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REVIEW ARTICLE

Phytotherapy and pain management

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ABSTRACT

When it comes to pain, patients resort to complementary methods as well as pharmacological treatments. Among these methods, phytotherapy is the most widely used. The aim of this mini-review is to identify the herbs used in the treatment of pain-related disorders in the world and to review the available preclinical and clinical information about these herbs. For this mini-compilation, we discussed the plants used in traditional medicine in the treatment of pain in the world; We reviewed scientific databases of herbs (Pubmed, CINAHL; Web of Science, Ulakbim, EBSCOHost MEDLINE; Ovid and Bibliothecal digital) analyzed in preclinical studies and used in pain treatment using related terms, and obtained information from published books.

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INTRODUCTION

Phytotherapy (phytos=plant, therapy=treatment) means herbal treatment and its history dates back to ancient times. It has been claimed that the term "phytotherapy", which can be explained as an approach to treating patients using plants, was first used by the French physician Henri Lenclerc, who lived between 1870-1953, in the journal La Presse Medical. The first written document on this subject, BC. Nineveh tablets dating back to 3000 BC prove that there were treatments with herbal and animal medicines in the Sumerian, Akat and Assyrian civilizations established in Mesopotamia. Hippocrates described nearly 400 herbal products in his books (1). The herbal medicine used today takes its source from China and India. Medicinal herbs, which were first used among the people in Western countries, started to be preferred by physicians as a complementary treatment in the following years. Commission E (German Federal Institute for Drugs and Medical Devices), which was established in Germany in 1978, prepared a report by evaluating the clinical effects of 300 plants, and in the following years, standardization of herbal treatments was tried to be achieved with this report (2,3).

According to the International Association for the Study of Pain (IASP), Pain; It is defined as "an unpleasant sensory and emotional experience that accompanies or can be defined by existing or potential tissue damage" (4). We know that the behavior of people around us towards painful events is different. Some are more durable, some are more sensitive. This condition, called the pain threshold, appears as a characteristic of the body. In determining the pain threshold, cultural characteristics, lifestyle, environment, education, gender, language, religion and many other beliefs are also effective (5). Pain is considered the third most common health problem after disabling heart disease and cancer-related diseases. Pain; It is a painful process that ends with stimulation, perception, and inhibition. Pain management is done with many complex arrangements. However, the fact that pain does not occur in a single event and that it is affected physically, mentally and socioeconomically has pushed researchers to work in a multidisciplinary field on evaluation and treatment processes. It is imperative that each discipline be aware of new developments while examining the pain complex. In order to cope with pain, which concerns a large part of the society, it is necessary to know the mechanisms of pain well and to reveal the detailed molecular mechanisms of pain in terms of pathophysiology.

Worldwide, the use of medicinal plants is increasing to relieve symptoms associated with pain. However, there is little scientific evidence to confirm the effectiveness of these herbs. This evidence needs critical review and further study to provide scientific support for their use. Although pain management of pharmacological drugs provides significant relief in various pain-based diseases, many patients turn to complementary and alternative medicine support. Botanical herbs used in the treatment of pain can contribute to the recovery of a patient's quality of life or enhance by influencing traditional pain management. Today, the use of herbal analgesics has become widespread in many pain-related diseases such as rheumatologically diseases, back pain, cancer, diabetic peripheral neuropathy and migraine.

1/4 of the existing drugs are of herbal origin, and in most of them, the active ingredient desired to be obtained from the plant is copied in the laboratory environment. Almost one third of pharmaceutical drugs are derived from plants. In addition, another issue to be considered is that plants can interact with each other and with drugs. More than 50% of the population in Europe, North America and other industrialized regions use at least one of the complementary or alternative medicine methods. In San Francisco, London and South Africa, 75% of people with HIV/AIDS use conventional/alternative medicine. Between 1995 and 2000, the number of doctors encountering those taking natural medicines almost doubled (6) Although the majority of medical practices in the United States of America (USA) are traditional, approximately 70% of health care services are provided by alternative practices throughout the world (7). When the studies are examined, it is noteworthy that although it is so widely used, there is still no specific protocol in many phytotherapy applications, the studies were conducted with a small sample group, and there are uncertainties about how and how often it will be used in which patient group. Although its general prevalence in Turkey is not known exactly, phytotherapy application is available in the treatment of pain (8). When we review plant-derived anesthetic agents, phytochemicals with anesthetic activity and their products, the precise pharmacological mechanisms of general anesthesia are still a closed box. Currently used general anesthetics and anesthesia-related drugs (sedatives, anxiolytics or co-anesthetics) are thought to target inhibitory GABA A receptors and excitatory NMDA receptors (9).

