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Current Neuropharmacology, **2021**, *19*, **553-588**

SYSTEMATIC REVIEW ARTICLE

A Systematic Review of Traditionally Used Herbs and Animal-Derived Products as Potential Analgesics

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Abstract: Pain is a distressing but fundamental manifestation that prepares the body for potentially detrimental stimuli while ensuring its protection. Plant and animal products have traditionally been used to relieve pain for centuries. However, no attempt has been made to compile a single report of plant and animal products possessing analgesic properties. This review enadeavours to recover data from published articles to establish a collective literature review on folk remedies from plant and animal sources used as analgesics and in the treatment of pain-related conditions, identifying gaps in existing knowledge and future works. Relevant information was systematically retrieved using the PRISMA method. In this review, in total, 209 plants were found to be either used raw or prepared by decoctions or maceration. Administration was either oral or topical, and they were predominantly used in Asian countries. *In vivo* studies of plants with analgesic properties, which were tested using different methods including acetic-induced writhing test, hotplate test, tail-flick test, and formalin-induced pain test, were compiled. Animal products with analgesic properties were obtained mainly from compounds present in venom; their bioactive compounds were also identified. In the literature search, certain gaps were noted, which could be reviewed in future studies. For instance, there was a disparity of information regarding the traditional uses of medicinal plants. In this review, an attempt was made to critically assess and describe the pharmacological properties and bioactive composition of indigenous plants, some animal species, and animal venom by scrutinizing databases and looking for published articles. Therefore, it can be concluded that the compounds obtained from these sources can serve as important ingredients in therapeutic agents to alleviate pain once their limitations are assessed and improved upon. In the literature search, certain gaps were noted, which could be reviewed in future studies.

ARTICLE HISTORY

Received: March 22, 2020
Revised: May 10, 2020
Accepted: June 21, 2020

DOI:
10.2174/1570159X18666200808151522

Keywords: Traditional medicine, pain, analgesics, pharmacological, plants, animals.

1. INTRODUCTION

The ubiquitous nature of pain is complex. It entails both the peripheral and central nervous systems with multiple neurotransmitters and receptor-mediated events. In addition, emotional and psychological modifiers participate in the experience [1]. Pain is a distressing but fundamental manifestation that prepares the body for a potentially detrimental stimuli, while ensuring its protection. This notion highlights the biological importance of pain, which is relevant when acute pain is experienced. Basically, acute pain occurs for a short duration and can be attributed to diseases or injury. Nonetheless, pain can also last for a longer duration than the predicted prognosis; this pain is termed chronic or persistent pain. In this condition, pain no longer plays a role as a signal for impeding danger [2].

The International Association for the Study of Pain describes the term "pain" as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Consequently, pain is a term that has evolved from a mono-dimensional to a multidimensional entity entailing several aspects, such as sensors, cognition, motivation, affection, behavior, and spirituality [3]. Pain is often subjected to each individual's perception of their experience related to injury or physical

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1570-159X/21 $65.00+.00

damage. Pain can be classified based on pain physiology, intensity, temporal characteristics, type of tissue affected, and syndrome.

Despite the fact that pain is regarded with such significance, chronic pain is considered a plague. It is quite perplexing to evaluate, manage, and treat it as a multifactorial condition [4]. A statistical report stated that more than 1.5 billion of the global population suffers from this agonizing condition [5]. Regardless of the alarming prevalence of chronic pain, the mechanisms underlying the transition from acute to chronic pain are still unclear. The amplification of pain is multifactorial. Risk factors contributing to the severity of the condition include genetic predisposition, age, gender, previous experience, and attitude toward pain [6]. Some of the most commonly experienced pain-related conditions include back pain, headaches, migraines, angina pectoris, arthritis pain, nerve damage pain, and cancer pain. In other conditions, such as fibromyalgia, patients experience pain at a significantly higher level [7]. Therefore, pain relief and management are a matter of great importance and have been regarded as one of the uttermost human equity.

Moreover, pain can also be trivial and transient; thus, the ascendency and favorable outcomes of folk remedies or conventional methods for its treatment cannot be left unnoticed [8]. Nevertheless, at times, pain may be perpetual, and conventional methods, including opioid and non-opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids, among others, are less potent [9]. Medications commonly used to alleviate pain include drugs such as ibuprofen, naproxen, aspirin, acetaminophen, anti-depressants, and anti-seizure medications [10]. However, conventional therapies have been linked with multiple challenges including long-term efficiency, dosage, and tolerance issues and other side effects [11]. These limitations have led to an increased prevalence of folk remedies as supported by numerous anecdotal accounts [12, 13]. The use of folk remedies in recent times is correlated with psychosocial factors, ethnic and cultural characteristics, accessibility to healthcare resources, and individual perceptions of physical and medical conditions [14]. The most acknowledged therapies used for pain management are herbal remedies.

Herbal medicine has been a tradition for centuries. Some terrestrial plants are considered medicinal owing to their

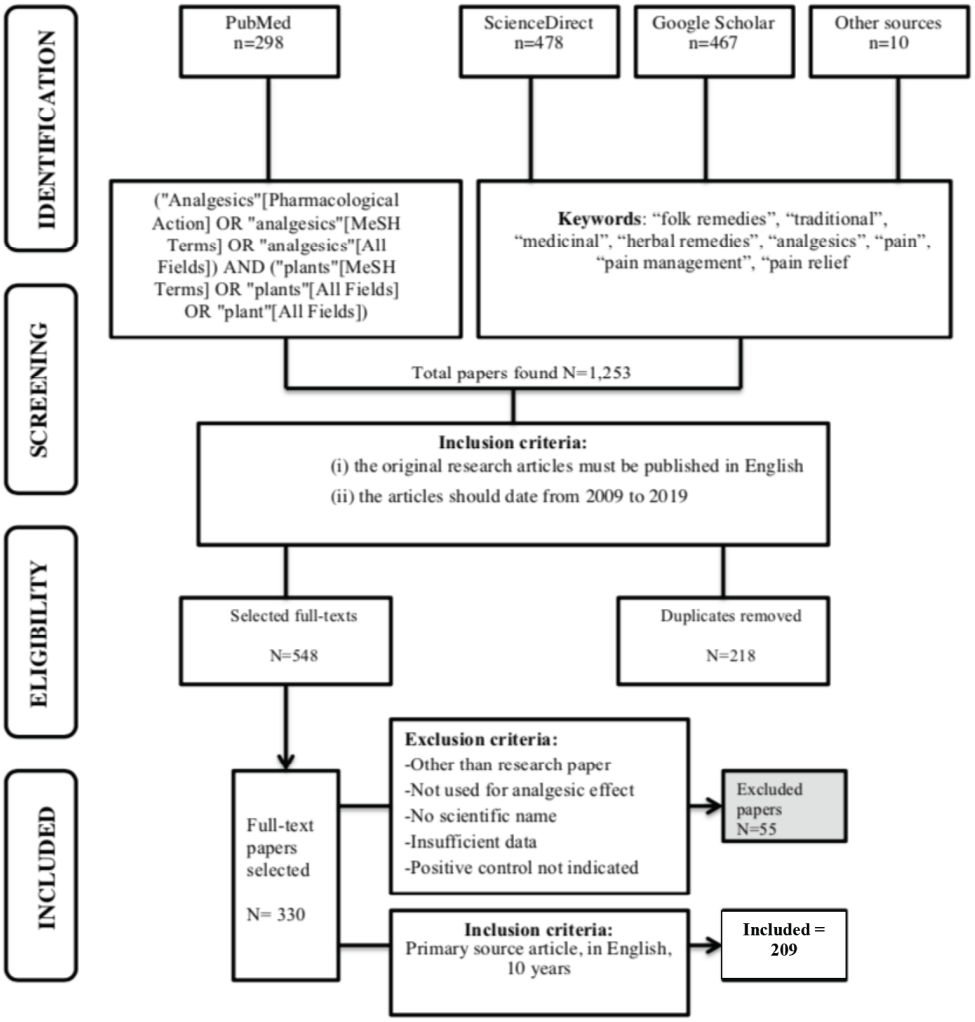

Fig. (1). Flowchart of selection process.

analgesic properties. Some of the most commonly used analgesics from food plant sources are moringa/drumstick (*Moringa oleifera*), guava (*Psidium guajava*), turmeric (*Curcuma longa*), and ginger (*Zingiber officinale*) for abdominal pain; potato (*Solanum tuberosum*) for headache; carrot (*Daucus carota*) for painful urination; and celery (*Apium graveolens*) for labor and joint pain [13, 15-18].

Numerous studies have emphasized the application of countless medicinal plants for pain management in different regions. However, an updated compilation of the available literature on plants, animals, and related products that are used as analgesics across the world as well as their pharmacology is lacking. In this context, we aimed to recover data from numerous published articles to establish a collective literature review on folk remedies from plant and animal sources used as analgesics and in the treatment of pain-related conditions.

2. METHODOLOGY

2.1. Search Strategy

Relevant information was systematically retrieved using the PRISMA method. Databases such as PubMed/Medline, Science Direct, and Google Scholar were scrutinized. Alternate sources, including books, dissertations, and online published material, were considered as well. Scientifically, a plant was identified according to the International Plant Name Index (www.ipni.org) and The Plant List database (theplantlist.org). The main chemical constituents of each plant were identified using the PubChem database. Similarly, potential pain killers from animal origin were searched and their chemical constituents were identified.

Databases were scrutinized using numerous keywords, such as “medicinal plant,” “traditional,” “medicinal,” “herbal remedies,” “analgesics,” “pain,” “pain management,” and “pain relief;” additionally, at times, a combination of keywords was used. The published literature was mainly taken from primary sources. *In vitro*, *in vivo*, and clinical studies were taken into consideration, and the literature search was limited to the English language. The search strategy for Medline (by PubMed) was (“analgesics” [Pharmacological Action] OR “analgesics” [MeSH Terms] OR “analgesics” [All Fields]) AND (“plants” [MeSH Terms] OR “plants” [All Fields] OR “plant” [All Fields]).

2.2. Study selection

Studies were selected according to two inclusion criteria. First, the original research articles must be published in English; second, the articles should date from 2009 to 2019. To ensure consistency, reproducibility of the process, and transparent reporting, the recommendations of the PRISMA statement were followed [19]. The selection process of the articles is represented in a flowchart (Fig. **1**).

2.3. Data Extraction and Description of Sections

In this review, we evaluated the traditional uses, chemical composition, and pharmacological properties of various plants used as analgesics. After screening the articles, the data was extracted and tabulated (Table **1**) with regard to the ethno-pharmacological uses of the medical plants used for pain management; the data included the plant family, scientific name, common name, country, method of preparation/dosage, ailments, and references to provide an overview of the various applications of the plants used for pain relief. Section 3 provides a comprehensive and critical analysis of the pharmacological properties of each plant (Table **2**), with regard to the chemistry and traditional uses.

3. RESULTS AND DISCUSSION

3.1. Traditional Remedies Made with Plants Presenting Analgesic Properties

In ancient times, the diverse population of plants represented medicinal wealth for indigenous people. While searching ways to relieve pain and cure diseases, traditional healers discovered new plants that could serve as analgesics. In total, 209 ethnomedicinal studies demonstrated the different uses of combinations of wild and domestic plants for pain relief, which are summarized in Table **1**. The study results are presented in alphabetical order of plant families, with their respective scientific name, local name, plant parts used, therapeutic use, mode of preparation, and route of administration for ethnomedicinal application. Most methods of preparation involved decoction or maceration; alternatively, the plants were used in their raw form. The administration was either oral or topical. These medicinal plants were used predominantly in Asian countries, such as India, Nepal, Pakistan, Iran, and Myanmar, and African countries (Table **1**).

Accordingly, stomach pain, earache, and joint pain were the most common types of pain that were targeted. As per the study of Bhatia *et al*. [20], *Justicia adhatoda* was used to alleviate headaches using fresh leaves that were topically applied on the forehead. In the same study, when mixed with other medicinal plants, *Justicia adhatoda* was also reported to cure fever, herpes, and pneumonia. Thus, the study showed that plants can have multiple functions by acting at different targets to cure diseases. Recently, Ong *et al*. [21] have identified wild medicinal plant species and evaluated their properties and uses among the local population. The herb *Acorus calamus* was reported to relieve earache and toothache when the rhizome extract is applied as a drop and drunk as a decoction, respectively. Other plants, such as *Sansevieria trifasciata, Spondias pinnata, Chrysanthemum indicum*, *Ananas comosus* (pineapple), *Matricaria chamomilla* (Camomile flower*), Costus speciosus* (Crêpe ginger), *Cuscuta europaea*, and *Cymbidium aloifolium*, were found to alleviate ear pain by the application of ear drops prepared by macerating the parts of the plants [15, 22].

Furthermore, Aloe vera (leaves) juice, Matricaria chamomilla (leaves and aerial part), Calendula officinalis (flower), Fumaria indica (whole plant), Geranium wallichianum (root), Alstonia scholaris (bark and sap), Holarrhena pubescens (bark), [17, 18, 23] have been identified as plants with analgesics effects. Ayyanar and Ignacimuthu [12] categorized and grouped various ailments with regard to the human anatomy, and the associated pain was reported in the different sections: stomachache in general health, earache in ear problems, breast pain as genito-urinary ailments, chest

Table 1. Traditional remedies of plant used to relieve pain.

