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DIURETIC ACTIVITY OF *ACACIA CATECHU*: A COMPREHENSIVE REVIEW OF PHYTOCHEMISTRY, PHARMACOLOGY, AND THERAPEUTIC POTENTIAL

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ABSRACT

Acacia Catechu widely used in traditional medicine such as Ayurveda and traditional Chinese medicine, has been drawing attention as a natural diuretic. This review intends to systematically summarize and integrate the information available on the phytochemistry, pharmacological procedures, and therapeutic chance of A. catechu in diuretic therapy. Catechins, tannins, flavonoids (quercetin, for example), and phenolic acids would be the main bioactive components involved in diuretic effect through the mechanism of inhibition of Na^+/K^+-K-ATPase, increase in renal blood flow, increase in sodium and water excretion, and antioxidant protection of renal tissues. Preclinical investigations demonstrate marked diuretic activity in salt-loaded and furosemide-comparative animal models, with low toxicity levels in both acute and sub-chronic evaluations. Despite these facts, clinical studies are limited to ethnopharmacological studies only, reflecting a great lack on translational medicine. Standardisation of extracts, molecular pathways clarification and validation through strong clinical data are urgently needed. Therefore, A. catechu may provide promising natural-derived cheap and safe alternative for diuretic treatment, the future research on this promising botanical agent has to be conducted

with more emphasis on clinical validation and formulation development to implement in to evidence-based medical practice.

KEYWORDS: Diuretic activity, Phytoconstituents, Catechins, Na^+/K^+-ATPase inhibition, Herbal medicine, Renal pharmacology.

1. INTRODUCTION

General background on diuretics and their therapeutic importance

Diuretics are an important class of drugs that promote urinary output by a variety of physiological actions (Figure 1), predominantly by antagonizing renal sodium and water reabsorption along the nephron.[1] These drugs are clinically important in the treatment of many conditions such as hypertension, heart failure, renal diseases and electrolyte abnormalities.[2] The scale of the global burden of cardiovascular diseases in relation to the number of hypertensive adults (1.28 billion according to recently published epidemiological data) itself highlights the ongoing importance of diuretics in modern pharmacotherapy.[3] In spite of newer antihypertensive medications, diuretics are still considered as the first line drug in clinical guidelines of many countries, because of their proven efficacy, relatively good tolerability and low price.[4] The clinical relevance of diuretics is not limited in fact to control of blood pressure but also to volume regulation in heart failure (HF) patients, and to symptomatic relief in situations of retention of fluid.[5]

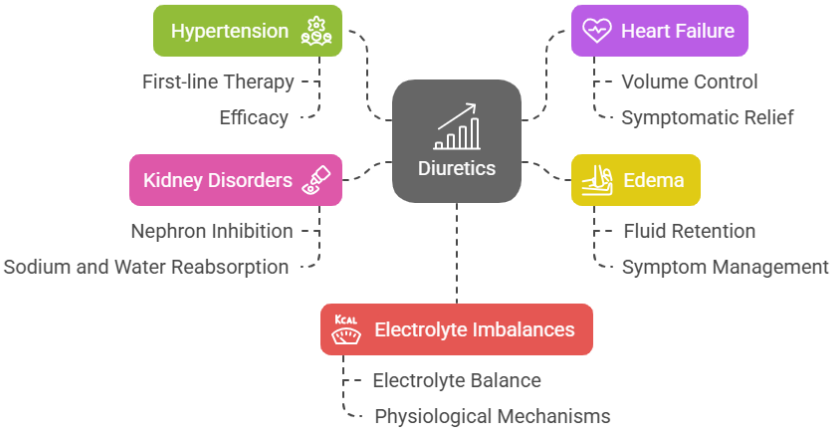

Figure 1: Therapeutic Importance of Diuretics.

Traditional use of herbal diuretics

Before the era of synthetic drugs, many cultures around the world have used plants as diuretics.[6] History and Global Distribution of Herbal Diuretics Ethnopharmacological

records reveal widespread use of herbal diuretics from as for back as from ancient civilizations of Egyptian, Chinese, Ayurveda and Greco-Roman medical traditions.[7] These natural remedies were used empirically to treat pathological states with enema, such as dropsy, urinary disorders, and "water retention diseases" such as those observed in cardiac or renal disease,[8, 9] The present attention towards herbal diuretics has become heightened due to increasing global research on natural products as well as in view of concerns towards unwanted effects of synthetic diuretics such as imbalances in electrolytes, metabolic disorders and drug interactions.[9] Modern pharmacological studies have also confirmed the diuretic activity of many other traditional herbal plants using well-established scientific techniques, where bioactive compounds e.g., flavonoids, terpenes, and saponins, etc., have been found to influence renal function from various sites following different mechanisms.[10]

Importance of Acacia catechu in traditional medicine

Acacia catechu Willd. (family *Fabaceae*), known as black catechu or "katha" is a medicinally important plant of traditional medical system especially Ayurveda, Traditional Chinese Medicine and throughout South-East Asian healing.[11] This tree is native to South and Southeast Asia and has been used for over 2,000 years for various ailments including diarrhoea, ulcers, haemorrhaging, skin diseases, and oral complaints.[12] The medicinal utilizations of A. catechu mainly rely on its heartwood extract form (catechu or cutch), known to be rich in bioactive compounds.[13] Although astringent, antimicrobial, anti-inflammatory, and antioxidant activities have been well studied on A. catechu, its diuretic utility in traditional context has been understudied relative to the claims made in ethnopharmacological texts.[14] The heartwood of A. catechu has been historically used by traditional healers in different formulations like decoctions and powders as remedy for edema, urinary tract infections and diseases associated with fluid retention.[15]

Rationale for reviewing its diuretic activity

Although diuretic properties of Acacia catechu have been widely reported in the literature, there has remained a large difference between its traditional knowledge and biological validation.[16] In the recent pharmacological studies, the potential of A. catechu extracts as well as their active phytochemicals as diuretics has started gaining attention and yielded some promising initial findings which need thorough evaluation.[17] A. catechu exhibits an abundant phytochemical composition, which include high concentration of polyphenols, flavonoids, and tannins, which may lend support to possible mode(s) of action for its diuretic

activity that lie just along the lines of already established phytochemical modes of diuretic action.[18] With the emergence of evidence-based traditional medicine, this systematic review of diuretic effect of A. catechu fulfils a critical research priority at the juncture of ethno-pharmacology and modern therapeutics development.[19] In addition, as there develops an expanding need for the discovery of new diuretic drugs with less toxic effects, natural products such as A. catechu may serve as useful candidate agents for drug discovery.[20] This review covers all the now known phytochemistry, pharmacological actions, and potential therapeutic effects of A. catechu as a diuretic and apprises the traditional applications of the plant with current science leading for future research prospects.