Most of the anesthetic agents currently used are derived from or related to natural products, particularly plants, as evidenced by the thymol and eugenol found in cocaine and thyme, isolated from coca (*Erythroxylum coca*, *erythroxylaceae*) and becoming the prototype of modern local anesthetics. (*Thymus vulgaris*, *Lamiaceae*) and clove (*Syzygium aromaticum*, *Myrtaceae*), both structurally and mechanically similar to intravenous phenolic anesthetics. Although it is a similar derivative of the coca plant, it also has a calming effect (10). It was first brought to Europe from Peru (*Erythroxylaceae*). In 1860, Albert Nieman of Göttingen reported that chewing coca leaves had the tongue feel and taste. He isolated an active ingredient from them and called it "cocaine." Sigmund Freud, the founder of psychoanalysis, read Niemann's report and considered using cocaine to overcome his morphine addiction. However, he encouraged his colleague Carl Koller, who resided in ophthalmology in Vienna, to participate in the cocaine study. Koller conducted experiments on animals and humans by dripping a solution of cocaine into the eyeballs and found the numbing effect of cocaine on the eye. Shortly after,

in 1884, he successfully performed cataract surgery using cocaine as a topical anesthetic (11). The beginning of modern local anesthesia began when Carl Koller, an ophthalmologist, showed in 1884 that topical cocaine produced surgical anesthesia in the eye. Following this, the most important discovery was August Bier's first surgical spinal anesthesia by administering 0.5% cocaine intrathecally in 1898(12). In 1898, Richard Willstätter structurally identified cocaine as methyl ester (1R, 2R, 3S, 5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo [3.2.1]octane-2-carboxylate.

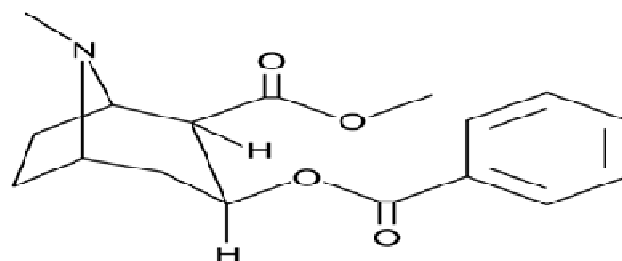


Figure. Cocaine Structure

Representative drugs of plant origin include anticholinergic atropine (from *Atropa belladonna*, *Solanaceae*), antimalarial quinine (from *Cinchona officinalis*, *Rubiaceae*), cardiotonic digitoxin (from *Digitalis purpurea*, *Plantaginaceae*), antitussive codeine (from *Papaver somniferum*, *Papaveraceae*), and analgesic salicylate and its derivative aspirin (from *Salix alba*, *Salicaceae*). Plants and herbs are sources of not only crude drugs, but also bioactive compounds that can lead to new drug structures (13). Osteoarthritis, a fairly common musculoskeletal disease, is the most common joint disease that can lead to chronic pain and severe disability. Nonsteroidal anti-inflammatory drugs used in conventional therapy have well documented existing side effects. However, Devil's Claw (*Harpagophytum procumbens*), a traditional South African herbal medicine used for rheumatic disorders, can be used in alternative phytotherapy as a safer treatment option. Its effectiveness in osteoarthritis has been evaluated in 14 clinical studies to date (14).

