Research Article

Phytochemical Constituents And Pharmacological Potential Of Neolamarckia Cadamba: A Comprehensive Review

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Abstract

Neolamarckia cadamba (Roxb.) Bosser, commonly known as Cadamba, is a fast-growing tropical tree belonging to the family Rubiaceae and has a long history of use in traditional medicine across South and Southeast Asia. Various plant parts, including bark, leaves, fruits, and roots, have traditionally been used for managing diabetes, liver disorders, inflammation, infections, wounds, and other chronic conditions. The plant contains diverse bioactive constituents, including flavonoids, phenolic compounds, steroids, fatty acids, indole alkaloids such as cadambine and iso-cadambine, and triterpenoids such as cadambagenic acid and betulinic acid.

Experimental pharmacological studies have demonstrated a broad range of biological activities of N. cadamba. These include antioxidant, antimicrobial, antifungal, anti-inflammatory, analgesic, hepatoprotective, anticancer, antidiabetic, anticonvulsant, and wound-healing effects. Its anticancer potential has particularly been associated with apoptosis induction and modulation of cell-cycle pathways. These findings indicate that N. cadamba may serve as a promising source of pharmacologically active compounds.

However, its translation into clinical applications remains limited due to insufficient human clinical trials, inadequate toxicological evaluation, variability in extraction methods and phytochemical composition, and incomplete understanding of its mechanisms of action. Therefore, systematic research is required to establish scientific evidence supporting its traditional uses. Future investigations should focus on standardized extraction procedures, phytochemical standardization, detailed toxicity studies, mechanistic investigations, and well-designed clinical trials to validate its therapeutic potential and facilitate evidence-based pharmaceutical development.

Keyword: Neolamarckia cadamba, Phytochemicals, Antioxidant activity, Antimicrobial, Antifungal, Anti-inflammatory, Analgesic, Anticancer, Apoptosis, Cell cycle arrest, Antidiabetic, Wound healing, Antipyretic, Toxicological evaluation, etc.

1. Introduction

Medicinal Plants are still among the most important resources for curing and preventing different types of disease today. Various Traditional Medical Systems around the world use these plants to this day, such as Ayurveda, Traditional Chinese Medicine (TCM) or Unani Medicine. With the worldwide resurgence of interest in natural and holistic methods of health care, there has been a renewed focus on the medicinal plants used by Ethnomedicine practitioners, in addition to promoting clinical research and drug development in the field of Western medicine (1) as well.

The therapeutic use of plants dates back to ancient civilizations. For example, Ebers Papyrus from Egypt (c. 1500 BCE) lists hundreds of plant-based remedies, while texts like the Charaka Samhita and Shennong Ben Cao Jing documented comprehensive knowledge on medicinal herbs in India and China, respectively. The fact that many contemporary medications, such as salicylic (made from birch bark), caffeine (made from the plant cinchona), while narcotics (made from silk flower), were first made from plants is evidence of the long-standing connection between plants along with health (2).

Neolamarckia Cadamba (Roxb.) Bosser, also referred to as Cadamba or Kadamba, is one of the plants that is particularly notable for its extensive ethnomedical use and increasing scientific attention (3). Cadamba is a tropical tree that originated from Southeast and South Asia. It has the ability to help individuals suffering from a variety of ailments including but not limited to fever, pain, liver issues, infections and metabolic disorders. Cadamba is recognized as a medicine in the tradition of Traditional Chinese Medicine, as well as in the folk traditions of various cultures that exist in regional areas. In addition to being valued as a medicinal plant, Cadamba also holds great cultural significance; it has been mentioned in many religious texts and ceremonies in cultures such as India and Indonesia (4).

Cadamba botanically classified under the Rubiaceae(5) family and previously recognized as Anthocephalus cadamba, it is a fast-growing, deciduous tree reaching up to 45m, identifiable by its large, glossy leaves and unique globular inflorescences. Its broad ecological distribution includes tropical India, Bangladesh, Sri Lanka, Nepal, Myanmar, Malaysia, Indonesia and southern China, thriving in humid, alluvial soils along river banks and community woodlands(3,6).

A long history of practical application and an increasing number of studies have led to continued scrutiny of a variety of natural products (secondary metabolites) that exist within the plant such as alkaloids (in particular cadambine & iso-cadambine), triterpenes, saponins, flavonoids, steroids, phenolics and fatty acids isolated from various tissues (7). The existence of bioactive compounds in these classes of compounds provides an opportunity for researchers to substantiate the purported pharmacological attributes of the plant (i.e. antioxidants, antimicrobial, anti-inflammatory, hepato-protectant, anticancer, antidiabetic and wound healing) in both in-vitro and in-vivo studies (3,8). These compounds are the source of ongoing molecular research, extraction and development of therapeutic products from the plant (9).
Nonetheless, there is a clear difference between the increasing number of animal studies verifying the effectiveness of Cadamba's various medicinal stem and the relatively few clinical studies assessing its human use, a lack of toxicological data to support safety and a lack of consistent extraction techniques and variability in the types of phytochemicals extracted from Cadamba, all of which impede product development and create a need for a complete overview of the current state of the area to evaluate Cadamba's potential efficacy and develop an integrated research plan to promote scientific progress through application of scientific evidence to practice (3,10).
This investigation aims to provide a comprehensive summary of Neolamarckia cadamba's phenolic composition, medicinal properties, ethnomedical history, alongside floral characteristics. This page aims to assist doctors, researchers and product manufacturers in realizing Cadamba's full medicinal value by compiling results from centuries of reputable studies, pointing out gaps in studies and providing suggestions for further study.

2. Botanical Profile and Traditional Uses

2.1 Botanical Description

The tree Neolamarckia cadamba (Roxb.) Bosser is a tree species found within the Rubiaceae (5) family that can reach heights of about 45m under good environmental conditions and grows quickly and naturally as an evergreen or deciduous tree. The tree has a straight cylindrical trunk, grey bark and broad, lush opposite leaves up to 30 cm long. However, it can also be identified as having a distinctive cluster of round-shaped (globular) flower clusters and having an aromatic smell.
The yellow-orange flowers are small, bisexual and densely clustered into globular heads, often appearing after the onset of monsoon rains. Fruits are capsule-like, containing numerous minute seeds dispersed by wind or water. Microscopically, the plant displays specialized laticifers canals and abundant parenchyma, with glandular structures frequently observed within its leaf and bark tissues attributes that contribute to its phytochemical richness(8,11).

2.2 Geographic Distribution and Ecological Habitat

The cadamba tree is found across much of the tropics and subtropics, especially in South and Southeast Asia. The main countries where the cadamba tree is located include India, Bangladesh, Nepal, Sri Lanka, Myanmar, Southern China, Malaysia, Thailand, and Indonesia. It thrives best in damp and very rich soils that have excellent drainage. Generally, these types of soils are located near rivers, within lowland forests and adjacent to forested areas managed by the community. Due to its fast growth and dense canopy, this tree is one of the main trees chosen in reforestation and agroforestry projects. It benefits the environment by helping reduce soil erosion and providing microhabitats (12,13).

2.3 Traditional Medicinal Uses

Numerous cultures have historically used the different sections of the cadamba plant to heal a multitude of ailments, thereby establishing it firmly within Ayurvedic and Unani as well as in other ethnomedical traditions.
Bark: Bark is often used to make herbal teas for many different health issues, including treating rashes, providing fever relief, aiding digestion and healing wounds. Bark also has a stringent quality to help close off the tissue it is applied to (both the cut or the mucous membrane) by causing them to contract. The astringent feature also decreases seeping from that area and prevents any blood loss due to the closing off of the area that receives the bark. Additionally, it is occasionally used as an emetic to induce vomiting, which is believed to occur through stimulation of the gastric mucosa or the chemoreceptor trigger zone (CTZ) in the brain, promoting expulsion of harmful substances from the stomach. The bark's antipyretic and digestive effects may be linked to its ability to modulate inflammatory mediators and enhance gastrointestinal function(14–16).
Leaves: When crushed, leaves can help reduce swelling, redness and pain because the chemical compounds in the leaves stop skin from releasing compounds that cause inflammation (like histamine) at the site. Crushed leaves also have healing properties and will help treat infections (from boils or ulcers) by promoting tissue regeneration, thus reducing the chance of getting an infection. It is highly probable that the leaves are a natural insect deterrent because they would contain volatile oils like terpenoids that would affect the insect's sensory mechanism preventing them from biting or getting close enough to the leaves. When ingested, the leaves will be able to regulate blood sugar levels due to their effects on insulin production and glucose absorption in cells as well as inhibiting certain enzymes needed to digest carbohydrates. Extracts of the leaves are also believed

to have anti-effect on microbes causing gastrointestinal issues like diarrhoea and dysentery as well as muscle relaxing or preventing contraction of the intestines, therefore their contents would help maintain fluid loss (7,17,18).

Fruits: The fruits components are taken fresh or incorporated into traditional formulations due to their well-known anti-inflammatory, diuretic and antipyretic properties. Their anti-inflammatory properties are thought to entail the suppression of pro-inflammatory mediators such as prostaglandins and cytokines. As diuretics, they encourage the elimination of excess fluids and salts by increasing urine output and affecting renal function. The antipyretic effect is assumed to be caused by the inhibition of prostaglandin synthesis in the hypothalamus, which aids in the regulation of body temperature during fever(12,19,20).

Roots and Flowers: The roots and flowers of the plant are used less frequently than other parts, yet they have traditional value. Roots are occasionally utilized in wound healing because of their antibacterial and tissue-regenerative qualities, which may improve speedier recovery by increasing cell proliferation and lowering local inflammation. While flowers are mostly used in cultural rituals and prized for their aromatic properties, they may also contain volatile chemicals with moderate medicinal effects such as mood elevation or antibacterial action via disruption of microbial cell membranes(4,21,22).

The way that Cadamba medications are produced in remote Indian communities with significant populations of Nepalese constitutes a rich market for producing medications (according to Malaysian ethno-botanicals). The tree also has cultural significance in Hinduism, with many references to the tree found in myths and family holidays like the "Kadamba tree festival", demonstrating its importance in society (3).

2.4 Ethnopharmacological Insights

Recent surveys suggest that more traditional remedies have a relationship to new research done on medicines. An example of this is using leaf pastes on wounds and ulcers, which coincides with earlier studies showing that the leaves have antimicrobial properties and promote healing of wounds. The cardio-protective properties of leaf decoctions and their ability to help with fever and skin conditions as a result of their anti-inflammatory and antioxidant properties also have support in the scientific literature. This overlap between what is traditionally used and what has been demonstrated in the laboratory provides additional support for conducting more research on the phytochemical and pharmacological effects of medicinal plants. Cadamba, with its rapid growth, adaptability and cultural integration, is valued not only for medicinal and ecological applications, but also plays an important socioeconomic role, providing timber, pulp and environmental renewal, reinforcing its status as a "miraculous multipurpose tree."(21,23).

3. Phytochemistry of Neolamarckia cadamba

The pharmacological effects of Neolamarckia cadamba are facilitated by a pool of chemically varied secondary metabolites. Several kinds of bioactive chemicals have been identified by phytochemical studies and they are dispersed differently throughout the bark, leaves, roots, fruits and flowers of the plant. A thorough description of the main phytochemical groups and their importance may be found below:

A. Alkaloids

Alkaloids are nitrogen-containing compounds that represent a significant portion of Cadamba’s bioactive profile. The principal alkaloids isolated include:(3)

Cadambine and Iso-cadambine: The main class of bioactive substances found in plants are indole alkaloids, which are primarily found in the bark and leaves. These alkaloids, which showed notable pharmacological properties like antibacterial, anti-inflammatory and cytotoxic actions, were among the first phytochemicals to be found. Antibiotics are capable of: interfering with the synthesis and function of microbial cell walls by interacting with key cellular targets; stopping the action of pro-inflammatory mediators (such as prostaglandins and cytokines) by blocking COX and NF-κB pathways; and inducing apoptosis in cancerous cells through activation of caspases and disruption of mitochondrial function. The multi-factorial nature of their therapeutic effects against inflammation, neoplasia and infectious disease highlights the potential of these antibiotics to be used as a treatment approach for these three classes of illness (21,24).

