Exploring the Multifaceted Potential of *Alnus Nitida*: A Comprehensive Review of Its Pharmacognostic and Pharmacological Significance

KhuvRaj[1] , Shavinder Kumari[1*], Shubham Garg, Shiv Kumar Kushawaha[1], M.S. Ashawat[2]

1. *Department of Pharmacology, Laureate Institute of Pharmacy, Kathog, H.P., India, 176031*
2. *Department of Pharmaceutics, Laureate Institute of Pharmacy, Kangra 176031*

Corresponding Author:

Shavinder Kumari

Assistant Professor

Department of Pharmacology

Laureate Institute of Pharmacy

Orcid Id: 0000-0002-1167-6642

Abstract

Alnus nitida, commonly known as the West Himalayan alder, is a deciduous tree indigenous to the Hindukush Mountain range, spanning from the Yamuna River to West Kashmir. Traditionally, it has been extensively used in folk medicine for treating various ailments, yet its pharmacological properties have only recently been scientifically explored. This comprehensive review evaluates the pharmacognostic, phytochemical, and pharmacological significance of *Alnus nitida*, shedding light on its medicinal applications and therapeutic potential. The plant is rich in bioactive compounds such as flavonoids, tannins, terpenoids, and phenolic acids, which contribute to its diverse pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and anticancer properties. This review discusses the molecular mechanisms underlying these therapeutic effects, particularly focusing on oxidative stress modulation, inflammatory pathway inhibition, and apoptotic regulation in cancer cells. Additionally, the review highlights the emerging role of nanoformulations in enhancing the bioavailability and therapeutic efficacy of *Alnus nitida-derived* compounds. Given the limitations associated with traditional herbal formulations, nanotechnology-based delivery systems offer a promising approach to improve drug stability, solubility, and targeted delivery.

Keywords: *Alnus nitida*, Anti-inflammatory**,** Antioxidant properties**,** Nanoformulations, Molecular signaling.

1. Introduction

Alnus nitida (Spach) Endl (syn. Clethropsis *nitida* Spach.), sometimes referred to as West Himalayan alder or sharol/seril, is a deciduous woody tree found in the Hindukush Mountain range in the Western Himalayas, extending from the Yamuna River to West Kashmir (1). It is generally known in Pashto and Urdu as Geiray is a member of the Betulaceae family. This is found around the world in about thirty species that resemble shrubs and trees. It is found in Pakistan's Murree, Dir, and Swat departments. This tree, which is deciduous and woody, may grow to a height of 20 meters or more. It thrives in moist soil and may tolerate shade. Although the species is widespread, it is most frequently seen near riverbanks. The Himalaya's temperate regions are also home to its growth. Typically, it happens between 1000 and 3500 meters above sea level in height (2)**.** The main phytochemicals identified from Alnus species are diarylheptanoids. Flavonoids, glycosides, phenols, alkaloids, coumarins, saponins, anthraquinones, and tannins are also present (3)The stem bark of *A. nitida* has long been used in medicine to relieve pain, swelling, and injuries. It is used to treat health issues including cancer, hypertension, and anthelmintic, reproductive, and central nervous system illnesses, according to reported research. The local population also uses *A. nitida* stem bark to alleviate inflammation-related issues. The presence of polyphenols and other substances like sterols and terpenoids, which reduce inflammation and function as mediators of pain, maybe the cause of the therapeutic action(4). Terpenoids, saponins, coumarins, phenols, and flavonoids were evident in the methanol extract, and its fractions were extracted from *A. nitida* stem bark. With strong antioxidant and hepatoprotective properties against CCl4-induced hepatotoxicity shown in the rat model, its high level of total phenols (TPC) and total flavonoids (TFC) is noteworthy (5).

The taxonomy of *Alnus nitida* (West Himalayan Alder) is as follows:

- Kingdom: Plantae
- Phylum: Tracheophyta
- Class: Magnoliopsida
- Order: Fagales
- Family: Betulaceae
- Genus: *Alnus*
- Species: *Alnus nitida*

1.2 Traditional Use: *A. nitida* leaves as a decoction or infusion to treat individuals with diabetes. This is accomplished by either boiling or soaking crushed leaves in water for the whole night, and the resulting extract is utilized in the morning(6). *A. nitida* stem bark is used to treat bone fractures, edema, pain, and injuries (7). The extract or fractions of *A. nitida* stem bark demonstrated strong analgesic and anti-inflammatory effects (8), (9).

