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An Examination of the Bleeding Complications Associated with Herbal Supplements, Antiplatelet and Anticoagulant Medications

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Dental professionals routinely treat patients taking prescription, nonprescription, and herbal medications that are known or have the potential to alter bleeding. Prescription anticoagulant and antiplatelet medications, as well as over-the-counter drugs such as aspirin, are typically taken to reduce the risk of thromboembolic events, including stroke. Herbal supplements are widely used for a variety of indications, and both patients and health care practitioners are often unaware of the anticoagulant and antiplatelet effects that occur as either predictable pharmacologic effects or adverse side effects of herbal medicines. In addition, patient use of these herbal supplements is usually undisclosed to health care providers. The purpose of this literature review is to examine the mechanisms of action of drugs and herbs that alter bleeding, and to educate dental professionals as to the proper care and management of patients using these medications. Decision-making strategies, including interpretation of laboratory tests, and when to discontinue the use of these medications are discussed. Patients undergoing routine dental and dental hygiene procedures do not need to discontinue the use of anticoagulant and antiplatelet medications. However, alterations in drug use may be required for those patients undergoing invasive surgical procedures. It is recommended that herbal supplements must be discontinued 2 weeks prior to receiving invasive surgical procedures. Dental practitioners must learn to weigh the risks of discontinuing drug therapy against the potential risks to patients, and implement risk reduction strategies to minimize adverse bleeding complications associated with dental treatment.

Keywords: Anticoagulants, Antiplatelet medications, Aspirin, Bleeding, Clotting, Dental treatment, Garlic, Ginger, Ginkgo biloba, Ginseng, Herbal supplements, NSAIDS, Platelets, St. John's wort, Warfarin

Introduction

Cardiovascular disease, including ischemic coronary heart disease, stroke, and peripheral vascular disease, is the leading cause of death in the United States.¹ Stroke is the third leading cause of death, and is the primary cause of adult disability.² Yearly, over 1 million Americans experience new or recurrent myocardial infarction (MI) or fatal coronary heart disease. Most of these events occur in the elderly or in those with known risk factors for cardiovascular disease.³ The age-adjusted mortality rate due to coronary heart disease, cerebrovascular disease and atherosclerotic disease is 194 per 100 000 cases, which translates to more than 500 000 deaths per year.¹ These leading causes of death correspond directly to chronic

conditions experienced by many patients, especially the elderly, who may live for decades with illnesses that are typically controlled with medication use.^{2,4}

Given these disease trends, dental professionals are seeing more patients taking anticoagulant and/or antiplatelet medications to prevent arterial or venous thrombosis and stroke.⁵ Controversy and confusion persist as to whether these medications actually pose a risk for significant postoperative bleeding following invasive dental procedures. However, excessive or life-threatening bleeding caused by medication use in the dental office is an extremely rare event, even among patients at risk.^{6,7}

Determining the proper management strategy to safely treat patients taking anticoagulant and antiplatelet medications must take into account the risk of thrombus formation in the patient. The clinician must weigh the risks of potential bleeding complications against the potential risks associated with altering the medications used to reduce significant cardiovascular risk.⁶ According to Little and associates (2002), risk of "thrombosis is of greater overall clinical importance in terms of morbidity and mortality than all of the hemorrhagic disorders combined."⁵

The decision to alter the patient's medication regimen, by either lowering the dosage of or discontinuing the medication prior to dental treatment, is not supported by clinical studies in the literature.^{6,8,9} Yet, many dental clinicians continue to recommend medication alteration as a management strategy, with the belief that they are promoting patient safety. Proposed regimens are based on case reports, opinions published in the literature, and habit, and are not supported by clinical data.^{6,9}

The justification for reducing or withdrawing anticoagulant medication prior to dental treatment can be dated back to a time when less than a dozen case reports in the literature reported excessive bleeding following dental treatment in patients taking warfarin. However, it is important to note that during the timeframe when those case studies were published, the prothrombin time test (PTT) was used to evaluate the effectiveness of warfarin; but, testing was not yet standardized, and variations in clinical efficacy were bound to occur.^{6,10,11} Today, standardized measures, such as the International Normalized Ratio (INR), are used to assess coagulation time in patients taking warfarin, and guidelines for therapeutic ranges of anticoagulation have been established.¹² These guidelines make it easier for the clinician to predict the risks for bleeding in medicated dental patients.

A variety of other medications can contribute to bleeding complications in dental patients, including nonsteroidal anti-inflammatory analgesics, hormones, herbs, and dietary supplements. It is critical that dental professionals conduct a pharmacologic history review as a component of a comprehensive review of systems for all patients who present for oral health care. Assessing the patient's prescription and over-the-counter (OTC) medication use provides important information about the patient's current medical status, disease severity, compliance with drug and treatment recommendations, and orientation to health and wellness.¹³

Understanding medication use helps dental professionals anticipate and prevent oral and systemic complications associated with adverse drug events.¹⁴ Drug-induced adverse bleeding events can happen outside of the dental office, as well as during treatment. Assessing potential bleeding complications associated with medication and supplement use is a vital service that dental professionals provide to their patients.¹⁴ Most dental patients taking prescription medications are aware of the bleeding risks associated with their drugs, and in fact, are monitored routinely to detect alterations in coagulation before complications arise. However, these same patients may not fully understand how their lifestyle, including diet, alcohol use, and the use of OTC medications, can alter the bleeding effects of their prescription medications.

In addition, dental professionals must remember to ask their patients about the use of herbs, vitamins, and dietary supplements when assessing medication use. Surveys estimate dietary supplement usage by 12% to 24% of the general population.¹⁵ In addition, usage doubled for individuals aged 65 years and older from 1999 to 2002.¹⁶ Recent estimates suggest that over 15 million Americans take herbs, vitamins, or both, along with their prescription medications.¹⁷ Since these supplements are available OTC, many patients do not include these products when listing medications on health history forms. For example, over 51% of patients scheduled to undergo surgical procedures in a Colorado hospital were taking herbal

medications, some of which may alter blood coagulation.¹⁸ Further, in a preanesthesia interview at a university medical center, nearly 70% of patients taking herbal medications did not report their usage.¹⁹

Several herbs contain substances that have coumarin, salicylate, or antiplatelet properties, such as garlic, ginkgo, and ginseng.²⁰ Although no definitive studies have been performed to show a direct cause and effect of herbal use and bleeding complications, the literature suggests that this is a phenomenon of increasing concern due to the extreme popularity and increasing use of these products.

During January 2005, the National Institutes of Health (NIH) conducted a joint conference with the National Heart, Lung and Blood Institute (NHLBI), the Office of Dietary Supplements (ODS), the NIH Clinical Center (CC), the National Center of Complementary and Alternative Medicine (NCCAM), the National Institute of Neurological Disorders (NINDS), the NIH Foundation, and the Office of Rare Diseases (ORD) at the NIH that specifically addressed this issue as a public health concern. The conference goal was to "increase our understanding of the potential for dietary supplements to interfere with hemostasis and antithrombotic therapies."¹⁵

According to the Natural Medicines Comprehensive Database, approximately 180 dietary supplements have the potential to interact with warfarin, and more than 120 may interact with aspirin, clopidogrel (Plavix®), or dipyridamole (Aggrenox®). The 2005 NIH conference specifically identified the following supplements as having this interaction potential:

Anise

Dong Quai

Omega-3 fatty acids in fish oil

Ajoene in Garlic

Ginger

Ginkgo

Vitamin E

Fucus

Danshen

St. John's Wort

American Ginseng

In addition, the following herbs may affect blood clotting, which is dependent on vitamin K:

High dose vitamin E (specific dosage not indicated), a vitamin K antagonist

Alfalfa -high vitamin K content

Coenzyme Q10 - dependent on vitamin K

Several of these listed herbs are consistently among the top sellers. Data from the Centers for Disease Control and Prevention (CDC) in 2002 included ginseng, ginkgo biloba, and garlic as the dietary supplements with the 2nd, 3rd, and 4th highest sales, respectively. St John's wort was 6th and ginger was 9th.²¹ The popularity of herbs with anti-coagulation potential was further validated by *HerbalGram's* report of dietary supplement sales in mainstream retail stores in 2004. Garlic was the top seller with ginkgo at 4th, ginseng at 7th, St John's wort at 9th, and ginger at 20th.²² Clearly, the popularity of these herbs has not waned.

Of the 11 herbs highlighted during the NIH conference, this article will only focus on garlic, ginkgo, ginseng, ginger, and St John's wort for several reasons. First, as indicated above, these herbs consistently rank high in sales, indicating

predominant usage. Second, the amount and quality of scientific evidence is more prevalent on these botanicals as compared to other herbs.

Health care professionals have an increasing responsibility to understand the rationale for use of these herbal medications and their reported effects on the body, given the large percentage of patients who take them. Unfortunately, it is challenging to locate accurate, consistent, and comprehensive information pertaining to herbal medications and their supposed mechanisms of action. While the knowledge base pertaining to herbs and other dietary supplements continues to grow, there are few studies that have determined conclusively how these products alter bleeding or interact with other herbals and prescription anti-thrombotic medications.²³ Speculation and case reports from the literature have provided clues as to the purported mechanisms of action; however, relatively few clinical trials have been conducted to formally examine these issues. Further, case reports in the literature sometimes fail to take into account other herbals or drugs that the patient may have been taking. Therefore, it is difficult to credit the results of a case study to one definitive herbal action.

