Neolamarckia cadamba and Kidney Health: A Review on its Antioxidant and Anti-fibrotic Phytochemical Promise

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Chronic Kidney Disease (CKD) is increasingly getting of concern because continued destruction of kidney by continued oxidative stress and inflammation is irreversible and current methods of control are insufficient to halt this process. *N. cadamba* that has industrial application in traditional medicine in treatment of wounds, fevers and inflammation has various bioactive compounds including cadambagenic acid, quinovic acid, indole alkaloids, phenolics and flavonoids. The significance of these natural antioxidants is due to the fact that oxidative damage has a significant role to play in CKD. Recent cell and animal studies demonstrate that N. cadamba extracts have the capability of interacting with the Keap1-Nrf2-ARE pathway, which enhances the antioxidant defence of the body such as HO-1, NQO1, catalase, and SOD. N. cadamba can be useful in reducing the cell damage by reactive oxygen species in the kidney cells by raising the level of these enzymes. The review examines how the plant can counter oxidative stress as well as fibrosis that are one of the major contributors to CKD that begins when the kidney fibroblasts transform and synthesize excess of the matrix because of TGF-1. Even though few studies have been conducted on the anti-fibrotic effects of *N. cadamba* in kidney models, its compounds have demonstrated high anti-inflammatory effects including inhibiting NF-KB and the down regulation of inflammatory cytokines like IL-6 and TNF-a. This could assist in breaking the perpetration of inflammation and fibrosis. Other organs have already demonstrated the anti-fibrotic action of terpenoids and chlorogenic acid of *N. cadamba*, so that they may also provide help to the kidneys. In general, the existing data indicate that *N. cadamba* may be a potential solution to new CKD therapies by enhancing the antioxidant defences and decreasing the inflammation. More studies should be conducted to identify the most promising anti-fibrotic agents and to evaluate whether they are able to prevent or restore kidney damage in CKD.

Keywords: *Neolamarckia cadamba*, Chronic Kidney Disease, Renal Fibrosis, Oxidative Stress, Nrf2 Pathway, Anti-fibrotic.

Introduction

Chronic Kidney Disease (CKD) is a disease that is defined as a structural or functional abnormality of the kidney, taking a prolonged period of three months, and accompanied by health outcomes [1]. It is a pandemic part of the non-communicable disease that is projected to affect over 10 percent of the total population of the world and its prevalence is increasing extraordinarily in developing nations due to the high prevalence of Type 2 Diabetes Mellitus (T2DM) and hypertension [2]. CKD is also a preventable risk factor, that results in cardiovascular mortality and progression to End-Stage Renal Disease (ESRD) is costly and requires a costly renal replacement (dialysis or transplantation) process imposing a substantial economic strain on any healthcare system in the globe [3].

Pathogenesis:

The progressive renal failure irrespective of the primary insult (diabetic nephropathy, hypertensive nephropathy, or glomerulonephritis) is linked to a common pathophysiological mechanism that is mediated by a triad of molecular events [4]:

1. **Oxidative Stress:** The metabolism and oxygen consumption of the kidney, particularly the proximal tubule, is high and thus highly susceptible to damage by the Reactive Oxygen Species (ROS) [5]. The imbalance is brought about by mitochondrial dysfunction, stirring up NADPH oxidase, and reduced endogenous antioxidant capacity that leads to the accumulation of ROS in CKD [6]. This oxidative stress limits cell lipids (MSD) and proteins and DNA as well as directly induces cell death of the tubular and glomerular cells directly [7].
2. **Chronic Inflammation:** Pattern recognition receptor (PRR) activation is due to the oxidative damage that evokes the pro-inflammatory-transcription factor, such as Nuclear Factor kB (NF-kB) [8]. NF-kB increases the production and excretion of the inflammatory cytokines (TNF- a, IL- 6) and of the chemokines (MCP-1), which attracts macrophages and T- cells [9]. It is inflammation that is long-lasting, low-grade, and aggravates tissue destruction and initiates tissue repair [10].
3. **The Final Pathway Renal Fibrosis:** It is the accumulation of Extracellular Matrix (ECM) proteins (collagen I and fibronectin) leading to glomerulosclerosis and interstitial fibrosis

[11]. Transforming Growth Factor-b1 or (TGF-b1) is the general regulator of this process and increases the differentiation of resident fibroblasts and pericytes into pathogenic a-smooth muscle actin-expressing myofibroblasts [12]. Renal fibrosis is the most good predictor of ESRD progression [13].

