

## RESEARCH PAPER

# Phytosomal Drug Delivery Systems of *Pinus roxburghii* (Sarg) Extractives: A Promising Approach for Epilepsy Management

Neetu Rani<sup>1</sup>, Dr. Vipin Kumar<sup>2\*</sup>, Dr. Ashwani Kumar<sup>2</sup>

<sup>1</sup> Research Scholar, Department of Pharmaceutical Sciences, Gurukula Kangri (Deemed to be University), Haridwar-249404, Uttarakhand.

<sup>2</sup> Assistant Professor, Department of Pharmaceutical Sciences, Gurukula Kangri (Deemed to be University), Haridwar-249404, Uttarakhand. Email: [vipin@gkv.ac.in](mailto:vipin@gkv.ac.in)

Corresponding Author: Dr. Vipin Kumar

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## ABSTRACT

Epilepsy is a chronic neurological disorder characterized by recurrent unprovoked seizures, caused by aberrant neuronal excitability and network hyper-synchronization. Despite advances in antiseizure medications (ASMs), approximately one-third of patients develop drug-resistant epilepsy, while many others experience dose-limiting adverse effects and inadequate brain bioavailability. These limitations underscore the need for innovative therapeutic strategies that combine multi-target pharmacology with improved central nervous system (CNS) delivery. *Pinus roxburghii* Sarg. (chir pine), widely used in traditional South Asian medicine, possesses a diverse phytochemical profile including flavonoids, phenolic acids, terpenoids, and lignans. Preclinical studies suggest that its bioactive constituents exhibit antioxidant, anti-inflammatory, and neuroprotective properties, as well as potential anticonvulsant effects in experimental seizure models. However, poor aqueous solubility, rapid metabolism, and limited blood–brain barrier (BBB) penetration restrict the translational utility of these phytoconstituents. Phytosomal drug delivery systems—molecular complexes of phytochemicals with phospholipids—offer a promising platform to enhance solubility, membrane permeability, metabolic stability, and systemic bioavailability. By improving lipid compatibility and facilitating transport across biological membranes, phytosomes may increase CNS exposure of *P. roxburghii* bioactives while enabling sustained release and reduced systemic toxicity. Evidence from other phytosomal formulations supports improved pharmacokinetics and enhanced neuroprotective efficacy. This review critically examines the pharmacological basis of *P. roxburghii* in epilepsy management and evaluates the rationale for phytosomal formulation as a strategy to overcome current biopharmaceutical limitations. Future investigations integrating mechanistic studies, optimized formulation design, and translational validation are warranted to establish phytosomal *P. roxburghii* as a potential adjunct or alternative approach in epilepsy therapeutics.

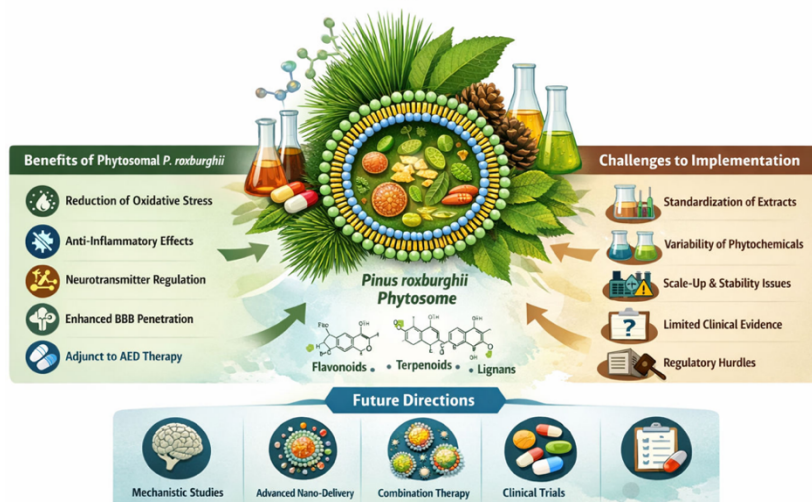
**Keywords:** *Pinus roxburghii*, Epilepsy, Antiepileptic activity, Phytosomal drug delivery, Neuroprotection, Blood–brain barrier

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## Graphical Abstract

Encapsulation of *Pinus roxburghii* extractives into phospholipid-based phytosomes enhances solubility, membrane affinity, and systemic bioavailability of bioactive phytoconstituents. Improved pharmacokinetic properties may facilitate transport across the blood–brain barrier, increasing central nervous system exposure. The delivered phytochemicals exert antioxidant, anti-inflammatory, and neuromodulatory effects, targeting key epileptogenic pathways. Phytosomal delivery therefore represents a mechanistically grounded and translationally promising strategy for adjunctive epilepsy management.

## Phytosomal *Pinus roxburghii* for Epilepsy



## 1. Introduction

Epilepsy is a type of the most common chronic neurodegenerative disease, which is evidenced by an incessant predisposition to incite unprovoked seizures and closely connected neurobiological, cognitive, psychological, and social impacts [1,2]. Epilepsy has been one of the most significant global public health issues, causing a significant burden with regard to disability and early deaths [3]. According to the latest projections by the Global Burden of Disease (GBD) Study, around 50 million people in the world are affected by potentia, with the burden considerably high in low- and middle-income countries (LMICs) [4]. Although there are limited positive results in the diagnosis and treatment, years lived with disability and epilepsy-related mortality rates are not low, and reflect the continued treatment and access disparities [5].

According to the World Health Organization, almost 80% of individuals with epilepsy live in LMICs, in which a high percentage of them would not take medication because of the limited healthcare facilities, the expensive medicine, the lack of specialists, and the stigma surrounding their condition [6]. Therefore, epilepsy is a neurological disease that is also a health priority in the world and needs therapeutic methods that are affordable, scalable, and culturally acceptable [7].

### *Problematic Aspects of Existing Antiseizure Medications*

The latest antiseizure drugs (ASMs) have enhanced the management of seizures in most people, though, in about a third of the cases, people develop drug-resistant epilepsy (DRE) [8]. The International League Against Epilepsy has developed the term DRE to signify the inability to attain long-lasting freedom from seizures following proper trials of two suitably chosen and tolerated ASMs [9]. When two regimens have failed, the chance of attaining seizure remission using later pharmacotherapy reduces significantly [10].

DRE patients are at risk of injury, psychosocial impairment, sudden unexpected death in epilepsy (SUDEP), and lower quality of life [11,12]. Even with the development of precision medicine, neuromodulation, and surgical treatment opportunities, the general population-based outcomes have not improved significantly [13]. Moreover, ASM treatment is often restricted by side effects, including mental retardation, psychiatric side effects, weight alterations, teratogenicity, and multiple

drug-drug interactions [8]. Such constraints pose a serious challenge, especially in resource-constrained environments where therapeutic monitoring is impeded [14].

