The use of herbal therapies is fast becoming widespread in both developed as well as developing countries. These “natural” therapies are considered beneficial, but more often than not their adverse effects and potential interaction with other drugs are not appreciated. Surveys in many developed countries have shown that the incidence of herbal medicine use ranges from 12% of the population in Australia to 37% in the USA. In South Africa it is estimated that as much as 27% of the population use herbal preparations as well as prescribed antihypertensive therapy to control their blood pressure. It is thought that as much as one fifth of all patients on prescription medication also use herbal remedies, high dose dietary supplements, or both. These figures may be as high as 80% or even higher when patients taking traditional herbal medication are included.

A distinction needs to be made between herbal, alternative and traditional medicines since the setting is South Africa.

Herbal therapies are defined as plant-derived products that are indicated for medicinal or health purposes. Herbal therapies have been part of human existence since the beginning of time. They span the spectrum from home-brewed teas prepared from collected leaves and herbs to products with official approved status granted by drug-regulating authorities.

More than 122 distinct plant derived chemical entities with pharmacological action are known. About 25% of drugs listed in the pharmacopoeias of developed countries were isolated from plant origin, while another 25% are modifications of molecules first found in plants.

A recent survey suggests that as much as 51% of patients use herbal medication in the two weeks preceding surgery. Of the drugs reported, 27% altered clotting, 30% had direct influence on cardiac rhythm, rate, blood pressure or serum electrolytes, and 20% would increase sedation.

The use of herbal medicines becomes problematic in the peri-operative setting for a number of reasons:

**Disclosure of use to health care practitioner**

- Herbal medicines are perceived as “natural” and therefore safe, and more than 70% of patients do not voluntarily disclose the use of these drugs to their physicians. Inadequate knowledge of this nature may prove detrimental to peri-operative outcome.

- Physicians may not be familiar with the mechanism of action of a specific herb, and may well underestimate the clinical effect of the drug.

**The influence on pharmacokinetics and –dynamics**

- The degree of alteration in pharmacodynamics and –kinetics of concomitantly administered drugs are often unknown, making prediction of clinical and side effects impossible. Induction and inhibition of both hepatic and intestinal drug metabolising enzymes have been suggested in numerous studies. Oral administration of herbs may alter gastric pH and motility and accelerate or impair drug delivery to the duodenum. Enterocytes are the first barrier that has to be crossed for absorption. These cells express high levels of CYP3A4 and P-glycoprotein, and the interplay of these are needed to determine bioavailability of many drugs. Modulation of these factors will determine enhanced or reduced bioavailability of co-administered substances.

- Of concern to the anaesthetist is the effects these medications may have on hepatic metabolism. St John’s wort is known to induce the CYP3A4 enzyme system, accelerating the metabolism of certain drugs such as amitriptyline. Other herbal drugs compete for the same cytochrome pathway as commonly used anaesthetic agents (e.g. echinacea competes with lignocaine for clearance via the CYP3A4 system). This may slow down clearance of the anaesthetic drug, predisposing the patient to toxic effects because of elevated plasma concentrations.

- Drug interactions between herbal medicines and conventional drugs are often not appreciated. Examples include St John’s wort and monoamine oxidase inhibitor interaction precipitating serotonin syndrome, or the additive effect on platelets that garlic and the nonsteroidal anti-inflammatory drugs have. This is dangerous especially when the conventional drug has a narrow therapeutic index (e.g. ginseng and warfarin), and relatively small alterations in concentration may have profound clinical consequences.

- The nett result of interaction may not be predictable because interaction may take the form of synergism, antagonism, inhibition or even acceleration of metabolism of either product. This will lead to pharmacological chaos.

**The risk of systemic toxicity**

- Another sinister complication refers to the ability of a herbal drug to enhance the organ toxicity of a concomitantly
administered drug. A herb such as echinacea increases the hepatotoxicity of drugs such as methotrexate and anabolic steroids,\(^{20}\) while halothane will elicit severe dysrhythmias when the patient has been using ephedra.\(^{21}\) Contaminants found in samples of herbal medication of questionable origin may include herbicides, pesticides, radio-isotopes, heavy metals and plant derived toxins, all adding to a confusing clinical picture when the patient become ill because of use of these drugs.\(^{22}\)

**Multiple adverse effects**

- Adverse events may include increased bleeding, cardiovascular complications, prolonged sedation, suppression of the central nervous system, and liver or renal dysfunction with derangement of drug metabolism and elimination.\(^{23}\)
- Adverse effects presenting peri-operatively due to the use of herbal medications may not be considered until late in the event process. And even when herbal therapies are considered in the aetiology of an adverse event, the response to standard emergency therapy (cardiovascular support drugs or haemostatic agents) may not be as expected.\(^{24}\)
- Many herbal substances may have multiple actions on one physiological system – for example, decreased activation of clotting by inhibition of von Willebrand factor, and decreased platelet aggregation due to glycoprotein receptor interference – or, conversely, act on more than one system simultaneously, such as effects on both the cardiac contractility and haemostasis.