Neolamarckines: The plant's methanolic extracts have been shown to include novel alkaloids that are structurally similar to cadambine but differ in certain substituents that increase its pharmacological potential and biological variety. Their affinity for biological targets is influenced by these structural differences, which results in a wider range of activities. These alkaloids work by inhibiting microbial enzymes, preventing infections from replicating their DNA and altering inflammatory signalling pathways. These variations are thought to create oxidative stress or interact with DNA and thus can trigger apoptosis in cancerous cells and provide a type of selective cytotoxicity. The differences in their structure are not only used as tools to help identify lead compounds for drug development but also provide an opportunity for expanded therapeutic use (4,17).

Neocadambines A–D: In-vitro cytokine suppression studies have recently showed the promise anti-inflammatory action of monoterpenoid indole alkaloids that were extracted from leaf extracts. Due to the presence of a monoterpenoid moiety that increases their bioactivity and cell permeability, these chemicals constitute a unique subclass of indole alkaloids. They work by

blocking important signalling pathways like NF-κB and MAPK, which suppresses pro-inflammatory cytokines like TNF-α, IL-1β and IL-6. As a result, inflammatory mediators and enzymes like COX-2 and iNOS are expressed at lower levels.
These alkaloids successfully reduce the inflammatory response by focusing on these molecular pathways, thereby bolstering their potential as treatment agents for inflammatory conditions(11,25).

B. Triterpenes and Saponins
Cadamba houses a range of triterpenoid and saponins, known for their membrane-modulating and cytoprotective properties. Notable compounds include:(3)
Cadambagenic acid: The bark and roots of the plant contain a pentacyclic triterpenoid alkaloid that has been shown to have powerful anti-inflammatory and hepatoprotective activity. The compound has strong biological activity and consists of the core five ring triterpenoid with multiple functional groups (including nitrogen). In addition to having inhibitory effects on key inflammatory mediators, including prostaglandins, IL-6 and TNF-α, through inhibition of the NF-κB and COX-2 signalling pathways. The compound also mediates its hepatoprotective activity through prevention of lipid peroxidation and the elevation of liver enzymes (ALT, AST) as well as the enhancement of antioxidant defence mechanisms (GSH, SOD). Together, these activities reduce inflammation and protect hepatic tissues from oxidative and toxic injury (14,15).
Quinovic acid: Quinovic acid, a triterpenoid and plant-derived steroids are among the compounds that have been isolated from the bark and have shown significant immunomodulatory and cytotoxic effects in addition to broad-spectrum anticancer activities. The majority of the anticancer effects of Quinovic acid occur as a result of the induction of apoptosis via mitochondrial pathways resulting in DNA damage and activation of caspases in cancer cells. Quinovic acid also stimulates macrophage and NK cell activity and modulates the immune response, which facilitates the inhibition of tumour growth. Plant steroids, particularly for hormone-dependent cancers, prevent cancer cell growth via modulation of hormone receptor signalling, as well as inducing cell cycle arrest. In addition, these compounds reduce oxidative stress and inhibit pro-inflammatory cytokines, which contributes to both their cytotoxic and immune-modulatory properties. Together, these bioactive compounds provide a multi-faceted therapeutic option for the prevention and treatment of cancer (26, 27).
β-Sitosterol: The pharmacological profile of Cadamba is greatly influenced by one of the most prevalent plant sterols, which is extensively dispersed throughout the leaves and bark. This sterol has strong immunomodulatory, hypocholesterolaemic and anti-inflammatory properties. Its mode of action involves downregulating the COX and NF-κB pathways, which inhibits inflammatory mediators such prostaglandins and cytokines. As a hypocholesterolaemic drug, it lowers blood cholesterol levels by competing with dietary cholesterol for intestinal absorption. Additionally, it enhances macrophage activity and lymphocyte proliferation, which regulates immunological responses. This sterol enhances the overall pharmacological potential of Cadamba by acting in concert with other phytochemicals in addition to contributing to specific therapeutic benefits(28,29).

C. Flavonoids and Phenolics
Extensive studies have identified numerous polyphenolic compounds in Cadamba, predominantly in leaves and fruits:(3)
Quercetin, Caffeic acid, Syringic acid, Tannic acid and Chlorogenic acid: Phenolic and flavonoid compounds in cadamba have significant antioxidant characteristics and play an important role in scavenging free radicals and reducing inflammation. Quantitative methods have revealed that cadamba extracts contain large amounts of total phenolic content (TPC) and total flavonoid content (TFC), with higher levels found in ethanolic and hydroalcoholic extractions, which is highly related to the increased ability to scavenge free radicals. The directly scavenged reactive oxygen species (ROS) and the chelation of metal ions that catalyse oxidative processes are accomplished through a mechanism that upregulates endogenous antioxidant enzymes, such as glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD). Additionally, these compounds may inhibit inflammation by inhibiting pro-inflammatory signalling pathways, such as NF-κB, that are activated by oxidative stress. As a result, cadamba may have great therapeutic potential in the treatment of diseases associated with oxidative stress and will enhance cellular defence mechanisms (8,30).

D. Fatty Acids and Other Constituents
According to GC-MS analysis, the leaf extracts of Cadamba mostly include fatty acids such n-hexadecenoic acid (palmitic acid), octadecanoic acid ethyl ester (ethyl stearate) and similar derivatives. The antibacterial and anti-inflammatory qualities of the plant are mostly attributed to these fatty acids. They work by breaking down the membranes of microorganisms, which allows their contents to escape and stops them from growing. Furthermore, they control inflammatory reactions by downregulating the COX and NF-κB pathways, which prevents the synthesis of pro-inflammatory mediators such prostaglandins, cytokines and nitric oxide (NO). By providing both therapeutic and preventive actions against inflammatory diseases and microbial infections, these bioactive fatty acids improve the pharmacological profile of the plant(3,31,32).
Environmental elements like geographic location, climate, plant age and seasonal fluctuations have a big impact on Cadamba's phytochemical profile. These factors can affect the form and content of active substances like phenolic, flavonoids and

triterpenoids. Weather conditions, rainfall levels and soil characteristics can influence the metabolic responses of plants producing varying levels of intensity and quantity of polyphenols. Differences in seasonality will impact the biosynthetic processes of plants, thereby indicating the optimal time to harvest. Standardized methods for harvesting and extracting plant materials are required to ensure research has consistent and reproducible results. In addition, standardization will facilitate the development of effective and high-quality herbal medicines and provide scientific support for Cadamba as a source of therapeutic benefits (19, 33).

4. Analytical and Extraction Techniques

The phenolic yield varies significantly depending on the removal technique. Methanol or ethanol are suggested fluids for the broad-spectrum separation of semi polar chemicals like phenols, phenolics, while opiates, whereas hexane and chloroform have fewer polar components.

Analytical methods applied include:

1. Thin Layer Chromatography (TLC): As a preliminary qualitative profiling method for Cadamba extracts, Thin Layer Chromatography (TLC) has been used, especially to detect and separate different types of phytochemicals like alkaloids, flavonoids, triterpenoids and phenolic compounds. Different bands corresponding to particular phytoconstituents have been seen under UV light or following derivatization with reagents such as ferric chloride (for phenolics) or Dragendorff's (for alkaloids) using various solvent systems and visualizing agents.

To evaluate the chemical variety of Cadamba, TLC is a quick, economical and effective method that allows comparison of extracts (such as methanolic, ethanolic and hydroalcoholic) and directs additional purification and structural clarification of bioactive chemicals(33,34).

2. Gas Chromatography–Mass Spectrometry (GC-MS): For the investigation of volatile chemicals and fatty acid profiling in Cadamba, especially in leaf and bark extracts, Gas Chromatography–Mass Spectrometry (GC-MS) is commonly used. Important bioactive components such as n-hexadecenoic acid, octadecanoic acid ethyl ester, phytol and other fatty acid methyl esters can be identified and measured using this method. Because of its excellent sensitivity and specificity, GC-MS is perfect for identifying thermally stable, low molecular weight molecules. By identifying the presence of fatty acids, esters and terpenoid derivatives, the GC-MS profile of Cadamba offers important information on the plant's antibacterial, anti-inflammatory and antioxidant qualities. This analytical method is essential for confirming traditional applications and directing the creation of standardized herbal mixtures(5,35).

3. Liquid Chromatography Mass Spectrometry (LC MS): The analytical technique, Liquid Chromatography- Mass Spectrometry (LC–MS), is an extremely powerful analytical method that provides precise measurements of a wide variety of chemical substances in Cadamba (e.g., flavonoids, triterpenes, phenolic compounds). Due to LC–MS' unique characteristics (i.e., sensitivity, specificity and resolution), this technique is the most appropriate method for identifying and quantifying compounds that vary greatly in size, structure and thermal properties. The use of LC–MS has identified pentacyclic triterpenoids, numerous pharmacologically active flavonoid glycoside compounds and more recently, the indole alkaloids (i.e., cadambine derivatives) from Cadamba. The ability of LC–MS to provide molecular weights, fragmentation data and specific structural information has facilitated the characterization of bioactive compounds from Cadamba. Hence, LC–MS not only supports the standardization and quality assurance of phytochemical analysis, but also provides a greater understanding of the medicinal value of plants from a pharmacological and phytochemical perspective (23,36).

4. Fourier Transform Infrared Spectroscopy (FT-IR): Functional groups found in the phytoconstituents are identified by the use of Fourier Transform Infrared Spectroscopy (FT-IR) for the initial structural characterization of Cadamba extracts. This approach gives an individual spectral fingerprint for different types of chemicals through vibrational transitions in molecular interactions. Using FT-IR analysis on Cadamba's leaves, bark & roots, the following key functional groups have been discovered - hydroxyl (-OH), carbonyl (C=O), amine (-NH) & alkene (C=C).

These functional groups suggest the corresponding presence of phenolics, flavonoids, alkaloids & triterpenoids. The plant's antibacterial, anti-inflammatory and antioxidant properties are supported by the presence of these functional groups. Thus, FT-IR complements other cutting-edge analytical methods and provides a quick, non-destructive means of verifying the chemical makeup of the bioactive chemicals in Cadamba(25,37).

5. Nuclear Magnetic Resonance (NMR) Spectroscopy: A crucial method for verifying the molecular structure of the bioactive chemicals that have been extracted from Cadamba is Nuclear Magnetic Resonance (NMR) Spectroscopy. NMR determines the molecular structure, functional groups and stereochemistry of complex phytochemicals by examining the magnetic characteristics of atomic nuclei, mainly hydrogen (^1H) and carbon (^13C). NMR has proven crucial in Cadamba's study for clarifying the structures of flavonoids, triterpenoids and indole alkaloids (such cadambine and its derivatives).

It provides conclusive evidence of compound identity by assisting in the precise location of substituents, ring structures and conjugation patterns. The pharmacological potential of Cadamba's phytochemicals must be confirmed by this high-resolution structural analysis in order to direct the creation of synthetic or semi-synthetic drugs based on these natural leads(38,39).

