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Analgesic Potential of Extracts and Derived Natural Products from Medicinal Plants

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Abstract

Since ancient times, plants have always been a reliable and important source of bioactive compounds used to treat several diseases, and thus play a central role in human health. In addition, medicinal plants are a rich source of bioactive secondary metabolites that have a wide range of medicinal uses. This is the reason why, currently, 90% of drugs come from natural or semisynthetic origins. Chemical diversity of plants made them one of the main sources for the extraction and purification of secondary metabolites. On the other hand, pain has always been a cause of concern to humans who searched for a remedy from natural sources, mostly from plants. In this respect, substances that relieve pain (algesia) can be described as analgesics (painkillers). Chemically diverse structures have been identified as pain relievers; they relieve pain through various mechanisms and act either centrally (opioids receptor agonism) or peripherally. Therefore, this chapter is intended to summarize the literature pertaining to plants and their constituents discovered with analgesic potential in the last four decades.

Keywords: medicinal plants, analgesics, extract, derived natural products

1. Introduction

Medicinal plants are a rich source for making phytochemicals with great efficiency and selectivity. Since the middle of the nineteenth century, many natural products were obtained in a pure form from plants; most of these products are available to be used as active agents in modern medication. Despite the significant advances in synthetic drugs, side effects remain that necessitate the search for effective, inexpensive, and more accessible drugs. Medicinal plants may provide such valuable therapeutic alternatives. Use of traditional medicinal plants with

analgesic effects has recently gained popularity worldwide because of their natural origin and fewer side effects [1]. Moreover, medicinal plant extracts and their fractions are used by 80% of the world population for their simple health care necessities. They are the significant source of natural drug molecules and secondary metabolites which can be used in modern medicine for the cure of various diseases. Throughout history, people relied on an old-style traditional system of medicine to cure diseases and disorders, which with time has gained popularity and global significance. Present approximations suggest that in numerous developing countries, a large proportion of the population seriously trusts traditional specialists and local healers in addition to trusting medicinal plants and medicinal plants-derived drugs to cure diseases, though modern drugs may be accessible in these countries. However, herbal medicines must be approved by local authorities before being prescribed.

Native people and early civilizations tested different plants and animal parts to determine what effect they have. Using trial and error methods, local healers and shamans found that particular plants or parts had therapeutic activity. These indicated the first crude drugs and this knowledge was passed down through the generations and arranged similar to the old-style Chinese medicine as well as Ayurveda [2, 3]. Many traditional medicines have actual and useful effects, and extracts of these medicines have led to the discovery of bioactive molecules and to the growth of current chemically active pure drug discovery [3].

Recently, several people in developed countries have turned to complementary treatments including the use of therapeutic herbs [2]. In this context, the term Ayurvedic medicine has been introduced which is mainly in the form of a crude extract that consists of a mixture of several compounds; however, when the active agents are isolated and purified, they individually fail to give the desired activity. Therefore, pharmacological data on several medicinal plants and isolated compounds are required to regulate active compounds with the desired biological potency. Furthermore, modern methods of production, purification, and standardization should be followed to obtain plant-derived materials of high quality [3]. In ancient times, humans extracted chemicals from plants for treatment of various diseases, and kept records of useful properties and uses of medical plants, such as willow bark and *Papaver somniferum*, used as pain killers. It is now documented that willow bark contains acetylsalicylic acid, the active ingredient in aspirin [3].

Due to its frequent occurrence, pain is a public health problem with considerable socioeconomic effects. It is an indication of several illnesses and it is predicted that about 80–100% of the population will experience, for example, back pain once in life [4]. Pain treatment requires analgesics including, anti-inflammatory medicines, which at maximum doses have analgesic properties. In this respect, inhibition of nitric oxide (NO) and prostaglandin E2 production has been reported as a potential therapy for different inflammatory disorders [5]. Though several anti-inflammatory and analgesics drugs exist on the shelves, current drug therapy is related to certain adverse effects such as gastrointestinal irritation [6], bronchospasm, fluid retention, and extension of bleeding time. Consequently, it is necessary to discover new drugs with fewer adverse effects. Accordingly, people resort to medicinal plants for discovery and development of new drugs [7]. In addition, scientists discovered that extracts from medicinal plants can be a significant source of natural and safer new drugs for the treatment of inflammation and pain [8, 9].

