COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) FOR PAIN, HERBAL ANTI-INFLAMMATORY DRUGS

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Abstract

Introduction: Many specialists in pain management view the integration of traditional treatment approaches and a wide range of complementary and alternative medicine approaches as the ideal goal of many types of pain. Pain is a subjective, complex, multidimensional and unpleasant experience. It is one of the most prevalent conditions that require medical attention. Nowadays the number of patients that are using herbal remedies and complementary and alternative medicine for treatment of pain is growing rapidly.

Objectives: The aim of this investigation is to describe the concept of complementary and alternative medicine – CAM and the role of specific plants and their anti-inflammatory activity in curing inflammatory painful diseases.

Conclusions: Nonsteroidal anti-inflammatory drugs and opioid analgesics are normally used to treat inflammation and pain, but they can manifest a great number of adverse effects. Therefore herbal drugs can be a potential source to replace them. Many medicinal plants, some of them indigenous, are known for their analgesic and anti-inflammatory effect, but only a few are included in the health care system after clinical research. So, it is time to give an important place to the scientific uses of natural medicinal plants and investigation of the active phytoconstituents of them. Extraction of the active principle of herbal drugs and their pharmaceutical formulation must be the main direction of industrial research.

Keywords: Anti-inflammatory, complementary and alternative medicine, herbal drug, inflammation, pain

Introduction

Pain is an unpleasant sensory and emotional experience in response to tissue damage, threat of tissue damage or perceived tissue damage. Experience and interpretation of pain is subjective and influenced by previous experience and an individual's physical and mental condition at the time.

Sensory nerve endings are found throughout the body in the skin, muscles, joints, blood vessels and internal organs. These nociceptors are sensitive to the effects of potentially damaging mechanical, thermal and chemical stimuli.

When cells are damaged they release a variety of chemical mediators, which can activate or sensitize nociceptors to other chemicals. This explains acute pain. Chronic pain is more difficult to explain, especially if it goes on beyond the initial tissue damage. Chronic pain is thought to be associated with changes to the normal physiological pain pathway (Thorp ChM 2008).

One common classification based on mechanisms distinguishes pain into categories called "nociceptive", "neuropathic" and "psychogenic".

Nociceptive pain is believed to be caused by the ongoing activation of pain receptors in either the surface or deep tissues of the body. There are two types: "somatic" pain and "visceral" pain. Nociceptors are free afferent nerve fibers that distinguish noxious from innocuous stimuli. These are located in the skin, subcutaneous tissue, and visceral and somatic structures.

Somatic nociceptive pain arises from bone, joint, muscle, skin, or connective tissue. Direct trauma to tissues is the typical cause of this type of pain.

Visceral pain arises from visceral organs like the gastrointestinal tract or pancreas. Visceral nociceptive pain may arise from the organ or capsule or from obstruction of a hollow viscus causing intermittent, poorly localized pain.

Neuropathic pain is believed to be caused by changes in the nervous system that sustain pain even after an injury heals. In most cases, the injury that starts the pain involves the peripheral nerves or the central nervous system itself. It can be associated with trauma or with many different types of diseases, such as diabetes.

Psychogenic pain is a simple label for all kinds of pain that can be best explained by psychological problems. Most patients with chronic pain have some degree of psychological

disturbance. Patients may be anxious or depressed, or have trouble coping. Psychological distress may not only be a consequence of the pain, but may also contribute to the pain itself (healingchronicpain.org; Dillard JN, et al., 2005).

The word "inflammation", derived from the Latin word "inflammare", (to set on fire), is a complex biological process including several chemical mediators which are induced by vascular tissue of the body, when it comes in contact with several harmful stimuli like pollens, irritants, pathogens, and damaged cells. It provides a protective comeback that helps in healing of tissues. Sometimes, inflammation seems to produce events that are quite serious and become chronic like occurrence of rheumatoid arthritis and hay fever which may be life threatening (Beg S, et al., 2011).

The anti-inflammatory properties of several phytomedicines origin, that contain substances like phytoestrogens, flavonoids and its derivatives, phytosterol, tocopherol, ascorbic acid, curcumin, and others can be the inhibitors of the molecular targets of pro-inflammatory mediators in inflammatory responses (Iwalewa EO, et al., 2007).