Summary Table: Principal Phytochemicals of Neolamarckia cadamba

Compound/Class	Plant Part(s)	Reported Activities
Cadambine (Alkaloid)	Bark, Leaves	Antimicrobial, Anti-inflammatory, Cytotoxic
Iso-cadambine (Alkaloid)	Bark, Leaves	Anti-inflammatory, Analgesic
Neolamarckines	Leaves	Anti-inflammatory
Cadambagenic acid	Bark, Roots	Hepatoprotective, Anti-inflammatory
Quinovic acid	Bark	Anticancer, Hepatoprotective
β-Sitosterol	Bark, Leaves	Anti-inflammatory, Hypocholesterolaemia
Quercetin	Leaves, Fruits	Antioxidant, Anti-inflammatory
Caffeic acid	Leaves, Fruits	Antioxidant, Antimicrobial
n-Hexadecenoic acid	Leaves	Antimicrobial, Antioxidant

5. Pharmacological Activities of Neolamarckia cadamba

Numerous studies have been conducted to evaluate the various pharmacological effects of Neolamarckia cadamba. Numerous isolated compounds, fractions, especially extracts have shown encouraging biological activity both in-vitro as well as throughout in-vivo. This section summarizes recent research in various pharmacological categories, emphasizing experimental strategies, significant findings, as well as, when applicable, mechanistic insights.

1. Antioxidant Activity

Oxidative stress contributes significantly to the pathophysiological features of many chronic diseases, such as cardiovascular disease, diabetes, cancer and the neurological diseases. Neolamarckia cadamba has garnered attention in recent years because of its potent antioxidant properties. A number of studies have demonstrated the antioxidant effects of cadamba extracts, which are primarily attributed to their phenolic and flavonoid compounds. These compounds possess the ability to neutralize ROS, reduce lipid peroxidation and enhance the activity of naturally occurring antioxidant enzymes (SOD and CAT). The ability of cadamba to mitigate oxidative stress supports its potential for therapeutic use in the treatment and prevention of common chronic diseases associated with oxidative stress (20,40).

In-vitro assessments: Different in-vitro assays have been carried out to evaluate Neolamarckia cadamba's antioxidant properties, including tests based on hydrogen peroxide radical scavenging and those measuring FRAP (ferric reducing antioxidant power), ABTS radical scavenging and DPPH radical scavenging capabilities. Results showed that ethanolic and hydroalcoholic extracts of Cadamba leaves and fruits exhibit strong antioxidant activity in a dose dependent manner. IC_{50} values for all components ranged from 15-40 µg/mL, indicating substantial capacity for free radical neutralisation. This substantial capacity for antioxidant action directly correlates to Cadamba's high phenolic and flavonoid concentrations suggesting that it has great potential as a natural medicine for the treatment of diseases caused by oxidative stress (20,40).

Structure-activity relationship (SAR): Research that applied the structure activity relationship approach demonstrated that total flavonoid and polyphenol concentrations in Neolamarckia cadamba show a solid correlation with the total antioxidant capacity of cadamba. Findings from this research demonstrate the significance of certain chemical substances found in N. cadamba for bioactivity; for instance, these include quercetin, caffeic acid and chlorogenic acid. The primary reason these compounds exert antioxidant functions is due to the presence of structural hydroxy groups on the compounds, which are capable of reactively scavenging for free radicals and stabilising them. In addition, they may enhance antioxidant activity through the modulation of the activity of distinct antioxidant enzymes and by chelating (binding) metal ions. The importance of phenolic compounds as functional components of cadamba and as such, the potential use of cadamba to treat diseases resulting from oxidative stress, is indicated by the SAR results obtained.

Biological Significance: The scientific research showing that Neolamarckia cadamba has been able to help in protecting against oxidative damage (through both cellular and animal models) shows that antioxidants found in cadamba are biologically important. Antioxidants help reduce oxidative stress by removing reactive oxygen species (ROS), decreasing lipid peroxidation, as well as keeps cellular structure intact. Therefore, extracts of cadamba have shown positive results in providing protective effects when used in experimental models of cardiovascular disease, neurodegeneration and liver toxicity. Collectively, this evidence supports that cadamba has therapeutic value for treating and preventing disorders associated with oxidative stress such as; diabetes mellitus, malignancies, neurological diseases and cardiovascular disease (19,41).

2. Antimicrobial and Antifungal Activities

Neolamarckia cadamba is an antibiotic that inhibits multiple different types of pathogens, including many types of bacteria (both Gram-positive & Gram-negative), fungi and some types of viruses. The rich chemical compounds found in the plant, including alkaloids, phenolics, flavonoids and fatty acids are believed to have antimicrobial effects as they disrupt the integrity of the cell wall of the microbes, impair the functions of important enzymes necessary for the viability of the pathogens and prevent the synthesis of their nucleic acids. The plant has long been used to treat wounds and infections and studies have demonstrated that extracts from various plant parts, particularly the bark and leaves, can dramatically lower microbial growth. This wide-ranging action demonstrates Cadamba's potential as a supplementary or natural antibacterial treatment agent(7,27).

Bacterial inhibition: The bark, leaf and fruit extracts of the Neolamarckia cadamba tree possess significant antibacterial properties against several different harmful microorganisms, for example, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Bacillus subtilis. Chloroform and methanol extracts, in particular, showed a strong inhibition against bacteria when compared with extracts from other solvents. Some Minimum Inhibitory Concentration (MIC) results from the extracts are identical to those of many recognized types of antibiotics; therefore, there is a high probability that the antibacterial properties result from the presence of several bioactive constituents, such as flavonoids, triterpenoids and alkaloids. It is believed that these compounds interfere with or damage the structural integrity of bacterial cell walls, inhibit protein synthesis by target bacteria and disrupt various metabolic pathways within the target bacteria. Therefore, the current research supports earlier research that suggests Neolamarckia cadamba trunk and herb may be a potential source of antimicrobial compounds (3,42).

Antifungal activity: Neolamarckia cadamba has been shown to have antifungal activity against pathogenic fungi including Aspergillus Niger, Candida albicans and more. The antifungal activity of cadamba is attributed to its bioactive triterpenes and alkaloids, which can damage the integrity of fungal cell membranes, inhibit ergosterol synthesis and block critical enzymatic processes. In-vitro studies using bark and leaf extracts have shown evidence of antifungal activity as visible zones of inhibition have been demonstrated by limiting fungal growth. These studies demonstrate the potential of cadamba for developing natural antifungal therapies especially considering the increased resistance to traditional antifungal treatments (7,19).

Mechanism of Antifungal activity: Four distinct mechanisms have been described that cadamba has an antibacterial effect through damaging bacteria cell membranes thereby leaking cellular components leading to cell death; preventing Quorum sensing which regulates the levels of virulence and biofilm formation by pathogens; inhibiting microbial enzymes important for continued survival and reproduction; and possibly other effects yet to be identified. The broad range of effects that cadamba has on fungi is a result of the four mechanisms described above. When cadamba is combined with certain prescribed antibiotics there appears to be a synergistic effect increasing the overall effectiveness of each antibiotic alone; therefore, cadamba may assist in improving antimicrobial therapy and combating antibiotic resistance (7,19).

Limited Antiviral data: Antiviral research is still scarce, despite the fact that cadamba has been thoroughly investigated for its antibacterial and antifungal qualities. Preliminary screens suggest that some extracts may have antiviral qualities, perhaps by preventing viral entry, replication or protein synthesis. However, these findings are still early, as well as aren't enough comprehensive studies that identify specific active ingredients in addition to their mechanisms of action. The plant's rich phytochemical profile especially broad-spectrum antimicrobial activities may pave the way for the creation of plant based antiviral therapies, so further investigation into its antiviral potential is required (43,44).

3. Anti-inflammatory and Analgesic Effects

A biological reaction that is essential to many illnesses is inflammation. Cadamba's anti-inflammatory activity supported by research using a variety of in-vivo models. The results of several different studies have been performed using rodent models to demonstrate that both aqueous and methanolic extracts from Neolamarckia cadamba (both bark and leaves) provide both potent anti-inflammatory and analgesic effects. In evaluating the formalin test for pain (formalin) and the paw edema model (carrageenan), all extracts were able to decrease paw edema and suppress nociceptive responses. These effects indicate a significant peripheral and central modulation of pain. The effects of Neolamarckia cadamba were similar to those of commonly used anti-inflammatory and analgesic drugs, such as diclofenac and aspirin. As a result, the traditional use of Neolamarckia cadamba for the treatment of inflammation and pain is supported by the results obtained in these previous studies and by the presence of alkaloids, flavonoids and triterpenoids in Cadamba, all of which may act through inhibition of prostaglandin synthesis and inhibition of the pathways associated with inflammatory signalling (8,14).

Molecular Targets: The mechanisms behind the anti-inflammatory effects of Neolamarckia cadamba have been elucidated by the identification of the monoterpenoid indole alkaloids Neocadambines A-D. Neocadambines A-D were observed to significantly diminish pro-inflammatory cytokines IL-1β and TNF-α in studies with cultured macrophages. In addition to inhibiting these pro-inflammatory cytokines, Neocadambines A-D also inhibit cyclooxygenase-2 (COX-2) expression, an important inflammatory mediator. The combined action of cytokine inhibition in addition to COX-2 suppression highlights the potential of Cadamba's alkaloids to alter inflammatory responses at the molecular level, thereby increasing their therapeutic value in the management of chronic inflammatory disorders (31, 33).

Mechanistic studies: Mechanistic research on Neolamarckia cadamba has shown that several molecular pathways mediate its antioxidant and anti-inflammatory properties. Notably, it has been demonstrated that extracts and isolated chemicals suppress the NF-κB signalling pathway, a crucial regulator of inflammation, which lowers the expression of pro-inflammatory enzymes and cytokines like COX-2, IL-1β and TNF-α. Cadamba has been shown to significantly reduce markers associated with oxidative stress by increasing both its levels of enzymatic antioxidants (i.e., catalase and superoxide dismutase) and through glucan polymer's ability to enhance the functioning of those enzymatic antioxidants (3,31,33). The findings thus demonstrate the value of Cadamba as a therapeutic agent for treating chronic inflammatory and oxidative-stress related diseases due to the demonstrated ability of its anti-inflammatory and antioxidant properties to work together to elicit its therapeutic responses.

4. Anticancer Potential

Several studies highlight Cadamba's cytotoxicity against various cancer cell lines and elucidate possible apoptotic mechanisms.

In-vitro cytotoxicity: Neolamarckia cadamba bark extracts and their extracted triterpenoid saponins have shown strong dose-dependent cytotoxic action against a range of human cancer cell lines, including colorectal (HCT116), prostate, lung (A549), liver (HepG2) and breast (MCF-7) cancer cells. According to in-vitro research, these extracts frequently have IC_{50} values less than 50 µg/mL, which suggests that they have substantial anticancer potential. It is thought that processes like apoptosis induction, mitochondrial membrane potential disturbance and caspase pathway activation contribute the cytotoxic effects. These results demonstrate the possibility of chemicals obtained from Cadamba bark as viable options for the creation of plant-based anticancer treatments(35,45).

Apoptosis and Cell Cycle Arrest: Studies on the anticancer properties of Neolamarckia cadamba have demonstrated that its bioactive constituents, particularly triterpenoid saponins, induce apoptosis through a range of cellular mechanisms. One of the key findings is the activation of the caspase-3 especially caspase-9 enzymes, which are critical for the apoptotic execution phase. Additionally, by raising pro-apoptotic proteins like Bax in addition to lowering anti-apoptotic proteins like Bcl-2, the administration of Cadamba extracts shifts the balance in favour of cell death. Additionally, cell cycle research has demonstrated arrest at crucial checkpoints, such as the G0/G1 and G2/M phases, which successfully stops the growth of cancer cells. Together, these molecular processes lend credence to Cadamba and its phytoconstituents' strong cytotoxic and cancer-inhibiting properties(45,46).

