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Gursimran Singh
Department of Pharmaceutical Sciences, Gurur Nanak Dev University, Amritsar, Punjab, India

Awais Ahmad Mubashir
Department of Pharmaceutical Sciences, Gurur Nanak Dev University, Amritsar, Punjab, India

Corresponding Author:
Gursimran Singh
Department of Pharmaceutical Sciences, Gurur Nanak Dev University, Amritsar, Punjab, India

Emerging neuroprotective roles of *Cnidium monnieri*: Modulation of oxidative stress and inflammation in CNS disorders

Gursimran Singh and Awais Ahmad Mubashir

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Abstract
Cnidium monnieri (L.) Cusson ex Juss a traditional medicinal herb rich in bioactive coumarins, flavonoids, and phenolic compounds, is gaining attention for its neurotherapeutic potential. Chronic neurodegenerative diseases such as Alzheimer's and Parkinson's are primarily driven by oxidative stress, neuroinflammation, mitochondrial dysfunction, and calcium dyshomeostasis. This review highlights the compound-specific and multi-target effects of *C. monnieri* in preclinical models of Alzheimer's disease, depression, and neuropathic pain. It includes mechanisms like COX-2 and iNOS inhibition, TRPV1 and p-ERK downregulation, and modulation of calcium signaling pathways (e.g., IP3R/SOCE). Moreover, the extract demonstrates promising antidepressant effects by restoring monoaminergic neurotransmission and exerting anti-inflammatory effects in key brain regions. Together, these findings validate traditional uses of *C. monnieri* and support its modern application as a multi-targeted phytotherapeutic agent for managing CNS disorders.

Keywords: *Cnidium monnieri*, Alzheimer disease, Parkinson disease, neuroprotective role, depression, neuropathic pain

Introduction
Chronic neurodegenerative diseases, such as Alzheimer's and Parkinson's, are characterized by neuroinflammation and mitochondrial dysfunction, leading to increased oxidative stress from reactive oxygen and nitrogen species (ROS and RNS). This oxidative stress promotes neuronal damage and inflammation, creating a vicious cycle of neurodegeneration. Tumor necrosis factor (TNF) plays a dual role, exacerbating inflammation and oxidative stress through TNFR1 while promoting neuroprotection and tissue regeneration via TNFR2 [1].
Multi-targeted herbal therapies offer promising alternatives for CNS disorders, addressing the limitations of GPCR drugs such as side effects and inconsistent efficacy by acting on multiple pathways [2].
It has been used historically to treat symptoms like headaches, light headedness, seizures, and memory loss, which are often associated with neurological imbalance. Its purported capacity to boost circulation and libido is also thought to be suggestive of neurovascular advantages. Modern research is starting to validate its neuropharmacological properties, such as neuroprotection, anti-inflammatory effects, and cognitive enhancement suggesting a possible scientific [3, 4].

CNS-Modulating Effects of C.M constituents
Cnidium monnieri (L.) Cusson ex Juss., a well-known plant in traditional Chinese medicine, is rich in coumarins and other bioactive compounds. Several of its phytoconstituents have shown promising neuroprotective effects through diverse mechanisms, such as antioxidant activity, anti-inflammatory action, cholinergic modulation, and synaptic plasticity enhancement.

Osthole
Mainly osthole are bioactive constituents whereas studies proves their neuroprotective effect. It shows neuroprotective effect through suppression of proinflammatory cytokines.

Moreover, it enhances survival rate of neuron via activating PI3K/Akt and ERK1/2 pathway. Osthole also contribute in downregulation of reactive oxygen species [5].

Imperatorin

Other form of furanocoumarin, imperatorin which are contribute in neuroprotection through inhibition of acetylcholinesterase enzyme responsible for maintaining acetylcholine level in CNS. It is also possessed in anti-oxidant properties which are responsible for reduction in neuroinflammation [6]. Xanthotoxin (Methoxsalen): Xanthotoxin demonstrate sedative and anticonvulsant effect, indicating its potential therapeutic application in epilepsy and anxiety-related disorders. Mechanisms contributes through involving interaction GABA-A receptors, which make more stability in neuronal activity and offering neuroprotective effect [7].

