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REVIEW ARTICLE: ANALGESIC ACTIVITY OF A POTENTIAL SOURCE OF MODERN MEDICINE

Amrita Asthana and Neeraj Sharma

Department of Pharmacy, Bhagwant University, Rajasthan Sikar Rode, Ajmer - 305004, Rajasthan, India.

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Correspondence to Author:
Amrita Asthana

Ph.D Scholar,
Department of Pharmacy, Bhagwant University, Rajasthan Sikar Rode, Ajmer - 305004, Rajasthan, India.

E-mail: amritaasthanaamh@gmail.com

ABSTRACT: Recently, scientific investigations of medicinal plants using indigenous medical systems have attracted a lot of attention in international investigation. Nature has imparted our planet with an enormous wealth of medicinal plants known for bestowing and are highly esteemed worldwide as a rich source of therapeutic agents for the prevention and cure of diseases and ailments. Since their chemical characterization in the 19th century, herbal bioactive compounds have fueled drug development. Herbal drugs can be potential drugs to replace them. Every year, many plants from the traditional medicinal system may be screened for their potential analgesic activity. Still, only a few of them only included in the health care system after clinical research. So this is time to give more emphasis on research work based on natural sources, investigate the active phytochemical constituents, and use them on a specific treatment.

INTRODUCTION: Plants have been important and basic of preventive and curative health care systems since ancient times. The disease is as old as mankind, and indigenous herbal medicines are a very ancient art and an entire part of treatment [1]. Traditional medicinal herbs have served as a potential source of alternative medicine and different healthcare products. From immemorial time Indian, Chinese, Egyptian, Greek, Roman, and Syrian medicinal system documented the use of different plant-based medicine for different diseases [2]. According to WHO, approximately 75-80% of the world population still depends on herbal medication.

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Active chemical constituents from plant sources directly used as therapeutic agents and phytoconstituents are also provided as lead molecules for synthesizing various drugs [2, 3]. Folk medicine and its use against diseases in different cultures are a vast traditional knowledge based on the necessities, instinct, aim, trial and error, and long experience of immemorial/tribal people [4]. Ayurveda is used to treat inflammation, anaemia, asthma, blood disorders, bronchitis, fever, urinary infection, and splenomegaly diseases [5].

Pain- Pain is a heterogenous phenomenon that accompanies the body's inflammatory response to tissue damage. The immune cells at the injury site actively release chemical mediators that result in vasodilatation, increased vascular permeability, and cellular infiltration [6]. The mechanism is conducive to scavenging necrotic tissue and promoting tissue healing. Pain is rightly defined as a: complex constellation of unpleasant sensory, emotional and cognitive experiences provoked by real or

perceived tissue damage and manifested by certain autonomic, psychological and behavioural reactions [7]. Inhibitory and excitatory pathways modulate the sensory and affective components of pain. Inhibitory neurotransmitters (noradrenaline and serotonin) and drugs (clonidine and dexmedetomidine) act as agonists on α2 adrenoceptors in dorsal horn cells of the spinal cord causing supraspinal analgesia [8]. The latest research has shown that non-steroidal anti-inflammatory drugs (NSAIDS) also facilitate noradrenergic activation of α1, α2C, and β-adrenoceptors in addition to their peripheral anti-nociceptive action [9]. COX inhibitors are an integral part of most analgesic actions. COX enzymes are in two forms, COX-1 and COX-2. COX-1 is constitutive and produces prostanoids essential for physiological processes, including the protection of gastric mucosa. COX-2 is inducible and synthesizes prostanoids that mediate inflammatory actions like pain, fever, tissue injury, and infection. Classic NSAIDs inhibit COX-1 and COX-2 and decrease pain in acute and chronic pain conditions across the entire spectrum of pain severity [10]. However, non-selective inhibition of COX interferes with physiological actions and causes adverse effects like peptic ulcers, platelet dysfunction, helicobacter pylori infection, and nephrotoxicity.

On the other hand, COX-2 inhibitors exhibit fewer gastrointestinal and other side effects but have similar anti-inflammatory, anti-pyretic, and analgesic properties [11]. In inflammatory states, the expression of COX-2 is accentuated centrally and peripherally under the proinflammatory cytokine IL-1-b. COX-2 inhibitors modulate nociception through differential activity at both sites [11]. Zaltoprofen, a preferential COX-2 inhibitor, is a potent anti-inflammatory and analgesic propionic acid derivative with novel anti-nociceptive properties. It decreases PGE2 production by acting at the COX enzyme and inhibits the bradykinin and lipoxygenase pathway of nociception.[12] The B2 receptor-mediated signaling pathway on the primary sensory neurons is attenuated without actual blocking of bradykinin receptors. It has a greater inhibitory effect on bradykinin-induced nociception than other NSAIDs.

