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A COMPREHENSIVE REVIEW ON *SWIETENIA MACROPHYLLA* KING: CHEMICAL CONSTITUENTS, PHARMACOLOGICAL ACTIVITIES, TOXICITY AND SAFETY ANALYSIS

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ABSTRACT: *Swietenia macrophylla* King, widely recognized as big-leaf mahogany or sky fruit, is a highly prized tropical hardwood species belonging to the Meliaceae family traditionally used for managing diabetes, hypertension, inflammation, and various other ailments. Despite growing research interest, existing studies remain fragmented, largely limited to in vitro and acute animal models, with significant variability in extract preparation and scarce standardized clinical data. This review systematically compiles, organizes, and critically analyzes the botanical description, taxonomic classification, ethnomedicinal uses, major bioactive compounds, broad spectrum of pharmacological activities, toxicity and safety analysis of *Swietenia macrophylla*. The plant is notably high in limonoids like swietenine, swietenolide, and various derivatives, which contribute to its significant pharmacological potential, including antidiabetic, anticancer, anti-inflammatory, antimicrobial, antioxidant, anti-aging, wound healing, and other effects. Pharmacological studies have demonstrated significant bioactivities through multiple mechanisms, notably modulation of Nrf2, NLRP3 inflammasome, PPARγ activation and related pathways. The present work offers a consolidated and up-to-date framework that addresses research gaps, variability in extract efficacy, and the need for further clinical validation, thereby facilitating evidence-based development and standardization of *Swietenia macrophylla* as a promising source of multi-target therapeutic agents.

INTRODUCTION: *Swietenia macrophylla* stands as a prominent tall hardwood tree indigenous to the tropical regions of Central and South America [1, 2]. It has been extensively introduced and cultivated in various parts of Southeast Asia, including Bangladesh, India, Indonesia, Malaysia and southern China for its valuable timber, reforestation efforts, and medicinal properties [3, 4].

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The fruits, popularly known as "sky fruit" due to their upward orientation, hold particular importance in traditional medicine for managing diabetes mellitus, hypertension, inflammation, and various other ailments [1, 5, 6].

In the context of increasing global demand for natural, multi-target therapeutic agents in the face of rising metabolic and inflammatory disorders, a systematic compilation of its phytochemicals and pharmacological activities is critically needed to bridge fragmented research and unlock its full therapeutic potential. Previous studies have documented the botanical features, traditional uses, and bioactivities of *Swietenia macrophylla*.

Milestone review papers successfully mapped its complex, limonoid-rich chemistry and broad pharmacological spectrum [2, 7]. Recent works have focused on specific aspects such as neuroprotective potential against Alzheimer's disease [3], anti-aging and wound healing potential [8, 9], antidiabetic effects of seed extracts [6] and swietenine [10], and nanoparticle-enhanced antimicrobial [11] and anticancer activities [12]. While these studies have advanced understanding of individual bioactivities, most research remains limited to *in-vitro* and acute animal models, with variability in extract preparation and efficacy across plant parts, and standardized clinical data still scarce. These limitations justify the need for a current and comprehensive review that brings together the available knowledge on *Swietenia macrophylla*. In this review, we systematically synthesized data from peer-reviewed literature. This approach provides a more integrated and up-to-date resource than previous fragmented or narrowly focused reviews. The present work contributes by offering a consolidated framework that highlights the major bioactive constituents listed in **Table 1**, underlying mechanisms of various pharmacological activities, the toxicity & safety analysis of *Swietenia macrophylla*. Expected outcomes include facilitating evidence-based development of phytopharmaceuticals, guiding standardization efforts, and promoting the sustainable utilization of this valuable medicinal timber species.

Botanical Description: *Swietenia macrophylla* is a tropical, tall, evergreen to occasionally semi-deciduous or deciduous hardwood timber tree belonging to the Meliaceae family [4, 6, 7, 13]. The species typically attains a height of 30-60m, occasionally exceeding 50m [2, 5, 7, 14], with a girth of 3-4m [2, 7]. It features a straight cylindrical trunk measuring 100-200 cm in diameter at breast height [5, 15] and an umbrella-shaped crown [7, 13]. The outer bark is scaly, thick, and deeply furrowed, varies from brownish-grey to reddish-brown [5], whereas the inner bark appears pinkish-red to red-brown [5, 16]. The paripinnate leaves measure 12-45 cm long and consist of 3-6 pairs of asymmetrical, lanceolate or ovate leaflets that are dark green and shiny when mature [5, 17]. Small, unisexual, yellow-cream colored flowers are produced in large branched inflorescences [5]. The fruit is a woody ovoid capsule, 11.6-38.7 cm long, light grey to brown in color, and features 4-5 valves [5, 13]. It opens to release 22-71 samaroid (winged) seeds per fruit [5, 13]. The seeds are chestnut to reddish-brown, typically 7-12 cm long (maximum15 cm) and 2-2.5 cm wide, featuring a hard outer shell, a distinctive odor, and a bitter taste [13, 18, 19]. The fruits are widely recognized as "sky fruit" due to their characteristic upward growth toward the sky [5, 7, 12, 20, 21]. The species is indigenous to the tropical regions of the Americas, with its primary distribution in Central and South America, including Bolivia and Mexico [4, 7, 22]. It has been widely introduced and cultivated in Southeast Asia, Bangladesh, India, southern China, and other tropical or subtropical areas [7, 23] for timber, reforestation, and medicinal purposes [5, 23].

Taxonomic Classification: *Swietenia macrophylla* is taxonomically classified under the Kingdom of Plantae, Phylum of Tracheophyta, Class of Magnoliopsida, Order of Sapindales, Family of Meliaceae, and Genus of Swietenia [7, 22]. It belongs to the subfamily Swietenoideae within the Meliaceae family [4, 17]. The genus *Swietenia* consists of three primary species- *Swietenia macrophylla*, *Swietenia mahagoni*, and *Swietenia humilis* along with two natural hybrids, including *Swietenia x aubrevilleana* [24, 25].

Synonyms: The accepted synonyms include *Swietenia macrophylla* King var. *marabaensis*, *Swietenia krukovii* Gleason, *Swietenia candollei* Pittier, *Swietenia tessmannii* Harms and *Swietenia belizensis* Lundell [4, 7]. The word "macrophylla" derives from the Greek terms makros (big) and phyllon (leaf), reflecting its exceptionally large leaves [4, 6].

Vernacular Names: In English, it is commonly called big-leaf mahogany, Honduran mahogany, sky fruit, genuine mahogany, large-leaved mahogany, broad-leaved mahogany, Brazilian mahogany, tropical American mahogany, or bastard mahogany [7, 19, 22]. Regional names include "pokok buah tunjuk langit", "tunjuklangit", or "Cheria mahogany" in Malaysia [4, 6, 26], "Mahoni" in Indonesia [7], "Baramahauni", "Bara Mahauni", "Bara-mahagony", or "Mahagni" in Bangladesh [7, 27], "xiangtianguo" in China [7, 28], and "tettankotai" in Tamil [7, 26]. International names include West Indian mahogany (England), Colombian mahogany

tree, and Brazilian mahogany tree; Echtesmahagoni (Germany); Mogano (Italy); Mogno (Portugal); Mahokkani-bailek or Mahokkani (Thailand); Mahok/Mahonie (Netherlands); and Acajou du Honduras or Acajou du Venezuela (France) [4, 7]. In Myanmar it is commonly known as Mahogany while in Mexico it is locally known as "caoba" [29, 30]. These names consistently reflect the species economic importance as a high-quality timber tree and the distinctive upward orientation of its fruits, popularly known as "sky fruit" [4, 7].

Traditional / Ethnomedicinal Use: The seeds, commonly known as mahogany seeds, are the most extensively used part in traditional medicine. In Malaysia and Indonesia, they are primarily employed for managing diabetes mellitus [13, 23], hypertension [31, 32], and pain relief [20, 33]. They are typically consumed raw (chewed or swallowed), as powder, or as decoctions [20, 26]. In Indonesia, the seeds are also traditionally used for malaria, diarrhea, and hypertension [7, 13, 34]. In India, the plant is used for diabetes, diarrhea, skin diseases, and wounds [35, 36]. In Bolivian Amazonian communities (Tacana), the seeds have been used as an abortifacient and for treating leishmaniasis [1, 7]. The fruits, commonly referred to as "sky fruits," are traditionally used in Malaysia and the Solomon Islands for diabetes, hypertension, and as a natural painkiller [37, 38, 39, 40]. Fruit preparations are also valued for improving blood circulation and skin condition [37, 41, 42]. The bark is traditionally employed for wounds as an astringent, as an antipyretic, febrifuge, and tonic [7, 30]. It is also occasionally employed for tanning leather due to its high tannin content and red pigmentation [7, 30, 43]. Leaf decoctions or infusions have been used for diarrhea, fevers, colds, catarrh, and nerve disorders [30]. Across Asia and other regions, *S. macrophylla* has been traditionally valued for its antimicrobial, antioxidant, anti-inflammatory, antidiabetic, anticancer, antitumor, and antimutagenic properties [13]. It has also been used to manage malaria, anemia, dysentery, cough, fever, chest pain, intestinal parasitism, ulcers, eczema, and rheumatism [44, 45]. The plant forms an important component of traditional jamu preparations in Indonesia and other Southeast Asian folk systems [43, 46].

