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Deciphering Pain: A Multidimensional Comprehensive Review of Nociceptive, Neuropathic, And Nociplastic Types, Herbal Supervision Methodology

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Abstract:

Pain is a complex and multidimensional biological experience with sensory, emotional, and neurophysiological aspects, which can be categorized into nociceptive, neuropathic, and nociplastic (depending on the underlying mechanisms and not on the symptoms) in general. This review paper is a unanimous synthesis of experimental results of validated animal models to explain the molecular, inflammatory, oxidative, and neuroplastic pathways involved in such categories of pains. Paradigms of carrageenan-induced inflammation, chronic constriction injury, spared nerve injury and fibromyalgia-like models have identified important biological targets in NF- B, COX-2, 5-LOX, TRPV1 channels, NMDA receptors, ERK/MAPK signaling cascades, and glial activation markers. Preclinical studies have shown that herbal bioactives, including curcumin, resveratrol, boswellic acids, withanolides, and quercetin, among other phytochemicals, have a multimodal analgesic mechanism involving inhibition of pro-inflammatory cytokines, inhibition of oxidative stress, ion channel modulators and ion channel regulation. The review also highlights the significance of a pharmacokinetic profiling, safety and toxicity assessment, dose translation plans, and phytochemical standardization to improve the translational reliability. This paper combines mechanistic knowledge with methodological adequacy and suggests a more systematic herbal supervision model to promote the evidence-based, integrative, and mechanism-centred approaches to holistic and precision-focused pain management

Keywords: Nociceptive Pain, Neuropathic Pain, Nociplastic Pain, Herbal Analgesics, Central Sensitization, NF-Kb Pathway, Pharmacokinetics, Pain Management.

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1. INTRODUCTION

Pain is a universal biological process witnessed among different species of living organisms as an essential survival mechanism, which notifies an organism of potential or actual tissue injury. Nociception- the neural processing and encoding of noxious stimuli- in animals has been widely studied to determine the evolutionary causes and adaptation of pain[1]. Since invertebrates can experience reflex withdrawal to mammals being capable of providing complex affective and cognitive reactions, pain is a multidimensional experience that occurs in sensory, emotional, and behavioral levels. The animal models have been, and continue to be, important in the explanation of the mechanisms of molecular pathways, neurotransmitters, and inflammatory mediators of pain perception, such as the presence of prostaglandins, cytokines, ion channels, and central sensitization mechanisms. These models of experimentation have helped researchers to define pain into specific groups, such as, nociceptive, neuropathic, and more recently, nociplastic based on underlying pathophysiology, but not based on symptom expression.

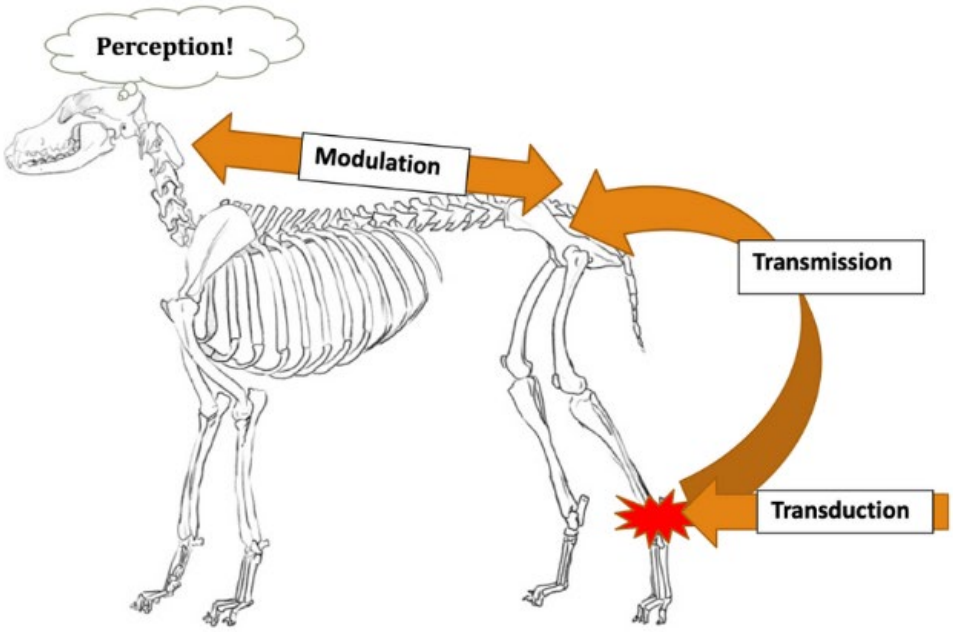

Figure 1: The 4 Pain Pathways[2]