1.2 Standard Therapy disadvantages and Rationale of Ethnomedicinal Agents

The current treatments of CKD have a major goal of controlling the main risk factors, and they involve blood pressure and glucose levels, with the primary method involving RAAS blockade (i.e. ACE inhibitors and ARBs) [14]. Though they aid in the slowing down of the progression, by lowering proteinuria and glomerular capillary pressure, they cannot prevent active developing fibrosis when it already has fully developed [15]. The greatest weakness of conventional drugs is the fact that they only mediate on a single target and the oxidative stress, inflammation, and fibrotic signalling pathways are interdependent and complex [15]. This loophole has created a mad-cap interest particularly in the scientific studies to use the natural products in order to produce next generation and multi-target nephroprotective drugs [16]. Plants produce thousands of secondary metabolites (phytochemicals) in response to the environmental stress and most of them possess the inherent capability to:

- Antioxidant activity (radical scavenge of the free radicals).
- NF-kB signal (anti-inflammatory effect).
- Inhibit TGF-b1 signal (anti-fibrotic activity).

The rationale behind this is that a complex plant extract which is extremely synergistic in phytochemicals may provide the multi-dimensional blockade that is required to disrupt the CKD cascade more effectively than the mono-target synthetic drugs [17].

1.3 *Neolamarckia cadamba:* Traditional Use

Medicinal plants have been very significant in treatment of diseases in human history. *Neolamarckia cadamba* (Roxb.) is one of the enormous numbers of medicinal flora. It also called *Anthocephalus cadamba* (Roxb). It has a prestigious seat in the tropical Asian ethnomedicine. The tree is known as Kadamba locally, and is appreciated as not only having pharmacological value, but also having rich cultural and mythological value. Kadamba has a close connection with the Hindu Lord Krishna and the goddess Durga and its spherical and fragrant flowers symbolize devotion and purity [18]. In India, various tribal communities have traditional healers who use various components of the Kadamba tree in treating various diseases including fever and inflammation among skin and liver diseases [19,20]. Kadamba is an ingredient in classical preparations, like Dashamoola (ten roots), and Kadamba Pushpa Churna, which are used to treat illnesses like pitta roga (bilious disorders), kushta (skin diseases), and prameha (diabetes) [21]. It is embraced by a variety of indigenous systems - such as Ayurveda, Siddha, Unani, and other folk systems and

it is clear that this is due to its adaptability and its continued therapeutic applicability.

Kadamba use was first recorded in ancient Sanskrit materials, including the Charaka Samhita and the Sushruta Samhita, which talks of using it in the treatment of wounds and as a febrifuge [22]. Kadamba extracts are still used as home remedies to gastrointestinal and dermatological disorders in rural India and adjacent areas of Bangladesh and Nepal [23]. The use of the Kadamba decoctions to treat diarrhoea, malaria, and purifying the blood has been noted as a consistent pattern in the Santali, Bhil, Khasi, and Munda tribes, in ethnobotanical field survey [24,25].

N. cadamba has recently come under a fresh research interest as the use of herbs has reemerged globally as a field of interest. Scientific research has identified bioactive compounds that cause the pharmacological effect of the plant. Indole alkaloids, cadambine and isocadambine, have anti-inflammatory and antimicrobial properties [26]; triterpenoids and flavonoids have a role in hepatoprotective and antioxidant properties [27]. Combining the traditional knowledge and the modern analysis tools, such as high-performance liquid chromatography (HPLC), LC-MS, and GC-MS profiling, has enriched the knowledge about the complex chemistry of the plant [28].

N. cadamba is a perfect example of ethnopharmacological integration because of its therapeutic diversity. Antipyretic, anti-diarrhoeal, and wound-healing properties of the extracts of the barks and leaves are attributed to traditional healers, although the implementation of anti- inflammatory, anti-microbial, and antioxidant effects substantiates the traditional effects [29,30]. This convergence indicates that indigenous knowledge is credible and promotes scientific research on how it works. Table 1 summarizes the relationship between the parts of *Neolamarckia cadamba* and their potential relevance to kidney health is as follows

Table 1: *Neolamarckia cadamba* and Potential Traditional Uses.