2. Analgesic (painkiller)

Analgesics drugs include paracetamol (acetaminophenol), in addition to the nonsteroidal anti-inflammatory drugs (NSAIDs) such as salicylates, and morphine and oxycodone isolated from opium. There are many classes of drugs available for treatment of pain. Each class has a dissimilar history of uses for treatment of different types of pain and in different types of people.

Analgesic selection is governed by the type of pain. For example, for neuropathic pain, traditional analgesics are less effective, whereas drugs that are not normally mentioned as analgesics, such as tricyclic antidepressants and anticonvulsants medicine, are more effective as pain killers [10]. In general, pain killers are not used if there have other serious side effects. For pain relief, drugs are classified based on either their chemical structures or on their uses for different classes of medical illnesses. Moreover, some drugs are arranged according to the requirements of people who use them. In other cases, these drugs are listed based on accessibility in a geographical zone, possibly to stop obtaining drugs which are prohibited there.

2.1. Acetaminophen

Acetaminophen (paracetamol) is a common medication to treat fever and pain [11]; this medicine is mostly used for slight and moderate body pain. On the other hand, paracetamol in combination with opioid are used for severe pain, such as pain after surgery [12]. Acetaminophen is used orally or taken intravenously [12] and its effect lasts between 2 and 4 hours. Acetaminophen is classified as slight analgesic [13] and is harmless at the recommended doses [13, 14].

2.2. NSAIDs as analgesics drug

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of medications that provide antipyretic and analgesic effects, and in higher doses have anti-inflammatory potential. They are among the most commonly used analgesics for arthritic pain worldwide. The prominent members of this group of drugs are ibuprofen, aspirin, and naproxen, which are available and used in most countries [15]. Analgesic NSAIDs are nonnarcotic and are used as a nonaddictive alternate to narcotics.

2.3. Archetypal opioids

The archetypal opioids (morphine) and all similar extracts, as well as other opioids, affect the cerebral opioid receptor coordination [16, 17]. Tramadol is a serotonin-norepinephrine reuptake inhibitor (SNRI) through feeble μ -opioid receptor agonist actions, whereas buprenorphine is a partial agonist of the μ -opioid receptor [18]. Tramadol and venlafaxine are structurally very close to codeine that exerts analgesia not by individual opioid-like properties but through less agonism of the μ -opioid receptor and by acting as a serotonin-releasing agent and a norepinephrine reuptake inhibitor [19–22]. Opioids, though very active analgesics, might have certain unfriendly side effects. Those patients starting morphine might experience vomiting and nausea [23].

2.4. Alcohol compounds as analgesics

Alcohol compounds are also documented to treat pain [24]; however, alcohols have biological, mental, and social properties that affect the significance of their use for treatment of pain [25]. Although reasonable usage of alcohol can reduce certain kinds of pain under certain conditions [26], the use of alcohol to cure pain, however, is encountered by the negative effects of extreme drinking [27].

2.5. Cannabis and cannabinoids as analgesic

Cannabis or medical marijuana is related to the use of cannabis and isolated cannabinoids to cure diseases and relieve pain [28]. In addition, cannabis and its compounds are used to treat chronic pain. The best-known analgesic of these cannabinoids for treatment of pain is tetrahydrocannabinol, or the best known as THC [29–31].

In comparison, numerous mixtures of analgesic drugs have been determined to have insufficient effectiveness compared to similar doses of their separate mechanisms. Furthermore, these analgesic mixtures frequently result in consequences such as unintentional overdoses, often owing to misperceptions that arise from the many mentioned compounds and combinations [32]. Countless people use alternative medicine for pain relief. There are indications that some medications relieve some kind of pain more efficiently than others [33]; however, additional research would be essential to improve comprehension of the uses of many alternative medicine [34].