Clinicians encounter this same phenomenon with their own patients. When asked, a patient may know a product's brand name, but cannot identify the multiple herbs that are contained within that same product. Further, it is not unusual for a patient to take upwards of 7 individual dietary supplements at the same time, but often on an inconsistent basis. When the CDC last reported on dietary supplement usage (1988-94), 14.4% of respondents reported usage of 3 or more supplements.²⁴ The highest segment of users (22%) was among those aged 40 years and older. More recently, the Hartman Group, a research firm, surveyed 43 000 U.S. households, and found that 31% reported using 7 or more supplements.²⁵ These statistics may not reflect, and in fact may underestimate, the growing use of combination products, or supplements that contain multiple herbs as well as vitamins. Given these trends, it is highly likely that an individual is unknowingly taking several herbs that have either anticoagulant or antiplatelet activity. Therefore, use of dietary supplements has the potential to a) cause a bleeding condition, b) exacerbate an existing bleeding condition, or c) alter the effectiveness of other OTC and prescription medications being taken concurrently. Obviously, the resulting complications may be potentially serious.

The purpose of this article is to assist dental professionals with understanding the mechanisms of action of popular prescription and herbal medications that alter bleeding. Drug and herbal interactions will also be discussed. Finally, practice management considerations for medicated patients and strategies for risk reduction will be presented to increase the dental professional's confidence in making treatment decisions for patients taking these medications.

Blood Clotting

There are over 50 substances in the blood that affect blood coagulation by acting as either procoagulants or anticoagulants. Normally, the anticoagulant substances predominate, keeping blood clots from forming. However, when a blood vessel is ruptured, procoagulant substances in the area of the damaged vessel become activated and override the effects of the anticoagulant substances, allowing a blood clot to form.²⁶

When clotting poses risk to a patient, anticoagulant or antiplatelet drug therapy is used to reduce the risk for thromboembolism. A thrombus is an abnormal clot that forms in a blood vessel. When the velocity of the blood flowing past the clot breaks the clot free from its attachment to the vessel wall, the free floating clot is referred to as an embolus. Clots that originate on the left side of the heart on the arterial side of the circulation clog arteries and arterioles that feed organs, resulting in ischemia and permanent damage to the organ tissue. Clots that originate on the venous side of the circulation or on the right side of the heart flow through the pulmonary arteries to the lungs, resulting in pulmonary embolism (PE). Risk for PE is high for patients who are immobile or bedridden, as intravenous clotting forms in the legs due to blood pooling in the lower extremities. This condition is known as deep vein thrombosis (DVT), a problem that can also occur in those traveling for long periods of time sitting in a motor vehicle or airplane.

Dental hygienists should be aware that circulating bacteria and bacterial endotoxins can also activate clotting mechanisms, producing small but numerous clots that plug blood vessels in the periphery, depriving many tissues of oxygen and other essential nutrients.²⁶ This is why patients who develop bacterial endocarditis are treated with anticoagulants as well as antibiotics: the antibiotics kill the causative bacteria, while the anticoagulants help to prevent clotting and ischemia initiated by bacterial endotoxins.

Parenteral Anticoagulants

Heparin

Heparin is an endogenous substance produced by many cells in the body, but is primarily made by mast cells found in the connective tissue surrounding capillaries in the body. These mast cells continuously produce small quantities of heparin that diffuses into the circulation. Basophils in the blood also release heparin into the plasma. The concentration of heparin in the blood is normally very low, and only produces significant anticoagulant effects under specific circumstances. It is used medically in much higher concentrations to prevent intravascular clotting.²⁶

Heparin itself is not an anticoagulant; however, by binding to antithrombin III, it serves as a catalyst to enhance the inactivation of multiple coagulation factors, including thrombin. Heparin also prevents the conversion of fibrinogen to fibrin, thus inhibiting clot formation.^{5,26} Unfractionated heparin (Hep-Lock®, heparin sodium, heparin calcium) has been used in medicine since the 1920s, and is used primarily in hospitalized patients to treat thromboembolism and PE.²⁷ High-dose therapy is used for DVT and PE, while low-dose therapy is used preventively.⁵

Both warfarin (Coumadin®) and heparin therapy are started on the first day of treatment, and the overlap allows for the 4 days to 5 days needed for warfarin to take effect. Heparin inactivates existing coagulation factors relatively quickly, while warfarin therapy blocks the synthesis of new clotting factors by the liver. In older adults undergoing general surgery, prophylaxis with low-dose unfractionated heparin (LDUH) or an intermittent pneumatic compression device, such as compression elastic stockings, is recommended to prevent DVT and venous thromboembolism (VTE).²⁸ Heparin is also used to prevent clot formation in catheters, shunts, pumps, and infusion machines (eg. dialysis machines).⁶

Standard heparin is comprised of an unfractionated heterogeneous mixture of polysaccharide chains with mean molecular weights ranging from 12 000 to 16 000 daltons. Heparin is administered parenterally, usually by intravenous injection, which results in an immediate anticoagulant effect.^{5,27,29} When administered by intravenous infusion or as a deep subcutaneous injection, onset of action occurs anywhere from 20 minutes to 30 minutes.^{27,29} Response to heparin is varied and unpredictable; therefore, patients receiving heparin are monitored with an aPTT (activated partial thromboplastin time) test.^{5,27}

Most patients receiving heparin will be treated in the hospital setting, and invasive dental procedures should be avoided during active treatment. Dental emergencies in these hospitalized patients must be treated carefully and conservatively.⁵ The most common dental patients taking heparin seen outside of the hospital setting are those who are undergoing hemodialysis, who receive heparin on an outpatient basis. As heparin has a half-life of 1 hour to 2 hours, its effects last for only a few hours after dialysis has been completed. It is safe for these patients to receive invasive dental procedures on the day following dialysis.⁵

Heparin may induce thrombocytopenia in up to 30% of users; however, for most affected patients, this adverse event is not clinically significant. However, heparin may induce an immunologically-mediated thrombocytopenia in 1% to 2% of users that causes a marked decrease in platelet count, leading to thromboembolic complications, such as PE, skin necrosis, and gangrene.²⁹ Daily platelet counts for the first week following the initiation of drug therapy can help to detect this condition.

Hemorrhage, including gingival hemorrhage, is another risk associated with heparin. This risk is increased by the use of other anticoagulant medications, thrombolytic agents and drugs that alter platelet function (see below). It is important to note that heparin is often used in conjunction with thrombolytics and during the initiation of warfarin therapy to assure adequate anticoagulation. Certain cephalosporins and parenterally administered penicillins may also increase risk for hemorrhage in heparinized patients.²⁹

Low Molecular Weight Heparins

Low molecular weight heparins (LMWHs) are the preferred method for prophylaxis for elective hip replacement surgery, started preoperatively or immediately after surgery, as these drugs have been found to be very effective in preventing asymptomatic VTE.³⁰ For elective knee replacement or hip fracture surgery, LMWH or adjusted-dose warfarin may be used.²⁸ Routine prophylaxis for VTE with LDUH or LMWH is recommended for patients with ischemic stroke and impaired mobility. These agents are also recommended for patients with other risk factors for VTE including immobility, cancer, heart failure, and severe lung disease.²⁸

LMWHs act in a similar manner to standard heparin, by inhibiting activated factor X and thrombin; however, they produce a lesser effect on the inhibition of thrombin.^{31,32,33} LMWHs are formed by depolymerization of unfractionated heparin side chains, producing "smaller" heparin fragments, with mean molecular weights ranging from 1000 daltons to 10 000 daltons.²⁷

LMWHs are administered subcutaneously, and exhibit a better bioavailability than standard heparin, as they are less bound to plasma proteins, endothelial cells and macrophages. They also have a longer half-life (2 hours to 4 hours) than heparin, and dosage is based upon body weight. Because LMWHs produce a more predictable anticoagulant response, laboratory monitoring during treatment is generally not necessary.^{5,27} Dental professionals do not need to order laboratory testing for patients taking these drugs for routine dental care.

For patients undergoing orthopedic surgery to the lower extremities, the optimal duration of prophylaxis is unknown.²⁸ Risk for DVT following surgery is related to the length of time that the patient remains immobile and other risk factors; risk persists for up to 2 months following total hip replacement surgery.^{28,34,35,36,37} Six randomized double-blind controlled clinical trials demonstrated reduced risk of total and proximal DVT by at least 50% for patients with total hip replacement who received prophylaxis with either LDUH or LMWH for 5 weeks beyond the hospital stay.³⁰

LMWHs can be provided on an outpatient basis, and patients taking these drugs have lower risks for hemorrhage and heparin-induced thrombocytopenia, as compared to patients taking heparin. Risks for bleeding increase when the LMWHs are used with thrombolytic agents, oral anticoagulants, and drugs that alter platelet function, although they are frequently used during initial therapy with oral anticoagulants to ensure proper anticoagulation. There are 3 FDA approved LMWHs in the United States: dalteparin (Fragmin®), enoxaparin (Lovenox®), and tinzaparin (Innohep®).^{27,29} Enoxaparin is the most widely used LMWH, and has been shown to prevent ischemic complications associated with unstable angina and non-Q wave myocardial infarction (MI).^{5,29,38}

Patients on LMWHs who present to the dental office can usually receive invasive dental treatment without any modifications necessary to their medication regimen. Should excessive bleeding be anticipated, as with oral or periodontal surgery, a physician consultation is warranted to determine whether the medication should be temporarily discontinued prior to performing the dental procedure. Given the short half-life of these drugs, high dose LMWH can be stopped for one day on the day before the surgery; then, therapy is resumed following hemostasis on the day of surgery. However, the best option is to wait until LMWH therapy has been completed before attempting any elective dental surgery.⁵

Antithrombotic Agents

There are 3 FDA approved antithrombotics that are used for the prevention of postoperative deep vein thrombosis (DVT), and for the treatment of heparin-induced thrombocytopenia and related thromboembolic complications. These drugs are argatroban (no brand name), danaparoid (Orgaran®), and lepirudin (Refludan®).

