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Review Article

A Review on *Citrus maxima*: Phytochemical, Pharmacological and Therapeutic Perspectives

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ABSTRACT

Citrus maxima (Burm.) Merr., widely known as pomelo, is the largest naturally occurring species in the Rutaceae family. Revered for centuries across Asian healing traditions, this plant has recently gained significant scientific traction owing to the remarkable diversity of its secondary metabolites. The present review endeavor to bring together scattered findings from botanical, ethnopharmacological, and biomedical literature into a coherent narrative. Phytochemical characterisation of leaves, peel, pulp, seeds, and roots has revealed an abundance of biologically active molecules—chief among them being the flavanones naringin and naringenin, polymethoxylated flavones such as nobiletin and tangeretin; the monoterpene limonene; a suite of phenolic acids, including chlorogenic and ferulic acid; and nutritionally significant quantities of ascorbic acid, potassium, and dietary pectin. These constituents collectively underpin a broad spectrum of experimentally validated activities: free-radical scavenging, broad-spectrum antimicrobial activity, suppression of inflammatory signalling cascades, modulation of glycemic control pathways, selective cytotoxicity toward malignant cells, protection of hepatic parenchyma, regulation of lipid metabolism, and preservation of neuronal integrity under oxidative challenge. The review also draws attention to an under-discussed but clinically critical concern. The capacity of pomelo-derived furanocoumarins to inhibit intestinal CYP3A4, with consequent implications for drug bioavailability. Research gaps, particularly the near-absence of human clinical data, are identified, and priority areas for future investigation are outlined.

INTRODUCTION

Among the many genera that populate the family Rutaceae, citrus stands out as a major agricultural product and a source of important medicinal compounds. Within this genus, Citrus maxima (Burm.) Merr., known as the pomelo or pummelo, holds a special place. It is not only the oldest

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cultivated citrus species but also the largest, with mature fruits often exceeding 25 cm in diameter and weighing more than one kilogram. Burman first brought this species to scientific attention in the eighteenth century, and it was later reclassified by Merrill. Today, it is widely recognized as the ancestor of many hybrid citrus types, especially the commonly known grapefruit (Citrus paradisi).

Healers across India, China, Southeast Asia, and the Pacific Islands have long recognized the medicinal value of this fruit's diverse organs. From dried peel preparations dispensed in traditional Chinese pharmacies for respiratory complaints to leaf decoctions consumed postpartum by women in Malaysia and Indonesia, the plant's therapeutic applications are as geographically widespread as its cultivation. This gathered knowledge, developed over generations and across cultures, offers a strong base for modern pharmacognosy to grow from.

Contemporary pressures on pharmaceutical systems—the emergence of antimicrobial resistance, the chronic disease burden of ageing populations, and a documented consumer shift toward plant-derived health Products have collectively intensified interest in scientifically validating traditional remedies. C. maxima has attracted substantial research effort in this context. Investigations conducted over the past two decades have identified structurally diverse bioactive compounds and documented their activities across multiple disease models. The present review synthesizes this body of knowledge systematically, evaluates its quality and limitations, and proposes productive avenues for advancing the science of C. maxima toward clinical application.

2. BOTANICAL DESCRIPTION AND TAXONOMIC CLASSIFICATION

Citrus maxima is a slow-growing, well-branched evergreen tree. It typically reaches heights of 5 to 15 meters when cultivated and can sometimes grow taller in undisturbed forest areas. The root system is deep and wide, allowing the tree to tolerate occasional dry spells. However, it does not thrive in waterlogged conditions. The bark is grey-brown and somewhat rough on the main trunk, becoming smoother on younger branches. Thorns, when they appear, are axillary, solitary, and stout, reaching lengths of up to five centimeters. This trait is important both for classification and practical use, as it helps distinguish many wild variants from thornless cultivated ones.