2. Phytochemical Compounds

2.1 Phenolic Compounds: PCs are widely found in the majority of plant tissues, including edible portions like fruits, seeds, leaves, stems, roots, and so on. In their structure, all PCs have at least one aromatic ring with a single hydroxyl group. There are more than8000 distinct plant PCs with a wide range of structural variations that may be divided into two primary categories: flavonoids and nonflavonoids (10).

Table .1 Phenolic Phytochemical Compounds in *Alnus nitida*

Sr.No.	Identification Compound	Pharmacological Properties	Reported By
1.	Malic acid	Antioxidant	(11)
2.	Chlorogenic acid	Antioxidant, Anti-inflammatory	(9)
3.	Quercetin	Antioxidant, Anti-inflammatory	(12)
4.	Ellagic acid	Antioxidant	(13)
5.	Pyrogallol	Antioxidant	(11)

6.	Epigallocatechin gallate	Anticancer, Neuroprotection	(14)
7.	Vitamin C	Antioxidant	(15)

2.1.1Malic Acid: A naturally occurring chemical component found in Alnus nitida, malic acid has been researched for possible antioxidant benefits that may help disorders like neurological diseases that are associated with oxidative stress (16). Malic acid's significance in promoting mitochondrial activity and strengthening the body's antioxidant defense system are two of the underlying processes that are frequently studied (17). The chemical structure of malic acid is shown in Fig.2.

2.1.2 Chlorogenic acid: CGAs are a series of esters that are created when quinic acid and certain trans-cinnamic acids combine typically, the only commercially accessible CGA is 5-O-caffeoylquinic (18). The primary polyphenolic component of many fruits and drinks, especially coffee, is chlorogenic acid, which also has antioxidant properties linked to the scavenging of free radicals and inhibits lipid peroxidation and anticancer activity (9). A recent study examined CGA's protective impact against oxidative damage to neuronal cells and discovered that it significantly reduced hydrogen peroxide-induced apoptotic nuclear condensation in neuronal cells (19). The chemical structure of chlorogenic acid is shown in Fig.2.

2.1.3 Quercetin: A popular natural flavonoid included in many fruits and vegetables, such as apples, berries, onions, and capers, is quercetin (3,5,7,3,4-pentahydroxyflavone) (12). The actions of quercetin include anti-oxidative, anti-apoptotic, anti-inflammatory, anti-cancer, antithrombotic, anti-aggregatory, and vasodilating mechanisms (20). The chemical structure of quercetin is shown in Fig.2.

2.1.4 Ellagic acid: Ellagic acid may be found in a wide variety of fruits, seeds, and vegetables, including pomegranates, persimmons, raspberries, black raspberries, wild strawberries, peaches, and plums (21). It has two lactones and four hydroxyl groups in its hydrophilic moiety, as well as two hydrocarbon rings in its lipophilic moiety. Due to this, ellagic acid has the ability to engage in antioxidant redox processes and receive electrons from many substrates(13) ellagic acid, which is a derivative of chromene-dione (2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde]chromene-5,10-dione; C14H6O8; mw:302.194g/mol), is shown in Fig. 2.

2.1.5 Pyrogallol: Pyrogallol is a common phenolic moiety found in flavonoids and polyphenols, which are found in a variety of food plants, such as chocolate, nuts, fruit peels, vegetables, and medicinal plants (22). In an alkaline solution, pyrogallol (benzene-1,2,3-triol) is a potent reducing agent that takes in oxygen from the atmosphere. It is frequently used as an antibiotic, a photographic developing agent in the hair dyeing business, and a tool to measure

the quantity of oxygen in the air because of its ability to produce oxygen radicals (23).The chemical structure of pyrogallol is shown in Fig.2.