Chemical Constituents: *Swietenia macrophylla* is renowned for its rich array of secondary metabolites, primarily limonoids (tetranortriterpenoids) characterized by a furan ring at the C-17 position, along with extensive oxidation and skeletal rearrangements, dominate the phytochemical profile across seeds, fruits, leaves, bark, roots and terminal shoots [3, 23, 47]. Seeds are abundant in swietenine ($C_{32}H_{40}O_9$), swietenolide ($C_{27}H_{34}O_8$), 3-O-tigloylswietenolide, khayasin T, 3,6-O,O-diacetylswietenolide, and related derivatives, alongside steroids such as stigmasterol and β-sitosterol [21, 48]. Fruits yield mexicanolide-type limonoids, while bark contains mexicanolide-type and andirobin-type limonoids (e.g., swietemicrolides A-D), phenolics (catechin, epicatechin), and the first reported grandifotanecore limonoid in the genus [40, 49]. Leaves and shoots feature phragmalin-type limonoids and sesquiterpenes like germacrene D [15, 50].

Qualitative screening of seeds indicates alkaloids, phenolics, flavonoids, terpenoids, steroids, and tannins, with high total phenolic (78.409% GAE) and flavonoid (96.167% RE) contents [51]. Over 160 limonoids have been identified from the Swietenia genus, with more than 100 reported from *Swietenia macrophylla*, including fatty acids, polyacetylenes in roots, and coumarins like scopoletin [2, 52, 53]. Over the past decade, there has been growing research interest and awareness regarding *Swietenia macrophylla*. The chemistry of its various plant parts has undergone extensive investigation over recent decades, resulting in the discovery of numerous isolated pure compounds possessing a broad spectrum of pharmacological properties. Among these, the major pharmacologically active compounds are presented in **Table 1** and some chemical structures in **Fig. 1.**

TABLE 1: PHARMACOLOGICALLY ACTIVE MAJOR CHEMICAL CONSTITUENTS ISOLATED FROM *SWIETENIA MACROPHYLLA*

Chemical Constituents	Chemical Class	References
Swietenine	Limonoid	6, 41, 54
Swietenolide	Limonoid	21, 55, 56
3,6-O,O-Diacetylswietenolide	Limonoid	6
Khayasin T	Limonoid	41

6-Deoxyswietenine (Febrifugin)	Limonoid	41
Proceranolide	Limonoid	41
β-Sitosterol	Sterol	51,57
Stigmasterol	Sterol	58
Fucosterol	Sterol	51
3β-Hydroxystigmast-5-en-7-one	Sterol	58
β-Sitostenone (β-cytostenone)	Sterol	58
Germacrene A	Sesquiterpene	3, 58
Germacrene D	Sesquiterpene	3, 58
β-Amyrin	Triterpenoid	59
Olean-12-ene	Triterpenoid	44
2,4-Di-tert-butylphenol	Phenolic	44
Swieteliacate B	Limonoid	26
3β,6-Dihydroxydihydrocarapin	Limonoid	34
7-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one	Flavonoid	34
3',4',7-Trihydroxyisoflavanone (THF)	Isoflavanone	60
Alternariol 9-methyl ether (AME)	Polyketide	60
Catechin	Flavonoid	40
Epicatechin	Flavonoid	40
Chlorogenic acid	Phenolic acid	4
Gallocatechin	Flavonoid	4
Saponins	Saponins	61

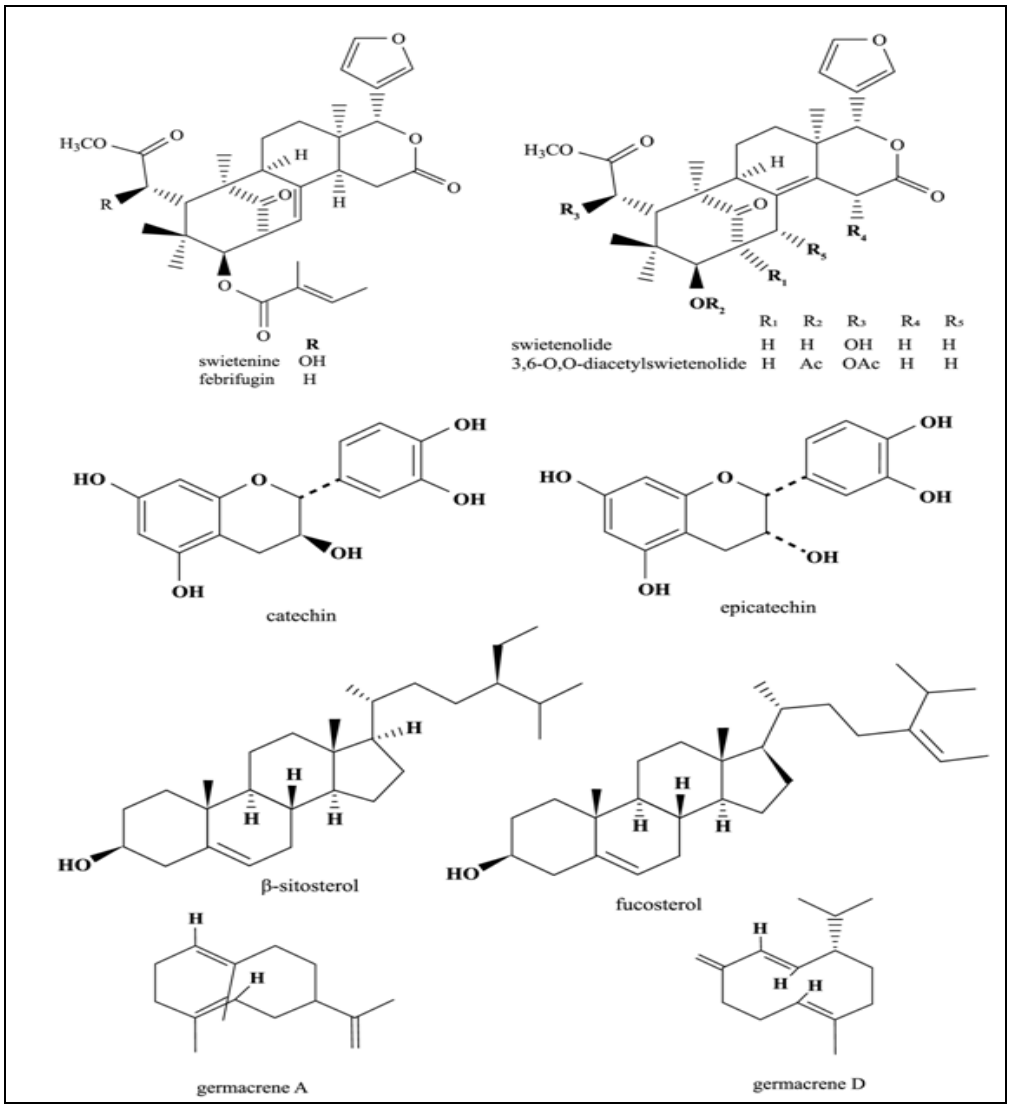

FIG. 1: CHEMICAL STRUCTURES OF SOME MAJOR CHEMICAL CONSTITUENTS ISOLATED FROM *S. MACROPHYLLA*

Pharmacological Activities of *S. macrophylla:*

Anti-diabetic/ Anti-hyperglycemic Activity: The standardized ethanolic seed extract (SMEE) produced significant anti-hyperglycaemic effects in Goto-Kakizaki rats (a non-obese T2DM model closely resembling human disease), reducing fasting blood glucose at 500 mg/kg with markedly improved oral glucose tolerance and minimal weight gain, while limonoids like swietenine and 3,6-O,O-diacetyl swietenolide enhanced glucose utilization, activated PPARγ, inhibited superoxide and nitric oxide production, and promoted GLUT4 translocation [6].

Complementary evidence from hydroalcoholic leaf extract (HASM) exhibited strong *in-vitro* inhibitory activity against α-glucosidase (IC50 of 107.11 µg/mL) and α-amylase (IC50 of 75.69 µg/mL) [27]. In STZ nicotinamide diabetic rats, oral HASM (for 21 days, 200- 400 mg/kg/day) dose-dependently lowered the fasting glucose (to 179-158 mg/dl vs. 327 mg/dl in controls), improved glucose tolerance, restored body weight and lipid profiles, normalized liver/kidney markers, reduced LDH, and promoted pancreatic β-cell regeneration and islet restoration, notably at 400 mg/kg [27]. In alloxan-induced diabetic rats, bark extracts also showed clear hypoglycaemic activity [62], while other extracts demonstrated multi-mechanistic hypoglycaemic effects in neonatal diabetic models via glucokinase activation, β-cell regeneration, and reduced renal glucose excretion, favouring insulin centric pathways over glucosuria [46].