The leaves are among the most readily identifiable features of the species. They are alternate, broadly ovate to elliptic, measuring between five and twenty centimeters in length, with a distinctly winged petiole—often broader than the petioles of other Citrus species—representing a key diagnostic characteristic for field identification. The lamina is coriaceous, dark glossy green above and paler beneath, with translucent oil glands visible when held against light. Flowers are bisexual, actinomorphic, white to slightly cream-colored, intensely fragrant, and borne singly or in axillary clusters of two to ten. Petals are four to five in number, thick, and waxy. Numerous stamens surround a single pistil with a large, mucilaginous stigma. The fruit is a hesperidium—the type characteristic of the genus—but of exceptional dimensions. It may be globose, oblate, or pyriform in shape, depending on the cultivar. The exocarp (flavedo) is pale yellow, greenish-yellow, or pale pink at maturity, studded with prominent oil glands. The mesocarp (albedo) is white, spongy, and extraordinarily thick, sometimes constituting fifty per cent or more of the total fruit weight. It is this tissue that accumulates high concentrations of naringin, pectin, and essential oils. The endocarp consists of

eleven to eighteen segments filled with large juice vesicles and separated by papery membranes of pronounced bitterness. Seeds are polyembryonic and variable in number. Taxonomically, the species falls within Kingdom Plantae, Division Magnoliophyta, Class Magnoliopsida, Order Sapindales, Family Rutaceae, Genus Citrus, and Species maxima.

3. GEOGRAPHIC DISTRIBUTION AND AGRONOMY

The primary centre of origin of C. maxima is broadly placed in the Malay Archipelago, encompassing present-day Malaysia, Indonesia, and the southern Philippines, from where the species spread through human migration and trade into mainland Southeast Asia, China, India, and eventually beyond Asia entirely. Today, commercial cultivation occurs across a wide band of tropical and warm subtropical latitudes. China—particularly the provinces of Fujian, Guangdong, Guangxi, Yunnan, and Sichuan—remains the dominant producer and consumer, with pomelo holding deep cultural significance as a New Year gift symbolising prosperity and familial unity.

Beyond China, substantial cultivation exists in Thailand, Vietnam, Cambodia, Indonesia, Malaysia, the Philippines, Bangladesh, India (principally in Assam, Meghalaya, Kerala, and the Andaman Islands), and Japan. Outside Asia, pomelo is grown commercially in Israel, parts of the Arabian Peninsula, Trinidad, and Japan. Outside Asia, pomelo is grown commercially in Israel, parts of the Arabian Peninsula, and Trinidad, with a climate of annual rainfall between 1,200 and 2,000 mm and deep, well-drained loamy soils with a slightly acidic pH of 5.5 to 7.0. It is frost-intolerant, restricting cultivation to regions where minimum temperatures remain above ten degrees Celsius. Propagation is mainly through grafting or air-layering to preserve cultivar characteristics, as seedling progeny are variable due to polyembryony.

4. TRADITIONAL AND ETHNOMEDICINAL USES

The documentation of C. maxima's traditional therapeutic applications across independent cultural systems lends considerable ethnopharmacological weight to modern scientific inquiry. In Traditional Chinese Medicine, dried pomelo peel—commercially available as hua ju hong—is classified as a phlegm-resolving and qi-regulating herb. Practitioners prescribe it for productive cough, nausea, distension, and indigestion, typically in decoctions combined with other botanicals. The fruit itself is considered cooling in thermodynamic character and is recommended for fever, thirst, and internal heat conditions.

In Ayurvedic and Unani medicine practiced on the Indian subcontinent, leaf and bark preparations of C. maxima appear in formulations addressing epilepsy, joint inflammation, skin disorders, and digestive sluggishness. The juice is consumed medicinally as a diuretic and mild laxative. In rural communities of Northeast India, tribal healers use root bark decoctions applied externally for managing rheumatic swellings and internally for malaria. In Peninsular Malaysia and Java, a postpartum ritual involving bathing water infused with pomelo leaves, lemongrass, and other aromatics is widespread and believed to cleanse the uterus, contract abdominal muscles, and ward off evil spirits. Lactating mothers consume the cooked young shoots as a galactagogue.