2.1.6 Epigallocatechin gallate: Epigallocatechin gallate (EGCG) is a flavonoid that is an esterified form of gallic acid and a member of the chemical family known as flavan-3-ols (catechins). Although a range of vegetal foods and beverages, including fruits, chocolate, wine, and tea, contain catechins, the primary catechin in green tea is EGCG. The most abundant and physiologically active catechin in green tea is epigallocatechin-3-gallate (EGCG), whose potential to treat cancer has been thoroughly investigated (24). The chemical structure of epigallocatechin gallate is shown in Fig.2.

2.1.7 Vitamin C: Ascorbic acid, often known as vitamin C (abbreviated as AA), is a substance that is generated by the majority of animals and plants (25). It is a vitamin for humans since the gluconolactone oxidase gene, which codes for the last enzyme in the AA synthesis pathway, has undergone mutations that make it non-functional (26). Water-soluble vitamin C (ascorbic acid) serves a variety of purposes in the body, including facilitating iron absorption and playing a crucial part in the hydroxylation processes required for collagen creation and carnitine synthesis(27),((28)The chemical structure of vitamin C is shown in Fig.2.

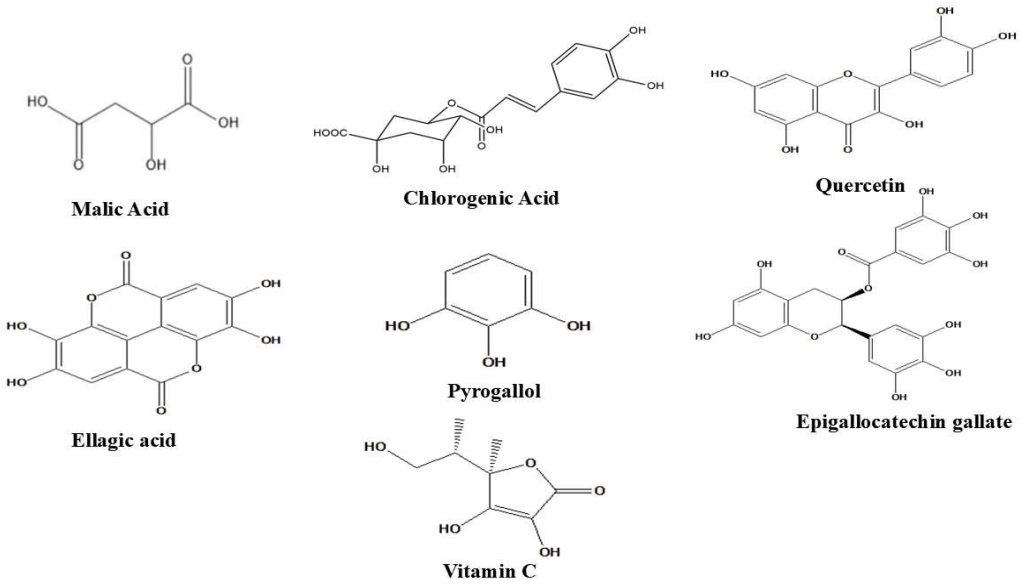

Fig.1 Chemical structure of Phytoconstituents

3. Pharmacological Activities of *Alnus Nitida*

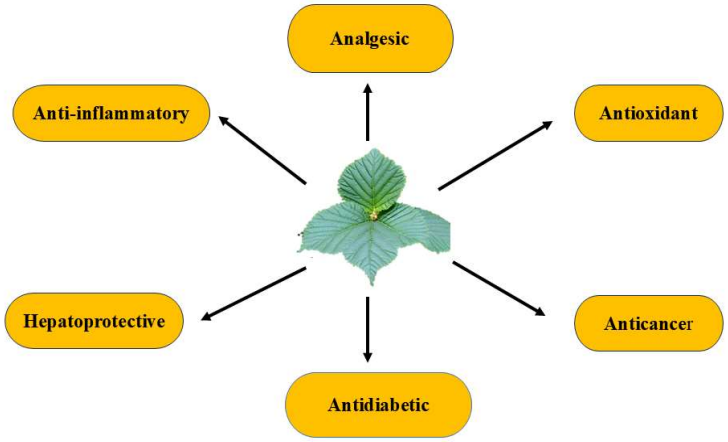

Fig.2 Pharmacological Action of *Alnus nitida*

3.1 Analgesic and Anti-inflammatory Activity: A. nitida stem, bark, and leaf paste are applied topically to treat boils and lessen discomfort and swelling. According to the literature search, the anti-inflammatory properties of *A. nitida* bark were assessed using the carrageenan-induced paw, Freund's complete adjuvant-induced arthritis, histamine-induced paw, and xylene-induced ear edema techniques (29). The herb's anti-inflammatory impact appears to be achieved via inhibiting nitric oxide synthesis in the chosen cell lines, which is triggered by inflammatory stimuli like PMA or LPS, as well as by inhibiting NF-κB transcriptional activity (30). *A. nitida* anti-inflammatory properties through iNOS suppression in LPS-induced macrophages (31).

3.2 Antioxidant Activity: In vitro antioxidant tests have revealed the antioxidant properties of A. nitida stem bark in rats (32). Antioxidants have long been recognized for their ability to safeguard the biological system by preventing or inhibiting oxidative stress caused by reactive oxygen compounds generated during routine metabolic processes or environmental influences (33). The presence and combined effects of phenolic and flavonoid chemicals, in addition to any other active compounds present, may be responsible for the antioxidant activity of Alnus species (34).

3.3 Antidiabetic Activity: Hyperglycemia and the antidiabetic properties of A. nitida leaves caused oxidative damage in rats by suppressing DPP-4, α-amylase, and α-glucosidase activity using in vitro tests. In rats given alloxan to produce diabetes, serum analysis was performed on several indicators, and the antioxidant activity of *A. nitida* in the liver, pancreas, and kidneys was also assessed (35).