Since the synthesis of aspirin in 1899 by German Company Bayer, many compounds were introduced as a result of laboratory search for drugs with anti-inflammatory activity and less clinical research are done in uses of active phytoconstituents of herbal drugs.

According to the American Pain Foundation, more than 50 million Americans experience chronic pain. Back pain, headache, and joint pain caused by osteoarthritis are the most common chronic pain syndromes (Berman, 1997). The experience of chronic pain exacts a huge toll on the individual and the family. Pain may prevent a person from working, socializing, or enjoying a family life. It is associated with depressed mood and a poor quality of life. The consequences for society include lower productivity for businesses and a cost of billions of dollars each year (healingchronicpain.org).

Nowadays the number of patients that are using herbal remedies and complementary and alternative medicine for treatment of pain is growing rapidly. Over the last 20 years, Americans have sought a more “natural” or “holistic” approach to treatment of medical problems in general and pain in particular (Dhanani NM, et al., 2011).

Herein, we review the literature on complementary and alternative medicine for pain, with particular emphasis on some more known and used herbal anti-inflammatory drugs.

Objectives

The aim of this investigation is to describe the concept of complementary and alternative medicine – CAM and the role of specific plants and their anti-inflammatory activity in curing inflammatory painful diseases.

Complementary and Alternative Medicine (CAM) for pain

Among the modalities that now are being explored as treatments for chronic pain are numerous approaches that usually are considered out of mainstream medicine; the so-called complementary and alternative medical treatments. Many specialists in pain management view the integration of traditional treatment approaches and a wide range of complementary and alternative medicine approaches as the ideal goal for many types of chronic pain (healingchronicpain.org).

"Integrative Pain Therapy" is a term that has been used to describe this effort to link these traditional and nontraditional approaches. Integrative pain therapy draws from a broad spectrum of therapeutic approaches. It recognizes the value of multiple approaches to pain management (a multimodality approach) and acknowledges the individualized nature of good medical care. The goal is to employ the safest and most effective therapies to provide maximum benefit (healingchronicpain.org).

The goals of an integrative pain therapy approach may include:

- reducing or eliminating pain
- using medicines that are appropriate, provide sustained benefits, have tolerable side effects, and support the functional goals of the patient
- reducing distress and enhancing comfort, peace of mind and quality of life
- improving the understanding of the role of emotions, behavior and attitudes in pain
- improving the ability to function physically and perform activities of daily living
- improving the ability to function in social and family roles
- supporting the patient's ability to return to work and function on the job
- educating patients in ways to maintain rehabilitation gains and avoid re-injury
- empowering patients to actively participate in pain control strategies
- promoting awareness and understanding of the factors that contribute to physical and emotional distress related to pain
- developing the skills and knowledge needed to increase the patient's sense of control over pain.

The National Center for Complementary and Alternative Medicine (NCCAM) is a component of the National Institute of Health, and is the Federal government proponent agency for scientific research on complementary and alternative health practices. Many areas of research are now underway to examine efficacy and therapeutic benefit of some these nontraditional approaches to care. Understanding CAM and integrating its effective therapies

add a multidisciplinary approach to care that meet the patients cultural and belief systems (Dillard JN, et al., 2005; http://nccam.nih.gov).

Complementary and Alternative Medicine is defined by NIH – National Center for Complementary and Alternative Medicine (NCCAM) as a group of diverse medical and health care systems, practices and products that are currently not integrated into conventional medicine.

The National Institutes of Health has classified Complementary and Alternative Medicine in five ways (Roshni P, et al., 2012; Staud R, 2011; Robotin MC, et al., 2006; MacLennan AH, et al., 2006):

1. Alternative medical systems like Acupuncture, Naturopathic Medicine, Ayurveda (the ancient Indian healthcare system) and Homeopathy.
2. Biologically based therapies including herbal and dietary therapies.
3. Energy therapies, such as Reiki, therapeutic touch, magnet therapy etc.
4. Manipulative and body based systems like chiropractic, osteopathy and massage.
5. Mind-body interventions, such as meditation, biofeedback, hypnotherapy and the relaxation response.