Endophytic fungi associated with the seeds further contribute to the plant's anti-diabetic potential, ethyl acetate extracts from *S. macrophylla* seeds isolated *Alternariaalternata* BRN05 displayed potent α-glucosidase inhibition, with quarter strength medium extract (EQS) achieving an IC50 values of 0.01482 ± 1.809 mg/mL substantially superior to full strength extract and the standard acarbose (IC50 values of 0.494 ± 0.009 mg/mL) [60]. UHPLC-ESI-QTOF-MS identified 19-20 metabolites where molecular docking and MD simulations confirmed superior binding affinities for several compounds, notably, alternariol 9-methyl ether (AME; -7 kcal/mol) and 3', 4', 7-trihydroxyisoflavanone (THF; -7.5 kcal/mol) position THF as a promising lead compound for novel α-glucosidase inhibitors that may involve fewer gastrointestinal side effects [60]. Swietenine, the predominant limonoid in *S. macrophylla* seeds has been repeatedly validated as a central bioactive principle [63]. Swietenine improved cardiac function in diabetic complications in high glucose-stimulated H9C2 cardiomyocytes and db/db mice [63]. It also exerted dose-dependent hypoglycaemic activity in neonatal STZ type 2 diabetic rats (25-50 mg/kg), comparable to glibenclamide [54], and produced synergistic glucose lowering effects with metformin in STZ induced models, restoring normoglycaemia where either agent alone was insufficient [64].

Other limonoids (e.g., compounds 1, 2, 3) demonstrated concentration-dependent α-amylase inhibition [47], while swietenine, swietenolide, khayasin T, 6-deoxyswietenine, and proceraolide enhanced glucose uptake in insulin-resistant HepG2 cells, upregulated PPARγ and PDX-1 expression, protected β-cells against oxidative stress, and boosted insulin secretion [21, 41]. Seed extracts additionally target the hexosamine biosynthetic pathway by inhibiting glutamine:fructose-6-phosphate amidotransferase (GFAT), with swietenine, swietenolide, β-sitosterol, and fucosterol showing strong binding affinities (-6.58 to -7.71 kcal/mol) [51]. In STZ-induced rats, ethanolic seed extracts (50-300 mg/kg) consistently reduced fasting blood glucose, elevated serum insulin, liver glycogen, and haemoglobin, and lowered glycosylated haemoglobin [2, 36, 65, 66] and restored carbohydrate metabolism by increasing glucokinase/hexokinase activity while suppressing gluconeogenic enzymes like fructose-1,6-bisphosphatase and glucose-6-phosphatase [36, 65].

The 100 mg/kg dose often produced near normalisation with histological evidence of β-cell preservation [36, 65]. Methanolic extracts lowered cholesterol and triglycerides [4], while petroleum ether extracts enhanced peripheral glucose utilization via insulin mimetic effects, increased muscle glucose uptake, and reduced serum lipids [15] without significant intestinal α-glucosidase inhibition [57]. Aqueous extracts reduced fasting glucose and improved muscle glucose utilization [26], and nanoparticle formulations of ethanol extract further amplified efficacy at 300 mg/kg [66]. These extracts also inhibited α-amylase (ethanol extract,

IC50 value of 0.069 mg/mL, comparable to acarbose) [30] and α-glucosidase, delayed postprandial hyperglycaemia [67], and upregulated PPARγ, adiponectin, adipsin, and GLUT4 [32, 61] while downregulating PEPCK and RBP4 [7, 68]. Saponins derived from the seeds improved insulin sensitivity and reduced HOMA-IR [61], while specific alkaloids and flavonoids isolated from seeds stimulated insulin release and demonstrated significant hypoglycemic activity [69, 70]. Saponins are also recognized for their overall hypoglycemic properties in blood sugar management [17]. One study noted no significant α-glucosidase inhibition by certain seed compounds under optimized assay conditions [71], highlighting the need for standardized methodologies. Recent studies in human relevant T2DM models [6] and the identification of high potency fungal metabolites [60] further strengthen its therapeutic promise.

Anti-hyperlipidemic Activity: Swietenine significantly lowered elevated serum total cholesterol from (62.33 ± 6.22) mg/dl to (49.00 ± 5.06) mg/dl and triglycerides from (158.7 ± 7.94) mg/dl to (81.83 ± 3.55) mg/dl, supporting its role in improving diabetic dyslipidemia [10]. In type 2 diabetic rat models, both swietenine and methanol seed extract effectively lowered serum cholesterol and triglyceride levels and restored liver glycogen content to normal values [2, 54], with dose-dependent reductions in triglycerides (10.41-45.41%) and cholesterol (18.56-29.12%) observed for methanolic seed extract (300 mg/kg) and swietenine (25-50 mg/kg) respectively [7]. In a dose-dependent manner, treatment with swietenine increased HDL levels, and potentiated the lipid regulating effects of metformin [64]. Similarly, seed alkaloid extracts enhanced lipid profiles by markedly lowering total triglycerides, LDL, and cholesterol while elevating HDL levels by up to 53.7%, although excessive doses were noted to potentially induce pro-oxidant effects that could reverse triglyceride reduction [61, 70]. Aqueous seed extract markedly reduced plasma levels of total triglycerides, cholesterol, and LDL cholesterol in diabetic rats [72]. Likewise, alcoholic seed extract (50-200 mg/kg) over 45 days markedly reduced total cholesterol, triglycerides, LDL, and VLDL in plasma, liver, and kidney tissues while elevating HDL, with the 100 mg/kg dose showing the most pronounced normalizing effect [65].

The leaf extract of *Swietenia macrophylla* (SLE) demonstrated hepatoprotective potential against MASLD by significantly reducing lipid accumulation in primary mouse hepatocytes where at 40 μg/mL, SLE suppressed protein expression and SREBP-1c mRNA by 48.07% and 60.69% respectively [73]. Its active limonoid constituent, senegalension B, showed comparable inhibition (34.34% protein and 55.42% mRNA) and suppressed SREBP-1c promoter activity where molecular docking and dynamics simulations indicated direct interaction of senegalension B with SREBP-1c [73].

Antihypertensive Activity: Cycloartane triterpenoids isolated from *Swietenia macrophylla* leaves exhibit potent ACE inhibitory activity, with the most active compound displaying mixed-type inhibition (IC50 = 57.7 ± 6.07 μM) by competitively occupying the enzyme's active site through hydrogen bonds along with hydrophobic interactions as potential antihypertensive agents [74]. Ethanol and 50% ethanolic seed extracts demonstrate significant vasorelaxant and antihypertensive effects in isolated rat aortas and hypertensive animal models where these extracts induce potent, dose-dependent vasorelaxation (EC_{50}= 0.007 ± 0.002 mg/mL for the 50% ethanolic extract) through multi targeted pathways, primarily involving blockade of voltage operated calcium channels, opening of multiple potassium channels (K_{Ca}, K_V, K_{ir}, K_{ATP}), IP3 receptor inhibition, and activation of endothelium dependent and independent mechanisms including the NO/sGC/cGMP pathway and β_2-adrenergic receptors [75]. In addition, chronic oral administration also significantly lowers both systolic and diastolic blood pressure [75]. Furthermore, seed extracts may contribute to hypertension management by modulating carbonic anhydrase (CA) activity, given the association of elevated CA levels with high triglycerides and malondialdehyde in hypertensive conditions [72].

Cardioprotective Activity: *Swietenia macrophylla* demonstrates substantial cardioprotective potential, particularly in diabetic cardiomyopathy (DCM), where swietenine alleviates cardiomyocyte inflammation, attenuates myocardial hypertrophy, and reduces fibrosis by upregulating NAMPT and SIRT1 protein levels, thereby ameliorating cardiac

dysfunction and safeguarding heart tissue from high glucose induced damage [63]. In STZ induced diabetic rat models, *S. macrophylla* extract nanoparticles exert dose-dependent cardioprotection by specifically lowering serum cardiac injury markers such as lactate dehydrogenase (LDH) and creatine kinase myocardial band (CK-MB), effectively preventing cardiac tissue necrosis and preserving normal cellular structure [76].

Ether seed extract and its 28 tetranortriterpenoids (structurally related to swietenine/swietenolide) further contribute by strong inhibition of platelet aggregation induced by PAF (platelet-activating factor) was observed both in vitro and in vivo [4]. These benefits are reinforced through attenuation of apoptosis in cardiac related cell models and alignment with traditional use in hypertension management, achieved by downregulation of the pro-apoptotic protein Bax together with upregulation of the anti-apoptotic protein Bcl-2 inhibits the mitochondrial apoptosis pathway, thereby maintaining cellular integrity against oxidative insult [21]. Constituent notably swietenine, additionally regulate lipid profiles by lowering LDL, triglycerides, and cholesterol while raising HDL, conferring cardioprotective advantages in diabetes where sustained hyperglycemia drives long term cardiovascular compromise [64].