Plant Part	Traditional Indication	Contextual Relevance to CKD Pathology	Primary Phytochemical Class	References
Bark	Febrifugal (Anti-fever), Tonic, Dysentery	Anti-inflammatory and detoxification mechanisms; potential for and modulation.	Triterpenoids (Quinovic Acid)	[31]
Leaves	Wound healing, Ulcers, Diabetes	Anti-inflammatory, antioxidant, and tissue regeneration properties; relevant to epithelial repair and oxidative stress.	Flavonoids, Phenolics	[32]

Root/Root Bark	Urinary disorders (*Mutrakrichchhra*), Renal calculi	Direct historical influence on urinary tract and kidney function, suggesting diuretic and anti-urolithiatic activity.	Alkaloids, Saponins	[33]
General Extracts	Anti-inflammatory, Antiseptic	Broad-spectrum inflammation and infection control, crucial for interrupting the inflammation-fibrosis cascade.	All major classes	[34]

1.4 Plant Profile

Neolamarckia cadamba (Roxb.) Bosser is a member of the Rubiaceae family, which is one of the biggest groups of flowering plants. Based on studies of both molecular and morphological traits, the genus Neolamarckia was split off from Anthocephalus. *Neolamarckia cadamba* is the most well-known species in this group [35].

Taxonomical classification

Table 2 indicates *Neolamarckia cadamba taxonomical classification as follows* [36]*:*

Table 2: Neolamarckia cadamba taxonomical classification

Taxonomic Rank	Classification
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Gentianales
Family	Rubiaceae
Genus	*Neolamarckia*
Species	*N. cadamba* (Roxb.) Bosser
Common Names	Kadamba (Hindi), Vellaikadambu (Tamil), Burflower tree (English), Kadam (Bengali)

Morphological characteristics

N. cadamba is a straight-cylindrically upright-trunked tree and is an evergreen tree and is used to a height of 45 meters with broad top. **Leaves:** Opposite, large (15-50 cm), glossy, dark green, elliptic to ovate-shaped and having very strong veins [37]. **Flowers:** Large, fragrant, tubular, and growing in dense and spherical heads of orange-yellow color (3-5 cm diameter) [38]. **Fruits:** The various fruits are globose and consist huge amount of tiny and winged seed filled tiny capsules [39]. **Roots:** Strong taproot system where it can be stressed even during times when soil is saturated [40].

1.5 Geographical and ecological distribution

N. cadamba is native to tropical and subtropical South and Southeast Asia and can be grown in damp forests

and riverbeds of tropical environments and altitudes up to 1000 m above the sea level. Other countries which are natural occurrences include India, Bangladesh, Nepal,

Myanmar, Thailand, Malaysia, Indonesia, Sri lanka and part of China. Central America and Africa also have it in the production of timber and shade [41].

2. Traditional Uses and Ethnomedicinal Uses.

N. cadamba is used in the Ayurveda, Unani, and Siddha systems, which are traditional systems, and has been found to provide multi-targeted treatment [42]. The Ayurvedic classical texts (18 th
-19 th century) state that its bark (kadamba twak) is cooling, bitter and astringent and should be used in the treatment of pitta and kapha diseases. Its flowers (kadamba pushpa) are scent, which are used to treat headaches and insomnia, whereas its fruits are used to treat digestive problems [43]. The tree is considered a holy one in India; as Lord Krishna is believed to have had his Rasa Leela under a Kadamba tree [44]. This symbolism of the culture strengthens its ritual and medicinal role. Table 3 and 4 indicates entire *N. cadamba* plant ethnomedicinal applications are as follows:

Table 3: *N. cadamba* plant Part-wise ethnomedicinal applications

Plant Part	Traditional Uses	Mode of Preparation	References
Bark	Fever, diarrhoea, malaria, wound healing, liver disorders	Decoction, paste, or powder applied externally or consumed orally	[45]
Leaves	Ulcers, boils, skin infections, inflammation, pain relief	Leaf paste applied topically; juice for wounds	[46]
Flowers	Antipyretic, diuretic, sedative, headache relief	Dried flower powder in water or milk	[47]
Fruits	Digestive stimulant, antidiabetic, astringent	Fruit pulp eaten fresh or dried; juice used for dysentery	[48]
Roots	Stomachache, fever, blood purification	Decoction or root paste with honey	[49]

