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*Original Article*

# Medicinal and Dietary Plants as Dual Modulators of Pain and Central Nervous System Activity: Phytochemical Basis, Mechanisms of Action and Preclinical Evidence

**Tejasvi U. Dalavi*, Ushahprabha S. Potphode, Mayuri L. Pawar, Pratiksha K. Mohite, Shivani G. Mohite, Shreya A. Bele**

*Department of Pharmacology, PES Modern College of Pharmacy, Moshi, Pune,.*

## ABSTRACT

Pain and anxiety or other central nervous system (CNS) disturbances frequently coexist and share neurobiological substrates, yet existing analgesics, benzodiazepines and opioids are limited by adverse effects, dependence and poor tolerability. Medicinal and dietary plants are rich in flavonoids, alkaloids, terpenoids and phenylpropanoids and are attractive sources of agents that act on both pain and CNS pathways. This review summarizes the phytochemical basis, mechanisms of action and preclinical evidence for such dual activity. The most frequently reported mechanisms are positive modulation of GABA-A receptors, regulation of ion channels (TRPV1, ATP-sensitive K+ and voltage-gated Na+/Ca2+ channels), opioidergic and nitrergic signalling, and inhibition of cyclooxygenase-mediated inflammation, with antioxidant activity as a contributing factor. Extracts of *Tragia involucrata*, *Cajanus cajan*, *Aloysia gratissima* and *Passiflora incarnata* show antinociceptive and/or anxiolytic-sedative activity in rodents, and dietary herbs such as ginger, turmeric, black pepper and lavender provide translational support. Most evidence comes from acutely dosed crude extracts, with limited compound-level validation, small groups and scarce pharmacokinetic and blood-brain barrier data. Standardized extracts, ARRIVE-compliant reporting, mechanism-confirmatory studies and well-designed clinical trials are needed to translate these findings.

**Keywords:** Medicinal plants, Dietary herbs, Analgesia, Anxiolytic, GABA-A receptor, Phytochemicals, Preclinical studies

## INTRODUCTION

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [1]. Its emotional dimension helps explain why persistent pain so often coexists with anxiety and depression. A World Health Organization study in primary care found that persistent pain was associated with psychological illness across countries [2], and the literature on depression and pain describes a bidirectional, mutually worsening relationship [3].

The standard drug classes for these overlapping conditions each carry liabilities. Non-steroidal anti-inflammatory drugs increase vascular and upper gastrointestinal risk [4], opioids are associated with misuse and dependence in chronic pain [5], and benzodiazepines cause dependence and cognitive and psychomotor harm [6]. Such limitations sustain interest in alternatives, and natural products have long been a productive source of new drugs [7].

Plant-derived compounds and extracts have been reviewed extensively as analgesic leads [8–10] and as anxiolytic or sedative agents [11–13]. Fewer reviews consider both activities together. In this article, a "dual modulator" means a plant, extract or constituent for which both antinociceptive and CNS-depressant, anxiolytic or sedative effects have been reported, ideally through shared mechanisms such as GABAergic or ion-channel modulation. We examine (i) the phytochemical classes involved, (ii) proposed mechanisms of action, (iii) the preclinical evidence for medicinal and dietary plants, and (iv) the methodological and translational gaps that currently limit clinical application.

### 2. Methodology of Literature Search

**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Relevant literature for this review was collected systematically, following the PRISMA approach. We searched PubMed/MEDLINE, ScienceDirect and Google Scholar thoroughly for studies on medicinal and dietary plants with analgesic, anxiolytic, sedative and other central nervous system activities. To widen the coverage, we also looked at other sources, including books, dissertations and material published online. We drew mainly on primary sources, meaning original research articles that reported the data directly. In vitro, in vivo and clinical studies were all considered, so that the review would cover the full path from laboratory findings to human evidence. Only articles published in English were included. Review articles were used mostly to understand the background and mechanisms, and the findings reported in the primary studies were given priority in the discussion.

## 3. Phytochemical Basis

Four chemical groups account for most of the activity reported for dual-acting plants (Table 1). Phytochemical screening in the primary studies is usually qualitative, so assignment of activity to a specific constituent should be treated with caution until isolation or standardized chemical profiling supports it.

### *3.1 Flavonoids and other phenolics*

Flavonoids are the best-characterized group. Several act as ligands at the benzodiazepine site of the GABA-A receptor and show anxiolytic and sedative effects [14]; apigenin, from *Matricaria recutita*, was an early example of a flavone with central benzodiazepine-receptor affinity and anxiolytic activity [15]. In *Passiflora incarnata*, anxiolytic activity in the mouse elevated plus maze has been traced to defined fractions [16] and to the GABAergic system [17]. Flavonoids are also central to the antinociceptive profile of seed extract of *Cajanus cajan*, in which rutin, quercetin, luteolin, pinostrobin, biochanin A, formononetin and apigenin were identified by HPLC-DAD [18]. Phenolic-rich extracts with antioxidant and anti-inflammatory activity, such as grapevine leaf extract characterized by LC-MS/MS, add an inflammatory-pathway component to analgesia [19].