Translational applicability of animal research has contributed immensely to drug discovery in comprehension of mechanisms of chronic pain, especially in how to understand neuroinflammatory processes, glial response, peripheral and central sensitisation and changes in pain modulation circuits. Research in rodent models of inflammatory injury, nerve ligation and stress-induced hyperalgesia has shown that pain processing goes beyond tissue damage. These findings have changed the paradigm of a purely biomedical approach to a biopsychosocial approach which incorporates neural plasticity, psychological stressors, and environmental factors.

Furthermore, the increased attention to complementary and herbal medicine has prompted preclinical studies of plant-derived bioactive compounds with analgesic, anti-inflammatory and neuroprotective effects. These changes offer a scientific premise toward discussing herbal supervision methodologies in pain management.

1.1 Background Information and Context

Pain is conventionally divided into nociceptive pain, caused by tissue damage and palpation of peripheral nociceptors, neuropathic pain, caused by damage or dysfunction of the somatosensory nervous system, and nociplastic pain, which is the abnormal nociception without an apparent tissue injury or nerve damage. Whereas nociceptive pain is typically related to inflammation, trauma or surgery, neuropathic pain is related to maladaptive neural adaptations including demyelination, ectopic firing and central sensitization. The conceptualization of nociplastic pain is rather recent, as it is seen in such relatively recent conditions as fibromyalgia and chronic primary pain syndromes in which the systems of pain processing are disturbed. The traditional pharmacological methods used are usually nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, anticonvulsants, and antidepressants, which are usually limited in their efficacy and have side effects, dependence, and inconsistent effects on patients. As a result, more scientific attention is given to integrative and herbal-based approaches to addressing inflammatory mediators, oxidative stress pathways, ion channels, and neuroimmune interactions as potentially less harmful and multimodal options of therapy[3].

1.2 Objectives of the Review

The primary objectives of this review are to:

- To systematically classify and differentiate nociceptive, neuropathic, and nociplastic pain based on their underlying pathophysiological mechanisms and molecular targets.
- To critically analyze animal models used in pain research and evaluate their relevance in understanding inflammatory, neuropathic, and central sensitization processes.
- To examine the mechanistic role of herbal bioactives in modulating inflammatory pathways, oxidative stress, ion channels, neurotransmission, and glial activation in different pain conditions.
- To assess pharmacokinetic, safety, and dose translation considerations necessary for bridging preclinical herbal findings to clinical application.
- To propose a structured herbal supervision methodology that integrates phytochemical standardization, mechanistic validation, and translational rigor for evidence-based pain management.

1.3 Importance of the Topic

Chronic pain is a significant health problem in the world, as it impacts physical functioning, psychological and socio-economic productiveness[4]. The wrong interpretation of the types of pain usually results in an inappropriate approach to treatment, extended pain, and higher expenses related to healthcare services. Multidimensional perception of nociceptive, neuropathic, and

nociplastic pain is thus required to deal with precision-based management. Moreover, the side effects and restrictions of long-term traditional medicine with pharmacotherapy have increased the need to find alternatives, which are more sustainable and safer. With increasing pharmacological and molecular data backing herbal medicine, there is a promising adjunctive or alternative approach that is capable of suppressing inflammatory cascades, oxidative stress, the work of neurotransmitters, and neuroimmune responses[5]. The study of these methods in the frames of a systematic supervisory approach to the investigation is capable of not only closing the gap between traditional and contemporary science but also playing a part in the formation of integrative and patient-focused pain management practices.

2. ANIMAL EVIDENCE IN PAIN RESEARCH: NOCICEPTIVE, NEUROPATHIC, AND NOCIPLASTIC MODELS

Animal models continue to be useful to the mechanistic understanding of the basis of nociceptive, neuropathic, and nociplastic pain and to how to assess herbal therapeutic interventions.

