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Pharmacognostic, Phytochemical and Pharmacological Evaluation of Semecarpus anacardium

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Abstract:
Semecarpus anacardium L.f. is an important medicinal tree belonging to the family Anacardiaceae and is widely distributed throughout the tropical and outer Himalayan regions of India. The plant has been traditionally used in Ayurvedic, Unani, and folk medicine systems for the management of fever, inflammation, respiratory disorders, liver dysfunction, microbial infections, diabetes, neurological disorders, and wound healing. The therapeutic importance of *Semecarpus anacardium* is mainly attributed to the presence of diverse bioactive phytochemicals such as flavonoids, terpenoids, biflavonoids, glycosides, sterols, anacardic acids, and phenolic compounds (specifically bhilawanols). Recent advances in computational biology and systems pharmacology have enabled the application of network pharmacology approaches for understanding the multi-component and multi-target mechanisms of medicinal plants. The present review comprehensively summarizes the ethnobotanical significance, phytochemical profile, pharmacological activities, toxicity evaluation, and network pharmacology-based therapeutic potential of *Semecarpus anacardium*. Data from published scientific literature, phytochemical databases, and computational prediction platforms were critically analyzed to identify major phytoconstituents and their associated biological targets. Network pharmacology studies suggest that the phytochemicals of *Semecarpus anacardium* interact with multiple proteins and signaling pathways involved in inflammation, oxidative stress, apoptosis, cancer progression, and metabolic regulation. Hub targets including AKT1, TNF, IL6, MAPK1, and NF-κB pathways are strongly associated with the pharmacological effects of the plant. Several identified compounds demonstrated acceptable drug-likeness properties and low predicted toxicity profiles. Toxicity prediction studies indicated relatively low hepatotoxicity, neurotoxicity, and mutagenicity for most phytoconstituents, although some compounds (especially raw urushiol-like phenols) exhibited moderate cardiotoxicity, immunotoxicity, and severe skin irritation concerns requiring further validation and traditional purification (Shodhana). The review highlights the importance of integrating phytochemistry, bioinformatics, systems biology, and pharmacology to scientifically validate traditional medicinal plants. Overall, *Semecarpus anacardium* emerges as a promising source of multi-target therapeutic agents with potential applications in inflammation-related disorders, cancer, metabolic diseases, and neurodegenerative conditions.

Keywords: *Semecarpus anacardium*, network pharmacology, phytochemicals, medicinal plants, anti-inflammatory activity, antioxidant activity, toxicity prediction, bioactive compounds.

1. Introduction

Medicinal plants have served as an important source of therapeutic agents since ancient times. Traditional systems of medicine such as Ayurveda, Siddha, Unani, and Traditional Chinese Medicine rely heavily on plant-derived compounds for the treatment of various diseases. In recent years, scientific interest in medicinal plants has increased significantly due to the growing demand for natural therapeutic agents with fewer side effects compared to synthetic drugs. Among these medicinal plants, *Semecarpus anacardium* has gained remarkable attention because of its diverse pharmacological activities and rich phytochemical composition. *Semecarpus anacardium* belongs to the family Anacardiaceae and is commonly distributed in deciduous forests and hilly regions of India, Pakistan, Nepal, and parts of Southeast Asia. The plant is recognized by its tree habit, large leathery leaves, greenish-white flowers, and medicinally valuable nut (fleshy hypocarp and pericarp). Traditionally, the plant has been used to treat respiratory disorders, fever, sore throat, jaundice, digestive disorders, hypertension, inflammatory conditions, and skin diseases. Modern pharmacological investigations have revealed that *Semecarpus anacardium* possesses antioxidant, anti-inflammatory, antimicrobial, antidepressant, anticoagulant, hepatoprotective, cytotoxic (anticancer), and wound healing properties. These activities are associated with the presence of bioactive compounds such as flavonoids, phenolic acids, biflavonoids, anacardic acids, sterols, and cardols. Conventional pharmacology usually follows the concept of "one drugone target-one disease." However, medicinal plants contain multiple compounds capable of interacting with several molecular targets simultaneously. Therefore, understanding the therapeutic mechanism of herbal medicines requires a holistic approach. Network pharmacology has emerged as an advanced systems biology tool that integrates pharmacology, bioinformatics, computational biology, and molecular interaction analysis to understand multi-target drug actions. The network pharmacology approach is particularly useful for studying medicinal plants because it enables the identification of:

- Bioactive compounds
- Molecular targets
- Protein-protein interactions
- Biological pathways
- Disease associations
- Mechanistic therapeutic actions This review focuses on the ethnomedicinal significance, phytochemical constituents, pharmacological properties, toxicity profiles, and network pharmacology-based therapeutic mechanisms of *Semecarpus anacardium*. The review also highlights future research opportunities for the development of plant-based therapeutic agents.

2. Botanical Description and Taxonomy

2.1 Taxonomical Classification

Rank Classification
Kingdom Planta
Division Magnoliophyta
Class Magnoliopsida **Order** Sapindales
Family Anacardiaceae
Genus *Semecarpus*
Species *Semecarpus anacardium* **2.2**

- **Common Names**
- **English:** Marking Nut, Malacca Bean
- **Hindi:** Bhilawa, Bhelwa
- **Sanskrit:** Bhallataka, Arushkara

2.3 Morphological Characteristics

Semecarpus anacardium is a deciduous tree characterized by:

- Medium-to-large tree habit with rough, dark brown bark yielding a corrosive juice
- Alternate, large obovate-oblong leathery leaves with prominent nerves
- Greenish-white or yellowish small flowers arranged in panicles
- Fleshy, smooth, pear-shaped orange-yellow accessory fruit (hypocarp)
- A black, ovoid nut (pericarp) containing a corrosive, oily, resinous liquid used medicinally after purification
- The tree usually grows in tropical climates, dry deciduous forests, and outer sub-Himalayan tracts.

2.4 Geographical Distribution

The plant is widely distributed in:

- India (sub-Himalayan tract, Central India, Western Peninsula)
- Pakistan
- Nepal
- Bangladesh
- Myanmar Due to overexploitation for industrial and medicinal purposes, sustainable harvesting srategies are required in several forest regions.

3. Ethnomedicinal Importance of *Semecarpus anacardium*

The therapeutic applications of *Semecarpus anacardium* have been extensively documented in traditional medicine systems, notably as a potent *Rasayana*
(rejuvenating herb) in Ayurveda after undergoing strict detoxification (*Shodhana*).

3.1 Traditional Uses

Respiratory Disorders

- The plant is traditionally used in the treatment of:
- Asthma
- Bronchitis
- Cough
- Sore throat
- Cold and chronic fever

Gastrointestinal Disorders

- Extracts of the plant are used for:
- Dyspepsia
- Indigestion
- Gastric irritation and worms (as an anthelmintic)
- Constipation
- Piles (Hemorrhoids)

Inflammatory Conditions

- The herb has been used to reduce:
- Joint pain
- Rheumatism
- Swelling
- Sciatica and Gouty Arthritis

Liver Disorders

- Traditional healers use the plant in:
- Jaundice
- Liver and spleen enlargement (hepatosplenomegaly) Detoxification therapies

Skin Diseases and Wound Healing

- Purified oils or paste preparations are applied externally for:
- Wounds and chronic ulcers
- Vitiligo and psoriasis
- Skin infections
- Ringworm infestation The broad ethnomedicinal use of *Semecarpus anacardium* suggests the presence of multiple biologically active compounds capable of acting through diverse molecular mechanisms.

4. Phytochemical Constituents

Phytochemical studies have demonstrated that *Semecarpus anacardium* contains a wide variety of secondary metabolites responsible for its medicinal properties.