In the Philippines, fresh leaf sap is dabbed directly onto insect bites, minor cuts, and fungal skin patches. Thai traditional practitioners incorporate pomelo peel oil into formulations for massage and

inhalation therapy aimed at stress reduction. In Bangladesh and West Bengal, regular consumption of pomelo is popularly associated with weight control, diabetes prevention, and cardiovascular health—an empirical observation that has since found partial biochemical support. The breadth and consistency of these applications across geographically distant and culturally independent traditions strongly suggest genuine pharmacological activity and justify systematic scientific exploration.

5. PHYTOCHEMICAL CONSTITUENTS

The phytochemical landscape of C. maxima is remarkably rich and extends across multiple structural classes of secondary metabolites. Distribution of these compounds is organ-specific, with the peel, particularly the albedo, constituting the most pharmacologically dense tissue. A comprehensive account of the major compound classes follows.

5.1 Flavonoids

Flavonoids constitute the single most pharmacologically significant class of compounds in C. maxima and have been the subject of exhaustive chemical and biological investigation. Naringenin (4',5,7-trihydroxyflavanone) and its 7-O-neohesperidoside, naringin, dominate the flavanone fraction, occurring in the highest concentrations in the peel and juice of the fruit. Naringenin is widely recognised as a potent antioxidant. anti-inflammatory and metabolic modulator, while naringin carries the characteristic bitter taste associated with pomelos and related citrus. Hesperidin (hesperetin-7-O-rutinoside) and its aglycone, hesperetin, are present in peel and leaf fractions and have been associated with vasoprotective and lipid-modulating activities. Among the polymethoxylated flavones—a subclass particularly concentrated in citrus peel—nobiletin (5,6,7,8,3',4'-hexamethoxyflavone), tangeretin, sinensetin, 5-demethylnobiletin, and 3,3',4',5,6,7,8-heptamethoxyflavone have been isolated and characterised. These highly lipophilic molecules demonstrate superior cellular penetration and have attracted disproportionate research interest for their anticancer, neurological, and anti-inflammatory properties. The flavonol rutin, quercetin-3-O-rutinoside, and its aglycone quercetin, along with kaempferol, apigenin, luteolin, and their glycosides, have been detected in leaf extracts, contributing additional antioxidant and anti-inflammatory capacity.

5.2 Essential Oils and Terpene Constituents

Cold-pressed and steam-distilled peel oils of C. maxima reveal a complex terpene-dominated volatile profile. d-Limonene invariably accounts for the largest proportion of the total volatiles, ranging between 60 and 90 per cent across different cultivars and extraction methods. This monocyclic monoterpene is responsible for the species' characteristic citrus aroma and has well-documented antifungal, anticancer chemopreventive, and gastroprotective properties. Other monoterpene hydrocarbons identified include alpha-pinene, beta-pinene, beta-myrcene, gamma-terpinene, alpha-terpinene, p-cymene, sabinene, and terpinolene. The oxygenated monoterpene fraction—linalool, geraniol, nerol, citronellal, citronellol, alpha-terpineol, and terpinen-4-ol—confers the floral and complex aromatic character of the oil and contributes meaningfully to antimicrobial and antifungal bioactivity. Sesquiterpenes, including beta-caryophyllene, germacrene D, alpha-humulene, and nerolidol, have been identified in smaller proportions.

5.3 Phenolic Acids, Coumarins, and Other Polyphenols

Hydroxycinnamic acids, such as ferulic acid, p-coumaric acid, caffeic acid, sinapic acid, and chlorogenic acid, are mainly found in the albedo and juice vesicle fractions. Chlorogenic acid stands out for its strong inhibitory effects on intestinal alpha-glucosidase and alpha-amylase. This supports traditional claims about C. maxima's role in managing high blood sugar. Among the hydroxybenzoic acid derivatives, researchers have identified gallic acid, protocatechuic acid, p-hydroxybenzoic acid, and vanillic acid. Coumarins, such as scoparone (6,7-dimethoxycoumarin), scopoletin, and the furanocoumarins bergamottin and 6',7'-dihydroxybergamottin, have been extracted from peel fractions. The latter two furanocoumarin compounds are important in clinical settings due to their effect on drug-metabolizing enzymes, as further discussed.