Table 4: Regional ethanomedicinal applications of *N. cadamba* plant

Region/Tribe	Traditional Practice	Reported Use	Reference
Assam (Bodo tribe)	Bark decoction for malaria	Antipyretic	[50]
Chhattisgarh (Baiga tribe)	Bark extract with honey	Wound healing, blood purifier	[51]
Odisha (Santal tribe)	Leaf paste	Skin infections	[52]
Tamil Nadu (Irula tribe)	Flower infusion	Sedative and headache remedy	[53]
Nepal Terai region	Fruit pulp	Diarrhoea, dysentery	[54]

2.1 Ayurvedic perspective

Neolamarckia cadamba (Roxb.) Bosser is a member of the Rubiaceae family, which is one of the biggest groups of flowering plants. Based on studies that combined molecular and morphological traits, the genus Neolamarckia was split off from Anthocephalus. Neolamarckia cadamba is the most well-known species in this group [55]. Table 5 indicates its use in ayurveda

Table 5: Ayurvedic applications of N. cadamba plant

Ayurvedic Attribute	Description	References
Rasa (Taste)	Tikta (Bitter), Kashaya (Astringent)	[56]
Guna (Properties)	Laghu (Light), Ruksha (Dry)	[57]
Virya (Potency)	Sheeta (Cooling)	[58]
Vipaka (Post-digestive taste)	Katu (Pungent)	[59]
Dosha action	Pacifies Pitta and Kapha	[60]
Therapeutic indications	Fever, liver disorders, prameha (diabetes), kushta (skin diseases), wound healing	[61]

3. *Neolamarckia Cadamba* Phytochemistry.

Phytochemistry

Neolamarckia cadamba has various secondary metabolites which have been credited with the pharmacological potential which primarily include alkaloids, triterpenoids, saponins, flavonoids, phenols, tannins, and glycosides. These bioactive compounds were identified by modern chromatographic and spectroscopic means in the barks, leaves, roots, flowers, and fruits. Its complicated phytochemical profile underscores the broad range of therapeutic applications of the plant and justifies several of its ethnomedicinal applications [62].

3.1 Phytoconstituents Major classes.

3.1.1. Alkaloids

Out of the bioactive compounds of *N. cadamba*, indole alkaloids hold the greatest importance. The most notable ones are cadambine, isocadambine, 3a-dihydrocadambine, cadamine, and isocephaline [63]. These compounds exhibit good anti-bacterial, anti-inflammatory and hepatoprotective effects. Indole nucleus of cadambine ($C_{28}H_{34}N_2O_4$) is quinolizing ring system; which is characteristic of alkaloids propagated by Rubiaceae. They are biosynthesized by the tryptamine-secologanin pathway, as other monoterpenoid indole alkaloids in the family [64].

3.1.2 Triterpenoids and steroids

N. cadamba has triterpenoids like ursolic acid, oleanolic acid, lupeol and betulinic acid in the bark and

leaves. They possess hepatoprotective, anti-inflammatory and antioxidant properties [65]. Methanolic extracts also contain steroidal compounds such as b-sitosterol, stigmasterol and campesterol [66]. Their presence allows the use of the plant in traditional medicine of the hepatic and inflammatory disorders.

3.1.3. Flavonoids and phenolics

The flowers and leaves have been isolated to produce flavonoids like quercetin, kaempferol and rutin. Phenolic acids such as gallic acid, caffeic acid, p-coumaric acid and ferulic acid are also involved in antioxidant activity and free radical scavenging. This synergetic effect of flavonoid and phenolic acids increases the protective activities of plants against oxidative stress and inflammatory diseases [67].

3.1.4. Saponins, glycosides and tannin.

Bark and fruit aqueous extracts have saponins, glycosides and tannins. The antimicrobial and expectorant actions of the traditional decoctions can be attributed to saponins, whereas the astringency effect and wound healing are due to tannins [68].

