Herbal Medicine and the Pharmacist

Common natural health products in your practice

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Lesson description

This lesson is designed to provide pharmacists with the knowledge and skills necessary to discuss natural health products (NHPs) with patients. Pharmacists will gain an understanding of the new Natural Health Products Regulations that were introduced by Health Canada. Latest research evidence on the role of the pharmacist with respect to NHPs will be provided. Pharmacists will learn about the safety and efficacy of common NHPs encountered in pharmacy practice. A special emphasis of the lesson will be drug interactions with NHPs.

Learning objectives

Pharmacists who successfully complete this lesson will be able to:

- describe the regulation of NHPs in Canada
- understand the role of the pharmacist with respect to NHPs
- provide information on the safety and efficacy of six common NHPs encountered in pharmacy practice, including saw palmetto, ginseng, garlic, glucosamine/chondroitin, hoodia, and melatonin
- identify drug interactions with NHPs
- discuss with patients issues associated with NHPs

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1. Introduction

Natural health products (NHPs) are widely available in Canadian pharmacies. They are defined by Health Canada to include vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines, probiotics, amino acids, and essential fatty acids.[1] A recent survey found that 7 in 10 Canadians (71%) have taken NHPs and many take them on a daily or weekly basis.[2] Use of NHPs appears to be more common among those with a higher level of education and household income, women, and those between the ages of 18 and 54.[2]

The use of NHPs has been studied within the wider context of complementary and alternative medicine (CAM). Researchers have identified two main explanations for why patients use CAM: 1) patients may be "pushed" toward CAM because of bad experiences with conventional medical treatment; or 2) patients may be "pulled" toward CAM because of their belief in the alternative paradigm of health and health care associated with CAM practitioners and therapies.[3] Many authors have identified the former, describing the increasing use of CAM as a product of consumer dissatisfaction with the present health care system.[3–7] Specific negative experiences leading to the use of CAM include the experience of conventional medical treatments as ineffective; experience with or concern regarding the adverse effects of conventional treatments; and poor patient-physician communication.[7] In addition, it has been noted that users of CAM report a significantly lower level of confidence in the efficacy of conventional medicine in general.[6,8]

Other researchers have investigated the concept that patients turn to CAM for ideological reasons.[3,5,7–10] A variety of reasons in this category have been identified, including a belief in the holistic understanding of health; the individual being responsible for health care decisions; and/or a general lifestyle orientation viewed to be "unconventional."[8,10]

2. Regulation of NHPs

All NHPs in Canada are now regulated by the Natural Health Products Directorate of Health Canada. The new Natural Health Products Regulations include provisions on product licensing, site licensing, good manufacturing practices, adverse reaction reporting, clinical trials, and labelling. The Regulations came into force on January 1, 2004 and apply to all NHPs as of this date. NHPs with a valid Drug Identification Number (DIN) have six years to obtain a product licence under the Regulations. Persons manufacturing, packaging, labelling, or importing a NHP before this date, have a transition period of two years to comply with the site licence requirements of the Regulations.[11]

2.1 Product licence

All NHPs require a product licence before they can be sold in Canada. In order to obtain a licence, detailed information on the product must be submitted to Health Canada, including medicinal ingredients, source, potency, non-medicinal ingredients, and recommended use. Once the product has been reviewed and approved by Health Canada for safety and efficacy, the product label will bear an 8-digit product licence number preceded by the distinct letters NPN or DIN-HM for homeopathic products.[11]

2.2 Site licence

All manufacturers, packagers, labellers, and importers of NHPs require a site licence. Sites must have procedures in place respecting distribution records and product recalls and for the handling, storage and delivery of their products, and demonstrate that they meet good manufacturing practice requirements.[11]

2.3 Good manufacturing practices (GMPs)

GMPs require that appropriate standards and practices regarding product manufacturing, storage, handling, and distribution of NHPs be met.[11]

2.4 Adverse reaction reporting

Health Canada has established an adverse reaction reporting system for the collection and evaluation of information relevant to the safe use of medicinal products, including NHPs. The Natural Health Products Regulations require the licensee or product licence holder to be responsible for reporting adverse reactions associated with the use of their licensed NHPs to Health Canada. Consumers and health care providers can also submit case reports directly to Health Canada.[12]

2.5 Labelling

Standard labelling requirements for NHPs have been established to ensure consumers make informed choices. Examples of the required label information include product name, contents and quantity of product in the bottle, recommended conditions of use (including use or purpose, dosage form, route of administration, dose, and any cautionary statements, warnings, contra-indications, and possible adverse reactions associated with the product), and any special storage conditions.[11]

3. The pharmacist's role in the use of NHPs

Pharmacists are increasingly identified as the most suitable health care professional to help consumers make safe and informed choices about NHPs.[13–17] A large proportion of Canadian and U.S. pharmacists reported receiving questions about NHPs from patients and other health care providers.[15] Of note in one Canadian study, 57% of community pharmacists reported being asked about herbal products several times a day and a further 15% are asked at least once a day.[18] In one U.S. study, 98% of community pharmacists and 58% of hospital pharmacists reported fielding questions from patients about herbals and other natural products.[19]