The other pharmacological obstacle is the blood-brain barrier (BBB), which is a selective endothelial barrier that controls exposure of the central nervous system (CNS) to the circulating compounds [15,16]. Active efflux transporters such as P-glycoprotein decrease brain penetration of various ASMs and could be the cause of pharmacoresistance [17]. The dysfunction of the BBB during seizures could further increase neuroinflammation and network hyperexcitability, and this feed-forward loop prevents the responsiveness to therapies [18]. Taken together, these problems justify the necessity of new delivery systems that can help to increase CNS bioavailability and reduce systemic toxicity [19].

### *Herbal medicine as Complementary therapies*

Considering such shortcomings of conventional ASMs, research interest in plant-derived therapeutics has increased [8]. Many phytochemicals, such as flavonoids, terpenoids, and phenolic acids, have anticonvulsant and neuroprotective effects in experimental models [66,67]. The compounds also regulate several epileptogenic processes, including the GABAergic and glutamatergic stress, the voltage-gated ion channels, oxidative stress, mitochondrial dysfunction, and neuroinflammation [20,21]. They are good adjunctive therapies because of their multi-target pharmacology.

Nevertheless, clinical use of herbal products is limited by such factors as phytochemical variability, no standardization, rapid metabolism, low aqueous solubility, and poor penetration through the BBB [22].

### *Pinus Roxburghii as a Candidate Botanical*

One of the recently discovered botanical candidates is *Pinus roxburghii* Sarg. (chir pine), which has been used in South Asian traditional medicine extensively [23]. Preclinical evidence shows that alcoholic extracts of the bark of trees minimise the severity of seizures in maximal electroshock and pentylenetetrazole-induced epilepsy [24]. These are the effects of phenolic acids and flavonoids like chlorogenic acid, rutin, and quercetin, which have antioxidant and anti-inflammatory properties [25]. Though with encouraging results, low solubility and unpredictable bioavailability of CNS face limitations to translatability [26].

*The justification of Advanced Drug Delivery Systems*

New nanotechnology and nanodelivery drug delivery systems (DDS), which are lipid-based, provide potential to improve the pharmacokinetics and brain delivery of synthetic drugs and complicated herbal extracts [27]. One of them, phytosomes - in the form of molecular complexes of phytoconstituents with phospholipids- is especially promising with respect to poorly soluble plant-derived compounds [28]. The phytosomes have enhanced absorption, metabolic stability, and systemic bioavailability by triggering lipophilicity and membrane affinity [29].

This platform is supported by the clinical efficacy of quercetin and curcumin phytosomal formulations under clinical studies, which reveal that the level of plasma exposure to the formulations is significantly superior to standard extracts [30]. Such findings do not necessarily rely on epilepsy, but they demonstrate that phytosomes can be used to deliver botanicals to the CNS [31].

Phytosomal delivery using *P. roxburghii* may be useful in enhancing solubility and permeability of bioactive compounds in epilepsy, stabilizing bioactive compounds during transit in the gastrointestinal tract, improving consistency of individual batches through standardized complexation, and may increase CNS exposure [32]. The combination of multi-target phytochemicals and the BBB-directed nanocarrier systems is a logical approach in line with the contemporary measures to deal with drug resistance and enhance the therapeutic specificity [33].

In general, the continued burden of epilepsy in the world population, existing shortcomings of ASMs, and the BBB-related pharmacoresistance make the development of novel platform delivery methods a consideration [18]. Mechanistically based Pinacol roxburghii Pinacol roxburghii extractives Phytosomal Particle Pinacol roxburghii extractives are a mechanistically-based and translationally plausible strategy forward on botanical therapeutics in the treatment of epilepsy [34].

## 2. Herbal Medicine and Epilepsy treatment

Herbal remedies have been used in traditional medicine systems, such as Ayurveda, Unani and Traditional Chinese Medicine (TCM), to treat neurological disorders, specifically seizures and epilepsy [35]. In the past, the extract of the plants was used to regulate the neuronal excitability, reduce convulsions and enhance mental ability. The multi-target nature of anticonvulsants derived

from plants has motivated further scientific interest over the last few decades as a result of their multi-target effectiveness behavior [36]. In contrast to most of the traditional antiseizure drugs (ASMs) that often have only a small number of molecular validated targets and are potentially linked to adverse effects/pharmacoresistance [37], phytochemicals often have extensive neuroprotective/modulatory effects [38].

Many of the bioactive plant nutrients show the anticonvulsant potential on experimental models [39]. They are flavonoids (e.g., quercetin, apigenin), terpenoids (e.g., linalool, borneol,  $\alpha$ -pinene), alkaloids (e.g., berberine and other indole derivatives) and even phenolic acids (e.g., chlorogenic acid) [40]. The compounds are commonly found in crude extracts as a combination and can also have a synergistic effect on effects on neuronal excitability and severity of seizures [41].

### 2.1 Overview of Plant-Derived Anticonvulsants

- *Flavonoids*

Flavonoids are polyphenols which are common in fruits and vegetables, and medicine plants [42]. A number of flavonoids have been shown to penetrate the blood-brain barrier (BBB) to different extents and engage it with the molecular targets involved in the pathogenesis of epileptic activity [43]. Mechanically, flavonoids promote GABAergic transmission, suppress supernumerary glutamatergic transmission, improve the scavenging of reactive oxygen species (ROS), and elevate endogenous antioxidant enzymes [44]. The preclinical evidence also suggests that flavonoid-containing extracts raise seizure threshold and decrease seizure severity, as well as prevent neuronal damages after status epilepticus [45]. Also, flavonoids can regulate a synaptic plasticity by controlling the calcium-calmodulin-dependent signaling as well as the expression of brain-derived neurotrophic factor (BDNF) [46].

- *Terpenoids*

The material is found in essential oils, resins, and aromatic vegetation in large amounts [47]. The Monoterpenes linalool, borneol, as well as  $\alpha$ -pinene can interact with the neuronal membrane and regulate the ion channels activity [48]. All of these compounds exhibit anticonvulsant activity in animal models, some of which is caused by improvements in GABAergic signaling and inhibition of excitatory currents [49]. On top of the suppression of

seizures, terpenoids have anti-inflammatory, antioxidant, and stabilizing properties of the mitochondria, that can disrupt the pathological events underlying epileptogenesis [50].