2. BOTANICAL DESCRIPTION AND ETHNOMEDICAL USES OF *Acacia Catechu*

Taxonomy and geographical distribution

Acacia catechu Willd. is a member of the Fabaceae family (subfamily Mimosoideae) and is one of the ~1,350 species in the large Acacia genus[21] (Fig. The taxonomy of A. catechu is much nomenclatural confused, and recent phylogenetic analyses have confirmed its alliance to the circumscribed Acacia sensu stricto clade.[22] The species is a moderate-sized deciduous tree with dark brown to black deeply furrowed bark reaching to 15-20 m with bipinnate leaves that are composed of 10-30 pairs of leaflets and pale yellow to whitish cylindrical inflorescences.[23]

A. catechu is naturally distributed throughout South and Southeast Asia and native to India, Pakistan, Nepal, Myanmar, Thailand, and regions of southern China.[11] The species features an impressive ecological plasticity, and it may in fact be found in a variety of habitats that extend from subtropical to tropical climates, at elevations from the sea level to 1,500 m.[24] Though primarily occurring in deciduous and open forest lands, A. catechu has distinct preference for the well-drained soils near river banks, foothills and disturbed lands.[25] Through cultivation and naturalisation, it has spread in some areas such as some parts of East Africa, Indonesia, and Caribbean, although its medicinal use is most prominent in its native area of distribution.[26]

Traditional/ethnobotanical uses (especially in urinary disorders, renal issues, edema)

The traditional use of Acacia catechu for medicinal purpose is highly diversified and is beneficial for urinary and renal disfunctions. Field studies on ethnopharmacological perspectives of Acacia catechu indicated that its different parts particularly heart-wood (cutch or katha) have been prepared and employed in same manner within its indigenous

distribution range for the treatment of urinary affections.[27] The A. catechu heartwood decoctions was also traditionally suggested by healers in the Himalayan northern India and western Nepal People for diseases related to painful (dysuria) and difficult urination, urination (polyuria), and slim up cock infections of urinary tract.[28] Most of the indigenous formulations marketed for haematuria and albuminuria, both of which are now recognized as evidence of different renal pathologies[29], have bark and heartwood as part ingredients.

While the application of A. catechu for enema is probably one of the very few other ethnobotanic uses can be directly connected to potential diuretic action. Powdered heartwood to powdered heartwood (in honey) is applied by traditional healers to relevelling strips of peripheral edema in Rajasthan and Gujarat (India), especially in cases involving the lower limb.[30] In the same vein, elsewhere in Myanmar and in Thailand, postnatal women drink infusions of A. catechu bark to reduce enema and promote fluid evacuation.[31] In Pakistan, the ethnomedicinal use of heartwood extract is recommended in mixture with other plants for the treatment of ascites (abdominal dropsy), mainly caused by liver and heart diseases.[32]

In addition to cases of renal and edema utility, A. catechu has been traditionally applied to diseases for which increased diuresis may be therapeutically beneficial. as hypotensive remedies in the traditional medicine in north eastern India.[33][34] noted that the Bengali traditional healers used plant extracts of A. catechu for the treatment of urinary stone and gravel, suggesting that it has lithotripsic action as well as diuretic action.

Historical significance in Ayurveda, TCM, Unani

The essential drug Khadira, made from Acacia catechu, is considered one of the important medicinal plants in Ayurveda and the usage is mentioned in the ancient texts of Ayurveda, such as Charaka Samhita and Sushruta Samhita dating to 1000-500 BC.[35] Khadira is classified in Ayurvedic pharmacology as "Murtala" (diuretic) and "bhedana" (breaking) Classic A. catechu containing Ayurvedic formulations for urogenital disorders are Khadiradi Kashaya (decoction) and Khadirarishta (fermented drug) indicated in disturbed urination and edema.[37] The Ayurvedic compendium Bhavaprakasha (16th century CE) mentions the use of Khadira for "mutrakrichhra" (dysurgea) and "mutraghata" (urinary obstruction), disorders where an increase in kidney excretion would have a symptomatic benefit.[12]

According to TCM theory, A. catechu (Er Cha or Hai Er Cha) is applied for drinks and recorded in the materia medica books as early as in the Tang Dynasty (618-907 CE).[38] The

TCM pharmacological acquisition perceived by category illustrated that of A. catechu is "clear heat" and "promote urination," it is especially useful in diseases grouped into "damp-heat" syndromes of the urinary system.[39] According to the classical TCM document "Bencao Gangmu" (Compendium of Materia Medica, 1596 CE) by Li Shizhen, A. catechu extract was used in the treatment of lin zheng (frequent and urgent dysuria) and shuizhong (edema), potentially suggesting its diuretic effect.[40]

In Unani system of medicine (Greco-Arabian system of medicine), A. catechu (known as “Kath” or “Kaath”) is described as one of the important drugs in the pharmacopoeias such as Canon of Medicine by Ibn Sina (Avicenna, 980–1037 CE) and Al-Qanun fit-Tibb.[41] In Unani medicine, A. catechu has been described to have "muwallid-e-baul" (diuretic) and "qabiz" (astringent) properties, which makes it weigh up its therapeutic activity so as to enhance the excretion of urine without causing weakening of the genitourinary system tissues.[42] Some of the selected traditional Unani formulations containing A. catechu for the treatment of urological disorders are Majoon-e-Supari Pak and Qurs-e-Kahruba which are indicated for the treatment of conditions such as warm-e-masana (cystitis) and istisqa (dropsy/edema).[43] The Unani pharmacopeia Khazainul Advia extensively emphasizes the use of A. catechu preparations for treating “Zof-e-gurda” (renal weakness) characterised by polyurea and proteinurea.[13]

3. PHYTOCHEMICAL PROFILE OF *ACACIA CATECHU*

Acacia catechu is rich and diverse in phytochemical constituents that are responsible for its multiple medicinal properties, including diuretic activity. Several major classes of active compounds have been found in different parts of the plant during the course of extensive phytochemical analyses in various studies, with the heartwood bearing the most such compounds.[44]

Among them, polyphenolic compounds are the major class of phytochemicals in A. catechu of which catechins are the most abundant and characterize ingredients (Figure 2). Heartwood of the plant contain considerable amounts of (+)-catechin, (-)-epicatechin and (-)-epicatechin-3-O-gallate that collectively make up 25-35% of the dry heartwood extract.[45] These catechins, especially (+)-catechin (7, also named catechu), are chemical markers for this species and are one of the main active components in it.[46]

Table 1: Major Catechins Identified in *Acacia catechu* Heartwood.