Argatroban is indicated for the prevention and treatment of thromboembolic complications in patients with heparin-induced thrombocytopenia. This drug is a highly selective thrombin inhibitor and binds reversibly to the active thrombin site of free and clot-associated thrombin. Drug administration is by IV, which produces an immediate onset of action. The drug inhibits fibrin formation, the activation of numerous clotting factors, and platelet aggregation.^{27,29}

Danaparoid (Orgaran®) is indicated for the postoperative prevention of DVT following elective hip replacement surgery. This drug prevents fibrin formation by inhibiting activated factor X by antithrombin. It is administered subcutaneously, with maximum effect occurring within 2 hours to 5 hours.^{27,29}

Lepirudin (Refludan®) is indicated for anticoagulation in patients with heparin-induced thrombocytopenia and related thromboembolic complications, and has investigational use for the prevention of ischemic complications associated with unstable angina. This drug is a highly specific inhibitor of thrombin, and is administered by IV. All antithrombotic agents have a risk for hemorrhage, which is increased with concurrent use of oral anticoagulants and drugs that alter platelet function.^{27,29}

Factor Xa Inhibitor

There is 1 antithrombotic agent in this new class of medications called fondaparinux (Arixtra®). This drug is indicated for prevention of deep vein thrombosis (DVT) in patients undergoing hip or knee replacement or hip fracture surgery. It may also be used for the treatment of acute pulmonary embolism (PE) or for treatment of acute DVT without PE. Fondaparinux is a synthetic pentasaccharide that inhibits activated factor X, which inhibits thrombin formation. It is administered subcutaneously, once daily. Risk for hemorrhage is increased when this drug is taken concurrently with oral anticoagulants, antiplatelet drugs, non-steroidal anti-inflammatory drugs (NSAIDS), salicylates, and thrombolytics.^{27,29}

Oral Anticoagulants

Warfarin

Warfarin (Coumadin®, Jantoven™) is an oral anticoagulant used for prevention and treatment of VTE, PE, atrial fibrillation with risk of embolism, and to prevent systemic embolism after MI.²⁹ Warfarin is also used for anticoagulation therapy in patients with prosthetic heart valves. Coumarin derivatives work differently than the other parenteral anticoagulants described above, by inhibiting the synthesis of vitamin K- dependent clotting factors.

Several clotting factors are dependent upon vitamin K for their synthesis in the liver. Warfarin binds to the liver microsomal enzyme vitamin K 2,3-epoxide reductase, and inhibits the production of the reduced form of vitamin K. Reduced vitamin K is a necessary cofactor in the gamma carboxylation of the 4 vitamin K-dependent clotting factors: factors II, VII, IX, X. Precursors to these 4 clotting factors undergo vitamin K-dependent modification to produce their active forms. By inhibiting the formation of reduced vitamin K, coumarins prevent the activation of these clotting factors. Thus, the clotting factors remain as inactive molecules that cannot participate in the clotting process, thereby stopping the formation of thrombin and fibrin.

Warfarin also depresses proteins C and S, which are endogenous anticoagulants. Levels of these 2 proteins may be depressed by warfarin prior to depression of the other clotting factors, resulting in a dangerous period of hypercoagulation for a short period of time. The anticoagulant effects of warfarin are not initially evident until 8 hours to 12 hours after oral administration, and given its 36 hour half-life, it may take up to 4-7 days of dosing to reach the desired target International Normalized Ratio (INR) value.²⁹ For this reason, heparin therapy (LDUH or LMWH) usually overlaps warfarin therapy for at least the first 2 days of oral anticoagulant therapy to allow for the warfarin to take effect and to achieve an optimal therapeutic range of anticoagulation.^{28,39} Heparin is discontinued after the INR has been in the therapeutic range for at least 2 measurements taken more than 24 hours apart.

Despite its widespread use, physicians often find it difficult to prescribe warfarin, given its narrow therapeutic index. It may take weeks of clinical testing (via the INR) to find the exact dose that results in the desired level of anticoagulation. Even small variations in dose can result in large clinical effects, including excess bleeding (over-anticoagulation) or inadequate anticoagulation, which places the patient at risk for developing clots.

Individuals taking warfarin vary in their response to given doses of the drug. It is known that a variation in the gene that encodes the CYP2C9 liver enzyme that metabolizes warfarin accounts for about 10% of the difference in response to the drug observed in warfarin users. Recently, investigators have identified another genetic variation in the VKORC1 gene (vitamin K epoxide reductase), which makes a protein that helps control clotting and is the target site of action of warfarin. By matching the genetic variations to the actual dose taken by study subjects, the researchers found that individuals with particular variations in the VKORC1 gene generally took similar doses of warfarin. Study results suggested that variation in this one gene accounted for 25% of the overall variance in warfarin dose. In the future, genetic testing could help to predict a person's response to warfarin, and could be used to determine the proper initial dose.⁴⁰

The major complication of anticoagulation therapy is bleeding. There is a positive relationship between the risk for hemorrhage and the intensity of anticoagulation.⁴¹ Patients on high-intensity warfarin therapy (INR>3.0) are at higher risk for hemorrhage as compared to warfarin therapy with an INR that falls between 2.0-3.0. The risk for intracranial hemorrhaging rises dramatically with an INR>4.0.^{41,42} The major determinants of warfarin-induced bleeding are the intensity of anticoagulation, unique patient characteristics, concurrent use of drugs that interfere with hemostasis (eg, aspirin), poorly controlled hypertension, and the duration of drug therapy.⁴¹ Multiple large, randomized controlled clinical trials support the use of combination therapy with aspirin plus warfarin (INR 2.0-2.5) in high-risk patients with atherosclerotic heart disease. Combination therapy increases the risk of both minor and major bleeding, but not intracranial bleeding in atherosclerotic patients. The most common bleeding complications include epistaxis (nosebleed), purpura (skin hemorrhages), gastrointestinal (GI) bleeding, hemoptysis (expectorating blood), and hematuria (blood in urine).^{42,43,44}

Unexpected elevations in the INR increase concerns for adverse bleeding events. Frequent monitoring of therapy, including the INR, is especially important in older adults, and adjustments to the treatment regimen are often necessary.⁴⁵ When the INR is elevated, but no bleeding is present, warfarin therapy can be reduced or stopped, which lowers the INR within 24 hours to 48 hours without returning it to baseline levels. In patients with non-life-threatening bleeding, a small dose of vitamin K₁ (1-2.5 mg) is administered orally or subcutaneously (SC). If urgent correction of the INR is needed, a larger dose of vitamin K₁ (2-4 mg) is given initially, with additional 1-2 mg doses given as needed. When the INR >9.0 and/or bleeding is life-threatening, warfarin therapy is stopped and large doses of vitamin K₁ (3-5 mg orally; 5-10 mg SC) are given. Fresh frozen plasma may also be given to replace the vitamin K-dependent clotting factors. Vitamin K₁ may also be given by IV in life-threatening situations, but it must be administered slowly and carefully monitored, given the risk for anaphylaxis.^{46,47,48,49,50,51,52}

Multiple factors can contribute to alterations in the INR. Poor compliance with warfarin therapy is the most common reason for fluctuations in anticoagulation therapy.⁵³ Switching between different brand names of warfarin product formulations has been shown to contribute to major medical complications, and patients are advised not to switch brands once the desired therapeutic effect has been achieved.^{29,54} Alterations in vitamin K intake, interference with intestinal bacterial synthesis of vitamin K, and impaired vitamin K absorption all cause significant fluctuations in response to warfarin.⁵⁵ Many common foods, especially dark green leafy vegetables and 4 plant oils (soybean, canola, cottonseed, and olive) serve as primary dietary sources for vitamin K.⁵⁶ Patients should maintain consistency in their diet and meet the recommended dietary allowance for vitamin K of 65 to 80 micrograms of phylloquinone per day.⁵⁶ Patients who increase their intake of "heart-healthy" green vegetables without informing their physicians may be inadvertently increasing their warfarin requirements; sudden decreases in vitamin K intake then increases the risk for hemorrhagic events.

Other factors that contribute to alterations in anticoagulation effects include illness, fever, thyroid disease, biliary disease, liver disease, malabsorption syndromes, congestive heart failure, malignancy, and diarrhea.^{6,55} Warfarin is also highly affected by medication use. In fact, more food and drug interactions have been reported for warfarin than with any other prescription medication.⁵⁷ Alcohol consumption has also been reported to increase bleeding in warfarin users.^{55,58}

Dental professionals should be aware that many commonly prescribed drugs used during dental treatment have the potential to alter the effects of warfarin. The dental drugs that have been reported to enhance the anticoagulant effect of warfarin include antibiotics (cephalosporins, macrolides, metronidazole, quinolones, penicillins, tetracyclines), analgesics

(acetaminophen, NSAIDS), prednisone, and the systemic azole antifungals (fluconazole, ketoconazole, itraconazole).^{29,55,59} Single-dose antibiotic prophylaxis for the prevention of endocarditis and prosthetic joint infection is not likely to alter the effect of warfarin, although 3 case reports have been reported in the literature describing elevations in INR following prophylactic antibiotic use.^{60,61} Salicylates and NSAIDS should be avoided in warfarin users, given their antiplatelet activity.⁶⁰ All dental professionals are encouraged to consult a drug reference guide prior to prescribing any medication to a patient taking warfarin to ensure drug compatibility and safety. Foods and herbs that alter warfarin activity are summarized in Table I.

Table I. Foods and herbs that alter warfarin activity.