- *Alkaloids*

The alkaloids are secondary nitrogenous metabolites having very varied neuropharmacological effects [51]. Berberine and other indoles affect GABAergic and glutamatergic loop, NMDA receptor, and also the voltage-gated sodium and calcium channels [52]. Even though not all alkaloids have large therapeutic indices, they have multi-modal actions and thus are prospective drug development templates and enhanced delivery patterns to enhance brain bioavailability and reduce the toxicity of the system [53].

## 2.2 Mechanisms of Action

- *GABAergic Modulation*

One of the key events in the anticonvulsant action of most phytochemicals is the enhancement of the inhibitory GABAergic transmission [13,16,36]. Some flavonoids and alkaloids also have actions as positive allosteric modulators of GABAA/transaminase or inhibitors of GABA transaminase, and thus augmenting synaptic GABA [16,43]. There are also some compounds that increase the endogenous GABA production by upregulating glutamic acid decarboxylase (GAD65/67) [13,43]. Together with actions that cause acute depression of seizures, these actions also help achieve neuronal network stabilization in the long run (Figure 1) [36].

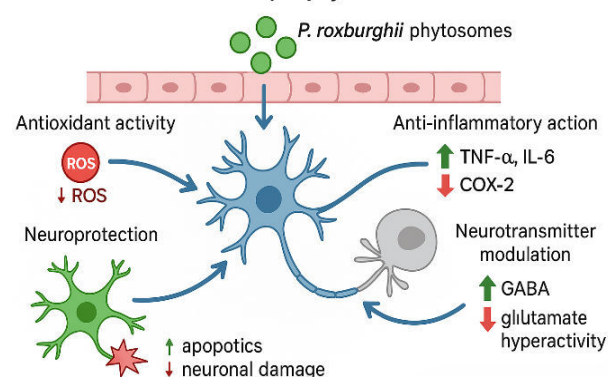
- *Anti-oxidant and Anti-inflammatory mitigation.*

One of the primary causes of the onset and further development of seizures is oxidative stress and neuroinflammation [20,15,35]. Most plant-derived compounds are also effective antioxidants due to their ability to scavenge ROS, prevent lipid peroxidation and improve native antioxidants, including superoxide dismutase and catalase [40-42]. At the same time, flavonoids, terpenoids and alkaloids inhibit the activation of pro-inflammatory signaling (NF- $\kappa$ B) as well as cytokine synthesis (e.g., TNF- $\alpha$ , IL-1 $\beta$ , IL-6) [20,15,35]. These compounds can reduce neuronal harm and restrain pathological network remodelling in chronic epilepsy by reducing the oxidative and inflammatory cascades [20,35,50].

- *Ion Channel Modulation*

Another significant mechanism of action of anticonvulsants is direct modulation of ion channels of cells under the neurons [7,36]. Voltage dependent sodium, potassium and calcium channels have been shown to be caused to change by terpenoids and alkaloids, which subsequently causes neuronal hyperexcitability to diminish [45,36]. Some monoterpenes increase potassium conductance and stabilize the resting membrane potential and others inhibit persistent sodium currents or T-type calcium channels [36]. These machineries should be seen as complementary to GABAergic and antioxidant activity, as multi-target anticonvulsant phenotypes [45,49].

**Mechanisms of Action of *Pinus roxburghii* Phytosomes in Epilepsy**



**Figure 1:** Mechanistic Overview of *P. roxburghii* Phytosomes in Epilepsy

## 2.3 Multi-Target Actions and Translational Implications

The analysis will combine the Multi-Target Actions and Translational Implications based on a concept of multi-target, which emphasizes the multiplicity in various fields.

One characteristic trait of herbal extracts is that they are polypharmaceutical [54]. One such extract is a flavonoid-bound extract, such as can be used to simultaneously promote inhibitory neurotransmission, minimize oxidative stress, inhibit inflammation, and stabilize ion channel function [55]. According to preclinical testing, this multi-target activity is capable of lowering the frequency of seizures, extending the interval to the manifestation of the seizure, enhancing neuronal preservation, and enhancing the cognitive capacity in test animals [56].

Nevertheless, translation to practice has been hampered by the fact that there are problems such as uncertainty in the extract composition, lack of oral bioavailability, incomplete pharmacokinetic characterization, as well as inadequate large-scale randomized controlled trials [57]. Strict standardization, dose optimization, and safety testing are mandatory in trying botanical anticonvulsants in clinical practice [58].

#### 2.4. Agents of Botanicals of Translational Potential.

Various plants have presented positive preclinical results in models of seizure:

- *Bacopa monnieri* (Brahmi): *Bacopa* is a natural herb that is abundant in bacosides and polyphenols and shows antioxidant, anti-inflammatory, and neuroprotective effects [69]. The effects of the status epilepticus on synaptic plasticity and hippocampal neuronal damage are improved in experimental studies [59].
- *Withania somnifera* (Ashwagandha): Withanolides have been shown to exhibit antioxidant and anti-inflammatory behavior. It is tested in the animal study, which demonstrates the inhibition and alleviation of seizures in hippocampal tissue and alleviates oxidative damage [60].
- *Passiflora incarnata*: It has flavonoids (e.g., vitexin, isovitexin), which increase the GABAergic neurotransmission. Preclinical models show a slow onset of the seizure or less mortality in the case of chemically induced seizures [61].
- *Morus alba* (White mulberry): Flavonoid-containing extracts mediated the decrease of the severity of seizure in pentylenetetrazole-induced models and mediated the GABAergic and glutamatergic pathways [62].

Though promising, these botanicals need to be standardized in formulations, have their pharmacokinetic assessment, and undergo clinical validation prior to application into routine therapeutic use [63].

#### 2.5 Pharmacokinetic and Formulation Considerations

One of the constraints to implementing herbal anticonvulsants in clinical practice is low bioavailability. The levels of polyphenols and alkaloids disappear at fast rates due to the first-pass metabolism, leading to low

systemic and CNS exposure. Complex delivery systems such as phytosomes, liposomes, polymeric nanoparticles, and intranasal formulations have been developed to improve absorption, preserve the labile compounds, and improve BBB penetration [64].

These technologies have the potential to optimize the therapeutic effect and minimize systemic toxicity, hence the combination of traditional phytotherapy and modern pharmaceutical innovation advances [65].