Carrageenan-induced paw edema in rats, the formalin test in mice/rats as well as the Complete Freund's Adjuvant (CFA) inflammatory model are usually included in the category of nociceptive pain models. The models model acute and subacute inflammatory responses and can be used to measure peripheral sensitization[6].

- **Neuropathic pain models:** Neuropathic pain models are Chronic Constriction Injury (CCI), Spared Nerve Injury (SNI), Streptozotocin-induced diabetic neuropathy, and Partial Sciatic Nerve Lamation (PSNL). These models recapitulate persistent hyperalgesia, allodynia and nerve degeneration in relation to peripheral and central sensitization.
- **Nociplastic pain models:** Other models of nociplastic pain including reserpine-induced models of fibromyalgia-like pain, acidic saline-induced models of chronic widespread pain and models of hyperalgesia induced by stress are used to replicate central sensitization without apparent peripheral tissue injury[7].

2.1 Key Herbal Interventions and Mechanistic Insights

The preclinical trials illustrate good responses of herbal bioactives to different types of pain:

- Curcumin suppressed TNF- A, IL-1b and cox-2 in carrageenan induced models of inflammation and suppressed central sensitization biomarkers in nociplastic models.
- Boswellia serrata extract reduced paw edema by inhibiting 5-LOX, which reduced the synthesis of leukotrienes.
- The formalin-evoked nociceptive behaviors in zingiber officinale were inhibited by the extract through the inhibition of the production of prostaglandins[8].
- Withania somnifera extract suppressed mechanical allodynia and oxidative stress indices of CCI-induced neuropathy.
- Resveratrol silenced the NF- hacia signaling and suppressed microglial activation of spinal tissues.
- Quercetin increased the nerve conduction velocity and lipid peroxidation was lowered.

- Hypericum perforatum reduced the nociplastic models with pain-like and depressive behaviors.
- Glycyrrhiza glabra regulated serotonergic as well as dopaminergic neurotransmission.

2.2 Strengths and Weaknesses of Animal Pain Models

- **Strengths:** Animals with pain models are reproducible with a well-defined biochemical and molecular endpoint[9]. They not only permit the use of behavioral testing (thermal and mechanical tests), which can be measured quantitatively, but also permit study of peripheral and central pain mechanisms. These models can also be used in the investigation of chronic interventions and therapeutic effects over a long period of time.
- **Weaknesses:** The acute models might not be representative of long-term human pains. Mechanisms of central sensitization are not appropriately included within some models. The lack of reliability in translation is caused by surgical variability, subjective behavioral interpretation, inadequate herbal standardization, inadequate bioavailability evaluation and inability to analyze sex behavior[10].

3. BIOLOGICAL TARGETS AND EXPERIMENTAL CONSIDERATIONS IN HERBAL PAIN MANAGEMENT

The herbal analgesic action in animal pain model includes inhibition of inflammatory (NF- B, COX-2, 5-LOX) and oxidative (NF-B, COX-2, 5-LOX) pathways, central sensitization (glial, NMDA, ERK/MAPK) and ion channels, neurotransmitter (TRPV1, sodium channels) regulation. But, the translation into clinical practice needs a better methodological rigor such as phytochemical standardization, phytochemical pharmacokinetic validation, and prolonged safety assessment[11].

3.1 Inflammatory and Oxidative Pathways

The key biological facets of the nociceptive and inflammatory pain models are inflammatory and oxidative pathways. The analgesic effects of herbal compounds are continually proven to be mediated by inhibition of nuclear factor-kappa B (NF- e K B) signaling cascade which is one of the key transcription factor that regulates pro-inflammatory cytokines including TNF -a, IL-1b and IL-6[12]. NF-kB activation is inhibited by phytochemicals such as curcumin which is found in Curcuma longa and resveratrol in Vitis vinifera thus lowering down stream inflammatory mediators. Furthermore, inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) causes a reduction of the production of prostaglandins and leukotrienes which inhibit peripheral sensitization. Herbs extracts are also very effective in lowering oxidative stress such as malondialdehyde (MDA) and increasing endogenous antioxidants enzymes such as superoxide dismutase (SOD) and catalase. The combined antioxidant and anti-inflammatory effect indicates a synergistic and multimodal analgesic effect, especially in inflammatory and chronic pain where oxidative stress is the source of the prolongation of tissue destruction and nociceptor activity[13].

