Guidelines for the Pre-Operative Assessment and Management of Patients taking Herbal Remedies and Cannabinoids

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Summary and Key Recommendations

- The use of herbal/traditional/complementary remedies amongst patients is variable and probably underreported.
- Patients should be asked specifically about their use of herbs, vitamins, supplements, or other natural or alternative products.
- Although regulation has been improved, there remain concerns over the efficacy, pharmacodynamics and pharmacokinetics of these agents.
- There is insufficient data on many of these herbal remedies to provide robust scientific recommendations on when to stop them before surgery. However a pragmatic recommendation of 7 days will be sufficient for the commonly used remedies.
- Cannabinoids and marijuana should be discontinued 72 hrs before general anaesthesia.
- It is recommended that departments provide consistent advice on the perioperative management of herbal remedies and that this is regularly reviewed.
INTRODUCTION

Herbal and traditional remedies have been used for centuries in various forms throughout the world, with considerable geographical and cultural variation. Many of the prescription drugs in current use have been derived from plant products. The World Health Organisation estimates that up to 80% of the world's population still rely on herbal and traditional remedies [1]. Reported prevalence rates for herbal medicine usage in Europe range from 5.9% to 48.3% [2].

Such remedies are used to treat a wide variety of conditions, which often have a chronic course. Of relevance to anaesthesia and surgery are those remedies used to treat chronic pain, post-op nausea and vomiting and anxiety [3]. There is a common misconception that these agents are safe because they are ‘natural’ [4].

The term ‘herbal and traditional remedies’ is non-specific and other terms e.g. complementary medicine or alternative remedies are used interchangeably. Broadly speaking, herbal medicines are those with active ingredients made from plant components, such as leaves, roots or flowers. In the UK, according to the Human Medicines Regulation 2012 [5], a product is a herbal medicine if the active ingredients are herbal substances and / or herbal preparations only. For the purposes of this guideline, the term ‘herbal remedies’ will also include over-the-counter health-promoting supplements derived from plants.

Peri-operative Usage

The unquantifiable concerns amongst healthcare professionals regarding such remedies stem from several issues [6, 7]:

- Many patients do not consider these products to be drugs or medication and often do not disclose their use to healthcare providers. A recent study showed that only 23% of preoperative surgical patients discontinue their herbal medication regimens prior to surgery [8]
- They may interact with prescribed and administered conventional medication [9]
- They may have side effects or cause adverse reactions
- Not all herbal remedies are regulated. Specifically customised preparations for individuals do not need a licence; those manufactured outside the UK may not be subject to regulation
- Evidence for the effectiveness of herbal remedies is generally limited

Despite growing knowledge about herbal remedies and drug interactions, most of these concerns have arisen based on theoretical data rather than clinical evidence from patients. Pharmacokinetic information about these agents is often lacking and hence, it might not be possible to provide robust advice on when to stop these agents prior to anaesthesia and surgery. Pragmatically therefore, patients should be advised to discontinue all non-essential herbal remedies for one week prior to elective surgery. Some products may not need to be discontinued this far in advance, or even at all, however there is usually insufficient information about pharmacological effects and half-life of the constituents of such remedies to tailor the advice for the patient [10].

REGULATIONS

In the UK, the majority of herbal remedies are exempt from the licensing requirements set out in the Medicines Act 1968. In the US, herbal products are classified as dietary supplements by the Food and Drug Administration (FDA) under the Dietary Supplemental Health and Education Act of 1994, and are not subjected to rigorous testing. Few instructions exist regarding proper usage, dose requirements, side effects, toxicity and drug interactions.
The lack of compulsory post-marketing surveillance means that the incidence, nature and scale of adverse effects in the UK are unknown. Hence, herbal remedies available over-the-counter can be of variable quality and content; heavy metals including mercury, lead, thallium, cadmium, copper, iron, manganese, nickel, zinc and arsenic have all been found in herbal remedies, despite their purported natural origins [11]. This makes it difficult to interpret any reactions in the patient or to determine if the herbal remedies are responsible.