3.4 Hepatoprotective Activity: The liver's critical activities include maintaining and restoring the body's equilibrium. It has a remarkable function in the human body, mediating a number of metabolic processes that include energy generation, disease defense, and feeding (36). The development of liver disorders is

mostly influenced by oxidative stress. The different harmful substances that are created by chemicals, viruses, or their bio-activation into chemically reactive metabolites are what cause liver damage. These metabolites may be free radicals, which work with cellular macromolecules to alter the biochemistry of the cells directly or trigger an immunological reaction. There is still a lack of a reliable synthetic liver defense medication, despite the intrusion into the contemporary medical system. Therefore, alnus nitida or extracts from these plants are thought to be useful in treating liver diseases (37). The phytochemical composition and to calculation the methanol extract *of A.nitida* stem bark's antioxidant and hepatoprotective properties against CCl4-induced hepatotoxicity in rats. HPLC-DAD analysis was performed to determine if polyphenolic components were present in the crude extract and its derived fractions, ethyl acetate, and residual aqueous fractions that showed strong antioxidant activity (38).

3.5 Anticancer activity: The malignant tumor with the greatest worldwide death rate is lung cancer, which is discovered later after the disease has advanced considerably. Lung cancer is caused by a number of variables, such as radiation, smoking, secondhand smoke, pollution, and exposure to metallic ions. Smoking is the main risk factor(39)**.** AKT and PI3K inhibitors can enhance the prognosis of cancer. Inflammatory reactions require the transcription factors p65 and NF-kB. It constantly activates genes related to cell survival and growth in malignant cells. B-cell lymphoma 2 (Bcl-2) coordinates anti-apoptotic effects via Bak and Bax, whereas Bcl-xL, a transmembrane protein located in mitochondria, regulates the mitochondrial release of cytochrome C and prevents apoptosis. These changes collectively demonstrated that the methanolic extract of the stem bark and leaf of *A. nitida* had antiproliferative and proapoptotic properties in patients with lung cancer (40).

4. *Alnus nitida* and Signaling Pathways :

4.1 NF-κB Pathway

The Nuclear Factor-kappa B (NF-κB) pathway is an essential modulator of inflammatory and immunological responses. Stress, cytokines, infections, and damage are some of the stimuli that activate it, causing the release of adhesion molecules, chemokines, and pro-inflammatory cytokines. Dysregulation of this pathway is associated with chronic inflammation and diseases such as cancer, autoimmune diseases, and cardiovascular disorders (41).

