin reduce neuropathic pain in rats, their antihyperalgesic and antinociceptive activities are attributed to protein kinase C inhibition and opioid system activation.[39] Activation of NMDA subtypes of glutamate receptors is associated with ischemia-induced neuronal cell damage and traumatic brain injury. While St. John's wort contains hyperforin and hypericin, their antagonistic effects on NMDA receptor responses may contribute to neuroprotection.

Herbs containing Na^+ channel blockers and vanilloid receptor activators: Quercetin, (–)-epigallocatechin-3-gallate and (+)-catechin block voltage-gated Na^+ channel currents of human cardiac channels.[40,41] Since St. John's wort, ginkgo, chamomile and green tea contain such Na^+ channel-blocking flavonoids, these herbs would interact with local anesthetics to increase anesthetic, antinociceptive and cardiac effects.

Menthol voltage-dependently blocks neuronal Na^+ channels and skeletal muscle Na^+ channels.[42] Spearmint containing this Na^+ channel blocker may interact with lidocaine, bupivacaine and mepivacaine to potentiate local anesthesia.

Ginsenoside Rb_1 reversibly blocks Na^+ channels in human brains,[43] and ginsenoside Rg_3 voltage-dependently inhibits peak Na^+ currents with greater potency than lidocaine.[44] Ginseng containing these Na^+ channel blockers would interact with local anesthetics to increase their effects.

Hyperforin and hypericin inhibit voltage- and ligand-gated channels including Na^+ channels in rat central and peripheral neurons.[45] Since St. John's wort contains such Na^+ channel blockers, this herb would interact with local anesthetics to increase anesthetic and cardiac effects.

Subcutaneously injected kavain produces local anesthesia in rats, and methysticin and kavain inhibit voltage-operated Na^+ channels in rat hippocampal neurons.[46] Kava containing these kavalactones would interact with local anesthetics to enhance anesthetic efficacy.

Capsaicin inhibits action potentials and voltage-gated Na^+ channels in rat trigeminal ganglion neurons. This phytochemical activates vanilloid receptors or transient receptor potential vanilloid type-1 (TRPV1) receptors, which are non-selective cation channels to modulate the nociceptive and pain transmission,[47] to exert analgesic or algesic effects depending on concentrations. The receptor channel TRPV1 is expressed in primary afferent sensory neurons of the pain pathway. Capsaicin is also able to transport Na^+ channel blockers like local anesthetics to nociceptors by opening TRPV1 channels to give them the access to cell interiors. Therefore, chili pepper containing capsaicin would interact with local anesthetics to increase anesthetic, analgesic and antinociceptive effects by different modes of interaction.

While the analgesic property of ginger is associated with Na^+ channel block, its component 6-gingerol and 6-shogaol effectively inhibit voltage-activated Na^+ currents.[48] Ginger containing these vanillyl ketones would interact with local anesthetics to increase anesthetic and analgesic effects.

VERIFICATION OF THE HYPOTHETICAL INTERACTIONS

The hypothetical interactions between herbal phytochemicals and anesthetic agents could be verified by case reports, preclinical trials and animal experiments in which herbs potentiate or attenuate anesthetic, sedative and analgesic effects.

St. John's wort and delayed emergence from anesthesia: A 21-year-old woman was admitted for incision, drainage and marsupialization of a Bartholin abscess.[49] She was administered fentanyl citrate (1 μg/kg, i.v.) followed by propofol (3 mg/kg, i.v.). Anesthesia was maintained with sevoflurane in oxygen and nitrous oxide. Total anesthesia time was approximately 10 min, but 30 min later, she could not be roused even when subjected to painful stimulation. At 90 min post-anesthesia, the patient was rousable with spontaneous eye opening. The patient denied taking any benzodiazepines, barbiturates, narcotics or cannabinoids preoperatively. For depression, she had been taking St. John's wort for the preceding three months and was self-administering St. John's wort tablet 1000 mg three times daily at the time of her surgical procedure.