In-silico studies: By showing that Neolamarckia cadamba's main phytochemicals, including cadambine and other triterpenes, exhibit substantial binding affinities to important cancer-related molecular targets, molecular docking studies have further validated the plant's anticancer potential. These comprise several protein kinases involved in cell survival and proliferation pathways, as well as enzymes such as topoisomerase I and II. Stable contacts at active sites are indicated by the docking data, indicating that these drugs may effectively limit target function. This computational data demonstrates the therapeutic potential of Cadamba in addressing molecular pathways linked to the advancement of cancer and validates the experimental results of cytotoxicity(47,48).

In-vivo data: Despite the paucity of in-vivo research on Neolamarckia cadamba, data from animal models has demonstrated encouraging hepatoprotective and anticancer properties, especially in xenograft tumour models. In support of its protective activity against chemically induced hepatic damage and cancer progression, these investigations have shown that Cadamba extracts can considerably reduce tumour volume and enhance liver function markers. The discovered in-vivo efficacy, which is in line with in-vitro results, suggests that the plant's bioactive components are not only pharmacologically active yet bioavailable as well as efficient in a living system. These results demonstrate the translational potential of Cadamba for future therapeutic applications and highlight the need for more clinical as well as preclinical studies (3,35).

5. Hepatoprotective Effects

Studies on animals with chemically induced liver damage support the liver protective function of cadamba.

Models used in experiments: Neolamarckia cadamba bark extracts have been demonstrated to have hepatoprotective properties in rat models. In studies where carbon tetrachloride (CCl_4) or paracetamol were used to induce hepatotoxicity, cadamba bark extracts significantly reduced in addition to normalized elevated liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), in addition to alkaline phosphatase (ALP). These biochemical alterations were supported by histopathological analyses and that showed reduced inflammation in addition to liver tissue damage. The hepatoprotective benefits of the plant are believed to be caused by the anti-inflammatory and antioxidant properties of its phytoconstituents, suggesting that it could be used as an organic remedy for liver diseases (15,43).

Histological improvements: Histological evaluation of the liver from studies that investigated the effects of Neolamarckia cadamba as a hepatoprotective agent shows substantial changes in the liver. Cadamba bark extracts decreased the amount of hepatic necrosis and inflammatory cell infiltration, including fatty infiltration, in animals where either carbon tetrachloride or paracetamol induced liver injury. The restoration of normal liver architecture indicates that Cadamba protects liver cells from oxidative as well as inflammatory injury and stimulates tissue regeneration. These findings provide additional evidence that Cadamba is a natural hepatoprotective agent with therapeutic potential in the treatment of liver disease (15,43).

Mechanism: Neolamarckia cadamba exhibits hepatoprotective effects due to cadambagenic acid (the major phytochemical in Cadamba), as well as numerous other flavonoids within Cadamba. The chemicals in cadamba can assist to improve liver protection by elimination of free radicals to develop antioxidant capability; enhancing lipid peroxidation; inhibiting reactive oxygen species (ROS); and returning the activity of endogenous antioxidant enzymes such as GSH, CAT and SOD, back to normal. In addition, the above nutrients act at the same time in producing anti-inflammatory effects in the liver by blocking or reducing pro-inflammatory cytokines and inflammatory pathways and enhancing the restoration and maintenance of healthy liver tissue. Therefore, these results provide a scientific basis to support the historical use of cadamba for treating liver disease and show that cadamba has potential as a modern hepatoprotective agent (15,43,49).

6. Other Pharmacological Activities

Antidiabetic effects: Neolamarckia cadamba has demonstrated excellent antidiabetic activity in preliminary studies conducted with animals. The leaf extracts have been found to have advantageous effects on insulin sensitivity and glycaemic control by improving these and other parameters of blood glucose regulation. It is believed that multiple mechanisms contribute to these benefits, one being the inhibition of the enzyme α-glucosidase, which reduces carbohydrate breakdown and glucose absorption. Also, both phenolic compounds within the plant as well as its flavonoids have remarkable antioxidant properties that may lower levels of oxidative stress, one of the primary causes of insulin resistance and dysfunction in pancreatic β-cells. Based on this evidence, it is possible that Neolamarckia cadamba could represent an integrated approach for the management of diabetes and its complications (3,22).

Diuretic Activity: The diuretic effects of Neolamarckia cadamba have been demonstrated in several studies, especially when both the leaf and the bark are used. When tested on animal model systems, both leaf and bark extracts produced increased volumes of urine and increased excretion of sodium and potassium in the urine, which suggests that both leaf and bark extracts may help improve renal function and maintain proper fluid balance. The diuretic action may be due to various bioactive compounds including flavonoids, saponins and alkaloids, which may also interfere with the reabsorption of fluid from renal tubules. This supports the traditional use of Cadamba for treating conditions such as edema, high blood pressure and urinary tract infections (3,50).

Antipyretic Activity: Neolamarckia cadamba has shown significant antipyretic activity in rodent models; its extracts have produced a substantial reduction in fever following experimental induction. Traditional pyrexia models such as Brewer's yeast-induced hyperthermia were used to assess these antipyretic effects and were comparable to those of conventional antipyretic drugs. This reduction in body temperature appears to be due to inhibition of prostaglandin synthesis within the hypothalamus, a major regulation centre for body temperature. The findings here add support for the use of Cadamba ethnomedically to treat fever by showing that it contains active compounds that can influence fever modulating biochemical pathways that closely correlate with traditional claims of medicine (3,17).

Wound healing: Neolamarckia cadamba leaves, when used as topical applications, as both leaf and bark extract, can be shown to promote the healing of wounds. When extracts of Neolamarckia cadamba are applied to wounds, they will influence both the speed at which the tissue regenerates, as well as the speed of closure due to increased collagen deposition and decreased localised inflammation associated with the wound. Bioactive substances with antimicrobial, anti-inflammatory, in addition to antioxidant qualities, such as flavonoids, triterpenoids, in addition to tannins, are responsible for the wound healing effects. These phytochemicals support extracellular matrix remodelling, fibroblast proliferation, in addition to wound infection prevention. These results demonstrate Cadamba's therapeutic potential in dermatological applications in addition to scientifically validate its traditional use in treating cuts, ulcers, especially skin injuries (9,51).

Additional activities: Research so far indicates Neolamarckia cadamba has multiple therapeutics uses apart from its known antibacterial and antioxidant activities. Its antipyretic, antispasmodic, immunomodulating and neuroprotective actions can be attributed to many different phytochemical components of substance, including alkaloids, flavonoids and triterpenoids. The preliminary experimental data available are also very promising; Cadamba appears to provide neuroprotective properties, modulate immune function (immunomodulant), relax smooth muscle and reduce fever. However, the mechanisms responsible for these effects are still not completely understood and require further validation from more thorough in-vivo studies and clinical trials. Further research is required to fully determine the therapeutic potential of Cadamba in these areas and to support its development into evidence-based pharmaceutical products. (3,52)

6. Mechanisms of Action of Neolamarckia cadamba Phytochemicals

To support traditional applications and direct future therapeutic development, it is crucial to comprehend the molecular and cellular mechanisms behind Neolamarckia cadamba's pharmacological actions. Despite the abundance of bioactivity data, mechanistic aspects are still not fully understood and are frequently deduced from related phytochemical families. The evidence currently known on important routes, targets and hypothesized mechanisms connected to the bioactive chemicals in Cadamba is summarized in this section.

1. Anti-inflammatory and Analgesic Mechanisms

A) Inhibition of pro-inflammatory cytokines: Neolamarckia cadamba, particularly Neo cadambines A–D, contains indole alkaloids that inhibit key pro-inflammatory cytokines, providing strong anti-inflammatory capabilities. These alkaloids, using cell cultures, have shown significant inhibition of cytokine release and signalling critical to start and maintain the inflammatory cascade (cytokines IL-1β, IL-6 and TNF-α). The key cytokine that regulates the master cytokine TNF-α promotes adhesion molecules, recruits immune cells and produces IL-1β and IL-6 to enhance the fever and inflammation signals. Neocadambines return the immune system to balance through the downregulation of IL-1β, IL-6 and TNF-α and therefore reduce tissue injury and excessive immune activation. There is in-vivo support for this mechanism, as these compounds decrease markers of oxidative stress, infiltration of cells and edema in models of inflammation. The therapeutic utility of the Cadamba alkaloids in treating chronic inflammatory disease is supported by this mechanism and may act through the modulation of NF-κB or MAPK intracellular signalling pathways that regulate cytokine gene transcription (8,14,31,33).

B) Downregulation of Cyclooxygenase-2 (COX-2): It has been shown that Neolamarckia cadamba extracts and isolated indole alkaloids can suppress the expression of cyclooxygenase-2 (COX-2), a crucial enzyme in the production of pro-inflammatory prostaglandins. The production of prostaglandins, which mediate pain, swelling and fever, is catalysed by COX-2, which is normally elevated in response to inflammatory stimuli. Cadamba alkaloids diminish downstream prostaglandin E2 (PGE2) production by inhibiting COX-2 expression, which reduces inflammation and related nociceptive responses. Non-steroidal anti-inflammatory medicines (NSAIDs), which similarly target COX-2 to produce analgesic and anti-inflammatory effects, work in a manner quite similar to this one. However, chemicals produced from cadamba may provide a more selective and possibly safer alternative for regulating inflammatory pathways than synthetic NSAIDs, which may non-selectively inhibit both COX-1 and COX-2 and hence pose a risk of gastrointestinal side effects(8,14,31,33).

C) NF-κB Pathway Modulation: Neolamarckia cadamba contains phytochemicals that have been demonstrated to disrupt nuclear factor-kappa B (NF-κB) activation, a key transcription factor that controls the expression of many pro-inflammatory genes. NF-κB is normally active and moved from the cytoplasm to the nucleus in inflammatory situations. There, it attaches itself to particular DNA sequences and starts the transcription of genes that produce inflammatory cytokines, chemokines and enzymes like COX-2 and iNOS. Compounds produced from cadmium effectively suppress the transcriptional activity of NF-κB by inhibiting this nuclear translocation. Consequently, the inflammatory response is attenuated due to a considerable decrease in the downstream production of inflammatory mediators. The potential of Cadamba phytochemicals as natural anti-inflammatory drugs with molecular targets comparable to those used by synthetic immunomodulators is highlighted by this modification of the NF-κB signalling pathway(8,14,31,33).

D) Antioxidant Contribution: Flavonoids and phenolic acids in Neolamarckia cadamba have potent antioxidant properties and also significantly augment the anti-inflammatory effects of the plant. They act as efficient free radical scavengers by neutralising increased concentrations of reactive oxygen species (ROS), which are commonly elevated during periods of oxidative stress and inflammation. In addition to causing direct damage to cells, excess ROS also act as signalling molecules that activate pro-inflammatory pathways including the MAPK and NF-κB signalling cascades. By reducing the concentrations of ROS, the flavonoids and phenolic compounds present in cadamba can inhibit the activation of these pro-inflammatory signalling pathways. This results in a reduction in the production of pro-inflammatory mediators and cytokines. This antioxidant-driven mechanism is crucial in preventing oxidative insult to tissue and regulating chronic inflammatory response and supports the traditional medicinal use of cadamba in treating inflammatory conditions (8,14,31,33).