4.1.1Mechanism of Action in Inflammation

IκB proteins (Inhibitors of κB) sequester NF-κB in the cytoplasm when inactive. IκB is phosphorylated and broken down by the proteasome when it is activated (for example, by TNF-α, IL-1, or oxidative stress). NF-κB dimers, primarily p65/p50, are released by this breakdown and go into the nucleus. NF-κB attaches itself to particular DNA sequences in the nucleus and triggers the transcription of genes related to inflammation (such as cytokines like TNF-α, IL-6, and IL-1β) (42).

4.1.1Impact of *Alnus nitida*

Extracts from *Alnus nitida* inhibit the degradation of IκB, preventing the translocation of NF-κB to the nucleus and thus reducing the expression of inflammatory genes (43).

4.2 MAPK Pathway

A number of kinases that transduce signals from the cell surface to the nucleus make up the MAPK (Mitogen-Activated Protein Kinase) pathway, which controls a number of biological functions such as inflammation, stress response, cell proliferation, and apoptosis. A variety of environmental stressors, including stress, cytokines, and growth hormones, can activate the primary MAPKs, which include p38 MAPK, JNK (c-Jun N-terminal kinase), and ERK (extracellular signal-regulated kinase) (44).

4.2.1 Mechanism of Action in Inflammation

When ligands (such as stress signals or cytokines) attach to cell surface receptors (such as growth factor or TNF receptors), MAPK is activated.Ras proteins are triggered by this, and MAPK kinases (MEK) are then triggered. These kinases phosphorylate and activate particular MAPKs (ERK, JNK, and p38), which phosphorylates downstream targets that regulate the expression of genes linked to inflammation. While ERK is more important in cell survival and proliferation, activated JNK and p38 MAPK promote the production of pro-inflammatory cytokines (45).

4.2.1Effect of *Alnus nitida*

By preventing the activation of particular MAPKs (including p38 and JNK), alnus nitida extracts may lower the synthesis of inflammatory mediators and enhance cellular defense against stress.

4.3 PI3K/AKT Pathway

The PI3K/AKT pathway is essential for protein synthesis, metabolism, growth, and cell survival. AKT (protein kinase B), which is essential for cell metabolism, survival, and proliferation, is activated when growth hormones or other extracellular signals trigger PI3K (phosphoinositide 3-kinase) (46).

4.3.1 Mechanism of Action in Cell Survival and Proliferation

Cell surface receptors, such as growth factor receptors like EGFR, activate PI3K. Phosphatidylinositol (PI) is changed into phosphatidylinositol-3,4,5-trisphosphate (PIP3) by this activation, which draws AKT to the plasma membrane (46). Once at the membrane, the PDK1 and mTOR pathways activate AKT, which has several effects:

1. **Cell survival:** AKT stimulates pro-survival proteins like mTOR and suppresses apoptotic proteins like Bad.
2. **Cell proliferation:** By activating cyclin-dependent kinases, AKT promotes the advancement of the cell cycle.

3. Metabolism: AKT controls the creation of proteins and the metabolism of glucose.

4.3.2 Impact of *Alnus nitida*:

Extracts from *Alnus nitida* may activate the PI3K/AKT pathway, leading to enhanced cell survival and proliferation, particularly in conditions of neuroprotection and cancer therapy.