Propofol is metabolized by CYP2C9 and CYP3A4 isozymes, which are inhibited by hyperforin and hypericin. Amentoflavone, quercetin, kaempferol, apigenin and luteolin are also potent inhibitors of CYP2C9 and CYP3A4 isozymes. These phytochemicals contained in St. John's wort would interact with propofol to increase its anesthetic effect. The $GABA_A$ receptor complex comprises allosteric binding sites for propofol, sevoflurane and nitrous oxide. Not only hyperforin has the high affinity to $GABA_A$ receptors but also quercetin and apigenin modulate $GABA_A$ receptors positively. Such $GABA_A$ receptor modulators in St. John's wort would also increase the anesthetic and sedative effects of different agents. Both pharmacokinetic and pharmacodynamic interactions are considered to underlie the delayed emergence from anesthesia.

St. John's wort and decreased effects of ketamine: In a placebo-controlled randomized cross-over study, 12 healthy volunteers orally received commercially available St. John's wort 300 mg or placebo three times per day for 14 days.[50] On day 14, *S*-ketamine (0.3 mg/kg) was orally administered. When determining plasma concentrations of ketamine, oral St. John's wort was revealed to alter its pharmacokinetic parameters. C_{max} was reduced from 16.2 ng/ml to 5.3 ng/ml, $t_{1/2}$ was shortened from 6.5 h to 4.2 h, and AUC-time curve was decreased by 58 %. There was a linear correlation between self-reported effects and C_{max} values of ketamine.

Oral administration of hyperforin- and hypericin-containing St. John's wort extracts to mice significantly increases the activity of CYP3A4 isozymes responsible for the metabolism of ketamine. St. John's wort medication induces CYP3A4 isozymes in healthy volunteers depending on hyperforin dose. Since hyperforin and hypericin potentially decrease in vivo ketamine concentrations, these phytochemicals contained in St. John's wort are considered to attenuate the clinical effects of ketamine by the pharmacokinetic interactions.

St. John's wort and increased effects of pentobarbital and diazepam: Mice were orally treated with St. John's wort extracts at 400 mg/kg four times in 24 h.[51] After pre-treatments with the extracts, mice received sodium pentobarbital (40 mg/kg, i.p.) or diazepam (3 mg/kg, i.p.). St. John's wort prolonged the duration time of and shortened the induction time of sleeping by pentobarbital, and also potentiated the impairment of motor coordination by diazepam.

St. John's wort contains flavonoid quercetin, kaempferol, apigenin and luteolin, phloroglucinol hyperforin, and naphthodianthrone hypericin. These phytochemicals inhibit CYP2C9,

CYP2C19, CYP2D6 and CYP3A4 activity. The metabolism of barbiturates is mediated by CYP2C9, CYP2C19 and CYP2D6 isozymes, and that of benzodiazepines, by CYP2C19 and CYP3A4 isozymes. CYP-inhibitory components in St. John's wort are considered to interact with pentobarbital and diazepam to increase their effects. Barbiturates and benzodiazepines act on $GABA_A$ receptors by binding to distinct sites. Not only quercetin and apigenin but also hyperforin and hypericin have the affinity to $GABA_A$ receptors. These $GABA_A$ receptor modulators contained in St. John's wort are also considered to contribute to increasing the effects of pentobarbital and diazepam.

Herbal terpenoids and prolonged propofol anesthesia: Mice intraperitoneally received carveol, menthol and borneol at 200 mg/kg for each, which are monoterpenes isolated from spearmint and ginger.[13] After 40 min, propofol (100 mg/kg, i.p.) was administered to mice and its effects were evaluated by observing the loss of righting reflex within the first few minutes after administration. All terpenoids significantly prolonged the time of propofol-induced anesthesia by at least 3-times compared with control.

Carveol and menthol effectively inhibit CYP-dependent aminopyrine-*N*-demethylase. Borneol is a potent inhibitor of CYP2B6 isozymes. These enzymes are responsible for the metabolism of propofol. Menthol and borneol also positively modulate $GABA_A$ receptors as well as propofol. It is considered that these terpenoids contained in spearmint and ginger prolong the duration time of propofol anesthesia by both pharmacokinetic interactions through CYP inhibition and pharmacodynamic interactions through $GABA_A$ receptor modulation.