2. Antioxidant Mechanisms

A) Direct Radical Scavenging: Neolamarckia cadamba is rich in phenolic and flavonoid constituents such as quercetin, caffeic acid and chlorogenic acid that provide antioxidant capacity by scavenging free radicals such as DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) through electron or proton donation, thus preventing oxidative damage to cellular components (i.e., lipids, proteins and DNA) from oxidative stress associated with the onset and progression of inflammation and many chronic diseases. The phenolic and flavonoid profile of cadamba supports its historical use as a natural remedy for diseases associated with oxidative and inflammatory processes through the reduction of oxidative damage and the prevention of cellular damage (19,20,40,41).

B) Enzymatic Antioxidant Induction: Studies indicate that Neolamarckia cadamba extracts enhance the body’s intrinsic antioxidant defence system by upregulating key endogenous enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). To eliminate the harmful effects of ROS, both inflammation and metabolic processes create SODs or superoxide dismutase. SODs convert the superoxide radical into hydrogen peroxide; this subsequently creates both water and oxygen through CATs and GPx actions. Through their actions, Cadamba extracts increase the levels and activities of SODs, CATs and GPxs. Thus, the use of Cadamba is substantiated by traditional practices for promoting health, longevity and its therapeutic potential for oxidative stress-related disease (19, 20, 40 & 41).

C) Metal Chelation: The antioxidant capacity of Neolamarckia cadamba is greatly enhanced by the metal-chelating qualities of some of its polyphenolic components. By binding transition metal ions like ferrous (Fe^{2+}) and cupric (Cu^{2+}), these polyphenols can stop them from taking part in Fenton and Haber-Weiss processes, which produce extremely reactive hydroxyl radicals (OH). One of the most harmful types of reactive oxygen species are hydroxyl radicals, which can cause protein oxidation, DNA strand breakage and lipid peroxidation. Cadamba-derived polyphenols efficiently block metal-catalysed oxidative processes by chelating these metal ions, lowering the total oxidative burden in cells and tissues. This method promotes Cadamba's use as a natural antioxidant agent and strengthens its preventive impact in illnesses linked to oxidative stress(19,20,40,41).

3. Anticancer Mechanisms

A) Apoptosis Induction: Experimental evidence has suggested that triterpene saponins and alkaloids from Neolamarckia cadamba can lead to apoptosis, also known as programmed cell death, through the intrinsic mitochondrial pathway of apoptosis. These bioactive compounds are able to affect multiple levels of apoptosis regulation by changing the levels of pro-apoptotic proteins such as Bax and anti-apoptotic proteins such as Bcl-2. Disruption of the mitochondrial membrane potential occurs when cytochrome-c is released into the cytoplasm as a result of these changes. Once cytochrome-c is released into the cytoplasm, it activates caspase-9 through mitochondrial disruption, leading to activation of executioner caspases such as caspase-3, resulting in apoptosis. If caspase-8 also is activated, the extrinsic pathway may be involved in apoptosis as well. The potential of Cadamba phytochemicals as anticancer therapeutics is reinforced by the evidence that Cadamba phytochemicals induce apoptosis in neoplastic or aberrant cells through activation of both the intrinsic and extrinsic apoptotic pathways (35,45–48).

B) Cell Cycle Arrest: According to reports, bioactive chemicals derived from Neolamarckia cadamba have antiproliferative effects by causing cell cycle arrest at various checkpoints, especially the G0/G1 or G2/M phases. Cellular proliferation is essentially stopped by this disruption in the regular process of the cell cycle, which stops cells from duplicating their DNA or going through mitosis. The process entails modifying cell cycle regulatory proteins, including cyclins, cyclin-dependent kinases (CDKs) and their inhibitors, which work together to regulate the cell cycle's transition between phases. Cadamba extract prevent the uncontrolled division of aberrant cells, which is a defining feature of malignant growth, by interfering with key regulatory processes. Their pro-apoptotic activity is complemented by this cell cycle stop, which strengthens the plant's medicinal promise for the prevention and treatment of cancer(35,45–48).

C) Inhibition of Oncogenic Signalling: Cadamba and other molecular dockings of the same chemical structure (from the plant Neolamarckia cadamba) show some of the strongest binding of their "league" to oncogenically active proteins critical for the proliferation and maintenance of cancer cells. The targets include kinases, such as phosphoinositide 3-kinase (PI3K), which mediate normal signalling pathways for cell growth and maintenance; transcription factors, which modulate the tissue-type specific expression profiles of tumours; and topoisomerases, that facilitate DNA replication and RNA transcription. The alkaloids of this tree may block necessary signalling pathways needed for cancer cell survival through the binding of the active sites of these proteins, thereby inhibiting their enzymatic activity or these molecules can break down the protein-DNA interactions. The molecular foundation of Cadamba's anticancer potential is supported by this in-silico findings, which also emphasizes Cadamba's potential as a source of lead chemicals for the creation of targeted cancer therapies(35,45–48).

D) ROS-mediated Cytotoxicity: After being treated with Neolamarckia cadamba extracts, cancer cells show increased reactive oxygen species (ROS) levels, which play a major role in cytotoxicity and apoptosis induction. Although cellular signalling is supported by moderate ROS levels, excessive ROS can upset redox equilibrium, especially in cancer cells that are already subjected to elevated levels of oxidative stress. The increase in ROS causes damage to vital macromolecules like proteins, lipids and DNA, which sets off pathways leading to oxidative stress-mediated cell death. Loss of membrane potential, mitochondrial malfunction and the activation of intrinsic apoptotic signals, such as the commencement of the caspase cascade, are caused by this imbalance. Increased ROS production thus becomes a key mechanism by which Cadamba chemicals specifically cause cancer cells to undergo apoptosis, thereby augmenting their therapeutic potential as natural anticancer drugs(35,45–48).

4. Hepatoprotective Mechanisms

A) Reduction of Oxidative Stress: By neutralizing reactive oxygen species (ROS), antioxidant phytochemicals found in Neolamarckia cadamba are essential for hepatic cell protection. Unchecked lipid peroxidation caused by these ROS damages the phospholipid bilayer of hepatocyte membranes and results in cellular malfunction. Flavonoids and phenolic acids, two of cadamba's bioactive substances, have potent anti-free radical properties. They stop the chain reaction of oxidative stress by donating electrons to unstable ROS, turning them into non-reactive species. This mode of action supports liver function, preserves cellular integrity, stabilizes hepatocyte membranes and inhibits lipid peroxidation(15,43,49).

B) Anti-inflammatory Effects: Flavonoids, triterpenoids and indole alkaloids (including Cadambine and Neocadambines) are bioactive metabolites found in Neolamarckia cadamba that affect liver inflammation by inhibiting critical pro-inflammatory signalling pathways. The bioactive metabolites will reduce inflammation by inhibiting COX-2 and iNOS gene expression by inhibiting the activation of NF-κB and MAPK signalling in the hepatic Kupffer cells and hepatocytes. This will inhibit the recruitment of inflammatory cells as well as their activation by inhibiting the release of cytokines (IL-1β, TNF-α, IL-6) from Kupffer cells. Therefore, these bioactive metabolites will protect the structure and function of the liver by reducing cytokine and oxidative and enzymatic damage to the hepatocyte membrane, inhibiting prostaglandin production via COX-2 and preventing an accumulation of cytokines in the liver (15,43,49).

C)Enhancement of Detoxification Enzymes: The Phytochemicals in Neolamarckia cadamba, particularly Flavonoids and Phenolic Compounds, enhance expression of the Glutathione-S-Transferase (GST), UDP-Glucuronosyltransferase (UGT) and NAD(P)H. Quinone Oxidoreductase 1 (NQO1) which promote hepatoprotection by conjugating hepatotoxic substances with endogenous compounds such as glutathione sulphate or glucuronic acid, enhancing solubility and facilitating excretion; a critical component of bio- transforming them so that they can be efficiently eliminated from the body. The Phytoconstituents in Cadamba activate Nuclear Factor Erythroid 2-Related Factor (Nrf2), a transcription factor that mediates the upregulation of proteins that detoxify or provide antioxidants; through activation of the Nrf2-Antioxidant Response Element (ARE) signalling pathway. This decreases the load on the liver through elimination of reactive and toxic compounds or metabolites and subsequent protection from cellular injury (15,43,49).

5. Antimicrobial Mechanisms

A) Membrane Disruption: Neolamarckia cadamba contains alkaloids and triterpenes that target the structural integrity of microbial cell membranes to produce strong antibacterial activity. These bioactive substances alter the structure of bacterial and fungal membranes by interacting with their lipid bilayer, which increases permeability. The disruption of the membranes of living bacteria due to the effect of the phytochemicals in cadamba causes both cell lysis and death of the bacteria, resulting in the leakage of vital components from the cell interior (proteins, & ions etc. as well as nucleotides). The phytochemicals in cadamba target the membranes of bacteria and thus contribute to the reduced chances of bacteria developing resistance to these agents while simultaneously compromising the viability of microorganisms, demonstrating their potential as natural antibacterial agents. (3,7,27)

B) Enzyme Inhibition: Phytoconstituents produced by Neolamarckia cadamba, such as indole alkaloids and triterpenoids, display antibacterial properties by blocking critical bacterial enzymes that are necessary for life. These compounds inhibit enzymes that are essential for bacterial DNA replication, folate metabolism and cell wall formation. The enzymes that participate in the metabolic processes of bacteria and play a role in the formation of peptidoglycan include DNA gyrase, dihydrofolate reductase and transpeptidases. By inhibiting these enzymes, the inhibition of energy production, nucleic acid production and the maintenance of structural integrity of the bacterial cell wall inhibits bacterial growth and ultimately destroys the cell. The enzyme targeting mechanism provides cadamba with broad spectrum antibacterial activity and thus represents a potential strategy for managing bacteria-related diseases (3,7,27,42).

C) Quorum Sensing Interference: Neolamarckia cadamba extracts have been shown to disrupt bacterial quorum sensing; a form of intercellular communication that regulates the expression of virulence factors and the formation of biofilms within a multicellular organism. Quercetin and many other flavonoids and alkaloids are present in the cadamba plant, which has the potential to inhibit signalling molecules - such as autoinducing peptides (AIPs) in Gram (+) bacteria and acyl-homoserine lactones (AHLs) in Gram (-) bacteria that regulate these processes. Using cadamba extracts to disrupt the quorum sensing signal pathways will reduce bacterial pathogenicity and toxin production, in addition to inhibiting the formation of protective biofilms created by bacteria to protect themselves from host defences and antibiotics. However, more information is still required about the molecular targets and mechanisms involved with the inhibitory effects of cadamba on bacterial quorum sensing, even though preliminary research indicates that they exist (3,7,27,42).

6. Antidiabetic Mechanisms

A) Enzyme Inhibition: Neolamarckia cadamba contains phytochemicals such as flavonoids and alkaloids that can reduce blood sugar levels by blocking the activity of critical enzymes that digest carbohydrates (e.g., α-amylase and α-glucosidase) to create postprandial glucose spikes. These enzymes break down long chains of carbohydrate molecules into smaller, absorbable units called monosaccharides. Cadamba compounds competitively bind to the active sites of the enzymes, therefore inhibiting intestinal glucose absorption and the breakdown of carbohydrates. By reducing blood glucose levels after meals, cadamba's enzyme-inhibitory effect makes it a viable natural treatment option for type-2 diabetes and related metabolic diseases(3,22,53,54).

B) Improvement in Insulin Sensitivity: Neolamarckia cadamba's anti-inflammatory and antioxidant qualities are essential for raising insulin sensitivity and boosting glucose metabolism. It is well recognized that oxidative stress and chronic inflammation degrade insulin receptor function and interfere with downstream signalling pathways including IRS-1/PI3K/Akt. Flavonoids, alkaloids and phenolic acids are among the bioactive substances found in cadamba that scavenge reactive oxygen species (ROS) and lower pro-inflammatory cytokine levels (such as TNF-α and IL-6), re-establishing cellular homeostasis and redox equilibrium. In metabolic diseases like type 2 diabetes, cadamba extracts assist maintain insulin receptor activation and facilitate efficient insulin signal transduction by reducing oxidative and inflammatory stress, this improves glycaemic control(3,22,53,54).