### *3.2 Terpenoids and essential oils*

Essential oils and their monoterpene, sesquiterpene and phenylpropanoid constituents have been reviewed for antinociceptive activity in animal models [20], and Lamiaceae species are a prominent source in pain therapy [21]. The sesquiterpenes guaiol and pinocamphone were identified in a supercritical CO2 extract of *Aloysia gratissima* leaves, which was antinociceptive in mice [22]. A standardized lavender oil preparation (silexan) was effective in a randomized, placebo-controlled trial in subsyndromal anxiety [23], which illustrates how an essential-oil product can progress from preclinical to clinical anxiolytic testing.

### *3.3 Alkaloids, lignans, vanilloids and cannabinoids*

Alkaloids, lignans and other secondary metabolites contribute to the analgesic and sedative effects of many extracts, as reviewed for plant-derived analgesic principles [8,9]. The ethanol extract of *Syringa oblata* heartwood, rich in lignans, produced analgesic and sedative effects in mice [24]. Pungent dietary vanilloids such as gingerols and piperine act at TRPV1 (Section 4.2). Cannabinoids (tetrahydrocannabinol and cannabidiol) are a clinically studied example of plant constituents used for chronic pain with comorbid mental health conditions [25].

**Table 1: Phytochemical Classes, Representative Sources and Principal Reported Targets**

| Class | Representative constituents / sources | Principal reported targets | Refs. |
|---|---|---|---|
| Flavonoids | Apigenin (*Matricaria recutita*); rutin, quercetin, luteolin, pinostrobin (*Cajanus cajan*); *Passiflora incarnata* fractions | GABA-A benzodiazepine site; COX-2 and μ-opioid receptor (docking); antioxidant | [14–18] |
| Terpenoids / essential oils | Guaiol, pinocamphone (*Aloysia gratissima*); Lamiaceae essential oils; lavender oil | ATP-sensitive K+ channels; multiple antinociceptive pathways; anxiolytic effect (lavender oil, clinical) | [20–23] |
| Vanilloids / phenylpropanoids | Gingerols (ginger); piperine (black pepper) | TRPV1 (agonism and subsequent desensitization) | [26,27] |
| Curcuminoids | Curcumin (turmeric) | Anti-inflammatory and antioxidant actions; low bioavailability | [28–30] |

| Class | Representative constituents / sources | Principal reported targets | Refs. |
|---|---|---|---|
| Lignans | Syringa oblata heartwood | Analgesic and sedative effects (mice) | [24] |
| Cannabinoids | THC, cannabidiol (*Cannabis sativa*) | Chronic pain with comorbid mental health conditions | [25] |

## 4. Mechanisms of Action

### *4.1 GABAergic modulation*

The GABA-A receptor carries several allosteric binding sites besides that for GABA itself [31], and many plant constituents interact with the benzodiazepine site or other modulatory sites [14]. A systematic review of GABA-modulating phytomedicines identified ten herbs, including valerian, passionflower, chamomile, ashwagandha, kava and lemon balm, for which both preclinical GABA-system interaction and human trials exist [32]. Preclinical reviews likewise report that GABA, through receptor binding, ion-channel modulation, or inhibition of GABA transaminase and glutamic acid decarboxylase, is the commonest mechanism among anxiolytic botanicals [12]. Because the GABA system takes part in pain, sleep and anxiety alike [32], it is the most plausible shared target for dual activity. Extracts that increase open-arm exploration in the elevated plus maze and also reduce writhing or formalin responses, as reported for *Tragia involucrata* [33], are consistent with this concept, although receptor-level confirmation (for example, flumazenil reversal or binding assays) is usually missing.

### *4.2 Ion channels*

Transient receptor potential (TRP) channels transduce noxious thermal and chemical stimuli [34], and TRPV1 was identified as the capsaicin receptor in nociceptors [35]. Piperine, the pungent principle of black pepper, activates human TRPV1 [27], and gingerols from ginger are vanilloid-receptor agonists [26]. Sustained TRPV1 activation can desensitize nociceptors, which offers a route to analgesia [34]. A review of 79 plant-derived compounds and extracts catalogued interactions with voltage-gated Na+, Ca2+ and K+ channels, TRP channels, P2X and acid-sensing ion channels [36]; related reviews focus on voltage-gated sodium and calcium channels [37] and on ion-channel modulation by traditional eastern medicine phytochemicals [38]. A single-plant example is *Aloysia gratissima*, whose antinociceptive effect in the formalin test was prevented by glibenclamide but not by naloxone, indicating ATP-sensitive K+ channel involvement without an opioid component [22].