Alcohol	Acute binge drinking increases PT/INR Chronic daily drinking decreases PT/INR
Foods rich in vitamin K	Decreases effect of warfarin
Vitamin C	Increases effect of warfarin
Cranberry juice	Increases effect of warfarin
St. John's wort	Decreases serum levels of warfarin
Alfalfa	Decreases effect of warfarin due to large amount of vitamin K
Coenzyme Q10	Decreases response to warfarin
Bromelain	Avoid concurrent use: antiplatelet action
Cat's claw	Avoid concurrent use: antiplatelet action
Dong quai	Avoid concurrent use: antiplatelet action
Evening primrose	Avoid concurrent use: antiplatelet action
Feverfew	Avoid concurrent use: antiplatelet action
Garlic	Avoid concurrent use: antiplatelet action
Green tea	Avoid concurrent use: antiplatelet action
Ginseng	Avoid concurrent use: antiplatelet action
Ginkgo	Avoid concurrent use: antiplatelet action
Horse chestnut	Avoid concurrent use: antiplatelet action
Red clover	Avoid concurrent use: antiplatelet action

Source: Wynn RL, Meiller TF, Crossley HL. Drug Information Handbook for Dentistry. 10th ed., Hudson:Lexi-Comp, Inc. 2005. ²⁹

Oral Antiplatelet Agents

Aspirin

Aspirin was first used as an analgesic and antipyretic drug in 1899, and has quickly become the most widely used drug in the history of medicine.⁶² During the 1960s, the antiplatelet properties of aspirin were discovered.⁶² Since then, aspirin has become the most comprehensively studied and least expensive of all antiplatelet medications.⁵ Aspirin blocks the synthesis of thromboxane A2 from arachidonic acid in platelets by inhibiting the enzyme cyclooxygenase 1 (Figure 1). Thromboxane A2 is necessary for platelet aggregation and promotes blood clotting. The inhibitory effect of aspirin on the formation of this substance is irreversible and lasts for the life of the platelet, which is 7 days to 10 days. In fact, a single dose of aspirin impairs platelet aggregation for up to 4 days, until new platelets enter the circulation in sufficient numbers to exert a thrombotic effect.⁶³

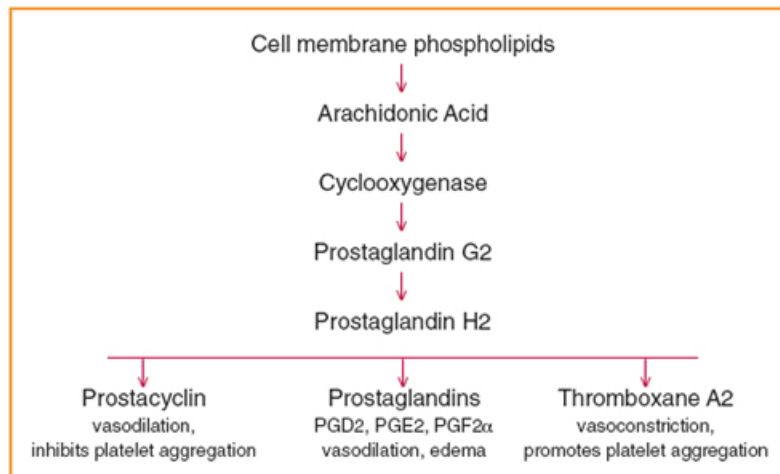


Figure 1. The arachidonic acid cascade.

Aspirin reduces mild to moderate pain, inflammation, and fever.²⁹ Aspirin is also used for the primary prevention of MI in patients at increased risk, and for the secondary prevention of ischemic cardiovascular events, such as stroke.⁶² Further, aspirin is used as an adjunctive therapy during revascularization procedures (eg, coronary bypass).²⁹ Aspirin should be available in the dental office as a pre-hospitalization drug for use in patients experiencing MI. It is thought that the fibrinolytic properties of aspirin, given at an 81-325 mg dose, may help to reperfuse the ischemic myocardium.⁶⁴

Despite the cardioprotective benefits of this drug, aspirin is still underused by many at-risk populations.⁶⁵ It is important to note that although aspirin is not approved for primary prevention of ischemic events, it may be possible for people who are at an even higher risk than those who have already experienced an adverse cardiovascular event to benefit from the effects of aspirin. The potential number of people in this highest risk category exceeds the number of people who are already taking the drug.⁶² Safety concerns, including risks for hemorrhage and gastrointestinal (GI) ulceration and bleeding, are thought to limit the recommendations of this drug by physicians to their patients.⁶² However, many patients choose to self-medicate with aspirin, and may be unaware of its potential adverse effects.

In addition to data that supports the benefits of aspirin in patients with cardiovascular disease, data from 55 000 individuals supports aspirin use for the prevention of first MI in healthy individuals, with an overall risk reduction of 32%.⁶⁶ Both the American Heart Association (AHA) and the U.S. Preventive Services Task Force (USPSTF) have published guidelines for the use of aspirin for the primary prevention of MI.^{3,67,68}

A meta-analysis of all available randomized, placebo-controlled clinical trials evaluating the effects of low-dose aspirin therapy for secondary prevention revealed that aspirin reduces the risk of death by approximately 20%. Further, aspirin also reduces the relative risk for cardiovascular events (eg, MI) and cerebrovascular events (stroke) by 20% to 30%.⁶⁹

The most common adverse event associated with aspirin use is GI ulceration and hemorrhage. These GI complications are attributed to aspirin's inhibitory effect on prostaglandin synthesis, which stops the production of protective prostaglandins that coat the walls of the stomach that normally form a barrier between the hydrochloric acid and the gastric mucosa. Further, aspirin inhibits the synthesis of prostaglandins that protect the kidney. Notably, chronic aspirin use can lead to kidney damage and renal failure. Hemorrhagic stroke is also a risk associated with long-term aspirin use. A meta-analysis of 16 clinical trials demonstrated an increased absolute risk of 12 hemorrhagic stroke events per 10 000 aspirin users.⁷⁰ Although aspirin increases risk for adverse bleeding events, the cardioprotective benefits of the drug outweigh these risks when used appropriately in at-risk patient populations.⁶²

Many adverse events caused by aspirin are dose-related and are extremely rare with low-dose therapy (81 mg per day). Bleeding risk increases with concurrent use of other medications that alter hemostasis, including NSAIDs, warfarin, and

alcohol. Drinking more than 3 alcoholic beverages per day significantly increases risk for GI hemorrhage. Aspirin use should be discontinued if patients develop tinnitus or hearing loss. Caution should be used when using aspirin in patients with bleeding or platelet disorders, peptic ulcer disease, and liver or kidney dysfunction.

Other serious reactions include hypersensitivity reactions and idiosyncratic reactions. Patients who are sensitive to tartrazine dyes, or who have nasal polyps or asthma are more likely to be sensitive to aspirin. In patients with bronchial asthma, aspirin and other NSAIDs may precipitate a condition known as aspirin-induced asthma (AIA), a syndrome characterized by aggressive and continuous inflammatory disease of the airways. AIA progresses from the upper to lower respiratory tract and affects women more than men, with an average age of onset at 30 years. Rhinorrhea and nasal congestion are the first symptoms, with asthma and aspirin hypersensitivity developing 2 years to 15 years later. Once developed, aspirin intolerance remains throughout life.⁷¹ Further, patients who are allergic to NSAIDs may not take aspirin or aspirin-containing products.²⁹

There is increasing concern about the number of individuals who exhibit aspirin resistance, also known as hypo-responsiveness, to the effects of aspirin. These individuals experience first MI or suffer a second adverse event while taking aspirin. For some reason, aspirin therapy is not enough to stop thrombotic activity. Three possible explanations have been offered to explain aspirin resistance: platelets become activated by pathways not blocked by aspirin; patients require a higher dose of aspirin to produce an effect; or patients generate thromboxane A2 despite aspirin therapy.⁷² Early data suggests that aspirin resistance may be dose related; resistance is found more often during low-dose therapy (< 100 mg daily) than at higher doses (> 300 mg daily). Platelet aggregation studies of these individuals reveal no biochemical activity of aspirin. Urinary concentrations of a thromboxane metabolite (11-dehydrothromboxane B2), a marker for aspirin resistance, may be used to identify potential aspirin-resistant individuals. Patients who are aspirin resistant should continue to take aspirin for its anti-inflammatory effects, but may require additional antiplatelet therapies for risk reduction.^{72,73}

Aspirin has many drug interactions, and dental professionals should consult a drug reference text prior to prescribing any medications to patients taking this drug. For example, concurrent use of aspirin with NSAIDs may decrease the serum concentration of some NSAIDs.²⁹ Dental professionals must remember that the effects of this drug are irreversible; therefore, additional bleeding will be evident during any invasive procedure. There is no evidence to support the discontinuation of low-dose aspirin therapy prior to dental procedures or dental surgery, as the risk for an adverse cardiovascular event outweighs the risk for intraoperative and postoperative bleeding in dental patients.^{8,29} Such bleeding can be managed locally with the use of hemostatic agents. However, a physician consultation is warranted to discuss whether patients who require major surgery require an alteration in aspirin therapy. The decision to discontinue therapy must take into account the risks to the patient. If the decision is to discontinue aspirin, the patient should stop taking aspirin 10 days to 14 days prior to surgery to allow for the synthesis of new platelets.

Dipyridamole

Dipyridamole (Persantine®) stimulates the release of prostacyclin or prostaglandin D2 (PGD2), inhibiting platelet aggregation and producing coronary vasodilation. The drug is primarily used to prevent angina pectoris, and to maintain the opening of the coronary arteries following bypass surgery. This drug is often used in combination with aspirin to prevent coronary artery thrombosis, or with warfarin, to decrease the risk of thrombosis in patients with mechanical heart valves. It may also be used prophylactically to prevent myocardial reinfarction.^{27,29} The drug is administered orally and intravenously.