C) Modulation of Glucose Metabolism: Neolamarckia cadamba may have antidiabetic effects by improving glucose absorption and encouraging the storage of glycogen in peripheral tissues including the liver and skeletal muscle. Hexokinase, glucokinase and glycogen synthase are important metabolic enzymes involved in the consumption and storage of glucose and it is believed that these enzymes are modulated to produce this effect. Cadamba may reduce blood glucose levels by facilitating the conversion of circulating glucose into glycogen through its influence on certain enzymatic processes. Comprehensive molecular research is still necessary to confirm the precise pathways and regulatory targets involved in cadamba's glucose-handling effects, even if preliminary findings support this process(3,22,53,54).

7. Immunomodulatory Effects

By controlling immune cell activity and cytokine release, phytochemicals found in Neolamarckia cadamba, such as indole alkaloids, flavonoids and triterpenoids, have shown immunomodulatory effects. A balanced production of pro-inflammatory cytokines like TNF-α in addition to IL-1β and anti-inflammatory mediators like IL-10 is the outcome of these substances' effects on the activation and proliferation of key immune cells like macrophages along with T-lymphocytes. By controlling this cytokine profile, preventing excessive inflammation and bolstering the body's defences, cadamba helps maintain immunological homeostasis. This immunoregulatory activity highlights cadamba's potential to treat diseases associated with the immune especially chronic inflammatory conditions (4,19,29).

7. Toxicological Evaluation and Safety Profile of Neolamarckia cadamba

To guarantee the safe therapeutic use of medicinal plants such as Neolamarckia cadamba (Cadamba), it is essential to evaluate their toxicity along with safety. Toxicological assessments of Cadamba are still relatively small but are progressively growing despite substantial pharmacological research. This section discusses genotoxicity and mutagenicity findings, highlights safety considerations for future clinical use, followed by summarizes the acute, subacute, especially chronic toxicity data available from preclinical studies.

1. Acute Toxicity Studies

Acute toxicity tests on mouse models have shown that Neolamarckia cadamba has a wide safety margin at therapeutic levels commonly used in traditional medicine. Mice as well as rats were administered single, high doses of various extracts, methanolic, ethanolic, as well as aqueous made from bark as well as leaves in these studies. For fourteen days, the animals were observed. The observed LD_{50} values above 2000 mg/kg body weight suggested low acute toxicity. Most of the time, there was no mortality along with significant adverse effects. These were gone by themselves from being there, even though they had some temporary changes in behaviour like less moving around and maybe a little sleepy; this is consistent with the safety of using cadamba extracts in traditional medicine and supports the need for further research for pharmacological properties (3,55,56).

2. Subacute and Chronic Toxicity

Numerous dose toxicity studies (from 28 days to 90 days) using mouse models have defined the long-term safety profile of Neolamarckia cadamba. These studies involved test subjects receiving daily doses, often via oral administration, of up to 500 mg/kg of either the standardized bark or leaf extracts (extractions usually methanolic or aqueous). Each of these extensive evaluations included: determining organ weights; clinical sign observation; measuring haematological parameters; testing serum biochemistry for liver function; testing serum biochemistry for kidney function and histological evaluation of critical organs. Based on all tested dosages to date, there have been no indications of any hepatotoxicity, nephrotoxicity or haematological abnormalities in any tested subject. Histopathological analyses of the liver, kidney, heart and lung tissues often showed no morphological changes or indications of inflammation, necrosis or fibrosis, while serum indicators like ALT, AST, ALP and creatinine stayed within normal ranges. The idea that cadamba extracts are well tolerated in subacute environments is supported by these results. Notwithstanding the positive outcomes, there is still a dearth of information on chronic toxicity, particularly for periods longer than 90 days. Given that cadamba may be used to treat inflammatory or chronic metabolic diseases, long-term safety research that includes evaluations of carcinogenicity, genotoxicity and reproduction is vital to confirming its therapeutic safety(14,55,56).

3. Genotoxicity and Mutagenicity

With so few research addressing this crucial issue, the genotoxic and mutagenic safety profile of Neolamarckia cadamba is still poorly understood. Testing cadamba extracts or isolated phytochemicals has shown either negative or minimal genotoxic effects in preliminary in-vitro studies, such as the Ames test using Salmonella typhimurium strains and the micronucleus assay in mammalian cells. DNA damage has a very low probability of occurring with this particular experimental arrangement in mind, based on this type of preliminary analysis; however, this initial assessment will not be sufficient for establishing conclusive evidence about the potential genotoxicity of cadamba, particularly with respect to prolonged exposure to high doses of

therapeutic cadamba products.
Therefore, comprehensive studies on the potential mutagenic or clastogenic properties of bioactive compounds such as indole alkaloids, including some triterpenoids with structures capable of binding to or disrupting cell cycle regulation of DNA, may offer valuable information in the evaluation of the potential genotoxicity associated with cadamba use, specifically for their growing use in anticancer research, where intercellular exposure duration is expected to be extended and cadamba's interaction with proliferating cells will likely occur as well. Accordingly, both in-vivo and in-vitro (e.g., comet assays, chromosomal variations) genotoxicity studies performed in accordance with OECD standards are needed to determine the potential genetic hazard posed by cadamba based treatments used in combination with chronic and high-risk medical conditions (14,55,56).

4. Safety Considerations and Drug Interactions

Although Neolamarckia cadamba has been used for centuries in traditional medicine to treat many health problems, there are still a very limited number of systematic research studies that have evaluated whether or not this plant will interact with any medication that is manufactured using modern processing methods. This creates a considerable void in demonstrating clinical safety when combining the use of cadamba in integrative medicine and allopathic medicine (modern medicine) where cadamba is potentially used with medications manufactured through modern processes. Some of the phytochemicals found in cadamba, including flavonoids, alkaloids and triterpenoids have previously been shown in different herbal systems to alter the functions of enzymes such as cytochrome P450 (CYP) enzymes and drug transporter proteins such as P-glycoprotein (P-gp) both of which are necessary for metabolizing and making effective many prescription medications (3,8,14).
Components of cadamba may alter the plasma concentration and therapeutic effectiveness of medications given at the same time as cadamba if they inhibit or induce specific CYP isoenzymes (e.g., CYP3A4, CYP2D6, CYP2C9) resulting in the potential for drug toxicity or therapeutic failure. Likewise, altering transporter proteins may have an impact on the distribution and absorption of drugs. The potential danger of herb-drug interactions is significant, especially with drugs that have a limited therapeutic index, even though there is little direct proof in the case of cadamba. Because cadamba has pharmacological properties that may overlap with those of anticoagulants (like warfarin), antihypertensives or antidiabetic medications such as anti-inflammatory, hypotensive or hypoglycaemic effects care should be used when taking it with these medications. These interactions may intensify the effects of the medication and raise the possibility of side effects like hypotension, hypoglycaemia or bleeding. Therefore, using cadamba with conventional medications at the same time should be done cautiously and with careful monitoring of clinical parameters and therapeutic results in the absence of thorough pharmacokinetic and pharmacodynamic interaction studies(14,55,56).

5. Recommendations for Future Toxicological Studies

Thorough toxicological studies are necessary to guarantee the safe pharmaceutical development of Neolamarckia cadamba. To evaluate long-term safety and detect any cumulative or delayed harmful effects, chronic toxicity studies involving several dosages over prolonged periods of time are required. Furthermore, assessing teratogenicity, developmental toxicity and reproductive toxicity is essential, especially to guarantee the safety of goods derived from cadamba in populations that are pregnant or nursing. To clarify the plant's absorption, distribution, metabolism and excretion (ADME) properties and gain knowledge about systemic exposure and possible bioactive metabolites, comprehensive pharmacokinetic and metabolic profiling is required. With the utilization of advanced in-vitro models, including organ-on-chip technology paired with Toxicogenomic screening, one can enhance the ability to predict human toxicologic responses and narrow the difference between preclinical data and clinical safety assessment. Therefore, in order to develop phytopharmaceuticals from Cadamba safely and effectively, standardized extracts and purified bioactive must be evaluated for their potential toxicity independently (i.e., don’t base all your conclusions upon the information provided by crude extracts) (3,8,56).

8. Clinical and Translational Perspectives of Neolamarckia cadamba

Neolamarckia cadamba's (Cadamba) preclinical success is now beginning to translate into clinical and commercial success, but continues to be a challenge at this stage of its development. This section provides an overview of current clinical evidence surrounding the use of Cadamba, as well as a discussion of relevant barriers to clinical translation and also an overview of the potential for the use of Cadamba in the development of phytopharmaceuticals, nutraceuticals and cosmetics.

1. Clinical Studies and Human Evidence

A) Existing Clinical Data: The clinical validation of Neolamarckia cadamba is yet largely unexplored, despite encouraging preclinical results. There are very few reliable human studies assessing the safety, effectiveness and proper dosage of cadamba preparations or isolated chemicals. The vast bulk of current research is restricted to animal models or in-vitro tests, which, although instructive, are not entirely capable of predicting human reactions. It is difficult to make firm judgments on its therapeutic potential in clinical settings due to the lack of well-designed randomized controlled trials (RCTs). Thorough clinical research is desperately needed to convert Cadamba's traditional and experimental usage into evidence-based therapy(3,4,11,19).

B) Case Reports and Traditional Usage: Long-standing traditional medical practices and anecdotal evidence support the use of Neolamarckia cadamba formulations to treat a variety of skin problems, diabetes and inflammation. Numerous ethnobotanical surveys in addition to observational studies have identified cadamba as an essential part of polyherbal formulations commonly used in traditional healing systems. One challenge when assessing the therapeutic efficacy of Cadamba is that the medicinal solutions may be comprised of a number of different plants as well as additional compounds; therefore, distinguishing the individual contribution of Cadamba to the overall therapeutic effect of a product will often be difficult. The absence of controlled clinical trials limits the ability to evaluate Cadamba's individual pharmacological effects. Traditional uses of Cadamba have demonstrated potential; however, the effectiveness of Cadamba and its importance as a modern therapeutic agent will require scientific research using appropriate experimental designs that are focused on validating its efficacy (3,21,50).

2. Challenges in Clinical Translation

A) Standardization Issues: Due to many different factors that affect the phytochemical composition of Neolamarckia cadamba, including harvest time, location, soil type and extraction processes, there is considerable variation in the content and composition of bioactive compounds from one sample to another. This variability creates a significant barrier to achieving consistent and reproducible results and standardizing dosage, both of which pose serious challenges for developing safe and effective medications derived from Cadamba. In addition, it is very difficult to convert Cadamba into a clinically useful medicine without proper quality control and standardization procedures in place. A number of problems need to be fixed in order to guarantee batch to batch consistency and transition Cadamba from conventional use to evidence-based phytopharmaceutical development (3,4,21,50).

B) Regulatory Hurdles: Neolamarckia cadamba is not becoming a widely used drug because of regulations requiring substantial evidence of safety, efficacy and quality control. Despite the fact that Cadamba is highly regarded in traditional medicine, modern regulatory bodies are unable to accept it due to the lack of comprehensive toxicological, pharmacokinetic and clinical data. Due to a lack of comprehensive research on its pharmacological profile, standardized extract safety, cadamba based products are often restricted to traditional or dietary supplement categories rather than being licensed as formal medicinal agents. Closing this regulatory gap necessitates systematic scientific evaluation in order to meet the stringent requirements set by international health authorities (3,4,21,50).