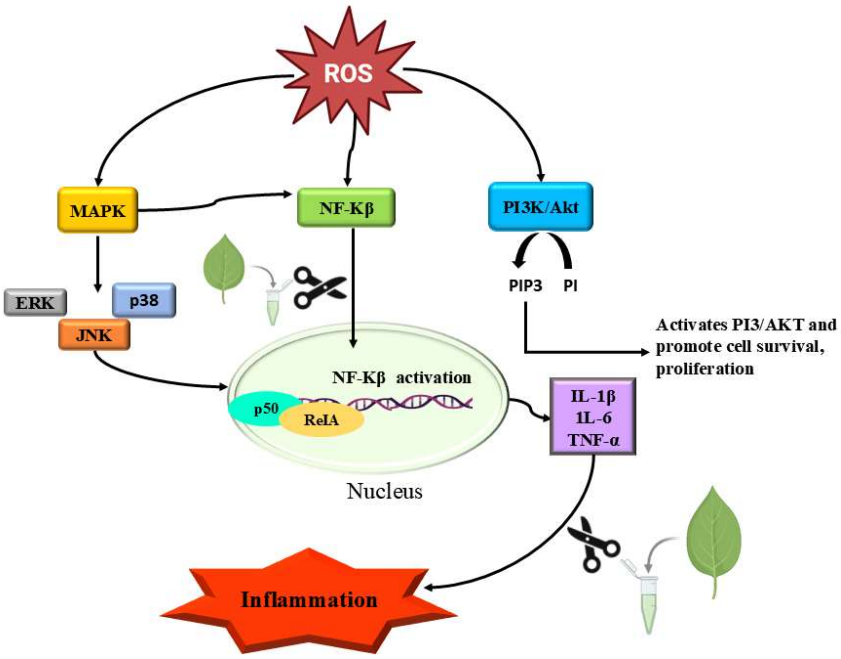

Fig.3. Illustration of oxidative stress and inflammation pathway: This highlights how ROS (Reactive Oxygen Species) activate key signaling cascades, including MAPK, PI3K/Akt, and NF-κB, leading to inflammation and cell survival. NF-κB activation, influenced by MAPK sub-pathways such as ERK, JNK, and p38, triggers the production of inflammatory cytokines like IL-1β, IL-6, and TNF-α. Additionally, the PI3K/Akt pathway is activated, promoting cell survival and proliferation. The presence of scissors and leaf icons suggests potential herbal interventions targeting NF-κB and inflammatory mediators to mitigate inflammation. This visual effectively represents the cellular response to oxidative stress, emphasizing the interconnected molecular mechanisms involved.

5 In silico studies

5.1 Docking

The majority of drug discovery investigations begin with docking. This tool provides crucial information on the inhibitor's optimal shape to suit the enzymes' active sites and is a crucial tool for ranking and comparing a list of potential inhibitors.

5.1.1 *In silico* anti-inflammatory properties of *Alnus nitida*

Palmitic acid and parthenolide were docked against inducible nitric oxide synthase (iNOS) to evaluate their binding interactions and inhibitory potential. Docking results indicated that parthenolide exhibited a more negative ΔG, signifying a stronger binding affinity compared to palmitic acid. This is attributed to parthenolide's α-methylene-γ-lactone moiety, which enables covalent and non-covalent interactions, including hydrogen bonding, π-π stacking, and hydrophobic forces, stabilizing its binding within the iNOS

active site. In contrast, palmitic acid, relying mainly on hydrophobic interactions and van der Waals forces, showed weaker binding due to its lack of strong polar functional groups and limited conformational fit. These findings suggest parthenolide as a promising iNOS inhibitor for further therapeutic exploration (1).

6. Different Species of *Alnus nitida*

Table .2 Various pharmacological effects produced by different species of *Alnus nitida*

Species	Natural Distribution	Pharmacological Activity	References
Alnus glutinosa (Black Alder)	Europe, from mid-Scandinavia to the Mediterranean, including northern Morocco and Algeria	Antibacterial, hepatoprotective, antioxidant, cytotoxic	(47)(48),(48)
Alnus incana (Gray Alder)	Scandinavia, and Baltic nations, thrive on acidic soils (pH as low as 4)	Anti-mycobacterial, used to treat TB-related symptoms	(49),(50),(51),(52),(53)
Alnus cordata (Italian Alder)	Mediterranean region, especially in nitrogen-deficient soils	Hepatoprotective, anti-inflammatory, anti-cancer, antioxidant	(54),(55)(56)(57) (58)
Alnus rubra (Red Alder)	Pacific Northwest, commonly used for commercial wood products (furniture, cabinets, paper)	Antibacterial, antioxidant, tumor cell-inhibiting, used for inflammation, hepatitis, cancer	(59),(60),
Alnus viridis (Green Alder)	Alpine conditions, heliophilous species, found in areas with low temperatures	Antibacterial, cytotoxic, antioxidant, anti-inflammatory	(61),(62),(63,64)