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Acanthaceae	*Justicia adhatoda* L.	Malabar nut, adulsa, adhatoda, vasa	Headache	India	Leaves	Fresh leaves are placed on forehead	Topical	[20]
Acoraceae	*Acorus calamus* L.	Sweet flag	Earache Toothache	Myanmar	Rhizome	Decoction	Rhizome extract as eardrop Oral	[21]
Agavaceae	*Sansevieria trifasciata* Hort. Ex Prain	Snake plant, mother-in-law's tongue, and viper's bowstring hemp	Earache	India	Stem	Maceration	Ear drops	[15]
Amaranthaceae	*Achyranthes aspera* L.	Chaff-flower, prickly chaff flower, devil's horsewhip	Toothache Abdominal pain	Pakistan	Leaves	Decoction	Oral	[24]
Amaranthaceae	*Aerva lanata* (L.) Juss.	Mountain knotgrass	Angina pectoris	India	Whole plant	Powder	Oral	[12]
Amaranthaceae	*Alternanthera sessilis* (L.) R.Br. ex DC.	Sessile joyweed anddwarf copperleaf	Eye pain	India	Leaf	Juice	Oral	[12]
Amaranthaceae	*Achyranthes aspera* L.	Chaff-flower, prickly chaff flower, devil's horsewhip	Toothache	India	leaves	Cotton soaked in leaf juice	Topical	[20]
Amaranthaceae	*Amaranthus viridis* L.	Slender amaranth or green amaranth.	Labor pain	India	Seeds	Seeds fried in clarified butter are given to pregnant ladies to curb	Topical	[20]
Amaricaceae	*Tamarix arceuthoides* Bunge	Gaz	Myalgia Back pain Hand and foot pain Knee pain	Iran	Stem Leaves	Decoction of mixed herb, Heated on embers	NI	[13]
Amaryllidaceae	*Allium oreophilum* C.A.Mey.	Pink lily leek	Abdominal pain Labour pain	Iran	Leaves Root	Raw	Oral	[13]
Anacardiacea	**Mangifera indica* L.	Mango	Abdominal pain	Nepal	Bark	Crushed	Oral	[17]
Anacardiaceae	*Spondias pinnata* (L.f.) Kurz	Wild (or forest) mango, Amda	Earache	India	Leaves	NI	NI	[22]
Anacardiaceae	**Mangifera indica* L.	Mango	Labor pain	India	Stem bark	Powder and paste	Oral	[12]
Anacardiaceae	*Pistacia atlantica* Desf.	Mt. Atlas mastic tree, Persian turpentine	Back pain Toothache Abdominal pain Arthralgia	Iran	Leaves, Fruits	Decoction, Pulverized, Burned on embers, Smoke Inhalation, Poultice, Liniment, Condensed	Topical	[13]
Anacardiaceae	*Pistacia khinjuk* Stocks	Kasour	Back pain Abdominal pain	Iran	Leaves, Fruits	Raw, Decoction, Pulverized, Poultice	Oral	[13]
Apiacea	*Prangos latiloba* Korovin	Paterk	Abdominal pain	Iran	Leaves, Stem	Raw taken with garlic	Oral	[13]
Apiacea	*Achillea eriophora* DC.	Anboul	Abdominal pain	Iran	Leaves, Stem	Decoction, Maceration, Pulverized	Oral	[13]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Apiaceae	**Foeniculum vulgare* Mill.	Fennel	Angina pectoris Renal pain	India	Seeds	Seeds boiled in milk	Oral	[23]
Apiaceae	**Daucus carota* L.	Carrot	Dysuria		Root	Extract	NI	[18]
Apiaceae	**Apium graveolens* L.	Celery	Arthralgia Myalgia Abdominal pain Labor pain	Iran	Aerial parts, Leaves, Seeds	Decoction, Pulverised, Poultice, Infusion	Topical	[13]
Apiaceae	*Bunium persicum* (Boiss.) B. Fedtsch.	Great pignut, black zira, earthnut	Toothache Renal pain Abdominal pain	Iran	Flower, Seeds	Decoction, Pulverised, Poultice Bath, Liniment	Topical	[13]
Apiaceae	*Dorema ammoniacum* D. Don	Poushk Oshterk	Toothache Renal pain	Iran	Aerial parts, Leaves	Decoction, Pulverised, Poultice	Topical	[13]
Apiaceae	*Ducrosia anethifolia* (DC.) Boiss.	Goatak	Abdominal pain Headache Renal pain Foot pain	Iran	Aerial parts, Leaves, Fruits	Decoction, Infusion, Pulverised,	Topical	[13]
Apiaceae	*Achillea wilhelmsii* K.Koch	Berenjask	Abdominal pain	Iran	Aerial parts, Leaves, Fruits	Decoction, Maceration, Pulverised	Topical	[13]
Apiaceae	*Acroptilon repens* (L.) DC.	Russian knapweed	Hands and foot pains	Iran	Aerial parts	Heated on embers	Topical	[13]
Apiaceae	*Artemisia deserti* Krasch.	Drannag	Abdominal pain	Iran	Aerial parts, Leaves, Flower	Decoction, Maceration, Pulverised	Topical	[13]
Apiaceae	*Cousinia pseudomollis* C. Winki	Polouah	Headache, Hand and Foot pain	Iran	Aerial parts	Vapour bath	Topical	[13]
Apiaceae	*Echinops endotrichus* Rech.f.	Chazhou	Abdominal pain	Iran	Rhizome	Decoction	Topical	[13]
Apiaceae	*Pulicaria gnaphalodes* (Vent.) Boiss.	Boumadran	Abdominal pain	Iran	Aerial parts	Decoction, Infusion, Raw, Maceration, Liniment	Topical	[13]
Apiaceae	*Dorema ammoniacum* D.Don	Poushk Oshterk	Toothache Renal pain	Iran	Aerial parts, leaves	Decoction, Infusion, Raw,	Oral	[13]
Apiaceae	*Ducrosia anethifolia* (DC.) Boiss.	Goatak	Abdominal pain Headache Renal pain Foot pain	Iran	Aerial parts, leaves, fruits, seeds	Decoction, Infusion, Pulverised	Topical	[13]
Apiaceae	*Scorzonera tortuosissima* Boiss.	Marooba	Abdominal pain	Iran	Aerial parts, leaves	Raw	NI	[13]
Apiaceae	*Centella asiatica* (L.) Urb.	Centella	Myalgia	Nepal	Leaves	Crushed	Oral	[17]
Apocynaceae	*Alstonia scholaris* (L.) R. Br.	Blackboard tree, devil tree, ditabark, milkwoodpine, saptparni, shaitan tree, white cheesewood	Myalgia Back pain	Nepal	Bark and sap	Bark placed into water and slightly cut stem to get sap	Oral	[17]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Apocynaceae	*Holarrhena pubescens* Wall. ex G.Don	Big tiger milk	Myalgia Abdominal pain	Nepal	Bark	Dry, pulverize and mix with water	Oral	[17]
Apocynaceae	*Calotropis gigantean* (L.) Dryand	Crown flower	Myalgia	Nepal	Latex, leaves, bark, stem and root	Crushed	Topical	[17]
Apocynaceae	Carissa carandas L.	Kalakkai	Abdominal pain	India	Fruit	Pickle	Oral	[12]
Araceae	*Rhaphidophora peepla* (Roxb.) Schott	Mini Monstera	Toothache	Myanmar	Leaves	Boil leaves and gargle	Gargle	[21]
Asclepiadaceae	*Calotropis procera* (Aiton) Dryand	Apple of Sodom, king's crown, rubber tree	Arthralgia	India	Leaves	Leaves soaked in hot mustard oil are fastened on joints	Topical	[20]
Asphodelaceae	**Aloe vera* (L.) Brum.	Aloe vera	Myalgia	Nepal	Leaves	Pound and drink juice	Oral	[17]
Asteraceae	*Chrysanthemum indicum* L.	Indian chrysanthemum	Earache	India	Leaves	Maceration	Ear drops	[15]
Asteraceae	*Arctium lappa* L.	Greater burdock	Myalgia	India	Leaves, Root	Paste	Topical	[23]
Asteraceae	*Taraxacum campylodes* G.E.Haglund	Common dandelion	Labor pain	India	Leaves	Cooked as vegetables and given to pregnant ladies	Oral	[23]
Asteraceae	*Taraxacum campylodes* G.E.Haglund	Common dandelion	Labor pain	India	Leaves	Cooked	Leaves are cooked as vegetable and given to pregnant ladies at the time of delivery for reducing labour pains	[18]
Asteraceae	*Achillea nobilis* L.	Noble yarrow	Dysmenorrhea	India	Aerial parts	Infusion	Oral	[18]
Asteraceae	*Artemisia maritima* L.	Sea wormwood, old woman	Arthralgia	DeosaiPlateau	Leaves	Infusion	Oral	[25]
Asteraceae	*Erigeron multiradiatus* var. *multiradiatus*	Himalayan fleabane	Abdominal pain	DeosaiPlateau	Leaves	Paste	Oral with water	[25]
Asteraceae	*Matricaria chamomilla* L.	Chamomille	Myalgia	Deosai Plateau	Leaves Aerial part	Paste Infusion	Oral	[25]
Asteraceae	*Achillea millefolium* L.	Common yarrow	Toothache	India	Root	Cotton soaked in fine root paste	Topical	[20]
Berberidaceae	*Berberis integerrima* Bunge	American barberry or Allegheny barberry	Myalgia	Iran	Fruit	Tablets, Mashed, Condensed	Oral	[13]
Bignoniaceae	*Millingtonia hortensis* L.f.	Indian cork tree	Abdominal pain	India	Root	Maceration	Oral	[15]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Bignoniaceae	*Oroxylum indicum* L. Kurz	Midnight horror, oroxylum, Indian trumpet flower, broken bones	Myalgia	Nepal	Bark	Crushed	Topical	[17]
Bombacaceae	*Bombax ceiba* L.	Red cotton tree	Abdominal pain	Nepal	Resin, bark and root	Crushed	Oral	[17]
Boraginaceae	*Alyssum meniocoides* Boiss.	Espantan koohi	Angina pecto-ris	Iran	Fruits	Decoction, Infu-sion	NI	[13]
Boraginaceae	*Clypeola jonthlaspi* L.	Toutary	Abdominal pain, Angina	Iran	Fruits	Decoction, Infu-sion	NI	[13]
Boraginaceae	*Descurainia Sophia* (L.) Webb ex Prantl	Flixweed,herb-Sophia and tansy mustard	Abdominal pain	Iran	Seeds	Syrup	Oral	[13]
Brassicaceae	*Descurainia Sophia* (L.) Webb ex Prantl	Flixweed,herb-Sophia and tansy mustard	Myalgia	India	Whole plant, seeds	Whole plant decoction Seeds powder	Oral	[23]
Brassicaceae	*Megacarpaea poly-andra* Benth.	Barmoola	Abdominal pain	India	Roots	NI	NI	[22]
Brassicaceae	*Lepidium sativum* L.	Garden Cress	Labor pain	India	Seeds	Seed decoction in milk and clarified butter curbs	Oral	[20]
Bromeliaceae	**Ananas comosus* (L.) Merr.	Pineapple	Earache	India	Leaves	Maceration	Ear drops	[15]
Buxaceae	*Sarcococca saligna* var. chinensis Franch.	Sweet box or Christmas box	Arthralgia	India	Roots	NI	NI	[22]
Caesalpiniaceae	*Cassia tora* L.	Sickle Senna	Abdominal pain	India	Seeds	Seeds taken with water Relieve side stomach pain	Topical	[20]
Cannabaceae	*Cannabis sativa* L.	Cannabis	Myalgia	India	Leaves	Juice	Leaf juice obtained after crushing leaves is spread on a cloth which is then tied around limbs to relieve severe pain	[23]
Caricaceae	*Carica papaya* L.	Papaya, Pawpaw	Abdominal pain	India	Root	Maceration	Topical	[15]
Chenopodiaceae	*Chenopodium album* L.	Lamb's quarters, melde, goosefoot, manure weed, and fat-hen	Abdominal pain	Pakistan	Whole plant	Cooked juice	Oral	[24]
Chenopodiaceae	*Chenopodium album* L.	Lamb's quarters, melde, goosefoot, manure weed, and fat-hen	Arthralgia	Nepal	Tender shoots, whole plant	Pound	Oral	[17]
Combretaceae	*Terminalia bellirica* (Gaertn.) Roxb.	Bahera or beleric or bastard myrobalan, Aksh	Headache	Nepal	Fruit, leaves	Roast (fruit) and pound (leaves and bark)	Oral	[17]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Combretaceae	*Terminalia chebula* Retz.	Black-or chebulic myrobalan	Headache	Nepal	Fruit, leaves and bark	Roast (fruit) and pound (leaves and bark)	Oral	[17]
Compositae	*Artemisia indica* Willd.	Artemisia indica	Headache	Nepal	Leaves	Pound	Oral	[17]
Compositae	*Calendula officinalis* L.	Calendula	Myalgia	Italy	Flower	Poultices	NI	[17]
Convolvulaceae	*Datura Stramonium* L.	Jimsonweed or devil's snare, hell's bells, devil's trumpet, devil's weed, *tolguacha*, Jamestown weed, stinkweed, locoweed, pricklyburr, devil's cucumber	Knee pain	India	Leaves	Paste	Topical	[26]
Convolvulaceae	*Cuscuta capitata* Roxb.	Cuscuta capitata	Angina pectoris	India	Whole plant	Juice	Oral	[23]
Convolvulaceae	*Ipomoea carnea* Jacq.	Pink morning glory	Arthralgia	India	Leaves	Leaves soaked in hot mustard oil are fastened	Topical	[20]
Convolvulaceae	*Convolvulus arvensis* L.	Lesser bindweed, European bindweed, small-flowered morning glory, creeping jenny, and possession vine	Angina pectoris	Iran	Aerial parts, leaves	Decoction, Infusion	NI	[13]
Costaceae	*Costus speciosus* (J.Koenig) Sm.	Crêpe ginger	Earache	India	Stem	Maceration	Ear drops	[15]
Crassulaceae	*Sedum quadrifidum* Pall.	Sooru	Headache Abdominal pain	India	Tender shoots	NI	NI	[22]
Crassulaceae	*Rhodiola imbricata* Edgew	Rhodiola imbricata	Headache	Deosai Plateau	Root	Powder	Oral with milk	[25]
Crassulaceae	*Sempervivum tectorum* L.	Sopravvivo	Headache	Italy	Aerial part	Used to be beaten and placed on the brow with a handkerchief	NI	[17]
Cucurbitaceae	**Luffa cylindrical* (L.) M.Roem.	Smooth luffa, Egyptian luffa, dishrag gourd, gourd loofa	Arthralgia	India	Leaves	Maceration	Topical	[15]
Cucurbitaceae	**Luffa cylindrical* (L.) M.Roem.	Smooth luffa, Egyptian luffa, dishrag gourd, gourd loofa	Abdominal pain	India	Fruit	Boiled with milk	Oral	[18]
Cucurbitaceae	*Solena heterophylla* Lour.	Creeping Cucumber	Toothache Arthralgia	Nepal	Leaves, fruit and root	Crushed	Oral	[17]
Cucurbitaceae	*Bryonia multiflora* Boiss.	Bryony	Bladder pain	Iran	Fruits	Poultice	NI	[13]
Cucurbitaceae	*Citrullus colocynthis* (L.) Schrad.	Colocynth, biter apple, bitter cucumber, desert gourd, wild gourd, vine of Sodom	Hand and foot pain Arthralgia Toothache	Iran	Aerial part, leaves, fruits, seeds	Poultice, Liniment	NI	[13]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Cupressaceae	*Juniperus communis* L.	Common juniper	Causalgia	Pakistan	Fruit	Powder	NI	[27]
Cuscutaceae	*Cuscuta europaea* L.	Greater dodder	Earache	India	Stem	NI	NI	[22]
Dilleniaceae	*Dillenia pentagyna* Roxb.	Dillenia pentagyna	Myalgia	Nepal	Bark	Dry and grind	Oral	[17]
Dioscoraceae	*Dioscorea alata* L.	Purplpe yam, Ube	Abdominal pain	Myanmar	Root	Crushed root	Topical	[21]
Dioscoreaceae	*Dioscorea esculenta* (Lour.) Burkill	Lesser yam	Causalgia	West Bengal	Tuber roots	Apply grated tuber on swellings	Topical	[27]
Dipsaceae	*Scabiosa olivieri* Coult.	Brik dal	Foot pain Knee pain	Iran	Aerial parts	Decoction	Topical	[13]
Ebenaceae	*Diospyros cordifolia Roxb*	Rajaan	Toothache	-	Twig	Brushing teeth with twig	Topical	[20]
Ephedraceae	*Ephedra intermedia* Schrenk & C.A.Mey.	Houmok Khoumok	Abdominal pain	Iran	Aerial parts	Decoction, Poultice, Pulverised, Condensed	Oral	[13]
Ericaceae	*Rhododendron campanulatum* D. Don	Shamru	Myalgia Throat pain	India	Flowers and roots	NI	NI	[22]
Euphorbiaceae	*Justicia gendarussa* Burm.f.	willow-leaved justicia	Renal pain	India	Leaves	Paste	Topical	[26]
Euphorbiaceae	*Ricinus communis* L.	castor bean or castor oil plant	Arthralgia, Myalgia	India	Seed	Raw	Topical	[12]