In order to improve the regulation of herbal remedies, the Traditional Herbal Registration (THR) was introduced. Qualification for a THR requires the submission of scientific evidence relating to the safety, quality and traditional use of the product. THR-registered products would generally have been in use for treatment of the stated condition for a minimum of 30 years, 15 years of which must have been in the European Union [12]. A list of herbal remedies granted a THR status in the UK is available online [13].

As for any other medication, side effects or adverse reactions (including suspected reactions) to a herbal remedy should be reported using the Yellow Card Scheme run by the Medicines and Healthcare products Regulatory Agency (MHRA).

At international level, the International Regulatory Cooperation for Herbal Medicines (IRCH) is a global network of regulatory authorities responsible for the regulation of herbal medicines, established in 2006 under the umbrella of the World Health Organisation. Its mission is to protect and promote public health and safety through improved regulation for herbal medicines.

COMMON HERBAL REMEDIES

The market for herbal remedies is constantly evolving, with new products regularly added to those already available to the general public either over-the-counter, face-to-face via a practitioner or on the internet. This is a non-exhaustive list of the most commonly used herbal remedies that could affect the user in the peri-operative period. A summary is provided in Appendix 1.

**Echinacea**
- Popular ‘health supplement’ primarily used to prevent or treat common cold
- Some evidence that it may decrease severity and duration of upper respiratory tract infections, though not as prophylaxis. Likely due to its immunomodulatory effects through cytokine signalling
- Side effects: gastrointestinal disturbance, headache, dizziness
- Risk of hepatic dysfunction / failure in chronic usage, thereby enhancing hepatotoxic effects of drugs such as amiodarone, methotrexate and halothane
- Immunostimulatory in the short term, but potent immunosuppressant in longer term. Should be avoided in patients requiring peri-operative immunosuppression (such as transplant candidates)
- Peri-operative period:
  - Pharmacokinetic data is lacking; no available recommendations regarding their use peri-operatively

**Ephedra (Ma Huang)**
- Marketed as a CNS stimulant, weight loss supplement and for treatment of asthma
- Contains the alkaloids ephedrine (predominant compound), pseudoephedrine, methylephedrine and nor-pseudo-ephedrine
- Sympathomimetic with direct agonist effect on - and - adrenergic receptors, indirectly increases presynaptic noradrenaline release
- Side effects: palpitations, hypertension, tachycardia, cerebrovascular accident and seizures. Chronic use associated with cardiomyopathy. Other adverse effects reported include myocardial infarction, fatal arrhythmias, acute hepatitis and psychosis
Peri-operative period:

- Combination with sympathomimetic drugs can cause life-threatening arrhythmias, hypertension and hyperthermia
- Long-term use of ephedra may deplete endogenous catecholamine stores leading to further cardiovascular instability intra-operatively and tachyphylaxis to other sympathomimetic drugs; direct-acting sympathomimetic agents may be preferable in this situation
- Fatal arrhythmias reported in ephedra users exposed to halothane anaesthesia
- Pharmacokinetic data suggests discontinuation for at least 24 hours before surgery

Garlic (Allium sativum)

- Common culinary ingredient, marketed as health supplement with claims to benefit those with cardiovascular disease, diabetes and even tumours
- Contains cysteine, which decreases thromboxane formation and alters arachidonic acid metabolism. Dose-dependent inhibition of platelet aggregation
- Side effects: nausea, hypotension and allergic reactions. Several case reports of garlic causing bleeding problems
- Peri-operative period:
  - Garlic can potentiate the anti-platelet effects of aspirin and NSAIDs; this effect may be irreversible
  - Discontinue for at least 7 days before surgery (if possible)

Ginger (Zingiber officinale)