7. Prospects for Drug Development

7.1 Lead Discovery

Bioactive phytochemicals, including catechins and rutin, which have strong pharmacological effects, are found in Alnus nitida. Because of their many therapeutic benefits, several substances show promise as potential drugs:

7.2 Rutin

This strong flavonoid has hepatoprotective, antioxidant, and anti-inflammatory properties. It is essential for illnesses like chronic inflammation and liver disorders because it stabilizes free radicals and regulates oxidative stress (65,66).

7.3 Catechins

The antioxidant activity of many plants is enhanced by catechins, which also have anti-inflammatory and anti-cancer properties. Their ability to shield liver cells and lower inflammation makes them viable options for treating liver disease (67).

8. Formulation Strategies for *Alnus nitida* :

Table 3: Formulation Strategies of *Alnus nitida* extract and their applications

Formulation Strategy	Type	Description	Key Bioactive Compounds	Potential Applications	References
Phytopharmaceuticals	**Oral Formulations**	Standardized extracts in tablets, capsules, or syrups for long-term use.	Flavonoids, Diarylheptanoids	Treatment of liver fibrosis, hepatitis, oxidative stress, and inflammation.	(67)
	Injectable Formulations	Purified extracts for intravenous or intramuscular use, ensuring fast absorption.	Stabilized bioactive compounds	Acute liver damage, severe inflammation.	
Nano Formulations	**Liposomes & Nanoparticles**	Encapsulation for controlled release and protection of bioactives.	Rutin, Catechins	Targeted delivery to oxidative or inflammatory tissues.	(68),(69)
	Nanogels & Nanoemulsions	Improves absorption of hydrophobic compounds and sustains therapeutic activity.	Polyphenols	Localized inflammation management, enhanced bioavailability.	(70)
Topical Applications	**Anti-inflammatory Creams**	Reduces swelling and discomfort in chronic inflammatory skin conditions.	Phenolics	Arthritis, skin irritation.	(71)
	Wound-healing Gels	Enhances tissue repair and reduces microbial infections.	Bioactive wound-healing agents	Promotes cell regeneration and wound healing.	

9. Future Prospective

The prospects of *Alnus nitida* lie in advancing pharmacological research, optimizing drug formulations, and ensuring sustainable utilization. Comprehensive in vivo and clinical studies are essential to validate its efficacy, safety, and long-term therapeutic potential. Enhancing bioavailability through nanoformulations, encapsulations, and targeted drug delivery systems could improve its medicinal applications. Further research into its molecular mechanisms, including immune modulation, neuroprotection, and metabolic regulation, will provide deeper insights into its pharmacological effects. Biotechnological advancements, such as genetic engineering and tissue culture techniques, may enhance the production of key bioactive compounds. Sustainable harvesting and agroforestry practices are necessary to prevent overexploitation and ensure environmental conservation. Additionally, *A. nitida* has strong commercial potential, with opportunities for integration into pharmaceutical and nutraceutical markets. Collaboration with the pharmaceutical industry and regulatory bodies will facilitate its transition from traditional medicine to mainstream therapeutic applications. With continued research and innovation, *A. nitida* could become a valuable

natural resource for developing novel, effective treatments for various diseases, reinforcing the role of medicinal plants in modern healthcare.

10.Conclusion:

A.nitida exhibits a unique pharmacological profile, offering strong anti-inflammatory, hepatoprotective, antioxidant, and anticancer properties. Its bioactive compounds play a crucial role in mitigating oxidative stress, reducing inflammation, and promoting cellular repair. The modulation of key molecular pathways further supports its therapeutic applications. The integration of novel formulation approaches, such as nano-based delivery systems, could enhance its bioavailability and clinical utility. Future research should focus on optimizing extraction methods, conducting in vivo studies, and developing standardized pharmaceutical formulations to fully harness the medicinal potential of *A. nitida.*

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