RESEARCH PAPER

# CHITOSAN-BASED NANOCARRIER FOR THE DELIVERY OF ACORUS CALAMUS NANOEMULSION IN THE MANAGEMENT OF TRIGEMINAL NEURALGIA

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**Abstract**
Trigeminal neuralgia (TN) is a chronic neuropathic pain disorder marked by sudden, severe, and recurrent episodes of facial pain, often refractory to long-term conventional therapies. Plant-derived bioactives with neuromodulatory, antioxidant, and anti-inflammatory potential are increasingly being explored as safer therapeutic alternatives. *Acorus calamus*, a medicinal plant widely used in traditional systems, exhibits analgesic, anti-inflammatory, and neuroprotective properties; however, its clinical translation is limited by poor aqueous solubility, low oral bioavailability, and rapid systemic metabolism. Nanoemulsion-based formulations provide an efficient platform to overcome these challenges by enhancing solubility, absorption, and sustained release. Chitosan, a natural biodegradable and biocompatible polysaccharide, further improves therapeutic delivery owing to its mucoadhesive properties, ability to facilitate controlled release, and capacity to cross biological barriers. The design of a chitosan-based nanocarrier encapsulating *Acorus calamus* nanoemulsion could significantly enhance drug stability, prolong systemic circulation, and enable targeted delivery to neural tissues. This approach is expected to improve therapeutic efficacy, reduce dose frequency, and minimize systemic adverse effects in TN management. Such a strategy combines the neuroprotective potential of *Acorus calamus* with the advanced delivery capabilities of chitosan nanotechnology, presenting a novel, safe, and patient-friendly alternative for effective neuropathic pain therapy.
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## 1. INTRODUCTION

The International Association for the Study of Pain defines trigeminal neuralgia as a sudden, unilateral, severe, brief, stabbing, and recurrent pain along the course of the distribution of the trigeminal nerves. Neuropathic pain in trigeminal neuralgia is evoked by stimuli known as trigger factors, which include routine daily activities like washing, shaving, smoking, talking, brushing of teeth, or can also occur spontaneously without a known trigger factor(Zakrzewska 2002).

The etiology of trigeminal neuralgia is still not established; the most acceptable hypothesis is the Ignition Hypothesis proposed by George Wegal and Kan Cassay, which proposes that there is a compression caused by the blood vessels over the trigeminal nerve in its course from the brain to the ganglion (Devor, Govrin-Lippmann, and Rappaport 2002). This compression usually occurs at any area of transition of the central myelin to peripheral myelin at the root entry zone. This persistent, continuous, mechanical pressure of the blood vessel on the nerve results in loss of myelin sheath, which leads to abnormal impulse transmission, which is called ephaptic transmission, or in other words, transmission of a normal impulse to a severe pain-transmitting impulse.

The right side of the face is commonly affected than the left side of the face. Bilateral simultaneous pain is quite rare. 75% of the patients affected with TN are in the maxillary and mandibular branches of TN, and the than 25% is the Ophthalmic artery (Xu et al. 2025). The International Headache Society (IHS) diagnostic criteria for diagnosis of classical TN are as follows: (a) paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of the trigeminal nerve. (b) pain has at least one of the following characteristics: (i) intense, sharp, superficial, or stabbing, and (ii) precipitated from trigger areas or by trigger factors, (c) attacks are stereotyped in the individual, (d) there is no clinically evident neurological deficit, (e) not attributed to another disorder.

Assessment of TN pain is carried out with various scales and questionnaires such as the Visual Analog Scale for pain, the Numeric Rating Scale for pain, and the Chronic Pain Grade Scale. McGill used the Questionnaire and the short form of the McGill Pain Questionnaire. Chronic Pain Grade Scale (CPGS) is a

widely accepted, comprises questions to quantify the pain as well as QoL. It is a multidimensional assessment that measures the pain intensity and pain-associated disability, which is best suited to assess chronic musculoskeletal pain (VandeVyver et al. 2008) (Haanpää et al. 2011).