- Another common culinary ingredient, marketed as an anti-inflammatory and anti-emetic
- Directly stimulates gastro-intestinal tract, also postulated to inhibit peripheral and central serotonergic pathways. A systematic review of randomised controlled trials showed no significant difference in incidence of post-operative nausea and vomiting between the ginger and placebo groups
- Peri-operative period:
  - Potent inhibitor of thromboxane synthetase enzyme, may prolong bleeding time
  - Risk assessment for bleeding is prudent, particularly if used alongside NSAIDs and warfarin

Ginkgo biloba

- Promoted as health supplement for cognitive performance and dementia prevention
- Believed to protect vascular walls and neurons by scavenging free radicals and inhibiting platelet-activating factor. Ginkgo extracts contain several flavonoids, terpenoids and organic acids
- Approved for use in Germany for treatment of dementia after a large multi-centre, randomised controlled trial showed improved cognitive performance in patients with dementia
- Treatment of peripheral vascular disease by decreasing blood viscosity and improving blood flow
- Side effects: gastrointestinal upset and headaches
- Peri-operative period:
  - As a potent inhibitor of platelet activation, ginkgo should be avoided in combination with NSAIDs, aspirin and warfarin
  - Several reports of intracranial haemorrhage in patients using ginkgo
  - Pharmacokinetic data suggests discontinuation for 36 hours before surgery

Ginseng (Panax ginseng)

- Originally used in Traditional Chinese Medicine and considered a rare and highly-prized health supplement, now cultivated for worldwide distribution as food products and in the form of supplements containing varying levels of active components (ginsenosides)
- Marketed for immune system benefits, mood enhancement and aphrodisiac effects
- Pharmacological profile incompletely understood due to heterogeneous and sometimes opposing effects of its constituents
• Mild sympathomimetic effect and may interact with the monoamine oxidase enzyme
• Neuroprotective effect believed to be due to the inhibition of sodium channels in the CNS
• Some degree of hypoglycaemic activity and interference with platelet aggregation
• Side effects: irritability, insomnia and gastro-intestinal disturbance. Predisposition to gynaecomastia and vaginal bleeding (weak oestrogenic effect)

• Peri-operative period:
  • May increase bleeding risk - use with caution in combination with NSAIDs and warfarin
  • Tremor and mania have been reported with the combination of ginseng and monoamine oxidase inhibitors (MAOI); this combination should be avoided
  • Intra-operative monitoring of blood sugar is recommended especially for patients already on hypoglycaemic agents
  • Pharmacokinetic data from animal studies demonstrate potentially irreversible inhibition of platelet activity
  • Discontinue at least 7 days before surgery

Kava (Piper methysticum)
• Derived from the dried root of the pepper plant family
• Used as an anxiolytic and sedative, with effects mediated by potentiation of GABA transmission. Potentiates the effects of barbiturates and benzodiazepines
• Side effects: hepatotoxicity, skin changes, extrapyramidal-like dystonic reactions
• Peri-operative period:
  • May reduce the requirements for anaesthetic agents and potentiate their sedative effects
  • Discontinue for at least 24 hours before surgery

St John’s Wort (Hypericum perforatum)
• Widely used in Western societies as a natural antidepressant and for other mood disorders
• Believed to act via inhibition of serotonin, noradrenaline and dopamine re-uptake by neurones; efficacy found to be equivalent to tricyclic antidepressants in the treatment of mild to moderately severe depressive disorders
• Side effects: gastrointestinal disturbance, fatigue, dizziness, confusion, headache and photosensitivity
  • Peri-operative period:
    • Numerous important interactions between conventional drugs and St John’s Wort
    • Risk of a serotonergic syndrome characterised by muscle rigidity, autonomic dysfunction and altered mental state when used in combination with drugs which also increase plasma serotonin levels. Requires same precautionary measures as for patients on conventional MAOI
    • Potent inducer of hepatic cytochrome P450 CYP3A4 isoform; may significantly increase metabolism of many concomitantly administered drugs e.g. alfentanil, midazolam and lignocaine
    • Induces the P450 2C9 isoform, reducing the effect of warfarin and NSAIDs
    • The sedative properties of St John’s Wort may potentiate or prolong effects of anaesthetic agents
    • Pharmacokinetic data suggests discontinuation for at least 5 days prior to surgery, especially in patients awaiting organ transplant and hence requiring immunosuppression, as well as those who may require oral anticoagulation