Aspirin with dipyridamole

Combination aspirin with extended-release dipyridamole is an antiplatelet drug known as Aggrenox®. Aggrenox® is used to reduce the risk of stroke in patients who have had either transient brain ischemia or an ischemic stroke due to thrombosis. The drug contains 25 mg of aspirin and 200 mg of dipyridamole. The aspirin inhibits platelet aggregation by inhibiting platelet cyclooxygenase and the generation of thromboxane A2. Dipyridamole stimulates the release of prostacyclin, the antagonist of thromboxane A2. The antithrombotic effects of this drug are irreversible, given the aspirin component of the drug.^{27,29}

Clopidogrel

Clopidogrel (Plavix®) inhibits platelet aggregation by a different mechanism than aspirin. This drug inhibits the binding of ADP to its platelet receptors, which prevents the binding of fibrogen between platelets, reducing platelet adhesion and aggregation. Clopidogrel also blocks the amplification of platelet activation caused by released ADP. Plavix® is used as an antithrombotic for the prevention of myocardial infarction, stroke and vascular death in patients with atherosclerosis. It is also prescribed for the prevention of thromboembolic events following the placement of coronary stents.^{27,29}

Plavix® was developed for use for patients who are unable to tolerate the adverse gastrointestinal effects of aspirin, and has recently replaced ticlopidine (Ticlid®) as the drug of choice for patients who are allergic or intolerant to aspirin.²⁷ Evidence supports that both clopidogrel and ticlopidine are more effective than aspirin in preventing stroke and other serious vascular events in high risk patients.⁷⁴ Like aspirin, this drug produces irreversible effects that last for the life of the platelet. Patients can receive routine dental procedures, including oral prophylaxis, without altering the dose of the drug.^{5,8} However, patients that are scheduled to undergo invasive surgical procedures, including dental surgery, are advised to discontinue the drug for 7 days prior to surgery.⁵ Consultation with the patient's physician prior to discontinuing the drug is warranted to ensure patient safety.

Risk for hemorrhage is associated with this drug and bleeding may occur at any site, including the oral cavity. Risk for hemorrhage increases with concurrent use of other drugs that alter hemostasis, including anticoagulants and antiplatelet drugs. Avoid the use of herbs that demonstrate antiplatelet activity (Table I). Concurrent use of clopidogrel with naproxen has resulted in GI blood loss. Cases of thrombotic thrombocytopenia purpura have been reported with use of this drug, usually occurring within the first 2 weeks of therapy.²⁹

At high doses, clopidogrel may alter the metabolism of some NSAIDs, which can result in toxicity reactions. Finally, CYP3A4 inhibitors, including the macrolide antibiotics, may decrease the effects of clopidogrel. Dental patients who are prescribed these antibiotics should be closely monitored.²⁹

Cilostazole

Cilostazole (Pletal®) is an oral antiplatelet drug used to manage the symptoms of peripheral vascular disease. This drug and its metabolites inhibit phosphodiesterase III, which increases cyclic adenosine monophosphate (AMP), causing inhibition of platelet aggregation and vasodilation. Inhibiting phosphodiesterase III increases cardiac contractility, atrioventricular (AV) nodal conduction, ventricular automaticity, heart rate, and coronary blood flow.²⁹

The blood levels of cilostazole may be increased by erythromycin. Increased blood concentrations of this drug are observed with concurrent use of CYP3A4 inhibitors, including the macrolide antibiotics and the systemic azole antifungals. Inhibition of platelet aggregation caused by aspirin is potentiated with concurrent use of cilostazole.²⁹

Ticlopidine

Ticlopidine (Ticlid®) is an irreversible platelet aggregation inhibitor used to reduce the risk for thrombotic stroke. The other primary indication for use is to reduce the incidence of thrombotic complications in patients with coronary stents. Use of this drug is typically reserved for patients who are intolerant to aspirin, and for those whose aspirin therapy has failed. Ticlopidine has a mechanism of action that is unique from other platelet aggregation inhibitors. While the drug inhibits adenosine diphosphate (ADP) platelet receptor fibrinogen binding (like Plavix®), this drug also significantly increases bleeding time. The increase in bleeding time can be further prolonged by the addition of aspirin.²⁹

Ticlopidine has been associated with life-threatening hematologic disorders, including neutropenia and thrombotic thrombocytopenic purpura.⁷⁵ Thus, use of clopidogrel has surpassed this drug due to a better safety profile. Ticlopidine use may increase the effect and risk for toxicity of aspirin, anticoagulants, and NSAIDs.²⁹

NSAIDS

Nonselective NSAIDS, such as ibuprofen, inhibit both cyclooxygenase 1 and 2, and thus alter thromboxane A₂ synthesis and platelet aggregation (Figure 1). However, unlike aspirin, the effects of these drugs are reversible and last for a shorter period of time, based upon the half-life of the individual drug.²⁷ When the drug is removed from the body, platelet function is restored. A recent study demonstrated that platelet function returned to normal within 24 hours of discontinuation of ibuprofen use in healthy individuals.⁷⁶ Many professionals continue to recommend discontinuing the use of NSAIDS at least 7 days prior to surgery, when in fact, a much shorter timeframe may suffice. Practitioners should look up the half-life of the NSAID to determine how long it will take for the drug to clear from the body.

The degree of platelet inhibition seems to vary among different nonselective NSAIDS, but for most drugs, this effect does not appear to last throughout the length of the dosing period. For example, taking naproxen 500 mg twice daily inhibits platelet aggregation throughout the dosing period, versus ibuprofen, which achieves adequate platelet inhibition at peak levels, but is not sustained, given the short half-life of the drug. Further, data suggests that the antiplatelet effects of naproxen are significant and comparable to those produced by aspirin, but are less with ibuprofen and diclofenac.⁷⁷ This suggests that naproxen may have greater cardioprotective properties than other NSAIDS. The variance in effect on platelet inhibition is among the many reasons why NSAIDS are not used for cardioprotective therapy.

A large epidemiologic study found no evidence of cardioprotective effects of traditional NSAIDS.⁷⁸ Several studies concluded that current use of NSAIDS does not substantially reduce the risk of acute myocardial infarction (MI).^{79,80,81,82} Given the effects of naproxen, several investigations examined whether naproxen therapy could reduce the risk for MI; study results were inconclusive.^{80,81,83,84,85,86,87,88} There is also increasing evidence that concurrent use of NSAIDS with aspirin may decrease the cardioprotective effects of aspirin.^{89,90,91}

A recent retrospective case-control analysis of 8688 case patients with first-time acute MI revealed that current use of NSAIDS does not alter the risk of acute MI. Further, the risk for acute MI was higher among subjects who stopped taking NSAIDS within 2 months before the MI occurred. The authors hypothesize that current NSAID use does offer some protective effect, such as reducing MI risk related to chronic inflammation, but that this effect only occurs while the drug is being taken.⁹²

Selective NSAIDS, known as the COX-2 inhibitors (eg, Celebrex®, Vioxx®, Bextra®), inhibit cyclooxygenase 2 without affecting cyclooxygenase 1. Thus, their effects predominantly alter prostacyclin versus thromboxane A₂ (Figure 1). Studies in healthy volunteers show that treatment with COX-2 inhibitors decreases systemic production of prostacyclin with no effects on platelet-derived thromboxane A₂ synthesis.^{79,93}

Expression of cyclooxygenase 2 is increased during ischemia, which is thought to be a protective mechanism against vascular injury, causing increased prostacyclin synthesis, resulting in vasodilation and decreased platelet aggregation to facilitate blood flow. Inhibition of the COX-2 enzyme blocks these protective effects, and because platelet thromboxane A₂ is unaffected, the balance of the equilibrium maintained between these 2 prostanoids becomes disrupted. This allows the influence of thromboxane to predominate, increasing vasoconstriction and clotting. This is the mechanism thought to underlie the adverse hypertension and stroke events found with long-term use of COX-2 inhibitors (eg, Vioxx®)

Herbal Supplements

Physicians closely monitor patients taking prescription medications that alter bleeding, because the effects of these medications are known. Unfortunately, patient use of OTC medications that alter bleeding, including the use of dietary supplements, is not supervised as closely, especially since many patients do not report taking these medications. In fact, use of any form of alternative medicine is not disclosed to health care providers over 60% of the time.¹⁷

A study in England documented that a significant number of patients may be co-ingesting herbal medicines with warfarin. One thousand three hundred and sixty patients from 35 different medical practices were surveyed about the use of garlic,

ginseng, ginkgo biloba, feverfew, ginger, and St. John's wort. One hundred and nineteen patients (8.8% of the respondents) reported taking one or more of these herbs. When asked if they had discussed their herbal use with any health care professional, 92.2% reported that they had not. The authors concluded that all general practitioners prescribing warfarin should always ask about the use of herbal medications. They also added that there are risks involved with any herbal preparations, and charged that physicians, as well as their patients, share a joint responsibility to discuss potential herb-drug interactions.⁹⁴ Dental professionals are also well positioned to help patients understand the vital nature of this type of disclosure along with responsible product use.

Both the desired and adverse effects caused by prescription medicines are predictable, as they are manufactured and tested according to exacting standards. The effects of herbal phytotherapies, including adverse reactions, are hard to foresee. The FDA does not regulate herbal product manufacturing, nor is safety testing required, so it is challenging to find documented safety and efficacy information. However, the popularity of these products has dictated the need for further study to gain a better understanding of how herbs affect the body, and significant improvements in both herbal manufacturing and research have occurred in recent years.

Unlike prescription drugs, individual herbal preparations are often a mixture of more than one active ingredient. Thus, it is difficult to determine which or how many constituents of the herbal product are pharmacologically important. In addition, comparable herbal products vary in formulation, and their undefined composition makes analysis of the active constituents extremely complex.⁹⁵ This further confounds the understanding and utility of findings gleaned from research studies about the effects of herbal drugs.