**Manufacturing standards and regulatory challenges**

- Because of poor regulation of herbal medicine manufacture, true content of different preparations vary greatly between different manufacturers.\(^{25,26}\) Therefore estimation of total daily dose consumed is often very difficult to calculate.
- A single herb usually contains a number of bioactive components, each of which may contribute in varying degrees to the observed pharmacological effect and interactions. This, in turn, leads to difficulties in predicting and explaining possible mechanisms for herb–drug interactions.\(^{27}\)
- Most clinical trials on the efficacy of herbal medication are of limited value because of poor study design, small sample size and poor quality control.\(^{28}\)
- Legislation prohibits manufacturers of herbal medication claiming clinical indications for their products. However, they are not prohibited from stating physiological effects for herbal drugs.\(^{29}\) Unfortunately, this leads to biased reporting where positive effects are overemphasised, while side effects are underreported and sometimes not even mentioned, perpetuating the notion that these drugs are safe, and their use has no negative consequences.

**The systemic effects of herbal medication**

An overview of clinical effects that commonly used herbal preparations have on different physiological systems is presented in Table 1.

Many plants are used in blood-related therapies, including as blood tonics, to prevent excessive bleeding and as wound dressings. The safety and efficacy of these therapies are not always scientifically defined, and as such may be associated with increased peri-operative blood loss.\(^{30}\) The key is to understand whether the preparations have a direct effect on the coagulation system, or if disruption is due to drug interaction.

The main direct effect centres on decreased platelet activation and aggregation. Mechanisms to explain disaggregation include:

- Microtubule stabilization\(^{31}\)
- Increased membrane fluidity
- Reduced tyrosine phosphorylation limiting calcium mobilization, arachidonic acid liberation\(^{32}\)
- Decreased / inhibited activation of tissue factor,\(^{33}\) thrombin,\(^{34}\) plasminogen activator phospholipases, thromboxane \(A_2\),\(^{21}\) Co-enzyme A and HMG CoA reductase\(^{35}\)
- Potentiation of heparin co-factor II\(^{33}\)
- Increased fibrinolysis\(^{36}\)

Increased aggregation or coagulation may be explained through:

- Increased network protein synthesis and
- Increased erythrocyte aggregation\(^{37}\)
- Activation of several clotting factors or platelets due to glycoconjugates\(^{38}\)

Recent literature reviews have attributed adverse coagulation effects due to drug–herb interaction in a number of specific herbal remedies.\(^{41,42}\) The interaction of these preparations with warfarin especially seems to be of significance because of the narrow therapeutic index of warfarin. Of specific concern to the anaesthetist is the interaction between aloe vera and Sevoflurane.\(^{41,44}\)

**Herbal drugs and the heart**

Although epidemiological data support the cardiovascular benefits afforded by antioxidants and flavonoids\(^{45}\) present in many herbal preparations, clinical trials with purified, single compound material have yet to show any benefit.\(^{46}\) In fact, botanical preparations are many times more likely to induce adverse cardiovascular effects including arrhythmias, hypertension\(^{47}\) and sympathomimetic effects.\(^{48}\) Reports of interference with coagulation, platelet activity and drug metabolism (especially where drugs with narrow therapeutic windows are used) exist almost exclusively as case reports, and it is well known that adverse events of this nature is vastly underreported.\(^{49}\) Further effects include direct inhibition of contractility, interference with conduction (prolonged QT interval), additive effects to cardiac drugs used (especially cardiac glycosides) and vasoconstriction or –dilatation.\(^{50}\) All of these may cause severe intra-operative complications.

**Central nervous system effects of herbal preparations**

Many herbal preparations are indicated for their sedating and anti-depressive effects.\(^{51,52}\) Since their effects are mediated by GABA receptor activation or by serotonin re-uptake inhibition (amongst other mechanisms), there is great potential for interaction with anaesthetic agents.\(^{53}\) Apart from prolonged sedation or the risk of serotonin syndrome, some of these drugs may also precipitate seizures\(^{54}\) (due to direct inhibition of anti-convulsive therapy, accelerated anti-convulsive metabolism, or additive excitatory effects with mood stabilizers like trazodone, buspirone and fluoxetine). L-Dopa efficacy may be compromised, resulting in worsening symptoms of Parkinsonism.\(^{55}\)

**Hepatic effects of herbal medicines**

As many as 60 herbal preparations are known to cause derangement of hepatic function.\(^{56}\) This does not include hepatic damage attributed to contaminants, impurities, misidentified herbs and solvents used in extraction of the active ingredients. Herbal therapies may alter drug metabolism by the influence they exert on the glucuronidation process, the cytochrome p450 (CYP) and other hepatic enzyme systems. CYP inhibition will decrease
### Table 1: Commonly used herbal drugs with indications, active ingredients and drug interactions