Euphorbiaceae	*Ricinus communis* L.	castor bean or castor oil plant	Arthralgia	India	Leaves	Leaves soaked in hot mustard oil are fastened on joints	Topical	[20]
Euphorbiaceae	*Phyllanthus emblica* L.	Emblic, India gooseberry, Malacca tree, amla, amalaki	Abdominal pain Headache	Nepal	Fruit, leaves, stem and root	Crushed	Oral	[17]
Euphorbiaceae	*Phyllanthus emblica L.*	Emblic, India gooseberry, Malacca tree, amla, amalaki	Abdominal pain Headache	Nepal	Fruit, leaves, stem and root	Crushed	Oral	[17]
Fabaceae	*Alysicarpus vaginalis* (L.) DC.	Alyce clover, buffalo clover, buffalo-bur, one-leaf clover, and white moneywort	Abdominal pain	India	Whole plant	Maceration	Topical	[15]
Fabaceae	*Mimosa pudic* L.	Sensitive plant, sleepy plant, action plant,Dormilones, touch-me-not, shameplant, zombie plant, or shy plant	Dysuria	Myanmar	Whole plant	Decoction	Oral	[21]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Fabaceae	*Clitoria ternatea* L.	Asian pigeonwings, bluebellvine, blue pea, butterflypea, cordofan pea and Darwin pea	Throat pain	India	Leaf	Paste	Oral	[12]
Fabaceae	*Alhagi pseudalhagi* (M.Bieb.)	Taranjabi	Bladder pain	Iran	Stem, Seeds	Decoction, Mix with milk, Infusion, Poultice	Oral	[13]
Fabaceae	*Astragalus fasciculifolius* Boiss	Gonjed	Abdominal pain Toothache	Iran	Stem, Seeds	Decoction, Mix with milk, Infusion, Poultice	NI	[13]
Fabaceae	*Astragalus podolobus* Boiss	Katek	Abdominal pain	Iran	Aerial parts, Leaves, Flower	Decoction, Raw	Oral	[13]
Fabaceae	*Glycyrrhiza glabra* L.	Liquorice	Hand and foot pains	Iran	Aerial parts, Flower	Decoction, Pulverised	Topical	[13]
Fabaceae	*Sophora alopecuroides* L.	Kor, Sophora	Renal pain	Iran	Aerial parts, Leaves	Decoction, Pulverised	Oral	[13]
Fagaceae	*Quercus leucotrichophora* A. Camus	Banjh oak, Banj	Toothache	India	Bark	Decoction	Topical	[20]
Fumariaceae	*Corydalis cornuta* Royle	*Corydalis cornuta*	Abdominal pain	India	Leaves, roots,	NI	NI	[22]
Fumariaceae	*Fumaria indica* (Haussk.) Pugsley	Fumitory or fumewort	Myalgia	India	Whole plant	Filtrate	The filtrate is used for bathing to cure rheumatic pain	[18]
Fumariaceae	*Fumaria asepala* Boiss.	Shah tare	Abdominal pain	Iran	Aerial parts, Leaves, Flower	Decoction		[13]
Gentianaceae	*Gentiana kurroo* Royle	Gentiana kurroo	Abdominal pain	Pakistan	Flower	Infusion	Oral	[25]
Geraniaceae	*Geranium wallichianum* D.Don ex Sweet	Geranium	Myalgia	India	Root	Herbal tea prepared from roots curbs	Oral	[23]
Labiatae	*Colebrookea oppositifolia* Sm.	Colebrookea oppositifolia	Myalgia	Nepal	Leaves, tender shoots and root	Pound	Topical	[17]
Labiatae	*Ocimum sanctum* L.	Holy basil, *tulasi*	Throat pain	Nepal	Leaves	Crushed	Topical	[17]
Labiatae	*Pogostemon benghalensis* (Burm.f.) Kuntze	Pogostemon	Headache	Nepal	Leaves	Crushed	Inhale	[17]
Lamiaceae	*Clinopodium vulgare* L.	Wild basil	Abdominal pain	India	Leaves, Flowers	Powder	Oral	[23]
Lamiaceae	*Ocimum tenuiflorum* L.	Holy basil, *tulasi*	Headache	Myanmar	Leaves, Fruits	Boil leaves and fruits	Eat boiled leaves and fruit	[21]
Lamiaceae	*Leucas aspera* (Willd.)	Thumba	Eye pain	India	Leaf	Paste	Oral Topical	[12]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Lamiaceae	*Isodon rugosus* (Wall. Ex Benth.) Codd	Isodon	Toothache	Pakistan	Dried leaves	Dried	Oral	[25]
Lamiaceae	*Ajuga bracteosa* Benth.	Bugleweed, ground pine, carpet bugle, bugle	Headache	India	Leaves	Crushed	Topical	[20]
Lamiaceae	*Colebrookea oppositi-folia* Sm.	Colebrookea, Chitti Suaali	Arthralgia Myalgia	India	Leaves	Leaves soaked in hot mustard oil are fastened on the affected part	Topical	[20]
Lamiaceae	*Vitex negundo* L.	Chinese chaste tree	Toothache	India	Twig	Brushing teeth with twig checks	Topical	[20]
Lamiaceae	*Marrubium anisodon* K.Koch	Hoarhound, Esped rosh, Kharek barei	Abdomial pain Headache Hand and Foot pain	Iran	Aerial parts, Leaves, Flower	Decoction, Poul-tice, Heat	Topical	[13]
Lamiaceae	*Mentha longifolia* (L.) L.	Horse mint	Abdomial pain, Hands and Foot pain Renal pain Labor pain	Iran	Aerial parts, Leaves, Flower	Decoction, Poul-tice, Heat Raw, Vapour bath	NI	[13]
Lamiaceae	*Rydingia persica* (Burm.f.) Scheen	Golder	Hand and Foot pain	Iran	Aerial parts, Leaves, Flower	Decoction, Mac-eration, Pulverised	NI	[13]
Lamiaceae	*Perovskia atriplicifo-lia* Benth.	Russian sage	Abdominal pain Hand and Foot pain	Iran	Aerial parts, Leaves, Flower	Decoction, Poul-tice	NI	[13]
Lamiaceae	*Salvia macrosiphon* Boiss.	Mor danag	Abdomial pain, Hands and Foot pain Renal pain Labor pain	Iran	Aerial part, Seeds, Leaves	Decoction, Poul-tice, liniment	NI	[13]
Lamiaceae	*Salvia mirzayanii* Boiss.	Mor	Abdomial pain	Iran	Leaves	Decoction, Poul-tice, Maceration	NI	[13]
Lamiaceae	*Salvia rhytidea* Benth	Mor	Abdomial pain	Iran	Leaves	Decoction	NI	[13]
Lamiaceae	*Ziziphora clinopoides* Lam.	Gole lala, Chai ka	Abdomial pain, Headache	Iran	Aerial parts, Leaves, Flower	Decoction, Infu-sion	NI	[13]
Lamiaceae	*Ziziphora tenuior* L.	Chahi ka	Abdomial pain	Iran	Aerial parts	Infusion	Oral	[13]
Lamiaceae	*Salvia macrosiphon* Boiss.	Mor danag	Abdomial pain, Angina pectoris	Iran	Aerial part, Seeds	Decoction, Poul-tice, Liniment	Oral	[13]
Lamiaceae	*Salvia mirzayanii* Rech.f.	Mor	Abdomial pain, Hands and Foot pain Renal pain Labor pain	Iran	Leaves	Decoction, Poul-tice, Maceration, Pulverised	Oral	[13]
Lauraceae	*Litsea cubeba* (Lour.) Pers.	Mountain pepper	Abdomial pain	Myanmar	Fruits, seeds	Powder	Oral	[21]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Leguminosae	*Mimosa rubicaulis* Lam.	Mimosa rubicaulis	Back pain Throat pain	Nepal	Tender and root	Crushed	Topical	[17]
Liliaceae	**Allium sativum* L.	Garlic	Arthralgia	India	Bulb, seeds	Cooked	Seeds deep-fried in ghee are eaten to curb arthralgia.	[18]
Liliaceae	*Aloe barbadensis* L.	Aloe vera	Headache	India	Leaves	NI	Latex is applied on forehead to get relief from headache	[18]
Liliaceae	**Allium sativum* L.	Garlic	Arthralgia	India	Bulbs	Curry prepared	Oral	[20]
Lythraceae	*Lagerstroemia hy-poleuca* Kurz	Andaman Crape Myrtle	Abdomial pain	India	Leaves	Paste	Topical	[15]
Lythraceae	*Leucas aspera* (Wild.) Link	Thumba	Myalgia	India	Leaves	Paste	Topical	[26]
Lythraceae	*Woodfordia fruticosa* (L.) Kurz	Dhataki	Abdomial pain	Nepal	Flower	Crushed	Oral	[17]
Magnoliaceae	*Michelia champaca* L.	Champak	Eye pain	India	Leaf	Decoction	Topical	[12]
Meliaceae	*Azadirachta indica* A.Juss	Neem, nimtree or Indian lilac	Myalgia	India	Seed	Maceration	Topical	[15]
Meliaceae	*Melia azedarach* L.	Chinaberry tree, cape lilac, Pride of India, bead tree, Persian lilac, Syringa berry tree	Abdominal pain	India	Leaf, stem	Juice Paste	Oral Topical	[12]
Meliaceae	*Melia azedarach* L.	Chinaberry tree, cape lilac, Pride of India, bead tree, Persian lilac, Syringa berry tree	Headache	India	leave	Leaves are stitched to make a cap and worn on head	Topical	[20]
Moraceae	*Ficus religiosa* L.	Sacred Fig, Bodhi tree, Bodhi tree, pippala tree, peepul tree, peepal tree, ashwattha tree	Angina pectoris	India	Leaf	Powder	Oral	[12]
Moraceae	*Ficus racemosa* L.	Cluster fig, Indian fig tree, goolar fig	Abdominal pain	Nepal	Plant sap, resin	Cut stem slightly	Oral	[17]
Moraceae	*Morus nigra* L.	Shah toot	Abdominal pain	Iran	Leaves, Fruits	Raw, Decoction, Infusion, Pulver-ised	-	[13]
Moringaceae	**Moringa oleifera* L.	Moringa, drumstick tree, horseradish tree, ben oil tree	Abdominal pain	India	Root	Maceration	Oral	[15]
Myrtaceae	*Premna barbata* Wall.	*Premna barbata*	Headache	India	Raw fruit	Applied on fore-head	Topical	[20]
Myrtaceae	**Psidium guajava* L.	Common guava, lemon guava, yellow guava	Abdominal pain,	Nepal	Leaves and bark	Boil	Oral	[17]
Myrtaceae	**Syzygium cumini* (L.) Skeels	Jambolan, Java plum, black plum	Abdominal pain	Nepal	Fruit, seed and bark	Dry (fruit) and pound (bark)	Oral	[17]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Nitrariaceae	*Peganum harmala* L.	Espantan, Doudny	Abdominal pain, Toothache Hand and Foot pain	Iran	Aerial part, Leaves, Fruits	Decoction, Maceration, Pou, Raw, Pulverised,	NI	[13]
Nyctaginaceae	*Mirabilis jalapa* L.	Marvel of Peru, Galwasi	Myalgia	India	Leaves	Boiled leaves are eaten to reduce body pains	Oral	[20]
Orchidaceae	*Cymbidium aloifolium* (L.) Sw.	*Cymbidium aloifolium*	Earache	India	Leaves	Maceration	Ear drops	[15]
Oxalidaceae	*Oxalis corniculata* L.	Creeping woodsorrel, procumbent yellow sorrel, sleeping beauty	Myalgia	Nepal	Whole plant	Crushed	Oral	[17]
Paeonaceae	*Paeonia emodi* Wallich ex Royle	Dhandra, Chandra	Abdominal pain	India	Leaves, flowers and fruits	NI	NI	[22]
Papaveraceae	*Fumaria indica* (Hausskn.) Pugsley	Fumitory	Myalgia	India	Whole plant, leaves	Decoction	Decoction of the aerial parts is filtered and the filtrate is used for bathing	[23]
Papilionaceae	*Indigofera heterantha* Brandis	Himalayan indigo	Angina pectoris	Pakistan	Rhizome	Powder	Oral	[24]
Papilionaceae	*Oxytropis lapponica* (Wahl.)	*Oxytropis lapponica*	Arthralgia	Pakistan	Aerial parts	Decoction	Oral	[25]
Phytolaccaceae	*Rivina humilis* L.	Dogblood	Dysmenorrhea	Jamaica	Whole plant	Decoction	Oral	[16]
Pinaceae	*Pinus kesiya* Royle ex Gordon	Khasi pine, Benguet pine, three-needle pine	Abdominal pain Toothache	Myanmar	Wood resin	Powder	Topical	[21]
Pinaceae	*Cedrus libani* A.Rich.	Cedar of Lebanon, Lebanon cedar	Abdominal pain	India	Resin, seeds	Cataplasm Decoction Smear	Topical	[18]
Piperaceae	*Piper betle* L.	Betel leaves, paan	Myalgia	India	Leaves	Maceration	Oral	[15]
Piperaceae	**Piper clematis* Trel.	Pepper	Toothache	Myanmar	Leaves	NI	Chew fresh leaves	[21]
Poaceae	*Cynodon dactylon* (L.) Pers.	Bermuda grass, *Dhoob,* dog's tooth grass, scutch grass	Myalgia		Whole plant	Decoction	Oral	[12]
Poaceae	*Stipa arabica* Trin.	Vasht, Kok Kartek	Hand and Foot pain	Iran	Aerial part	Heat	NI	[13]
Polygonaceae	*Persicaria hydropiper* (L.) Delarbre	Marshpepper knotwood	Dysmenorrhea	India	Leaves, stem	Leaves extract	Oral	[23]
Polygonaceae	*Rheum ribes* L.	Pil goshk	Arthralgia, Kidney pain	Iran	Leaves, stem	Raw, Pulverised, Decoction	NI	[13]
Polygonaceae	*Persicaria amphibia* (L.) Delarbre	Chusmin	Abdominal pain	Pakistan	Leaves	Infusion	Oral	[25]
Pteridaceae	*Adiantum capillus-veneris* L.	Siah lengok	Hand and Foot pains	Iran	Aerial parts, Leaves	Decoction, Infusion	Topical	[13]
Pteridaceae	*Pteropyrum aucheri* Jaub.	Karvankosh, Patont	Abdominal pain, Foot pains	Iran	Aerial parts, Leaves, fruits, flower	Decoction, Maceration, Pulverised, Poultice, Condensed	NI	[13]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Ranunculaceae	*Aquilegia pubiflora* Wall. ex Royle	Domba	Toothache	Pakistan	Dried root	Dried	Topical	[25]
Rhamnaceae	*Rosa beggeriana* Fisch	Khar golok	Abdominal pain	Iran	Stem, Fruits	Tablets, Condensed	Oral	[13]
Rhamnaceae	*Amygdalus scoparia* Spach	Goatam	Hand and Foot pain	Iran	Leaves, Fruits	Decoction, Infusion, Bath, Poultice	Topical	[13]
Rosaceae	*Prunus armeniaca* L.	Apricot	Arthralgia	India	Seeds	Seeds along with kernel are burnt to ash	Topical	[23]
Rosaceae	*Rubus ellipticus* Sm.	Golden Himalayan raspberry, yellow Himalayan raspberry	Abdominal pain	Nepal	Root	Crushed	Oral	[17]
Rubiaceae	*Adina cordifolia* (Roxb.) Hook. f.	Kadam	Eye pain	Nepal	Tender leaves and bark	Crushed	Oral	[17]
Rubiaceae	*Gaillonia macrantha* Blatt.	Toso Bodako Khar tos	Abdominal pain, Renal pain	Iran	Aerial part, Leaves, Flower,	Decoction, Pulverised, Infusion	Oral	[13]
Rutaceae	*Citrus medica* L.	Citron	Arthralgia, Headache	India	Fruit	Paste	Topical	[15]
Rutaceae	*Murraya koenigii* (L.) Spreng	Curry tree	Eye pain	India	Leaf	Paste	Oral	[12]
Rutaceae	*Aegle marmelos* (L.) Corrêa	Bael, golden apple, wood apple	Headache	Nepal	Fruit and leaves	Cut and squeeze the fruit and boil the leaves	Oral	[17]
Rutaceae	*Aerva javanica* (Burm.f.) Juss. Ex Schult	Kapok bush, desert cotton	Arthralgia	India	Leaves	Paste	Topical	[26]
Salicaceae	*Salix alba* L.	White willow	Leg pain	India	Leaves	Decoction	Oral	[23]
Salicaceae	*Salix acmophylla* Boiss.	Bid	Myalgia	Iran	Leaves	Heat on embers	Topical	[13]
Sapindaceae	*Aesculus hippocastanum* L.	Horse chestnut, Buckeye	Back pain	India	Seeds	Oil extract	Topical	[23]
Sapindaceae	*Cardiospermum halicacabum* L.	Ballon plant, love in a puff	Labor pain	India	Leaves	Juice	Oral	[12]
Sapindaceae	*Stocksia brahuica* Benth	Kotour	Abdominal pain Myalgia	Iran	Aerial part, leaves	Poultice	Topical	[13]
Saururaceae	*Hyptis suaveolens* (L.) Poit.	Pignut, chan	Myalgia	India	Leaves	Decoction	Oral	[26]
Saxifragaceae	*Bergenia stracheyi* (Hook.f.) Engl.	Khichlay	Abdominal pain	Pakistan	Leaves	Infusion	Oral	[25]
Scrophulariaceae	*Verbascum carmanicum* Bornm.	Mor , Lu leng	Hand and foot pains	Iran	Leaves	Pulverised	Topical	[13]
Solanacea	*Lycium ruthenicum* Murray	Russian box thorn	Abdominal pain	Iran	Fruits	Decoction, Poultice	Oral	[13]
Solanacea	*Solanum nigrum* L.	Angour toul	Bladder pain	Iran	Aerial part, fruits, leaves	Decoction	Oral	[13]