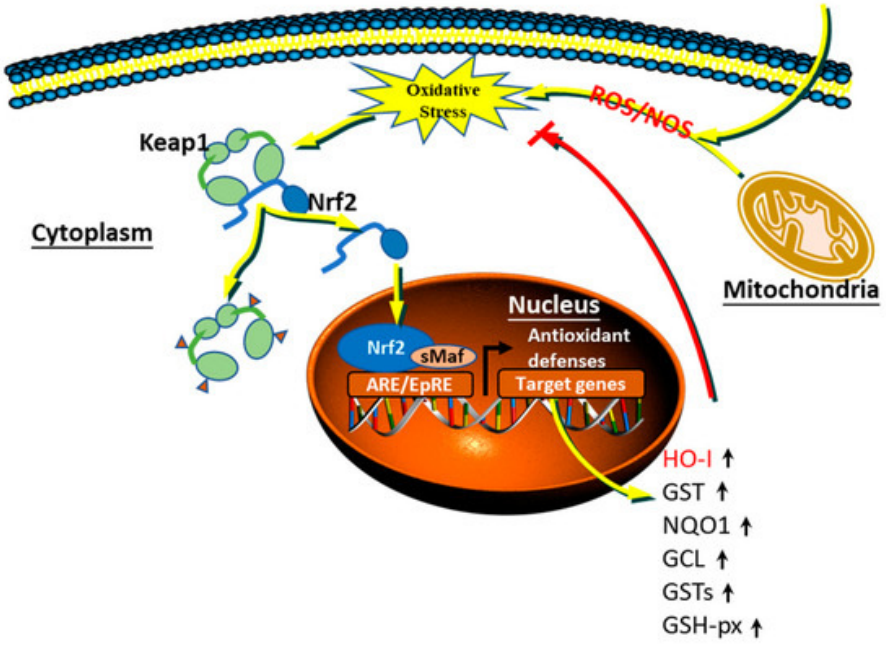

Figure 2: Oxidative Pathways[14]

3.2 Central Sensitization and Glial Modulation

Central sensitization is a key role in chronic pain conditions in the neuropathic and nociplastic pain models. There is an emerging body of animal evidence that suggests that herbal compounds regulate neuroinflammatory responses in the central nervous system. The indicators of activation of microglia and astrocytes (Iba1 and glial fibrillary acidic protein (GFAP)) are significantly inhibited after using bioactive phytochemicals like resveratrol and curcumin. This glial inhibition suppresses the pro-inflammatory cytokines and neuroexcitatory mediators release in the spinal cord[15].

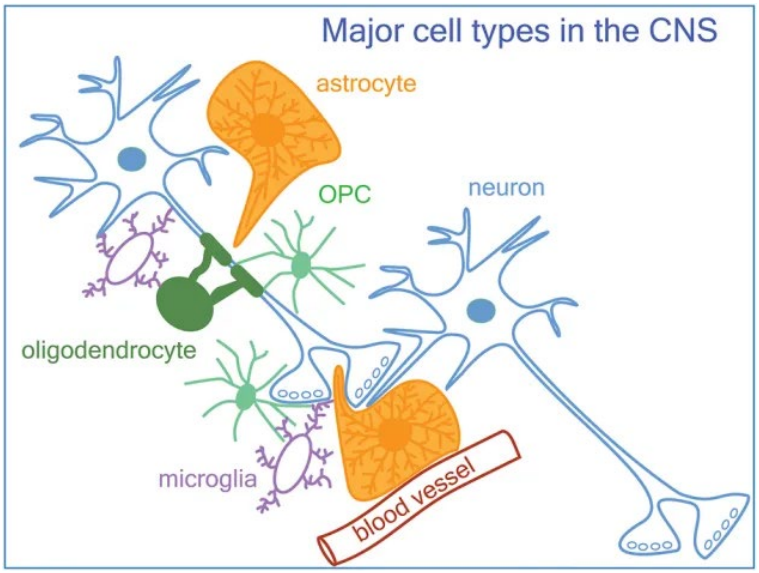

Figure 3: Glial Modulation[16]

Moreover, herbal medicines suppress phosphorylation of N-methyl-D-aspartate (NMDA) receptors, which would inhibit excitatory transmission of synapses related to amplification of chronic pain. Intracellular signaling pathways including extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) are also modulated to help them regulate central sensitization. Taken together, these results imply that herbal treatments have the potential to have neuroprotective properties, which are not limited to peripheral anti-inflammatory activities but can also control maladaptive central neural plasticity[17].