Evidence also indicates that consumers view pharmacists as trustworthy and knowledgeable about NHPs. The 2005 Baseline Natural Health Products survey found that 43% of Canadians are most likely to say that they completely trust the NHP information provided by their pharmacists, and 18% identified pharmacists as primary sources of information on NHPs.[2] In one U.S. study, 37% of the respondents agreed that pharmacists' advice is important for alternative therapies and 30% relied on pharmacists for herbal choices.[20]

The pharmacist's role in the use of NHPs is evolving. In a recent study to explore consumer and pharmacist views on the professional responsibilities of the pharmacist with respect to NHPs, the majority of consumers and pharmacists were found to agree that pharmacists should be knowledgeable about NHPs and that pharmacists should be able to manage drug-NHP interactions as well as to identify and evaluate the variety of information available to help consumers make informed decisions. Pharmacists should also explain to patients that NHPs are not always safe just because they are natural.[16] In a systematic analysis of Canadian pharmacy policies and guidelines, it was found that most policy documents indicate that pharmacists should inquire about NHP use when counselling patients and, when asked, should provide accurate information regarding the efficacy, toxicity, side effects, or interactions of NHPs.[14] As such, pharmacists need to have knowledge about the common NHPs used by their patients. This requires significant commitment on the part of the pharmacist to obtain adequate training and resources on the subject of NHPs.

The following 6 cases are designed to introduce common NHPs encountered in pharmacy practice. The cases are structured in the following manner: introduction to the case; clinical monograph of relevant NHP; and then a sample response to the clinical situation described in the case. It should be noted that the clinical monographs focus on the use of the NHP for the conditions described in each case and are not intended to be comprehensive reviews. Readers are encouraged to formulate their own response to the situation described in the introduction to the case as they read the clinical monograph and then to compare it with the sample response given. The responses outlined for each case are suggestions only and other appropriate responses may be possible.

4. Case 1

A middle aged man comes up to the counter with a bottle of saw palmetto. He tells you he would like to try using this product for benign prostatic hyperplasia but wonders if it would affect his sexual function like other conventional drugs. What do you tell him?

4.1 Clinical monograph: Saw palmetto
(Serenoa repens (Bartram) Small)

Family: Arecaceae (also known as Palmae)

Synonyms: American dwarf palm tree, Curbicin, dwarf palm, dwarf palmetto, Elusan Prostate, fan palm, IDS 89, LSESR, PA 109, Palmae, palmetto scrub, palmier de l'Amerique du Nord, palmier nain, Permixon®, PRO 160/120, sabalfruchte, *sabal fructus*, *Sabal serrulata* Schultes & Schultes, savpalme, saw palmetto berryserenoa, *Serenoa serrulata*, *Serenoa serrulata* Hook F., SG 291, SPE, Strogen Forte®, Talso®, WS 1473, zwegpalme[21]

Standard doses: 160 mg liposterolic extract twice daily[21] (80% to 95% standardized).

Saw palmetto is best known today as a treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH).[22–24] However, historically the dark, wrinkled, oblong berries, which are the part used medicinally,[25] were partially dried and used for a variety of conditions of the bladder, urethra and prostate.[22] Saw palmetto was considered primarily a "male" remedy and was used to "improve flagging reproductive function" as well as "debility and senility in men."[26]

Pharmacology

Most commercial saw palmetto products are "liposterolic extracts" that contain the fatty acids and sterols from the fruit of the plant.[22] These constituents are believed to exert their therapeutic action in the management of BPH via a variety of mechanisms, including blockade of androgen

receptors, 5 alpha-reductase inhibition, and disruption of the arachidonic cascade by inhibition of both the cyclooxygenase and lipoxygenase pathways.[21,27–31] Saw palmetto also appears to compete with endogenous estrogens for receptor sites.[32,33]

Clinical trials

A number of randomized controlled trials and one meta-analysis have reported positive results for saw palmetto for the treatment of benign prostatic hyperplasia.[34–45] In particular, the meta-analysis of 21 randomized controlled trials concluded that saw palmetto was effective at reducing symptom scores, increasing both peak and mean urine flow rates, and decreasing bladder residual volume compared to placebo. There was no significant difference between saw palmetto and a conventional medical treatment finasteride with respect to changes in symptom score, urine flow, or residual volume. As such, saw palmetto appears to be as effective as finasteride for the treatment of benign prostatic hyperplasia. However, saw palmetto was not found to be able to decrease prostate size.[45]

Adverse effects

The most commonly reported adverse effects associated with saw palmetto use are mild gastrointestinal complaints such as abdominal pain, nausea and vomiting, and diarrhea. Headaches/dizziness and hypertension have occasionally been documented. Saw palmetto appears to have little or no impact on sexual function.[21,46]

Cautions/contraindications

Individuals with known allergy or hypersensitivity to plants of the Arecaceae family should avoid saw palmetto. Safety has not been established in pregnancy and lactation.[21]

Drug interactions

There has been no clinical trial evidence or case reports of drug interactions with saw palmetto.[47]

Response

Current evidence suggests that saw palmetto is likely effective in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia with little or no impact on sexual function. This is a significant advantage given that conventional medications for this condition, such as finasteride and tamsulosin, have been known to cause erectile and ejaculation disorders.