Ciocon and colleagues have stated "that certain herbals have been associated with increased risk of bleeding by inhibiting platelet function, platelet aggregation and thromboxane synthesis, thrombin and thromboplastin mechanisms, and by those which contain coumarin-like effects, and salicylate-like effects."⁹⁶ They propose a mnemonic of a "Few G's" to help health professionals remember a list of herbs that are known to alter bleeding. The Few G's include fever**f**ew, plus g**ink**go biloba, g**ing**er, g**ar**lic and g**in**seng. They add that when the "g" is followed by a vowel (eg, g**ink**go), the herb is associated with this adverse effect. When an herb that starts with the letter "g" is followed by a consonant (eg, green tea), there is not a concern for bleeding.⁹⁶ This mnemonic can also be used to remember the herbs that are most likely to interact with anticoagulant and antiplatelet agents.

It is important to note that other herbal products have been implicated in causing adverse bleeding effects as well (Table II).²⁹ However, this article will focus on 5 herbs that are widely used and have some scientific evidence to support the effects described here.

Table II. Herbs with anticoagulant/antiplatelet properties.

Alfalfa
Anise
Bilberry
Bladderwrack
Bromelain
Cat's claw
Celery
Coleus
Cordyceps
Dong quai
Evening primrose
Fenugreek
Feverfew
Garlic*
Ginger*
Ginkgo biloba*
Ginseng*
Grape Seed
Green tea
Guarana
Guggul
Horse chestnut seed
Horseradish
Horsetail rush
Licorice
Prickly ash
Red Clover
Reishi
St. John's wort*
Sweet clover
Turmeric
White willow

*Herbs discussed within this article

Source: Wynn RL, Meiller TF, Crossley HL. Drug Information Handbook for Dentistry. 10th ed., Hudson:Lexi-Comp, Inc. 2005.*

Garlic Allium sativum

Recommended Dosage for general use: Extract, aged: 4 ml daily; Fresh: 4 g daily; Oil: 10 mg daily

Garlic is a perennial bulb with reported uses as an antilipidemic, antimicrobial, anti-asthmatic and anti-inflammatory. The bulb contains alliin and degradation products such as allicin, polysulfides, ajoenes, mercaptanes, thioglycosides, thiosulfinates, adenosine, and selenium.⁹⁷ The primary chemical components that have been implicated in bleeding include volatile oil and ajoene. The antiplatelet effect of garlic has been demonstrated by studying some of its pure isolated components on human platelet aggregation. Ajoene apparently functions as the chemical component responsible for these effects.⁹⁸ Ajoene is an unsaturated sulfoxide disulfide and is a component of allicin, a sulfanyl compound that gives garlic its strong odor and flavor. Like aspirin, the effect of ajoene appears to be irreversible, which lasts for the life of the platelet, and may potentiate the effect of other platelet inhibitors.²⁰ Several sulfur-containing compounds isolated from garlic have also demonstrated significant inhibition of human platelet aggregation.⁹⁹

Garlic oil exerts its effects on the arachidonic acid pathway (Figure 1). Garlic interrupts the synthesis of thromboxane, and stimulates the synthesis of prostacyclin. By reducing thromboxane and increasing prostacyclin, garlic decreases platelet aggregation and increases bleeding. Further, garlic inhibits platelet aggregation in a dose-dependent fashion. Case reports support that both dietary garlic and garlic supplements demonstrate these effects.¹⁰⁰ Further, the constituents of garlic, particularly alliin/allicin, also inhibit the production and/or release of chemical mediators such as platelet-aggregating

factor and adenosine, which decreases platelet function.¹⁰¹ Interestingly, many herbalists feel that the best quality, most consistent, and strongest source of *allium sativum* is the natural garlic clove itself.

Harenberg and colleagues (1988) studied the effects of dried garlic intake on blood coagulation, fibrinolysis, platelet aggregation, serum cholesterol levels and blood pressure in 20 patients with hyperlipoproteinemia. During a 4-week study period, subjects received 600 mg (200 mg bid) of dried garlic in a sugar-coated pill. After 4 weeks of garlic use, both fibrinogen and fibrinopeptide A levels significantly decreased by 10%. Streptokinase-activated plasminogen and fibrinopeptide B beta 15-42 significantly increased by 10%. Serum cholesterol levels significantly decreased by 10%, and both systolic and diastolic blood pressure decreased.¹⁰²

In another *in vivo* study, 6 subjects were given 5.0 g of crushed garlic bulbs daily for a 3-week study period. Fasting blood samples were taken at baseline and at weekly intervals to assess the level of serum triglycerides. Results showed that the addition of garlic in the diet resulted in significantly lower levels of serum triglycerides and an increase in blood fibrinolytic activity by the end of the second and third weeks.¹⁰³

Case reports in the literature also suggest that ingesting garlic while taking warfarin (Coumadin®) may result in over-anticoagulation. One case report documented that the INR of a previously stabilized patient on warfarin had more than doubled and that hematuria occurred 8 weeks after commencement of ingesting 3 garlic tablets a day.⁹⁷ Izzo and Ernst (2001) cite 2 case reports suggesting that the concomitant use of warfarin and garlic resulted in an increased INR.⁹⁵ It is evident that this popular herb has the potential to cause adverse bleeding effects.

Ginkgo Ginkgo biloba

Recommended Dosage for general use: Standardized extract: 40 mg tid

Ginkgo is a tree native to Asia and is now also found in the United States. The primary use of ginkgo is to prevent decreased cerebral functioning and peripheral vascular insufficiency associated with Alzheimer's disease or age-related dementia. Other reported uses are summarized in Table III.

Table III. Additional indications for the use of ginkgo.

antioxidant
peripheral artery disease
circulatory problems
depressive mood disorders
sexual dysfunction ("herbal Viagra")
asthma
glaucoma
menopausal symptoms
multiple sclerosis
headaches
tinnitus
dizziness
arthritis
altitude sickness
intermittent claudication

Components of ginkgo include flavonoids (ginkgo-flavones) and terpenoids (ginkgolides and bilobalide). The ginkgo leaf is processed and often standardized to 24% ginkgo flavonglycosides and 6% trilactones (terpene lactones). The primary chemical component that has been implicated in bleeding is the terpene ginkgolides. Ginkgolides, a terpene lactone, are potent and specific platelet activating factor (PAF) antagonists. Their effects are long lived and are rapidly established after oral dosing.¹⁰⁴ Ginkgolide B, one component of ginkgo, inhibits platelet activating factor by displacing it from its receptor binding site, resulting in reduced platelet aggregation.¹⁰⁵ In laboratory tests, ginkgo increases prothrombin time (PT), and blood salicylate levels, and may decrease platelet activity.¹⁰⁶

Ginkgo holds particular interest to the baby boomer and geriatric populations as its cerebral and vascular benefits continue to be researched. Whereas earlier and better known research focused on older and cognitively impaired individuals, a recent review in *Herbalgram* provided a comprehensive report of its successes with "healthy and cognitively intact adults." Both short- and long-term studies resulted in positive benefits of ginkgo in the improvement of processes such as memory, attention, and speed of processing.¹⁰⁷

Case reports document dangerous bleeding episodes following the regular use of ginkgo: intracranial bleeding (4 cases), spontaneous hyphema (hemorrhage within the anterior chamber of the eye) (1 case), and postoperative bleeding after cholecystectomy (1 case).⁹⁶ One of these reports occurred when a 70-year-old man presented with bleeding from the iris into the anterior chamber of the eye just 1 week after beginning a self-prescribed regimen of a concentrated ginkgo extract twice daily. He was also taking 325 mg of aspirin daily and had done so for 3 years. It is interesting to note that when he discontinued taking the ginkgo, but not the aspirin, the bleeding resolved. There was no recurrence of bleeding 3 months later.¹⁰⁸

Another case is a 61-year-old man who developed subarachnoid hemorrhage after consuming 40 mg of ginkgo 3 or 4 times per day for more than 6 months. No other medication was used. The patient's bleeding time increased to 6 minutes but normalized to 3 minutes within 4 months after discontinuing the ginkgo.¹⁰⁹

A systematic review by Izzo and Ernst discusses 2 case reports documenting that patients taking warfarin and aspirin had experienced severe spontaneous bleeding after self-prescribing ginkgo at recommended doses.⁹⁵ A fatal intracerebral mass bleeding was reported in a 71-year-old man who had taken ginkgo in conjunction with ibuprofen. He was previously in excellent health. He had been taking ginkgo for 2 ½ years for self-reported dizziness and had added ibuprofen 600 mg daily for osteoarthritis of the hip just 4 weeks prior to his death.¹¹⁰ This is a good example of an otherwise healthy older patient self-medicating with fatal consequences.

A 40-year-old woman was admitted to the hospital with an acute subdural hematoma with no history of head trauma, falls, alcohol abuse, or bleeding disorders. Her hematoma was evacuated via burr holes, yet her blood results, especially the INR, were difficult to stabilize. After treatment and questioning, it was revealed that she had been taking 40 mg of ginkgo twice daily for the past 2 months to "assist her while studying." Disturbingly, her family continued to give her the herb while in the hospital, stating that they were "just herbs." Once the herb was discontinued, the blood results returned to normal.⁹⁷

Clearly, ginkgo has tremendous potential for causing bleeding complications, and with its broad range of claimed benefits, the use of this herb is attractive to many. With a growing geriatric population and baby boomers wishing to preserve cognitive function, it is safe to expect use of this herb to increase.