Swietenine specifically attenuates cardiac pathological remodeling by reducing myocardial cell enlargement and suppressing hypertrophic biomarkers like brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) through repression of Akt and CREB phosphorylation signaling pathways, thereby intervening early to prevent heart failure progression [77]. By lowering the atherogenic index of plasma (AIP), which is defined as log (TG/HDL), the seeds enhance this activity and leveraging antioxidant mechanisms to inhibit LDL oxidation, which delays atherosclerosis and ischemic heart disease [61]. Fruits of the species support improved blood circulation and treatment of hypertension related conditions, with limonoids such as swietemacrolide C and swieteliacate D exhibiting protective effects against apoptosis induced by H_2O_2 in human umbilical vein endothelial cells (HUVECs) avert vascular dysfunction and heart failure [42].

The vasorelaxant and blood pressure lowering actions of the 50% ethanolic seed extract underpin broader cardiovascular protection through modulation of multiple ion channel and signaling pathways [75].

Renoprotective Activity: *Swietenia macrophylla* effectively alleviates tubular injury through enhanced mitophagy, which restores mitochondrial function and reduces ROS production *via* activation of the PINK1/PHB2/Acsf2 signaling pathway, as confirmed by Mdivi-1 and siRNA studies [78]. *S. macrophylla* extract provides renoprotection by downregulating SGLT2 expression, preserving brush borders, reducing inflammation, epithelial thinning, and intraluminal casts, while its saponin content suppresses TGF-β1 and fibronectin to limit fibrosis [46]. Natural swietenine further reduces diabetic nephropathy through inhibition of NF-κB signaling and NLRP3 inflammasome in mesangial cells by improving renal parameters such as uric acid, urea nitrogen, creatinine, and protein excretion [79].

Antioxidant Activity: *Swietenia macrophylla* bark extract exhibits strong DPPH radical scavenging, with water extracts displaying the highest overall capacity (27.22 µmol TE/g) despite lower phenolic and flavonoid contents than ethanol extracts which suggests that water soluble compounds, including dihydropyridine alkaloids, are major contributors [62]. Further differentiation within the bark reveals that the outer layer outperforms the inner bark owing to elevated total phenolic content, particularly catechol, whose ortho-hydroxyl configuration facilitates efficient ROS neutralization, a strong linear correlation between phenolic levels and DPPH activity confirms phenolics as the dominant mechanism [80]. Electrochemical analyses using cyclic and differential pulse voltammetry corroborate the presence of multiple redox active antioxidants in bark extracts, with lower oxidation potentials correlating to higher capacity [81]. Hydroalcoholic leaf extract (HASM) yields IC50 values of 74.75 ± 1.33 µg/mL (DPPH), 94.77 ± 1.08 µg/mL (nitric oxide scavenging), and 82.29 ± 1.40 µg/mL (FRAP), values indicative of potent free radical scavenging linked to its phenolic and flavonoid profile [27]. Methanolic leaf extract achieves even greater potency (IC50 values of 7.67 ± 0.29 µg/mL

in DPPH assay), surpassing the reference catechin and again attributed to tannins and flavonoids [39]. Aqueous leaf extracts (decoctions or infusions) maintain high total phenolic content (228.10-245.15) mg GAE/g and TEAC values (2.11-2.43) mmol TE/g, comparable to other polyphenol rich Amazonian species, with preparation method exerting negligible influence on efficacy [82]. Ethanolic seed nanoparticles (300 mg/kg) and crude extracts effectively scavenge ROS (O_2^-, OH^-, H_2O_2), lower kidney MDA, and elevate SOD and GPx in streptozotocin-induced diabetic rats [66], with effects driven by phenolics, limonoids, and swietenine [4, 66] and likely involving Nrf2 pathway activation [66]. Supercritical CO_2 extracted seed oil outperforms Soxhlet ethanol extraction in DPPH scavenging (45.95 ± 0.3 % inhibition) [13], while untreated seed oil reaches 87.69 % DPPH inhibition, with total phenolics contributing to overall capacity [33].

Among isolated compounds, khayanolide B demonstrates superior activity (IC50 values of 3.18 µg/mL vs. 7.18 µg/mL for ascorbic acid), with DFT computations reveal that mechanisms are environment-dependent, featuring hydrogen atom transfer in non-polar solvents and sequential proton loss electron transfer in polar media where both focused at the centered C-6 methine, which presents the lowest BDE of 72.9-73.8 kcal/mol. [83]. Swietemacrophyllanin, isolated from bark but also relevant to seed fractions, records an IC50 values of 56 µg/mL in DPPH assay, outperforming trolox [84]. Swietenine activates the AKT/Nrf2/HO-1 pathway in H_2O_2-stressed HepG2 cells, promoting AKT phosphorylation, nuclear translocation of Nrf2, and upregulation of HO-1 [85].

In LPS-stimulated macrophages, it also activates the NRF2/HO-1 antioxidant pathway, upregulating HO-1 and NQO-1 [85, 86]. Pharmacological inhibition of PI3K/AKT or Nrf2 silencing abolishes this protective antioxidant effect [85]. Hyperglycemia (from 209.9 ± 7.71 to 98.67 ± 9.11 mg/dL) is reversed in diabetic C57BL/6J mice (induced by a high-fat diet plus streptozotocin) following the oral administration of swietenine (80 mg/kg on alternate days for 8 weeks) [10], restores serum GSH (from 0.71 ± 0.18 to 2.02 ± 0.08 nmol/µL) and TAC (from 143.90 ± 17.36 to 310.50 ± 17.65 nmol/µL), and lowers MDA (from 7.98 ± 2.74 to 3.45 ± 0.49 nmol/µL) [10] *via* Nrf2-driven gene expression [10, 21]. Swietenolide similarly reverses hyperglycemia induced redox imbalance in db/db mice and HT22 cells by elevating SOD and GSH while suppressing MDA [87]. Synergistic enhancement occurs when swietenine is combined with metformin, further elevating TAC and GST while reducing MDA [64]. *In-vivo* evidence consistently supports translational relevance where ethanolic seed extract elevates vitamins C and E alongside glutathione in plasma, kidney, and liver of streptozotocin diabetic rats [7]. In the same model, administering the seed extract (at an optimal dose of 100 mg/kg) for 45 days restores enzymatic and non-enzymatic antioxidants while suppressing lipid peroxidation in the kidney, liver, and plasma [65]. Seed extract administration also lowers systemic MDA, a major lipid peroxidation biomarker, in diabetic rodents [88].

Silver nanoparticles synthesized from the plant extract display moderate DPPH, ABTS, superoxide, and hydroxyl scavenging, attributable to surface bound polyphenols and flavonoids [11]. The water fraction (SMWF) additionally exhibits dose-dependent DPPH/ABTS scavenging and ferrous-iron chelation, correlated with high phenolic content and distinct from the weaker activity of the hexane fraction [8].

Anti-inflammatory Activity: Swietenine separated from *S. macrophylla* exerts strong anti-inflammatory effects in diabetic cardiomyopathy by significantly reducing cleaved Caspase-1 p20, pro and mature IL-1β, and IL-18 levels where this effect is mediated *via* upregulation of the NAMPT/SIRT1 pathway, where NAMPT knockdown abolishes the protective effects, while SIRT1 activation restores them [63]. Similarly, swietenolide (Std) demonstrates neuroprotective anti-inflammatory activity in diabetic models by dose-dependently reducing pro-inflammatory cytokines such as TNF-α and IL-1β through Nrf2 activation, that suppresses the TXNIP/NLRP3 inflammasome pathway in both db/db mouse hippocampus and high glucose treated HT22 cells [87]. Crude extracts and isolated compounds from different parts of the plant also inhibit upstream inflammatory processes. At 1,000 mg/kg, the ethanolic seed extract achieved 79% suppression of carrageenan-induced paw edema in mice, outperforming methanol fraction (60%) and hexane

fraction (23%) [7]. Additionally, six limonoids from the fruit methanolic extract (ethyl acetate fraction) potently inhibited superoxide anion generation in human neutrophils (IC50 ≤ 35.7 μM) [7]. Comparable efficacy was reported for the crude ethanol seed extract (1 mg/g body weight), which produced 79% inhibition of carrageenan induced inflammation, with solvent fractions showing lower activity (methanol 60%, hexane 23%) [89]. At a lower dose (100 mg/kg), the seed extract still yielded 47.06% inhibition, comparable to ibuprofen, while isolated fruit limonoids suppressed superoxide anion generation, thereby limiting pro-inflammatory responses [15]. Limonoids, such as swietemacrophin, swietemahonin E, 3-O-tigloylswietenolide, swietenine, and several acetylated derivatives (e.g., 3-O-tigloyl-6-O-acetylswietenolide, 6-O-acetyl-3'-demethyl-swietephragmin E, 3,6-O,O-diacetylswietenolide, and 6-O-acetylswietemahonin G), consistently exhibit strong inhibition of nitric oxide (NO) production in LPS-stimulated murine macrophages [90] and generation of superoxide anions in fMLP-stimulated human neutrophils [53].