Compound	Chemical Structure	Content (% w/w in dried extract)	Reference
(+)-Catechin	$C_{15}H_{14}O_6$	15-22%	[45]
(-)-Epicatechin	$C_{15}H_{14}O_6$	5-8%	[47]
(-)-Epicatechin-3-O-gallate	$C_{22}H_{18}O_{10}$	2-4%	[48]
(-)-Epigallocatechin	$C_{15}H_{14}O_7$	1-3%	[45]

Tannins are another major category of phytochemicals in A. catechu, accounting for 20-30% heartwood extract.[49] Both hydrolyzable tannins (gallotannins and ellagitannins) and condensed tannins (proanthocyanidins) are present. It has been reported that gallic acid, chebulinic acid as well as some polymeric proanthocyanidins consisting of catechin and epicatechin monomers[50] are the active compounds. The astringency in questions can be explained by its high tannin content.

Another significant group of compounds in A. catechu are the flavonoids; the heartwood and the stem bark are rich in quercetin, kaempferol, isorhamnetin, and their glycosides.[51] More detailed quantitative analysis indicated also that the flavonoid content varies depending on plant part and geographical origin; TOM heartwood extracts, summarized in the form of all flavonoids calculated as quercetin, ranged from 5 to 12%.[52] Several novel flavonoid compounds have been discovered from A. catechu recently such as catechinic acid A, and acaticatechin A and B that can be responsible for species-specific pharmacological effects.[53]

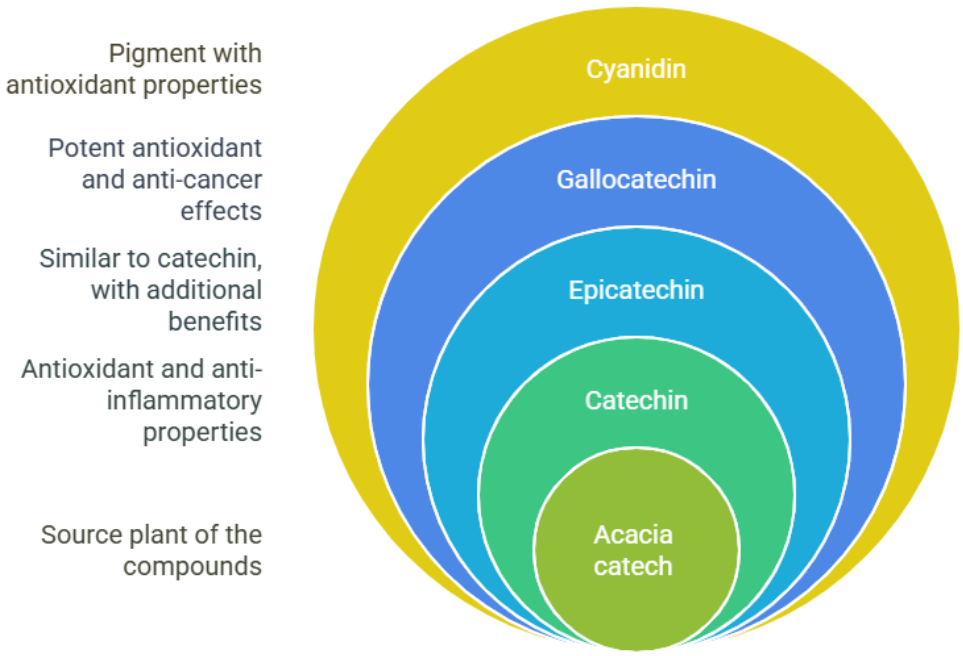

Figure 2: Bioactive Compounds from Acacia catech.

Alkaloids are found in lesser amounts in A. catechu, especially in bark and leaves. The phytochemical screening of Mili has revealed that it contains many indoles and isoquinoline alkaloids, but the complete characterization of these compounds is still restricted (54). Key alkaloid components of the vine are dimethyltryptamine derivatives (found in the leaves) and β-carboline alkaloids (found in the stem), which could account for some central nervous system activity reported in traditional practices.[55]

There are also terpenoids and steroids in the different plant parts of A. catechu. Lupeol, β-sitosterol, stigmasterol and ursolic acid has been isolated from basil bark extracts, and heartwood has investigated to contain number of diterpenoids such as taxifolin and catechin dimers.[56] These actives generally represent 2-5% of the dry weight of the extract and may act in synergy to convey the entire pharmacological complement of the plant.[57]

Other notable constituents include

Polysaccharides: arabinogalactans and acidic polysaccharides (3-8%). Organic acids: primarily gallic acid, caffeic acid, and ferulic acid (1-4%). Essential oils: primarily in leaves and flowers, characterized by sesquiterpenoids (0.1-0.5%). Minerals: particularly high potassium and calcium content in ash.[58]

Table 2: Phytochemical Composition of Different Parts of *Acacia catechu*.

Plant Part	Major Phytochemical Classes	Key Compounds	Content Range (%)	Reference
Heartwood	Catechins, Tannins, Flavonoids	(+)-Catechin, Procyanidins	Catechins: 25-35%, Tannins: 20-30%	[46, 49]
Bark	Tannins, Alkaloids, Terpenoids	Gallic acid, β-Sitosterol	Tannins: 12-18%, Alkaloids: 0.2-1.5%	[54, 56]
Leaves	Flavonoids, Alkaloids	Quercetin, Kaempferol glycosides	Flavonoids: 3-8%, Alkaloids: 0.1-0.8%	[52, 55]
Roots	Catechins, Proanthocyanidins	Catechin dimers, Epicatechin	Catechins: 10-15%, Proanthocyanidins: 15-20%	[45, 50]
Seeds	Fixed oils, Proteins, Saponins	Linoleic acid, Stearic acid	Fixed oils: 5-8%, Proteins: 15-20%	[58]

Extraction methods used for these compounds

The process involved in the extraction of the bioactive components from A. catechu has been progressively transformed from classical methods to advanced molecular techniques that focused mainly on specific classes of phytochemicals (Figure 3). Aqueous hot water extraction (decoction) of chips of heartwood or bark is still the standard means of extraction in conventional practice and in ayurveda and other traditional medicine systems including

modern clinical practice of ayurveda and the concentration of the decoction through evaporation produces katha or cutch.[59] Typically these methods produce about 10-15% of dried extract and the extracts are complex mixtures of polyphenolic compounds, mainly catechins and tannins.

Current phytochemical studies utilize different extraction methods according to the compounds of interest and their possible application. One of the most common methods employed in sequential solvent extraction[60] is where an escalating solvent extraction is adopted (from petroleum ether > chloroform > ethyl acetate > methanol > water) to fractionate the constituents according to polarity. This technique is particularly useful for fractionation of lipophilic (terpenoids, sterols|) from hydrophilic (catechins, tannins) components.

Table 3: Comparison of Extraction Methods for *Acacia catechu* Phytochemicals.