Ginseng Panax quinquefolius Panax ginseng

Recommended dosage for general use: Capsules: 200-500 mg extract daily; Powdered root: 1-4 g daily; standardized extract: 200-500 mg daily; Tincture: 1-2 ml extract daily (1:1 dilution)

Ginseng is one of the most popular, well-known, and valued herbs worldwide. *Panax Ginseng* has been used medicinally in Asia for more than 5000 years and, in China, it is more highly valued than gold.¹¹¹ The Chinese believe that ginseng can fight cancer, slow aging, protect one against heart attack and other sudden illnesses, strengthen digestion, and reduce high blood pressure, among numerous other benefits.¹¹² The Asian population is significant in the United States. According to the US Census 2000, almost 12 million Asians are living in the United States, and the Asian population increased faster than the total population between 1990 and 2000.¹¹³ With the increasing interest in both alternative medicine and traditional Chinese medicine, the use of ginseng will continue to be strong by a large segment of the population.

The word *Panax* is derived from the Greek word for panacea, as the herb is considered a cure-all, ie, good for all parts of the body. In fact, the plant itself resembles a human figure. According to Chinese sages, ginseng replenishes vital energy,

increases production of vital body fluids, and promotes health and longevity. This is the concept of a tonic or adaptogen, which our culture has little understanding of.

Standardized ginseng extracts contain 5% ginsenosides, an aglycone chemical component believed to act as a stimulant. Ginsenosides act on the hypothalamus-pituitary-adrenal cortex axis, stimulating the secretion of adrenocorticotropic hormone (ACTH), which increases production of the adrenal hormones (eg, cortisol, sex hormones, aldosterone). Thus, ginseng produces central nervous system (CNS) stimulating effects, estrogen-like effects, and elevates blood pressure.²⁹ Ginseng is also thought to restore and strengthen the body's immune response, and promotes growth of normal cells.¹⁰⁴

The ginsenosides are also believed to have the potential to inhibit platelet-activating factor.¹⁰⁶ Ginseng has been reported to inhibit platelet-activating factor (PAF), platelet aggregation, thrombin and thromboplastin, and can cause further bleeding when combined with aspirin, heparin, warfarin, and non-steroidal anti-inflammatory drugs.¹¹⁵

There are only a few kinds of "true" ginsengs in the botanical genus *Panax*. There are other plants that are in the ginseng family, but they are more distantly related to ginseng botanically, such as *eleuthero* or *Siberian Ginseng*. These other ginsengs affect the body in similar ways. They are not as powerful as "true" ginsengs, but they are less costly. True ginsengs in the *Panax* category include: Oriental, Chinese, Korean and American ginseng.¹¹²

The effects of ginseng are supported by hundreds of laboratory experiments, but there are very few controlled human studies.¹¹² Two laboratory studies assessed the potential for ginseng to cause bleeding. Chung and colleagues (1987) examined the effect of a ginkgolide mixture (BN 52063) in antagonizing skin and platelet responses to PAF in human subjects. The ginkgolide significantly inhibited PAF-induced platelet aggregation in platelet-rich plasma ($p < 0.001$). The researchers concluded that the BN 52063 "seems to be an antagonist of PAF in man."¹⁰⁵

There is some research to suggest that Oriental ginseng (*Ginsana*) may antagonize the anticoagulant effects of warfarin. In 1 case report, the INR of a 47-year-old man who had been receiving warfarin for 9 months (7.5 mg every Tuesday and 5 mg on all other days) to prevent thrombotic complications associated with a mechanical heart valve was stabilized at 3.9 - 4.0. The patient began taking Oriental ginseng, and within 2 weeks, his INR fell to 1.5. The patient denied any other changes in his medication regimen, including the use of other nonprescription or herbal products, diet, alcohol consumption, or other lifestyle factors that may have affected his response to warfarin. The patient's INR returned to therapeutic level (3.3) 2 weeks after he stopped using ginseng.¹¹⁶

Ginseng possesses a paradoxical effect. Despite ginseng's anticoagulant potential, it has been noted to decrease the effectiveness of warfarin. Yuan and colleagues (2004) conducted a study with 20 healthy volunteers to assess this potential drug-herb interaction. Subjects had no medical conditions requiring warfarin, nor had they taken warfarin or ginseng. During the 4-week study period, all of the volunteers were given warfarin. During the second week, the researchers randomly assigned each volunteer either a placebo or ginseng, taken in addition to the warfarin. Subjects had their blood clotting times tested using the INR. Results of the study revealed that the subjects taking ginseng had lower blood levels of warfarin, thus compromising anticoagulation.¹¹⁷

As previously stated, ginseng increases the production of adrenal hormones, including the sex hormones, leading to estrogen-like effects. There is a case report of postmenopausal bleeding that was attributed to the use of topical ginseng. A 44-year-old woman used a ginseng face cream from China in the hopes of relieving some post-menopausal symptoms. After using the cream, she experienced 2 episodes of spotting and her follicle-stimulating hormone (FSH) dropped significantly. After one month of discontinuing the product, the bleeding stopped and her FSH returned to previous levels. The authors concluded that ginseng appeared to have an estrogen-like effect on genital tissues.¹¹⁸ With its broad range of claimed benefits from increased physical endurance to improved ability to cope with stress, it seems reasonable to expect that all ginsengs will continue to be a popular choice in an increasingly fast-paced society.

Ginger Zingiber officinale

Recommended dosage for general use: Dried ginger capsules: 1 g/day; Dried root equivalent: 500mg bid-qid; Fluid extract: 0.7-2ml/day (1:2 dilution); Tablets/caps: 500 mg bid-qid; Tincture: 1.7-5 ml/day (1:5 dilution)

Ginger is primarily used to relieve motion and morning sickness, and preliminary research documents its efficacy in decreasing pain and inflammation associated with arthritis and other joint disorders.¹⁰⁶ Traditionally, in herbal folklore, ginger is best known for settling upset stomachs. The major constituents of ginger are pungent principles (gingerol, shogaol, zingerone), volatile oils (bisabolene, zingiberene, zingiberol), and proteolytic enzymes. Many people consider ginger to be a root, but it is actually a rhizome. *Zingiber* comes from the Sanskrit word for ginger, *singabera*, meaning "shaped like a horn."¹¹⁹

The research on ginger is mixed and limited to a few case reports, small scale in vivo studies and some *in vitro* studies. In one laboratory test, aqueous ginger extract reduced platelet thromboxane and also inhibited platelet aggregation.¹²⁰ In a small study of 8 healthy male volunteers, subjects ingested either 2 grams of dried ginger in capsule form or a placebo. Bleeding time, platelet count, thromboelastography, and whole blood platelet aggregometry were performed before, 3 hours, and 24 hours after ingestion. It was concluded that the effect of ginger on thromboxane synthetase activity was dose dependent and only occurs with fresh ginger, and that up to 2 grams of dried ginger is unlikely to cause platelet dysfunction when used therapeutically. Data obtained from case reports and studies with very small sample sizes (eg, N=7) suggest that ginger's antiplatelet effect exists with raw ginger only. For example, in one case report, an unspecified amount of marmalade with 15% raw ginger was consumed leading to inhibition of platelet aggregation. One week after discontinuing ginger, platelet function was described as spontaneously returning to normal.¹²¹ It is important to note that these are very small sample populations, and additional study is needed to further define the effects of ginger on platelet function.

Despite the lack of substantial evidence, ginger continues to be included in published literature reviews that detail the ability of herbal therapies to increase clotting time either alone or together with another herb or prescription drug.^{96,114,122} Further, as one of the "few G's," health care professionals need to be aware of the potential for adverse bleeding events.

St John's wort Hypericum perforatum L

Recommended Dosage for general use: 300 mg hypericum extract, standardized to 0.3% hypericin, tid

St John's wort is a popular herb used to manage mild to moderate depression. Depression is a silent health threat and statistics from the NIH indicate the highest risk is among middle-aged adults, aged 45 years to 64 years.¹²³ Depression is considered to be of epidemic proportion among adolescents in the United States, and is more common in women. This herb is one of few herbs with a significant body of research to support its efficacy. Given its popularity and numerous adverse effects, there are significant risks associated with undisclosed usage among patients.

St John's wort has had a colorful history. Ancient Europeans believed it had magical protective powers against disease and evil. Ancient herbalists from Hippocrates to Dioscorides valued St John's wort not only for the treatment of "melancholia" and other emotional disorders, but also for burns, wounds (especially those involving nerve injuries), neuralgia or nerve pain, inflammation, ulcers, and more. Today, it is used as an antidepressant. The major constituents of the herb include: hypericin, hyperforin, pseudohypericin, flavonoids, xanthenes, and essential oils.

A meta-analysis of 23 randomized European clinical investigations involving a total of 1757 patients concluded that standardized St. John's wort extract was significantly more effective than placebo and just as effective as standard antidepressant medications in the treatment of mild or moderate depression.¹¹⁹ Since 1998, 7 case reports were received by the Medical Products Agency (MPA) in Sweden that demonstrated a reduced anticoagulant effect of warfarin (decreased INR) associated with the concomitant use of St John's wort. This is the opposite of the other herbal interactions previously discussed, and is actually more dangerous, as the effect would be to potentially increase clotting. The reduced anticoagulation effect of warfarin is likely caused by induction of the liver enzyme cytochrome P450 2C9, which increases the metabolism of warfarin, thus decreasing its effect.¹²⁴ None of the patients in these studies developed thromboembolic complications,

but the decrease in INR was thought to be clinically significant. The INR returned to target values either after the warfarin dose was increased or the St John's wort was withdrawn.

The induction reaction of hepatic cytochrome P450 has been attributed to the hypericum extracts from St. John's wort, which may double the metabolic activity of the liver, and thus reduce the effects of many drugs.¹²⁵ For example, use of St John's wort (900 mg per day of hypericum extract LI160) resulted in a significant decrease of digoxin when compared to placebo in subject taking 0.25 mg of digoxin per day.¹²⁶ Digoxin is a drug that is used for the treatment of congestive heart failure and various types of arrhythmias.²⁹ It is easy to see that the adverse metabolic effects of this herb can cause many significant complications in patients with heart disease.