The first-line treatment for patients with classic TN and idiopathic TN is pharmacologic therapy. The most commonly used medication is the anticonvulsant drug carbamazepine (Gambeta, Chichorro, and Zamponi 2020). Carbamazepine - therapeutic range is normally between 800mg – 1200mg. Oxcarbazepine – an alternative should there be medication interaction issues with carbamazepine. The therapeutic range is normally between 1200mg – 1800mg. Another adjuvant medication may be added, Lamotrigine, which can be used in combination with carbamazepine, recommended to increase the dose escalation up to a maximum of 200 mg twice daily. Baclofen can be used in combination with carbamazepine /oxcarbazepine; the therapeutic range is normally between 40-80 mg, total daily dose split over 4 separate doses. Gabapentin - can be used in combination with carbamazepine/oxcarbazepine or as monotherapy. The therapeutic range is normally between 900-3600mg. Pregabalin - can be used in combination with carbamazepine/oxcarbazepine or as monotherapy, and recommended dose escalation up to a maximum of 300 mg twice daily (Moore et al. 2019). Maragathavalli et al. conducted a study on the incidence of trigeminal neuralgia and found that 83.3%, whereas the incidence of other orofacial neuralgia was found to be 16.7%. The majority of the study population was in the age group of 41-70 years. Males (54.1%) dominated the study population over females (45.8%) (*Incidence Trigeminal Neuralgia University Hospital Setting -A Retrospective Analysis*, n.d.). Maheswari et al. conducted a study on the prevalence of trigeminal neuralgia in a private institution and found that the majority of the affected individuals are in the age groups of 30-60 years, and there is a slightly greater female predilection than males. These people are mostly prescribed carbamazepine along with mecobalamin in the management of trigeminal neuralgia (Murugesan, T N, and Ramalingam 2024). Arvind et al. conducted a study on nerve involvement and distribution of pain in trigeminal neuralgia and found that the most common site of involvement is the right side rather than the left side, and it is most common in the male population (Priyanka, Arvind, and Priyanka 2020).

Carbamazepine is both an anticonvulsant and an antiepileptic drug, considered a gold standard in the treatment of trigeminal neuralgia. It can be given at a maximum dosage of 1200 mg per day. Although it has the property of calcium channel inhibition, it has a common side effect of bone marrow suppression, agranulocytosis, and drowsiness. There is a need for an alternative to minimize the side effects of carbamazepine.

*Acorus calamus* is a well-known medicinal plant used in traditional medicine for the management of liver and hepatobiliary carcinomas. It has a literature name of vacha. A wide variety of metabolites have been used previously in the management of cancers. Root rhizomes of the *Acorus calamus* have a property such as anticancer, antioxidant properties, as well, and neuroprotective properties by inhibiting the action of calcium channels, which is the main responsible of the pain conduction pathway (Rajaulla Naikwadi 2024). By inhibiting the calcium channel inhibitory action, it greatly reduces the pain intensity as well. Before moving on to the *Acorus calamus*, there is a need to check for cytotoxic properties and antioxidant properties. The main aim of the study is to prepare the nanoemulsion of the *Acorus calamus* and assess of cytotoxic activity of the prepared nanoemulsion.

## 2. MATERIALS AND METHODS:

### 2.1.1. Materials

Tween 80 was obtained from LOBA Chemie Private Limited, Mumbai, India. Eucalyptus oil was collected from a natural-based products shop in Chennai, India. *Acorus calamus* rhizome was collected from a garden at ECR Chennai-Pondicherry Highway, India.

2.1.2. Plant Material

*Acorus calamus* rhizomes were purchased from a nursery garden located in Chennai, India. The flowers and leaves were removed from the plant, and it was thoroughly washed with water. A known number of leaves and flowers were dried in an oven at 40 °C for 24 h. After drying, the preparation was pulverized in a grinder.