Curcumin, an effective anti-inflammatory component found in turmeric, plays an important role in protecting joints against destructive factors. Ginger and piperine are potent components of ginger and black pepper and can potentially enhance and sustain the effect of curcumin in this direction. To determine the effect of supplementation with turmeric extract, black pepper and ginger on prostaglandin E 2 (PGE 2), sixty patients with two different levels of knee osteoarthritis (Grade 2 and 3) were included in the study in patients with chronic knee osteoarthritis, in a study comparing Naproxen. Randomly selected daily for 4 weeks to take turmeric extract, ginger and black pepper together or Naproxen capsule. PGE2 was evaluated by ELISA method. All of the participants completed the study. PGE 2 was significantly decreased in both groups ($p < .001$), but there was no significant difference between the groups. The results of this study showed that twice daily intake of selected herbs for 4 weeks can improve PGE 2 levels in patients with chronic knee osteoarthritis, similar to the drug Naproxen. The first attempts at surgical anesthesia began centuries ago with herbs of antiquity. Mandragora or mandrake was used as a sedative and as a pain reliever for surgical procedures. It has been depicted on tablets and friezes since the 16th century BC and was used by Hannibal (2nd century BC) for its soothing effects against his enemies. The Romans used

mandrake for surgery. The Arabs translated the scientific works of the Ancients and expanded their knowledge. They developed *Spongia Somnifera*, which contains the juice of the mandrake plant. After the conversion of the Islamic cities of Europe to the Christians, scientific studies were translated into Latin and *Spongia Somnifera* was used in Europe until the discovery of the use of ether for surgical anesthesia (16). *Spilathes acmella* (Asteraceae), a plant that grows in the tropics, is used for rheumatism, sore throat and toothache. Eating its leaves and flowers is known to numb the tongue. He tested the local anesthetic activity of *Spilathes acmella* with an intracutaneous swelling assay. They injected 0.2 mL of aqueous extracts from their aerial parts into the backs of guinea pigs and observed the pinprick response of the raised areas. 10% and 20% extract injections provided 70% and 87% local anesthesia, respectively, while 2% lidocaine showed 97% local anesthesia (17).

It has been found that when aromatherapy massage with essential oils is applied to the abdominal region, menstrual pain decreases. It is stated that especially the use of lavender oil is more beneficial (18). In a study conducted to evaluate the effect of turmeric on premenstrual syndrome (PMS), it was seen that turmeric reduces PMS symptoms. Researchers attributed this result to the effect of turmeric on neurotransmitters and anti-inflammatory agents (19). In a systematic review evaluating the effect of aromatherapy on menopausal symptoms, stress, pain and depression when applied with products such as rose, lavender, jasmine, eucalyptus, chamomile by massaging the arm and back areas or by inhalation for varying durations from 15 minutes to 60 minutes. It was concluded that it was effective in reducing the symptoms (20). It has been stated that *Actaea racemosa* (Black snake root) plant significantly reduces premenstrual discomfort, dysmenorrhea and menopausal symptoms (21). In one of the studies conducted during the postpartum period, incision sites were observed in a placebo-controlled, single-blind, experimental study in which sixty primiparous patients were included. It was concluded that less redness, edema and pain developed in the incision area in the lavender-thymol group compared to the placebo group, and the use of analgesics decreased especially on the 1st and 2nd days postpartum (22). It has been observed that aromatherapy massage with lavender oil and rose water inhalation application reduce the level of pain and anxiety due to burns, and that aromatherapy massage is more effective than aromatherapy inhalation (23). It has been stated that lavender inhalation is an effective method for reducing pain when cannulae insertion into arteriovenous fistula in hemodialysis patients (24). Aromatherapy massage with lavender oil has been found to be effective in reducing pain when applied to the knees of patients with osteoarthritis (25).

CONCLUSION

Phytotherapy is among the complementary treatment methods used in addition to the traditional approach in pain treatment. Today, interest in herbal treatments has increased. It is widely used in many fields and in the treatment of diseases.

Although herbal treatments have been reported to have beneficial effects in general, herbal treatments can also have serious side effects and interactions with drugs. For this reason, health personnel should be knowledgeable about the effects and possible side effects of phytotherapy applications. In particular, it should be strictly questioned whether patients use an herbal treatment method and, based on evidence, herbal

medicines that have been shown to be effective should be allowed to be used under the control of the healthcare team. When the studies are examined, it is noteworthy that although it is so widely used, there is still no specific protocol in many phytotherapy applications, the studies were conducted with a small sample group, and there are uncertainties about how and how often it will be used in which patient group. As a result of bibliographic research, we can say that phytotherapy products can be useful in addition to the methods used in traditional medicine for the treatment of pain.

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