The National Center for Complementary and Alternative Medicine is studying the effects of St John's wort for a wide spectrum of mood disorders. Positive research findings will likely lead to renewed interest in this herbal remedy.

Practice Considerations for Dental Professionals

The most important risk reduction strategy implemented by dental professionals is the completion of a comprehensive health history for every patient on a regular basis. The review of systems allows for the discovery of systemic conditions that alter bleeding, or that require the use of drugs that alter bleeding. Systemic causes of bleeding include liver disease, kidney disease, chronic alcoholism, bone marrow suppression, blood dyscrasias, Vitamin K deficiency, and inherited coagulopathies.^{127,128} As most clotting factors are formed by the liver, liver disease can greatly affect bleeding tendencies. Dental patients may present with liver disease caused by a variety of conditions, most commonly alcoholism, cirrhosis, and/or infections, such as hepatitis.

Intestinal bacteria continually produce Vitamin K, thus, a deficiency is rarely seen in a normal person due to an absence of Vitamin K from the diet. Exceptions are those with gastrointestinal diseases that result in poor fat absorption, as Vitamin K is fat-soluble and is absorbed into the blood along with dietary fats. One of the most common causes of Vitamin K deficiency is failure of the liver to secrete bile into the gastrointestinal tract, as lack of bile prevents fat digestion and absorption, thus reducing Vitamin K absorption as well.²⁶

Dental professionals should remember to question patients about recent illnesses, changes in health behaviors, or modifications to their diets. Intestinal viruses that cause vomiting or diarrhea, changes in the intake of green leafy vegetables, or the use of medications can dramatically alter the patient's response to warfarin. Fluctuations in the patient's INR may be seen for several days, even weeks, following illness, dietary, or medication changes. It is essential to ask all patients taking warfarin about the results of their most recent INR. A follow-up with the patient's physician may be warranted.

At every appointment, patients should provide a list of all of the medications and herbs that they take, including dosing schedules. This medication list should be documented in the treatment record at every appointment. Follow-up questioning of the patient is conducted as a component of the comprehensive health history to ensure that this list is accurate and complete. It is important to note that many patients think of some herbs as merely popular cooking ingredients (eg, garlic and ginger) and/or that these plant-derived substances are all natural, and must therefore be "safe" health products for ingestion. For this reason, patients must often be prompted to disclose the use of herbal medications. Remember that many herbal preparations contain multiple herbs within one supplement and that patients may not always know what herbs they are consuming in these products. While clearly herbs provide substantive and beneficial health properties, consuming herbs on a regular basis from either supplement use or cooking can potentially alter bleeding.

It is imperative that dental professionals have access to a good drug reference guide, either as a chairside reference text or in the form of an electronic database, to assist with completing an accurate medication list. Many popular dental drug resources also contain information on herbal medications, although dental professionals may find it helpful to also have a resource that is strictly devoted to herbal supplements. Resources provide valuable information about drug dosing, common side effects, drug interactions, and precautions for treating patients using these medications. Dental professionals should look up all medications that a patient is taking prior to prescribing other medications to ensure safety and compatibility. Text versions of reference guides should be replaced on an annual basis, as the field continuously evolves

and changes. The advantages to electronic databases include speed of access to and the immediate availability of a vast quantity of information, and access to the most current drug data. Suggested resources for dental professionals are listed at the end of this paper. **(Please see Resources for Dental Professionals.)**

Dental professionals should also observe their patients for physical manifestations of bleeding complications. Signs of altered bleeding may include excessive or diffuse bruising, petechial hemorrhaging, prolonged bleeding following dental procedures, and spontaneous gingival bleeding. Patients may report bruising easily or noticing an increase in bleeding with toothbrushing and flossing. Bruising is frequently observed in elderly patients taking antiplatelet and anticoagulant medications, who also demonstrate epithelial thinning as a normal part of aging. Clinical signs from observation and symptoms described by the patient should be documented in the treatment record.

Whenever there is doubt as to the patient's safety and/or the stability of his current medical status, the patient's physician should be contacted. The dental professional must be prepared to discuss the nature of the concern and proposed dental treatment with associated or potential risks, then request any information needed to safely proceed with treatment. Results from recent, relevant laboratory tests should be obtained for the treatment record. Copies of any test results ordered by the dentist that are required prior to initiating dental treatment should be forwarded to the patient's physician as needed. Conversations with the patient's physician must be documented in the treatment record.

As previously discussed, few anticoagulant and antiplatelet medications require discontinuation prior to routine dental treatment. Exceptions have been previously noted elsewhere in this paper. However, discontinuation may be required prior to invasive dental surgery. Herbal supplements should always be discontinued prior to any type of surgery, including dental surgery. Different herbs possess specific safety windows that range from 24 hours (ephedra) to 7 days to 14 days (garlic and ginseng) prior to undergoing surgery.²⁰ Patients taking herbal supplements that possess anticoagulant and/or antiplatelet properties should be advised to discontinue use at least 2 weeks prior to having a surgical procedure until more is definitively known about the potential for bleeding complications.^{6,29} This 2 week to 3 week safety window is suggested by the American Society of Anesthesiologists (ASA).²⁰ It is important to note that the safety window also takes into account other herbal side effects that may increase surgical risk, such as the ability to recover from general anesthesia. A discussion of these and other effects is beyond the scope of this paper. The reader is referred to Ang-Lee et al (2001) for a detailed discussion of these considerations.

Despite careful planning and precautions, the potential for an unexpected bleeding event always exists for patients taking these medications. Therefore, it is essential that dental professionals have access to local hemostatic agents for use in the operatory. There are a variety of pharmacologic agents that are available for this purpose; however, a complete discussion about these products is beyond the scope of this paper. The reader is referred to Burrell and Glick (2003) for a review of hemostatic agents used in dentistry.¹²⁹ Invasive procedures should be performed with as minimal trauma to the tissues as possible. Careful post-surgical monitoring is advised.⁶

To determine whether increased gingival bleeding is caused by a medication side effect, or is a manifestation of gingival disease, a thorough oral examination should be performed at each visit. Patients should be taught proper oral hygiene techniques to decrease etiologic bacteria that cause gingival inflammation. Manual plaque removal may be improved through the use of power-assisted toothbrushes, floss aids, and oral irrigators. Chemotherapeutic agents that exhibit antimicrobial properties are useful adjuncts to kill residual organisms that brushing and flossing may leave behind. Broad-spectrum antimicrobial agents, such as chlorhexidine, essential oil mouthrinse, and triclosan toothpaste, have demonstrated efficacy in reducing supragingival plaque and gingivitis, and resultant gingival bleeding. Improving oral hygiene reduces gingival inflammation, thus eliminating the primary etiologic factor for gingival bleeding. It is important to teach patients that gingival bleeding is not "normal," as so many patients mistakenly believe, so that gingival bleeding as a complication of medication therapy can be quickly and accurately identified.

Dental hygienists possess an important role in educating patients about bleeding effects that may affect the oral cavity and the provision of oral health care services. Patients should be taught about the importance of accurately reporting their medication and herbal use, compliance with their medication regimens, and routine monitoring with blood tests as prescribed by their physicians. Patient education may also include dispelling myths about the need to discontinue medication use prior to undergoing routine oral care. Many patients discontinue their medications on their own, without consulting their

physicians or dental professionals, because they are worried about a bleeding complication. It is important to educate patients about how bleeding is adequately managed in the oral health care setting, provide reassurance, and how, if needed, their medications should be discontinued.

Resources for Dental Professionals:

National Center for Complementary and Alternative Medicine<http://nccam.nih.gov>

Food and Drug Administrationwww.fda.gov www.cfsan.fda.gov

Websites

American Botanical Council (publishes Herbalgram)

American Holistic Medical Association

Consumer Labs - Independent testing on herbs/supplements

Food and Nutrition Information Center

HerbMed

Herb Research Foundation

Lexi-Comp, Incorporated

Medline

Medline Plus

Mosby

Pubmed

Pubmed - screened for alternative medicine

RxList Alternatives

WebMD

Brochures

American Society of Anesthesiologists. Phone: 847-825-5586. "What You Show Know About Herbal Use and Anesthesia."
"What You Should Know About Your Patient's Use of Herbal Medicine." www.asahq.org.

Journals and Newsletters

Herbalgram - The Journal of the American Botanical Council and the Herb Research Foundation - published quarterly (\$50/year = four issues) Phone: 800-373-7105 www.herbalgram.org

Self Healing - Andrew Weil, MD newsletter - Phone: 1-800-523-3296 www.drweilselfhealing.com

Books

LaValle J Krinsky D, Hawkins E, Pelton, R, Willis, N. Natural Therapeutics Pocket Guide. 2nd ed. Hudson: Lexi-Comp, Inc., 2003.

Skidmore-Roth L. Mosby's Handbook of Herbs and Natural Supplements. 3rd ed. Littleton: Mosby, 2006.

Wynn RL, Meiller T, Crossley HL. Drug Information Handbook for Dentistry, 11th ed. Hudson: Lexi-Comp Inc., 2006.
Brinker F. Herb Contraindications and Drug Interactions. 3rd ed. Sandy: Eclectic Medical Publications, 2002.
Hobbs C. Herbal Remedies for Dummies. Foster City: IDG Books Worldwide, 1998.

Journal Full Issues and Articles

The Journal of the American Medical Association - Volume 280, No. 18 - November 11, 1998. Entire issue devoted to comprehensive alternative medicine research and editorials.

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