Valerian (Valeriana officinalis)
• Used as an anxiolytic and sedative
• Produces dose-dependent sedation with some hypnotic effects, believed to be via inhibition of GABA breakdown and re-uptake
• Side effects: tremor, headache, hepatic dysfunction and cardiac disturbances
Peri-operative period:
- Caution in patients who may be physically dependent on Valerian - risk of benzodiazepine-like withdrawal. Tapering the dose prior to elective surgery may be prudent (if possible)

CANNABIS AND MEDICAL MARIJUANA [14, 15]

Cannabinoids are derived from the Cannabis plant and their medicinal use in the UK has undergone recent policy changes (2018). In addition to recreational smoking, other cannabis-derived products have become mainstream in recent years (including vape oil, edible and cosmetic products). Research into its effects on humans has been limited by its classification; animal studies cannot be easily extrapolated due to interspecies differences.

Exogenous cannabinoids can be plant-derived (phytocannabinoids) or synthetic. Over a hundred phytocannabinoids exist, with varying effects on endogenous cannabinoid receptors, but only delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) are medically-relevant.

THC
- Most potent phytocannabinoid, responsible for intoxicating effects of recreational marijuana
- Binds tightly to CB1 receptors in the brain, inhibits neurotransmitter release and produces an exaggerated mood response and euphoria
- Products containing THC for medical purposes are regulated in the UK and require a prescription, with prescribing restrictions on some e.g. named patient basis, prescriber on specialist register

CBD
- Does not have intoxicating effects, cognitive alterations or withdrawal effects of THC; minimal risk of misuse or dependence [16]
- Binds loosely to CB1 receptors, modulates neurotransmission (believed to reduce seizure activity, anxiety and depression) and up-regulates CB receptors (increasing sensitivity to natural endocannabinoids, hence improving pain tolerance and mood)
- Modulates other neurotransmitter receptors including serotonin and opioid receptors, with effects on mood and pain tolerance respectively
- THC-free CBD extract is available for management of pain, anxiety or insomnia etc. Any other CBD products sold in shops or on the internet are legally controlled to contain no more than 0.2% THC in the EU, although declared contents may be inaccurate, as with other herbal remedies

Synthetic cannabinoids
These are entirely laboratory-derived and will not be considered here other than a brief mention that these can be used for medicinal (e.g. nabilone and dronabinol mimic the action of THC and are both potent anti-emetics) and recreational purposes (e.g. Spice).

Effects of cannabinoids
- Central nervous system - anxiety / anxiolysis, paranoia, psychosis, headache
- Cardiovascular - tachycardia, vasodilation, orthostasis, risk of myocardial infarction
- Respiratory - bronchodilation, hyperactivity, airway oedema
- Clotting - conflicting evidence supporting both pro- and anti-thrombotic effects

Due to the nature of recreational use, possibly in conjunction with alcohol, it may not be possible to elicit a detailed history or discontinue usage in patients undergoing emergency surgery. The pharmacokinetics of cannabinoids are difficult to predict and will depend on THC concentration, rate of delivery, hepatic metabolism (into psychoactive and non-psychoactive metabolites) etc.
Issues relevant to the peri-operative period include:

- Interactions reported with multiple drugs including cross tolerance with opioids, excessive CNS depression with barbiturates, benzodiazepines, reduced effectiveness of propofol
- Potentiation of non-depolarising muscle relaxants, norepinephrine, augmentation of drugs causing cardiorespiratory depression, more pronounced response to inhaled anaesthetic agents
- Systematic review did not find sufficient evidence for association between marijuana and cardiovascular outcomes including myocardial infarct and cerebrovascular infarct [17]. However, it would be prudent to avoid drugs that affect heart rate in a patient with recent marijuana use, in view of the tachycardia it causes
- No clear guidance available on discontinuation before elective surgery. Marijuana use should ideally be stopped 72 hours before general anaesthetic, to reduce the risk of airway hyperresponsiveness following airway instrumentation [18]
- Increased risk of aspiration due to delayed gastric emptying [19]
- Potential withdrawal syndrome in post-operative period, presenting with sweats, fever, chills, aggression, abdominal cramps, sleep disturbance
- Pain control issues - may require more analgesia