2.6. Plants as new sources of pain killers

Numerous medicinal plants and their derived phytochemicals were evaluated for their analgesic and anti-inflammatory effects. For example, extracts of bark as well as terpenoids obtained from *Combretum molle* (Combretaceae), β -glucopyranosyl, and other isolated compounds have been documented to have an excellent potential against carrageenan-induced paw edema in rats [7]. Similarly, *Millettia versicolor* crude extract and its isolated phytochemicals were found to inhibit 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced acute ear edema and phospholipase A₂ acute mouse paw edema [8]. Furthermore, chemical constituents isolated from various parts of *Millettia griffoniana*, *Erythrina addisoniae*, and *Erythrina mildbraedii* have been reported to exhibit significant anti-inflammatory activity on induced-paw edema and induced-ear edema in mice [8], whereas compounds isolated from *Erythrina sigmoidea* have been shown to possess anti-inflammatory activity against 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced ear edema [8]. Based on the above facts, the present chapter will focus on documenting the recent literature pertaining to medicinal plants and their phytochemicals and extracts as analgesics and in the treatment of inflammation.

2.7. Other natural products with analgesic properties

Natural products play a key role for living organisms. Primary metabolites are defined by Kossel as the main components of metabolic paths that are compulsory for life. Primary metabolites

are related to important cellular roles, such as energy production, assimilation of nutrients, and development/growth. Secondary metabolites, in contrast to primary, are not essential and not required for the survival of living organisms [35–38].

Interestingly, secondary metabolites possess a broad range of functions. They comprise pheromones, which can act as community gesturing molecules with additional individuals of the same species [39–41]. Communication molecules entice and stimulate a symbiotic organism and agents to solubilize and transport various nutrients, including siderophores, as well as good arms such as venoms, repellants, and toxins, which are used as a prey and predators competitors [42]. It has been documented in the literature that nearly 10 million organic compounds have been discovered and many new and novel compounds are still being isolated and characterized in various parts of the world.

Regarding these compounds, one hypothesis is that they present a good benefit to the living organism which makes them. Another view says that these compounds have similarity to the immune system of living organisms, and although they have no function, yet they can afford assorted bioactive compounds which have important biological activity [42].

Naturally obtained agents such as aspirin, morphine, codeine, thebaine, and others have been reported to have analgesic activity. Aspirin derived from salicylic acid extracted from barks of the willow tree (*Salix alba*) is one of the most extensively used compounds for the managements of mild pain. On the other hand, morphine codeine and thebaine isolated from plants are used as analgesics (**Figure 1**) [43, 44].

Different types of active phytochemicals, such as steroids, alkaloids, tannins, phenol, and polyphenols are produced by medicinal plants [45–49]. In addition, a large number of plants that have been investigated are reported to have less pharmacologically active secondary metabolites identified. Plant-derived molecules are mainly reported for their medical importance; this includes morphine, nicotine, quinine, steroidal, and many others [50]. A large number of presently recommended drugs have been derived from natural medicinal plants; some characteristic examples are given in next sections.

2.7.1. Salicin

It has been reported in the literature that extracted natural products possess analgesic activity. The bark of willow trees has been recognized for pain-relieving properties. It has been further reported that willow bark contains a bioactive compound, salicin, which hydrolyses into salicylic acid. As we know that derivative acetylsalicylic acid is known as aspirin and is used as a pain killer, the main mechanism of its action is inhibition of the cyclooxygenase enzyme (COX). There are two types of cyclooxygenase-2 enzyme isozymes; COX-1 (PTGS1) and COX-2 (PTGS2). It is nonselective and permanently inhibits both form, but it is weakly more selective for COX-1. COX produces prostaglandins most of them are pro-inflammatory and thromboxanes, which promote clotting [51].

Nonsteroidal anti-inflammatory drugs (NSAIDs) act via inhibition of cyclooxygenase enzyme (COX). Research findings suggest the opposing effects of nonsteroidal anti-inflammatory