5. Case 2

A well-dressed executive walks in the store and asks you about taking ginseng products, in particular COLD-fX®, to treat his cold which he just came down with today. How do you advise him?

5.1 Clinical monograph: Ginseng

Although many different kinds of "ginseng" are commercially available in Canada, two species are commonly seen in pharmacy practice: *Panax ginseng* C.A. Meyer (also called Panax, Ginseng, Chinese Ginseng, Korean Ginseng or Oriental Ginseng) and *Panax quinquefolius* (also called American or Canadian Ginseng). Another product available in Canada is *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Siberian Ginseng or Eleuthero), which is in the same family (Araliaceae) but is not a true ginseng (member of the *Panax* genus). COLD-fX® contains CVT-E002™, a proprietary ChemBioPrint® (CBP®) product containing greater than 80% poly-furanosyl-pyranosyl-saccharides extracted by an aqueous method from *Panax quinquefolius* L. (North American ginseng, root). It is widely marketed to help reduce the frequency, severity, and duration of cold and flu symptoms by boosting the immune system.

(*Panax ginseng* C.A. Meyer)

Family: Araliaceae

Synonyms: Asian ginseng, Chinese ginseng, ginseng, Korean ginseng, Panax schinseng Nees, Asiatic ginseng, Oriental ginseng, Ginseng radix, Ren shen, Ninjin, insam, white ginseng[48]

Standard doses: 100 mg to 500 mg standardized extract (4% to 8% ginsenosides) one to three times daily (usually taken for 15 to 20 days followed by a two week resting period).[48] *Panax ginseng* C.A. Meyer is the most widely used and most extensively studied species of ginseng.[49,50] The roots from 4- to 6-year-old plants are harvested in September or October and used medicinally. Many ginseng products available in Canada are made from *Panax ginseng* grown in the Orient. By contrast, *Panax quinquefolius* is native to eastern North America and is cultivated to be sold primarily for medicinal products in the Orient. The red and white forms of ginseng commonly available in Canada are obtained via two different processing procedures. Drying the root produces white ginseng, and a steaming process (often with other herbs) produces a caramel-coloured root known as red ginseng.[50] Although differences in pharmacological action have not been reported in the literature, according to traditional Chinese medi-

cine philosophy, red ginseng is more "heating" (more "yang" in nature) than white ginseng.

Within the traditional Chinese medical paradigm, ginseng is considered to be an adaptagen, which means that it is thought to maintain balance within the organism, especially during stressful times.

Traditionally it was used as a tonic to "increase strength, increase blood volume, promote life and appetite, quiet the spirit, and give wisdom."[51]

Ginseng has been widely studied, yet it is still difficult to distinguish between substantiated therapeutic properties and fictitious claims. Lack of human studies, lack of quality control, different extraction processes, adulterants, investigations of single ginseng constituents, and use of different species of ginseng have contributed to the inconsistent study results. *Panax ginseng* has been reported to have anti-cancer properties and immunostimulating effects.[48,52]

Pharmacology

It has been hypothesized that the possible anti-cancer effects of ginseng may be due to its stimulating effects on the immune system.[52] Ginseng appears to enhance antibody response, increase natural killer cell activity, stimulate macrophage activity, stimulate lymphocytes *in vitro*, stimulate the reticuloendothelial system, increase proliferation of T cells and B cells, and increase the production of interferon.[52]

Clinical trials

Cancer prevention

In three large (n=1810, n=3974, n=4634) case-control studies, intake of ginseng has been shown to be associated with a decreased risk (odd ratios of 0.40 to 0.56) of being diagnosed with a variety of cancers.[53–55] A dose-response relationship was found between ginseng and cancer prevention in all three studies.[53–55] Two studies found that ginseng extract and powder were more effective than fresh sliced ginseng, the juice, or tea in reducing the odds ratio of cancer.[53,54] One study noted that ginseng intake appeared to be associated with a decreased risk of cancers of the lip, oral cavity, pharynx, esophagus, stomach, colorectal, liver, pancreas, larynx, lung, and ovaries, but there was no decrease in the incidence of female breast cancer or cancers of the uterus.[54] Another study noted a decreased risk of gastric cancer and lung cancer among those ingesting ginseng.[55] Additional research is needed to determine the appropriate dose and to confirm these results in randomized studies in humans.

Immunostimulant

Two trials in humans found that ginseng stimulated the immune system by increasing the number and circulation of immune cells.[56,57] In a double-blind, randomized, placebo-controlled trial, *Panax ginseng* extracts taken for 8 weeks were found to stimulate an immune response in healthy adult subjects (n=60). The researchers observed enhanced chemotaxis of circulating polymorphonuclear leukocytes, phagocytosis index, phagocytosis fraction, intracellular killing, and blastogenesis, and there were increases in total lymphocytes and T helper cells.[56] In a multicentre, randomized, placebo-controlled, double-blind study, volunteers ingested either 100 mg ginseng extract (n=114) or placebo (n=113) once daily for 12 weeks and received an anti-influenza polyvalent vaccination at week 4. There was a significantly lower incidence of influenza or colds from week 4 to week 12 in the ginseng group when compared to the placebo group. In addition, antibody titres and natural killer activity levels were significantly higher in the ginseng group.[57] Additional research is necessary to confirm these findings.