3.3 Ion Channel and Neurotransmitter Modulation

In addition to the effects of control of inflammation, phytochemicals can affect ion channels and neurotransmitter systems that mediate nociceptive transmission[18]. Transient receptor potential vanilloid 1 (TRPV1) channel modulates have been experimentally observed to mediate both thermal and inflammatory hyperalgesia, which are essential mediators. Some of the compounds of vegetal origin inhibit the overactivation of TRPV1, and thus nociceptor excitement. Also, blockage of voltage-gated sodium channels also leads to the slower conduction of action potentials in peripheral nerves, which diminishes the transmissions of neuropathic pain. Herbal constituents too have been revealed to increase serotonergic and occasionally noradrenergic neurotransmission in descending inhibitory circuits to reinforce endogenous mechanisms of pain control. These multimodal actions on ion channels and neurotransmitter systems can be used to explain the decreased hyperalgesia and allodynia in the chronic pain models, and illustrate the integrative aspect of the pharmacodynamic of herbal analgesics[19].

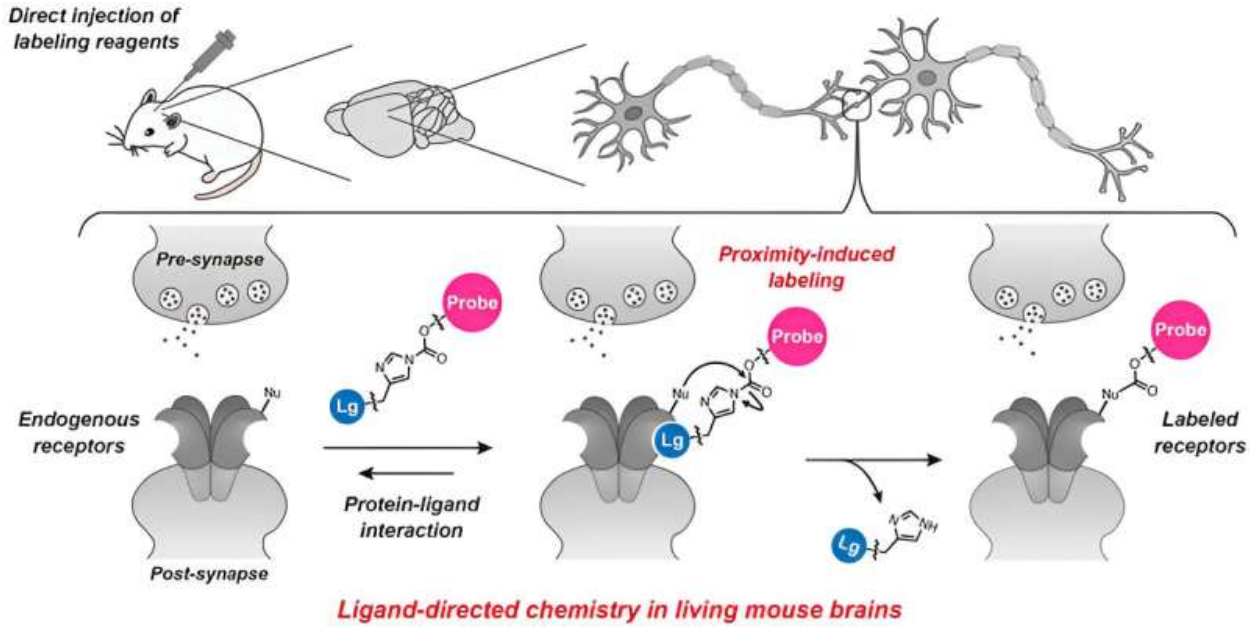

Figure 4: Neurotransmitter[20]