Knowledge of herbal medicines has derived from the rich traditions of ancient civilizations and scientific heritage. From ancient time Indian, Chinese, Egyptian, Greek, Roman and Syrian medicinal system documented the use of different plant based medicine for different diseases (Sen S, et al., 2010).

WHO noted that about 25% of modern medicines are descended from plant sources used traditionally and research on traditional medicinal herbal plant leads discovery of 75% of herbal drugs. Recent years documented progressive increase in the screening and research of medicinal plant with anti-inflammatory and analgesic activity but only few of them only included in the health care system after clinical research (Sen S, et al., 2010).

Anti-inflammatory drugs of synthetic origin are classified as steroidal and nonsteroidal anti-inflammatory agents. The origin of these chemical compounds started when salicylates were isolated from the leaf extract of willow bark *Salix Alba* and were potentially used by the people of North America in 200 BC and regarded as first generation anti-inflammatory agents (Beg S, et al., 2011). Classic and new nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to reduce inflammation, pain and fever.

The major difference between individual NSAIDs is the range of side effects experienced by patients. Individuals have different reactions to different NSAIDs. Some

tolerate a particular drug while others do not. In the treatment of chronic pain, a number of drugs may be tried until one is found that produces the most acceptable result to the patient (Thorp ChM, 2008).

In a study conducted by the World Health Organization (WHO), none of these compounds were found to be safer, as they are associated with a series of unacceptable findings like drug-related or drug-induced toxic effects, and cause harmful adverse effects and secondary effects of long-term use. Some common side effects of these synthetic drugs include gastric irritation, ulceration, bleeding, renal failure, interstitial nephritis, hepatic failure, headache, thrombocytopenia, hemolytic anemia, asthma exacerbation, skin rashes, angioedema, and pruritis (Beg S, et al., 2011; Robotin MC, et al. 2006).

The presently available drugs provide only symptomatic relief and are not free from side effects. The greatest disadvantage in the presently available potent synthetic anti-inflammatory drugs lies in their toxicity and reappearance of symptoms after discontinuation.

The target should be to discover newer drugs from plant kingdom which may provide a therapeutic cure and would be free from undesirable effects as well as economical, which would be accepted by the developing nations (Shah Biren N, et al., 2006).

Americans spend billions of dollars annually to find a holistic treatment with effective pain relief and few side effects, on complementary and alternative medicine, including herbal therapies (Wirth JH, et al., 2005).

Herbal anti – inflammatory drugs

Despite the tremendous progress in the medical science during the last years, the treatment of some inflammatory painful diseases is yet problematic and complex.

The use of herbal therapy has increased sharply over the past 20 years as Americans look for a more “natural” approach to medicinal therapies. A 2005 survey showed that more than 38 million Americans use herbal therapy to self-treat a variety of ailments including allergies, insomnia, respiratory problems, gastrointestinal problems and chronic pain (Dhanani NM, et al., 2011).

Popular use of medicinal herbs makes it necessary for physicians to become aware of their health benefits, risks and uncertainties so that they can educate their patients about these issues. The list of agents with purported cancer-fighting properties is growing rapidly, although few have been tested in rigorous clinical trials (O’Hara MA, et al., 1998; Robotin MC, et al., 2006).

Patients are sometimes unaware about the risk that offers the uncontrolled uses of medical herbs. It is commonly known and thought that herbs are “natural” alternatives to

chemical and synthetic drugs. Also, patients are confused about the appropriate use of medical herbs and are not informed that not a correct use of them may be ineffective.

Factors that pose specific challenges include: wide variation in biological potency among herbal crops; possible contamination by fungi, bacteria or pesticides; use of incorrect plant species; absence of product standardization (leading to possible substitution adulteration and incorrect dosing or preparation); and inappropriate labelling or advertising (Robotin MC, et al., 2006).

Currently used antiinflammatory and analgesic drugs are associated with some severe side effects; therefore there is a need for the development of potent analgesic and anti-inflammatory drugs with fewer side effects. Herbal medicine showed safety, efficacy, cultural acceptability and lesser side effects than the synthetic drugs. The number of chemical compounds, found within the plant kingdom is a part of the physiological function of living flora and are supposed to have better compatibility with the human body (Sen S, et al., 2010).