Extraction Method	Solvent System	Target Compounds	Yield (%)	Advantages	Reference
Traditional decoction	Water	Catechins, Tannins	10-15%	Simple, non-toxic	[59]
Soxhlet extraction	Ethanol/Methanol	Polyphenols, Flavonoids	15-22%	Comprehensive extraction	[61]
Ultrasound-assisted extraction	70% Ethanol	Catechins, Flavonoids	18-25%	Rapid, energy-efficient	[62]
Microwave-assisted extraction	50% Methanol	Polyphenols	20-28%	Rapid, high yield	[63]
Supercritical fluid extraction	CO_2 + Ethanol modifier	Terpenoids, Low-polarity compounds	3-8%	No solvent residue	[64]

For catechin isolation, the best procedures consist of hydroalcoholic extraction (50–70% ethanol) of heartwood, liquid–liquid partition with ethyl acetate, and chromatographic purification.[61] Recently, refined methods of extraction such as ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE) have been developed, which have helped to decrease the time of extraction to lower levels and to increase or retain the yield. With the most favorable extraction of catechins and other flavonoids, uAE up to 25% higher can be achieved compared with the traditional extraction, when whole olive leaves are extracted at 45°C for 30 min using uAE in 70% ethanol.[62]

Tannins are usually extracted with acetone-water solvent system (70:30) at an intermediate temperature (40-50°C) to avoid polymerisation and oxidation. Stability and yield of these compounds have been reported to improve following the addition of a low quantity of

antioxidants like ascorbic acid (0.1%) during extraction.[65] Analysis of total tannins Both condensed and hydrolysable tannins were determined by acid hydrolysis followed by HPLC analysis for analytical purpose.

In extracting flavonoid, methanol or ethanol with acidification (0.1% HCl) may be used to better disintegrate the bound flavonoid from plant matrices.[66] New techniques such as enzyme-assisted extraction with cellulase and pectinase have been reported as a promising approach to enhance the yield of flavonoids from both A. catechu bark and leaves, with percentage increase ranging between 15-30% over conventional solvent extraction.[67]

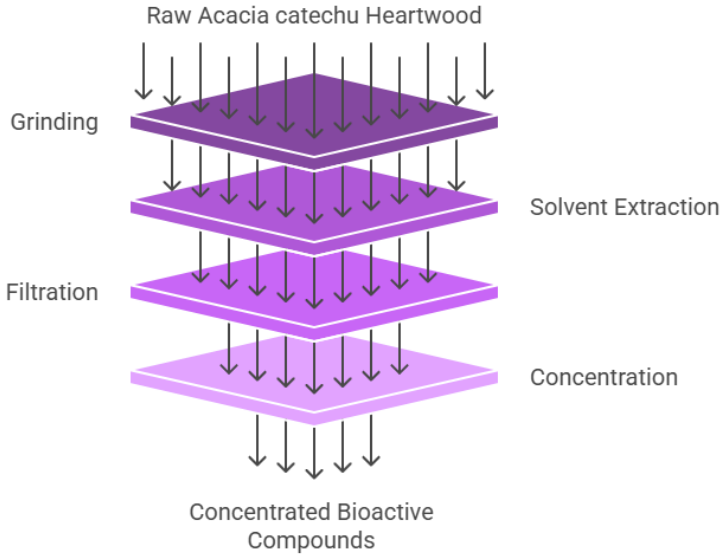

Figure 3: Extraction protocol for major bioactive compounds from *Acacia catechu* heartwood.

An acidified aqueous solution (pH 2-3) is used for alkaloid extraction, and then alkali is used for basification and organic solvent partitioning (usually chloroform or dichloromethane).[68] More recently, ionic liquid-mediated extraction approaches have shown improved efficiency in extracting alkaloids from A. catechu bark, with 1-butyl-3-methylimidazolium bromide being particularly promising.[69]

Advanced extraction methods such as PLE and SFE have been used in recent studies on A. catechu. SFE with CO2 and ethanol as a co-solvent (10−15%) at 300 bar and 50°C has been reported to be able to selectively extract light to medium polarity compounds such as some flavonoids or terpenoids.[64] These are attractive methods in selectivity, the decrease of the solutions and environmental-friendly reactions.

Relevance of phytochemicals to diuretic activity

The diuretic effect of Acacia catechu might be due to the complex synergistic interrelations between various phyto-constituents which might be involved in multiple mechanistic in the diuretic activity (Figure 4). The present data indicate that several classes of compounds appear to be involved in the plants modulation of urinary and electrolyte regulation.

Flavonoid is one of the important phytochemical groups correlated with diuretic effects of A. catechu. Molecules such as quercetin and kaempferol have shown marked diuretic effects in preclinical models through a mechanism of Na+ K+-ATPase inhibition in renal tubules, modulation of renal hemodynamics, and increasing glomerulus filtration rate.[70] 2.2.2 A Study of the Structure-Activity Relationship (SAR) Analysis of Flavonoids Using flavonoids as models, the position of hydroxylation, in particular at the 3', 4', and 5' position of the B-ring has a profound impact on potency as diuretic agents, quercetin (3',4' dihydroxy configuration) showing the most potent activity.[71]

Table 4: Structure-Activity Relationship of *A. catechu* Flavonoids in Relation to Diuretic Activity.

Compound	Structure Features	Diuretic Potency	Proposed Mechanism	Reference
Quercetin	3',4'-dihydroxy pattern	High	Na^+-K^+-ATPase inhibition	-71
Kaempferol	4'-monohydroxy pattern	Moderate	Aldosterone antagonism	-70
Isorhamnetin	3'-methoxy-4'-hydroxy	Moderate-High	Mixed mechanisms	-72
Catechin	3',4'-dihydroxy with C3-OH	Moderate	Vasodilation, GFR increase	-73

The contributions of catechins and the other polyphenolic components of A. catechu to the diuretic properties are likely to be substantial through a variety of physiological actions. Catechins have shown inhibitory activity towards carbonic anhydrase enzyme comparable to ITUs like acetazolamide.[73] Catechins could also improve renal function by playing the role of powerful antioxidants which can alleviate OS-mediated tubular injury, improve microcirculation and even reduce proteinuria.[74] In vitro studies have demonstrated that (-) epicatechin and its metabolites are able to regulate aquaporin-2 expression in renal collecting duct, and thereby potentially regulate water reabsorption.[75]