(Table 1) contd….

Family	Scientific Name	CEM/VN	Type of Pain	Region	Part of Plant Used	Method of Preparation	Administration	Refs.
Solanaceae	*Solanum virginianum* L.	Surattense nightshade, yellow-fruit nightshade, yellow-berried nightshade, Thai green eggplant, Thai striped eggplant	Toothache	Myanmar	Fruits, seeds	Ashes	Apply ash of burnt fruits and seeds	[21]
Solanaceae	**Capsicum frutescens* L.	Chilli pepper	Labor pain	India	Fruit	Paste	Oral	[12]
Solanaceae	*Solanum surattense* Burm. f.	Neeli Kandiari, Kandiari	Arthralgia	India	Leaves	Leaves soaked in hot mustard oil are fastened on joints	Topical	[20]
Solanaceae	**Solanum tuberosum* L.	Potato	Headache	India	Tuber	Paste	Topical	[20]
Solanaceae	*Solanum diffusum* Roxb	Solanum diffusum	Toothache	Nepal	Fruits	Burn	Inhale	[17]
Solanaceae	*Hyoscyamus malekianus* Parsa	Kermoshan	Toothache	Iran	Aerial part, seeds	Burn	NI	[13]
Solanaceae	*Hyoscyamus pusillus* L.	Dantan shan Kermoshan	Toothache	Iran	Seeds	Decoction, Infusion, Mouthwash	NI	[13]
Taxaceae	*Taxus wallichiana* Zucc.	Himalayan yew	Abdominal pain	Myanmar	Bark	Paste	Add water to powdered bark, apply as paste	[21]
Tiliaceae	*Grewia optiva* J.R.Drumm. ex Burret	Grewia optiva	Arthralgia	Pakistan	Leaves, bark	Decoction, bark extract	NI	[27]
Urticaceae	*Urtica dioica* L.	Common nettle, Stinging nettle	Myalgia	India	Whole plant	Whole plant is rubbed on the body	Topical	[23]
Verbenaceae	*Vitex negundo* L.	Chinese chaste tree, five-leaved chaste tree, or horseshoe vitex	Myalgia	India	Leaf	Decoction	Topical (bath)	[12]
Verbenaceae	*Callicarpa macrophylla* Vahl	Callicarpa macrophylla	Throat pain	Nepal	Root	Boil decoction	oral	[17]
Verbenaceae	*Premna barbata* Wall. Ex Schauer	Gineri	Abdominal pain	Nepal	Bark, leaves and flowers	Chew (bark) and dip into water (leaves and flowers)	Oral	[17]
Vitaceae	*Vitis parvifolia* Roxb.	Creeping grape	Renal pain	Pakistan	Fruit, Leaves	Leaves extract	NI	[27]
Zingiberaceae	**Curcuma longa* L.	Turmeric	Abdominal pain Arthralgia Myalgia Headache	India	Rhizome	Paste Maceration	Topical Oral	[15]
Zingiberaceae	**Zingiber officinale* Roscoe	Ginger	Abdominal pain	Jamaica	Rhizome	Decoction	Oral	[16]

Keywords: CEN-common English name, VN-vernacular name, NI-not indicated.

pain as respiratory systems disorders, and headaches and body pain as skeleton-muscular system disorder. In this particular survey, commonly used medicinal plants were identified among the Kani tribals (India). Interestingly, pickle was one of the peculiar preparation methods used to cure stomachaches using the fruit Carissa carandas.

In addition, Maleki and Akhani [13] investigated the flora in Iran, where herbs and shrubs are usually used in folk medicine. A remarkable therapy was documented in the same study for the alleviation of muscular, skeletal, and rheumatic pains termed by the local people as “cholzadan.” In this unusual method, the heat arising from burnt plants

Table 2. Analgesic properties of plants.

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Amaranthaceae	*Cyathula prostrate* L. Blume	Whole plant	*In vivo* Wistar rats (100-200g) and Swiss albino mice (20-30g)	AWT HPT	Methanolic	Acetylsalicyclic (10mg/kg) Morphine (10mg/kg)	AWT: It showed maximum inhibitory response (50%) at the dose of 200mg/kg. The inhibition elicited by the extract at 200mg/kg was however lower than that observed for acid at a dose of 10 mg/kg (63%). HPT: It showed a dose dependent effect with maximum inhibition (44%) at the highest dose of 200 mg/kg while Morphine showed a significant protective effect (62% inhibition.	[71]
Amaranthaceae	*Celosia argentea* L. *var. cristata* (L.)	Flower	*In vivo* Albino mice	AWT	Ethanolic	Diclofenac sodium (50 and 100 mg/kg) Tramadol (5 and 10 mg/kg)	AWT: At a dose of 200 mg/kg and 400 mg/kg, the aqueous extract was effective and showed a % percentage protection of 51% and 63% respectively.	[72]
Amarantharceae	*Aerva monsoniae*	Whole plant	*In vivo* Wistar albino rats (150-200 g) and Swiss albino mice (25-30 g) of either sex	HPT	Petroleum ether	Diclofenac sodium gel (100 mg/mL)	HPT: The plant extract was an effective analgesic agent at lower dose of 100mg/kg. The animals treated with 250 mg/kg exhibited poor reaction time.	[73]
Anacardiaceae	*Antrocaryon klaineanum* Pierre	Stem	*In vivo* Mus musculus white mice (18-25 g) and Wistar albino rats (90- 150 g) aged of 60 days	AWT FT HPT	Methanolic	Paracetamol, 50 mg/kg Morphine, 5 mg/kg	AWT: A decrease in the number of abdominal constrictions induced by acetic acid by 46% at a dose of 600 mg/kg FT: Oral administration of methanol extract of *A. klaineanum* significantly inhibited the neurogenic phase of formalin-induced nociceptive response by 59% at a dose 600 mg/kg. HPT: At doses of 400 and 600 mg/kg the latency time increased from 3.29 ± 0.26 s to 21.46±0.27 s and from 3.08±0.14 s to 22.90± 1.00 s (n=7) respectively 3 h after treatment. This increasing of the latency times might be due to the central analgesic effect of the extract.	[46]
Anacardiaceae	*Lannea coromandelica* (Houtt.) Merr.	Leaves	*In vivo* Swiss albino mice (20-25 g) of both sex	AWT FT	Ethanolic	Diclofenac sodium	AWT: At 50, 100, and 200 mg/kg doses caused a significant reduction in the number of writhing FT: At 50, 100, and 200 mg/kg dose caused a significant dose-dependent inhibition of both neurogenic (0-5 min) and inflammatory (15-30 min) phases	[74]

(Table 2) contd….

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Anacardiaceae	*Mangifera indica* L.	Leaves	*In vivo* Swiss albino mice of both sexes weighing between 25 g and 30 g and Wistar Albino rats of either sex weighing between 150 g and 200 g	AWT	Methanolic	Diclofenac Sodium (40mg/kg)	Leaves extract reduced the writhing count from 66.75±2.28 to 29.5±2.72/20 minutes.	[75]
Annonaceae	*Annona squamosal* L.	Bark	*In vivo* Male Swiss albino mice (20-25 g each) and Wistar rats (150-200 g each)	HPT AWT	Crude petro-leum ether	Pentazocin (50mg/kg) Aspirin (100mg/kg)	The maximum activity was observed with caryophyllene oxide (25mg/kg body wt., i.p.) at the 120min time interval, which is comparable to the standard pentazocin. t the dose of 25mg/kg body wt., caryophyllene oxide inhibited the writhing re-sponse almost to the same degree as aspirin (74.41%).	[76]
Apiaceae	*Heracleum persicum*	Fruits	*In vivo* Male Wistar rats weighing 150-200g and male Swiss mice (25-35 g)	AWT FT	Essential oil Hydroalcoholic	Indomethacin (10 mg/kg) Morphine (10 mg/kg)	AWT: Oral administration of Heracleum persicum essential oil at doses of 50-200 mg/kg and Heracleum persicum hydroalco-holic extract at doses of 250 and 500 mg/kg significantly reduced acetic acid-induced abdominal constrictions FT: Both extracts significantly attenuated the pain response of the second phase of formalin test.	[77]
Apocynaceae	*Ichnocarpus frutescens*	Roots	*In vivo* Swiss Albino mice, weighing 20-25 g	AWT	Methanolic	Diclofenac (10 mg/kg)	59%, 51% and 46% inhibition of writhing at 1, 3 and 6 mg/kg dose with much improved level of pain killing effect.	[45]
Aracaceae	Areca cate-chu Linn.	Seeds	*In vivo* Male and female Swiss albino mice (25-30 g) and Wistar albino rats (250- 300g)	HPT FT	Hydroalcoholic	Pentazocine (10 mg/kg) Aspirin (300 mg/kg)	HPT: A dose of 1000 mg/kg exhib-ited highest analgesic (54%) at 60 min and which was gradually de-creased at 90min. FT: At a dose of 500 mg/kg, it exhibited 92% of during the second phase (20-25min).	[78]
Araceae	*Typhonium trilobatum* L. Schott	Leaves	*In vivo* Swiss-albino mice (both sexes) weighing between (18-25 g) and Wistar rats of the either sex (180-200 g)	AWT	Ethanolic	Diclofenac sodium (10 mg/kg)	50% and 65% writhing inhibition at the doses of 250 and 500 mg/ kg body weight respectively, which was comparable to the standard drug diclofenac sodium that caused 71% inhibition.	[79]
Asclepiadaceae	*Pergularia daemia*	Roots	*In vivo* Wister albino rats of either sex weighing about 150- 200 g and adult albino mice of either sex weighing 25 -30 g	HPT AWT	Ethanolic	NI	The highest reaction time was ob-served for ethanol extract of *P. daemia* (9.08 sec.) at a dose of 200 mg/kg.	[80]

(Table 2) contd….

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Asparagaceae	*Sansevieria roxburghiana* Schult.	Whole plant	*In vivo* Young Swiss-albino mice of either sex aged 4-5 weeks, average weight 20-25 g	AWT	Ethyl acetate, Chloroform, Methanolic	Diclofenac sodium	The ethyl acetate, the chloroform and the petroleum-ether soluble fraction of crude methanolic extract of S. roxburghiana demonstrated significant analgesic activity with writhing inhibition of 63%, 60% and 57% respectively	[81]
Asteraceae	*Matricaria pubescens* (Desf.)	Whole plant	*In vivo* Swiss albino mice weighing18-25 g	AWT	Crude	Acetyl salicylic acid	Abdominal contortion inhibiting power was observed in mice treated with 200 mg/kg of *M. pubescens* alkaloids followed by those treated with 100 mg/kg, with percentages of 33.07 and 31% respectively	[82]
Asteraceae	*Ageratum conyzoide* L.	Leaves	*In vivo* Swiss-albino mice aged 4e5 weeks (either sex), average weight 20-25 g	AWT	Ethanolic	Diclofenac Sodium (250 and 500 mg/kg-bw)	% of writhing inhibition was highest (45%) at a dose of (500 mg/kg)	[34]
Asteraceae	*Mikania cordifolia* L.	Leaves	*In vivo* Swiss-albino mice aged 4-5 weeks (either sex), average weight 20-25 g	AWT	Ethanolic	Diclofenac Sodium (250 and 500 mg/kg-bw)	% of writhing inhibition was highest (42%) at a dose of (500 mg/kg)	[34]
Asteraceae	*Inula cuspidata*	Stem Root	*In vivo* Male Swiss Albino mice (Mus musculus) weighing 25-35 g and Wistar albino rats (Rattus norvegicus) weighing 150-200 gm	HPT AWT	Methanolic	Tramadol 10 mg/kg Acetyl salicylic acid 100 mg/kg	HPT: The methanol extracts at both the doses 100, 200 mg/kg exhibited a significant effect at 60 and 90 min readings as compared to control. AWT: All the tested extracts of stem and roots significantly exhibited dose dependent reduction in number of writhes within the 30 min of injection of acetic acid	[83]
Asteraceae	*Achillea fragrantissima* (Forssk.)	Whole plant	*In vivo* Mature albino mice and Wistar rats (27-30 g and 150-180 g, respectively) of both sexes	HPT AWT	Ethanolic	Indomethacin (20mg/kg)	HPT: Maximum protection against the thermal stimulus was seen at 90 at a dose of 400 mg/kg of the non-polar extract (81%), which was not statistically different compared to the reference drug (89%) AWT: Maximum protection was observed with a polar extract dose of 400 mg/kg (55%), which was not statistically different than the acetyl salicylic acid reference drug (58%)	[84]
Betulaceae	*Alnus nitida* (Spach) Endl.	Stem bark	*In vivo* Six weeks old (180 - 200 g) Sprague Dawley male rats	HPT AWT	Methanolic	Morphine (10 mg/kg)	HPT: Administration of extract at 50 mg/kg, 100 mg/kg and 200 mg/kg has elevated the latency by 56%, 58% and 61% after 120 min of the test sample administration. AWT: At 50 mg/kg (68%), 100 mg/kg (75%) and 200 mg/kg (79%), the extract exhibited the moderate level of analgesic activity.	[85]

(Table 2) contd….