Ginkgo and decreased effects of phenobarbital: Rats were given feed containing 0.1–1.0 % ginkgo extracts for two weeks and then, administered phenobarbital elixir (90 mg/kg, p.o.).[52] The extracts (0.5 and 1.0 %) delayed the onset time of and shortened the duration time of sleeping by phenobarbital.

Barbiturates act on $GABA_A$ receptors through their specific binding sites, whereas bilobalide, ginkgolide A and ginkgolide B negatively modulate or antagonize $GABA_A$ receptors. Bilobalide also induces hepatic CYP2B isozyme responsible for barbiturate metabolism. These terpenoid components in ginkgo are considered to interact with phenobarbital pharmacodynamically and pharmacokinetically, resulting in a decrease of its sleep-inducing effects.

Valerian and increased effects of thiopental: Mice were treated with the aqueous phase obtained from 1 g of valerian (150 mg of dry *Valeriana wallichii* residue/kg, i.p.) or hesperidin (2 and 4 mg/kg, i.p.) isolated from valerian, and after 20 min, with sodium thiopental (35 mg/kg, i.p.).[53] Both valerian fraction and hesperidin significantly increased the duration time of sleeping by thiopental. The hypnotic effect of hesperidin (2 mg/kg, i.p.) was potentiated by co-injection with another valerian component 6-methylapigenin (1 mg/kg, i.p.).

Valerian contains valerenic acid to modulate $GABA_A$ receptors positively, 6-methylapigenin to be a ligand of the $GABA_A$ receptor benzodiazepine binding site, and hesperidin to have the sedative property. These phytochemical components in valerian are considered to interact synergistically with thiopental on $GABA_A$ receptors to potentiate its sleep-enhancing effects.

Synergism between valerian and diazepam: Hesperidin isolated from *Valeriana wallichii* and diazepam were injected (alone or combined) to mice 20 min before pharmacological tests.[31] The combination of hesperidin (2 mg/kg, i.p.) and diazepam (0.3 mg/kg, i.p.) significantly increased the time of sleeping induced by sodium thiopental (35 mg/kg, i.p.). Hesperidin and diazepam also showed the synergism in sedation. Blood concentrations of diazepam (5 mg/kg, i.p.) 15–90 min after injection were not altered by co-injection with hesperidin (20 mg/kg, i.p.).

Hesperidin has sedative and sleep-enhancing effects, although it is not a ligand for the benzodiazepine-specific binding site of $GABA_A$ receptors.[53] Hesperidin contained in valerian is considered to bind to a new site of the $GABA_A$ receptor subtype and interact synergistically with diazepam to potentiate sedation.

Chili pepper and prolonged local anesthetic nerve block: After anesthesia of rats with 1–2% of sevoflurane, 0.2 ml volumes of bupivacaine (0.25 %) and lidocaine (2 %) were injected at the sciatic notch of the left hind limb.[54] All drugs were given alone or co-administered with chili pepper capsaicin at 0.05 %, and the co-administration was performed either 10 min after the first drug injection or simultaneously. When followed by capsaicin injection, bupivacaine and lidocaine produced predominantly nociceptive-specific block and their nerve-blocking effects were prolonged.

Capsaicin has the property to block voltage-gated Na^+ channels and induce sensory/nociceptor-selective nerve block. Capsaicin also activates TRPV1 receptors to induce analgesia and effectively transports Na^+ channel blockers to nociceptors through TRPV1 channel opening. Such a neuro-active phytochemical contained in chili pepper is considered to cause the cooperative interactions with local anesthetics to produce long-lasting nerve block.