5.4 Alkaloids, Nutritional Constituents, and Miscellaneous Compounds

Root bark and leaf extracts of C. maxima have yielded acridone alkaloids and quinolone derivatives, including 1-methyl-2-quinolone, arborine, and arborinone, which display moderate antimicrobial activity. The edible pulp provides substantial nutritional value: ascorbic acid content typically falls between 40 and 60 milligrams per 100 grams of fresh weight, making pomelo a meaningful dietary source of this essential vitamin and antioxidant. B-group vitamins—thiamine, riboflavin, niacin, pantothenic acid, and folate—are present in nutritionally relevant concentrations. The mineral profile is dominated by potassium, with significant contributions from magnesium, phosphorus, and calcium, and trace quantities of zinc, manganese, copper, and iron. Pectin, concentrated in the albedo, constitutes a commercially valuable dietary fibre with well-established prebiotic, hypocholesterolemic, and glycemia-moderating effects. Lycopene, beta-carotene, and beta-cryptoxanthin contribute antioxidant carotenoid content to red- and pink-fleshed cultivars.

6. PHARMACOLOGICAL ACTIVITIES

6.1 Antioxidant Activity

Free radical-mediated oxidative injury to lipids, proteins, and nucleic acids is now firmly established as a contributory mechanism in the initiation and progression of cardiovascular disease, type 2 diabetes mellitus, hepatic injury, neurodegenerative disorders, and carcinogenesis. The antioxidant potential of C. maxima has been assessed across a wide range of extraction solvents and plant organs using assays including DPPH radical scavenging, ABTS decolourization, ferric reducing antioxidant power (FRAP), phosphomolybdenum reduction, and metal chelation. In virtually all comparative studies, peel extracts—particularly methanolic and ethanolic preparations of the albedo—demonstrate significantly higher radical scavenging efficacy than juice, pulp, or seed extracts, a pattern attributable to the greater phenolic and flavonoid density of the peel tissue. Total polyphenol contents of peel extracts ranging from 80 to 320 milligrams gallic acid equivalents per gram of dry extract have been reported, varying with cultivar, solvent polarity, and extraction technique. Naringenin, naringin, nobiletin, rutin, chlorogenic acid, and ascorbic acid have been identified through bioassay-guided fractionation as the principal antioxidant contributors. In vivo corroboration has come from rodent models of chemically induced oxidative stress, where oral administration of C. maxima extracts significantly restored depleted hepatic and renal glutathione levels, elevated superoxide dismutase and catalase activities, and suppressed the accumulation of

malondialdehyde—a lipid peroxidation byproduct.

6.2 Antimicrobial Activity

The antimicrobial properties of C. maxima, particularly its essential oil and flavonoid-enriched extracts, have been systematically documented against clinically and agriculturally significant pathogens. Cold-pressed peel oil has demonstrated bactericidal and bacteriostatic activity against Staphylococcus aureus (including methicillin-resistant strains in select studies), Bacillus cereus, Streptococcus pyogenes, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Salmonella typhi, with minimum inhibitory concentrations (MICs) generally falling between 0.5 and 4.0 milligrams per millilitre depending on the organism and oil composition. Antifungal activity has been demonstrated convincingly against Candida albicans, Candida tropicalis, Aspergillus flavus, Aspergillus niger, and dermatophytes. Trichophyton rubrum, Trichophyton mentagrophytes, and Microsporum canis. The mechanisms underlying these effects include disruption of cytoplasmic membrane integrity by limonene and linalool (resulting in leakage of intracellular contents), interference with ergosterol biosynthesis, inhibition of efflux pumps that confer drug resistance, and suppression of biofilm formation. Naringenin and naringin have been found to potentiate the activity of tetracycline and ampicillin against resistant staphylococci in checkerboard assays, suggesting potential application in combination antimicrobial strategies.