The most active compounds, 3-O-tigloyl -6-O-acetylswietenolide and 6-O-acetylswietemahonin G, displayed IC50 values of 27.6 ± 1.7 μM and 27.9 ± 2.4 μM, respectively [53]. These limonoids also down regulate pro-inflammatory cytokines (IFN-γ, IL-6, IL-1β, and TNF-α), COX-2, and NF-κB expression while up regulating Nrf2, thereby combating oxidative stress [9, 86]. In RAW 264.7 cells, phragmalin-type and Mexicanolide-type limonoids from leaves and fruits likewise inhibit NO production[40]. Formulation strategies further enhance efficacy in nano-emulsion delivery of seed oil increased paw edema inhibition to 76.4% compared with raw oil [9], and a 10% bark extract gel reduced carrageenan induced rat paw edema by 41.93%, nearly matching the commercial corticosteroid desoximetasone (44.38%) [43].

The anti-inflammatory effects displayed by the separated new compounds 1, 2, and 3 revealed that compounds 2 and 3 showed significantly higher efficacy in preventing protein denaturation than compound 1, with compound 3 exhibiting a clear concentration-dependent increase in activity [47]. Polyphenols such as catechin contribute to synergistic effects by inhibiting cyclooxygenase and lipoxygenase enzymes, significantly reducing leukocyte infiltration following muscle injury [91]. Aqueous leaf extract (AEML, 50 mg/kg) administered orally in a 6-OHDA-induced Parkinson's disease model reduced IBA-1$^+$ microglial cells and GFAP$^+$ astrocyte expression, indicating beneficial modulation of neuroinflammation attributable to the extract's phenolic constituents [92]. Moreover, acute anti-inflammatory effects have been confirmed in indomethacin induced animal models [17].

Hepatoprotective Activity: Investigations have demonstrated that the plant effectively protects the liver against carbon tetrachloride (CCl_4)-induced damage, where 25% CCl_4 in liquid paraffin was administered intraperitoneally at 5 mL/kg body weight to male albino rats weighing 130-140 g [17].

Neuroprotective Activity: Swietenolide (Std) protects against diabetes-related cognitive dysfunction by improving memory and spatial learning while preserving hippocampal neuronal integrity, mitigating oxidative stress and inflammation through Nrf2 pathway activation and TXNIP/NLRP3 inflammasome inhibition (increasing SOD and GSH while reducing MDA and proinflammatory cytokines), effects that are abolished by ML385 [87]. It demonstrates promising neuroprotective potential against Alzheimer's disease by multiple ameliorative mechanisms, primarily targeting cholinergic deficits, apoptosis, mitochondrial dysfunction, neuroinflammation, and oxidative stress, with these properties position it as a candidate for adjunctive therapy, where current treatments like acetylcholinesterase inhibitors (AChEIs) provide only symptomatic relief with notable side effects [3].

Seed triterpenoids swietenine and khayasin T outperform latrepirdine in stabilizing bovine serum albumin to prevent protein aggregation in neurodegenerative diseases, forming more stable complexes with higher binding occupancy and lower conformational fluctuation [48]. Seed extract (SMSE) protects against lead induced degeneration by improving spatial memory, learning, and motor coordination, while reducing systemic lead and nitrate levels, suppressing TNF-α-mediated inflammation, clearing β-amyloid plaques and microglial activation, and preserving hippocampal

architecture [93]. These effects are supported by antioxidant and anti-apoptotic mechanisms, including Caspase-3 inhibition and Bcl-2/Bax regulation [21], with fruits contributing bioactive ingredients, although isolated compounds showed no obvious acetylcholinesterase inhibition [71]. Leaf aqueous extract (50 mg/kg/day) confers neuroprotection in 6-OHDA induced parkinsonian mice through phenolic compounds that combat oxidative stress and inflammation, partially preserving the nigrostriatal dopaminergic pathway and improving behavioral outcomes [92]. The ethyl acetate fraction (SMEAF) displays significant neuroprotective activity in primary neuronal cells [8], substantially enhancing viability against TBHP induced oxidative stress in MTT assays [94].

Anti-cancer Activity: Biosynthesized silver nanoparticles (SM-AgNPs) prepared from *S. macrophylla* exhibit markedly enhanced potency compared with crude extracts or conventionally synthesized nanoparticles where SM-AgNPs showed potential cytotoxic activity against MCF-7 breast cancer cells with an IC50 value of 2.1 µg/mL, selectivity index = 5 [11] and antiproliferative effects against A549 lung adenocarcinoma cells (IC50= 7.54 ± 0.07 µg/mL) via ROS induced oxidative stress, mitochondrial membrane sensitization, DNA damage, nuclear morphological changes, and S phase cell cycle arrest leading to apoptosis [95]. Similarly, ZnOnano-rice particles biosynthesized using the ethyl acetate fraction (SMEAF) showed superior anticancer activity against HCT-116 colon cancer cells compared to SMEAF or chemically synthesized ZnO alone, attributed to improved phytochemical delivery and synergistic nanoparticle extract interactions [12].

Crude and fractionated extracts, particularly ethanolic seed extracts and their ethyl acetate fraction (SMEAF), have been extensively evaluated, SMEAF consistently produced the strongest cytotoxicity against HCT-116 cells (IC50 = 35.35 ± 0.50 µg/mL) and demonstrated activity against additional lines including KB (Oral cancer), Ca Ski (Cervical cancer), and MCF-7 [4, 7]. The ethyl acetate fraction triggers apoptosis through DNA fragmentation, phosphatidylserine externalization, sub-G1 cell cycle arrest, mitochondrial membrane potential collapse, intracellular glutathione depletion, p53 upregulation, subsequent activation of the caspase cascade (caspases-9, caspases-3, and caspases-7), along with an increased Bax/Bcl-2 ratio [2, 38, 96]. Chloroform seed extracts (SMCE) and the isolated limonoids swietenine and swietenolide further inhibit HCT-116 proliferation by suppressing the MDM2-p53 signaling pathway, with swietenolide proving more potent (IC50 = 5.6 µM; selectivity index = 12.8) than swietenine or the crude extract [55]. Leaf extracts and the isolated limonoid L1 specifically target HCT-116 colorectal cancer cells, inducing DNA damage and apoptosis by down regulating anti-apoptotic BCL2 while up regulating pro-apoptotic TP53, ATM, and CASP3, resulting in G2/M phase arrest and significant inhibition of colony formation [97].

Subfraction 7b of ethyl acetate seed extracts achieved 76.49% growth inhibition at 50 µg/mL against MCF-7 breast cancer cells [98]. Isolated compounds and specific structural classes such as polyacetylenes from roots displayed selective cytotoxicity against hepatocellular, myeloid leukemia, and gastric carcinoma lines, with compounds 1 and 6 showing the strongest effects (IC50 range 14.3 µM to 45.4 µM), the epoxy group in compound 6 appears to enhance genotoxicity [52]. Against HL-60 leukemia (IC50 = 32.9 µM) and SW480 colon cancer (IC50 = 30.6 µM) cells, compound 2 isolated from fruits demonstrated moderate cytotoxicity [99]. Swieteliacate B demonstrated activity against SW480 and HL-60 lines [26], while limonoid compound 19 potently inhibited A375 melanoma cells (IC50 = 9.8 µM), outperforming dacarbazine through G2/M phase arrest and apoptosis induction [40].

In contrast, five isolated limonoids (1-5) lacked significant cytotoxicity against KB carcinoma and A549 lung cancer cells [49]. Additional limonoids, including 6-O-acetylswietephragmin E, have been highlighted for colorectal cancer potential [45], and compounds like swietenolide, methyl angolensate, 7-deacetoxy-7α-hydroxygedunin, and swietenine acetate have shown activity against HuH-7 liver cancer cells [26]. Silico evidence supports the experimental findings where docking of 80 seed compounds against breast cancer receptors (ER-α, PR, IGF-1R, VEGFR2, FGFR1) identified 12 lead molecules whose binding profiles align with observed cytotoxicity against MCF-7 (IC50 = 34.11 µg/mL), colorectal, and melanoma cells

where the main leads 3β,6-dihydroxy-dihydrokarapin, 7 – hydroxyl – 2 - (4 – hydroxyl-3-methoxyphenyl)-chroman-4-one, and stigmasterol mimic established clinical inhibitors at hormone binding or allosteric sites and are predicted to possess oral bioavailability despite minor Lipinski violations [34]. Additionally, crude extracts and fractions display antitumorpromoting activity through the inhibition of TPA (12-O tetradecanoylphorbol-13-acetate) induced EBV-EA (*Epstein Barr* virus early antigen) activation [15, 89].