<table>
<thead>
<tr>
<th>Name</th>
<th>Indications</th>
<th>Active constituents</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aloe vera</strong> (Aloe vera)</td>
<td>Oral – laxatives, Topical – creams</td>
<td>Polysaccharides, Acetylated mannans, Inhibits arachidonic acid synthesis</td>
<td>Additive to sevoflurane effect on platelets - inhibition of GPIIb/IIa receptors on platelet - inhibition of GPIA interaction with intercanalicular system Poor platelet plug formation – increased risk of haemorrhage</td>
</tr>
<tr>
<td><strong>Chamomile, German</strong> (Matricaria recutita)</td>
<td>Restlessness, Insomnia, Gastrointestinal upset</td>
<td>Azulene constituents, Sesquiterpene, Bisabolol and coumarin constituents</td>
<td>Central nervous system depressants (e.g., opioids, benzodiazepines) – increased sedation Warfarin, aspirin and NSAIDs – increased risk of bleeding from presence of coumarin in chamomile</td>
</tr>
<tr>
<td><strong>Echinacea</strong> (Echinacea angustifolia, E. purpurea, and E. pallida)</td>
<td>Oral – prevent and treat common cold and upper respiratory tract infections, immunostimulant, Topical – wound healing, burns, abscesses, eczema, herpes simplex virus</td>
<td>Choricic, echinacisides, polysaccharides, polyacetylenic compounds, ketoalkenes and ketoalkynes</td>
<td>Immunosuppressants (e.g., cyclosporine, prednisone, azathioprine) – decreased immunosuppressant effects due to possible immunostimulation Hepatotoxic agents (e.g., acetaminophen, methotrexate, amiodarone) – additive hepatotoxicity resulting from glutathione depletion Inhibition of CYP3A4 and CYP1A2 increasing levels of drugs metabolized by these enzymes</td>
</tr>
<tr>
<td><strong>Evening primrose oil</strong> (Oenothera biennis)</td>
<td>Premenstrual syndrome (PMS), Menopausal symptoms, Atopic eczema, Rheumatoid arthritis, Raynaud's syndrome, Multiple sclerosis, Hypercholesterolemia, Diabetic neuropathy</td>
<td>Gamma-linolenic acid (GLA) – rapidly metabolized to Dihomogammalinolenic acid (DGLA) Linoleic acid</td>
<td>Anticonvulsants – risk of seizure Anticoagulants and antiplatelet agents – increased risk of bleeding Anaesthetics – risk of seizure Phenothiazines – report of seizures with concomitant use</td>
</tr>
<tr>
<td><strong>Feverfew</strong> (Tanacetum parthenium)</td>
<td>Oral – prevent migraine used for fever, arthritis, tinnitus and vertigo, Topical – toothache and insect bites</td>
<td>Parthenolide – a sesquiterpene lactone</td>
<td>Anticoagulants, antiplatelet agents, and NSAIDs – inhibition of platelet aggregation and risk of bleeding</td>
</tr>
<tr>
<td><strong>Garlic</strong> (Allium sativum)</td>
<td>Hypertension, Hyperlipidemia, Coronary heart disease, Bacterial and fungal infections, Prevention of atherosclerosis</td>
<td>Powdered extract - 1.3% alliin Fresh garlic contains 1% alliin, allicin, and other organosulphur constituents</td>
<td>Protease inhibitors – decreased levels - treatment failure, risk of viral resistance Non-nucleoside reverse transcriptase inhibitors (NNRTI) – decrease serum levels - treatment failure, risk of viral resistance Cyclosporine – decrease levels, risk of transplant rejection Anticoagulants and antiplatelet agents – increased risk of bleeding Insulin and antihyperglycemic – enhanced hypoglycaemic action Oral contraceptives – possible contraceptive failure</td>
</tr>
<tr>
<td><strong>Ginger</strong> (Zingiber officinale)</td>
<td>Nausea, Arthritis</td>
<td>Gingerols, Gingerdione, Galanolactone, Zingerone</td>
<td>Antacids, H2 antagonists, proton pump inhibitors – ginger increases stomach acid while these medications suppress it Anticoagulants, antiplatelet medications, NSAIDs – increased risk of bleeding Sedatives, barbiturates, benzodiazepines, alcohol – enhanced effect Blood pressure medications – ginger alters blood pressure and interferes with therapy Cardiac glycosides – inotropic effect; can alter contractility Diabetes medications – additive hypoglycaemic effect</td>
</tr>
<tr>
<td><strong>Ginkgo</strong> (Ginkgo biloba)</td>
<td>Oral – memory loss, Alzheimer’s disease, circulatory disorders, intermittent claudication and tinnitus, Topical – frostbite and wound dressings</td>
<td>Terpene lactones, Ginkgo flavone glycosides, Isohammetin, Quercetin, Kaempferol, and Proanthocyanidins Bilobalide Primary terpenoids are ginkgolides A, B, C, M, and J</td>
<td>Thiaziade diuretics – increased blood pressure Anticoagulants, antiplatelet agents, NSAIDs – increased risk of bleeding Buspirone and fluoxetine – possibility of hypomania Trazodone – associated with coma Insulin – altered insulin secretion, leading to altered blood glucose levels Anticonvulsants – decreased efficacy Mild inhibitor of CYP3A</td>
</tr>
<tr>
<td><strong>Ginseng</strong> (Panax quinquefolius)</td>
<td>Enhanced stamina, concentration, energy, immune response, and stress response, Antidepressant, Diuretic, Acute respiratory illness, Diabetes, Impotence</td>
<td>Ginsenosides – Rb-1 Panaxosides</td>
<td>Digoxin – increased effects Anticoagulants – decreased efficacy Monoamine oxidase inhibitio – insomnia, headache, tremor, agitation, and worsening of depression Diabetes medications – increased risk of hypoglycaemia Opioids – decreased analgesic effect Oestrogen – additive estrogenic effect</td>
</tr>
<tr>
<td><strong>Kava</strong> (Piper methysticum)</td>
<td>Oral – anxiety, insomnia, restlessness, muscle pain, headaches, Topical – wound healing</td>
<td>Kava-lactones and -pyrones, Kawai, Dihydrokawai, Methysticin, Dihydroxymethysticin, Vangonin</td>
<td>Benzodiazepines – increased lethargy and disorientation Levodopa – decreased effectiveness CNS depressants, alcohol – additive drowsiness, and depression of motor reflexes</td>
</tr>
</tbody>
</table>
metabolism of competing drugs dependant on the specific enzyme, whereas induction of the CYP enzyme will accelerate metabolism in a similar fashion (e.g. St John’s wort and amitrypteline57). Some therapies (on their own or additive to other hepatotoxins) may cause direct hepatocellular damage,66 while others are known to protect against hepatotoxicity by inhibiting enzymes responsible for metabolism of a compound into a toxic metabolite (garlic protecting against paracetamol toxicity).19