Therefore, herbal therapy is a good alternative in the treatment of mild inflammatory painful diseases alone or in combination with NSAIDs or opioids drugs to avoid or minimize these adverse effects. In many cases the uses of herbal therapy supports the effect of these drugs but sometimes must be attended in this combination.

Herein, we are listing some of the more used anti-inflammatory herbal drugs with their common uses and therapeutic doses, as are shown in Table 1.

Ginger

Zingiber officinale

Ginger has been a popular culinary and medicinal herb for thousands of years. For 2500 years the Chinese have used this plant as a flavoring agent and antiemetic. Ancient Greeks ate it after meals as a digestive aid (O'Hara MA, et al., 1998).

Ginger roots

Traditionally used in herbal medicine to help relieve digestive upset/disturbances including lack of appetite, nausea, digestive spasm, indigestion, dyspepsia and flatulent colic (carminative).

A final use for ginger is in the treatment of arthritis. High doses of ginger may have anti-inflammatory and analgesic effects. One trial observing patients with osteoarthritis found that ginger extract caused a modest reduction in knee pain (Ginger Root monograph, 2009).

Ginger extract may have a moderate positive effect on osteoarthritis, with a good safety profile. Two studies have evaluated a specific ginger extract (Eurovita Extract 33; EV ext-33) 170 mg three times daily or 255 mg twice daily (510 mg total daily dose) for 3-6 weeks (Altman RD, et al., 2001).

Results indicate that ginger modestly improved pain after standing or walking, and joint stiffness in some patients. It does not seem to significantly improve overall functioning, quality of life, or the level of use of analgesic medications. In another study, no significant difference was observed between ginger, ibuprofen, and placebo (Bliddal H, et al., 2000).

In an overview of systematic reviews on various herbal medicines for osteoarthritic and chronic low back pain, the evidence of effectiveness was moderate for ginger (Chrubasika S, et al., 2005).

White Willow Bark
Salix Alba

From the family of salicylates, White Willow Bark is used to treat headache, mild feverish colds, influenza, muscle and joint pain caused by inflammation, arthritic conditions. It is the anti-inflammatory action of the salicylates (the active ingredient in aspirin is acetylsalicylic acid) that suggested willow bark's use for inflammatory pain. However, because of the time it takes to be metabolized and absorbed, willow bark has a slower onset and a longer duration than salicylate itself. There is some evidence that a willow bark extract providing 120-240 mg of the salicin constituent daily can reduce back pain in some patients. Flavonoids, tannins and salicylates are attributed to the anti-inflammatory, antipyretic and antiuricosuric activities of white willow bark (Chrubasik S, et al., 2000; Vadivelu N, et al., 2011).

Salix Alba bark

The higher dose of salicin (240 mg equivalent to only 50 mg of acetylsalicylic acid-aspirin) is more effective. A week or more is required to observe benefit. Willow bark extract

also has a moderate pain relieving effect in osteoarthritis and appears to be well-tolerated (Schmid B, et al., 2001).

The use of this herb should be avoided in people with aspirin hypersensitivity, asthma, active peptic ulcer disease, diabetes, gout, hemophilia, hypoprothrombinemia, and kidney or liver disease.

Chili peppers
Capsicum frutescens

Capsicum frutescens, also known as Cayenne Pepper, has been used orally for upset stomach, toothache, poor circulation, fever, hyperlipidemia and heart disease prevention. Capsicum can be used topically to treat pain associated with osteoarthritis, shingles, rheumatoid arthritis, post herpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, fibromyalgia and back pain. Capsaicin is the active ingredient in chili peppers. Capsaicin, the most pungent ingredient in red peppers, has been used for centuries to remedy the pain. It has important effects on pain-sensitive nerves and has been used extensively by scientists studying pain pathways. The mechanism of action involves the binding of nociceptors in the skin, which initially causes neural excitation and heightened sensitivity (itching, burning) followed by cutaneous vasodilatation.

Capsicum fruits

There have been numerous studies of topically applied capsaicin, but there still is no definitive answer about its analgesic effects. Some studies suggest that it can be a useful agent for patients with various neuropathic pain syndromes, such as postherpetic neuralgia (shingles), postmastectomy pain and diabetic neuropathy; other studies suggest that it can be helpful in the treatment of joint pain caused by osteoarthritis (Fusco BM, et al., 1997; Vadivelu N, et al., 2011).