Anti-melanogenic Activity: In zebrafish models, *Swietenia macrophylla* seed extract significantly reduced melanin content and tyrosinase activity, producing a whitening effect comparable to the standard control phenylthiourea (PTU) and the crude extract, hexane fraction outperformed, indicating possible synergistic interactions among its phytocompounds [23]. Proteomic analysis and molecular docking studies further revealed that specific limonoids in the extract effectively downregulate major melanogenic proteins and exhibit stronger binding affinities to TYRP-1 (Tyrosinase-related protein 1) compared to kojic acid, supporting their potential as effective natural candidates for skin whitening [23]. Additionally, *S. macrophylla* seed extracts can inhibit unwanted melanin accumulation, which commonly results from UV radiation exposure and subsequent activation of the melanogenesis pathway [9].

Antibacterial Activity: Silver nanoparticles synthesized with *S. macrophylla* extract (SM-AgNPs) exhibit clear dose-dependent antibacterial activity against major pathogens such as *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Salmonella typhi*, *and Pseudomonas aeruginosa*, outperforming conventional silver colloids in bactericidal effectiveness [11]. Methanolic seed extracts produce significant dose-dependent inhibition against *S. aureus* and *Escherichia coli*, achieving peak zones of 16 ± 1.15 mm and 15 ± 0.33 mm at 80 mg/mL, respectively, with activity linked to bioactive secondary metabolites and comparable to streptomycin [19]. Methanol extracts consistently outperform aqueous counterparts across multiple pathogens (*P. aeruginosa*, *Bacillus cereus*, and *K. pneumoniae*), with *Escherichia coli* MTCC 443 particularly susceptible [7]. Crude methanolic extracts from seeds show the highest inhibitory efficacy against *E. coli* and *S. aureus* (peaking at 50 µg/mL) compared with leaf or central fruit axis fractions [100]. Broader seed extract studies confirm activity against clinical wound pathogens, with greater potency against gram-positive bacterial strains (*Bacillus cereus*, *Bacillus subtilis*, and *Staphylococcus aureus*) and concentration-dependent time kill kinetics achieving 99.9% reduction in *B. subtilis* within six hours at MBC levels [16].

Crude alkaloid fractions from seeds further demonstrate strong broad-spectrum effects, often surpassing leaf alkaloids, with inhibition zones up to 21 mm against *S. aureus* and MIC/MBC values ranging from 12.5-50 mg/mL [14]. Ethyl acetate seed extract enhances *Caenorhabditis elegans* survival against *P. aeruginosa* infection by upregulating innate immunity genes such as lys-7 [2], and certain limonoids reduce MRSA virulence in vivo despite limited direct in vitro growth inhibition [9]. Seed oil studies reported activity against *P. aeruginosa*, *S. typhimurium*, and *S. aureus* (max 20 mm zones), though *E. coli* showed complete resistance in some assays [31, 101]. The optimized 5% (w/v) acetone bark extract produces clear zones of 21 mm against *Bacillus* sp. and 18 mm against *S. aureus* but shows no effect on gram-negative *E. coli* or *Serratia marcescens* [81].

Leaf extracts exhibit more variable activities. Some demonstrate selective gram-positive inhibition with no activity against gram-negative strains [39, 102], while others show broad spectrum effects against *E. coli*, *Salmonella typhi*, and, *S. aureus* with ethyl acetate and methanol fractions achieving 17-20 mm zones and MIC/MBC ranges of 50-200 mg/mL [103]. Petroleum ether leaf extracts provide strong dose-dependent protection (up to 20%) against *E. coli*, *P. aeruginosa*, and MRSA, with ethanolic fractions matching chloramphenicol potency against MRSA [35]. Ethanolic leaf extracts additionally inhibit foodborne pathogens such as *Salmonella typhimurium*, *E. coli*, *Shigella sonnei*, and *P. aeruginosa*, with MIC values as low as 31.25 µg/mL for *E. coli* and *P. aeruginosa* [44]. Limonoids isolated from *Swietenia macrophylla*, such as swietenolide and the more potent 2-hydroxy-3-O-tigloylswietenolide exhibits strong antibacterial effects across eight distinct bacterial strains [56]. Swietenine and swietenolide are credited with

broad-spectrum effects, demonstrating effectiveness against multiple drug-resistant strains such as *Klebsiella pneumoniae* and *Streptococcus pneumoniae* [9]. Both swietenine and swietenolide exhibit notable antimicrobial properties, with swietenolide in particular demonstrating potent growth-inhibitory effects against a broad range of pathogens, specifically four gram-positive and four gram-negative bacterial strains [4, 21]. Flavonoids from seeds exert concentration-dependent effects, showing greater efficacy against gram-negative *E. coli* (18.50 mm) than gram-positive *B. cereus via* β-glucuronidase mediated conversion to toxic metabolites [104]. In contrast, certain isolated compounds tested at 50 mg/mL produced negligible zones (<7 mm) against *S. aureus* and *Ralstonia solanacearum* [71], indicating structure and concentration specific limitations. Endophytic fungi and host microbe interactions further expand the plant's antimicrobial activity. *Aspergillus* sp. IBRL MP15 CCL metabolites exhibit concentration-dependent bacteriostatic to bactericidal effects, with host extracts markedly boosting potency [105]. Ethyl acetate extracts of leaf endophytes demonstrate wider inhibitory ranges against gram-negative and gram-positive pathogens, such as MRSA, *P. aeruginosa*, and *B. subtilis*, than methanolic fractions [106].

Antifungal Activity: Methanol extracts inhibit *Fusarium* sp., *Alternaria* sp., *Helminthosporium* sp., and the yeast *Candida utilis*, with efficacy increasing linearly with concentration [9, 17]. Similarly, both methanol and aqueous fractions are effective against *Aspergillus flavus*, *A. niger*, *Cryptococcus albidus*, and *Candida albicans*, with *C. albidus* showing the greatest susceptibility and methanol extracts proving superior [7]. Ethyl acetate and aqueous fractions of the seeds further exhibit pronounced activity against clinical isolates of *C. albicans*, *A. niger*, and *A. flavus* where among isolated compounds, swietenolide is the most potent, but swietenine acetate displays no inhibitory effect [107]. Limonoid fractions from seeds produce zones of inhibition exceeding 11 mm against *C. albicans* and >29 mm against *Aspergillus fumigatus*, values comparable to Caspofungin, these fractions also exhibit synergistic enhancement when combined with *Triphasia trifolia* extract, achieving a MIC (minimum inhibitory concentration) of 31.25 mg/mL [108].

The isolated limonoid khayanolide B exhibits remarkable broad-spectrum suppression of mycelial growth in a dose-dependent manner against *Sclerotium rolfsii*, *Fusarium oxysporum*, *Botrytis cinerea*, and *Phytophthora* species [25]. However, not all limonoid preparations are uniformly active, certain compounds screened at 50 mg/mL against *Fusarium oxysporum f.* sp. *vasinfectum* and *Fusarium oxysporum f.* sp. *cubense* produced inhibition zones <7 mm, indicating negligible antifungal effect [71], and isolated triterpenoids (compounds 1-3) similarly failed to inhibit *A. niger* at concentrations of 0.05-0.2 mg [47]. Leaf extracts achieve complete growth inhibition of *C. albicans*, *Aspergillus* species, and the dermatophyte *Trichophyton mentagrophytes* at concentrations as low as 83 µg/mL, with activity increasing dose-dependently up to 333 µg/mL [35]. Triterpenoids and limonoids function as constitutive defense compounds, effectively targeting the groundnut rust *Puccinia arachidis* and *C. albicans* [15]. Endophytic fungi harbored within the plant display targeted fungicidal activity against yeasts (*Cryptococcus neoformans* and *C. albicans*, MIC 250 µg/mL) but are largely ineffective against filamentous species such as *A. fumigatus*, a selectivity attributed to eukaryotic cell wall similarities between the endophyte and non-susceptible fungi [105]. Endophyte isolates also inhibit *A. fumigatus*, *Microsporum fulvum*, *T. rubrum*, and *Rhizopus* sp., although secondary screening frequently reveals reduced potency, possibly due to the high chitin content and structural complexity of fungal cell walls [106]. Silver nanoparticles synthesized using *S. macrophylla* (SM-AgNPs) have shown significant antifungal action against *Fusarium graminearum*, *Alternaria alternata*, and *C. albicans* [11]. In parallel, the swietenolide isolated from mature seeds produces a 30 mm clearing zone (activity index 2.0) against the dermatophyte *T. mentagrophytes* at 90 µg and its monoacetyl and diacetyl derivatives are markedly less potent, and the parent compound is inactive against *C. albicans* [109].