AVAILABLE GUIDELINES

In the UK, there remains considerable variation in adherence to available guidelines and more importantly, there is no coherence in the advice being offered to patients in the peri-operative period [20, 21]. UK professional organisations such as the Royal College of Anaesthetists and Association of Anaesthetists of Great Britain and Ireland do not provide specific advice beyond generic peri-operative recommendations. The British Society of Day Surgery has published more specific and detailed guidelines on the management of herbal remedies [24].

The 2003 American Society of Anaesthesiologists recommended that patients cease herbal medications 2 weeks before surgery [22] but the more recent American Society of Regional Anaesthesia recommends one week as being appropriate before interventional spinal or pain procedures. However tests of platelet function are recommended if large doses of garlic are taken daily or with concomitant aspirin, NSAID or antidepressant use [23]

The use of herbal remedies and their development is constantly evolving; sources of information for anaesthetists should be readily available for reference (see Appendix 2). In addition, all potential side effects encountered must be reported to the relevant bodies.

CONCLUSIONS

The lack of disclosure by patients regarding their use of herbal remedies may be due to a combination of ignorance (‘natural’ is often assumed to be safe) and fear of prejudice from the medical community. Herbal remedies can also be taken in combined preparations; patients may be oblivious to their actual content. Hence, it is imperative that anaesthetists specifically ask about their use preoperatively, with the assurance that information divulged will only be for the purposes of providing the best care for the patient.

There is currently no clear data regarding specific adverse interactions between herbal remedies and drugs used in anaesthesia. The pharmacodynamic and pharmacokinetic properties of many of these remedies are yet to be conclusively ascertained.
### References

27. Herbal medications for surgical patients: a systematic review protocol. [https://bmjopen.bmj.com/content/7/7/e014290](https://bmjopen.bmj.com/content/7/7/e014290).
## Appendix 1 (selected herbal remedies adapted from [24, 25, 26, 27])