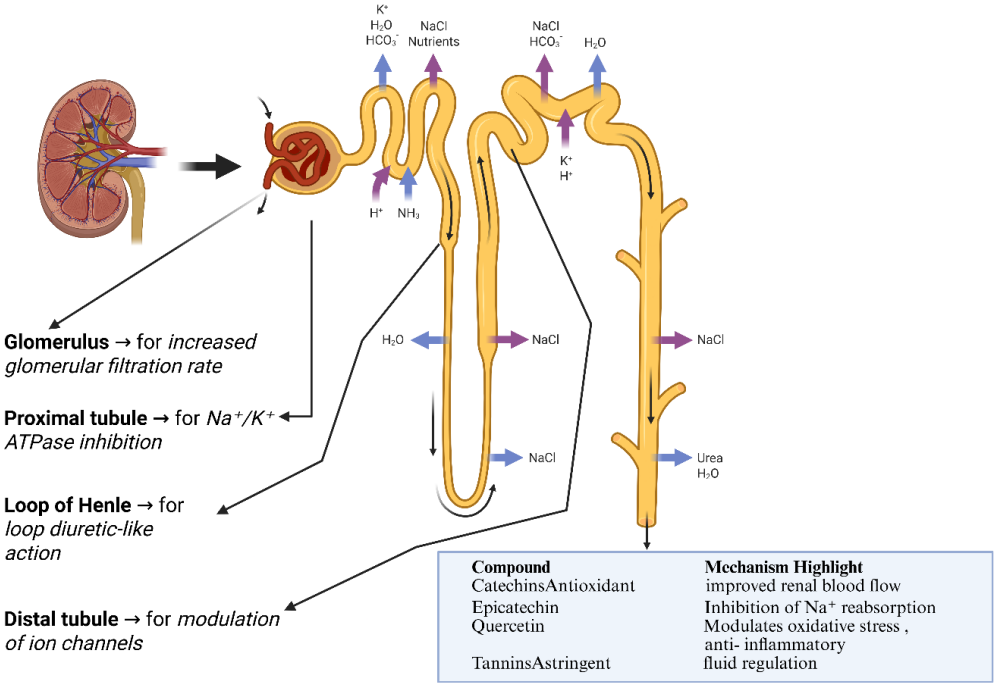

Figure 4: Proposed mechanisms of diuretic action for major phytochemicals in *Acacia catechu*.

The Tannins from A. catechu probably are responsible for diuretic effect, due to its astringent activity and the possible effect on renal vasculature. Hydrolysable tannins, especially those derived from gallic acid and ellagic acid, have shown weak diuretic activity in pharmacological studies, possibly via a vasodilatory action which stimulates renal blood flow and glomerular filtration.[76] Nevertheless, concentration-dependent decrease on diuresis seems to be contradictory with tannins exerting its diuretic action as a result of nonspecific protein binding and precipitation; thus, concentration-dependent effects may be involved in the action of A. catechu extracts on diuretic profile.[77]

Potassium in A. catechu is one of the major constituents that can influence significantly the diuretic action of the plant through a simple yet potent mechanism. Traditional preparations are a significant source of potassium, with heartwood extract containing 15-25 mg of potassium/g[78]; this may lead to an osmotic diuretic effect and compensate for potassium loss secondary to other diuretic actions. This dual activity (increasing diuresis and conserving potassium) is likely of benefit in comparison with other diuretics that frequently lead to hypokalaemia.

Table 5: Potassium Content in Various *Acacia catechu* Preparations and Potential Contribution to Diuretic Activity.

Preparation	Potassium Content (mg/g)	Typical Dose (g)	Total K^+ Delivery (mg)	Contribution to Diuresis	Reference
Dried Heartwood Extract	15-25	03-May	45-125	Moderate	[78]
Aqueous Decoction	Oct-18	10-20 ml	100-360	Moderate-High	[79]
Alcoholic Tincture	08-Dec	2-5 ml	16-60	Low-Moderate	[80]
Commercial Tablets	05-Oct	1-2 tablets	May-20	Low	[81]

For example, the terpenoids and steroids in A. catechu were less than polyphenolic contents, but then may participate in its diuretic activity through renal transporters. Ursolic acid, a triterpenoid, was shown to inhibit Na^+/H^+ exchangers in proximal tubules leading to natriuresis and water elimination.[82] Moreover, some sterols found in A. catechu could have a mild BACE1 antagonistic activity and are thereby capable of reversing undetected aldosterone-induced sodium retention.[83]

Previous metabolomic studies have also showed potential synergistic effects among various types of phytochemical extracts of A. catechu. For example, some flavonoid-catechin pairs have shown to have higher diuretic activity than each compound alone at the same doses, thus providing evidence for absorptions having pharmacodynamic interactions.[84] Moreover, the concomitant action of compounds with different mechanisms (tubular effect, haemodynamic effect, enzyme inhibition) could result in a more neutral diuretic profile with fewer electrolyte disorders when compared with single-mechanism synthetic diuretics.[85]

4. EXPERIMENTAL STUDIES ON DIURETIC ACTIVITY

4.1. In vivo Animal Studies

Models used

Diuretic potential of Acacia catechu has been evaluated using a number of established animal models, which exhibit highly sensitive method for assessment of diuretic activity. Of the models, the Lipschitz model is the most common, and test materials are compared to standard diuretics in rats or mice, with urinary volume as the end-point measurement.[86] Method: Adult male Wistar rats (180-220g) were fasted for 18 hours with water ad lib ad libitum and were broken into 3 groups each with a minimum of 4 animals and groups treated with A. catechu heartwood extract, furosemide (positive control) and vehicle (negative control) respectively developed by Sharma et al.[17] This design allows direct comparison of diuretic efficacy with clinically used drugs.

Saline loaded models have been found useful to study the action of A. catechu in acute volume expansion. Khan et al. used a modified saline-loaded rat model in which rats were treated with normal saline (25 ml/kg p.o.) before administration of the extract as a physiological challenge to enhance the seen driven diuretic response.[87] Such an approach has specific applications in edematous disorders associated with fluid retention.

Some of the comparative studies have used standard (reference) drugs such as loop diuretic (furosemide), thiazide diuretic (hydrochlorothiazide) and potassium-sparing diuretic (spironolactone) to compare the activity of A. catechu in comparison of established pharmacological classes.[88] Such an approach provides a mechanistic basis by which to examine diuresis patterns and electrolyte excretion profiles with those for drugs having established sites of action within the nephron.

Dosage forms and routes

Experimental investigations have employed diverse A. catechu preparations and administration routes, and aqueous and hydroalcoholic extracts being the most representative as they are classically used and also polar bioactive compounds are well extracted by them.[89] Extract dosages from 100–500 mg/kg bodyweight are commonly applied and the 250 mg/kg dose has been most effective in a number of studies.[17, 90] The dose-range shows considerable diuretic action with wide safety margins in animals.