CONCLUSIONS

We have hypothetically reviewed that herbal medicines and supplements affect anesthesia, sedation and analgesia by their component phytochemicals to interact with anesthetics and anesthetic adjuncts pharmacokinetically and pharmacodynamically. Table 1 summarizes the herb and anesthetic interactions, including possible clinical concerns, relevant phytochemicals and presumable mechanisms. Considering that many herbs to contain enzyme-acting and neuro-active phytochemicals are being utilized currently, they may influence the intrinsic effects of anesthetic agents more frequently than anticipated. The resultant anesthetic failure and insufficient efficacy can be prevented or improved by discontinuing the use of herbs preoperatively for a fixed period of time.

Herb	Anesthetic agent	Clinical concern	Relevant phytochemical	Interaction mechanism
St. John's wort	Propofol Barbiturates Benzodiazepines Ketamine	Potentiate or prolong anesthesia, sedation and analgesia Delay emergence from anesthesia	Amentoflavone Quercetin Kaempferol Apigenin Luteolin Hyperforin Hypericin	Pharmacokinetic (CYP inhibition)
St. John's wort	Propofol Sevoflurane Nitrous oxide Barbiturates Benzodiazepines	Potentiate anesthesia, sedation and analgesia	Quercetin Apigenin Hyperforin Hypericin	Pharmacodynamic ($GABA_A$ receptor positive modulation)
St. John's wort	Ketamine	Attenuate ketamine's effects	Hyperforin Hypericin	Pharmacokinetic (CYP induction)
St. John's wort	Local anesthetics	Increase anesthetic and cardiac effects	Quercetin Hyperforin Hypericin	Pharmacodynamic (Na^+ channel block)
Ginkgo	Propofol Barbiturates Benzodiazepines Ketamine	Potentiate or prolong anesthesia, sedation and analgesia	Amentoflavone Quercetin	Pharmacokinetic (CYP inhibition)
Ginkgo	Sevoflurane Propofol Barbiturates Benzodiazepines Ketamine Local anesthetics	Reduce anesthetic, sedative and analgesic efficacy	Bilobalide Ginkgolide A Ginkgolide B	Pharmacokinetic (CYP induction)
Ginkgo	Propofol Sevoflurane Barbiturates Benzodiazepines	Potentiate anesthesia and sedation	Quercetin	Pharmacodynamic ($GABA_A$ receptor positive modulation)
Ginkgo	Propofol Sevoflurane Barbiturates Benzodiazepines	Reduce anesthetic and sedative efficacy	Ginkgolide A Ginkgolide B Ginkgolide C	Pharmacodynamic ($GABA_A$ receptor negative modulation)
Ginkgo	Local anesthetics	Increase anesthetic and cardiac effects	Quercetin	Pharmacodynamic (Na^+ channel block)
Chamomile	Propofol Barbiturates Benzodiazepines	Potentiate or prolong anesthesia and sedation	Quercetin Kaempferol Chrysin Apigenin Luteolin	Pharmacokinetic (CYP inhibition)
Chamomile	Propofol Sevoflurane Barbiturates Benzodiazepines	Potentiate anesthesia and sedation	Quercetin Apigenin	Pharmacodynamic ($GABA_A$ receptor positive modulation)
Chamomile	Local anesthetics	Increase anesthetic and cardiac effects	Quercetin	Pharmacodynamic (Na^+ channel block)
Valerian	Propofol Etomidate Sevoflurane Barbiturates Benzodiazepines	Potentiate anesthesia, sedation and analgesia	Valerenic acid 6-Methylapigenin Hesperidin	Pharmacodynamic ($GABA_A$ receptor positive modulation)
Ginseng	Propofol Barbiturates Benzodiazepines Ketamine	Potentiate or prolong anesthesia and sedation	Ginsenoside Rd Ginsenoside Rb_2 Ginsenoside Rg_3 Ginsenoside Rh_2	Pharmacokinetic (CYP inhibition)
Ginseng	Local anesthetics	Increase anesthetic and cardiac effects	Ginsenoside Rb_1 Ginsenoside Rg_3	Pharmacodynamic (Na^+ channel block)
Kava	Propofol Barbiturates Benzodiazepines Ketamine	Potentiate or prolong anesthesia and sedation	Kavain 7,8-Dihydrokavain Methysticin 7,8-Dihydromethysticin	Pharmacokinetic (CYP inhibition)
Kava	Local anesthetics	Increase anesthetic effects	Kavain Methysticin	Pharmacodynamic (Na^+ channel block)
Garlic	Propofol Barbiturates Benzodiazepines Local anesthetics	Reduce anesthetic and sedative efficacy	Diallyl monosulfide Diallyl disulfide Allyl methyl sulfide	Pharmacokinetic (CYP induction)