Cnidilin, a relatively less studied coumarine compound found in *cnidium monnieri* has demonstrated anti-inflammatory and antioxidant aactivites in early pharamcological studies. Although its neuroprotective potential to mitigate systemic inflammation implies a possible therapeutic role in managing neuroinflammatory conditions [8]. Isopimpinellin is a polyoxygenated coumarin recognized for its ability to modulate cytochrome P450 enzyme which perform function by reducing neurotoxin aggregation as well as it also contributes in free radical scavenging activity which are responsible for neuroprotection [9]. Bergapten (5-methoxypsoralen) play vital role in treatment of Parkinson like disease which are originated due to MAO present in brain. Whether it also possess anti-oxidant property which are helpful in neuroprotection [10]. Umbelliferone has demonstrated excitotoxicity protection by inhibiting glutamate-induced neuronal death. It also reduces nitric oxide (NO) production and oxidative stress, suggesting its therapeutic potential in stroke and neurodegeneration [11].

Beyond osthole, imperatorin, and xanthotoxin, *Cnidium monnieri* contains several other coumarins, flavonoids, and phenolic compounds that contribute to its neuroprotective activity through multiple mechanisms including anti-inflammatory, antioxidant, anti-apoptotic, and neurotransmitter-regulating effects. Columbianetin, a dihydrofuranocoumarin, exhibits notable anti-inflammatory effects via inhibition of COX-2 and iNOS expression, leading to reduced prostaglandin and NO production. This contributes to its ability to protect neurons from inflammatory damage [12].

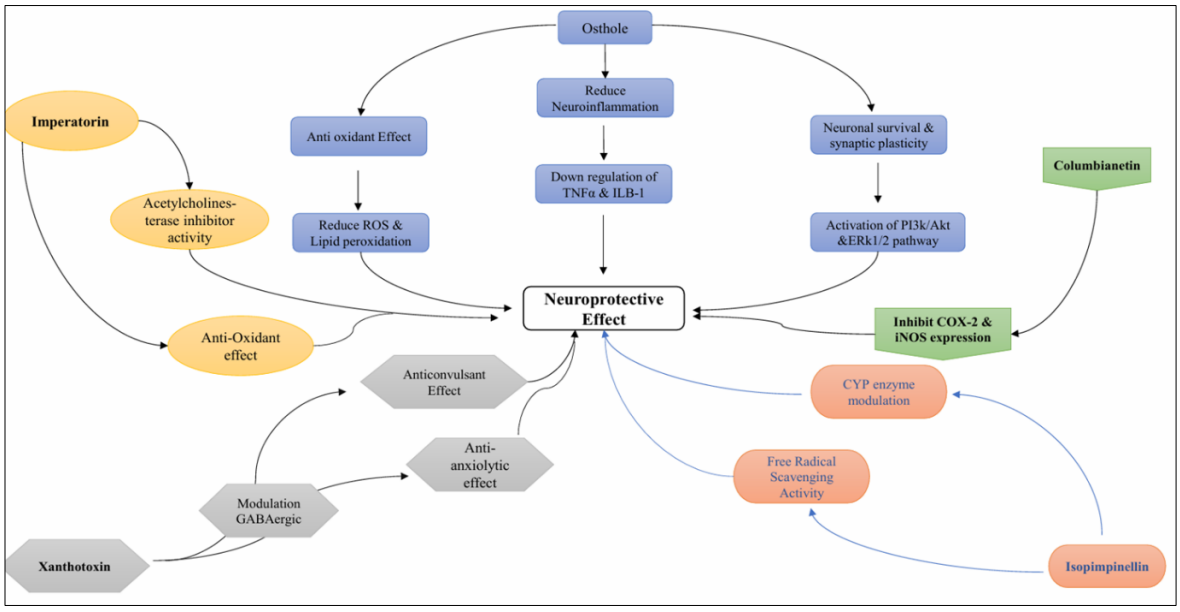

Fig 1: Effect of *Osthole, Isopimpinellin, Xanthotoxin, Columbianetin, Imperatorin* role for neuroprotection in brain

Columbianadin is structurally similar to osthole and exhibits both antioxidant and anti-inflammatory activity. It suppresses NF-κB signaling and reduces ROS levels, suggesting utility in oxidative stress-driven neuronal injury [13]. Scopoletin is a coumarin derivative with MAO-B inhibitory properties, which may help in dopaminergic neuroprotection. It also improves mitochondrial membrane potential and attenuates neuronal apoptosis [14].

Isobergapten (5-methoxy-8-isopentenylpsoralen) shows potential for cholinesterase inhibition and ROS scavenging, although more CNS-specific studies are needed. Preliminary work suggests it could reduce neuronal aging markers [15].