Herbal effects on the immune system

Many so-called immune boosters have yet to be proven effective in clinical trials. Most of these drugs only decrease the severity of the symptoms, but do not in fact alter the duration of the disease.60 Important to note is the fact that these drugs interact with immune modulating agents in a way that poses significant danger to the patient.61 Alteration in CYP metabolism leads to a decrease in the efficacy of immunosuppressant drugs like cyclosporine (narrow therapeutic window), increasing the risk for rejection in organ transplant patients.56,63 Furthermore, a herb such as garlic decrease the bioavailability of anti-retroviral drugs such as sequinavir and ritonavir, thus rendering therapy ineffective and increasing the risk of viral resistance.10

Endocrine and electrolyte effects of herbal preparations

The effects on the endocrine system are varied and specific to relevant herbs,19 and include hyper- and hypoglycaemia,64 oral contraception failure with some preparations,55 impaired corticosteroid synthesis66 and hypokalaemia.69

Conclusion

Herbal medicine usage is very common. The anaesthetist will be confronted more and more with patients using these drugs. It is true that our knowledge of the clinical effects of many of the preparations is still incomplete. However, there is a growing body of evidence regarding drug interactions and side-effects concerning these drugs. Specific enquiry during history taking may alert and prepare the peri-operative physician for the most likely adverse events. Where unexpected complications occur, one must have a high index of suspicion that the patient omitted to reveal the usage of herbal medication. No guidelines from scientific societies have been published as yet, but most authorities agree that all herbal supplements and drugs be stopped at least 2 weeks prior to surgery.68

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Herbal and alternative medicine: the impact on anesthesia


Operation Smile is a non-profit, volunteer medical services organization providing free reconstructive surgery in over 60 countries around the world, including 13 in Africa. Our mission principle is: No child, in any community, should have to live with the pain and isolation caused by a correctable facial deformity.

About us:
Operation Smile South Africa (OSSA) was registered as the regional hub for Central and Southern Africa in 2006. Our inaugural medical mission, which initiated the long term commitment from Operation Smile to South Africa, was conducted in September 2006 in Empangeni, KwaZulu Natal.

Since 1982, Operation Smile, through the help of dedicated medical volunteers has provided 220,000 free surgical procedures for children and adults. Our work creates a lasting global impact.

OSSA also conducts several medical training programs throughout the year including programs in American Heart Association (AHA) Basic Life Support (BLS) and Pediatric Advanced Life Support (PALS). OSSA educational programs have benefitted more than 400 health care professionals across South Africa.

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