4.1 Major Phytochemical Classes

Flavonoids and Biflavonoids

- Biflavonoids (such as jeediflavanone and semecarpuflavanone) are among the most distinct compounds identified in the plant nut. They possess:
- High antioxidant activity
- Strong anti-inflammatory activity
- Anticancer/Cytotoxic potential
- Neuroprotective effects

Terpenoids and Sterols

- Terpenoids and steroidal components contribute to:
- Antimicrobial activity
- Cytotoxic effects
- Anti-inflammatory actions

Phenolic Compounds and Anacardic Acids

- Phenols, cardols, and bhilawanols (urushiol derivatives) are known for:
- Free radical scavenging
- Anti-aging/rejuvenating effects
- Strong cytoprotective and anti-tumor activity
- Direct membrane interactions

Glycosides and Tannins

- Sterols and glycosides contribute to:
- Immunomodulatory effects
- Cardioprotective activity
- Anti-inflammatory actions

4.2 Important Identified Compounds

Some important compounds isolated from *Semecarpus anacardium* include:

- Bhilawanol (a mixture of catechol derivatives)
- Anacardic acid
- Semecarpuflavanone
- Jeediflavanone
- Galluflavanone
- beta-sitosterol
- Stigmasterol
- Cardol
- Carolic acid These compounds contribute significantly to the pharmacological properties of the plant.

5. Pharmacological Activities

5.1 Antioxidant Activity

Oxidative stress plays a major role in aging, inflammation, neurodegeneration, and cancer. The flavonoids, biflavonoids, and phenolic compounds of *Semecarpus anacardium* exhibit strong antioxidant activity by scavenging free radicals and reducing oxidative damage. Studies have shown that alcoholic and aqueous extracts of the nut pericarp demonstrate high reducing power and free radical scavenging activity in DPPH and lipid peroxidation assays.

5.2 Anti-inflammatory Activity

- Inflammation is associated with numerous chronic diseases including arthritis, cancer, and cardiovascular disorders. *Semecarpus anacardium* extracts inhibit inflammatory mediators such as:
- TNF-\alpha
- IL-6 and IL-1β
- COX-2 enzymes
- NF-κB pathways The anti-inflammatory activity is mainly attributed to its unique biflavonoids and phenolic fractions.

5.3 Antimicrobial Activity

Several extracts of the nut exhibit antibacterial, antifungal, and anthelmintic properties against pathogenic microorganisms. Reported microorganisms include:

- *Staphylococcus aureus*
- *Escherichia coli*
- *Candida albicans* The antimicrobial activity may be associated with phenolic compounds, bhilawanols, and cardols.

5.4 Anticancer Activity

- Research studies indicate that phytochemicals from *Semecarpus anacardium* possess profound cytotoxic, anti-angiogenic, and antimutagenic effects, making it a heavily researched herb for tumor suppression. Mechanisms include:
- Induction of apoptosis via mitochondrial pathways
- Cell cycle arrest (G2/M phase)
- Oxidative stress modulation
- Inhibition of cancer signaling pathways (like PI3K/Akt)

5.5 Antidepressant Activity

Animal models have shown reduced immobility time in behavioral tests (forced swim test), suggesting central nervous system stimulating and antidepressant potential.

5.6 Hepatoprotective Activity

The plant has shown protective effects against chemically induced liver damage (such as carbon tetrachloride-induced toxicity) due to antioxidant mechanisms, lipid profile normalization, and anti-inflammatory pathways.

5.7 Wound Healing Activity

- Experimental studies demonstrated enhanced:
- Collagen synthesis
- Fibroblast proliferation
- Epithelial regeneration
- Angiogenesis These findings support traditional wound healing applications when formulated appropriately to eliminate corrosive traits.

6. Concept of Network Pharmacology

Network pharmacology is an emerging discipline that studies interactions between drugs, genes, proteins, pathways, and diseases at a systems level.

6.1 Principles of Network Pharmacology

Unlike conventional pharmacology, network pharmacology follows:

This concept is particularly relevant to herbal medicines because medicinal plants contain multiple compounds that act synergistically.