Ferulic Acid (Minor Component) although not a primary component, ferulic acid has been detected in trace amounts in *Cnidium monnieri* extracts. It is a well-established antioxidant and anti-apoptotic agent in models of neurodegeneration [16].

Ligustilide is occasionally co-extracted with *Cnidium monnieri* in Chinese formulations. It modulates calcium homeostasis, inhibits apoptosis, and shows promise in cerebral ischemia [17]. Umbelliprenin is a prenylated coumarin isolated from *Cnidium monnieri* that has been shown to modulate apoptotic pathways, particularly via caspase inhibition and Bcl-2 upregulation, indicating neuroprotective potential in oxidative stress induced neuronal injury [18]. Auraptene is a geranyloxycoumarin present in *C. monnieri* extracts and also abundant in other Rutaceae family members. It has been shown to cross the blood-brain barrier and exert anti-inflammatory effects on microglia, along with neurotrophic factor induction (e.g., BDNF expression) [19]. Panaxynol (Trace Component) although more commonly associated with *Panax* species, panaxynol or similar polyacetylenes have been detected in complex *C. monnieri* decoctions. It displays anti-

inflammatory effects via NF-κB inhibition, helping suppress microglial activation in neurodegenerative settings [20].

Psoralen is a linear furanocoumarin found in both *Cnidium monnieri* and *Psoralea corylifolia*. It exhibits neuroprotective and antiepileptic effects, likely due to its modulation of ion channels and antioxidant capacity. However, its potential for photosensitization limits its clinical utility unless chemically modified [21]. Cnidicin, another structurally related coumarin, is known to act as a vascular relaxant and calcium channel blocker. These properties may reduce excitotoxicity and cerebral ischemia-related damage by improving blood flow and stabilizing intracellular calcium levels in neurons [22].

Marmesin is a coumarin precursor with reported free radical scavenging ability. Though CNS-specific studies are sparse, its antioxidant role implies a potential for reducing oxidative stress induced neuronal injury [23]. Prenylated Phenylpropanoids recent LC-MS/MS studies of *C. monnieri* extracts have identified prenylated phenylpropanoids, including prenyl ferulate derivatives. These have shown strong radical-scavenging and anti-apoptotic activities in SH-SY5Y neuronal cells under oxidative stress [24].