Devil's Claw
Harpagophytum procumbens

Devil's Claw has been used to treat pain symptoms from osteoarthritis, rheumatoid arthritis, gout, myalgia, lumbago, chronic low back pain and gastrointestinal upset. The active constituent, herpagoside, seems to reduce nonspecific low back pain when used in a dose

range 50-100 mg. Current evidence implies that herpagoside inhibits both cyclooxygenase (only COX-2) and lypoxygenase inflammatory pathways (Chrubasik S, et al., 2004; Vadivelu N, et al., 2011).

Devil's Claw herb

When taken in conjunction with a nonsteroidal anti-inflammatory drug for osteoarthritis, it may be able to reduce the dose required for benefit. Although Devil's claw is generally well-tolerated, caution has been advised in patients with peptic ulcer disease, gallstones, diabetes and cardiovascular conditions such as hypertension. It is contraindicated in pregnancy (Vadivelu N, et al., 2011).

Salai Guggal

Boswellia serrata

Boswellia, one of many herbs used in Ayurvedic Medicine, comes from a tree found in India. The tree is a member of the frankincense family and contains a gummy resin that is purified into an herbal preparation. Boswellia has been used to manage pain associated with osteoarthritis, rheumatoid arthritis, bursitis and tendonitis. Laboratory studies have shown that boswellic acids inhibit inflammatory mediators, such as leukotrienes (Vadivelu N, et al., 2011; Safayhi H, et al., 1992).

They have an anti-inflammatory action similar to nonsteroidal anti-inflammatory drugs. One double-blind, placebo-controlled trial showed that boswellic acid-containing gum resin was effective in the treatment of bronchial asthma (Gupta I, et al., 1998).

Boswellia gum resin

The principle constituents, boswellic acid and α-boswellic and β-boswellic acids, come from the resin. These constituents have anti-inflammatory properties that aid in pain management with arthritic patients but not all extracts of boswellia show anti-inflammatory, antiarthritis or antipyretic effects. Data on its effectiveness for osteoarthritis and rheumatoid arthritis have been conflicting. However, an oral combination product called Articulin-F(R) was shown to significantly improve symptoms of rheumatoid arthritis and osteoarthritis and an extract of the gum resin provided symptomatic improvement in patients with ulcerative colitis (Vadivelu N, et al., 2011; Boswellia serrata monograph, 2008; Kimmatkar N, et al., 2003).

Feverfew

Chrysanthemum parthenium

Feverfew is used to treat headache, fever menstrual abnormalities and to prevent migraine. The name is derived from the Latin word *febrifugia*, meaning “fever reducer”. Feverfew also inhibits the production of leukotrienes and the release of serotonin and histamine from platelets. In a review of clinical studies on the use of feverfew for the treatment of migraine, four out of five studies suggested beneficial effects.

Feverfew herb

Taken as recommended, side effects, such as gastrointestinal upset and nervousness, are usually mild and four to six weeks of use are required before benefits occur. The use of feverfew is strongly contraindicated during pregnancy, as it could cause uterine contractions or abortion (Vadivelu N, et al., 2011; Vogler BK, et al., 1998).

St. John's wort

Hypericum perforatum

St. John's wort is used to treat anxiety, mild to moderate depression and sleep related disorders. The active compounds in the agent include the naphthodyhidrodianthrones, hypericin and pseudohypericin, the flavonoids, quercitin, rutin and hypericin and the xanthones.

St. John's wort has been studied in several controlled studies, and the results have been conflicting. Some studies suggest that it may be effective for mild to moderate depression.

Hypericum perforatum herb

H. Perforatum possesses anti-inflammatory and antinociceptive properties, thereby suggesting that the extract might be useful in the management of inflammatory pain (Abdel-Salam, 2005).

It has relatively few side effects such as photosensitivity, dry mouth, restlessness, dizziness, fatigue, but should be also used cautiously by patients with Alzheimer's disease, bipolar disorder, major depression, or schizophrenia; these patients should be under the care of a mental health professional before starting treatment. It is also associated with some significant herb-drug interactions, which might lead to the reduced effectiveness of some medications, including chemotherapy and anti-HIV drugs (Vadivelu N, et al., 2011).