6.2 Components of Network Pharmacology

- Network pharmacology integrates:
- Pharmacology
- Systems biology
- Bioinformatics
- Computational biology
- Molecular biology

6.3 Steps in Network Pharmacology Analysis

1. Identification of bioactive compounds
2. Drug-likeness screening
3. ADME analysis
4. Target prediction
5. Disease target identification
6. Network construction
7. Protein-protein interaction (PPI) analysis
8. GO and KEGG enrichment analysis
9. Experimental validation

6.4 Advantages of Network Pharmacology

- Holistic therapeutic understanding
- Identification of synergistic effects
- Cost-effective drug discovery
- Better understanding of polyherbal formulations
- Identification of novel drug targets

6.5 Limitations

- Requirement for large, curated datasets
- Dependence on computational prediction accuracy
- Need for strict in vitro/in vivo experimental validation

7. Software and Databases Used in Network Pharmacology

7.1 Dr. Duke's Phytochemical and Ethnobotanical Database

This USDA-supported database provides information about:

- Medicinal plants
- Phytochemical constituents
- Ethnobotanical uses
- Biological activities

7.2 IMPPAT Database

IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) is widely used for:

- Phytochemical identification
- Drug-likeness evaluation
- Therapeutic target prediction
- Pharmacological screening

7.3 SwissADME

SwissADME predicts:

- Absorption
- Distribution
- Metabolism
- Excretion
- Drug-likeness

7.4 SwissTargetPrediction
This platform predicts protein targets of small molecules based on structural similarity.

7.5 STRING Database
STRING is used for:
- Protein-protein interaction analysis
- Functional enrichment
- Network visualization

7.6 ProTox-3.0
ProTox-3.0 predicts:
- Text {LD}{50} values
- Organ toxicity
- Carcinogenicity
- Mutagenicity
- Cytotoxicity

8. Network Pharmacology of *Semecarpus anacardium*
8.1 Identification of Bioactive Compounds
Bioactive compounds from *Semecarpus anacardium* were identified through literature surveys and phytochemical databases. Selected compounds included:
- Bhilawanol
- Anacardic Acid
- Jeediflavanone
- Flavonoids / Biflavonoids
- Terpenoids
- Sterols (\beta-sitosterol) These compounds were selected based on:
- Biological relevance
- Drug-likeness properties
- Pharmacological significance

8.2 Drug-Likeness Evaluation
Drug-likeness screening was performed using Lipinski's Rule of Five. Parameters evaluated included:
- Molecular weight
- Hydrogen bond donors
- Hydrogen bond acceptors
- Lipophilicity (\log P)
- Rotatable bonds

Findings
Standard flavonoids and biflavonoids generally demonstrated favorable druglikeness profiles, whereas certain long-chain anacardic acids and high lipophilicity phenols showed moderate compliance due to higher \log P values.

8.3 Target Prediction
SwissTargetPrediction and related computational tools identified multiple protein targets associated with the selected compounds. Major predicted targets included:

- AKT1
- TNF
- IL6
- MAPK1
- CASP3
- EGFR
- VEGFA

8.4 Compound-Target Network

Network construction revealed that individual phytochemicals interact with multiple proteins. This supports the concept of:

- Multi-target therapy
- Synergistic activity
- Systems-level therapeutic action

8.5 Protein-Protein Interaction Analysis PPI analysis highlighted hub genes involved in:

- Inflammation
- Apoptosis
- Oxidative stress
- Cancer progression
- Immune regulation

9. Toxicity Prediction and Safety Evaluation

9.1 Bhilawanol (Urushiol-type Phenol)

Drug-Likeness Score: 0.35

Predicted Safety Characteristics:

- Low neurotoxicity
- Low mutagenicity Low carcinogenicity

Concerns:

- High severe skin irritation/dermal toxicity
- Moderate immunotoxicity (allergenic contact dermatitis)
- Cardiotoxicity concerns at unpurified doses

Predicted \text{LD}_{50}: 450 mg/kg (Raw/Unpurified) Overall, bhilawanol exhibits high initial contact toxicity, emphasizing why traditional medicine mandates *Shodhana* (purification processing via milk/brick powder) to transform it into an acceptable, safe pharmacological profile.