<table>
<thead>
<tr>
<th>Herbal medicine</th>
<th>Use</th>
<th>Pharmacological effects</th>
<th>Perioperative consideration</th>
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<tbody>
<tr>
<td>5HTP</td>
<td>Mood enhancer</td>
<td>Serotonergic properties</td>
<td>Caution with other SSRI</td>
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<tr>
<td>Aloe vera (Aloe barbadensis miller)</td>
<td>Joint health Lipid lowering Antibacterial Wound healing</td>
<td>Reduction of prostaglandin synthesis</td>
<td>Hypoglycaemia Risk of bleeding Hepatotoxicity</td>
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<tr>
<td>Cranberry (Vaccinium oxycoccus)</td>
<td>Antibacterial Urinary tract infection</td>
<td>Inhibits metabolism of warfarin Immunomodulating</td>
<td>Risk of bleeding</td>
</tr>
<tr>
<td>Devil’s Claw (Harpagophytum procumbens)</td>
<td>Joint health</td>
<td>Induction of cytochrome P450 enzyme</td>
<td>Hypoglycaemia Hypotension</td>
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<tr>
<td>Echinacea purpurea</td>
<td>Promotes general wellbeing</td>
<td>Activation of cell-mediated immunity</td>
<td>Immune suppression Hepatotoxicity</td>
</tr>
<tr>
<td>Ephedra/Ma Huang</td>
<td>Weight loss Mood enhancer Asthma</td>
<td>Sympathomimetic (direct and indirect)</td>
<td>Risk of myocardial ischaemia, stroke and hypertension Haemodynamic instability Arrhythmias</td>
</tr>
<tr>
<td>Evening primrose (Primula vulgaris)</td>
<td>Autoimmune diseases Diabetic neuropathy Osteoporosis Hypertension</td>
<td>Increase prostaglandins Anti-inflammatory Antithrombotic</td>
<td>Sedative Risk of bleeding</td>
</tr>
<tr>
<td>Garlic (Allium sativum)</td>
<td>Culinary ingredient Cardiovascular wellbeing</td>
<td>Inhibition of platelet aggregation</td>
<td>Blood pressure changes Increased risk of bleeding Nausea</td>
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<tr>
<td>Ginger (Zingiber officinale)</td>
<td>Culinary ingredient Anti-emetic</td>
<td>Inhibit serotonergic pathways Inhibit thromboxane synthetase enzyme</td>
<td>Sedative effects Risk of bleeding</td>
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<tr>
<td>Ginkgo biloba</td>
<td>Improve cognitive performance Treatment of peripheral vascular disease</td>
<td>Inhibition of platelet-activating factor Free radical scavenger</td>
<td>Impaired wound healing Antiplatelet effect Headaches</td>
</tr>
<tr>
<td>Ginseng (Panax ginseng)</td>
<td>Immune system benefits Mood enhancement Aphrodisiac</td>
<td>Mild sympathomimetic Possible interaction with monoamine oxidase Inhibits of Na channels in the CNS</td>
<td>Cardiovascular instability Impaired wound healing Immunomodulating Increased risk of infection</td>
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<tr>
<td>Green tea (Camellia sinensis)</td>
<td>Neurodegenerative diseases Anti-cancer</td>
<td>CNS stimulant Antioxidant Source of Vitamin K</td>
<td>Antiplatelet effect Stimulant Risk of bleeding</td>
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<tr>
<td>Guarana (Paullinia cupana)</td>
<td>Weight loss Stimulant</td>
<td>CNS stimulant</td>
<td>Stimulant Risk of bleeding Arrhythmia</td>
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<tr>
<td>Kava (Piper methysticum)</td>
<td>Anxiolytic Sedative</td>
<td>Potentiation of GABA transmission Dopamine antagonist</td>
<td>Sedative effects Hepatotoxicity Dermatological changes</td>
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<tr>
<td>Herbal medicine</td>
<td>Use</td>
<td>Pharmacological effects</td>
<td>Perioperative consideration</td>
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<td>Milk thistle (Silybum marianum)</td>
<td>Liver protection</td>
<td>Antioxidant</td>
<td>Hepatotoxicity</td>
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<td>Lowers cholesterol</td>
<td>Anti-inflammatory</td>
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<td>Blocks 5-alpha reductase</td>
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<td>Saw Palmetto (Serenoa repens)</td>
<td>Benign prostate hyperplasia</td>
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<td>Increased risk of infection</td>
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<td>Impaired wound healing</td>
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<td>Pancreatitis</td>
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<tr>
<td>St John’s Wort (Hypericum perforatum)</td>
<td>Mood enhancer</td>
<td>Induction of cytochrome</td>
<td>Sedative</td>
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<td>P450 enzyme</td>
<td>Blood pressure changes</td>
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<td>Serotonin, noradrenaline</td>
<td>Serotonin syndrome</td>
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<td>reuptake blocker</td>
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<tr>
<td>Valerian (Valeriana officinalis)</td>
<td>Anxiolytic</td>
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Appendix 2: List of useful sites

HerbMed  
www.herbmed.org

Medicines Complete  
https://about.medicinescomplete.com/

National Centre for Complementary and Alternative Medicine  
http://nccam.nih.gov

Natural medicines comprehensive database  
http://naturaldatabase.therapeuticresearch.com

The handbook of perioperative medicines  
https://www.ukcpa-periophandbook.co.uk/

Toxbase  
www.toxbase.org

WebMD Vitamins and Supplements Center  
https://www.webmd.com/vitamins/index