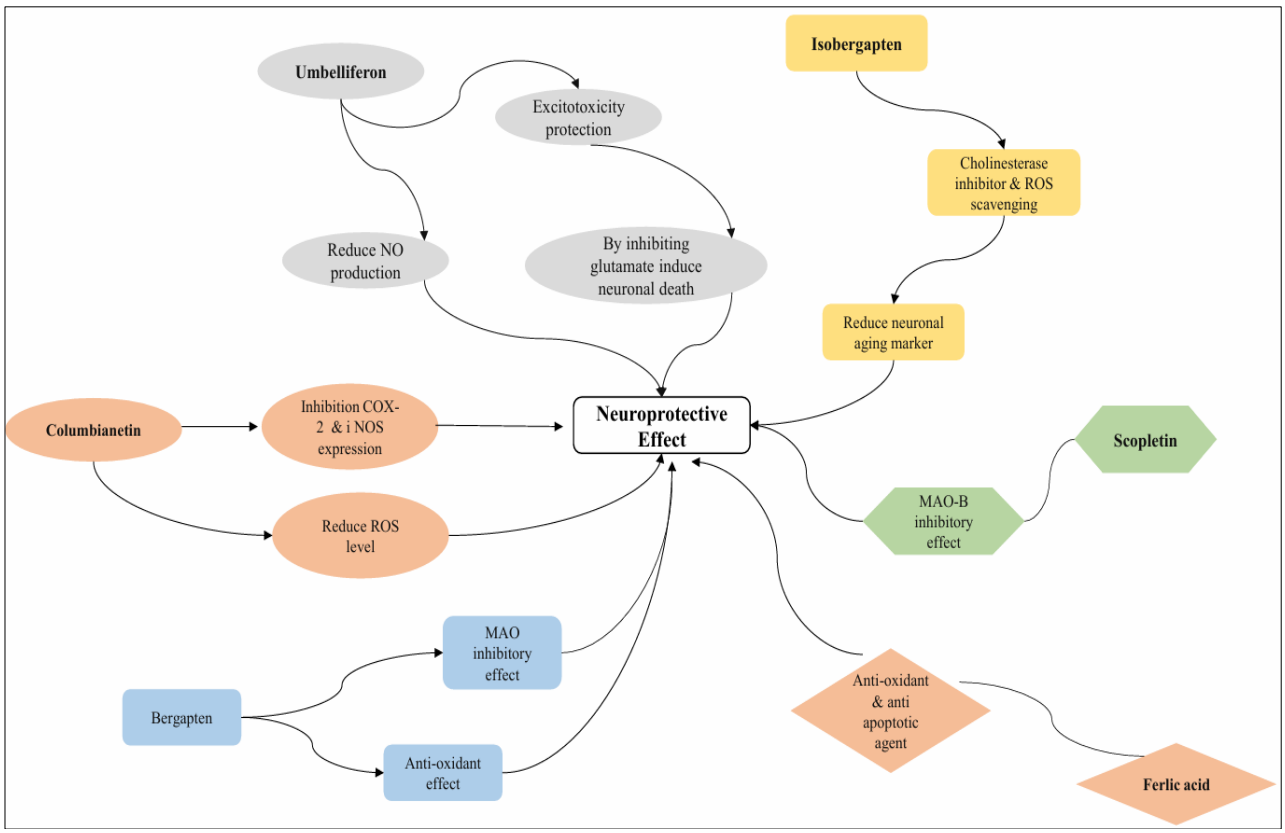

Fig 2: Effect of columbianetin, Scopletin, Ferlic acid & Bergapten role for neuroprotection in brain

Application in CNS Disorders

Alzheimer's disease (AD) is a progressive neuro-degenerative disorder primarily characterized by memory loss and cognitive impairment, often associated with the accumulation of amyloid-beta (Aβ) peptides, particularly $A\beta_{1-42}$. These peptides initiate a cascade of pathological events including oxidative stress, neuroinflammation, mitochondrial dysfunction, and dysregulation of intracellular calcium (Ca^{2+}) homeostasis, ultimately leading to synaptic damage and neuronal apoptosis. Among various mediators of calcium signaling, the inositol 1, 4, 5-triphosphate receptors (IP3Rs) and store-operated calcium entry (SOCE) pathways play a pivotal role in Aβ-induced neurotoxicity. Recent evidence suggests that 2-APB exhibits significant neuroprotective effects by attenuating Aβ-induced Ca^{2+}overload, reducing reactive oxygen species (ROS) generation, and mitigating endoplasmic reticulum (ER) stress. Moreover, 2-APB downregulates pro-inflammatory cytokines such as TNF-α and IL-1β, suppresses microglial activation, and restores synaptic plasticity markers including PSD-95 and synaptophysin. Whereas therapeutic potential of 2-APB as a calcium signaling modulator in preventing or alleviating Aβ-induced cognitive deficits and provide a mechanistic basis for its further exploration in Alzheimer's disease management [25].

Depression

Cnidium Monnieri extract can enhance the levels of monoamines, including serotonin (5-HT), dopamine (DA), and norepinephrine (NE), in key brain regions implicated in depression, such as the hippocampus and prefrontal cortex. These changes are believed to occur partly through the inhibition of monoamine oxidase enzymes (MAO-A and MAO-B), reducing neurotransmitter degradation. Additionally, *Cnidium monnieri* exhibits antioxidant and anti-inflammatory properties, decreasing malondialdehyde (MDA) and pro-inflammatory cytokines like TNF-α, while increasing antioxidant enzymes such as superoxide dismutase (SOD). Importantly, treatment with *Cnidium monnieri* has been shown to upregulate brain-derived neurotrophic factor (BDNF), *Cnidium monnieri* may offer a promising natural approach for the management of depressive disorders, with a multi-target mechanism involving neurotransmitter modulation, oxidative stress reduction, and neurotrophic support [26].