6.3 Anti-inflammatory Activity

Inflammation, when it is chronic and out of control, plays a key role in the development of various conditions like atherosclerosis, type 2 diabetes, inflammatory bowel disease, asthma, rheumatoid arthritis, and some cancers. C. maxima extracts and isolated compounds affect inflammatory signalling through several pathways. In experiments using LPS-stimulated murine macrophages (RAW 264.7), naringenin reduced nitric oxide and prostaglandin E2 production in a dose-dependent manner. It also suppressed the secretion of IL-1β, IL-6, and TNF-α while downregulating iNOS and COX-2 protein expression. These effects mainly occurred by inhibiting IκB kinase phosphorylation, which blocked NF-κB from moving into the nucleus. Nobiletin additionally suppressed MAPK signalling pathways (ERK, JNK, and p38) that increase inflammatory gene transcription. In rodent models, C. maxima peel extract given at oral doses of 200 to 400 milligrams per kilogram reduced carrageenan-induced plantar edema in rats by 40 to 55 per cent four hours after injection, an effect similar to that of indomethacin at lower doses. Anti-arthritic effects were observed in models of Freund's adjuvant-induced arthritis, with treated animals showing reduced paw thickness, better joint histology, and lower levels of circulating inflammatory markers.

6.4 Antidiabetic Activity

Diabetes mellitus, especially type 2, caused by insulin resistance and issues with beta cells, is one of the biggest chronic health problems worldwide. Several studies have outlined how the components of C. maxima can lower blood sugar through different molecular pathways. Naringenin activates the peroxisome proliferator-activated receptor gamma (PPARγ), which is also targeted by thiazolidinedione insulin sensitisers. This activation helps fat cells take in glucose and improves insulin signalling in peripheral tissues. At the same time, naringenin inhibits enzymes in the liver that are responsible for making glucose, such as phosphoenolpyruvate carboxykinase and

glucose-6-phosphatase, and supports glycogen production. Naringin effectively blocks the activities of intestinal alpha-glucosidase and salivary alpha-amylase, reducing glucose absorption after meals in a way similar to the drug acarbose. Chlorogenic acid activates the liver's AMP-activated protein kinase (AMPK), which plays a key role in metabolism, leading to less fat and glucose production while encouraging the burning of fatty acids. Hesperidin and rutin protect the pancreas by reducing oxidative stress that can lead to beta-cell death, thus helping to maintain insulin production. In studies with diabetic rats treated with C. maxima extracts, researchers consistently found lower fasting blood sugar levels, better glucose tolerance tests, normalised glycated hemoglobin levels, reduced pancreatic inflammation in tissue samples, and a partial recovery of beta-cell mass.

6.5 Anticancer Activity

The investigation of C. maxima constituents as anticancer agents has gathered considerable momentum, with nobiletin occupying the center of research attention. This polymethoxylated flavone inhibits cancer cell proliferation across multiple tumor lineages, including colorectal (HCT116, SW480), breast (MCF-7, MDA-MB-231, T-47D), hepatocellular (HepG2, Huh7), gastric (AGS, MKN-45), lung (A549, H1299), and prostate (LNCaP, PC-3) carcinoma cell lines. Mechanistic dissection reveals that nobiletin induces G2/M cell cycle arrest by downregulating cyclin B1 and CDC2 expression, triggers intrinsic apoptosis through elevated Bax/Bcl-2 ratios, cytochrome c release, and caspase-3 and -9 activation, suppresses invasion and migration by reducing MMP-2 and MMP-9 secretion, and inhibits tumor angiogenesis by blocking VEGF and HIF-1alpha expression. Naringenin demonstrates selective cytotoxicity, showing significantly greater growth inhibitory effects toward MCF-7 and triple-negative breast cancer cells than toward normal human mammary epithelial cells—a selectivity index of considerable therapeutic relevance. D-Limonene, the dominant monoterpene in pomelo peel oil, has been evaluated in Phase I clinical trials in women with breast cancer recurrence risk; observational data suggest that regular dietary consumption is associated with reduced risk, and the compound has been proposed as a chemopreventive agent acting through induction of Phase II detoxification enzymes and modulation of Ras signaling. These converging findings from diverse cancer models position C. maxima's phytoconstituents as serious candidates for oncological drug discovery programs.