### 3. Phyto and Pharmacology of *Pinus roxburghii*

#### 3.1 Botanical Description and Distribution.

*Pinus roxburghii* Sarg. So-called chir pine is a big evergreen conifer with the family Pinaceae. The plants are usually 30-50 meters high and are straight, cylindrical, with a trunk, thick, fissured bark, and long, needle-like leaves in fascicles of three. Woody cones are big and generate winged seeds that are scattered by the wind and help them spread to a wide range of ecological locations [66]. *P. roxburghii* is a native of the Himalaya terrain, growing at altitudes around 450 to 2300m in the countries of Afghanistan, India, Nepal, Bhutan, and Myanmar [23,34]. It is most common in Uttarakhand, Himachal Pradesh, or Jammu & Kashmir in India. Other than its medicinal significance, chir pine is also geologically relevant in terms of conservation of the soil, slope control, and preservation of the integrity of the forest ecosystem [67].

#### 3.2 Traditional and Ethnopharmacological Uses.

*P. roxburghii* has traditionally found application in Ayurveda, Unani, and Himalayan folk medicine in the treatment of various ailments [23,34]. The therapeutic uses of various parts of the plants are the bark, needles, resin, and cones. Bark decoctions are also used traditionally as gastrointestinal, epilepsy, and diabetes treatment, and the resin (chir resin) topically, when treating wounds, skin infections, rheumatism, and joint pain [23]. Resin oil is also used as an expectorant in respiratory diseases, and needle extracts have been proven to have antimicrobial effects [34]. The powdered bark is also traditionally used to provide analgesic and anti-inflammatory effects [23,24]. These varied ethnomedicinal uses indicate that it could have systemic pharmacological activity, much of which has been confirmed by experimental studies [24,34].

### 3.3 Major Phytoconstituents

- Investigations of phytochemicals show that a rich repertoire of bioactive secondary metabolites [23,34] exhibited by *P. roxburghii* includes:
- Phenolic acids: Gallic acid, ferulic acid, chlorogenic acid, and caffeic acid are dominantly found in the extracts of bark, and have antioxidant and neuroprotective properties [20,25].
- Flavonoids: quercetin, rutin, catechin, and kaempferol, which all have antioxidant, anti-inflammatory, and neuromodulatory effects [20,25,40].
- Lignans: Secoisolariciresinol and matairesinol, which play a role in free radical scavenging and anti-inflammatory action [25].
- Terpenoids: a-pinene, b-pinene, longifolene, and abietic acid, which are mostly found in resin, are linked to antimicrobial, anti-inflammatory, and neuroactive effects [24,34].
- Triterpenoids: Lupeol and betulin, which exhibit hepatoprotective, antioxidant, and cytoprotective effects [38].

This varied phytochemical makes up a multi-target pharmacological profile, specifically applicable in epilepsy, in which oxidative stress, neuroinflammation, and excitotoxicity are interacting synergistically [15,21,35].

### 3.4 Reported Pharmacological Activities

#### *Antioxidant Activity*

Oxidative stress is important in neuronal hyperexcitability and neuronal damage caused by seizures [15,21]. Bark and needle extracts of *P. roxburghii* exhibit potent in vitro antioxidants, such as the DPPH radical and ABTS radical scavenging activity [20,25]. Reductions in lipid peroxidation and increases in endogenous antioxidant enzymes like superoxide dismutase and catalase [20,38] are demonstrated in the in vivo studies.

This redox-modulatory activity, in particular, can be applied to epilepsy, where oxidative damage leads to neuronal pathophysiology and epileptogenesis [15,21].

#### *Neuroprotecting and Anticonvulsant Effect*

The preclinical seizure models have also supported a neuroprotective and anticonvulsant effect of *P. roxburghii*.

Alcoholic extracts of the barks have a significant effect of suppressing the frequency of seizure and severity of the maximal electroshock (MES) models and pentylenetetrazole (PTZ)-induced seizure models [24]. These influences are probably mediated by stimulating GABAergic neurotransmission, or activation of voltage-gated ion channels and reduction of excitotoxic injury [36].

Also, the presence of sedative and analgesic effects in the experimental research is consistent with the conventional assertions of central nervous system use [23,34].

#### *Anti-Inflammatory Activity*

Neuroinflammation is involved in the development and dissemination of seizures. Bark and resin extracts prevent the development of carrageenan-induced paw edema in rodents and the expression of pro-inflammatory cytokine including TNF- $\alpha$ , IL-1 $\beta$  and IL-6. These effects are mostly caused by flavonoids and diterpenoids [68].

*P. roxburghii* can decrease the potential to develop seizures and prevent pathological remodeling that occurs in chronic epilepsy because it inhibits inflammatory cascades [69].

#### *Antimicrobial Activity*

These oils are essential oils that are produced out of needles and resin; they are antimicrobial agents towards Gram-positive and Gram-negative bacteria, along with a selective area of fungi. Although these effects are mostly beneficial in conventional topical applications, they indirectly inhibit the effects of infection-related neuroinflammatory incitations that may increase vulnerability to seizures [70].

#### *Antidiabetic and Metabolic Effects*

A potential clinical use of Bark extracts is hypoglycemic activity in streptozotocin-induced diabetic models, which is due to the presence of phenolic acids and flavonoids, which increase glucose consumption and glucose insulin sensitivity. Based on the two-way interaction between metabolic malfunction and neurological conditions, such other metabolic impacts could provide further therapeutic aspects in patients with comorbid epilepsy and metabolic syndrome [71].

#### *Hepatoprotective and Gastroprotective Effects*

Triterpenoid including lupeol, is hepatoprotective against liver injury caused by toxins. Also, mitigation of ethanol induced gastric ulceration gastric ulceration is attributed to

antioxidant action as well as cytoprotective influence of bark extracts [38,60]. Such systemic protection effects have the potential to increase the general treatment tolerability in the chronic treatment regimens [23,34].

The overall pharmacological relevance of the EPR to the epileptic condition is also affected by its connection to the dependent (epileptic) parameter, specifically. The overall pharmacological dependence on epilepsy is also influenced by the relationship between the EPR and the dependent variable (epileptic), that is, quasi-epilepsy.

It is the combination of antioxidant, anti-inflammatory, neuroprotective, metabolic, and ion-modulatory properties that place *P. roxburghii* as a potential adjunctive agent in epilepsy [57,59,60,66]. Its multi-component nature offers the ability to target essential processes which are epileptogenic at the same time, such as oxidative stress, neuroinflammation, and excitotoxicity [15,21,35].

Nevertheless, there are still translational issues, even though there is positive preclinical data. Fluctuation of extract composition, poor bioactivity of active constituents, and inadequate clinical testing should be discussed in order to adopt therapeutic use completely [20,36,45].

#### 4. Phytosomal Drug Delivery Systems

##### 4.1 Definition and Concept of Phytosomes

The concept and definition of the phytosomes are adapted to feature a phytosome that is recognized via the cell wall of the initial cell that attains the target analysis.