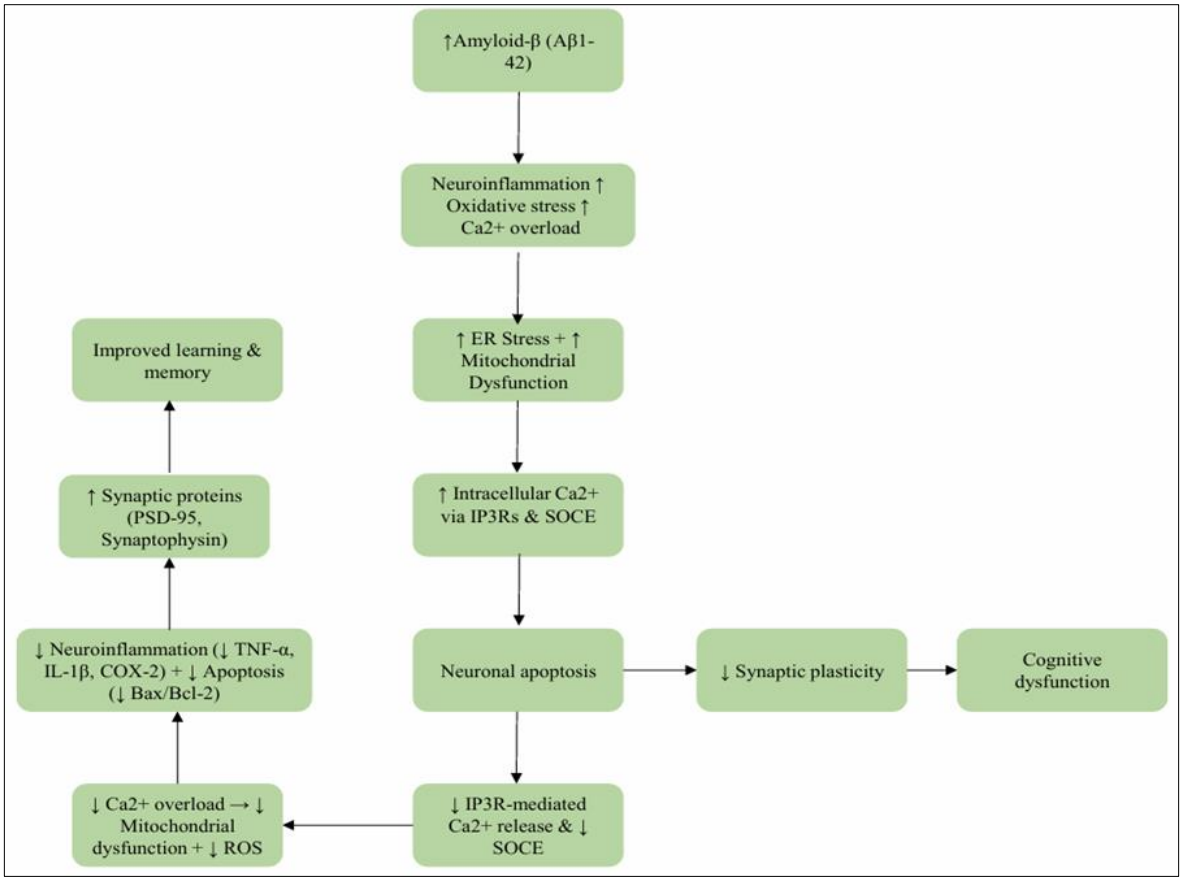

Fig 3: Represents effect of cnidium monnieri on amyloid induce Alzheimer disease

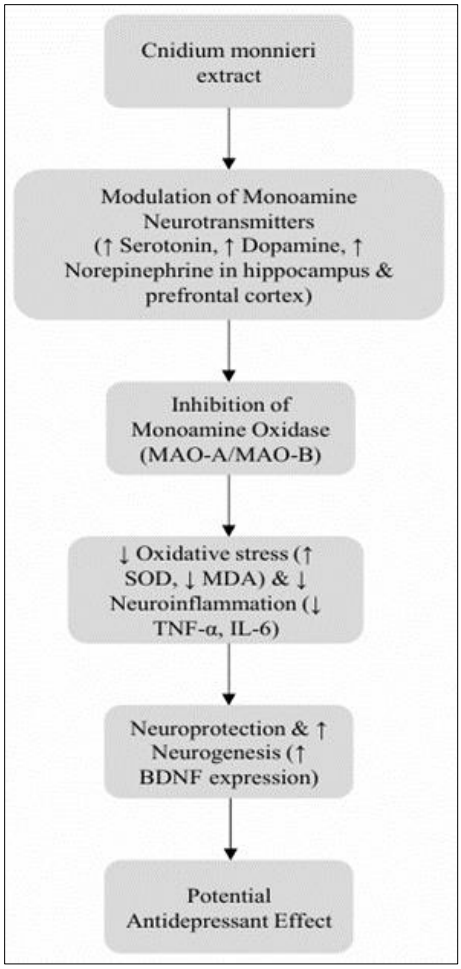

Fig 4: Represents the antidepressant effect is induced due to *Cnidium Monnieri*

Neuropathic pain

The extract significantly alleviates pain-related behaviors by targeting multiple pro-inflammatory mediators and pain signaling molecules, highlighting its broad-spectrum analgesic potential. Specifically, it down regulates the expression of cyclooxygenase-2 (COX-2), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β), which are key contributors to the inflammatory cascade and pain sensitization. COX-2 is known to facilitate the production of prostaglandins that sensitize nociceptors, while TNF-α and IL-1β enhance neuronal excitability and promote the recruitment of immune cells, further amplifying pain signals.