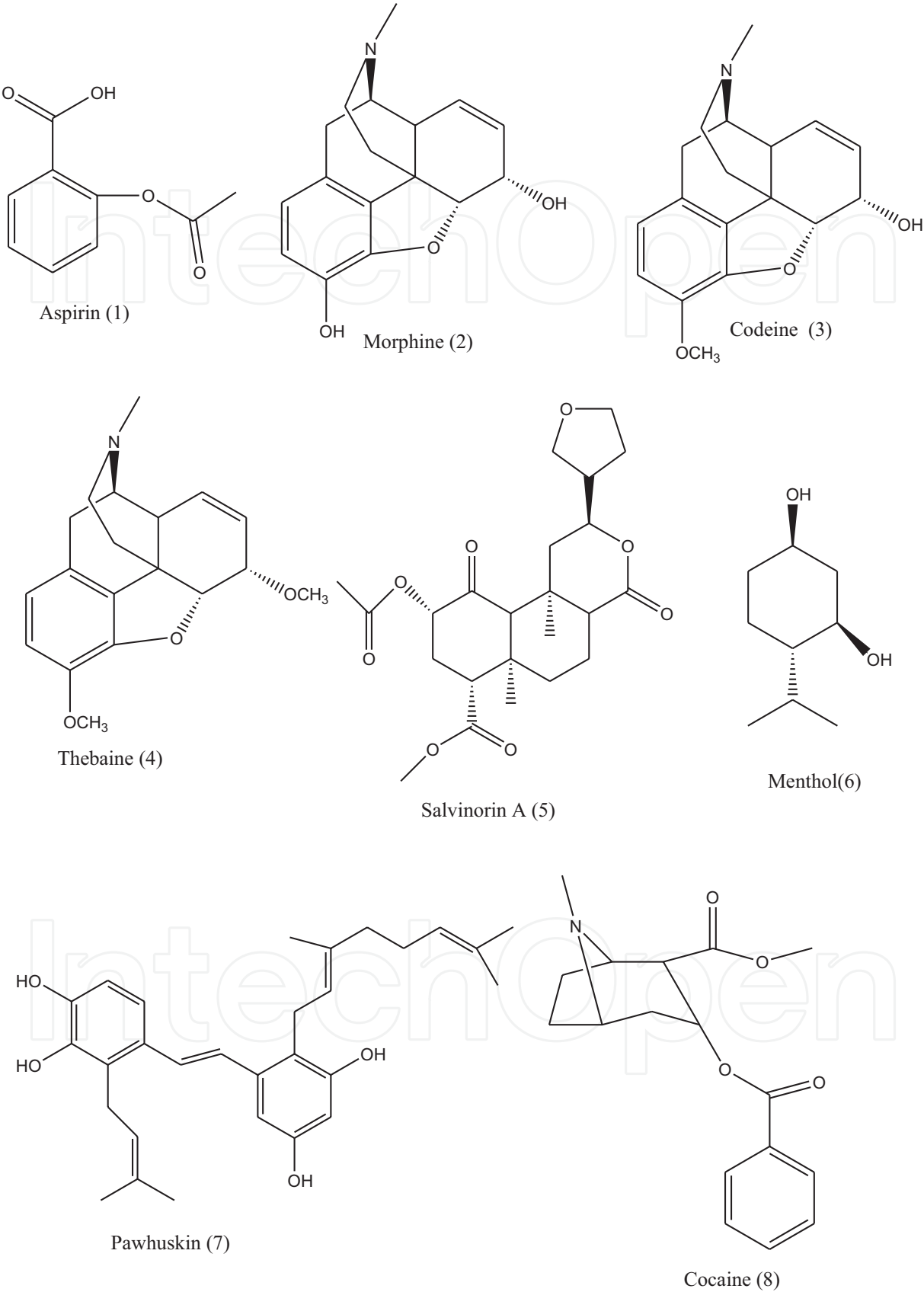


Figure 1. Chemical structures of analgesic compounds from medicinal plants.

drugs on COX. These drugs act by blocking the COX-1 enzyme, which catalyzes the production of prostaglandins that are involved in numerous physiological functions, such as (a) maintenance of normal renal function in the kidneys, (b) mucosal protection in the gastrointestinal tract, and (c) proaggregatory thromboxane in the platelets. However, COX-2 expression can be induced by cytokines and other inflammatory mediators in a number of tissues, including endothelial cells, and is believed to have a role in the mediation of pain, inflammation, and fever. COX-2 agents only inhibit the COX-2 enzyme, whereas traditional NSAIDs block both versions in general [16].