The phytosom is a modern form of lipid delivery that aims at addressing pharmacokinetic challenges facing numerous bioactive extracts of plants [72]. A phytosome is a molecular complex between a standardized plant extract or a botanical single phytoconstituent and a phospholipid, typically phosphatidylcholine. Compared to mere blends of simple physical mixtures, unbound physical mixtures, phytosomes have targeted chemical interactions, such as hydrogen bonding and polar associations between hydrophilic groups of phytochemicals and the polar head of phospholipids [73].

This interaction leads to a mixture of the interaction becoming an amphiphilic complex, which can be maintained in nano- or microscale vesicular structures in aqueous conditions, which increases the affinity of the membrane and biological incorporation [28-30,72,73]. Phytosome technology was initially created in the 1980s in order to enhance the bioavailability of silymarin and was later expanded to a wide range of polyphenols and flavonoids that are poorly soluble in water and are rapidly broken down by the human body, leading to their subsequent excretion [28-30,40,44].

Well-documented examples that exemplify that phospholipid complexation may largely increase systemic exposure and pharmacodynamic response are such compounds as quercetin and curcumin, catechins, and silymarin [25,38,40,41,44].

##### 4.2 Preparation Methods

Various methods of preparation have been devised, and their choice varies depending on the solubility, thermal stability, scalability, and desired particle properties [28–30,42,72].

##### Solvent Evaporation Method

The phytoconstituent and phospholipid get dissolved in a mutual organic solvent. After the removal of solvents under lower pressure, a thin film is created and then moistened to produce vesicles phytosomes [28-30].

- Anti-Solvent Precipitation: The phytochemical-phospholipid solution is added into a non-solvent medium, which precipitates the complex very fast [29].
- Lyophilization: Drying off phytosome suspensions with the help of freeze-drying gives way to homogenous dry powders that can be used in either capsules or tablets [42].
- Supercritical Fluid Method: In-Supercritical CO<sub>2</sub>-based methods offer a solvent-free, scalable method to produce homogeneous phytosomal nanoparticles with fine size dispersion, especially useful when handling thermolabile compounds [54].

The method of preparation, zeta potential, release kinetics, and entrapment efficiency are critically dependent on the size of the particles, which affect bioavailability and therapeutic performance indirectly [28-30,42].

#### 4.3 Benefits Compared to the Traditional Herbal Formulations.

Phytosomes have a number of benefits over crude extracts and standard preparations, especially the use of the CNS-targeted therapy [28-30,42]: Improved Solubility Phospholipid complexation enhances aqueous dispersibility and lipid solubility, and may result in better gastrointestinal absorption [37,42].

- Enhanced lipophilicity: Augmented bioavailability boosts membrane permeability and systemic exposure. At least, clinical trials using quercetin and curcumin phytosomes show much higher plasma levels than extracts that have not been formulated [29,42].
- Protective Effect on Metabolism: Complexation and resistance to enzymatic degradation and first-pass metabolism lengthen the systemic circulation [40,44].
- Potential Blood-Brain Barrier (BBB) Facilitation: Phytosomes are lipid and nano-sized and, therefore, may enhance the CNS delivery of specific compounds [29-33,45,46].
- Controlled Release and Reduced Toxicity: Sustained release schedules can lessen the fluctuations in the peak-trough curves, which can enhance drug tolerability and allow a lower dose to be administered [28-30].

Together, all these qualities put phytosomes at an advanced position to improve the translational viability of botanical therapeutics.

#### 4.4 Applications Successful Env Neurology.

There are a number of phytosomal preparations which reported promising results in neurological studies:

- Curcumin Phytosomes: A better systemic bioavailability and improved neuroprotection in preclinical models of neuroinflammation and neurodegeneration [43,44].
- Quercetin Phytosomes: An increase in plasma stability and neuroprotective activity of quercetin phytosomes in oxidative stress and seizure-related models [41,45].
- Silymarin Phytosomes: This group initially came into existence because of hepatoprotection, with a

subsequent study proposing that it could be useful in neuroprotection via antioxidant and anti-inflammatory activities [38,40].

Green Tea Catechin Phytosomes Green tea has already proven better CNS delivery and neuroprotection of experimental Parkinson's disease models [25,42].

Most of this evidence comes from the preclinical or non-epilepsy models, but these results support the idea that the phytosystem flowers can be used in CNS-targeted phytochemicals [28-30].

#### 4.5 Phytosomal *Pinus roxburghii* in Epilepsy.

*Pinus roxburghii* has flavonoids, phenolic acids, terpenoids, and lignans with proven antioxidant, antitumor and anticonvulsant properties in experimental research [23,24,25,38,40]. But, low solubility, stereotypical metabolism, and unpredictable CNS bioavailability limit its application as a drug [50-52].

Phytosomal formulations of *P. roxburghii* extracts have the potential of:

- Increase systemic contact and absorption through the intestines [28,29].
- Deter viable terpenoids against metabolic deterioration [29,42].
- Enhance membrane diffusion and potentially distributions in the CNS [29-33].
- empower long-term discharge and dose optimum [28-30]

Although concrete experimental data testing the usefulness of phytosomal *P. roxburghii* in epilepsy is not much, the already known advantages of the phytosome technology with structurally related phytochemicals offer a logical argument leading to further research [28-30,40,44].

Pharmacokinetic and Pharmacodynamic investigations should be conducted rigorously to prove the increased anticonvulsant effects compared to traditional extracts [50-52].

#### 4.6 Translational Perspectives and Future Directions.

Phytosomal technology provides an interface between the ancient phytotherapy and the current CNS drug delivery [28-30,45,46]. The research priorities in future are:

Enhancement of particle size, surface charge, and targeted ligand based on the optimization of CNS delivery [29-33].

- Determination of Pharmacokinetics and Biodistribution [28-30].
- Assessment in a proven seizure model with comparison of dose response [24,54].
- Security profiling and analysis of interaction with standard ASMs [8,9,63].
- Randomised controlled trials to evaluate clinical efficacy that are well designed [50-52].

In formulations with proven systemic pharmacological effectiveness, phytosomal phytoformulations of *P. roxburghii* would make a multi-target adjunctive approach in epileptic therapy.

## 5. Phytosomal Formulations of *Pinus roxburghii* for Epilepsy

### 5.1 Rationale for Phytosomal Formulation

The Phytosomal Formulation is rationalized because it reduces the adverse effects of employing synthetic stamping components.

Epilepsy is a periodic seizure that is caused by neuronal hyperexcitability, oxidative stress, neuroinflammation, and impaired neuronal transmission [74]. Even though traditional antiepileptic medications (AEDs) are the first-line treatment approach, they do not show effectiveness in a significant percentage of patients because of pharmacoresistance, drug side effects, drug-drug interactions, and suboptimal central nervous system (CNS) bioavailability [75].