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Buxaceae	*Sarcococca saligna* (D. Don) Mull.	Fruits	*In vivo* BALB/C mice of both gender, age 4-5 weeks and mean weight of 20- 25 g	AWT	Methanolic	Diclofenac sodium (10 mg/kg)	At a dose of 500 mg/kg, the highest % of writhing inhibition were observed withing 10 min.	[86]
Cactaceae	*Opuntia microdasys* (Lehm.) Pfeiff	Flower	*In vivo* Wistar rats and Swiss albinos mice of both sexes weighing 160-180 g and 18-25 g	AWT	Aqueous	ASL at 200 mg/kg	Doses of 50 (58%) and 100 mg/kg (72%) of aqueous extracts significantly decreased the writhing reflex.	[49]
Capparidaceae	*Cleome rutidosperma* DC.	Whole plant	*In vivo* Swiss Albino mice (20−25 g)	HPT TFT FT AWT	Methanolic	Morphine (5 mg/kg)	HPT: At the doses of 100 and 200 mg/kg respectively, MECR displayed the significant ability of sustaining the latency of reaction to thermal-induced nociception thoughout the 120 min experiment. TFT: There were no significant difference in the antinoceptive effect of 100 and 200 mg/kg. FT: a dose-dependent antinociceptive effect in both the neurological (0−5 min) and inflammatory (15−30 min) phase at 100 and 200 mg/kg. AWT: A significant inhibition (39% and 47%) of the writhing response at 100 and 200 mg/kg.	[40]
Chenopodiaceae	*Bassia eriophora*	Whole plant	*In vivo* Albino Wistar rats and albino Swiss mice	HPT AWT	Alcoholic	Indomethacin (4 mg/kg bw)	HPT: t 90 min, the mean reaction time for indomethacin of analgesia effect showed 9.18 ± 0.22 (n=5), while 250 and 500 mg/kg *B. eriophora* showed significant analgesic effect (8.10 ± 0.18 and 8.10 ± 0.12, n=5) respectively. AWT: The indomethacin was showed 86% inhibitions of analgesia, while 250 and 500 mg/kg *B. eriophora* showed 55% and 68% inhibitions of analgesia respectively	[87]
Cistaceae	*Cistus salviifolius* L. *Cistus monspeliensis* L.	Whole plant	*In vivo* Adult Swiss mice and adult Wistar rat	AWT TFT	Aqueous	Aspirin (150 mg/kg) Morphine (0.1 mg/kg)	AWT: Aqueous extracts of both plants (500 mg/kg) caused significant inhibition of writhes 49% compared to the standard drug aspirine hat produced 40% inhibition at 150 mg/kg bw. TFT: Both extracts (500 mg/kg) have maximum effect at 60 min; their effects at 120 min were less than those of the control drug morphine.	[88]
Clusiaceae	*Garcinia lanceifolia* Roxb.	Whole plant	*In vivo* 20-25 g Swiss-albino mice (aged 4-5 weeks)	Peripheral: AWT method Central: TFT	Methanolic	Peripheral: Diclofenac (50 mg/kgbw) Central: Morphine	In peripheral antinociceptive activity, 400 and 200 mg/kg of extract exhibited significant inhibition of writhing with 59% and 49% respectively. In central antinociceptive activity, the extract (400 and 200 mg/kg) exhibited significant analgesic activity having 78% and 90% elongation of reaction time respectively in 90 min.	[35]

(Table 2) contd….

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Convolvulaceae	*Rivea hypo-crateriformis*	Leaves	*In vivo* Albino rats of Wistar strain (250 - 300 g)	TFT	Ethanolic	Ibuprofen	Doses of 400 mg/kg increased the pain threshold significantly after 30 min, 1,2 and 4 hours.	[89]
Cucurbitaceae	*Citrullus colo-cynthis* Schrad.	Immature seeds Ripe seeds Immature fruits Ripe fruits Stems Roots	*In vivo* Male adult Wistar rats weighing 160-180 g and Swiss albinos mice (weighing 18-25g)	AWT	Aqueous extract	Acetyl sali-cylate of lysine 200mg/kg	The immature fruits and seeds possess the highest analgesic properties; the most active of them were immature fruits as well as at 0.1 mg/kg (94%)	[37]
Cuucurbitaceae	*Momordica dioica* Roxb.	Seed	*In vivo* Albino mice (Swiss strain) weighing 25-30g either sex	AWT HPT	Methanolic	Paracetamol (50 mg/kg) Pentazocine 10 mg/kg	AWT: At a dose of 50 and 100 mg/kg, the extract showed a reduction in number of writhing, which is 4% and 12% respec-tively. HPT: A dose of 50 mg/kg was found effec-tive at 60 and 90 minutes.	[90]
Cyperaceae	*Cyperus routunds* Linn.	Whole plant	*In vivo* Ani-mals (albino mice of either sex; weight 25-30 gm)	TFT	Ethanolic	Diclofenac sodium (50 m/kg)	The reaction time (1 to 4 hours) to pain stimulus was increased after crude extract administration (300mg/kg)	[86]
Dilleniaceae	*Dillenia indica* f. elongata (Miq.)	Bark	*In vivo* Ethyl acetate extracts	HPT TFT FT	Ethyl ace-tate extracts	Pentazocine 30 mg/kg and 25 mg/kg Indomethacin (10 mg/kg	HPT: Ethyl acetate extract of *D. indica* f. elongata (300 mg/ kg) showed significant analgesic activity at 60 min respectively. TFT: *D. indica* f. elongata (100 mg/kg) possessed significant analgesic activity more than that of standard drug pentazocine at 1 h. FT: *D. indica* f. elongata (100 mg/kg) extracts were potent than indomethacin and decreased the number of paw lickings at the second phase.	[38]
Dipterocar-paceae	*Shorea robusta* Gaertn.	Bark	*In vivo* Ethyl acetate extracts	HPT TFT FT	Ethyl ace-tate extracts	Pentazocine 30 mg/kg and 25 mg/kg Indomethacin (10 mg/kg	HPT: *S. robusta* was effective at a dose of (300 mg/ kg) at 30 min. TFT: Ethyl acetate extract of *S. robusta* (100 and 300 mg/kg) showed significant analgesic activity which was more potent than standard pentazocine from 0.5 h to 1 h. FT: *S. robusta* at 300 mg/kg was more effective than the indomethacin.	[38]
Fabaceae	*Cassia siamea* Lam.	Stem	*In vivo* Male and female Wistar rats (200-350 g)	HPT	Ethanolic	Morphine (2mg/kg)	At a dose of 200 and 400 mg/kg, the ethanol extract was more effective.	[91]
Fabaceae	*Senna singueana* Del. Lock	Leaves	*In vivo* Swiss albino mice (20-25gm)	AWT HPT FT	Methanolic	Diclofenac sodium (10 mg/kg) Morphine sulfate (5 mg/kg)	Percentage maximum inhibition of writhing response was 80% at a dose of 400 mg/kg. A combination of drug and the plant extract was found more effective in all three methods.	[92]

(Table 2) contd….

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Flacourtiaceae	*Scolopia crenata* (Wight & Arn.) Clos.	Stem bark and leaves	*In vivo* Swiss albino mice (25-30g)	AWT HPT	Methanolic	Indomethacin (5mg/kg) Morphine (5 mg/kg	The oral administration of methanol extract of leaf and bark at higher dose of 400mg/kg reduced the number of writhings from 65.33 (induced) to 12.83 (80%) and 17.17 (74%), respectively. An increase in the response latency time at 30 min, which persisted in a dose dependent manner of 200 and 400mg/kg.	[93]
Lamiaceae	*Hyptis suaveolens* L. Poit.	Whole plant	*In vivo* Male Swiss albino mice (25-30 g)	HPT	Ethanolic	Morphine (5 mg/kg)	AEHS (400 mg/kg) had produced higher latency time at 120 min (after treatment) and mean latency time was 5.30 ± 0.36 s	[36]
Lamiaceae	*Mentha rotundi-folia* L.	Leaves	*In vivo* Swiss albino mice (25- 30 g)	AWT	Methanolic	Aspirin (150 mg/kg)	Doses of 200, 400, and 600 mg/kg bw had significantly analgesic effects and dose dependent with inhibition percentages from 79% to 85%. The analgesic effect of the extract (at 600 mg/kg bw) was greater than the Aspirin (150 mg/kg bw)	[32]
Lamiaceae	*Stachys lavan-dulifolia* Vahl.	Whole plant	*In vivo* Young-adult male Swiss mice (28-33 g)	FT CNT	Essential oil	Morphine (3mg/kg)	FT: Higher dose (50 mg/kg) produced significant inhibitory (35.50 ± 4.405) ef-fects on nociceptive face-rubbing behav-ioral response in the first phase. CNT: All doses (78.50 ± 12.68 and 63.00 ± 9.495; or 59.50 ± 13.57 and 48.50 ± 11.48, (n=6)respectively) inhibited nociceptive behavior in mice.	[43]
Lamiaceae	*Mentha arvensis* L.	Whole plant	*In vivo* Swiss albino mice of either sex (20-29 g body weight)	AWT	Ethanolic	Diclofenac sodium (25 mg/kg of body weight)	The extract produced 46% and 64% writh-ing inhibition in mice at oral doses of 250 mg/kg and 500 mg/kg body weights of mice respectively while the standard drug exhib-ited inhibition of 77% at a dose of 25 mg/kg body weight	[44]
Leguminosae	*Dalbegia saxatilis*	Leaves	*In vivo* Wistar rats and mice of both sexes weighing 100-150 g and 20-25 g	AWT HPT	Methanolic	Aspirin (300 mg/kg) Morphine (10 mg/kg)	AWT: The extract significantly decreased the number of writhes caused by acetic acid in a dose independent manner. HPT: The methanol leaf extract signifi-cantly increased the reaction. At 30 min, there was significant increase in reaction time in the 500 mg/kg and 1000 mg/kg.	[94]
Leguminosae	*Albizia lebbeck* Benth.	Bark	*In vivo* Long-Evans rats (150-200 g) and Swiss albino mice (25- 30 g)	AWT TFT	Petroleum ether, ethyl acetate and methanolic	Aminopyrine (50mg/kg) Morphine (2mg/kg)	AWT: Inhibition of writhing was 52% at 400mg/kg. TFT: % elongation was highest (61.48) using 400 mg/kg at 30 min.	[95]
Leguminosae	*Acacia ferruginea* DC.	Leaves Bark	*In vivo* Wistar albino rats (180-220 g, Male) and Swiss albino mice (25- 40 g)	HPT AWT	Hydroalco-holic	Tramadol (10 mg/kg) Aspirin (5 mg/kg)	HPT: Bark extract at the same dose of 100 mg/kg showed higher inhibition (8.85 ± 0.45 min) of thermal stimulation as com-pared to leaf extract (6.79 ± 0.29 min) at a response time of 90 min. AWT: The maximum protection was ob-served at a dose of 100 mg/kg in both leaf (91%) and bark extracts (90%) against acetic acid, which was com- parable to standard aspirin (51%).	[96]

(Table 2) contd….

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Liliaceae	*Polygonatum verticillatum* L.	Roots	*In vivo* Swiss albino mice (20-25g) and Wistar rats (210-270g	AWT FT	Methanolic	Aspirin (300 mg/kg) Morphine (10 mg/kg)	AWT: The analgesic response of PR at 200 mg/kg was quite similar to the positive control (77% at 100 mg/kg) FT: At a dose of 200 mg/kg, the extraxt was effective.	[97]
Malvaceae	*Microcos paniculata*	Bark Fruits	*In vivo* Swiss albino mice, 6-7 weeks old, weighting 25-30 g	FT AWT TFT	Methanolic	Aspirin (1.0 ml) Diclofenac sodium (100 mg/kg) Tramadol (10 mg/kg)	FT: Bark extract of 400 mg/kg showed the maximun percentage inhibition (78%) of paw licking in mice in the last phase of formalin injection. AWT: The highest percentage inhibition of writhing resulting from treatment with plant extracts (54%) was obtained by fruit extract at 400 mg/kg. TFT: AT 60 min, the maximum effects of bark extracts at 400 mg/kg, and fruit extract at 200 and 400 mg/kg had significant analgesic activities.	[42]
Moraceae	*Ficus racemosa* Linn.	Whole plant	*In vivo* Young Swiss-albino mice of either sex aged 4- 5 weeks, average weight 20-25 g	HPT AWT	Ethanolic	Diclofenac sodium 10 mg/kg	At 90 minutes, the percent inhibition of two different doses (100 and 200 mg/kg body weight) was 50% and 57%.	[98]
Moringaceae	*Moringa oleifera* Lamarck	Leaves	*In vivo* Male and female Wistar rats weighing 180-200 g	FT	Hexane	Naproxen (10 mg/kg)	During phase I, significant effect was observed at a dose of 30 mg/kg resembling the effect of the positive control.	[99]
Myrtaceae	*Psidium cattleianum* Sabine	Leaves	*In vivo* Male albino mice (20-25 g)	AWT HPT	Hydroalcoholic	Indomethacin (5 mg/kg) morphine (5 mg/kg)	AWT: The inhibition percentage of the number of writhing of acetic acid-induced writhing in mice was 86, 91, 81, 99, and 73% at doses of 60, 80, 100, 200, and 400 mg/kg, respectively. HPT: No analgesic effect on the central nervous system that would contribute to its peripheral analgesic effect.	[39]
Myrtaceae	*Syzygium calophyllifolium* Walp.	Bark	*In vivo* Healthy Wistar albino rats (100-150g) and Swiss albino mice (20-25 g), of either sex	AWT HPT FT	Methanolc	Aspirin (150 mg/kg) Pentazocine (5 mg/kg)	AWT: The extract displayed profound analgesic activity (6.75 ± 1.38, n=6) at a higher dose (200 mg/kg). HPT: Oral administration of 200 mg/kg methanol extract showed a sig- nificant capacity to inhibit the pain sense by 81%. FT: A dose of 200 mg/kg increased the latency period (9.00 ± 0.82 s), thereby increasing the heat tolerance of the mice by 54%	[100]
Nymphaeaceae	*Nymphaea nouchali* Burm.f.	Flower	*In vivo* Swiss albino mice of either sex, 3-4 weeks of age, weighing between 20-25 g	TFT AWT	Methanolic	Diclofenac sodium (50 mg/kg) Morphine (25 mg/kg)	TFT: The highest dose (400 g/kg) exhibited effective analgesic effect from 60-120 min. AWT: The methanolic extract produced 60% and 65% writhing inhibition at oral doses of 200 mg/kg and 400mg/kg.	[101]

(Table 2) contd….

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Oleaceae	*Jasminum sambac* L.	Roots	*In vivo* Healthy Charles Foster albino rats (150-200 g) and Swiss albino mice (20-30 g) of either sex	AWT	Ethanolic	Diclofenac (10 mg/kg)	At 400 mg/kg, p.o. reduced writhing counts up to 49%.	[102]
Oleaceae	*Jasminum* abyssinicum Hochst. ex. DC.	Roots	*In vivo* Healthy Swiss albino mice, weighing 25-35 g and aged 6-8 weeks	AWT	Methanolic	Aspirin (150 mg/kg, 100 mg/kg)	The percentage inhibition for the extract was 38.7%, 70.6% and 66.8% at 50 mg/kg, 100 mg/kg and 200 mg/kg respectively. The extract at doses of 100 mg/kg and 200 mg/kg showed a better effect than aspirin (which had a percentage inhibition of 56%)	[103]
Oleaceae	*Nyctanthes arbortristis* Linn.	Leaves	*In vivo* Male albino mice (Swiss strain) weighing 25-28 g	HPT AWT	Petroleum ether extract	Paracetamol (50mg/kg)	Petroleum ether, chloroform and ethyl acetate extracts (50 mg/kg) produced significant inhibition of writhing reaction induced by acetic acid compared to the control group β-Sitosterol (5, 10 and 20 mg/kg, i.p., each) isolated from petroleum ether extract showed comparable activity with standard drug paracetamol.	[104]
Passifloraceae	*Passiflora subpeltata* Ortega	Leaves	*In vivo* Male Swiss albino mice (20-25 g) and Wistar rats (140-170 g)	AWT FT	Acetone	Morphine (10 mg/kg)	AWT: At doses of 200 and 400mg/kg reduced the number of writhes to 8.5 ± 0.29, n=3 (51% inhibition) and 3 ± 0.82 (83% inhibition) respectively. At a dose of 400mg/kg showed higher analgesic activity. FT: The extract possessed only mild inhibitory effect deter- mined from the licking response at the dose of 200 and 400 mg/kg.	[105]
Pinaceae	*Pinus roxburghii* Sarg.	Stem	*In vivo* Wistar rats (150-250gm) and Swiss albino mice (20-25 gm) of either sex	AWT TFT	Alcoholic	Diclofenac Sodium (50mg/kg)	AWT: Doses of 100, 300, and 500 mg/kg significantly and dependently reduced the number of abdominal constrictions induced in mice. TFT: The extract showed a significant elongation of reaction time after 30 min to 90 min at 500 mg/kg.	[106]
Piperaceae	*Piper nigrum* L.	Fruit	*In vivo* Swiss albino mice of both sex weighing 25-30 g and Swiss albino rats of both sex weighing 150-200 g	TFT Analgesymeter HPT AWT	Crude Ethanolic Hexane	Diclofenac sodium (5 mg/kg) Acetyl salicylic acid (10 mg/kg)	TFT: Piperine exhibited maximum activity after 120 min at a dose of 5 mg/kg. The hexane extract showed maximum analgesic activity at a dose of 10 mg/kg after 60 min. Ethanol extract was effective at doses of 5, 10 and 15 mg/kg. Analgesy-meter: ethanol extract exhibited maximum analgesic activity at a dose of 10 mg/kg after 60 min. HPT: Maximum analgesic effect was noted at a dose of 10 mg/kg after 120 min for piperine. AWT: Piperine and ethanol extract (10 mg/kg) showed 100% protection. Hexane extract exhibited 99% at 10 mg/kg.	[107]

(Table 2) contd….