3.4 Methodological Considerations in Herbal Supervision

Although there are encouraging preclinical results of herbal pain studies, the methodological constraints remain serious in herbal pain studies. One of the biggest issues is that phytochemical standardization is not achieved in all studies and causes inconsistencies in extract composition and

therapeutic effects[21]. The systematic pharmacokinetic validation is usually missing in dose translation between the animal models and human equivalents, which is problematic to clinical application. Moreover, there is scanty information on bioavailability, metabolism, and chronic toxicity, which are necessary in determining safety profiles[22]. To enhance scientific integrity, the proposed studies should include blinded behavioral measurements to reduce the observer bias, random assignment of animals to experimental groups in order to guarantee experimental validity, and the standard characterization of extracts through analytical methods, including high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS). Widely conducted pharmacokinetic profiling and chronic toxicity testing is also needed to bridge the gap between experimental data and clinical practice[23].

4. PHARMACOKINETICS, SAFETY EVALUATION, AND DOSE TRANSLATION IN ANIMAL-BASED HERBAL PAIN RESEARCH

The pharmacokinetic (PK) analysis is crucial to the study of herbal analgesics in animals to learn about the absorption, distribution, metabolism, and excretion (ADME) of bioactive phytochemicals. Most herbal compounds like curcumin and resveratrol show promising analgesic and anti-inflammatory effects in preclinical models, but their practical utility depends on poor oral bioavailability, a high metabolic rate, and low systemic stability[24]. Animal PK tests assist in finding plasma concentration-time and tissue distribution (in neuropathic pain models, blood-brain barrier intrusion), and metabolism. High-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS) are the common techniques used in order to measure phytoconstituents and their metabolites and guarantee reproducibility and mechanism validation.

Another important element of herbal analgesic studies is safety evaluation[25]. Even though the compounds derived in plants are generally believed to be harmless, toxicity profiles should be strictly evaluated by conducting acute, subacute, and chronic toxicity tests on animal models. Hematological indices, liver and kidney functioning parameters, histopathology and behavioral changes are systematically measured to ascertain no-observed-adverse-effect levels (NOAEL). Long-term administration needs special care especially with models of chronic pain, where there can be cumulative toxicity, organ damage, or herb-drug interaction. Reproductive toxicity and genotoxicity tests also provide a more solid framework of safety before the human experimentation[26].

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In general, the combination of the sound pharmacokinetic profiling, toxicity evaluation, and scientifically supported dose translation methodology is essential to closing the gap between the knowledge obtained on animals and safe and effective application of herbal analgesics to humans[29]. Enriching these translational elements will increase reproducibility, regulatory acceptability, and future chances of using herbal treatment approaches as an evidence-based element in pain management guidance.

Table 1: Summary of Selected Literature on Pain Mechanisms and Modulating Factors[30]

Author(s) & Year	Study Title	Focus Area	Methodology	Key Findings
Proietti et al. (2024)[31]	Online Questionnaire with Fibromyalgia Patients Shows Negative Correlations between Disease Severity and Adherence to Mediterranean Diet	Fibromyalgia severity and dietary patterns	Online questionnaire-based cross-sectional study; correlation analysis between Mediterranean diet adherence and symptom severity	Higher adherence to the Mediterranean diet was negatively correlated with fibromyalgia severity, suggesting anti-inflammatory dietary patterns may reduce pain and fatigue symptoms.
Ren et al. (2025)[32]	Role of Microbiota in Pain: From Bench to Bedside	Gut microbiota and pain modulation	Comprehensive review integrating preclinical and translational research findings	Altered gut microbiota influenced pain through immune regulation, cytokine signaling, microglial activation, and gut–brain axis communication; microbiome-targeted therapies showed potential in pain management.
Shapoo et al. (2025)[33]	Cancer Pain Is Not One-Size-Fits-All: Evolving from Tradition to Precision	Cancer-related pain heterogeneity and precision medicine	Analytical review of pain phenotypes and precision-based treatment approaches	Cancer pain involved inflammatory, neuropathic, and treatment-induced mechanisms; personalized analgesic strategies based on biomarkers