The multi-target pharmacological characteristics of natural products are the reason why they have become complementary therapeutic candidates [65,67]. *Pinus roxburghii* (chir pine) has been reported to have flavonoids, phenolic acids, terpenoids, and lignans, which exhibit antioxidant, anti-inflammatory, and neuroprotective properties [23,24,25,38,40]. The translational potential of the same phytoconstituents is limited, however, by low aqueous solubility, chemical liabilities, high metabolic rate, and questionable blood-brain barrier (BBB) permeation [19,50–52].

Phytosomal drug delivery systems are a logical approach to effective management of such limitations [28–30,42]. The phytosomes can increase the affinity of phytochemicals to membranes through the creation of molecular complexes, the enhancement of absorption of

phytosomes, and the enhancement of absorption of phytochemicals [28-33]. The *P. roxburghii* extract formulation into phytosomes could thus maximize the pharmacokinetics and increase the therapeutic efficacy of phytosomes in seizure disorders [28-30].

### 5.2 Hypothesized benefits in seizure control

Epilepsy pathophysiology is associated with oxidative injury, excitotoxicity, neuroinflammation, and progressive neuronal injuries [116,35]. *P. roxburghii*. Given the potential advantages, the following may improve its effects on these mechanisms through phytosomal delivery of *P. roxburghii*:

#### *Lessening of Oxidative Stress*

Reactive oxygen species (ROS) also lead to neuronal damage caused by seizures [15,21]. The presence of flavonoids and phenolic acids in *P. roxburghii* has good antioxidant activities [20,25,40]. Phytosomal encapsulation can enhance systemic exposure and CNS availability to generate redox-modulatory effects [28-30].

#### *Anti-Inflammatory Modulation*

Neuroinflammation, a result of microglial activation and cytokine release, is a major contributor to epileptogenesis [15,35]. *P. roxburghii* exhibits anti-inflammatory effects through the work of terpenoids and polyphenols [23,38]. These effects can be enhanced by improved oncogenic delivery and sustained release by means of phytosomes [28-30].

#### *Neurotransmitter Regulation*

Some phytochemicals of pine can affect the GABAergic and glutamatergic pathways [36,61]. Improved infiltration using phytosomes may enhance their neuromodulatory action, which may capture the excitatory-inhibitory balance [13,16].

#### *Improved BBB Interaction*

Lipophilicity and compatibility with the membrane of phytosomes are enhanced by the phospholipid-based structure [28,29]. Though the improved penetration of the BBB depends on formulation, it is quite possible to have improved CNS penetration that needs to be proven by empirical means [29-33].

#### *ADS Synergy Adjunctives*

Phytosomal *P. roxburghii* can be used as an adjunctive treatment with the standard AEDs, probably resulting in a decrease of dosage and reduction of side effects, especially in drug-resistant epilepsy [8,9,75].

Generally, it is postulated that phytosomal delivery yields better therapeutic effects owing to the availability of better bioavailability, stability, and CNS targeting of bioactive constituents [28-30].

5.3 Preclinical and Experimental Evidence

Direct experimental analysis on phytosomal *P. roxburghii* has yet to be done on epilepsy models. Nevertheless, there are some pieces of evidence that favor the continued research:

- **Neuroprotective Effect and Antioxidant:** Traditional extracts of *P. roxburghii* suppress lipid peroxidation and improve endogenous antioxidant enzyme activities of rodent models [20,38].
- **Anti-Inflammatory Activity:** Pine flavonoid compounds suppress pro-inflammatory cytokines like  $\text{TNF-}\alpha$  and IL-6, and COX-2 that are intricately linked with the spread of a seizure [38,55].
- **Seizure Model Data:** The alcoholic extracts of the bark have shown anticonvulsant properties in maximum electroshocks (MES) and pentylenetetrazol (PTZ) tests [24,49].
- **Phytosomal Precedent:** Other phytosomal preparations such as curcumin, quercetin, and bacosides have demonstrated better brain absorption and increased protection of the brain against seizures or neurodegenerative processes [41,43,44,56].

Though intrinsic pharmacological activity and the previously known advantages of phytosomal delivery make the idea of combination and correction rather powerful, the ideas of extrapolation should be approached cautiously [28-30].

5.4 Comparative Perspective to other Phytosomal-based Neuroprotective Agents.

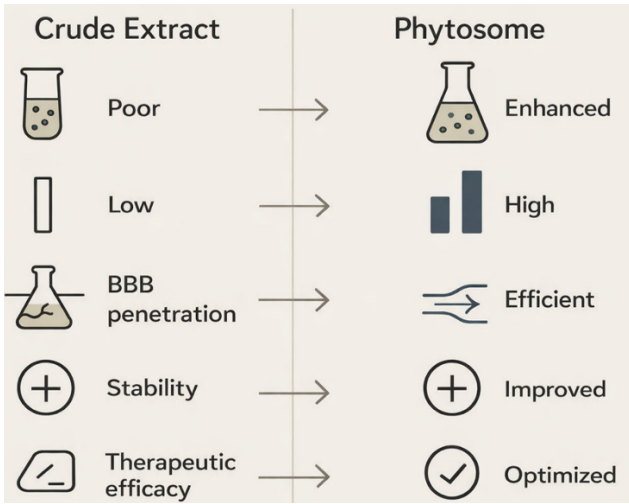
Translational Phytosomal botanicals have been shown to have translational feasibility in a number of situations:

- **Curcumin Phytosomes:** Greater bioavailability and anticonvulsant efficacy in experimental epilepsy [43,44].
- **Quercetin Phytosomes:** Greater antioxidant, anti-inflammatory activity with better pharmacokinetic properties [40,41].
- **Resveratrol Phytosomes:** Evidence of better CNS delivery and neuroprotection in seizure-related research [28-30].
- **Ginkgo biloba Phytosomes:** The business success in cognitive diseases points to the regulations and clinical practicability [28-30].
- **The Bacopa monnieri plant is referred to as the bacoside phytosomes:** Neuroprotective effects are enhanced as compared to crude extracts [59].

In comparison with these agents, *P. roxburghii* is at a select position of flavonoids, terpenoids, lignans, and phenolic acids, which are combined to work in concert to affect several epileptogenic pathways [23,25,38,40]. Nevertheless, in contrast to curcumin or quercetin, phytosomal *P. roxburghii* is on its own at a relatively hypothetical and preliminary level of research.

5.5 Summary and Positioning

The phytosomal formulation of *Pinus roxburghii* is a mechanically logical approach toward increasing the translational capabilities of the multi-component botanical [28-30].