Types of pain:

Somatic Pain: caused by the activation of pain receptors in either the body surface, which causes likes abnormalities, inflammation, repetitive trauma, excessive activity, vigorous stretching, and contractions due to paralysis.

Visceral Pain: It is associated with the damage of internal organs and is the most common form of pain, resulting from the activation of pain receptors in the chest, abdomen, and pelvic areas.

Neuropathic Pain: it is caused by injury or malfunction to the spinal cord and peripheral nerves associated with burning, tingling, shooting, stinging, pins and needles.

Acute Pain: acute pain is associated with tissue damage or injury, but usually goes away as the injury heals or the cause of the pain is short-lasting and usually manifests in ways that could be easily described and observed.

Chronic Pain: pain lasting for more than three months and more subjective; treating chronic pain poses a great challenge for physicians as it can change the function and quality of life.

TABLE 1: SOME OF THE COMMONLY USED ANALGESIC DRUGS AND THEIR ADVERSE EFFECT [13, 14, 15]

S. no.	Drug	Adverse Effect
1.	Fentanyl	sedation, sweating, headache, vertigo, lethargy, confusion, light-headedness, nausea, vomiting, respiratory depression
2.	Codeine	sedation, sweating, headache, dizziness, lethargy, confusion, light-headedness
3.	Methadone	light-headedness, dizziness, constipation, respiratory depression, sedation, nausea, vomiting, physical dependence
4.	Morphine sulfate	sedation, hypotension, increased sweating, constipation, dizziness, drowsiness, nausea, vomiting, dry mouth, somnolence, respiratory depression due to acute opioid poisoning, dysphoria
5.	Pentazocine	light-headedness, sedation, constipation, dizziness, nausea, vomiting, respiratory depression, and high doses increase blood pressure and can cause hallucinations, nightmares, dysphoria, tachycardia, dizziness
6.	Buprenorphine	light-headedness, sedation, constipation, dizziness, nausea, vomiting, respiratory depression

TABLE 2: SOME OF PLANT SOURCE WITH ANALGESIC ACTIVITY [16 -26]

S. no.	Botanical Name (Common Name) Family	Part used	Chemical Constituent	Activity
1.	*Sterculia foetida* (Jangli badam) Sterculiaceae	seeds	Fat, cycloprenoid fatty acids.	Antiinflammatory, Analgesics
2.	*Tridex procumbens* (Ghamra) Asteraceae	leaves	flavonoids, procumbentin and quercetin, βsitosterol	Antiinflammatory, Analgesics
3.	*Cissus rependa* (Panibel) Vitaceae	Root, Stem	Alkaloids, glycosides, saponins, tannins.	Antiinflammatory, Analgesic
4.	*Hedyotis puberula* (Surbuli) Rubiaceae	whole plant	Iridoid glycosides	Antiinflammatory, Analgesics
5.	*Eucalyptus citriodora* (lemon eucalyptus) Myrtaceae	essential oil	Terpenes, alkaloids, flavonoids, tannins, eucalyptol.	Antiinflammatory, Analgesics
6.	*Chococca brachiata* Rubiaceae	Root	Steroids, phenolic compounds, ligans	Antiinflammatory, Analgesics
7.	*Tanacetum artemisioides* (Paloyo Zoon)	whole plant	Asteraceae Flavonoids	Antiinflammatory, Analgesics
8.	*Kaempferia galangal* (Aromatic ginger) (Zingiberaceae)	fresh rhizome	ethyl-p-methoxycinnamate, methylcinnamate, Carvone, etc	Antiinflammatory, Analgesics
9.	*Clerodendrum phlomidis* (Arni) Verbenaceae	Stem bark	Alkaloids, glycosides, saponins, tannins	Analgesic
10.	31 *Cynara scolymus* (Globe artichoke) Asteraceae	Leaves	Sesquiterpenes, flavone glycosides, volatile oil.	Antiinflammatory, Analgesics
11.	*Elephantopus scaber* (Elephant foot) Asteraceae	Leaves	Glycosides, stigmasterol, deoxyelephantopin	Antiinflammatory, Analgesics
12.	*Bauhinia racemosa (*Kachnal) Caesalpiniaceae	Stem bark	Flavonoids, saponins, glycosides, tannins	Analgesic
13.	*Mikania glomerata* (sprengel) Asteraceae	Leaves	Coumarins.	Antiinflammatory, Analgesics
14.	*Sida acuta* (Bariara) Malvaceae	whole plant	alkaloids, flavanoids, steroids, tannins, terpenoids	Analgesic
15.	*Toona celiata* (Tun) Meliaceae	Heartwood	Phytosterols, coumarins, carbohydrates.	Analgesic
16.	*Baugainvilla spectabillis* (Booganbel) Nyctaginaceae	Leaves	flavanoids, Alkaloids, tannins, betacyanine, pinitol.	Analgesic
17.	*Ficus glomerata (*Cluster Fig Tree) Moraceae	Bark and leaves	Betasitosterol, lupeol, stigmasterol, leucoanthocyanins.	Analgesic
18.	*Polyalthia longifolia* (Devadaru) Annonaceae	Leaves	Diterpenes, alkaloids.	Analgesic
19.	*Tridax procumbens* (Tridax daisy) Compositae	leaves	Saponins, Alkaloids, Flavanoids, Proteins, Phytosterols,	Analgesic