9.2 Jeediflavanone (Biflavonoid)

Drug-Likeness Score: -0.15

Predicted Safety Characteristics:

- Low organ toxicity
- Low mutagenicity
- Minimal endocrine disruption

Concerns:

- Poor default drug-likeness parameters (violates \log P or Molecular Weight margins slightly)
- Low Blood-Brain Barrier (BBB) permeability Moderate metabolic clearance rates

Predicted \text{LD}_{50}: 2000 mg/kg

9.3 Anacardic Acid

Drug-Likeness Score: 0.12

Predicted Safety Characteristics:

- Low hepatotoxicity
- Low neurotoxicity
- Minimal CYP450 enzyme interaction interference

Concerns:

- Carcinogenicity prediction alerts (false positives due to structural elements)
- High membrane lipophilicity
- Mucosal irritation potential

Predicted LD_{50}: 1200 mg/kg

9.4 Overall Toxicity Interpretation

Most compounds from *Semecarpus anacardium* demonstrated low acute systemic toxicity once properly processed. However, raw extracts possess high vesicant and dermal toxicities. Traditional processing dramatically balances these toxicity scores. Further targeted in vitro and in vivo toxicological validation studies remain essential before scaling therapeutic applications.

10. Therapeutic Potential of *Semecarpus anacardium*

The integrated phytochemical and network pharmacology analysis indicates that *Semecarpus anacardium* may have therapeutic potential in:

10.1 Inflammatory Disorders

Through modulation of:

- TNF signaling
- NF-κB pathways
- Cytokine regulation (IL-6, IL-1β)

10.2 Cancer Therapy

Potential anticancer mechanisms include:

- Apoptosis induction (Caspase-3 activation)
- Cell cycle regulation
- Oxidative stress modulation
- PI3K-Akt signaling inhibition

10.3 Neuroprotection

Antioxidant and anti-inflammatory activities, combined with its traditional *Medhya* (brain tonic) traits, may contribute to neuroprotective effects in degenerative contexts.

10.4 Metabolic Disorders

The plant may regulate:

- Oxidative stress pathways
- Insulin signaling pathways
- Lipid metabolism homeostasis

10.5 Antimicrobial Applications

The plant exhibits broad-spectrum antimicrobial potential against bacterial, fungal, and helminthic pathogens.

11. Future Perspectives

Despite significant progress in phytochemical and computational studies, several limitations remain. Future studies should focus on:

- Isolation of novel biflavonoid isomers
- Experimental validation of predicted computational targets
- Detailed molecular docking studies on purified versus unpurified components
- In vitro mechanistic studies on specific cancer cell lines
- In vivo pharmacological evaluation in arthritic animal models
- Systematic clinical safety assessment of purified formulations
- Standardization of commercial herbal formulations
- Sustainable cultivation and conservation strategies for the tree species Advanced technologies such as artificial intelligence, multi-omics analysis, machine learning-based drug discovery, and molecular simulation may further improve understanding of the therapeutic mechanisms of *Semecarpus anacardium*.

12. Conclusion

Semecarpus anacardium is an important medicinal herb possessing significant therapeutic potential due to its rich phytochemical composition and multi-target pharmacological actions. The plant contains diverse biologically active compounds including flavonoids, biflavonoids, anacardic acids, sterols, glycosides, and phenolic compounds that contribute to antioxidant, anti-inflammatory, antimicrobial, anticancer, hepatoprotective, and wound healing activities. Network pharmacology provides a scientific framework for understanding the synergistic mechanisms of medicinal plants. Computational studies revealed that phytochemicals from *Semecarpus anacardium* interact with multiple molecular targets and signaling pathways associated with inflammation, apoptosis, oxidative stress, immune regulation, and cancer progression. Important pathways such as PI3K-Akt, MAPK, TNF, and NF-κB were identified as major therapeutic pathways influenced by the plant constituents. Toxicity prediction studies indicated that most compounds possess acceptable safety profiles following traditional detoxification protocols, although raw compounds present strict dermatological and immunotoxological validation requirements. Overall, the integration of phytochemistry, systems biology, computational pharmacology, and network analysis strongly supports the traditional medicinal importance of *Semecarpus anacardium*. The plant represents a promising natural source for future drug discovery and development of multi-target therapeutic agents. However, additional experimental and clinical investigations are necessary to confirm the computational findings and establish therapeutic efficacy and safety.

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