**Figure 2:** Comparative Advantages of Phytosomal Delivery vs Conventional Extracts

Phytosomes can address various shortcomings, including solubility, metabolic variability, and low CNS exposure, that can result in more predictable and more effective anticonvulsant activities (Figure 2) [28-30,50-52]. However, prior to clinical use, it is required that rigorous pharmacokinetic research, standard extract characterization, trials of comparative efficacy, and assessment of safety are undertaken [50-52].

## 6. Challenges and Limitations

### 6.1 Standardization of Herbal Extracts

**Herbal Extract Standardization:** The samples undergo extract preparation using acetic acid and 1:1 ethanol in distilled water, followed by evaporation in a low-pressure evaporator at 104 °C.

The initial problem in formulating the phytosomal preparation of *Pinus roxburghii* is standardisation of the herbal extract [63,65]. Which is directly associated with the qualitative and quantitative makeup of bioactive constituents; this is directly linked to the therapeutic efficacy of botanical medicines [63]. Nonetheless, the variable nature of plant material provides a possibility of inconsistency in the pharmacological results [65].

Geographical origin, altitude, soil structure, climate, harvesting date, age of plant, and after-harvest process are some of the factors that have a great impact on the concentration of flavonoids, terpenoids, phenolic acids, and lignans [23,63,67]. Moreover, the extraction parameters, such as the choice of solvent, temperature, period, and the method, have the capability to change the phytochemical profile significantly [63,64].

The standardization methods usually depend on chromatographic fingerprinting of compounds and quantification of markers [63,65]. This is even more crucial in phytosomal preparations since the phytochemical quality out of complexation, stability, and reproducibility requires constant phytochemical composition [28-30,42]. The lack of standardization can lead to the variability of solubility, bioavailability, and therapeutic effects, and the translational validity is compromised [63,65].

### 6.2 Phytotransvariability of Phytochemical Content.

In the same vein as standardization, there is natural variability between batches [63,65]. This cause can also be temporarily varying flavonoid and terpenoid contents even in the same species and in the same location of collection

[23,63]. This kind of variance can affect pharmacodynamics and pharmacokinetics [63,65].

Phytochemicals vary in preclinical research studies, making it difficult to interpret the mechanism and replicate the results of inconsistent phytochemical content [63,65]. Variability has potential risks that are based on unpredictable efficacy, changes in safety profile, or potential drug interactions with traditional antiepileptic drugs (AEDs) in clinical settings [8,9,71].

It is critical to contain these problems by having well-established quality control frameworks [63,50]. They consist of established techniques of analysis, high-performance liquid chromatography (HPLC) profiling, mass spectrometry, nuclear magnetic resonance (NMR) analysis, and quantitative biomarker standardization [63,65].

### 6.3 Scale-Up and Formulation Stability.

Even though phytosomes can exhibit good pharmacological properties at the laboratory level [28-30], application to the commercial level poses other challenges.

The impact of scale-up can include a change in particle size distribution, morphology, surface charge, and entrapment efficacy parameters that directly affect bioavailability and CNS distribution [28-30,42]. It is important to optimize the methods used to prepare it carefully in order to maintain consistency of every production batch, be it solvent evaporation, anti-solvent precipitation, lyophilization, or supercritical fluid processing [28-30,42,54].

Another important issue is stability in the course of storage. Phytochemicals tend to be strongly affected by temperature, humidity, and light, whereas lipid-based carriers could face oxidation, hydrolysis, or aggregation over time [28-30,42]. Antioxidant addition, lyophilization, peptide coating, and proper packaging are some of the strategies required to maintain structural integrity. The stability studies on the shelf life and storage conditions require accelerated and long-term stability studies [63,65].

### 6.4 Limited Clinical Evidence in Epilepsy.

Although *P. roxburghii* is showing positive preclinical results [24,49], there is limited clinical evidence that assesses the effect of *P. roxburghii*, especially in phytosomal form. The majority of the literature uses an in vitro assay or rodent seizure model, but also has little information dealing with the pharmacokinetics, safety, and

tolerability effects of these drugs in humans, as well as their therapeutic benefits [24,49,63,65].

This regulatory gap is a critical obstacle in the way of regulatory approval and clinical adoption [63,65]. In the absence of properly designed randomized controlled trials, clinicians will have no indication of the best dose, duration of treatment, safety during long-term treatment, and interaction with conventional AEDs [8,9,71].

Narrowing this gap will necessitate a gradual scale of clinical trials, which will first involve safety and pharmacokinetic studies and then proceed with proof-of-concept tests evaluating the frequency, severity, and quality-of-life results [63,65].

### 6.5 Regulatory Considerations

The *P. roxburghii* phytosomal formulations regulatory pathway is complicated [50-52]. Depending on the regulatory frameworks, herbal drugs and synthetic drugs may have different regulations, and hybrid systems like phytosomal nanocarriers can belong to unclear categories of classifications [563,65].

The regulatory bodies might insist on detailed documentation, which involves:

- Takaki phytochemical characterization.
- It involves standardized methods of extraction.
- Quality control in manufacturing in the Good Manufacturing Practices (GMP) [52].
- Preclinical toxicology and efficacy.
- Shelf-life and stability.
- Clinical development plans [63,65]

Depending on the jurisdiction, the regulatory requirements are quite different [52]. In certain zones, the herbal products may be governed as dietary supplements, but in other instances, advanced delivery systems can be regarded as novel drug entities that will require a stringent check-up [63,65]. Such processes can add to the cost of development and extend time.

### 6.6 Integrative Perspective

These challenges can only be addressed by the use of a multidisciplinary approach, which comprises of phytochemist, formulation scientists, pharmacologists, clinical experts, and regulatory professionals [63,65].

Phytochemical profiling and quality control require a high level of advanced analytical methods (HPLC, LC-MS/MS, NMR) [63,65]. Strategies to enhance CNS delivery, degradation reduction, and surface modification, such as ligand targeting, surface modification, and optimization of formulation, can be used [29-33,28-30].

Premature interaction with regulatory bodies may help clarify the pathways of classification, and the data needs to make translation between the bench and clinic easier [63,65]. Despite the significant obstacles still existing, high-quality standardization, validation, and translational research can unravel the therapeutic potential of phytosomal *P. roxburghii* as an epilepsy treatment [36-38,50-52].

## 7. Future Perspectives

### *The necessity of the Mechanistic Studies is appreciated*

The molecular mechanisms of the anticonvulsant action of phytosomal *Pinus roxburghii* formulations require further insight to facilitate their therapeutic development [57,58]. Although various phytochemicals have been shown to possess anticonvulsant, antioxidant, and anti-inflammatory activity [14-16,59,60,66], their mechanism of action at epileptogenic connections is not fully defined [13,72].