### 2.2. Pulverization

A known number of rhizomes were dried in an oven for 24 h at 40° C. The final rhizomes were pulverized in a grinder, and the final weight was recorded. The powder was stored separately in a Scott bottle at room temperature for further usage.

### 2.3. Extraction and sample preparation

Dried rhizomes were dissolved separately in distilled water, methanol, and hexane with a ratio of 1:20 (g/mL). The extract was treated with a 40°C horizontal bath shaker with a middle shaking speed for 3 h. Afterwards, the content was filtered using No.1 Whatman filter paper. The solvent was evaporated from the filtrate through a rotary evaporator at 40 °C for 40 min. For preparing a 100 mg/mL extract stock solution, a known amount of dried extract was dissolved in DMSO. The mixture was treated with ultrasonication for 30 min to achieve full dissolution. The membrane residue was used to remove the undissolved residues.

**2.4. Preparation of nanoemulsion**

The extraction process was performed using a Soxhlet apparatus. Here, a 10 g dried sample was used for the aqueous extraction of bioactive compounds. The extract was evaporated, and the powder was collected by using rotary evaporation. In order to prepare nano nanoemulsion, 10 mg of powder was added to 10 mL of water. To which 60 mL of palm oil and 30 mL of Tween 20 were added to prepare an oil-in-water emulsion. Then, the mixture was ultrasonicated for 60 min using an ultrasonics processor. The formation of a milky white coloured solution indicates the formation of an emulsion. The nanoemulsion formulation was further characterized by using various techniques. The size distribution of the droplet was identified by the dynamic light scattering method. The stability of the emulsion was determined by using a Zetasizer.

**2.5. Methodology**

Tween 20 was purchased from Loba Chemie Private Limited, located in Mumbai, India. Eucalyptus oil was purchased from a natural-based plant company, Chennai, India. Extract of *Acorus calamus* was collected from a naturally available herbal centre located at Madurai, India.

2.6. **Addition of Chitosan polymer to the prepared extract**

Total volume 20 ml

0.2ml 1% glacial acetic acid

Distilled water 9.8ml

10ml nanoemulsion

0.2ml 1% glacial acetic acid was added and heated for 2 hours at 70 °C, and then 10ml of *Acorus calamus* nanoemulsion. Spread the preparations in a Petri dish, and keep in the hot air oven at 120 degrees overnight. After getting the samples dried, allow the samples to the characterisation. Fig. 1 shows the resultant polymer preparation.

3. Results

3.1. Particle size distribution

The particle size distribution (Fig. 2a) is used to depict the particle size at which the nanoemulsion is dimensionally stable.

3.2. Zeta potential:

The zeta potential value rises when the particle size is at 31nm; the normal value of less than -30 up to +30 the value is unstable. The zetapotential (Fig. 2b) is used to determine whether the nanoemulsion prepared is dimensionally stable or not. But the nano emulsion of *Butea monosperma* is -32.9, which shows that the nano emulsion is dimensionally stable.

3.3. FTIR

Fourier Transform Infrared spectroscopy (FTIR) obtains an infrared spectrum of a substance, revealing information about its chemical composition and structure. FTIR spectroscopy is widely used in various fields for analysing organic and inorganic compounds. Figure 3 depicts that OH ions are emitted initially, followed by NH3 ions, showing that the sample dimensionally emits organic compounds.

3.4. TGA

Thermo-Gravimetric analysis (TGA) is a thermal analysis technique in which a sample's mass is tracked as its temperature varies over time. In addition to chemical events like chemisorptions, thermal breakdown, and solid-gas reactions (e.g., oxidation or reduction), this measurement offers information on physical phenomena like phase transitions, absorption, adsorption, and desorption (Rimal and Srivastava 2024). Figure 4 depicts that water molecules are excreted from the prepared sample initially, followed by nanoemulsion and aloe vera are excreted till 550 degrees centigrade. Shows that the prepared gel was resistant to heat till 550 degrees centigrade.