6.6 Hepatoprotective Activity

The hepatoprotective capacity of C. maxima has been demonstrated across multiple chemically induced liver injury models. In the well-characterised carbon tetrachloride model of acute hepatotoxicity, pretreatment and concurrent treatment with C. maxima peel extract attenuated the rise in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin concentrations and partially preserved normal hepatic histoarchitecture—reducing centrilobular necrosis, hepatocyte ballooning, and inflammatory cell infiltration. Naringenin has been specifically investigated in high-fat diet-induced non-alcoholic fatty liver disease (NAFLD), an increasingly prevalent hepatic pathology. In these models, naringenin supplementation significantly reduced hepatic triglyceride and cholesterol accumulation; attenuated activation of lipogenic transcription factors (SREBP-1c and ChREBP); downregulated pro-inflammatory cytokine expression within hepatic tissue (TNF-alpha, IL-6, and IL-1beta); and ameliorated markers of oxidative stress and

early fibrosis. These hepatoprotective properties appear to arise from the integration of antioxidant, anti-inflammatory, and lipid-regulatory activities, suggesting multi-target protection of hepatocytes.

6.7 Cardioprotective and Hypolipidemic Activity

Cardiovascular disease remains the principal cause of premature mortality worldwide, and dyslipidemia is a central modifiable risk factor. C. maxima flavonoids have been investigated in high-fat diet and Triton WR-1339-induced hyperlipidemic rodent models. Oral administration of naringenin, naringin, and nobiletin consistently produced reductions in total plasma cholesterol, triglycerides, and LDL cholesterol, accompanied by modest elevations in HDL cholesterol. The underlying mechanisms include suppression of HMG-CoA reductase activity (the rate-limiting step in de novo cholesterol biosynthesis), upregulation of hepatic LDL receptor expression, enhanced bile acid excretion in faeces via ABCG5/8 transporter induction, and inhibition of pancreatic lipase-mediated dietary fat absorption. Antihypertensive mechanisms for naringenin and hesperidin include endothelium-dependent relaxation of vascular smooth muscle through enhanced nitric oxide bioavailability, inhibition of angiotensin-converting enzyme (ACE), and reduced plasma endothelin-1 concentration. Antiplatelet activity through inhibition of collagen- and ADP-induced platelet aggregation reduces atherothrombotic risk. Taken together, these activities support the view of C. maxima as a potential multi-mechanism cardioprotective functional food.

6.8 Neuroprotective Activity

Neurodegeneration, characterised by progressive loss of neuronal structure and function, underlies conditions including Alzheimer's disease, Parkinson's disease, and vascular dementia, for which current pharmacotherapy remains inadequate. Nobiletin has emerged as a particularly promising neuroprotective agent from C. maxima. It inhibits amyloid-beta (Aβ) peptide aggregation, promotes its clearance via upregulation of neprilysin and IDE, suppresses tau hyperphosphorylation through GSK-3β and CDK5 inhibition, and attenuates neuroinflammation by reducing microglial NF-kappaB activation and pro-inflammatory cytokine release within brain tissue. In APPswe/PS1dE9 transgenic Alzheimer mouse models, chronic nobiletin administration significantly improved spatial learning and memory performance in Morris water maze protocols, reduced brain amyloid plaque load, and partially restored synaptic protein expression. Naringenin has been shown to cross the blood-brain barrier and protect primary cortical neurons against glutamate-induced excitotoxicity and hydrogen peroxide-mediated oxidative damage. In rodent models of Parkinson's disease induced by MPTP, naringenin preserved dopaminergic neuron populations in the substantia nigra and improved locomotor performance. The anxiolytic and mild sedative properties of C. maxima essential oil, demonstrated through elevated plus-maze and open-field behavioral tests, suggest additional CNS activities worthy of formal investigation.