Adverse effects

Insomnia is the most common adverse effect associated with *Panax ginseng*.[57] Although other adverse effects have been reported including diarrhea, skin eruptions, vaginal bleeding, breast tenderness, mania and Stevens-Johnson syndrome, it is difficult to assess the clinical relevance of these reports because the ginseng products were never tested for purity.[58–62]

"Ginseng Abuse Syndrome" includes a variety of symptoms that may occur in the overuse of the product, such as hypertension, diarrhea, restlessness, nervousness, euphoria, insomnia, and skin eruptions. However, this syndrome has only been reported in a study in which many of the participants were concurrently ingesting large amounts of caffeine; thus, this may be the result of an interaction with caffeine rather than a direct adverse effect of ginseng.[63,64]

Cautions/contraindications

Ginseng should be used with caution in hypertension, acute illness, premenopausal women with unstable hormonal cycles, controlled diabetics, and concomitant use of stimulants.[58] The safety of *Panax ginseng* has not been established in children or pregnant or lactating women. It is not advisable to ingest ginseng in the evening due to its ability to induce insomnia.[48]

Drug interactions

- Diuretics – Patients taking diuretics should avoid taking ginseng preparations because there has been one case report of diuretic resistance in a man who was taking ginseng along with diuretics for kidney disease who was hospitalized because of edema and hypertension.[65]
- Warfarin – Patients taking warfarin should avoid taking ginseng preparations because there has been one case report where the concomitant administration of ginseng and warfarin led to a decrease in INR.[66]
- Phenelzine – Patients taking phenelzine should use ginseng supplements with caution because two case reports indicated additive effects.[67,68]
- Drugs metabolized by enzymes in the cytochrome P450 1 family – An *in vitro* study found that standardized Asian and North American ginseng extracts inhibited CYP1 activity (i.e., CYP1A1, CYP1A2, and CYP1B1).[69]

5.2 Clinical monograph: COLD-fX®

CVT-E002™ – a proprietary ChemBioPrint® product containing greater than 80% poly-furanosyl-pyranosyl-saccharides extracted by an aqueous method from *Panax quinquefolius*

Standard doses: 200 mg twice daily[70]

COLD-fX® is recommended to help reduce the frequency, severity, and duration of cold and flu symptoms.[70]

Pharmacology

COLD-fX® has been shown by both experimental and clinical studies to stimulate the immune system. These effects were found on both the innate and the acquired immune system, and both cell-mediated and humoral (antibody)-mediated immunity have been shown to be enhanced. However, the active ingredients of COLD-fX®, polysaccharides, are very large molecules, which means they are unlikely to enter the bloodstream. It has been hypothesized that they exert immune-stimulating effects in the gastrointestinal tract, but additional studies are required to confirm the mechanism of action.[70]

Clinical trials

Several clinical trials have found COLD-fX® to be effective in reducing the frequency, severity, and duration of cold and flu symptoms.[71–74] One randomized, double-blind, placebo-controlled trial examined the efficacy of COLD-fX® in the prevention of acute respiratory illness in 43 community dwelling seniors aged 65 years or older. Ingestion of two capsules/day of COLD-fX® by immunocompetent seniors during a "cold and flu" season for four months was found to reduce the relative risk and duration of respiratory symptoms by 48% and 55%, respectively.[72] Similarly, a randomized, double-blind, placebo-controlled trial in institutionalized older adults demonstrated that taking COLD-fX® at a dose of 400 mg daily for 8–12 weeks significantly reduced the relative risk of developing laboratory confirmed influenza or respiratory syncytial virus illness by 89%.[71] A randomized, double-blind, placebo-controlled trial was conducted on 323 healthy adults (18–65 yrs) with a history of at least two upper respiratory infections in the previous year. It was found that COLD-fX® taken at 400 mg daily for 4 months reduced the severity of cold symptoms (31%) and the duration of symptoms (35%).[73] Two blood samples were collected before and after treatment from 42 of the 323 subjects recruited. COLD-fX® treatment was shown to increase the number of T-helper and natural killer cells and decrease the level of immunoglobulin A in the plasma.[74] However, additional research is necessary to confirm these findings.

Adverse effects

No adverse effects have been reported with taking COLD-fX®.

Cautions/contraindications

Safety has not been established in pregnancy and lactation. Individuals requiring anti-coagulant therapy such as warfarin should avoid the use of COLD-fX® because high doses of some forms of ginseng that are high in ginsenosides have been shown to affect the metabolism and effect of blood thinners such as warfarin. However, COLD-fX® is composed of molecules, polysaccharides, which are not thought to cause drug interactions. COLD-fX® is not recommended for individuals with impaired liver or renal function or known allergies to ginseng.[70]

Drug interactions

No drug interactions have been reported with COLD-fX®.