Aloe	Propofol Sevoflurane Barbiturates Benzodiazepines Ketamine Local anesthetics	Potentiate or prolong anesthesia, sedation and analgesia	Emodin Rhein Danthron Chrysophanol	Pharmacokinetic (CYP inhibition)
Chili pepper	Propofol Barbiturates Benzodiazepines Ketamine Local anesthetics	Potentiate or prolong anesthesia, sedation and analgesia	Capsaicin	Pharmacokinetic (CYP inhibition)
Chili pepper	Local anesthetics	Increase anesthetic, analgesic and antinociceptive effects	Capsaicin	Pharmacodynamic (Na^+ channel block, TRPV1 receptor activation and TRPV1 channel opening)
Ginger	Propofol Barbiturates Benzodiazepines Ketamine	Potentiate or prolong anesthesia, sedation and analgesia	6-Gingerol 8-Gingerol 10-Gingerol Borneol	Pharmacokinetic (CYP inhibition)
Ginger	Propofol Etomidate Benzodiazepines	Potentiate anesthesia and sedation	Borneol	Pharmacodynamic ($GABA_A$ receptor positive modulation)
Ginger	Local anesthetics	Increase anesthetic and analgesic effects	6-Gingerol 6-Shogaol	Pharmacodynamic (Na^+ channel block)
Echinacea	Propofol Barbiturates Benzodiazepines Ketamine	Potentiate or prolong anesthesia, sedation and analgesia	Dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamide Dodeca-2*E*,4*E*-dienoic acid isobutylamide	Pharmacokinetic (CYP inhibition)
Spearmint	Propofol Etomidate Benzodiazepines	Potentiate anesthesia and sedation	Menthol Carvacrol Carvone	Pharmacodynamic ($GABA_A$ receptor positive modulation)
Spearmint	Propofol	Potentiate or prolong anesthesia	Carveol Menthol	Pharmacokinetic (CYP inhibition)
Spearmint	Local anesthetics	Increase anesthetic and antinociceptive effects	Menthol	Pharmacodynamic (Na^+ channel block)
Green tea	Barbiturates Benzodiazepines Propofol Sevoflurane Ketamine	Potentiate or prolong sedation, anesthesia and analgesia	(–)-Epigallocatechin-3-gallate	Pharmacokinetic (CYP inhibition)
Green tea	Benzodiazepines	Potentiate sedation	(–)-Epigallocatechin-3-gallate	Pharmacodynamic ($GABA_A$ receptor positive modulation)
Green tea	Local anesthetics	Increase anesthetic and antinociceptive effects	(–)-Epigallocatechin-3-gallate (+)-Catechin	Pharmacodynamic (Na^+ channel block)

Table 1: Hypothetical interactions between representative herbs and anesthetic agents.

Official standards and guidelines are not available. Based on the half-life time of phytochemicals contained in representative herbs, patients should discontinue the use of herbs two or three weeks before anesthesia and operation until the safety against phytochemical and drug interactions is clearly determined. Despite the fact that patients including pre-surgical population daily use ginkgo, garlic, ginseng, aloe, chamomile, ginger, St. John's wort and other medicinal herbs, they do not necessarily disclose the use of such herbs to doctors or primary care physicians because of their misconception that herbal medicines and supplements are safe due to the natural origin. Surgeons and anesthesiologists should elicit and document a history of herbal medicines and supplements during the preoperative evaluation together with understanding the potential problems that arise from the interactions between herbs and anesthetic agents.

CONFLICTS OF INTEREST

All authors declare that they do not have any conflicts of interest.

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