3.5. Antimicrobial property

**Antimicrobial resistance** (**AMR** or **AR**) occurs when microbes evolve mechanisms that protect them from antimicrobials, which are drugs used to treat infections. Antimicrobial activity is useful in seeing if the prepared sample is resistant to microbial organisms. Figure 5 depicts that the prepared sample shows a very good zone of inhibition of the microbes, which shows that the prepared gel has antimicrobial activity. The test was performed in Staphylococcus aureus (S.aureus) and Escherichia coli (E.coli).

4. Discussion

The study aims the formulate of chitosan-based nanocarrier for the delivery of A*corus calamus* in the management of trigeminal neuralgia. Acorus calamus, commonly known as sweet flag, has been used traditionally for various medicinal purposes. Its rhizome contains bioactive compounds, including asarone, which are responsible for its therapeutic properties. Nanoemulsion technology has emerged as a promising approach to enhance the efficacy and delivery of these compounds (Nandakumar, Menon, and Shailajan 2013).

Alpha asarone is one of the major compounds found in A.*calamus*, 9.7% in the rhizome, and there is no Asarone content in the leaf part. (Shukla et al. 2009). The rhizome part of Acorus calamus was found to be less hydrophilic, so the extract preparation was done using water in oil type, followed under the reverse micelle principle. Rhizome of A.*calamus* naturally produces complex polyphenolic compounds, which might be the reason for the hydrophobic nature that exists with high affinity. Methanol was found to be the best solvent to extract the flavonoids of A.*calamus.*

Chitosan is a biodegradable polymer derived from chitin, found on crustacean cells. It has non-toxic, biocompatible, and anti-microbial properties, hence it is used as a polymer in our study. In our current study, the preparation was done for targeted delivery (Zhao,

C. Templonuevo, and Chun 2024). Nanoemulsion formulation could enhance the delivery of bioactive components from A.calamus to the trigeminal nerve, and contribute to reducing the inflammation and oxidative stress.

The current study examines FTIR, TGA, cytotoxic activity, zeta potential, particle size distribution, antimicrobial activity, and SEM image analysis. Neuroinflammation, peripheral sensitization, and ectopic neuronal discharges are the main causes of TN pain. The potential mechanisms of action of A.calamus nanoemulgel include: direct modulation of nociceptor excitability through plant alkaloids/flavonoids; enhanced drug residence and penetration from the gel matrix to perineural tissues; antioxidant activity—limiting oxidative stress that sustains neuropathic signaling; and local anti-inflammatory effects by reducing cytokine/mediator-driven sensitization.

Other bioactive chemicals found in the extracts were thought to have contributed to the antibacterial activity of A.calamus since the correlation data showed that the antibacterial activity of the plant was not concentration-dependent on TPC, TFC, or TAC. According to earlier research, extracts from A. calamus were found to have antibacterial activity. The abundance of flavonoids and phenolic compounds should theoretically be closely associated with A. calamus's antibacterial action (Shailajan et al. 2015). Given that phenolic acids from other plants, such as gallic acid and caffeic acid, have been shown to have antibacterial properties. Another active ingredient thought to be in charge of the antibacterial activity in this investigation was beta-asarone. In addition, Joshi et al. (2012) found that beta-asarone had comparatively greater antibacterial action than alpha-asarone. This finding provided evidence that beta-asarone, rather than alpha-asarone, was the primary chemical responsible for the antibacterial action of A. calamus extracts.\

In the present study, FTIR, TGA, antimicrobial activity, particle size distribution, zetapotential, SEM image analysis, and cytotoxic activity are studied. TN pain is driven by ectopic neural discharges, peripheral sensitization, and neuroinflammation. The limitations of the current study reveals that, as there are low number of evidence on the nanoemulsion, there is a need of more studies in the future.