C) Formulation and Bioavailability: Many of the bioactive phytochemicals in Cadamba have limited bioavailability along with poor water solubility, which severely restricts their medicinal potential in conventional formulations. To overcome the difficulties presented by creating more sophisticated drug delivery methods (i.e., solid dispersions; liposomes and nanoparticles), new delivery methods need to be developed that enhance the absorption of the drug; provide a more selective target; produce a prolonged release of the drug. However, the manufacturing of the delivery system is significantly more difficult when you want to create a stable, scalable, user-friendly and pharmacologically effective delivery system. The extensive clinical application of cadamba based treatments is further hampered by the high expense and technical know-how needed for the creation and validation of these systems (11,19,21,50).

D) Intellectual Property and Commercial Incentives: One major obstacle to the pharmaceutical development of botanical extracts, such those from Neolamarckia cadamba, is the lack of patent protection. In contrast to synthetic medications, which enjoy robust intellectual property rights, natural products frequently lack the exclusivity or novelty necessary for strong patenting. Because of this, businesses are less able to obtain returns on their investment, which lowers their commercial incentive to finance the expensive and time-consuming clinical trials required to prove efficacy and safety. Because of this, the development of clinically authorized medicines from Cadamba is still sluggish and underfunded, even though preclinical evidence of its pharmacological activities which range from antioxidant and hepatoprotective to anticancer and antibacterial properties is encouraging. Development obstacles are further increased by the necessity for standardization of phytochemical ingredients and regulatory complexity. Enhancing investment incentives and expediting the clinical validation of promising plants like Cadamba could be achieved by fortifying frameworks and policies that promote traditional and plant-based medicine(37,42,51,59).

3. Potential Applications

Phytopharmaceuticals: Bioactive compounds isolated from Neolamarckia cadamba, such as cadambine (an indole alkaloid) and cadambagenic acid (a triterpenoid), have great potential as lead molecules for drug development or as dietary supplements in the treatment of chronic illnesses, provided they are further purified and structurally characterized.

According to early pharmacological research, these substances have strong cytotoxic, antioxidant and anti-inflammatory properties that may make them useful as treatments for diseases like cancer, metabolic disorders and immune-mediated illnesses. These phytochemicals are especially appealing for additional preclinical and clinical testing due to their various modes of action, which include scavenging of reactive oxygen species (ROS) and altering inflammatory pathways. The integration of phytochemicals into innovative pharmaceutical formulations or integrative health strategies may be made possible by developments in phytochemical standardization and focused pharmacological screening(11,21,57,58).

Nutraceuticals and Functional Foods: Standardized extracts of Neolamarckia cadamba have the potential to be added to dietary supplements or functional beverages that promote overall health and prevent diseases linked to a lifestyle because of their significant antioxidant capacity and positive effects on metabolic parameters. Preclinical investigations have shown that Cadamba, which is rich in phenolic compounds, flavonoids and triterpenoids, can scavenge free radicals, modulate lipid profiles and enhance glycaemic control. These characteristics are especially important when it comes to treating metabolic imbalances and oxidative stress linked to non-communicable diseases including diabetes, heart disease and obesity. Cadamba-derived nutraceuticals, when prepared with standardized and confirmed phytochemical content, may provide a natural and efficient way to improve long-term health as consumer interest in plant-based preventive health products increases(11,21,24,57,58).

Cosmeceuticals: Neolamarckia cadamba's strong antibacterial and antioxidant qualities lend credence to its potential use in skincare products, especially for wound healing, acne treatment and anti-aging. Rich with flavonoids, triterpenoids and phenolic compounds, cadamba extracts support skin suppleness and rejuvenation by scavenging free radicals that cause cellular damage and skin aging. It is also positioned as a natural acne treatment option due to its antibacterial action against common skin infections like Propionibacterium acnes and Staphylococcus aureus. The use of Cadamba in topical formulations is further supported by its capacity to promote wound healing, which is ascribed to increased collagen synthesis and anti-inflammatory properties. Standardized Cadamba extracts could be included into contemporary skincare products with both medicinal and cosmetic effects in response to the increased consumer demand for plant-based and functional cosmetics(19,37,42,51).

Agricultural and Environmental: Neolamarckia cadamba is an important plant for sustainable agroforestry and timber industries, providing both ecological and economic benefits due to its quick growth rate and multipurpose utility. Cadamba is a rapidly growing deciduous tree that is commonly grown for its high-quality, lightweight wood, which is used to make plywood, paper and furniture. This helps to support rural livelihoods and green economies. Cadamba trees are ideal for planting in both reforestation and land rehabilitation due to their deep overhead canopy that allows them to sequester more carbon than any other plant; thus, they contribute greatly to stabilizing the soil via their extensive root systems. Additionally, their use as an intercrop enables the utilisation of a wider variety of species and natural resources, which also contributes to sustainable agricultural practices and therefore a more stable population and economic system in future generations. Finally, Cadamba's contribution to the environment beyond just their medicinal value add great stature to Cadamba from a holistic health and economic perspective (3,4,19,50).

4. Future Directions

Clinical Trials: Although there is some evidence that Neolamarckia cadamba works in rats, potential therapeutic value is not proven in humans because there is no human evidence available on this plant. Carefully designed clinical studies need to be conducted during both parts of development to assess Neolamarckia cadamba's risk-to-benefit profile, its optimal dosing intervals and its efficacy in treating humans. Such studies will provide information regarding the differences between established and modern uses of this plant in relation to the numerous biological effects its constituents (i.e., polyphenols) produce; most notably inflammation, metabolism and cancer. Accomplishing these goals will require cooperation between academia, pharmaceutical manufacturers and traditional physicians in order to combine available traditional knowledge and modern clinical practice. Such collaboration will help produce information about the toxicological properties of Neolamarckia cadamba that prove valuable and will facilitate the development of well-defined and documented medicinal plants that will conform to internationally accepted standards for clinical efficacy (11,21,24).

Quality Control and Standardization: Careful planning and implementation of Quality Assurance procedures with properly validated Quantitative Identifiers is essential to ensure safe and efficient applications of Neolamarckia cadamba in commercial and medical settings. To ensure consistency within each batch of Cadamba plant material for therapeutic effect and regulatory compliance, it is imperative that all batches of plant material are calibrated against a specific standard. The different natural compound mixtures contained within the Cadamba plant (phenolic compounds, cadambine and cadambagenic acid), have complex chemical structures; therefore, very sophisticated instrumentation such as HPLC, LC-MS and NMR must be used to accurately identify and quantify the compounds associated with biomarker molecules present in that batch of analysis. The development of quality control inspection protocols enhances both product security and efficacy as well as increases consumer confidence in Cadamba based products within the marketplace and in academic research. In addition to the creation of quality standards, Cadamba must also be manufactured according to established pharmaceutical and GMP standards in order for Cadamba products to be marketed globally through both retail and health care sectors (11,21,58).

Advanced Formulations: The potential therapeutic value of Neolamarckia cadamba can greatly increase by using advanced drug delivery techniques, such as packaging, nanotechnology and other innovative systems. Because of the poor solubility, stable state and permeability of many cadamba bio-active compounds (especially flavonoids and triterpenes) to produce their therapeutic effect, the use of polymers, lipids and nanocarrier-type materials can be an effective solution for preventing degradation, enhancing absorption or providing controlled or targeted release of drug compounds to specific organs. These methods can help to decrease the amount of medication needed for treatment, minimise unwanted side effects and improve drug kinetics. As the trend towards precision and plant-based medicine continues to grow around the world, fibres derived from cadamba herbal sources incorporated into nanocomposites may provide an effective treatment for medical conditions such as tumours, inflammatory diseases and cardiovascular disease (19,37,42,51).

Pharmacokinetic and Metabolomic Studies: To allow an appropriate use of the standard cadamba in medicine requires an in-depth study to clarify the intakes of the bioactive components, their kinetics, their standard dilution and their bioactive component outputs (ADME). While there exists an increasing volume of research demonstrating that cadamba has medicinal properties, the physiological role of the individual major components of cadamba, specifically phenolic compounds, cadambine and cadambagenic acid, are still largely unknown. There are multiple ways to determine the accessibility, toxicity risk, tissue concentrating abilities and efficient dosing techniques of cadamba's bioactive components by examining the pharmacokinetic parameters associated with them. These kinds of findings are crucial for directing the development of recipes and distribution strategies, in addition to maximizing the effects of therapy. Integrating ADME investigations with clinical and preclinical trials will eventually increase the rationale for Cadamba's use in evidence-based medicine, facilitating the drug's shift from a standard treatment to a licensed pharmaceutical component (3,4,19,50).

Regulatory Engagement: Immediate and open communication with statutory bodies is essential to accelerate the synthesis and marketing of natural pharmaceuticals using Neolamarckia cadamba. With the intricate nature of organic items, initial meetings can help define legal standards for safety, Caliber, utility and processing standards. Initial cooperation with agencies such as the FDA, EMA or AYUSH can help guide the onset of appropriate clinical trials, standardized protocols and standards controls and will save creation expenses and timelines. This participatory strategy is extremely helpful for plant medicines like Cadamba, whose standard usage exists but modern scientific proof remains in progress. The chance of an excellent authorization and the legitimacy and competitiveness of the pharmaceutical medicines created from Cadamba are both increased by early legal linkage (19, 37, 42, 51).

9. Research Gaps and Future Directions

The entire fulfilment of Neolamarckia cadamba's (Cadamba) clinical while economic viability is hampered by a number of crucial flaws, with the growing amount of study on the plant. The journey of exciting test outcomes to medically verified, safe and efficacious medicines will be accelerated by resolving these holes by concerted multimodal work.

1. Clinical Validation Deficiency

Lack of Controlled Human Trials: The majority of current research on Neolamarckia cadamba is limited to in-vitro tests and preliminary animal investigations, providing only a rudimentary summary of its potential for treatment. However, the lack of well-designed RCTs (randomized controlled trials) in healthy individuals significantly restricts the capacity to determine its effectiveness, tolerability features and ideal therapeutic volumes. Its integration into medical evidence and the development of regulations for its use as a regulated generic drug are severely hampered by this crucial evidence gap (35,37).

Epidemiological and Observational Data: While controlled clinical studies are necessary, Neolamarckia cadamba is not well-documented in terms of actual data or cultural usage habits. A few attempts were made to record results using approved clinical parameters, but unconfirmed and norms remain largely unclear. Local data collection and planned observations may help bridge the gap between traditional and contemporary treatment validity by improving after-sales safety management and encouraging the development of scientific hypotheses (51,52).

2. Standardization and Quality Control Challenges

Variability in Phytochemical Content: Neolamarckia cadamba's botanical composition may differ significantly due to geographic origin, harvest time, plant age and ways to extract it. Due to the varied level of bioactive elements and this volatility ultimately compromises the reliability and reproducibility of drugs. The substantial challenge this variation creates in defining solutions for study and medical use highlights the need for stringent inspection procedures and validated analytical techniques to ensure stability across investigations and clinical uses (11,19).

Lack of Established Quality Markers: Because there is no proven accord on traditional biomarkers or signature profile data, it is difficult to ensure consistent batch uniformity in Neolamarckia cadamba isolates or compositions. The lack of established scientific norms and clear standard substances hinders quality control and complicates the comparison of results. It affects the accuracy of physiological data and restricts the production of regulated pharmaceuticals. Establishing reliable chemistry and comprehensive plant profiling is essential for future health and business use to be reliable, safe and successful (3,50).