Response

Current evidence does not support the use of COLD-fX® for the treatment of cold or flu symptoms. COLD-fX® is recommended to be taken daily as a preventative to maintain an optimal immune system. A number of clinical trials have found COLD-fX® to be effective in reducing the frequency, severity, and duration of cold and flu symptoms.

6. Case 3

Jerry Smith, 37 years old, comes to renew his prescriptions for his HIV medications, saquinavir and ritonavir. He asks you about taking garlic to lower his cholesterol. How do you respond?

6.1 Clinical monograph: Garlic (*Allium sativum* L)

Family: Liliaceae

Synonyms: ail, ajo, ail commun, banlasun, camphor of the poor, dra thiam, foom, garlic clove, Gartenlauch, hom khaao, kesumphin, kitunguu-sumu, Knoblauch, dra thiam, l'ail, lahsun, lai, lashun, majo, naharu, nectar of the gods, ninniku, pas-se-waa, poor man's treacle, *Porvium sativum*, rason, rasonam, rasun, Russian Penicillin, rustic treacles, seer, skordo, sluôn, stinking rose, velluli, vellulli [75]

Standard doses: 3–30 g of fresh garlic daily; 600–900 mg/day of dehydrated garlic powder in tablet or capsule form; or other formulations containing 2–5 mg of allicin.[75]

Garlic is best known today for its use in lowering cholesterol.[75] It might also be useful for preventing colds, reducing blood pressure, inhibiting platelet aggregation, and enhancing fibrinolytic activity.[75]

Pharmacology

Allicin is thought to be the principle active component of garlic. Several mechanisms of action have been postulated, including increased bile acid excretion; reduced 3-hydroxy-3-methyl-glutaryl coenzyme A reductase activity; and inhibition of squalene epoxidase, the final enzyme in the synthetic pathway of cholesterol, by tellurium compounds found in garlic bulbs. All these mechanisms decrease the hepatic production of cholesterol. It has also been suggested that components of garlic may decrease the activity of lipogenic enzymes (e.g., glucose-6-phosphate dehydrogenase and malic dehydrogenase), which leads to a decrease in fatty acid synthesis. Another hypothesis is that components of garlic may exert cardioprotective effects by decreasing the levels of glycosaminoglycans (GAGs), which have been shown to be proportional to the susceptibility of different species to cholesterol-induced atherosclerosis.[76]

Clinical trials

Three meta-analyses assessed the cholesterol-lowering effects of garlic.[77–79] One included five trials and concluded that garlic has the ability to reduce serum total cholesterol levels in doses of about one half to one clove per day.[79] Another included 16 trials and concluded that a daily dose of 600–900 mg of garlic preparation for a period of 1–3 months was sufficient to lower total blood cholesterol levels.[77] The most recent one included 13 trials and showed that garlic caused a significant reduction in total cholesterol levels when compared to placebo. However, the authors concluded that the cholesterol-lowering effects of garlic were minimal and advised patients that such effects might not be clinically meaningful.[78] A number of other positive trials have been reported,[80–82] but several negative trials have also been published.[83–85]

Adverse effects

A common side effect of garlic is bad breath and body odour.[75] Postoperative bleeding has also been reported in several cases upon the ingestion of garlic.[75]

Cautions/contraindications

Garlic supplements should be used with caution by pregnant and lactating women and avoided before undergoing surgical procedures due to possible post-surgical bleeding. One author recommends caution after organ transplants because it has been reported that garlic enhances the activity of natural killer (NK) cells, which are largely responsible for tissue rejection.[76]

Drug interactions

- HIV medication: protease inhibitors (e.g., saquinavir and ritonavir) – Garlic has been shown to reduce blood levels of protease inhibitors.[86,87]
- Warfarin – Several reviews reported possible interactions between garlic and warfarin.[75]
- Anti-diabetic medications – Patients receiving hypoglycemic drugs should use garlic supplements with caution because it has been shown to reduce average blood sugar levels.[88]

Formulations

Odourless garlic supplements are available for patients who would like to avoid the bad breath and body odour due that fresh garlic can cause. When selecting garlic supplements, it is important to choose a product that specifies the allicin content.[75]

Response

Current evidence indicates that garlic is probably useful for lowering cholesterol. However, garlic has been shown to reduce blood levels of protease inhibitors, such as saquinavir and ritonavir, so this patient should avoid the use of garlic.

7. Case 4

A 54-year-old woman comes to the counter with a bottle of glucosamine, a bottle of chondroitin, and a bottle of glucosamine with chondroitin. She wants to know which one she should take for her knee osteoarthritis. What do you tell her?