Further studies need to consider:

- Recognition of particular molecular targets (an example, GABAA receptors subunits, NMDA receptors, voltage-gated ion channels) [13,16,72].
- Neuroinflammatory mediator and microglial activation effects [14,35].
- Modulation of network remodelling and synaptic plasticity in epileptogenesis [13,14].

The mechanistic validation with transcriptomic, proteomic, and metabolomic methods might also offer a clue about the engagement with the target and the pathway modification [53,54]. This kind of data would provide more strength to the biological plausibility and rational optimization of dose to the clinical development [50-52].

### 7.2 State-of-the-Art delivery technologies

Even though phytosomes greatly increase bioavailability [36-38,42], bioavailability can be enhanced further by using advanced nanotechnology to target the brain [29-33,45,46].

The emerging strategies are:

- Nano-phytosomes having guarded nanoscopic measurement and surface qualities [36-38].
- According to the ligand theory Surface functionalization with ligands (e.g., transferrin, lactoferrin, peptides) to increase receptor-mediated transcytosis across the blood-brain barrier [29-33].
- Nose-to-brain Intranasal delivery systems that overcome systemic circulation [29,32].
- Hybrid nanocarriers, Phytosomes mixed with liposomes in order to enhance stability and controlled release [29-31,45,46], polymeric nanoparticles, dendrimers.

These methods can lead to build up of CNS, decrease systemic exposure, and raise the therapeutic index [29-33]. The effect of the combination of these technologies has the potential to enhance the translational potential of phytosomal formulations in refractory epilepsy to a great extent [21-23].

The research has been integrated with conventional antiepileptic drugs, which is an important aspect that serves as a comparative tool between the research and the conventionally used medications (Evans, 2002).

A combination therapy can be viewed as a promising route, especially in patients with drug-resistant epilepsy [3,4].

- *P. roxburghii* formulations may:
- Add multi-target to traditional AEDs [65-67].
- cut down on doses of the synthetic drugs [71, 75].

Reduce oxidative stress and neuroinflammation that have not been comprehensively covered under existing ASMs [14,15,35].

- Perhaps enhance tolerability profiles [8,9].
- Nonetheless, a strict clinical research is required to test:
- Paraxanthine slows the absorption rate of theophylline [9,21-23].
- Hepatic metabolism effects and cytochrome P450 effects [9].
- Precautions during co-administration in long-term [8,71].
- Effect on the frequency, severity, and quality-of-life indices of seizures [71,75].

To test the synergistic potential appropriately and in a safe way, effective clinical trials should be developed [50-52].

#### 7.4 Translational Pathway: Bench to Bedside

To achieve successful clinical translation of phytosomal *P. roxburghii*, a step-wise approach towards its development has to be well organized [50-52]:

Full preclinical validation.

- Dose-response studies [57,58]
- Toxicological profiling [50-52]
- Pharmacokinetic analysis [36-38] and biodistribution analysis [36-38].
- Formulation optimization
- Particle size control [36-38]
- Dynamically stabilized surface charge [36-38].
- Shelf-life validation [50-52]

Regulatory alignment

- Compliance with good manufacturing practice (GMP) [52].
- Standard phytochemical fingerprinting [50,51].
- Stability and quality documentation [50-52].

Pipes of clinical development.

- Phase I: Safety and tolerability [50-52].
- Phase II: Proof-of-concept efficacy [50-52].
- Phase III: massive validation [50-52].

The partnership between formulation scientists, pharmacologists, clinician and regulatory authorities will be vital in terms of reproducibility, scalability, and clinical credibility [50-52].

Strategic Outlook

The use of *Pinus roxburghii* as phytosomal drug delivery is a move that is bringing together ancient herbal medicine and new nanopharmaceutical medicines [36-38]. Provided that there is a state of mechanistic clarity, formulation strength, and clinical validation, this one can provide a multi-target, safer, adjunctive approach to epilepsy management, especially in drug-resistant and resource-limited settings [3,4,20]

#### Conclusion

*Pinus roxburghii* represents a promising botanical candidate for adjunctive epilepsy management, supported

by its diverse phytochemical profile comprising flavonoids, terpenoids, lignans, and phenolic acids [23,24,25,38,40]. These bioactive constituents exhibit antioxidant, anti-inflammatory, neuroprotective, and neuromodulatory activities that target key mechanisms implicated in epileptogenesis, including oxidative stress, neuroinflammation, ion-channel dysfunction, and imbalance between excitatory and inhibitory neurotransmission [15–18,35,36].

Unlike many conventional antiepileptic drugs (AEDs), which primarily act through single molecular targets and are often limited by adverse effects, pharmacoresistance, and suboptimal brain penetration [3,5,8,17,19], *P. roxburghii* offers a multi-target pharmacological approach [65–67]. Such polypharmacology is particularly relevant in complex neurological disorders like epilepsy, where multiple pathological pathways interact [15,21].

However, the clinical utility of *P. roxburghii* extractives is constrained by poor aqueous solubility, limited bioavailability, metabolic instability, and variable blood–brain barrier (BBB) penetration [19,50–52]. Phytosomal drug delivery systems provide a rational and scientifically grounded strategy to overcome these limitations [28–30,42]. By forming phospholipid complexes, phytosomes enhance solubility, improve membrane affinity, increase systemic bioavailability, and potentially facilitate improved CNS delivery [36–38,29–33]. Precedents from other phytosomal formulations support the translational feasibility of this approach [41,43,44].

Despite encouraging preclinical evidence [24,49], several challenges remain before phytosomal *P. roxburghii* can be integrated into clinical practice. These include rigorous extract standardization [63,65], reproducible large-scale manufacturing [36–38], long-term stability validation [50–52], comprehensive toxicological assessment [50–52], and well-designed clinical trials to establish safety and efficacy [50–52]. Additionally, regulatory pathways for herbal nanomedicines require careful navigation to ensure compliance with quality, safety, and efficacy standards [63,65].

In summary, phytosomal delivery of *P. roxburghii* represents a scientifically plausible and strategically innovative approach for epilepsy management [28–30]. While current evidence remains largely preclinical [24,49], continued mechanistic studies, formulation optimization, and translational research may enable its evolution from a

conceptual framework to clinically validated adjunctive therapy [63,65]. With appropriate scientific rigor and regulatory alignment, this approach may contribute to expanding therapeutic options, particularly for patients with drug-resistant epilepsy and in resource-limited settings where treatment gaps remain significant [3,45,20].

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