### *4.3 Opioidergic and nitrergic signalling*

For *Cajanus cajan* seed extract, antinociception was blocked by pretreatment with naloxone or L-NAME, and docking suggested interaction of pinostrobin with the μ-opioid receptor, supporting opioidergic and nitrergic involvement [18]. Antagonist-reversal experiments provide pharmacological evidence of pathway involvement, but they do not prove receptor binding by a defined constituent, and non-specific effects on locomotion or arousal need to be excluded.

### *4.4 Inflammatory mediators and oxidative stress*

Inhibition of cyclooxygenase and phospholipase A2 is a frequent peripheral component of plant analgesia. In *Cajanus cajan*, docking indicated interaction of seed constituents with COX-2 and PLA2, in line with in vivo anti-inflammatory activity [18]. Anti-inflammatory and analgesic activity together with antioxidant capacity has been reported for grapevine leaf [19] and for *Syzygium cumini*, which also showed muscle-relaxant and sedative effects in mice [39]. Broader reviews connect phytochemical antioxidant and anti-inflammatory effects with pain relief [8,10] and with the neurochemistry of anxiety [11,13]. Such effects are better regarded as contributory than as primary dual-action mechanisms.

## 5. Preclinical Evidence

Table 2 summarizes selected rodent studies in which at least one nociceptive and one CNS endpoint, or a mechanistic analysis of analgesia, was reported. Several extracts produced both antinociceptive and anxiolytic or sedative effects in the same study, including *Tragia involucrata* [33], *Alpinia calcarata* [40], *Syringa oblata* [24] and *Pothos scandens* [41]. Others, such as *Cajanus cajan* [18] and *Aloysia gratissima* [22], illustrate mechanism-focused antinociception without a primary CNS-depressant profile. *Clerodendrum petasites* is notable because CNS safety was assessed explicitly alongside antinociception [42].

**Table 2: Selected Preclinical Studies on Dual or Mechanism-Defined Activity (Rodent Models)**

| Plant (part) | Reported activity | Key findings and proposed mechanism | Refs. |
|---|---|---|---|
| *Tragia involucrata* (leaves) | Anxiolytic, sedative, analgesic | Methanol, ethyl acetate and n-hexane extracts active in elevated plus maze, pentobarbital sleep, writhing and formalin tests in Swiss albino mice; heavy-metal content also quantified | [33] |
| *Cajanus cajan* (seeds) | Antinociceptive, anti-inflammatory | Writhing, formalin and hot-plate activity; blocked by naloxone and L-NAME; docking with μ-opioid receptor, COX-2 and PLA2 | [18] |
| *Aloysia gratissima* (leaves, supercritical CO2 extract) | Antinociceptive | Reduced writhing and formalin responses without altering locomotion or motor coordination; prevented by glibenclamide, not naloxone; no mortality in OECD 423 test | [22] |
| *Passiflora incarnata* | Anxiolytic | Fractions active in the mouse elevated plus maze; GABAergic mediation | [16,17] |
| *Syringa oblata* (heartwood) | Analgesic, sedative | Ethanol extract rich in lignans active in mice | [24] |
| *Syzygium cumini* | Anti-inflammatory, analgesic, muscle relaxant, sedative | Extracts active in mice | [39] |
| *Alpinia calcarata* (leaves) | Analgesic, anxiolytic, sedative-like | Activities reported in mice | [40] |
| *Ficus hispida* (bark) | Antinociceptive, anti-inflammatory, CNS effects | Extract active in experimental animal models | [43] |
| *Clerodendrum petasites* | Antinociceptive; CNS safety | Antinociceptive efficacy with CNS safety profile evaluated | [42] |
| *Pothos scandens* | Neuropharmacological, analgesic, anti-inflammatory | Acetone extract; constituents profiled by GC-MS | [41] |
| *Vitis vinifera* (leaves) | Antioxidant, anti-inflammatory, analgesic, antipyretic | Active constituents identified by LC-MS/MS | [19] |

Taken together, these studies support the plausibility of dual activity but do not establish it. Most are single-laboratory, acute-dosing experiments in small groups of mice, with crude extracts of variable standardization. Where a CNS endpoint is positive, the same sedation or motor impairment may itself reduce responses in reflex-based pain tests, so locomotor and motor-coordination controls, as performed for *Aloysia gratissima* [22], are essential before an effect is called analgesic.