7.1 Clinical monograph: Glucosamine

(2-amino-2-deoxyglucose)

Synonyms: glucosamine sulfate, glucosamine hydrochloride, chitosamine, n-acetylglucosamine[89]

Standard doses: 1500 mg daily taken in three divided doses[89]

Glucosamine is best known today for the treatment of symptoms of osteoarthritis.[89]

Pharmacology

Glucosamine is a precursor for glycosaminoglycans (GAGs), which are a major component of joint cartilage. Chondrocytes either obtain pre-formed glucosamine from the circulation or synthesize it from the amino acid glutamine and glucose. Glucosamine is used in the synthesis of GAGs, collagen, and hyaluronan. It is thought that taking glucosamine supplements may help stop cartilage breakdown, build cartilage, and decrease swelling.[89,90]

Clinical trials

A Cochrane review assessed the effectiveness and toxicity of glucosamine in osteoarthritis. Twenty studies with 2570 patients were included. Analysis restricted to eight studies with adequate allocation concealment failed to show benefit of glucosamine for pain and WOMAC function. The WOMAC Index is self-administered and assesses the three dimensions of pain, disability, and joint stiffness in knee and hip osteoarthritis using a battery of 24 questions. The 20 analyzed randomized controlled trials collectively favoured glucosamine with a 28% (change from baseline) improvement in pain and a 21% (change from baseline) improvement in function using the Lequesne index. However, the results were not uniformly positive. Glucosamine was as safe as placebo.[90]

Adverse effects

No significant adverse effects have been reported with taking glucosamine. Stomach upset has been reported but with the same incidence as the placebo group.[90]

Cautions/contraindications

Diabetics should use caution when supplementing with glucosamine products (especially injectable formulations) because, based on animal and test tube studies, glucosamine may prevent insulin secretion and therefore cause high blood sugar. Individuals with allergies to shellfish may also be allergic to glucosamine derived from shellfish. Safety of glucosamine in pregnancy and lactation has not been established.[89]

Drug interactions

Drug interactions with glucosamine have not been reported.

7.2 Clinical monograph: Chondroitin

Synonyms: dermatan sulfate (chondroitin sulfate B), chondroitin polysulfate (chondroitin sulfate D), chonsurid structum, chondroitin-4-sulfate (chondroitin sulfate A), chondroitin-6-sulfate (chondroitin sulfate C), chondroitin sulfuric acids[91]

Standard doses: 1000–1500 mg daily taken in three divided doses or 800–1200 mg daily taken in a single dose or divided doses.[91]

Chondroitin is best known today for the treatment of symptoms of osteoarthritis.[91]

Pharmacology

It is hypothesized that chondroitin sulphate will support or enhance macromolecular synthesis by chondrocytes (DNA, RNA, collagen, proteoglycans, matrix); inhibit degradative enzymes (e.g., collagenase, cathepsins, hyaluronidase, chondroitinases) or inflammatory mediators (e.g., interleukin-1, tumor necrosis factor, PGE2); and remove or prevent formation of fibrin, thrombi, plaque in synovium, and/or subchondral blood vessels.[91]

Clinical trials

Two meta-analyses have assessed the effectiveness of chondroitin sulphate for osteoarthritis.[92,93] One included seven trials of 372 patients taking chondroitin sulphate. All selected studies claimed to be randomized, double-blind designs in parallel groups. Following patients to 120 or more days, chondroitin sulphate was shown to be significantly superior to placebo with respect to the Lequesne index and pain VAS. The authors concluded that chondroitin sulphate may be useful in osteoarthritis, but further investigations in larger cohorts of patients for longer time periods are needed to prove its usefulness as a symptom-modifying drug in osteoarthritis.[92] A more recent meta-analysis included 20 trials of 3846 patients.

Studies were included if they were randomized or quasi-randomized controlled trials that compared chondroitin with placebo or with no treatment in patients with osteoarthritis of the knee or hip. A high degree of heterogeneity was found among the trials. Small trials, trials with unclear concealment of allocation, and trials that were not analyzed according to the intention-to-treat principle showed larger effects in favour of chondroitin than did the remaining trials. When the analysis was restricted to three trials with large sample sizes and an intention-to-treat analysis, chondroitin sulphate showed minimal symptomatic benefits.[93] Given the conflicting results, additional large-scale, methodologically sound trials are required.

Adverse effects

Mild stomach problems (e.g., nausea, stomach pain, vomiting, diarrhea) have been reported.[91]

Cautions/contraindications

Safety of chondroitin in pregnancy and lactation has not been established.[91]

Drug interactions

Drug interactions with chondroitin have not been reported.

7.3 Glucosamine and chondroitin combinations

Only a few trials have investigated the efficacy of glucosamine and chondroitin in combination for osteoarthritis.[94–96] In the multicentre, double-blind, placebo- and celecoxib-controlled Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), 254 patients were assigned the combination of 500 mg of glucosamine plus 400 mg of chondroitin sulfate three times daily. Exploratory analyses suggest that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain.[94] In a smaller randomized, placebo-controlled study of 93 patients, the combination of 1000 mg FCHG49 glucosamine HCl, 800 mg TRH122 low-molecular-weight sodium chondroitin sulphate, and 152 mg manganese ascorbate twice daily was found to be effective for the treatment of radiographically mild-to-moderate osteoarthritis of the knee.[95] Finally, a 16-week randomized, double-blind, placebo-controlled crossover trial of a combination of glucosamine HCl (1,500 mg/day), chondroitin sulfate (1,200 mg/day), and manganese ascorbate (228 mg/day) in 34 males with degenerative joint disease of the knee or low back found that the combination therapy relieved symptoms of knee osteoarthritis.[96] Given the small number of trials, additional research is required to make definitive conclusions.