Extraction Methodology: The variety and number of active substances that are extracted are impacted by the wide variation in Neolamarckia cadamba methods for gathering used in studies. Those distinctions can impact the medicinal properties reported and make valid comparisons of studies challenging. To advance its medical expansion, extraction approaches that are efficient, flexible and repeatable and closely linked to cellular processes are essential. Unifying these processes will support QC, enhance the reliability of test results and boost uniformity and efficacy of formulas for medical use (12,25).

3. Insufficient Mechanistic Understanding

Limited Molecular Target Identification: Although Neolamarckia cadamba's medicinal efficacy is receiving greater interest and comprehensive structural investigations are still scarce. A lot of research has not completely identified the specific molecules, signals or changes in genes that its distinct bioactive materials affect. This dearth of basic knowledge limits our ability to comprehend how its constituents have medicinal properties at cell and molecular levels. Extensive study on these chemical interactions is essential to assist rational drug design, validate curative claims and pave the way for targeted clinical applications of Cadamba-based therapeutics (5,39).

Synergistic and Antagonistic Interactions: Most studies on Neolamarckia cadamba have focused on isolated compounds or raw materials, neglecting the possibility of hostile or combined effects within the intricate botanical matrix. These relationships might have a major impact on the plant's overall medicinal properties and medicinal efficacy. The overlooked multimodal consequences make a thorough knowledge of its physiological properties difficult. Future studies ought to use holistic techniques to investigate the links of the material's numerous constituents so as to completely comprehend its curative properties and enhance packaging processes (3,6,59).

Pharmacokinetics and Metabolism: The majority of research on Neolamarckia cadamba has concentrated on single substances or raw ingredients, ignoring the potential for adverse or hybrid reactions within the complex plant network. These connections may significantly affect the plant's overall therapeutic qualities and effectiveness. A comprehensive understanding of its bodily features is challenging due to the neglected mixed implications. In order to fully understand the material's therapeutic qualities and improve processing procedures, future research should employ holistic methods to examine the connections between its many components (3,6,59).

4. Toxicological and Safety Evaluation Gaps

Long-Term and Specific Toxicity Studies: Neolamarckia cadamba has undergone preliminary ecological hazardous but comparatively few comprehensive studies assessing mutation, etiology, fertility toxicity and toxicity over time are being conducted. To fully understand the potential health risks associated with excessive or prolonged use, certain particular, ongoing safety assessments are required. A major barrier to medical use and regulatory acceptance is the absence of this type of knowledge, which diminishes confidence in its risk record. Hence, thorough research into these toxicology criteria is crucial to demonstrate that the plant's security for medical purposes and to encourage its integration into medical evidence (60,61).

Interaction with Conventional Drugs: Everything exists about likely herbal drug effects, given Neolamarckia cadamba's significance. Considering it might be used in combination with conventional medications, especially in polyherbal or holistic modalities, it is essential to comprehend any metabolic or behavioural conflicts. Hidden connections can alter a drug's efficacy or increase the likelihood of adverse reactions, which raises major health risks. To ensure safe combined use and provide medical guidance, extensive study on the effects of its active substances on drug metabolism enzymes and carriers is vital (15,43,49).

5. Commercialization and Regulatory Pathway Barriers

Product Development: It has taken a very long time for Neolamarckia cadamba to move from early studies on raw extracts to the creation of standardized, clinically verified products. The technical challenges of isolating and characterizing its diverse bioactive compounds, the high cost of advanced research and product development and the strict regulatory requirements for safety, efficacy and quality assurance are some of the reasons for this lag. All of these obstacles have slowed the rate at which formulations based on Cadamba can go from encouraging test results to authorized medicinal or nutraceutical uses on the market (3,8,14).

Intellectual Property Challenges: Commercialization efforts for Neolamarckia cadamba are further hampered by the exclusivity and patentability issues that are frequently encountered with botanical extracts. It becomes challenging to get robust intellectual property protection for plant-derived substances since they frequently occur in nature and are not unique in their unprocessed state. The financial incentive for pharmaceutical or nutraceutical businesses to spend in the costly research, clinical studies and manufacturing processes required to bring Cadamba based products to market on a big scale is diminished as a result of this limitation of market exclusivity (14,55,56).

Sustainability and Supply Chain: A well-managed supply chain and sustainable harvesting are crucial for Neolamarckia cadamba in order to provide a steady supply of premium raw materials. Premature or uncontrolled harvesting can result in variations in the phytochemical content, which could jeopardize the final formulations' safety and effectiveness. Standardized cultivation, harvesting and post-harvest processing methods, as well as traceable supply chain systems, would preserve natural populations while upholding the consistency and dependability needed for therapeutic or nutraceutical products based on Cadamba(15,43,49).

6. Underexplored Applications and Geographic Variation

Cosmeceutical and Nutraceutical Development: Preliminary research suggests that Neolamarckia cadamba may have potential benefits in skincare and functional foods because of its antibacterial, anti-inflammatory and antioxidant qualities, although these applications are still mostly unexplored. The development of economically viable products has been hindered by a lack of targeted clinical studies, limited formulation research and limited scientific validation. Cadamba may find new prospects in value-added health and wellness sectors if research in these areas is expanded(3,8,56).

Influence of Environmental Factors: The effects of location, soil composition, climate and cultivation methods on the phytochemical profile and bioactivity of Neolamarckia cadamba have not been thoroughly investigated. The concentration and makeup of its bioactive substances can be drastically changed by variations in these agronomic and environmental conditions, which will eventually impact the product's medicinal potential and consistency in performance. In order to create consistent cultivation procedures and guarantee reproducible quality in Cadamba based applications, thorough research into these factors is essential(8,14, 56).

7. Future Directions and Recommendations

Clinical Research: To go from preclinical promise to practical use of Neolamarckia cadamba must undergo carefully planned human clinical trials to thoroughly assess its safety, effectiveness and ideal dosage. Pharmacovigilance systems to track side effects and long-term safety, as well as patient-reported outcomes to record practical advantages and quality-of-life enhancements, should be used in conjunction with such research. The thorough body of evidence required for regulatory approval and wider adoption of Cadamba based products would be provided by this integrated approach(11,21,24).

Standardization: Establishing extraction and phytochemical fingerprinting procedures is crucial for Neolamarckia cadamba in order to guarantee the potency, consistency and repeatability of its bioactive components. Batch-to-batch variance would be reduced by standardizing the evaluation of raw materials and final products through the definition of certain chemical markers for quality control. In addition to promoting regulatory compliance, this standardization increases trust in the efficacy and safety of Cadamba based formulations for both commercial and therapeutic applications (24,57,58).

Mechanistic and Pharmacokinetic Studies: Utilizing cutting-edge molecular biology techniques in conjunction with genomics, proteomics, metabolomics and other omics technologies can significantly improve our comprehension Neolamarckia cadamba's mechanisms of action as well as the ADME (absorption, distribution, metabolism and excretion) profiles of its main bioactive compounds. Such methods would increase the scientific foundation for its therapeutic usage and direct the creation of optimal, evidence-based formulations by offering comprehensive insights into molecular targets, metabolic pathways and possible interactions (3,8,56).

Safety and Toxicology: A thorough toxicological program that goes beyond acute studies to include sub chronic (such as 90-day) and chronic (6–12 month) toxicity testing, reproductive and developmental toxicity, genotoxicity and carcinogenicity assessments is crucial for Neolamarckia cadamba. Safe exposure limits will be established with the aid of targeted studies of organ-specific toxicity and concurrent in-vitro and in-vivo safety pharmacology studies (cardiovascular, respiratory and central nervous system). To predict clinically meaningful interactions, it is essential to conduct a rigorous review of the potential for herb drug interactions, taking into account effects on important drug-metabolizing enzymes (CYPs), transporters (like P-glycoprotein) and pharmacodynamic interactions. The safety database required for regulatory submissions and informed clinical usage will be created by designing these studies in accordance with international criteria (OECD/ICH) and incorporating trustworthy biomarkers (21,24,58).

Formulation Development: Using nanotechnology and other innovative delivery methods presents a viable way for Neolamarckia cadamba to enhance the stability, bioavailability and therapeutic index of its main bioactive ingredients. Nano emulsions, liposomes, solid lipid nanoparticles and polymeric nanoparticles are examples of encapsulation techniques that can prevent labile constituents from degrading, improve solubility and absorption, allow for controlled or targeted release and possibly lower necessary dosages and off-target effects. More consistent pharmacokinetics and safer, more efficient Cadamba formulations for clinical and commercial uses will be made possible by combining these delivery systems with standardized extracts and clearly defined chemical indicators (15,43,49).

Sustainable Sourcing: To reconcile environmental preservation with increasing commercial demand, it is essential to develop and promote defined cultivation and harvesting rules for Neolamarckia cadamba. Sustainable agroforestry procedures, ideal planting densities, harvesting schedules based on peak phytochemical content and post-harvest handling techniques that maintain bioactive integrity should all be highlighted in such guidelines. These procedures can help preserve natural populations, sustain biodiversity, guarantee a consistent supply of high-quality raw materials and promote long-term viability for Cadamba based companies by coordinating conservation priorities with market demands(50,52).

Cross-disciplinary Collaboration: For Neolamarckia cadamba fostering collaborative partnerships among ethnobotanists, Phytochemists, pharmacologists, clinicians and industry stakeholders is essential to accelerate its journey from traditional use to validated therapeutic applications. Such interdisciplinary collaboration can integrate traditional knowledge with modern scientific approaches, streamline research workflows, ensure rigorous quality and safety standards and facilitate efficient translation of findings into market-ready products. By pooling expertise, resources and infrastructure, these partnerships can overcome developmental bottlenecks and unlock the full potential of Cadamba in healthcare and commercial sectors. By bridging these gaps, Neolamarckia cadamba can progress toward evidence based clinical use and commercial exploitation, blending traditional wisdom with contemporary science for improved healthcare outcomes (50,52,60).

10. Conclusion

Neolamarckia cadamba (Cadamba) is a tropical tree with medicinal significance, well-known for its varied phytochemical profile and long history of traditional use. It has phenolic compounds, flavonoids, triterpenoids and bioactive indole alkaloids that together provide a wide range of pharmacological actions including wound-healing, hepatoprotective, anti-inflammatory, anti-cancer, antidiabetic and antioxidant properties. Cadamba's diverse therapeutic potential is supported by the synergistic interaction of its bioactive constituents, which makes it a strong contender for novel phytopharmaceuticals and drug discovery based on natural products.

Despite encouraging in-vitro and in-vivo results, there are still a number of significant gaps that limit Neolamarckia cadamba's clinical translation. These include a lack of consistent extraction and formulation procedures, insufficient toxicological and pharmacokinetic analyses and a dearth of strong human clinical trials. Additionally, the processes behind its varied pharmacological effects are still not entirely understood and seasonal and environmental variations in phytochemical composition make it more difficult to guarantee constant quality and repeatable therapeutic efficacy.

To connect such disparities, cohesive, interdisciplinary study that places a high priority on comprehensive basic analysis, stringent quality assurance requirements and strong diagnostics is needed.

It is possible to create uniform, safe and efficient treatments using Cadamba standards by fusing modern scientific developments with established cultural skills. Using cutting-edge administration techniques may also enhance adherent patients, maximize medical results and boost solubility.

If Neolamarckia cadamba is thoroughly verified by biology and acquired responsibly, it offers great promise as a foundation of new drugs and in dietary and cosmetics products. By combining innovative methods of study with traditional ethnomedical expertise, Cadamba's medicinal properties can be successfully translated into modern treatment. This will open up new avenues for managing chronic and lifestyle-related diseases and enhance the health of millions of people worldwide.

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