				improved therapeutic targeting.
Şovăilă, Porcaro, & Neculau (2024)[34]	Chronic Pain: A Narrative Review for the Internist in 2024	Chronic pain classification and management	Narrative review synthesizing contemporary evidence	Chronic pain involved nociceptive, neuropathic, and nociplastic mechanisms; central sensitization and neuroimmune interactions were key contributors; multidisciplinary care was essential.
Sunzini (2024)[35]	Characterization of the Neurobiological Phenotype of Pain in Psoriatic Arthritis	Neurobiological pain phenotype in psoriatic arthritis	Doctoral research with phenotypic and neurobiological assessment	Psoriatic arthritis pain involved both inflammatory and neuropathic components; evidence supported altered central pain modulation mechanisms.

5. DISCUSSION

The data reveal that the mechanisms of nociceptive, neuropathic and naciplastic pain are similar with the animal studies demonstrating such targets as NF-kB, COX-2, TRPV1, and NMDA receptor. The curcumin and resveratrol, as herbal compounds, work with many multimodal mechanisms, including peripheral and central pain mechanisms. Even though their promises as safer adjuncts to traditional analgesics, they should be further standardized, pharmacokinetically validated, and their safety needs to be established over a longer period, and properly designed clinical studies that are bound to guarantee reliability and efficacy should be conducted[36].

5.1 Interpretation and Integration of Findings

The evidence reviewed points out that nociceptive, neuropathic, and nociplastic pain are different, but overlapping pathophysiological mechanisms that are characterized by inflammation, neural damage, oxidative stress, and central sensitization[37]. Animals models have played a significant role in defining the molecular targets which include NF- 0B, COX-2, 5-LOX, TRPV1, NMDA receptors, and ERK/MAPK pathways. The multimodal effects of herbal bioactives such as curcumin, resveratrol, boswellic acids, and withanolides were observed as a combination of inflammatory mediator, oxidative damage, and glial activation. This integrative process gives an

indication that herbal remedies can be useful in multifocusing both the peripheral and central aspects of the chronic pain, as opposed to a single pathway[38].

5.2 Implications and Significance

The results justify the possible significance of herbal supervision methodology in the mechanism-based pain management. Due to the restrictions and undesirable effects of long-term use of NSAIDs, opioids, and other synthetic analgesics, the phytotherapeutic interventions could be used as safer supplements or alternatives. The distinction between nociceptive, neuropathic, and nociplastic pain enables a more specific kind of therapeutic choice, which can enhance the accuracy of pain treatment. Dose standardization, pharmacokinetic validation and safety assessment all require proper evaluation of preclinical advantages to clinical practice[39].

5.3 Gaps and Future Research Directions

Although these results are promising, there are a number of gaps. Most of the researches are based on short-term animal models which may not be the accurate picture of chronic human pains. Translational reliability is limited by variability in the standardization of herbal extracts, a lack of bioavailability information and long-term toxicity testing. The forthcoming studies should be on standardized phytochemical profiling, sex-based analysis, sophisticated molecular research and designed clinical trials. Enhancement of such aspects will make them more reproducible and can help incorporate herbal therapies in modern pain management practices[40].

6. CONCLUSION

In conclusion, this review comprehensively demonstrates that nociceptive, neuropathic, and nociplastic pain are mechanistically distinct yet interconnected conditions driven by inflammation, oxidative stress, neural injury, and central sensitization. Evidence derived primarily from validated animal models highlights critical molecular targets such as NF-κB, COX-2, 5-LOX, TRPV1, NMDA receptors, and ERK/MAPK pathways, providing a mechanistic foundation for targeted intervention. Herbal bioactives including curcumin, resveratrol, boswellic acids, withanolides, and related phytochemicals exhibit multimodal analgesic effects through anti-inflammatory, antioxidant, neuroprotective, and neurotransmitter-modulating actions, suggesting their potential as complementary strategies in pain management. However, successful clinical translation requires rigorous phytochemical standardization, robust pharmacokinetic profiling, comprehensive safety evaluation, and scientifically justified dose optimization. Integrating these translational considerations within a structured herbal supervision methodology can strengthen evidence-based practice and contribute to the development of safer, mechanism-driven, and precision-oriented approaches for comprehensive pain management.

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