Response

Current evidence suggests that glucosamine and chondroitin alone or in combination might be useful for the treatment of the symptoms of osteoarthritis. It appears that the use of glucosamine alone has the strongest evidence for efficacy, and so it might be a better option in comparison to the others.

8. Case 5

A thin, tired-looking teenager asks you about the use of hoodia for appetite suppression. How do you advise her?

8.1 Clinical monograph: Hoodia

(*Hoodia gordonii* (Masson) Sweet ex Decne)

Family: Apocynaceae (also known as Asclepiadaceae)

Synonyms: bushman's hat, Kalahari cactus, Queen of the Namib, *Stapelia gordonii*, Xhoba[97–99]

Standard doses: 300 mg twice daily (maximum 600 mg/day)[98,99]

Hoodia is best known today for its use as an appetite suppressant.[100] It has also been used traditionally for abdominal cramps, hemorrhoids, tuberculosis, indigestion, hypertension, diabetes, and as a thirst quencher.[101]

Pharmacology

It has been hypothesized that specific steroidal glycosides in hoodia extract commonly called P57 are responsible for its appetite suppressant properties.[99,101] The central nervous system pathways are mediated by a variety of neuropeptides which serve as messengers to facilitate communication between the brain and the rest of the body. P57 appears to affect these neuropeptides and exert appetite suppressant effects.[99,101] P57 has also been found to increase the ATP content of the hypothalamus, which acts as a signal of energy-sensing satiety.[102]

Clinical trials

One small, unpublished human trial (n=18) completed by a company that makes hoodia products[100] and two animal studies suggested that hoodia can possibly suppress appetite and reduce body fat content,[102,103] but additional human evidence is required to make any definitive conclusions.

Adverse effects

Unwanted effects on the liver after ingestion of hoodia have been reported in some individuals, but these reports have not been well documented.[97]

Cautions/contraindications

Hoodia should not be taken by those with known allergy or hypersensitivity to flowering plants in the Apocynaceae family or those with liver abnormalities or eating disorders.[97] It should also be avoided by people with diabetes because it can theoretically lower blood sugar levels.[97] Safety has not been established in pregnancy and lactation.

Drug interactions

Drug interactions with hoodia have not been reported.

Response

Since hoodia is strictly contraindicated in those with eating disorders, it is the pharmacist's responsibility to determine if this customer has an eating disorder. If this is the case, the pharmacist must refuse to sell the hoodia and advise her to consult a physician.

9. Case 6

Gale Green, 26 years old, is going on her honeymoon to Australia in two days. She is concerned about jet lag. Her friend advised her to take melatonin and she wants to know if she should start taking it tomorrow night. How do you advise her?

9.1 Clinical monograph: Melatonin

(N-2-(5-methoxyindol-3-ethyl)-acetamide ($C_{13}H_{16}N_2O_2$))

Synonyms: Acetamide, BMS-214778, luzindole, mel, MEL, MLT N-acetyl-5-methoxytryptamine, 5-Methoxy-N-acetyltryptamine[104,105]

Standard doses: 0.5–5 mg at bedtime.[105] The 5 mg dose appears to be more effective for improvement of sleep quality and latency.[105] It is preferable to start with 2 or 3 mg because for many people 5 mg may be a higher dose than necessary.[106]

Melatonin is best known today for its use in preventing or reducing jet lag.[106] The timing of the melatonin dose is important. It should be taken at bedtime after darkness has fallen on the first day of travel and at the destination on the following few days at bedtime. If it is taken too early in the day, it can cause sleepiness and delay adaptation to local time. Taking melatonin before the day of travel is not recommended as it does not hasten or improve adaptation to local time at the destination.[106]

Pharmacology

Melatonin is a hormone released by the pineal gland. Its release is stimulated by darkness and inhibited by light. Melatonin appears to play a key role in regulating the body's circadian rhythms. A physiological dose of orally administered melatonin shifts circadian rhythms in humans according to a phase-response curve. It delays circadian rhythms when administered in the morning and advances them when administered in the afternoon or early evening.[105–107]

Clinical trials

A Cochrane review assessed the effectiveness of melatonin for the prevention and treatment of jet lag. Ten trials were included. They all compared melatonin with placebo and one in addition compared it with a hypnotic, zolpidem. Eight of the 10 trials found that melatonin, taken close to the target bedtime at the destination (10 pm to midnight), decreased jet lag from flights crossing 5 or more time zones. The authors concluded that melatonin should be recommended to adult travellers flying across 5 or more time zones, particularly in an easterly direction, and especially if they have experienced jet lag on previous journeys. Travellers crossing 2–4 time zones can also use it if necessary.[106]

Adverse effects

Evidence from a variety of clinical trials indicates that melatonin may cause a disorienting "rocking" feeling, decrease glucose tolerance and insulin sensitivity in postmenopausal women, increase triglyceride and VLDL cholesterol levels, increase luteinizing hormone (LH) levels in women, lower blood pressure, and cause mild stomach upset, including symptoms such as nausea, vomiting, abdominal cramps, heartburn, and flatulence.[105]