Alkaloid as Analgesic Used as Medicinal Plants: Crude alkaloids of medicinal plants showed famous analgesic potentials through inhibition of peripheral and central nervous system mechanisms. Further work is required for the isolation of the pharmacologically active constituents. These analgesic activities are associated with many adverse effects like intoxication, which cause physical dependence, tolerance, and addiction. NSAIDs are repeatedly associated with gastrointestinal disorders like gastric or duodenal ulceration [27]. This obligates the discovery of relatively safe alternatives for pain treatment. Medicinal herbs have been used for therapeutic purposes for centuries. Many of these herbs has been used for pain management without any evident adverse effects [28]. Ethno-pharmacologically guided research has brought considerable contributions to new drug development [29, 30]. There was an increasing interest in finding new and safe anti-inflammatory and analgesic drugs from natural sources, including medicinal plants [31]. Medicinal plants had been a very useful source of lead structure for subsequent synthetic modification and optimization of bioactivity. Alkaloids are naturally occurring active, diverse groups of secondary metabolites in plants that have been used in medicine for hundreds of years [32]. Plants like *Woodfordia fruticosa, Adhatoda vasica, Chenopodium ambrosioides, Viburnum*

cotinifolium, Vitex negundo, Peganum harmala and *Broussonetia papyrifera* have been investigated scientifically for the presence of alkaloids regarding their ethnopharmacological profile in pain management [33, 34, 35]. Analgesic activity of alkaloids isolated from plants is reported with different mechanistic approaches [36, 37]. The strong positive correlation of alkaloids in medicinal plants for analgesic activity persuades an intent to determine the possible analgesic activity of total alkaloids extracted from the mentioned medicinal plants using animals' model. Pain management sometimes requires more than one drug therapy. Thus the practice of polypharmacy carries risks of adverse drug reactions and side effects. Therefore, the search for new drugs with the same therapeutic impact with relatively less frequency of side effects is the need of the time [38, 39].

This study helped us understand the possible mechanisms of potential analgesic effects of the test alkaloids that work through inhibition of the central nervous system and peripheral nervous system. The abdominal constriction induced by acetic acid is thought to be due to the involvement of peripheral mechanisms. In contrast, tail immersion test model testing of analgesic activity thought to be due to central mechanisms [40]. Formalin test is used for both peripheral and central mechanisms [41]. The formalin test model is used to investigate the ability to draw peripheral and/ or central analgesic effects as it assays biphasic characteristics, labeled as the early and late phases resulting from formalin administration [42]. The early phases are neurogenic pain resulting from an acute response toward direct action of formalin on nociceptors within the intraplantar region. In contrast, the late phase is considered an inflammatory-mediated pain resulting from a tonic response due to the release of inflammatory mediators [43]. The crude alkaloidal extracts of different medicinal plants get analgesic potentials, possibly through inhibition of central and peripheral pain mediators. The antinociceptive activity confirms traditional uses of the aforesaid medicinal plants for pain management.

CONCLUSION: State-of-the-art clinical intervention studies, that is, randomized, double-blind placebo-controlled trials, are the gold standard for testing whether a substance has a therapeutical or preventive potential; this research area often suffers from either inadequately performed or a low number of studies. In this minireview, we did try not only to pinpoint deficiencies but also to highlight positive developments that will be bright and advance disease prevention or therapy.

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