7. DRUG INTERACTIONS AND SAFETY CONSIDERATIONS

A clinically important dimension of C. maxima consumption that warrants prominent discussion is its potential to alter the pharmacokinetics of co-administered drugs through inhibition of cytochrome P450 3A4 (CYP3A4)—the intestinal and hepatic enzyme responsible for first-pass metabolism of an estimated 50 per cent of clinically prescribed pharmaceuticals. Pomelo, like grapefruit, with which it shares structural and

genetic proximity, contains the furanocoumarins bergamottin and 6',7'-dihydroxybergamottin, which form mechanism-based irreversible inhibitor complexes with CYP3A4, thereby abolishing its metabolic activity for up to 72 hours following a single pomelo serving. The clinical consequence is a marked and unpredictable elevation in plasma concentrations of CYP3A4 substrates, including HMG-CoA reductase inhibitors (simvastatin, lovastatin, and atorvastatin); dihydropyridine calcium channel blockers (amlodipine, felodipine, and nifedipine); immunosuppressants (cyclosporine, tacrolimus, and sirolimus); antiretrovirals (saquinavir and indinavir); certain antihistamines; benzodiazepines; and several antiepileptics. Sources and analytical characterisation practices make cross-study comparison deeply problematic. Clinical human data, which alone can establish efficacy and safety in the target species, are conspicuously scarce—a gap that this review identifies as the foremost priority in the field. From a toxicological standpoint, acute and subacute rodent studies have not identified significant systemic toxicity at standard dietary doses; nonetheless, long-term safety data from human studies remain absent, and formal dose-ranging toxicology investigations using standardized extracts are a research priority.

8. DISCUSSION

The evidence assembled in this review paints a picture of C. maxima as a phytochemically sophisticated and pharmacologically versatile plant. The concordance between traditional therapeutic applications documented across multiple Asian cultures and the mechanistic activities uncovered in laboratory research is striking and lends credibility to both bodies of knowledge. The peel—abundant, inexpensive, and frequently discarded as agricultural waste—emerges from the available evidence as the single richest source of bioactive compounds, creating an attractive opportunity for value-added utilization within circular bioeconomy frameworks. Industrial extraction of naringenin, nobiletin, and essential oils from pomelo processing waste could simultaneously reduce agricultural waste burdens and provide cost-effective pharmaceutical or nutraceutical raw materials. However, several limitations of the current evidence base demand candid acknowledgement. The preponderance of studies is in vitro, conducted under conditions that do not replicate the complexity of whole-organism physiology—including gut absorption, systemic distribution, enzymatic biotransformation, cellular sequestration, and excretion. Animal model data, while internally consistent and encouraging, translate to human outcomes with well-known limitations of scale, metabolic rate, and pharmacogenomic differences. A quantitatively significant methodological problem is the inconsistent standardization of extracts used across studies: different extraction solvents, plant part ratios, cultivar sources, and analytical characterisation practices make cross-study comparison deeply problematic. Clinical human data, which alone can establish efficacy and safety in the target species, are conspicuously scarce—a gap that this review identifies as the foremost priority in the field.

10. CONCLUSION

Citrus maxima is a plant whose medicinal dimensions have been appreciated intuitively for centuries and are now being progressively illuminated through the tools of modern pharmacology. The chemical inventory of this species—spanning flavanones, polymethoxylated flavones, monoterpenes, sesquiterpenes, phenolic acids, furanocoumarins, alkaloids, and essential nutrients—provides an exceptionally broad

molecular basis for therapeutic activity. The convergence of antioxidant, antimicrobial, anti-inflammatory, antidiabetic, anticancer, hepatoprotective, cardioprotective, and neuroprotective activities in a single species, substantiated by an expanding body of in vitro and animal data, positions C. maxima as a compelling subject for pharmaceutical drug discovery and nutraceutical development. The peel, far from being waste, may prove to be the plant's most valuable tissue for pharmaceutical exploitation. Simultaneously, awareness of drug interaction risks through CYP3A4 inhibition must accompany any clinical development program and be communicated clearly to patients and prescribers. Realizing the full therapeutic potential of this remarkable species will require a concerted shift from discovery-phase laboratory investigation toward rigorously designed, well-powered human clinical research.

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