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Rhamnaceae	*Ziziyphus nummularia*	Leaves	*In vivo* Healthy Wistar rats of both sexes weighing 180-200 g and Swiss mice weighing 20-24 g	AWT TFT HPT	Ethanolic	Aspirin 100 mg/kg morphine 5 mg/kg BW	AWT: A reduce number of writhes was observed with an increased dose of plant extract. TFT&HPT: At a dose of 10 mg/kg, the latency time was 09.48 ± 0.34 s, n=6.	[108]
Rhamnaceae	*Ziziphus Xylopyrus*	Stem	*In vivo* Swiss albino mice (25-30g) and albino rats of Wistar strain (150-200g) of either sex	HPT TFT	Petroleum ether, cholo-form and methanolic	Morphine sulphate	HPT: The different dose of methanolic extract of *Z. xylopyrus* showed highly significant effect at 30, 60,120 and 180 minutes as compared with control group. The chloroform extract 200mg/kg showed a significant activity at 30minute and highly significant activity at 60,120 and 180 minutes. TFT: The methanolic extract of *Z. xylopyrus* at a dose of 200mg/kg showed peak effect of 13.6±0.173 at 180 minutes	[109]
Rubiaceae	*Hedyotis puberula* (G. Don) R. Br. ex Arn.	Whole plant	*In vivo* Male swiss albino mice (20-25 g) and wistar rats (120-150 g)	AWT HPT	Methanolic	Indomethacin (5 mg/kg) Pentazocine (30 mg/kg)	AWT: retreatment with methanol extract of *H. puberula* at doses of 200 and 400 mg/ kg reduced the number of writhes to 33.83 ± 2.70, n=6 (42% inhibition) and 21.00 ± 0.63 (64% inhibition). The extract dose 400mg/kg registered higher levels of analgesic activity than the positive control. HPT: At 400 mg/kg and 60 min reaction time, the analgesic activity (7.30 ± 0.20 s) of the test extract was higher than the positive control.	[110]
Rubiaceae	*Morinda citrifolia* L.	Fruits	*In vivo* Male mice	HPT	Ethanolic	Tramadol (30 mg/kg)	The application of 10% of the noni fruit puree concentrate in the drinking water of the mice for a period of 4 days prior to the experiment resulted in a reaction time of 9.2 s.	[111]
Rutaceae	*Clausena anisata* (Wild) Hook .F. ex Benth	Leaves	*In vivo* Swiss albino mice both male and female	AWT FT	Ethanolic	NI	AWT: At a dose of 39 mg/kg, the extract was effective for an interval of 15 min (8.11 ± 0.21, n=6) FT: At a dose of 78 mg/kg, the extract was found more effective (4.82± 0.98) than the standard drug (2.28± 0.22).	[112]
Sapindaceae	*Schleichera oleosa* (Lour.) Oken.	Stem	*In vivo* Wistar rats (150-180 g)	FT	Ethanolic	Indomethacin	The extract (400 mg/kg) produced a significant reduction in response time of the animals against pain, from 100 sec in control group to 38 sec	[113]
Scrophulariaceae	*Scoparia dulcis* L.	Whole plant	*In vivo* Young Swiss-albino mice of either sex aged 4- 5 weeks, average weight	HPT AWT	Ethanolic	Diclofenac sodium 10 mg/kg	At 90 minutes, the percent inhibition of two different doses (100 and 200 mg/kg body weight) was 55% and 62%.	[98]
Solanaceae	*Solanum paniculatum* L.	Leaves	*In vivo* Male Swiss Webster mice	AWT	Aqueous ethyl acetate	Acetaminophen (90, 180 or 360 mg/kg bw)	Treatment of mice with ethyl acetate partition (300 mg/kg bw) produced approximately 50% reduction in the writhing nociceptive response	[33]

(Table 2) contd….

Family	Plant	Part of Plant used	Model used *In vivo*	Test	Extract Type	Positive Control	Main Findings	Refs.
Solanaceae	*Schwenckia americana* L.	Whole plant	*In vivo* Male albino wistar rats, weighing 200-250g	AWT FT	Methanolic	Piroxicam (10 mg/kg)	AWT: The percentage inhibition (53.3, 58.0 and 86%) of the extract at 25, 50 and 100 mg/kg, respectively were significant. FT: The percentage pain inhibition between 0 and 10min (early phase) were 44.00, 56.04, and 56% for 25, 50 and 100 mg/kg intra-peritoneal doses. The percentage pain inhibition between 15 and 60 min (late phase) were 33.00, 36.63 and 60%, for 25, 50 and 100mg/kg intra-peritoneal doses of the extract	[114]
Vitaceae	*Vitis vinifera* L.	Leaves	*In vivo* Swiss albino mice (20-30 g)	FT AWT	Ethanolic	Morphine (10 mg/kg) Indomethacin (10 mg/kg)	FT: In the second phase, the middle, highest dose of the extract (200, 400mg/kg) and morphin all inhibited the licking response significantly the licking times were (33.35 ± 2.29 s), (23.79 ± 1.43 s), (20.32± 0.52 s, n=5) respectively. AWT: A peak inhibitory effect (66%) was observed at a dose of 400 mg/kg.	[41]
Vitaceae	*Cissus repanda* Vahl	Stem	*In vivo* Wistar strain albino rats of either sex weighing 200 ± 20g and Swiss albino mice of either sex weighing 30 ± 06g	TFT FT	NI	Pentazocine (20mg/kg) Indomethacin (10 mg/kg)	FT: A significant decrease in % inhibition of paw licking response (17.%) was seen after 24 hours TFT: Not effective	[48]
Zingiberaceae	*Alpinia nigra* (Gaertn.) B.L. Burtt	Leaves	*In vivo* 6-week-old Swiss albino mice of both sexes weighing 25-30 g	FT TFT	Methanolic	Diclofenac sodium (5 mg/kg)	FT: The extract at the dose of 200 mg/kg displayed inhibition of the late phase. TFT: It exhibited potent analgesic effect after 30 and 60 minutes of administration at a dose level of 200 mg/kg.	[48]

and charcoal in a grave-like pit is projected toward the body, which is simply covered with a blanket for approximately 45 minutes. This process is also known as "heated on embers."

3.2. Analgesic Properties of Plants

In the present review, we evaluated various studies in which pain asessments, such as tail-flick test, hotplate test, acetic-induced writhing test, and formalin test were included. The tail-flick test utilizes a spinal reflex that targets the μ_2- and δ-opioid receptors, whereas the hotplate test demonstrates the supraspinal reflex mediated by the μ_1- and μ_2-opioid receptors [28]. Writhing is induced by the intense intrinsic pain produced by the parenteral administration of acetic acid in mice, which persists for a prolonged period of time. The analgesic effect of a test compound is determined upon a decrease in writhing or inhibition of writhing [29].

Plants contain readily available polyphenols, including flavonoids that possess analgesic and anti-inflammatory properties [30]. Flavonoids cross the brain-blood barrier and manage pain using different mechanisms; they mainly affect the GABA A, opioid, and α-adrenergic receptors and inhibit enzymes that normally participate in inflammatory activities in the brain. They also exert their effects in several areas of the nervous system; inhibition of these receptors results in pain relief. Flavonoids can inhibit the release of cyclooxygenase in tissues and, thus, prevent the generation of prostaglandins. Prostaglandins play a role in stimulating the pain receptors [31].

Boussouf *et al*. [32] explained that analgesic properties can be assessed using the acetic-induced writhing test, which normally causes sensitization of the nociceptive receptor and the release of prostaglandins, in particular PGE2α and PGF2α, in peritoneal fluids. In their study, the analgesic effect of *Mentha rotundifolia* leaf extracts (600 mg/kg) was compared with that of aspirin (150 mg/kg). Interestingly, the plant extract was found to be more effective than the drug. In a recent study, de Souza *et al*. [33] analyzed the analgesic potency of the traditional medicinal plant *Solanum paniculatum*, which is native to Brazil. The writhing test showed that treatment with the aqueous extract of the plant leaf (partitioned with ethyl acetate) at a dose of 300 mg/kg-body

weight (bw) produced an approximately 50% reduction in the writhing nociceptive response.

In addition, Dewan *et al*. [34] investigated the analgesic potential of the crude ethanolic extract of two plants, *Ageratum conyzoides* and *Mikania cordifolia*. Ethanolic extract of both plants leaves were found to exert significant analgesic effects at a dose of 500 mg/kg-bw when the writhing test was performed; moreover, *A. conyzoides* was fairly stronger in terms of antioxidant potential. However, the positive control, diclofenac sodium (250 and 500 mg/kg-bw), showed a higher inhibition of writhing compared to the two plants extracts.

Ghosh *et al*. [35] evaluated the antinociceptive (peripheral and central) activity of the methanolic extract of *Garcinia lanceifolia* (whole plant). At doses of 200 and 400 mg/kg, the plant extract exhibited high antinociceptive activity. Notably, the plant extract demonstrated 50% and 60% of writhing inhibition at doses of 200 and 400 mg/kg, respectively, whereas the standard (diclofenac) showed 60% inhibition. The central antinociceptive activity was evaluated using the tail immersion method. The crude extract at doses of 200 and 400 mg/kg-bw showed significant analgesic activity, with 90% and 78.31% prolongation in the reaction time, respectively, in the 90 min after the sample was administered. This particular study confirmed that the analgesic effect of the plant was attributed to the presence of numerous flavonoids, saponins, terpenoids, diterpenes, and steroids that inhibited the synthesis of prostaglandins.

In the study by Begum *et al*. [36], the aerial parts of *Hyptis suaveolens* extracted in 80% aqueous ethanol demonstrated analgesic properties at 400 mg/kg; moreover, the petroleum ether and ethyl acetate extracts exerted remarkable central analgesic effects against heat-induced pain. Naloxone was used to antagonize the action of endogenous opioids; the results demonstrated that the antinociceptive effects of the extracts (400 mg/kg) and morphine (10 mg/kg) were reversed in the hotplate test.

Furthermore, Marzouk *et al*. [37] evaluated the analgesic properties of an aqueous extract of *Citrullus colocynthis* fruits and seeds. They found that immature seeds had the highest percentage of writhing inhibition (99%) at a dose of 8 mg/kg. Even at the lowest concentration (0.1 mg/kg), the percentage of writhing inhibition was 94% for the immature fruits. This demonstrates the strong analgesic capacity of these immature fruits and seeds; however, the active compounds (alkaloids, iridoids, flavonoids, steroids, *etc*.) change according to the maturation process of the fruits.

When evaluating the analgesic effects of the stem bark extracts of *Dillenia indica* f. *elongata* and *Shorea robusta*, Singh *et al*. [38] performed three tests: the hotplate test, tail-flick test, and formalin-induced pain test, in rats. The hotplate test confirmed the analgesic properties of the ethyl acetate extracts of *D. indica* f. *elongata* and *S. robusta* (300 mg/kg) at 60 and 30 minutes, respectively. Interestingly, the tail-flick test revealed that the analgesic effect of the ethyl acetate extract of *S. robusta* (100 and 300 mg/kg) was greater than that of the positive control (pentazocine) after 30 minutes. The formalin-induced pain test demonstrated that both plant extracts were more potent than the standard (indomethacin) during the second phase (15-30 min), as the number of paw lickings was significantly reduced. Thus, this study confirmed that ethyl acetate extracts of both plants have central and peripheral analgesic activity that can be attributed to the blockade of opioid receptors (κ, μ, and d), prostaglandins, and histamine.

In the study of Alvarenga *et al*. [39], the hydroalcoholic extract of the leaves of *Psidium cattleianum* was screened for *in vivo* analgesic activity. The results revealed that, in the acetic-induced writhing test, the extract had the highest percentage of inhibition (99%) at a dose of 100 mg/kg compared to the standard drug (indomethacin). Nonetheless, the hotplate test did not show any central analgesic effect. *Cleome rutidosperma*, which originated in Southeast Asia, is a medicinal plant used in folk medicine. The plant was tested for its analgesic effect, and positive results were obtained in different tests. Specifically, in the hotplate test, at a dose of 200 mg/kg, the methanolic extract of the plant (13.22 ± 0.52, n=5; 53.52%) could sustain the latency time at 30 minutes; this result was comparable to that of the positive control morphine (5 mg/kg; 15.35 ± 0.32, n=5; 67.27%). The results of tail-flick test showed no significant differences in the analgesic effects of the plant extract at the two doses (100 and 200 mg/kg), compared to the standard drugs. In the formalin-induced paw lick test, investigators found that, with the methanolic extract of the plant, the number of paw licks was significantly decreased in both the neurological and inflammatory phases, compared to the positive control. At the same doses, in the acetic-induced writhing test, the extract showed significant inhibition (40% and 47%, respectively) in a dose-dependent manner [40].

Furthermore, the effects of the hydroalcoholic leaf extract of *Vitis vinifera* (grapevine) were evaluated in the acetic-induced writhing test and formalin-induced paw lick test in mice. The results demonstrated that the extract at dosages of 100, 200, and 400 mg/kg-bw significantly decreased the acetic-induced writhing by 48%, 58%, and 68%, respectively. However, the low percentage of inhibition (50%) suggests that it is not a centrally-acting analgesic. Remarkably, the extract causes a dose-dependent inhibition of formalin-induced pain in the second phase [41].

Aziz [42] evaluated the analgesic properties of the methanolic extracts of the fresh bark and fruits of *Microcos paniculata*, which has been traditionally used in Bangladesh to treat several diseases such as fever, diarrhea, dyspepsia, heat stroke, colds, hepatitis and wounds. In the formalin-induced paw lick test in mice, it was observed that both extracts (400 mg/kg) showed an increase in the percentage inhibition of paw licking (with the highest inhibition at 78%) from the acute phase to the delayed phase; however, the percentage inhibition of paw licking was lowered in the late phase for the fruit extract. In the writhing test, the extract displayed a significantly higher percentage inhibition of writhing compared to the standard drug (diclofenac sodium, 100 mg/kg). Moreover, the fruit extract showed the highest percentage inhibition of writhing (54%) at 400 mg/kg. However, in the tail immersion test, the tramadol group (positive control group) showed a significant increase in latency after 30 minutes, compared to the plant extract.