Antibiofilm Activity: Biofilm formation by all four gram-positive pathogens (*Bacillus cereus* ATCC 11778, *Clostridium sporogenes* ATCC 13124, *Staphylococcus aureus* ATCC 33862, and

Streptococcus pneumoniae ATCC 19615) was significantly inhibited ($p < 0.05$) by the methanolic extract of *Swietenia macrophylla* leaves (SMME) in a non-concentration-dependent manner across 31.3-1000 µg/mL where the biofilm inhibition ranged from (8.27-66.34)% (*S. pneumoniae*), (68.93-82.50)% (*C. sporogenes*), (13.76-44.59)% (*B. cereus*), (41.49-61.65)% (*S. aureus*), and time-kill kinetics revealed inhibition of *S. pneumoniae* and *C. sporogenes* biofilms starting at 12 h. BIC50 values indicated highest potency against *B. cereus* (33.86 µg/mL), followed by *S. pneumoniae* (85.44 µg/mL), *S. aureus* (228.3 µg/mL), and *C. sporogenes* (>1000 µg/mL) where the antibiofilm effect was attributed to SMME's secondary metabolites, particularly β-amyrin (22.8%) [59]. The ethanolic extract also demonstrates potent antibiofilm properties by effectively inhibiting the formation of pellicles and reducing total biofilm biomass in foodborne pathogens where biofilm inhibitory concentration (BIC50) values for the ethanolic extract range between 5.19 and 42.47 µg/mL, where these activities are linked to compounds like 2,4-di-tert-butylphenol and olean-12-ene through affecting cell surface hydrophobicity and inhibiting the initial steps of biofilm adhesion [44].

Antiviral/ Anti-herpetic Activity: A study on *Swietenia macrophylla* identified secomahoganin and stigmasterol as promising inhibitors target ACE2, the SARS-CoV-2 entry receptor and molecular docking revealed superior binding affinities for both compounds (-10.50 and -10.34 kcal/mol, respectively) compared to the natural ligand MLN-4760 (-7.10 kcal/mol) as they share critical amino acid interactions with the reference ligand and exhibit stable binding, making them strong candidates for development as anti-SARS-CoV-2 agents [110]. Additionally, 7-deacetoxy-7-oxogedunin together with 3β-hydroxy-stigmast-5-en-7-one were identified as promising inhibitors targeting the SARS-CoV-2 papain-like protease (PLpro), with the former showing superior stability in molecular dynamics simulations [111]. The lignan 3-hydroxycaruilignan C from stem ethyl acetate fraction showed anti-hepatitis C virus activity by enhancing interferon stimulated gene expression and synergizing with interferon-α and viral inhibitors [2, 112]. Methanolic bark extract rich in chlorogenic acid, methyl esters, catechin, and gallocatechin displayed significant HIV-1 protease inhibitory activity [4], while tannins and beta carboline alkaloids further contribute to anti-HIV effects by inactivating various viruses including polio, herpes simplex, and inhibiting HIV-1 entry *via* gp41 [113]. Moreover, ethanol seed extract and isolated limonoids such as swietenine acetate, methyl angolensate, swielimonoid B, and swietenolide showed notable inhibitory effects against Dengue virus 2 with EC_{50} values of (3.5-12.5) µM and favorable selectivity indices [114].

Antimalarial Activity: Methanol seed and bark extracts showed notable efficacy against *P. vinckeipetteri*, with 73% inhibition at 250 mg/kg in rodent *in-vivo* models, and 78% inhibition against chloroquine-resistant *Plasmodium falciparum* strains at 100 µg/mL [4]. Aqueous seed extract additionally exhibited antibabesial effects [2]. Various plant extracts overall exhibited potent antimalarial activity in screened samples, with inhibition ranging from 89.6% to 100%, an effect largely attributed to the presence of limonoids [15].

Wound Healing Activity: *Swietenia macrophylla* extracts and fractions, including crude ethanolic extract (SMCE) and its water (SMWF), ethyl acetate (SMEAF), and hexane (SMHF) fractions, enhanced keratinocyte proliferation and migration *in-vitro*, with SMWF achieving the highest 74.68% wound closure at 50 µg/mL in a 24h scratch assay due to its strong antioxidant and iron chelating activities [8]. *In-vivo*, 10% w/w seed ointment promoted complete wound closure by day 15 in Sprague-Dawley rats where six days faster than controls *via* fibroblast proliferation, neovascularization, and organized collagen deposition, while also suppressing UVB mediated MMP-1 for photoaging reversal [9, 56]. Leaf extract (96% ethanol) showed dose-dependent wound closure in rabbit incision models, with 20% concentration yielding (21.46±1.49) % healing, comparable to positive controls [115]. Fractions rich in catechin further accelerated muscle regeneration through early fibroblast activity and robust collagen deposition [91]. Tannins contribute by forming a protective barrier against infection, aiding burns, bleeding control, and ulcer healing [113]. Histologically, the extract supports angiogenesis along with antimicrobial, anti-inflammatory, and analgesic effects for structured dermal recovery [56].

Anti-aging Activity: Molecular docking studies showing that *Swietenia macrophylla* seeds contain bioactive steroids and terpenoids, notably β-cytostenone, 3β-hydroxystigmast-5-en-7-one, and germacrenes A and D, which combat skin aging by inhibiting major degradative enzymes which mitigate up to 80% of UV-induced photoaging by blocking MMP-1 (matrix metalloproteinase-1) to preserve collagen, NEP to maintain elasticity, and PPO3 (tyrosinase) to prevent hyperpigmentation and reduce skin cancer risk [58]. As they largely follow Lipinski's rule of five, they exhibit high potential as drug-like agents for advanced dermatological anti-aging treatments [58]. Seed extracts, particularly the hexane (SMHF) and ethyl acetate (SMEAF) fractions, provide strong anti-aging effects by countering UVB-induced extrinsic stressors that cause wrinkles, sagging, and irregular pigmentation while UVB triggers oxidative stress, DNA damage, and MMP-1-mediated collagen breakdown, these fractions restore cellular homeostasis through dual-action mechanisms [9]. SMHF upregulates antioxidant pathways and heat shock proteins to aid protein repair, whereas SMEAF suppresses inflammation and prevents extracellular matrix degradation, by combining UV photoprotection with wound healing and cellular repair, they effectively mitigate skin structural decline, offering a potent natural alternative for advanced cosmeceutical formulations [86].

Anti-nociceptive and Analgesic Activity: Seed extracts are used as a natural method to manage chronic pain and clinical evaluations in albino rats using Novalgin as a reference have documented significant analgesic activity [17]. The aqueous and ethanolic extracts of *S. macrophylla* fruits demonstrate significant analgesic effects across chemical and thermal pain models, in acetic acid induced writhing tests, an oral administration of 200 mg/kg of the ethanolic extract notably reduces the frequency of writhes in animal models and this anti-nociceptive activity is further confirmed by significant responses in tail-flick and hot-plate tests [37].

Antidiarrheal Activity: Tannins within the plant serve as effective astringents for treating diarrhea. Unlike treatments that stop the flow of disturbing substances in the stomach, these tannins control irritation in the small intestine and provide immediate relief for dysentery [113]. At 100 mg/kg, the petroleum ether seed extract exhibited notable antidiarrheal activity comparable to standard drugs such as atropine sulphate and diphenoxylate, by reducing defecation frequency and improving fecal consistency in castor oil-induced models [15]. The petroleum ether extract mechanistically suppresses gastrointestinal motility, reducing intestinal transit by up to 34.60%, while significantly inhibiting castor oil-induced enteropooling (fluid accumulation), an effect linked to steroids that may promote intestinal absorption of water and sodium [116].

Anti-pyretic Activity: Antipyretic activity was evaluated in male albino rats using the yeast-induced hyperthermia model for 90% ethanol extracts of *Swietenia macrophylla* stem bark and leaves where only the leaf extract demonstrated a moderate antipyretic effect at an oral dose of 100 mg/kg body weight, significantly lowering rectal temperature with higher efficacy noted at the 2 hours interval (potency = 0.5 relative to paracetamol 20 mg/kg). Conversely, negligible activity was shown by the stem bark extract (potency ≈ 0.18), suggesting that the antipyretic constituents of *S. macrophylla* are mostly concentrated within the leaves [117].

Anti-snake Venom Activity: *Swietenia macrophylla* leaf extracts, particularly those rich in catechin (F5 fraction) and the polar fraction Sm13-16,23, effectively neutralize *Bothrops asper* venom by inhibiting phospholipase A_2 (PLA_2) enzymes and these extracts prevent cell membrane damage, cytotoxicity, myonecrosis, and neuromuscular dysfunction by blocking the hydrophobic channel upon forming hydrogen bonds with residues such as Asp49 at the PLA_2 active site [91, 118, 119]. *In-vitro* studies further showed that fraction Sm13-16,23 inhibits myotoxic PLA_2 and crotoxin from South American pit vipers (*Bothrops asper* and *Crotalusdurissus cumanensis*) with over 80% inhibition, demonstrating dose-dependent reduction in edema, cytotoxicity, and myotoxicity with greater potency against Lys49 than Asp49 variants [1, 118].