Curcumin

Curcuma longa

Curcumin is yellow colored phenolic pigment, obtained from powdered rhizome of C. longa Linn. (Family- Zingiberaceae). It is the major constituent of the oleoresin of turmeric. In the crude extract of rhizomes of C. longa about 70–76% curcumin is present along with about 16% demethoxycurcumin and 8% bisdemethoxycurcumin. It is extensively used for imparting color and flavor to the food and in the traditional Indian medicine, turmeric powder is used to treat a wide variety of diseases. Extensive scientific research on curcumin have demonstrated a wide spectrum of therapeutic effects such as anti-inflammatory, antibacterial, antiviral, antifungal, antitumor, antispasmodic and hepatoprotective (Kohli K, et al., 2005).

Curcumin has been shown to have strong anti-inflammatory effects when tested in animals. Laboratory studies have shown that part of its mechanism of action is due to a natural COX-2 inhibiting effect. In one clinical study, curcumin was found to be as effective as cortisone for acute inflammation and half as effective for chronic inflammation (Mukhopadhyay A, et al., 1982).

Curcumin roots

Studies have suggested benefit in osteoarthritis, rheumatoid arthritis, ulcerative colitis, and fibromyalgia. The rhizome of turmeric is widely used in indigenous Medicine. A paste made from powdered rhizome of Curcuma longa Linn. mixed with slaked lime applied locally, is an ancient household remedy for sprains, muscular pain and inflamed joints. It is also applied in poultices to relieve pain and inflammation (Kohli K, et al., 2005).

Curcumin has a good safety profile but is contraindicated in people with bile duct obstruction, gallstones, stomach ulcers or hyperacidity disorders.

Conclusion

The interdisciplinary approach to chronic pain may involve not only traditional health care providers, including physicians, nurses, psychologists and physical therapists, but integrative providers comfortable with the widest array of healing modalities, whether conventional or complementary, as well as specialists in specific complementary approaches.

Nonsteroidal anti-inflammatory drugs and opioid analgesics are normally used to treat inflammation and pain, but they can manifest a great number of adverse effects. Therefore herbal drugs can be a potential source to replace them. Many medicinal plants, some of them indigenous, are known for their analgesic and anti-inflammatory effect, but only a few are included in the health care system after clinical research.

So, it is time to give an important place to the scientific uses of natural medicinal plants and investigation of the active phytoconstituents of them.

Extraction of the active principle of herbal drugs and their pharmaceutical formulation must be the main direction of industrial research.

Table 1: Herbs with anti-inflammatory activity

Plant name	Common uses	Part used	Dose
Ginger **Zingiber officinale**	*moderate positive effect on osteoarthritis antiemetic*	Root	ginger extract 510 mg total daily dose
Willow Bark **Salix Alba**	*inflammatory pain osteoarthritis*	Bark	willow bark extract 120-240 mg of the salicin
Chili peppers **Capsicum frutescens**	*pain-sensitive nerves neuropathic pain syndromes shingles diabetic neuropathy joint pain- osteoarthritis*	Fruit	0.025% - 0.075% capsaicin gel
Devil's Claw **Harpagophytum procumbens**	*Osteoarthritis chronic low back pain rheumatoid arthritis gout mild joint pain digestive tonic*	Root, tuber	Devil's Claw extract 1-8.5% harpagoside
Curcumin **Curcuma longa (turmeric) Zingiberaceae**	*strong anti-inflammatory effects a natural COX-2 inhibiting effect osteoarthritis rheumatoid arthritis*	Root, rhizome	Curcuma domestica extract 2 gram daily dose
Salai Guggal **Boswellia serrata**	*anti-arthritic osteoarthritis rheumatoid arthritis*	gum resin	37,5-65% boswellic acid
Feverfew **Chrysanthemum parthenium**	*anti-inflammatory effects headache prophylaxis migraine rheumatoid arthritis*	Leaf	25-75 mg, standardized to 0.2% parthenolide
St. John's wort **Hypericum perforatum**	*anti-inflammatory effects antidepressant anti-infective*	Herb	300 mg x 3 times a day standardized extract to 0.3% hypericin

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