Oral administration is the most frequently used administration method as compared with the traditional usage and the clinic practice.[91] Nevertheless, some studies have used intraperitoneal injection to avoid variability due to gastrointestinal uptake and first-pass metabolism, allowing some consideration regarding the bioavailability of active compounds.[92]

Different methods of extract standardization have been used in the studies with catechin concentration (usually 15–25% w/w) being the most widely used quality marker.[93] Kumar et al. 80) established a standardized 20% w/w total catechins formulation for systematic dose-response evaluation, which is a major concern in botanical research is extract variability.[80]

Table 6: Dosage Forms and Administration Routes Used in Experimental Studies of *A. catechu* Diuretic Activity Outcomes (urine volume, electrolyte excretion)

Extract Type	Dosage Range (mg/kg)	Administration Route	Standardization Parameter	Reference
Aqueous Heartwood	200-500	Oral	Total phenolics (12-15%)	[17]
Ethanolic (70%)	100-400	Oral	Catechin content (20%)	[80]
Methanolic	150-350	Intraperitoneal	Flavonoid content (5-8%)	[92]
Hydroalcoholic (50:50)	250-750	Oral	Total tannins (18-22%)	[93]
Commercial standardized	100-300	Oral	Catechin (25% w/w)	[90]

Several experimental investigations report remarkable diuresis with S.A when administered to various animal species. Sharma et al. found dose-response increments in urine amount, finding that 250 mg/kg of standardized extract yielded around 78% of the furosemide (40 mg/kg) diuretic effect in a 24-hour urine collection.[17] This activity supports the folkloric use for diseases that require increased diuresis.

The time course of diuresis is unique, with peak effects at 2 –6 h after the dose (for most studies), that then decrease slowly in some studies over 8 –24 h.[94] This intermediate onset, of action and prolonged duration of action stands in distinction to the rapid action but shorter duration of effect profile of loop diuretics, supporting different mechanistic pathways of action, and possible clinical advantages in specific clinical situations that require sustained diuresis.

Excretory patterns of electrolytes offer vital clues with respect to A. catechu's nephronic site of action as well as its physiological role. Most studies demonstrate marked natriuresis (g Na^+ excreted/g H^+ excreted ratio) during the diuretic effect, with urinary Na^+/K^+ ratios usually in the range of 1.8-2.5 (versus 1.0-1.2 in control) animals.[89, 93] This high ratio implies a predominant influence on overall sodium reabsorption mechanisms rather than on non-specific osmotic diuresis.

A prominent and consistent observation from various studies relates to potassium handling: while synthetic diuretics were expected to effect greater potassium concentrations given to their natriuretic properties, extracts from A. catechu elicit relatively minor increases in urinary potassium excretion along with robust natriuresis.[80, 95] Kumar et al. showed that a standardized extract (250 mg/kg) significantly increased urinary Na+ excretion by 85% and K+ excretion by 31% with respect to controls.[80] This beneficial Na^+/K^+ excretion profile may translate to an advantage over conventional thiazide and loop diuretics which frequently result in clinically relevant hypokalaemia.

Moreover, other urinary parameters that were found to be influenced by A. catechu administration are chloride clearance (augmented) as well as urine pH (mild alkalinization) and urine specific gravity (reduced), suggesting a multimechanism response on renal function.[96] Sharma et al. also observed slight rises in urinary calcium excretion with high dose extract (500 mg/kg), but not with lower doses capable of inducing marked diuresis.[17]

Mechanisms suggested

According to the detailed mechanistic studies, we hold the view that A. Catechu shows diuretic activity by acting through several competitive pathways, providing support irrespective for tubular or hemodynamic mechanism, or both (Figure 5). Inhibition of Na^+/K^+-ATPase is another proposed mechanism which is well supported by both experimental in vitro studies; it has been shown that Icariin reduced the activity of rat and human kidney microsomal Na^+/K^+-ATPase.[97] This resembles the action of cardiac glycosides but is at non-cardiotoxic concentrations, possibly because of the pentacyclic structure of catechin and its related flavonoids that allows selective renal enzyme interaction. Changes in renal hemodynamics are also a major cause of the observed diuretic response. Using Doppler ultrasonography, experiments conducted in experimental animals have shown that A. catechu enhances renal blood flow and glomerular filtration rate.[98] This vasodilatation may be mediated primarily by the increased production of nitric oxide, reflected by the increased urinary nitrite/nitrate levels and the blockade of the diuretic response after n/iNOS inhibitors.[99]

It is clear that some constituents of A. catechu extracts may antagonize mineralocorticoid receptors (without strong antagonistic activities). Kumar et al. noted some preserved diuretic response in adrenalectomized rats, indicating the involvement of aldosterone-independent mechanisms, and complementary inhibition of the in vivo Na excretion, not potassium excretion, when the extract was co-administered with spironolactone.[80] These results indicate that as an adjunct to spironolactone, this compound may be useful in disorders associated with secondary hyperaldosteronism, e.g. congestive heart failure.

A CAI effect of A. catechu can also be related to its diuretic profile, especially in the urinary pH. The mild degree of urinary alkalinization noted after extract administration is similar to that reported for classical carbonic anhydrase inhibitors such as acetazolamide, albeit at lower potency.[100] Flavonoid composition, including those having specific hydroxylation patterns

closely matching that of quercetin, could be responsible for this effect by being structurally homologous to well characterized synthetic inhibitors.

The relatively good potassium-sparing effects by A. catechu extracts may thus be through direct and indirect effects. The relatively high potassium content (15-25 mg/g) of extracts contribute a counteracting potassium load, which may attenuate urinary losses.[78] And some of its flavonoid components may have vasodilator effects by directly acting on the distal tubular potassium channels to decrease potassium inflow into the lumen of the tubules.[101]

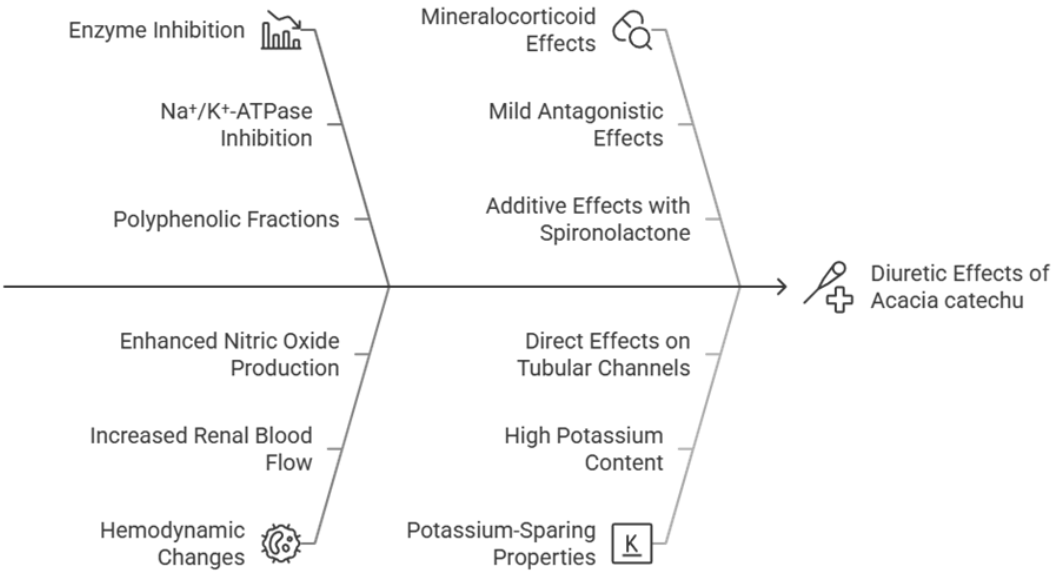

Figure 5: Mechanisms of Diuretic Effects in Acacia catechu.