Anthelmintic and Anti-parasitic Activity: Aqueous and alcoholic bark extracts of *Swietenia macrophylla* exhibit dose-dependent anthelmintic

activity against *Eisenia andrei* earthworms, with the alcoholic extract at 40 mg/mL proving the most potent (paralysis at 32.67 min; death at 34.67 min in test subject) [22]. While both extracts outperformed lower concentrations, they remained less effective than the reference drug albendazole, which induced death in 13.67 minutes, where these findings specifically highlighting the superior efficacy of the high concentration alcoholic extract [22]. Ethanol extracts of the leaves have demonstrated acaricidal activity, specifically showing effectiveness against *Varroa destructor* mites found within honeybee colonies [120]. The plant extracts were screened and showed a potent inhibition range of 84.2% to 98.1% against *Babesia gibsoni*, a parasite that causes erythrocyte lysis similar to malaria [15].

Mosquito Repellent Activity: Herbal mosquito repellent cones formulated with *Swietenia macrophylla* seed extract and natural binders exhibited strong efficacy, with formulation F5 (highest extract and gum acacia) showing optimal performance where 18 min burn time, 0.17g ash, pleasant odor, non-irritating smoke, and maximum repellency (4 mosquitoes repelled) [19]. Field trials in homes, labs, and classrooms confirmed effective mosquito control without irritation, positioning it as an eco-friendly, affordable, and biodegradable alternative to synthetics [19]. Additionally, seneganolide isolated from the plant, potent larvicidal activity against *Aedes aegypti* larvae was demonstrated with LC_{90} values of (57.3-65.1) µg/mL and LC_{50} values of (34.1-44.1) µg/mL after 24h and 48h exposure, respectively, highlighting its promise for vector control [83].

Antifeedant Activity: *Swietenia macrophylla* employs sophisticated chemical defense by concentrating phragmalin-type limonoids in mature leaves, exhibiting strong antifeedant and growth inhibitory activity against the shoot borer *Hypsipyla grandella*, thereby protecting mature foliage and forcing larvae to feed on vulnerable young shoots with lower limonoid levels [50]. Leaves also contain germacrene D and γ-himachalene, which attract *H. grandella* for oviposition [120]. From the fruit acetone extract, four limonoids (3,6-O,O-diacetylswietenolide, swietemahonin F, 6-O-acetylswietenolide, and swietenolide) exhibited strong antifeedant activity against *Spodoptera frugiperda* larvae, with swietenolide recording the highest index of 94.1% at 1,000 ppm [121]. Ethanol and hexane seed extracts further displayed antifeedant effects against *S. frugiperda* and striped cucumber beetle, albeit with moderate potency [15]. Moreover, the plant harbors B, D-secolimonoids like bussein and entandrophragmin, which display feeding inhibition in *Ostrinia nubilalis* larvae at 500 ppm along with growth inhibition at 50 ppm [122].

Anticoagulant Activity: The pulp and seed extracts of the *Swietenia macrophylla* fruit demonstrate significant anticoagulant effects on experimental rat blood. Experimental results indicate that ethanolic extracts are particularly potent specifically at an 80% concentration, these extracts significantly increased blood clotting time. This anticoagulation activity was consistent across different extraction mediums, though the efficacy varied based on the concentration levels (20%, 40%, 60%, and 80%) and the part of the fruit used [123].

Anti-mutagenic Activity: Research into the seeds of *S. macrophylla* has revealed anti-mutagenic properties, indicating a protective effect against genetic mutations [21]. *In-vitro* and animal studies indicate that the flavonoids in *S. macrophylla* possess antimutagenic activities, helping to protect genetic material from damage [113]. The ethanolic seeds exhibit notable antimutagenic activity, as evidenced by results from the micronucleus test, the frequency of micronucleated polychromatic erythrocytes induced by the known mutagen mitomycin C was decreased by roughly 50% through administration of the crude extract at a dose of 0.02 mg per gram of body weight [89].

Toxicity and Safety Analysis: Acute oral toxicity assessments consistently classify *S. macrophylla* seed, leaf, and fruit extracts as practically non-toxic. In female Swiss albino mice, the hydro-alcoholic seed extract (HASM) produced no mortality, behavioral changes, or delayed toxic signs up to 2000 mg/kg body weight (OECD 425) where the median lethal dose (LD50) was therefore >2000 mg/kg, indicating that HASM is non-toxic at the tested doses [27]. Comparable results were obtained with ethanolic or aqueous seed extracts in Sprague-Dawley rats and Balb/c mice (LD50> 2000 mg/kg), with no alterations in body weight,

food or water intake, hematological or biochemical parameters, or histopathology of vital organs [20, 37, 93, 94]. Leaf fractions (Sm13-16,23) showed no clinical or histopathological lesions at 300 mg/kg, although minor liver and kidney changes appeared at the limit dose of 2000 mg/kg [1]. Aqueous seed extracts similarly exhibited no toxicity [72]. These findings in together support a broad non-toxic therapeutic index for short-term exposure [57].

Subacute and repeated dose studies in diabetic and normal animal models further reinforce safety within effective dose ranges. Seed extracts (20-300 mg/kg) produced significant therapeutic effects without clinical signs or histopathological alterations in liver or kidney [32, 46]. Swietenine (20-40 mg/kg) reversed diabetes-induced renal markers (urea, creatinine) without adverse effects in normal rats [64]. Allometric conversion from a prior subacute trial supported a 50 mg/kg/day dose of aqueous leaf extract for Parkinson's models with no reported toxicity [92]. Ethanolic extracts showed only mild effects in long-term (72-day) nanoparticle studies [66, 76].

In-vitro cytotoxicity and genotoxicity data are concentration and solvent-dependent. Genotoxicity of silver nanoparticles (SM-AgNPs) was minimal at ≤5 µg/mL, supporting biocompatibility [11]. Zebrafish embryo assays (24 hpf, up to 100 µg/mL) revealed no mortality or morphological defects for crude ethanolic extract or fractions [23]. MTT assays on HaCaT keratinocytes demonstrated that crude seed extract (SMCE) was most cytotoxic (significant viability reduction from 12.5 µg/mL), while fractionated preparations, particularly the hexane fraction (SMHF), exhibited markedly lower or negligible toxicity up to 100 µg/mL [8, 86]. Aqueous extracts restored β-cell function in diabetic rats without histopathological changes [13]. Specific limonoids (e.g., swietemacrophin, swietenine) maintained high cell viability and showed no generalized cytotoxicity at pharmacologically active concentrations [90, 97]. Water extracts consistently displayed the lowest cytotoxicity among solvents tested [26].

Limited data exist on chronic toxicity or long-term human exposure. No chronic studies were identified in the reviewed literature [26]. Moisture content assessments of dried bark (6.95%) met Indonesian pharmacopoeial standards for safe storage [62]. Brine shrimp lethality and allelopathic assays indicated bioactivity but were not directly linked to mammalian toxicity [98, 120]. Clinical evidence introduces an important safety concern. Multiple case series from Singapore (2015-2018) documented herb-induced liver injury (HILI) following *S. macrophylla* seed consumption, presenting as hepatocellular or mixed injury (elevated ALT/AST, jaundice, occasional acute kidney injury) with onset typically 30-45 days post-ingestion [26, 28, 124]. Cases were idiosyncratic, RUCAM-classified as "probable" to "highly probable," and generally resolved upon discontinuation, though liver failure occurred in isolated instances where no fatalities were reported, and most patients had comorbidities (diabetes, hypertension). Moreover, in vitro HepG2 studies confirmed solvent-dependent cytotoxicity, with non-polar extracts more toxic than aqueous ones [26].

Preclinical acute and subacute toxicity profiles of *Swietenia macrophylla* extracts, fractions, and limonoids are consistently favourable. Multiple studies reported LD_{50} values >2000 mg/kg [20, 27, 94]. Genotoxicity was negligible at low concentrations [11, 23], while cytotoxicity was markedly reduced in aqueous extracts or fractionated forms [8, 86]. These data support safe use within traditional and experimental therapeutic ranges (20-300 mg/kg in animals). However, documented human cases of idiosyncratic hepatotoxicity necessitate caution, particularly with crude seed preparations, and highlight the absence of controlled chronic human trials. Future research should prioritize standardized extracts, long-term safety studies, and pharmacovigilance to fully establish the risk-benefit profile for medicinal applications.

CONCLUSION: *Swietenia macrophylla* emerges as a remarkable medicinal plant whose traditional applications across diabetes, hypertension, inflammation, infections, and wound healing are increasingly substantiated by robust preclinical evidence. Its rich limonoid profile, particularly swietenine and swietenolide, along with supportive phenolics and steroids, underpins a broad spectrum of pharmacological effects such as potent anti-diabetic, antioxidant, antimicrobial, anti-inflammatory, anti-cancer, and organ-protective

effects, often through regulation of major pathways including apoptosis, PPARγ, and Nrf2.

While acute toxicity studies affirm a generally favorable safety profile at therapeutic doses, isolated reports of herb-induced liver injury highlight the importance of standardized preparations and cautious use. Although substantial progress has been made, the full therapeutic potential of *Swietenia macrophylla* awaits confirmation through well-designed clinical trials, extract standardization, and deeper mechanistic insights. With sustainable cultivation and continued research, this valuable medicinal plant holds considerable promise as a source of effective phytopharmaceuticals and functional natural products for modern healthcare.

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