In neuropathic pain models, such as the chronic constriction injury (CCI) model, the extract from *Cnidium monnieri* exerts modulatory effects on central and peripheral pain mechanisms. It suppresses the expression of transient receptor potential vanilloid 1 (TRPV1), a non-selective cation channel involved in nociceptive transmission and thermal hyperalgesia. TRPV1 upregulation is typically associated with increased pain perception in chronic pain states. Moreover, the extract downregulates substance P, a neuropeptide involved in the transmission of pain and neurogenic inflammation. Concurrently, it inhibits the activation of phosphorylated extracellular signal-regulated kinase (p-ERK), a crucial component of the mitogen-activated protein kinase (MAPK) pathway, which plays a significant role in central sensitization and pain memory formation.

These molecular effects are particularly evident in both the dorsal root ganglia (DRG) and the spinal cord, indicating a dual action on peripheral nociceptors and central processing units of the pain pathway. The observed reductions in pro-

nociceptive mediators and signaling proteins suggest that the extract acts not merely as a symptomatic analgesic but as a disease-modifying agent capable of interrupting the chronic pain cycle. Together, these findings underscore the extract's potential in treating complex pain disorders by modulating inflammatory, neuropeptidergic, and kinase signalling pathways [27].

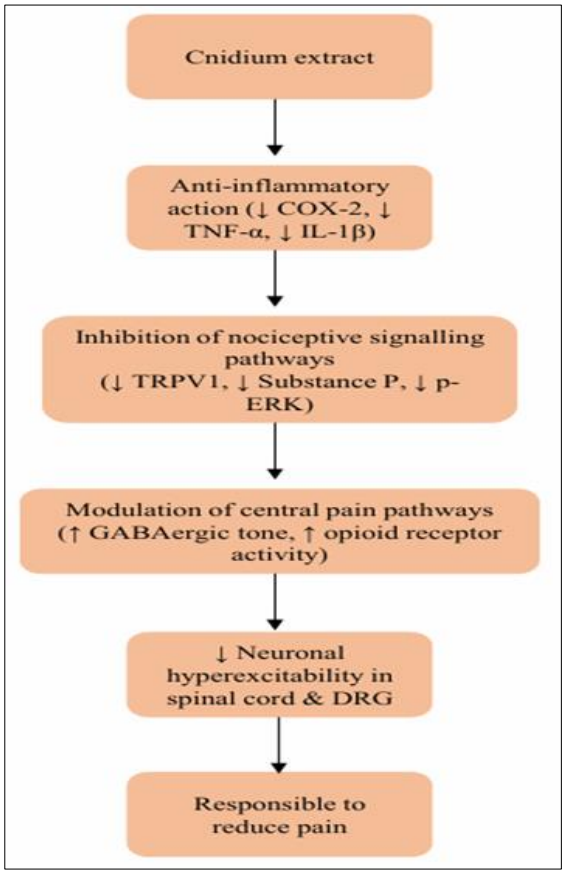

Fig 5: Figure demonstrate pathway follow up *C Monnieri* in neuropathic pain

Conclusion

The mounting preclinical evidence supports *Cnidium monnieri* as a promising neurotherapeutic agent capable of addressing the multifactorial pathophysiology of central nervous system disorders. Its diverse phytoconstituents act on several molecular targets, including pro-inflammatory cytokines, oxidative stress mediators, neurotransmitter systems, ion channels, and neurotrophic factors, contributing to its neuroprotective, antidepressant, and analgesic effects. By simultaneously modulating both central and peripheral pathways, *C. monnieri* offers a disease-modifying approach rather than mere symptomatic relief.

Given the limitations of current synthetic drugs such as poor efficacy, adverse effects, and single-target mechanisms the broad pharmacological actions of *C. monnieri* underscore its value as a safer and more holistic alternative for managing conditions like Alzheimer's disease, depression, and neuropathic pain. However, further clinical studies are essential to validate its efficacy, safety, pharmacokinetics, and therapeutic potential in human populations. Future research should also focus on standardization, active compound isolation, and molecular docking studies to fully harness the plant's neuropharmacological benefits.

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