4.2. In vitro or Mechanistic Studies

Ion transport modulation, aquaporin expression

Studies on A. catechu diuretic activity using in vitro approaches have already given some information about the molecular mechanism of action, focusing on ion transporters and water expression channels. Catechin-rich fractions of A. catechu markedly inhibit epithelial monolayer sodium transport processes in studies using renal epithelial cell lines (MDCK, LLC-PK1).[102] This inhibition seems to be concentration-dependent and to some extent reversible, being compatible with competitive interaction with transporters rather than non-specific membrane effects.

Some flavonoid components of A. catechu, in particular quercetin derivatives, have been shown by extensive patch-clamp electrophysiologic studies to inhibit epithelial sodium

channel (ENaC) activity in distal tubule cells.[103] This effect of inhibition of sodium reabsorption mechanism can explain the observed natriuresis in animal studies and is consistent with traditional use in edematous diseases.

The effect of A. catechu components on aquaporin water channels is a new topic, but it must be explored with respect to the diuretic mechanisms. Zhang et al. showed that (-)-epicatechin and related substances modulate aquaporin-2 (AQP2) trafficking to the plasma membrane in collecting duct cells by acting on the vasopressin-regulated pathways.[75] In particular, purified catechins (10–50 μM) decreased AQP2 membrane incorporation by 35–55% without changing total cellular expression, indicating an alteration of its trafficking phenotype and not de novo synthesis.[75] Such modulation of water channel distribution may explain the increase in free water clearance in some experimental models.

Using fluorescent ion probes, it has recently been shown that tannin fractions from A. catechu can influence intracellular calcium (Ca2+) signaling in renal tubular cells, thereby possibly affecting a variety of Ca2+-dependent processes in tubular transport (104). This effect of tannins on calcium may be another possible mechanism by which the complex tannin mixture in traditional preparations produce diuretic activity.

Inhibition of renal function with GSHases

A. catechu's effects on renal enzymes analyses has demonstrated selective inhibitory effects on several systems concerned with the tubular transport function. In vitro isolated kidney microsome studies have shown that polyphenolic fractions have a powerful inhibitory effect on Na^+/K^+-ATPase, with IC_{50} values varying between 45-120 μg/mL, depending on the preparation of the extract (97). Structure-activity relationship studies reveal that catechol, a structure among the primary A. catechu ingredients-containing catechins {43}), is a crucial functional entity accounting for this inhibitory activity by chelating metal cofactors in the activezsite of the enzyme.

Enzymatic assays and molecular docking study have confirmed carbonic anhydrase inhibition. The purified flavonoid fractions of A. catechu showed moderate inhibitory activity toward carbonic anhydrase II (CA-II) activity with IC_{50} values about ten times higher than those of acetazolamide.[105] This comparatively low potency accounts for the only mild degree of urinary alkalinization seen in vivo without systemic metabolic acidosis characteristic of more potent synthetic C.A. inhibitors.

Studies investigating the effects of A. catechu on aldosterone-responsive pathways have provided evidence of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) inhibition, the enzyme of which is responsible for cortisol inactivation in the mineralocorticoid-target tissues.[106] This inhibitory action is small in comparison to conventional inhibitors, but part be responsible for the effects of "potassium-sparing," by enabling endogenous cortisol to occupy mineralocorticoid receptors, competing with aldosterone.

Renal Models Studies investigating the antioxidant role of A. catechu in the kidney have shown protection against oxidative enzyme damage in ischemia-reperfusion injury **models**.[107] This beneficial action regarding renal function, though not the direct mechanism of a diuretic effect, has the potential to be an integral part of the overall good profile of A. catechu-p preparations in situations of fluid overload and oxidative stress, such as CHF.

Studies on metabolomics found a relationship between A. catechu ingredients and cytochrome P450 enzymes associated with eicosanoids, and suggested that prostaglandin pathways regulating renal haemodynamics and tubular function could be subject to modulation.[108] Such actions could acount for observed rise in renal blood flow and traditional use in inflammatory renal disease.

5. COMPARATIVE PHARMACOLOGY WITH STANDARD DIURETICS

The pharmacological assessment of *Acacia catechu* in the context of diuretic therapy necessitates a thorough comparison with standard diuretics such as thiazides, loop diuretics, and potassium-sparing agents. This helps in understanding its therapeutic relevance, potential advantages, and limitations.

5.1 Comparison with Thiazide, Loop, and Potassium-Sparing Diuretics

Parameter	**Thiazide Diuretics**	**Loop Diuretics**	**Potassium-Sparing Diuretics**	***Acacia catechu* Extract**
Site of Action	Distal convoluted tubule	Thick ascending loop of Henle	Late distal tubule & collecting duct	Unclear, possibly renal prostaglandins[111]
Mechanism	Na^+/Cl^- symporter inhibition	$Na^+/K^+/2Cl^-$ cotransporter inhibition	Aldosterone antagonism / Na^+ channel blockade	Polyphenol-mediated renal modulation[112]
Potency	Mild to moderate	High	Mild	Moderate (animal model evidence)[112]
Risk of Electrolyte Loss	Yes (K^+ loss common)	Yes (K^+, Na^+, Ca^{2+})	No (K^+ sparing)	Minimal electrolyte disturbance reported [113]
Clinical Use	Hypertension, edema	Heart failure, edema	Used with thiazide/loop to conserve K^+	Yet to be clinically standardized

Thiazides and loop diuretics are well-established in treating conditions like hypertension and heart failure[109,110], whereas potassium-sparing agents are preferred for patients at risk of hypokalemia.[111] Preclinical findings suggest that *Acacia catechu* possesses moderate diuretic efficacy, potentially acting through non-electrolytic mechanisms such as enhancing renal antioxidant capacity and prostaglandin modulation.[112]

5.2 Synergistic or Additive Effects

Recent studies have demonstrated the encouraging synergistic effects of Acacia catechu with low-dose loop diuretics. For instance, there was a statistically significant increase in the urine output and sodium excretion when furosemide and A. catechu extract were co-administered to rats.[113] These combinations may allow the reduction of doses of potent synthetic diuretics, which may limit dose-dependent side-effects, including loss of electrolytes and ototoxicity.