Barreto *et al*. [43] tested the analgesic effect of the extract of *Stachys lavandulifolia* essential oil, which is commonly used to treat orofacial pain in Turkish traditional medicine. Orofacial pain was induced using formalin in the perinasal area of a rat. The same process was repeated using capsaicin. The essential oil extract caused a decrease in the face-rubbing behavior induced by formalin. At elevated doses of the essential oil extract (50 mg/kg), the inhibitory effect was observed in both phases. Further, it was highlighted that the inhibition in both phases of the formalin test by monoterpenes may be attributed to the blockade of the voltage-dependent sodium ion channels (thus stabilizing the excitable membrane) or the involvement of the descending modulatory pain systems. The capsaicin test demonstrated strong analgesic activity at all doses. This model is relevant to the activation of the capsaicin vanilloid receptors, which elicit axon reflex vasodilation.

Moreover, *Mentha arvensis,* commonly known as wild mint in India and Bangladesh, was analyzed for its pain-relieving effects. The effects of the ethanolic extract of the plant were evaluated using the acetic-induced writhing test in mice. At oral doses of 250 and 500 mg/kg-bw, the extract displayed 46% and 64% writhing inhibition, respectively, whereas the standard drug, diclofenac sodium, exhibited 77% inhibition at a lower dosage of 25 mg/kg [44].

The root of the climber, *Ichnocarpus frutescens*, which originated in India, was evaluated for its analgesic efficacy. The methanolic extract of the root demonstrated positive analgesic effects against acetic-induced writhing; furthermore, it exhibited nociceptive peripheral pain effects and the highest percentage of inhibition (59%) at a dose of 1 mg/kg in an *in vivo* animal model. Therefore, the study confirms the role of the methanolic root extract of *Ichnocarpus frutescens* in the management of pain in arthritis, comparable to the compound dexamethasone like phytosterol property [45].

The indigenous African plant, *Antrocaryon klaineanum*, is traditionally used for the treatment of pain. Fongang *et al*. [46] assessed the analgesic properties of the methanolic extract of the stem bark in a rat model. In the acetic-induced writhing test, at a dose of 600 mg/kg, the extract caused a significant decrease in abdominal constriction at a percentage of 45%. In the formalin test, the plant extract inhibited the nociceptive response by 59% at the highest dose (600 mg/kg). In the hotplate test, at doses of 400 and 600 mg/kg, the extract caused an increase in the latency time, which explains its central analgesic properties. The experiments revealed that the plants could be used to treat acute and neurologic pain.

Sinomenium acutum is used in Chinese herbal medicine to treat rheumatoid arthritis. Sinomenine, a phytochemical compound isolated from the root of *Sinomenium acutum,* is responsible for its analgesic potential in relieving neuropathic pain. Gao *et al*. [47] confirmed this by performing the hotplate test and tail-flick test. The results of the hotplate test showed a latency time of 30 min at a dose of 40 mg/kg. In the tail-flick test, a change was observed at 30, 60, and 90 minutes using the same dosage. Harisha *et al*. [48] evaluated the analgesic effect of the folklore medicinal plant *Cissus rependa*, which originated in Orissa. The effects of the root and stem extracts were evaluated in the formalin-induced

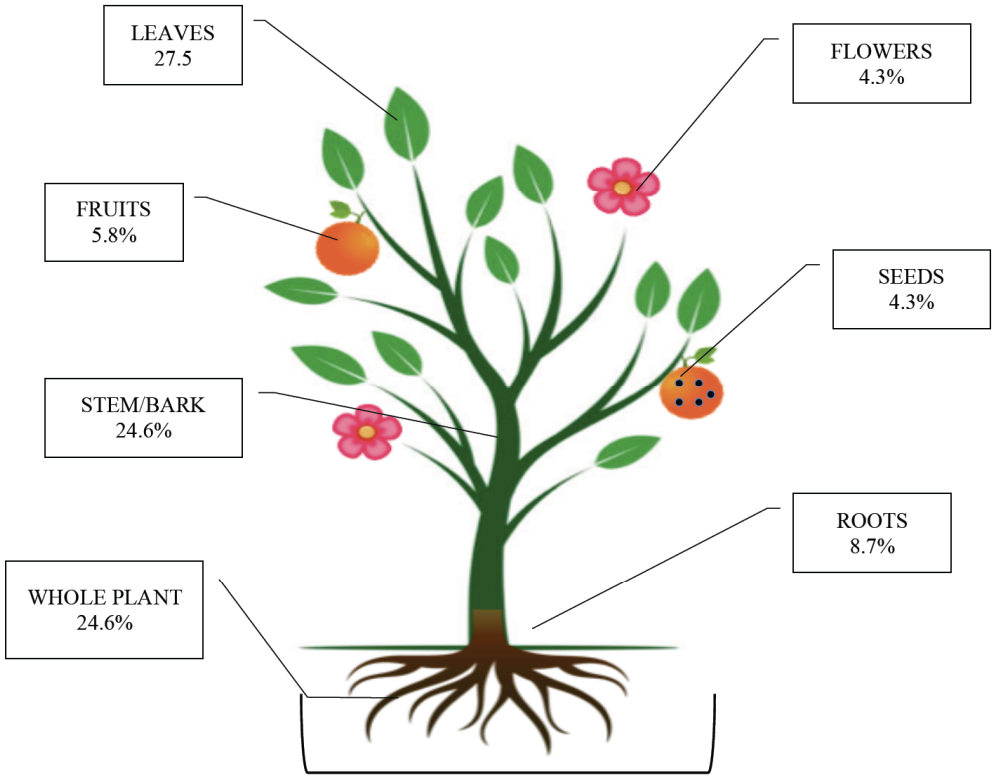

Fig. (2). Plant part used for analgesic activity.

pain test and tail-flick test. The root extract was effective in reducing the paw licking episodes in both phases. Nevertheless, the stem extract of the plant failed to antagonize this effect and no change was seen in the tail-flick test. The aqueous flower extract of *Opuntia microdasys* (100 mg/kg) reduced pain by inhibiting prostaglandin synthesis. Furthermore, the abundance of polyphenols and, especially, flavonoids, such as kaempferol (159±3 µg/g extract, n=6) and isorhamnetin (14 368±28 µg/g extract, n=6), in the *O. microdasys* flowers could be correlated with this significant pain-relieving activity [49].

In an experimental randomized study, complex behavior was observed when patients suffering from chronic pain due to fibromyalgia inhaled cannabinoids; only a minimal analgesic response was observed after a single inhalation. However, further detailed studies are necessary to determine if this could be used as a long-term treatment to manage pain [50]. Based on the reviewed literature, leaves (27.5%) (Fig. **1**) were the most common plant part studied for their analgesic activity, followed by stem/barks (24.6%) and whole plants (24.6%) (Fig. **2**). Other parts, such as seeds and flowers, as well as multiple plants parts, were the least used. This is explained by the fact that leaves are more available, compared to other plant parts, and their plucking would cause no severe harm or impair the survival of the plant or tree, as harvesting the root would [51]. Different types of extraction solvents were used for the different analgesic tests. The most frequently used extraction solvent was methanol (34%), followed by ethanol (29%). Other solvents, such as ethyl acetate (7%), petroleum ether (6%), hydroalcoholic (5%), crude (4%), aqueous (4%), alcoholic (3%), hexane (3%), essential oil (2%), and acetone (1%), were less frequently used (Fig. **3**).

3.3. Bioactive Constituents

Several studies have reported the pharmacological properties, including analgesic and anti-inflammatory effects, of plants utilized for their therapeutic benefits; the effects mentioned in these studies were supported by the presence of phytochemicals. Since ancient times, the most common and natural remedy for the treatment of pain was opium. Greek and Roman medical practitioners used opium as a pain reliever and sleep inducer. From the plant *Papaver somniferum*, bioactive compounds, such as morphine, codeine, and thebaine, were derived. Researchers have found that opioid analgesics evoke pain relief by the activation of opioid receptors such as the mu opioid peptide receptor. However, several side effects, such as constipation, respiratory problems, depression, and tolerance, were also attributed to opioid use [52]. *Mitragynine speciosa*, which originated in Thailand, was screened and an alkaloid called mitragynine was found. This compound displayed analgesic, muscle-relaxant, and anti-inflammatory properties. Nevertheless, its administration at high dosages was linked to anorexic effects, tolerance, and unpleasant withdrawal effects. Further, another compound, salvinorin A, derived from the plant *Salvia divinorum,* was found to be a kappa opioid peptide receptor agonist; this compound was previously used to aid in childbirth [53]. Quintans-Júnior *et al.* [54] demonstrated the analgesic activity of the monoterpene citronella from the plant *Corymbia citriodora*; its effect is also mediated *via* the opioid system.

Opioid peptides, such as beta-endorphin, enkephalin, and diamorphine, are broadly dispersed in the hypothalamus, brain, and spinal cord. Opioid peptides bind to opioid receptors (mu, delta, and kappa receptors) to diminish the release of nociceptive substances and cause a strong analgesic effect. The aromatic monocyclic monoterpene, *p*-cymene, which is naturally present in the volatile oils of certain plants, was antagonized by naloxone in a tail-flick test [55]. Furthermore, menthol from peppermint is commonly utilized for the relief of pain due to injuries and arthritis. Naloxone and nor-BNI serve as antagonists against the antinociceptive effect of menthol [56]. Quercetin, which is one of the major flavonoids present in allium species, was found to mitigate cancer

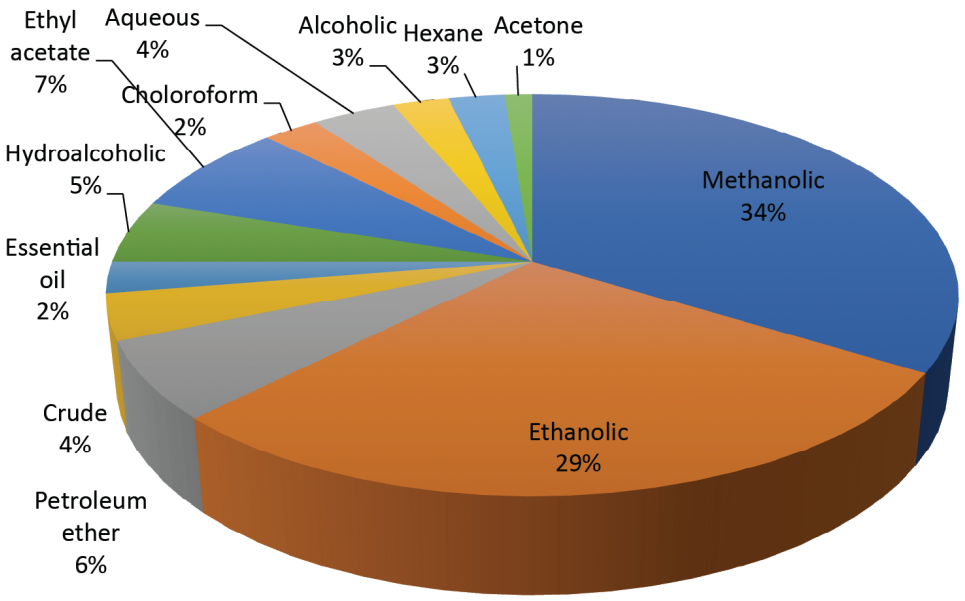

Fig. (3). Types of extracts used in analgesics tests.

pain and neuropathic pain in diabetic patients through an opioid-dependent analgesic mechanism [57]. Capsaicin, the dominant ingredient present in hot peppers or capsicum, was suggested to elevate proopiomelanocortin mRNA levels in the arcuate nucleus of rat models, suggesting that the analgesic properties of capsaicin are linked to the cerebral opioid system [58].

Indrayoni *et al* [59] studied the metabolic profile of *Justicia gendarussa*. The ethanolic extract of the *Justicia gendarussa* leaves was tested for its analgesic effect using the acetic-induced writhing and hotplate tests; positive results were obtained. This extract is traditionally used to treat rheumatic pain; the bioactive components present include friedelin, β-sitosterol, lupeol, apigenin conjugates, and justidrusamides A-D. Lupeol, isolated from the stem of *Diospyros mespiliformis*, displays pain-relieving properties [60]. It mediates the inhibition of interleukin-1 beta and tumor necrosis factor alpha synthesis. Likewise, fridelin, found in *Azima tetracantha*, and ursolic acid, found in *Cissus repens*, both displayed analgesic and anti-inflammatory activities [61, 62].

Calotropis gigantea leaves were used by the Bhil tribe in India to treat body pain [23]. Studies have reported that the leaves contain calotropagenin, calactin, calotoxin, calotropin, taraxasteryl acetate, beta-sitosterol, stigmasterol-alpha, and beta-amyrin [63, 64]. *Mimosa pudica* is an indigenous plant used for the treatment of arthritis in India, headaches in Panama, and stomach pain in Mexico [65]. The aqueous extract of the plant demonstrated antinociceptive activity in the hotplate test, tail-flick test, and acetic-induced writhing test. This extract contained beta-sitosterol, leucoanthocyanidin, dimethyl crocetin, quercetin, luteolin derivatives, mimosainic acid, and mimosinamine [66]. Further, Chan *et al*. (Chan *et al*., 2016) reported that the fruits of *Vitex trifolia* were used to treat headaches, migraines, and rheumatism in Asian regions. They reviewed the compounds that demonstrated analgesic potential and identified the presence of flavones, such as glycosides, luteolin, ursolic acid, and m-hydroxy benzoic acid, and flavonoids, such as casticin, vitexin, artemetin, corniferaldehyde, and vanillin.

In a recent review, [67] gave a detailed account of the pharmacological and remedial activity of several species of mushrooms. They confirmed the effects of the following species together with their respective bioactive compounds: *Pleurotus pulmonarius* (β-glucans), *Pleurotus florida* (hydroethanolic extract), *Pleurotus eous* (methanol and aqueous extract), *Agaricus brasiliensis* (fucogalactan), *Agaricus bisporus* var. hortensis (fucogalactan), *Agaricus macrospores* (agaricoglycerides), *Coriolus versicolor* (polysaccharopeptides), *Cordyceps sinensis* (cordymin), *Termitomyces albuminosus* (crude saponin and polysaccharide extract), *Inonotus obliquus* (methanol extract), *Phellinus linteus* (ethanolic extract), *Lactarius rufus* (soluble β-glucans), and *Grifola frondosa* (agarucoglycerides).

Wang *et al*. [68] studied the progress of analgesic components commonly used in traditional Chinese medicine and compiled all the compounds that were shown to produce a positive analgesic effect *in vivo*. The different compounds obtained from plants were categorized as alkaloids, flavonoids, terpenes, aromatic compounds, coumarins, and lignans. The following 39 alkaloids were reported: trilobine, palmatine, tetrandrine, berberine, rhoifoline A, dicentrine, govaniadine, sinomenine, tetrahydropalmatine, gelsemine, coronaridine, rutaecarpine, mitragynine, harmine, 21-O-syringoylantirhne, alangine, antirhine, harmane, norharmane, mesaconitine, yunaconitine, lappaconitine, bullatine A, aconitine, guiwuline, incarvillateine, 8-O-ethylaconosine, aconicarmisulfonine A, oxymatrine, spectaline, huperzine A, matrine, capsaicin, scotanamine B, skimmianine, veratraline A, veratraline B, veratraline C, and isomurrayafoline B. As for the flavonoids, 16 compounds were screened, including gossypin, hyperin, chrysin, lycopene, eupatilin, acacetin, ellagic acid, quercetin, rutin, kaempferol, hesperidin chalcone, hesperidin, curcumin, kempferol-3, 4′-di-Oα-L-rhamnopyranoside, and myricitrin. The terpenes consisted of 1,8-cineole, p-cymene, menthol, paeoniflorin, borneol, swertiamarin, geniposide, geraniol, 6-gingerol, and myrtenol. The aromatic compounds were paeonol, divaricatol, cinnamaldehyde, sinapyl alcohol, and caffeic acid. The ten coumarins were as follows notopterol, columbianadin, daphnetin, decursinol, 7-hydroxycoumarin, osthole, albiflorin, scopoletin, fumaric acid, and embelin. Finally, the only lignin was liriodendrin.