Cautions/contraindications

Melatonin should be used with caution while driving or operating heavy machinery. Safety has not been established in children and lactation. Melatonin should be avoided during pregnancy because it may cause hormonal disturbances. High levels of melatonin during pregnancy also increase the risk of developmental disorders in the fetus.[105]

Drug interactions

- Anti-seizure medications – Melatonin should be used cautiously by patients taking anti-seizure medications because it may increase the risk of seizures.[105,108]
- Nifedipine – Melatonin should be used cautiously by patients taking nifedipine because in one clinical trial, patients taking both nifedipine and melatonin for four weeks had increased blood pressure and heart rate.[109]
- Warfarin – Melatonin should be used cautiously by patients taking warfarin because evidence

from case reports indicated that patients taking both warfarin and melatonin experienced changes in bleeding.[106]

- Zolpidem – Melatonin should be used cautiously by patients taking zolpidem because increased daytime drowsiness, confusion, and nausea have been reported.[110]
- Drugs metabolized in the liver (CYP1A2 drugs) – Since melatonin is metabolized by CYP1A2, drugs that increase (e.g., carbamazepine, phenytoin, rifampin) or decrease (e.g., amiodarone, ciprofloxacin, clarithromycin) CYP1A2 activity may alter melatonin levels.[105]
- Sedative medications – Additional drowsiness may occur if melatonin is taken together with other sedatives, such as benzodiazepines, phenobarbital, narcotics, and alcohol.[105]

Response

Current evidence indicates that melatonin is likely effective for preventing and treating jet lag. It is not recommended to take melatonin before the day of travel because this does not hasten or improve adaptation to local time at the destination. If the patient is leaving Toronto about midday, the first dose of melatonin is taken on the plane soon after it gets dark to sleep on the way to Australia; the second dose is taken at bedtime after arrival the next day, again after dark.

10. Resources for Pharmacists

CAMline
www.camline.ca

Natural Medicines Comprehensive Database
www.naturaldatabase.com

Pharmacist's Letter
www.pharmacistsletter.com

Natural Health Products Directorate – Compendium of Monographs
www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_list-eng.php

National Centre for Complementary and Alternative Medicine (NCCAM)
nccam.nih.gov

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Questions

1. Which of the following is a reason why patients take natural health products?
   a. They are perceived to be natural and therefore safe.
   b. They have experienced adverse effects of conventional therapy.
   c. Natural health products are just part of a holistic paradigm of health care in which they believe.
   d. All of the above.

2. Which of the following is **not** part of the pharmacist's role with respect to natural health products?
   a. Helping patients make informed choices.
   b. Identifying interactions between drugs and natural health products.
   c. Providing accurate information regarding the efficacy, toxicity, and side effects of natural health products.
   d. Assuring patients that natural health products are always safe because they are natural.

3. Which of the following is **false** with respect to the Natural Health Products Regulations?
   a. All natural health products must have DINs.
   b. All manufacturers, packagers, labellers, and importers of natural health products require a site licence.
   c. Manufacturers must comply with good manufacturing practice guidelines.
   d. The licensee or product licence holder is responsible for reporting adverse reactions associated with the use of their licensed natural health products to Health Canada.

4. Which of the following drugs/natural health products may interact with melatonin?
   a. penicillin
   b. synthroid
   c. zolpidem
   d. COLD-fX®

5. Which of the following statements regarding garlic is **false**?
   a. A common side effect of garlic is bad breath and body odour.
   b. Garlic has been shown to reduce blood levels of protease inhibitors.
   c. It has been suggested that components of garlic may increase the activity of lipogenic enzymes.
   d. Garlic is best known today for its use in lowering cholesterol.

6. Which of the following is the most common adverse effects of *Panax ginseng*?
   a. diarrhea
   b. insomnia
   c. skin eruptions
   d. "ginseng abuse syndrome"

7. Which of the following statements regarding saw palmetto is **false**?
   a. Saw palmetto appears to have little or no impact on sexual function.
   b. Most commercial saw palmetto products are "liposterolic extracts" that contain the fatty acids and sterols from the fruit of the plant.
   c. There has been no clinical trial evidence or case report of drug interactions with saw palmetto.
   d. Saw palmetto is best known today for its use as a treatment of prostate cancer.

8. P57 is considered to be the main active constituent of which natural health product?
   a. hoodia
   b. melatonin
   c. garlic
   d. glucosamine

9. Which of the following statements regarding chondroitin is **true**?
   a. Chondroitin is effective for lowering cholesterol.
   b. Chondroitin has been shown to reduce blood levels of protease inhibitors.
   c. It is hypothesized that chondroitin sulphate will support or enhance macromolecular synthesis by chondrocytes.
   d. Chondroitin is effective for the treatment of jet lag.

10. Which of the following statements regarding glucosamine is **false**?
   a. Individuals with allergies to shellfish may also be allergic to glucosamine derived from shellfish.
   b. Individuals taking warfarin should avoid the use of glucosamine.
   c. The standard dose of glucosamine is 1,500 mg daily taken in three divided doses.
   d. Glucosamine is a precursor for glycosaminoglycans (GAGs), which are a major component of joint cartilage.