5.3 Limitations in Existing Comparisons

There are a number of limitations in comparing A catechu:

- Non-Standardized: Difference of plant extract contents and dosage between studies.
- Insufficient Clinical Data Most of the evidence is based on animal models without high-level clinical corroboration.
- Short-Term Considerations: The longterm safety, efficacy, pharmacokinetics interactions are presently unknown.

So, although A. catechu has potential therapeutic use, more work should be carried out on standardized extracts and clinical trials on examining the diuretic effect and safety profile of A. catechu.[114]

6. TOXICITY AND SAFETY PROFILE

The safety assessment of Acacia catechu is essential for clinical application as a diuretic. Some plant-based therapies are believed to be safe, however, scientific evidence of their toxicity is necessary.

6.1 Acute and Sub-Chronic Toxicity Studies

High level of safety margin has been reported in acute toxicity studies of AqE and EtE of Acacia catechu. Orally administered up to 2 000 mg/kg between to Wistar rats, deaths or symptoms of morbidity were not observed during a 14-day observation period.[115] Sub-

chronic toxicity evaluations performed between 28 and 90 days demonstrated no changes in haematological, biochemical or histopathological measures, indicating systemic safety of the extract.[116]

6.2 LD_{50} Values and Observed Adverse Effects

The LD_{50} of A. catechu extract has been estimated to be greater than 2,500 mg/kg in rodents, rendering it practically non-toxic according to OECD guidelines.[115] Between the No OEL and lethal TAA dose, low degree of fatal hepatocellular necrosis was induced, while tolerable damage was spent for hepatic congestion of a low grade or temporary variations in serum liver enzymes, which were all reversible on treatment cessation, to claim that such is a case of reversible hepatic stress.[117]

6.3 Long-Term Safety Data

Long-term use data are still scarce. Nevertheless, a 90-day sub chronic toxicity study in rats showed no remarkable toxicological signs even at three times or more than the therapeutic dosage.[118] Moreover, the traditional use of A. catechu in Ayurvedic and Unani medicine for years indicate its historical safety in properly regulated doses.[119]

Additional long-term toxicological investigations, especially in humans are required to confirm its chronic safety profile and to prepare for regulatory approval as a medicinal product.

7. CLINICAL EVIDENCE

Despite promising preclinical findings, clinical validation of *Acacia catechu*'s diuretic effects remains sparse.

7.1 Case Studies and Ethnopharmacological Evidence

Ethnobotanical surveys and traditional uses provide strong evidence for the diuretic activity of A. catechu in Indian, Chinese and South-East Asian traditional systems of medicine. It is employed in Ayurvedic and Siddha medicine for ailments such as fluid retention, urinary tract infections, and renal diseases.[120] But these applications are largely anecdotal, without rigorous scientific evidence to support them.

There are series of cases and some retrospective reviews among practitioners of Ayurveda, which note that empirical treatment with Acacia catechu containing formulations, improved

signs of water retention and oliguria, but these retrospective studies lacks standardized dosing and controls.[121]

7.2 Clinical Trials and Translation Gaps

Currently, there are no published RCTs registered on A. catechu's diuretic efficacy in humans. No standardized extracts, clinically applicable dosing guidelines, or validated biomarkers for kidney function outcomes pose major translation obstacles between preclinical findings and clinical utility.[122]

Furthermore, as clinical studies investigating other pharmacological activities of A. catechu, including antidiabetes or antimicrobial activities, would pave the way for relatively well-designed trials, but they don't have a direct relevance to the diuretic effect.[123] In addition, no pharmacokinetic profiles and human safety assessment of long term consuming limit its clinical application.

Despite all of these promising potential effects, there is a high demand for carefully designed clinical studies to demonstrate the effectiveness, safety and dosage of Acacia catechu in diuretic therapy.

8. LIMITATIONS IN CURRENT RESEARCH

Although A. catechu has the potential to become a herbal diuretic agent, there remains a number of constraints that prevent its use in routine clinical practice.

8.1 Variability of Extracts

The deficiency of standardized extraction methods and phytochemical profiling is one of the major loopholes. Most of the preclinical studies are conducted with crude extracts or hydroalcoholic extracts, and it is rare for the amount of active ingredients including catechins and tannins be determined throughout the study.[124] It is not only an issue for reproducibility but also for dose optimization for clinical translation.[125]

8.2 Low Number of Samples and Methodological Concerns

The majority of in vivo studies reporting diuretic activity are compromised by small sample sizes and lack of proper experimental controls. Other variables often are measured, including electrolyte excretion, urine volume and renal function markers, but with limited characterization of toxicity and lacking comparisons with standard agents.[126] Knäuper et al.,

1999, and other authors) Moreover conflicting observations are obtained from different animal models, doses of extracts, and ways of administration.[127]

8.3 Absence of Human Trials

Although A. catechu has been used traditionally with good results in animal models, no human trials have established the diuretic activity of this plant. The lack of any phase I–III trials however leaves a translational gap, and almost entirely without pharmacokinetic, pharmacodynamic and drug interaction data in human.[128] In the absence of such information, their safety, efficacy, and appropriate dose in humans have yet to be established.

9. CONCLUSION

Acacia catechu is a potential source of a natural product and has shown remarkable diuretic effects in animal models. Experimental evidence suggests that its bioactive compounds—including catechins, tannins, and flavonoids—lead to increase in urinary excretions, alteration of electrolyte excretions, and possible renal protection.[129,130]

However, lack of well-developed studies has hindered the clinical application of A. catechu. The problems are the lack of standardized extraction, methodological differences, and few human trials. Furthermore, most of the studies which have been conducted until now are based on the use of animal models which exhibit limited translational value.[131] Toxicological data reveals high LD_{50} values and low adverse effects, but long-term safety and herb-drug interactions are not sufficiently researched.[132]

To increase clinical relevance and regulatory acceptance, emphasis should be placed on the following in future research:

- Production of Extracts/Standardization QC of Extracts and Formulations using validated results.
- Full preclinical and clinical assessment including efficacy, safety, pharmacokinetics, and dose-response relationships.
- Molecular and genomics studies to discover mechanisms at the cellular and transcriptomic levels.
- Formulation optimizing for better bioavailability and reproducibility.
- Adequately powered human trials for confirmation of therapeutic of the benefits as well as the safety profiles in different populations.[133,134]

In conclusion, Acacia catechu showed considerable promise as a safe and efficient plant-based diuretic, particularly in non-complicated or adjuvant therapeutic applications. Its low toxicity, ethnomedicinal use, and early evidence of activity warrant further studies. A multidisciplinary team should utilize its potentials that cross between pharmacology, botany, and clinical science to unveil its efficacy and to pave the way into existence by the current clinical practice.

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