3.1.5. Volatility and non-volatility oil.

Volatile components (linalool, a-pinene, b-caryophyllene, nerolidol, and phytol) have been identified as essential oil components through the use of GC-MS [69]. These add to the smell and repelling insects of the plant. The seed oil contains non volatile lipophilic fatty acids such as linoleic acid, palmitic acid and oleic acid which is why it is used in skin disorders [70]. Damba is different according to the plant part and constituents required. Popular solvents are methanol, ethanol, chloroform and aqueous. The more recent extraction methods include Soxhlet extraction, microwave-assisted extraction (MAE) and ultrasound-assisted extraction (UAE) have enhanced yields and are less destructive of thermolabile compounds [71].

Alkaloids are normally collected by acid-base fractionation and then column chromatography is conducted on silica gel. TLC, HPLC, LC-MS/MS as well as NMR spectroscopy are used to identify and characterise [72]. The concentration of cadambine derivatives by advanced LC-MS fingerprinting can be applied to chemotaxonomic and pharmacological research [73]. The amount of phenolic and flavonoid in methanolic and ethanolic extracts. Research presents phenolic content of between 85-120mg GAE/g extract, flavonoid content of between 40-70mg QE/g extract [74]. These values are associated with a high level of antioxidant capacity using DPP.

These phytochemicals can be mechanistically explained in order to preserve the kidneys are as follows:

Antioxidant scavenging and Redox modulation: Flavonoids and phenolic acid in *N. cadamba* neutralize ROS and enhance antioxidant endogenous markers in vitro and in vivo (e.g., increase SOD, catalase, and reduce MDA). The answer to the prevention of the tubular epithelial cells under the AKI and slow down the frequency of oxidative stress-mediated fibrogenic signalling in CKD is the reduction of the oxidative stress [75].

Anti-inflammatory effects: Others of these extracts inhibit pro-inflammatory mediators and possess analgesic/anti-inflammatory activity in animal models - reducing the damage caused by cytokines that results in fibrotic cascades (e.g. TGF-b activation following inflammation) [76].

Plausibility against the fibrosis: Even though, there is little evidence to suggest that *N. cadamba* suppresses the classic fibrosis signalling (TGF-b / Smad, myofibroblast activation), the overarching antioxidant and anti-inflammatory activity of the plant suggests a scenario of potentially upstream inhibition of fibrogenesis. Preclinical nephroprotection Preclinical nephroprotection in models (see SS4) has been demonstrated by functional experiments, but needs to be supported by mechanistic experiments in fibrosis models [77].

4. Preclinical evidence

4.1 Cisplatin was found to cause nephrotoxicity

N. cadamba ethanolic root extract was very effective in preventing nephroprotective effects in cisplatin-treated Wistar rats: it decreased the serum creatinine/BUN, resulted in better histology, and balanced the oxidative stress indicators in comparison with cisplatin (which caused oxidative stress in rats). These authors came to the conclusion that interaction probably resulted in a protective effect due to antioxidant/nephroprotective phytoconstituents [78].

4.2 Nephrotoxicity caused by arsenic

Kidney architecture and markers were reported to be restored with aqueous/flower extracts in mice after exposure to arsenic with further positive outcomes in histology and oxidative stress biomarkers. These data demonstrate prophylactic action on different nephrotoxic offenses [79].

4.3 Anti-urolithiasis / CaOx was a research undertaking

The N. cadamba extract decreased calcium, oxalate, phosphorus deposition in kidney in a model of CaOx kidney stones, and prevented CaOx crystal formation in vitro- antioxidant activities and crystal nucleation/aggregation inhibition are possible. This is to mean that there may be some good on the side of the urinary stone disease and as such may lead to the damage of the second renal parenchyma [80].

4.4 Anti-oxidant /anti-inflammatory in other models

In a series of studies (wound healing, anti-inflammatory assays) the antioxidant activity and the reduced level of inflammatory cytokines through the use of *N. cadamba* extracts is recurrently

shown - which is in agreement with the general tissue-protective properties in kidneys. H and FRAP methods [81].

5. Conclusion

Neolamarckia cadamba is an antioxidant and anti-inflammatory phytochemically rich plant with reproducible activity in various studies; it has been shown to have nephroprotective activity in various preclinical nephrotoxicity and urolithiasis models. These results give a justifiable reason to declare it an encouraging target of the anti-fibrotic approaches to kidney disease, yet the direct evidence of anti-fibrotic action is already rather low. The next steps to be given priority are strict mechanistic research on chronic fibrotic renal models, guided discovery of active molecules by bioassays, and standardized toxicology/pharmacokinetics before any clinical implementation.

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