In India, spices are one of the pillars of tradition and are widely used in every Indian kitchen. Interestingly, in addition to providing taste and aroma, spices were found to be medically beneficial. Turmeric, which is also known as the golden spice, was found to cure rheumatic pain and gastrointestinal pain and have strong wound healing properties. *In vivo, in vitro,* and clinical studies have confirmed the efficacy of the different extracts of Curcuma species in osteoarthritic patients. The patients showed significant improvement in terms of pain relief, physical movement, and quality of life after the administration of curcumin. A decrease in the use of concomitant analgesics and side effects was also reported. *In vitro* research determined that curcumin possibly inhibits the apoptosis of chondrocytes, reduces the release of proteoglycans and metal metalloproteases, and suppresses the expression of COX, prostaglandin E2, and inflammatory cytokines in chondrocytes [69].

Ginger has been traditionally used as a painkiller. This is of interest as it is suggested that ginger can heal multiple types of pain. Ginger ointments are prepared by crushing ginger and then adding water (a little at a time); this preparation is then applied to the forehead to relieve headaches. Applying the same ointment to the gum helps alleviate toothaches. A few drops of ginger juice instilled into the ear can alleviate earaches. New compounds isolated from ginger rhizomes include cassumurins A, B, and C, which are found to have strong antioxidant and anti-inflammatory potential. Numerous spices are prospective sources of compounds useful for the treatment of pain. These include curcuma, black cumin, ginger, garlic, saffron, black pepper, and chilli pepper, which contain many effective bioactive compounds, such as curcumin, thymoquinone, piperine, and capsaicin. These bioactive compounds mainly exert their effects by interfering with various mechanisms such as apoptosis; suppressing proliferation, migration, and invasion of tumors; and sensitizing tumors to radiotherapy and chemotherapy [69, 70].

3.4. Animal-Derived Compounds with Analgesic Properties

Biologically active compounds isolated from animal sources were found to have potent effects. Zadeh-Ardabili and Rad [115] concluded that fish oil and Neptune krill oil could exert a potential analgesic effect by downregulating pro-inflammatory cytokines. Results showed that 500 mg/kg of fish oil and Neptune krill oil reduced the number of writhes by 22.5% and 50%, respectively, in the acetic-induced writhing test in mice. The analgesic effect of the crude petroleum ether and ether extracts of electric rayray fish (*Narcine brunnea*) was assessed using the hotplate test and tail clip method in rats. In the hotplate test, the petroleum ether extract and ether extract displayed a basal reaction time from 2.150±0.043 and 2.300±0.058 at 0 min to 6.102±0.037 and 8.783±0.070 at 120 min, respectively. In the tail clip method, a significant increase in the basal reaction time of 6.817±0.031 in petroleum ether and 8.852±0.043 in ether extract was observed at 120 min ($P<0.05$), compared to the control groups (2.233±0.061). The compounds, which are present in the crude extract of the electric ray and are responsible for its analgesic properties, were identified as 3, 5- dihydroxy phenyl acetic acid, N-methyl 2, 3- dihydro 3-but-2-enyl indole 5-sulphonic acid, and 3-but-2 enyl indole-5-sulphonic acid. Interestingly, the same compounds were also identified in other marine sources, such as herring, mackerel, cod liver oil, and shark liver oil [116].

Animal venoms are definite reservoirs for drug discovery and the enhancement of pharmacological tools [117]. Leite dos Santos and colleagues [118] investigated the antinociceptive potential of *Micrusrus lemniscatus* venom by performing the writhing test, formalin test, and tail-flick test *in vivo*. Oral administration of a dry crude extract of *M. lemniscatus* at a dose of 19.7-1600 µg/kg caused a significant inhibition of the abdominal constriction induced by acetic acid. In the formalin test, oral administration of 1600 µg/kg of the extract caused an analgesic effect in both the early and late phases in the central mechanism. An orally administered dose of 177-1600 µg/kg of venom extract enhanced the reaction time in the tail-flick test; this effect lasted for 5.5 hours. The *M. lemniscatus* venom acts in the opioid system *via* the µ-opioid receptor.

Saez and Herzig [119] reviewed the versatile repertoires of peptides in spider venom and their therapeutic effects for medicinal application. Some of the pain-relieving peptides are Pn3a (*Pamphobeteus nigricolor*), Cd1a (*Ceratogyrus darlingi)*, protoxin-III (*Thrixopelma pruriens*), CcoTx1 (*Ceratogyrus marshalli*), GpTx1 (*Grammostola porteri*), and Phα1β (*Phoneutria nigriventer*) [120-129].

The spider neurotoxin, PhTx3-6, is patented as an antinociceptive agent (Ph α1β). The analgesic effects were assessed using the formalin test in Wistar rats pre-treated with Phα1β (100 pmol/site); the nociceptive behavior was reduced by 72.0±7.8% (n=4-12 per group). Multiple isoforms of Phα1β have demonstrated to have analgesic potency, including PnTx3-3, PnTx3-4 and PnTx3-5 [127]. However, adverse effects, including body shaking and serpentine-like tail movements due to the high dose, have been documented [127]. Similar results demonstrating the synergistic analgesic activity of Phα1 β in combination with the TRPV1 blocker were confirmed in animal studies [130]. Furthermore, Deuis *et al*. [124] revealed that the original GpTx1 peptide from tarantula exerted analgesic effects when administered locally, but not systemically, as evaluated in an OD1-induced spontaneous pain rat model. Another novel neurotoxin, Huwentoxin-XVI (HWTX- XVI), extracted from the venom of the Chinese tarantula, *Ornithoctonus huwena*, was tested for its pain relief properties using the formalin test and hotplate test *in vivo*. A dose of 112.7 nmol/kg was intraperitoneally injected and the effect of the neurotoxin was evaluated in the formalin test; it was observed that pain was reduced only in the second phase. In the hotplate test, an acute thermal pain model was used; a dose of 56.3 nmol/kg of HWTX-XVI showed slight analgesic activity with a maximum effect of 68±7% (n=8) from 0.5 to 1 hour after injection. A plantar incision rat model was used to test the analgesic effect of the venom on mechanical allodynia. Intramuscular infusion of venom at a dose of 56.3 nmol/kg displayed a significant reduction of post-incision allodynia, reaching its maximum effect at 2.5 hours [131].

In a study by Maatooug *et al*. [132], a new scorpion toxin, *Buthus occitanus tunetanus* (BotAF), was analyzed for its potent analgesic effect in rodents. The antinociceptive writhing test revealed a positive analgesic effect up to 50%, even after 90 min after the BotAF (5 mg/kg; intraperitoneal) injection. This result also indicated that BotAF is a 2.3-fold stronger analgesic compound than the standard drug beta-endorphin for viscera-somatic pain. BotAF was tested using the hotplate method to evaluate its efficacy in reducing acute somatic nociception. The same dose had a maximum effect at 60 min after intraperitoneal injection. The analgesic activity was further evaluated using the tail-flick test and formalin test. The results of the tail-flick test revealed that a maximal antinociceptive effect was obtained at 60 min and was still significant up to 120 min after injection. The formalin test suggested that BotAF acted on both phases when injected locally; moreover, on average, BotAF was shown to be more efficient (2-fold increase) than morphine sulfate. Furthermore, the venom of scorpion *Buthus martensii* Karsch is traditionally used to treat several diseases; it has also been used as a painkiller. The peptide BmK AGAP-SYPU2 was assayed using the mouse-twisting model (pain in the internal organs) and the hotplate test (pain in the limbs) *in vivo*. In the mouse-twisting model, the peptide was intravenously injected at different doses; the maximum dose (0.35 mg/mL) showed an analgesic effect. The hotplate test demonstrated that 0.35 mg/mL of BmK AGAP-SYPU2 had a stronger analgesic effect than the positive control (morphine; 1.5 mg/kg). Therefore, the neuropeptide exhibited a powerful analgesic effect against both visceral and somatic pain [133].

Bee venom has been used in oriental medicine to treat several diseases and relieve pain through a chemical acupuncture point, termed apipuncture [134]. Shin *et al*. [135] studied the effectiveness of bee venom acupuncture for reducing pain and disability in subjects suffering from chronic lower backpain using a randomized, sham-controlled, triple-blind, two-group parallel clinical trial. Sixty participants

were randomly divided into a bee venom acupuncture group and a sham control group. In total, six acupoints (0.1 mL BVA for each acupoint) were injected for an interval of 4 weeks. Both groups responded positively without any adverse reactions and medical interventions showed improvements in pain intensity; thus, it was concluded that this therapy can be considered safe for managing pain. Jeong *et al*. [136] attempted to enhance the efficiency of bee venom acupuncture by loading the venom into biodegradable poly(d,l-lactide-co-glycolide) nanoparticles (BV-PLGA-NPs) using a water-in-oil-in-water-emulsion/solvent-evaporation technique. A formalin rat test was conducted and bee venom was injected into the Zusanli acupuncture, which significantly reduced pain behavior in the late phase; the effect lasted for approximately 12 hours.

Several bioactive compounds have been identified from amphibian skin secretions. Analgesin-HJ and analgesin-HJ (15T) are two novel analgesic compounds found in the skin of the tree frog *Hyla japonica*. Multiple tests, including the acetic-induced abdominal writhing test, formalin test, and thermal pain test, confirmed the efficacy of the compounds. In the acetic-induced writhing test, analgesin-HJ (1.25, 2.5, and 5 mg/kg) and analgesin-HJ (15T; 1.25, 2.5, and 5 mg/kg) were found to be more potent than the standard drug (morphine; 2.5 mg/kg). An intraperitoneal injection of analgesin-HJ significantly attenuated neurogenic and inflammatory pain responses. In the formalin-induced test, at doses of 1.25, 2.5, and 5 mg/kg, the licking time was reduced by ~106, 90, and 75 seconds, respectively, in a rat model. Applications of both analgesin-HJ and analgesin-HJ (15T) increased the tail-flick latency. The analgesic effect lasted for a minimum of 360 seconds. In the hotplate test, administration at various doses (1.25, 2.5, and 5 mg/kg) increased the latency time to 15, 17.5, and 19 seconds for analgesin-HJ and 16, 17, and 20 seconds for analgesin-HJ (15T), respectively [137].

Recently, a novel compound, anntoxin, has been identified in skin secretions of the amphibian *Hyla annectans* (Jerdon). Different pain tests were carried out in both male and female Kunming mice (20-25 g) using recombinant anntoxin at a dose of 2.5 g/kg. The recombinant anntoxin at a dose of 2.5 g/kg delayed the reaction time to 9 seconds after either 30 or 60 minutes of administration. In the hotplate test, the same dose delayed the reaction time to 22.5 seconds after 60 minutes of administration. In the formalin-induced paw licking test, anntoxin significantly inhibited the response time in the late phase. Lastly, in the acetic-induced writhing test, the analgesic effect of anntoxin was demonstrated as the number of writhings decreased from 72 to 39 with increased doses of anntoxin (0.625, 1.25, and 2.5 mg/kg body weight), compared to the control, which was 90 after 30 minutes of administration [138]. Therefore, it was noted that animal sources contain potent analgesic compounds that can be further evaluated for therapeutic consideration.

4. LIMITATIONS AND FUTURE WORK

In the literature search, certain gaps were noted, which could be reviewed in future studies. First, there was a disparity of information with regard to the traditional use of medicinal plants. Even though the analgesic effects of many indigenous plants were recorded, there was a paucity of information regarding the mode of administration, variety of plants used, dosage, and method of preparation; these details are essential when carrying out ethnomedicinal studies. It was also found that most studies were conducted in Asian and African regions (Table **1**). Furthermore, many studies were rejected as they did not match the inclusion criteria. Correct taxonomic nomenclature, including author citations, allows duplicability and documentation, reducing the risk of misinterpretation [139]. Similar vernacular names are frequently used for numerous species, which are generally not related to each other [140]. Additionally, vernacular names are termed in and within languages, which add further confusion.

Furthermore, it was found that many food plants were traditionally used for their analgesic properties. However, there was no pharmacological validation to critically analyze the data. Therefore, more studies (*in vitro, in vivo*, and clinical studies) should be carried out using traditional formulations to validate the different pharmacological properties. In the present review, many plants were found to have multiple therapeutic properties along with pain alleviating properties. Other data on the herb-drug interactions can help clarify the pharmacodynamics and pharmacokinetic interactions to limit toxicological issues. Analgesic compounds derived from animal sources remain an issue when it comes to ethics and dietary restrictions.

Maatoug *et al*. [132] stated that several analgesic compounds were derived from animals; however, to date, ziconotide is the only toxin-derived medicine used in clinics to treat pain. The major challenges posed when translating preclinical trials to therapeutics are: (i) reaching the right potency and selectivity and (ii) providing the correct target accessibility and coverage. Analgesics from venom sources and species require diverse screening strategies that are target-based, toxin-based, and activity-based.

In this review, we found that 24.6% whole plants and 8.7% roots were used to test for analgesics; thus, it should be noted that the extensive use of some plant species may disturb their ecological patterns and populations, leading to extinction. Considerable investigations should be directed to prevent such harm to the ecological patterns of medicinal plants [141]. Eventually, more than half of all hospitalized patients will suffer from pain in the last stages of their lives. Despite the therapies provided to alleviate discomfort and pain, especially for patients with cancer, studies show that 50% to 75% of patients still die in moderate to severe pain.

Preclinical studies aim to discover disease mechanisms and analgesic targets to implement new treatments and provide more sophisticated therapies; however, only a few new such therapies are being practiced in the medical domain. Other challenges include the translation of preclinical research in murine models to clinical studies in patients. Additionally, the complexity of pain makes it difficult to understand the dimensions of pain. Therefore, a better and more detailed comprehension of the role of reward/motivational circuits in pain could promote analgesic drug discovery in a purposeful way [142, 143]. Much work remains to be done to provide effective treatments using natural ingredients in conjunction with advanced technology.

CONCLUSION

In the present review, the pain was described as sensory occurrence; and was explained as an unpleasant sensory and emotional experience attributed to tissue damage, inflammation and other causative factors. Consequently, this multidimensional entity has been associated with multiple aspects, including sensors, cognition, motivation, affection, behavior, and spirituality. The mechanism of pain is complex, but the condition is still perceived as a plague despite being regarded with such significance. The WHO confirmed that approximately 80% of the global population is deprived of proper access to opioid analgesics for the treatment of pain. Despite the fact that opioids and non-steroidal anti-inflammatory drugs, such as morphine and aspirin, have proven efficacy, they are associated with potentially harmful side effects and societal drawbacks. In this review, an attempt was made to critically assess and describe the pharmacological properties and bioactive composition of indigenous plants, some animal species, and animal venom by scrutinizing databases and looking for published articles. It should be noted that the analgesic activities were highlighted and the *in vivo* results were also compiled. Therefore, it can be concluded that the compounds obtained from these sources can serve as important ingredients in therapeutic agents to alleviate pain once their limitations are assessed and improved upon.

AUTHORS' CONTRIBUTION

All authors were involved in conceptualization. F. Mahomoodally and T. Joaheer did the data mining. K. Rangasamy and Yansheng Zhang reviewed and edited the manuscript and language check. All authors were actively involved in the preparation of the first draft and editing.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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