The future scope of the current study involves performing the cell line studies followed by human trials to elaborate on the usage of the topical nanogel in the management of trigeminal neuralgia along with carbamazepine in a fixed dosage of 200mg/day.

## 5. Conclusion

When applied topically, a chitosan-based nanocarrier combined with an Acorus calamus nanoemulsion shows promise as an adjuvant treatment for trigeminal neuralgia. Because it targets the trigger zone specifically and helps to lessen the degree of pain, the topical application method is also recommended in therapy. More research is required to assess the pharmacological activities and mechanism of the created nanoemulsion as there are fewer studies and pieces of evidence.

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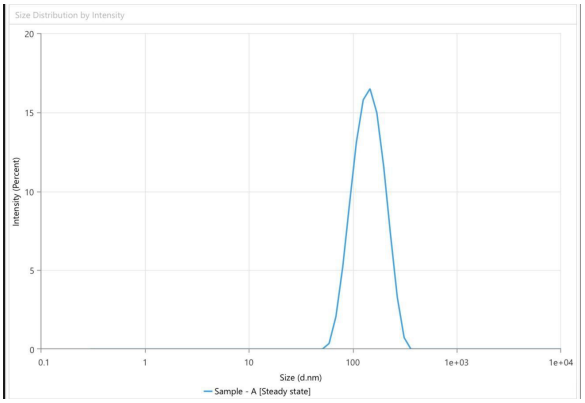
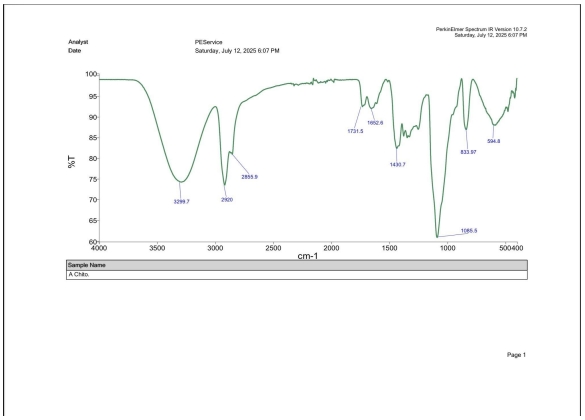
7. IMAGES

1a. Particle size distribution

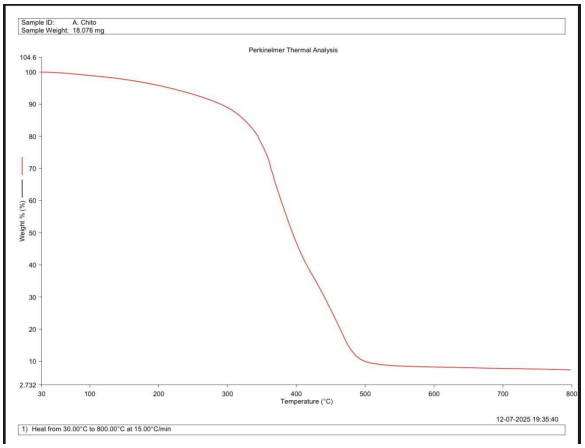



1b. Zeta potential

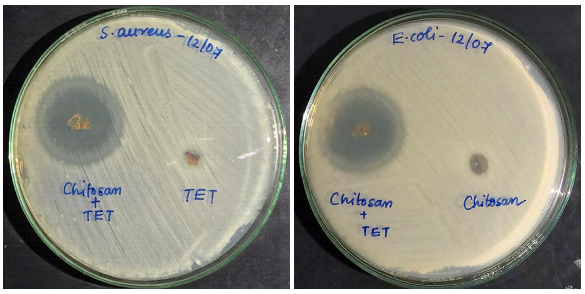

3. FTIR




4. TGA




5. ANTI-MICROBIAL ASSAY


S.aureus - 12/10/7
Chitosan + TET
TET
E.coli - 12/10/7
Chitosan + TET
Chitosan