After extensive acceptance of the cyclooxygenase enzyme (COX-2) inhibitors, it was revealed that many of the drugs in this class increase the risk of cardiovascular toxicity, which led to the removal of valdecoxib and rofecoxib, and others. On the other hand, etoricoxib appears comparatively safer to that of noncoxib NSAID diclofenac [17]. It is worth mentioning here that our research group has reported that pistagremic acid, a natural product isolated from *Pistacia integerrima*, can inhibit COX-2 enzyme owing to the hydrogen and hydrophobic contacts to significant active sites of molecule [17].

The key uses of NSAID medication are typically for joint- and spine-related pain. Its mechanism of action is through interaction with pro-inflammatory cytokines interleukin (IL-1a, IL-1b, IL-6) and tumor necrosis factor (TNF- α). Increased absorption of TNF- α is thought to produce the cardinal symptoms of inflammation. These pro-inflammatory cytokines result in chemo-attractants for neutrophils and help them to stick to the endothelial from migration. They also stimulate white cell phagocytosis and the production of inflammatory lipid prostaglandin E₂ (PGE₂). The ability of NSAIDs to interfere with the production of prostaglandin during inflammatory cascade is the major mechanism cited for success of pain of medication. In normal pain, the archidonic pathway proceeds and results in the production of highly reactive mediators that are prostaglandin, prostacycline, histamines, and many others. These mediators cause the start of pain in the body.

2.7.2. Morphine

An additional distinguished example is *P. somniferum*, a flowering poppy that yields opium, which contains a potent narcotic alkaloid constituent called morphine that acts as an opioid receptor [52]. Morphine binds to opioid receptors; molecular signaling activates the receptors to mediate certain actions. μ (Mu) receptors exist in the brain stem as well as in thalamus activation, these receptors result in relief of pain and sedation. Kappa receptor is found in the limbic system, part of forebrain, spinal cord, and brain stem. Activation these receptors result in relief of pain and sedation. Delta receptor found in brain, spinal cord, and digestive tract, stimulation of delta receptor leads to analgesic.

2.7.3. Ziconotide

Ziconotide, also known as SNX-111, is a novel nonopioid analgesic drug. It is a synthetic version of ω -conotoxin MVIIA (ω -MVIIA), which is a peptide that is found in the venom of the fish-eating marine snail, *Conus magus*. It is a powerful analgesic drug that acts through

a mechanism that involves selective block of N-type calcium channels. This action inhibits the discharge of pronociceptive neurochemicals such as glutamate, calcitonin gene-related peptide, and substance P in the brain and spinal cord, ensuing in pain relief. It has been approved for the treatment of severe chronic pain in patients only when administered by the intrathecal route. Importantly, prolonged administration of ziconotide does not lead to the development of addiction or tolerance [53].

2.7.4. *Salvinorin*

Salvinorin A is the main active psychotropic molecule in *Salvia divinorum*, a Mexican plant that has a long history of use as an entheogen by indigenous Mazatec shamans. Salvinorin A is considered a dissociative. It can produce psychoactive experiences in humans with a typical duration of action being several minutes to an hour [54, 55]. Furthermore, Salvinorin is a *trans*-neoclerodane diterpenoid, which acts as a κ -opioid receptor agonist. The mechanism of action of Salvinorin A on ileal tissue has been described as prejunctional, as it was able to adjust electrically made contraction, but not those of exogenous acetylcholine. A pharmacologically important feature of the contraction-reducing properties of ingested Salvinorin A on gut tissue is that it is only pharmacologically active on inflamed and not normal tissue, thus reducing possible side effects. Salvinorin produces a conditioned place aversion and decreases locomotors. It is able to modify dopaminergic pathway [55].

2.7.5. *Pawhuskin A*

Pawhuskin A is a bioactive naturally occurring stilbene reported from *Dalea purpurea*. Pawhuskin A has been recognized to function as an opioid receptor antagonist, with special binding to the κ receptor. Pawhuskin A is the most active natural compound making a small group of nonnitrogenous compounds with effect on the opiate receptor system [56].

3. Conclusions

This chapter has focused on information and relevant literature pertaining to analgesic plants and their explored chemical constituents. Furthermore, unexplored medicinal plants reported to be used in folk medicine have been highlighted. This chapter also provides references to research carried out on analgesic drugs. Additionally, this chapter describes the main mechanisms of action of natural products possessing analgesic properties.

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