## 6. Dietary Plants and Spices

*Ginger.* Clinical trials of ginger for pain have been summarized in a narrative review [44], and a separate review examined ginger and its sub-components in pain [45]. Mechanistically, gingerols are vanilloid-receptor agonists [26].

*Turmeric.* Curcumin has well-documented anti-inflammatory and antioxidant activity [28]. A systematic review and meta-analysis of randomized trials examined turmeric extracts and curcumin for joint arthritis symptoms [46], and a comprehensive review covered curcumin formulations in preclinical and clinical peripheral neuropathic and postoperative pain [29]. Bioavailability is the main obstacle [30].

*Black pepper.* Piperine activates TRPV1 [27] and, in a pharmacokinetic study in animals and human volunteers, increased curcumin bioavailability [47], which provides a rationale for pepper-containing curcumin combinations. Whether the combination yields additive analgesic or CNS effects still needs controlled testing.

*Tulsi, lavender and ashwagandha. Ocimum sanctum* (tulsi) has been reviewed for wide-ranging traditional and pharmacological uses [48]. Lavender oil (silexan) reduced anxiety in a randomized controlled trial [23], and a high-concentration ashwagandha root extract reduced stress and anxiety scores in adults in a double-blind, placebo-controlled study [49]. Lamiaceae species more broadly have been reviewed in pain therapy [21].

*Cannabis and diet in neuropathic pain.* Reviews of THC- and cannabidiol-based medicines address chronic pain together with mental health conditions [25], and a systematic review has evaluated diet and non-pharmacologic supplements in chronic neuropathic pain [50]. Botanical interventions for neuropathy and neuropathic pain were reviewed recently [51].

### 7. Preclinical Models and Standardization

Evidence for dual activity depends on matched nociceptive and CNS test batteries (Table 3). Acute toxicity is commonly assessed by the OECD 423 acute toxic class method [52], and plant material should be authenticated and quality-controlled according to WHO methods [53]. Animal models of pain capture only some aspects of clinical pain, and their predictive validity is limited [54].

**Table 3: Commonly Used Preclinical Tests in Dual-Activity Studies**

| Test | Domain assessed | Typical endpoint | Refs. |
|---|---|---|---|
| Acetic acid-induced writhing | Peripheral/visceral inflammatory nociception | Number of writhes | [55] |
| Hot-plate test | Supraspinal thermal nociception | Latency to response | [56] |
| Tail-flick test | Spinal thermal nociception | Latency to flick | [57] |
| Formalin test (biphasic) | Neurogenic (early) and inflammatory (late) pain | Licking/flinching time | [58,59] |
| Elevated plus maze | Anxiety-like behaviour | Open-arm time and entries | [60,61] |
| Open field / rota-rod | Locomotion and motor coordination (confound control) | Distance, time on rod | [22] |
| Acute oral toxicity | Safety | Mortality, clinical signs | [52] |

### 8. Safety, Bioavailability and Translational Considerations

Extract composition varies with plant part, solvent and origin, so batch standardization is a precondition for reproducibility [53]. Contaminants matter: the *Tragia involucrata* study quantified arsenic and iron in the leaves [33]. Compound-level pharmacokinetics are rarely reported, and poor bioavailability has been a recurring problem even for well-studied compounds such as curcumin [30], with co-administration of piperine as one proposed solution [47]. For dual activity specifically, evidence that active constituents reach the CNS is generally indirect and rests on behavioural effects. Because CNS effects may include sedation and motor impairment, developers need to define whether sedation is a wanted effect or an adverse event for the intended indication, and CNS safety should be assessed explicitly [42].

### 9. Limitations and Future Directions

Common weaknesses of the primary literature include crude extracts without chemical standardization, single acute doses, absent sample-size justification, non-blinded scoring and lack of mechanistic confirmation. Reporting according to the ARRIVE 2.0 guidelines would improve transparency and reproducibility [62]. Priorities for future work are: (i) bioassay-guided isolation linking defined constituents to GABAergic, ion-channel and opioidergic targets [8,36]; (ii) paired nociceptive and anxiety test batteries with motor controls [22]; (iii) models of chronic and neuropathic pain, where botanical evidence is still limited [50,51]; (iv) formulation strategies that improve bioavailability and CNS delivery [30]; and (v) randomized clinical trials of standardized preparations, building on the clinical experience with lavender oil [23], ashwagandha [49], ginger [44] and cannabinoid medicines [25].

## CONCLUSIONS

Medicinal and dietary plants contain flavonoids, terpenoids, vanilloids, lignans and other constituents that modulate GABA-A receptors, ion channels, opioidergic and nitrergic signalling and inflammatory mediators, giving a credible basis for combined effects on pain and CNS function. The preclinical evidence is encouraging but largely descriptive. Standardized, mechanism-confirmed and adequately reported studies are the next step toward clinical translation.

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