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Exploring phytochemistry and pharmacology of the Apocynaceae family: A comprehensive review

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ABSTRACT

The *Apocynaceae* family, one of the largest and most medically significant angiosperm families, encompasses over 400 genera and approximately 5,000 species worldwide. Renowned for their production of diverse secondary metabolites including indole and steroidal alkaloids, terpenoids, flavonoids, glycosides, phenolic compounds, lactones and cardiac glycosides. These plants have been integral to traditional medicinal practices and modern pharmacotherapy. This review synthesizes current knowledge on the phytochemical diversity, biological activities and therapeutic applications of major Apocynaceae crops such as *Catharanthus roseus*, *Rauvolfia serpentina*, *Nerium oleander*, *Plumeria species*, *Tabernaemontana* and *Vinca* species. Emphasis is placed on validated bioactivities including anticancer, antihypertensive, antimicrobial, anti-inflammatory and neuroprotective effects, as well as emerging areas like antiviral and sustainable agricultural uses. The complex chemical profiles often exhibit synergistic bio efficacies with reduced toxicity compared to isolated compounds. Advances in phytochemical characterization, molecular biology and DNA barcoding have enhanced taxonomic resolution and quality control, fostering reliable identification and safety assurance. Despite well-documented therapeutic potentials, challenges in standardization, toxicity evaluation, bioavailability and clinical validation persist. Future research should prioritize integrative approaches combining metabolomics, genomics and synthetic biology to optimize bioactive compound production and develop novel, safe, and effective phytomedicines. This review highlights the Apocynaceae family's continuing relevance and vast untapped potential in the discovery of innovative therapeutic agents and bioactive products for sustainable human health and agriculture.

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Keywords: Apocynaceae, Phytochemicals, Bioactivity, Alkaloids, Flavonoids, Anticancer.

INTRODUCTION

The Apocynaceae family, commonly known as the Dogbane family, stands as one of the largest and most pharmacologically significant families within the angiosperms. This diverse family encompasses over 400 genera and approximately 5,000 species, thriving predominantly in tropical and subtropical regions across Europe, Asia, Africa, Australia and the Americas. Members of the Apocynaceae are generally characterized by their production of milky latex and a remarkable diversity of secondary metabolites including alkaloids, terpenoids, steroids, flavonoids, glycosides, simple phenols, lactones and hydrocarbons. These compounds confer significant biological activities and medicinal properties [1,2].

Taxonomically, the family is subdivided into five subfamilies: Apocynoideae, Asclepiadoideae, Secamonoideae, Periplocoideae and Rauvolfioideae. These plants exhibit diverse morphological traits. Their perennial and evergreen life forms range from herbs to shrubs and trees with stems that are aerial, woody, herbaceous or smooth. Leaves exhibit great variation in shape, from simple ovate to lanceolate and linear forms [3]. Floral structures often feature twisted crowns, tightly clustered leaves and uniquely shaped pollinia that serve as key taxonomic identifiers. Pollination mechanisms predominantly involve insects, although a minority of species employ birds as pollinators, underscoring the ecological diversification within the family [4].

Apocynaceae plants have contributed substantially to traditional medicine. Their extracts and preparations address a wide array of ailments including skin infections, fever, pain, diabetes, gastrointestinal disorders, malaria, epilepsy and cardiovascular diseases [5]. The milky latex contains proteases such as cysteine and serine types that are stable under various environmental conditions, with promising applications extending to industrial uses like milk coagulation [6].

Phytochemically, the Apocynaceae family is a prolific source of biologically active metabolites. Documented chemical classes include alkaloids especially indole, steroidal and terpene alkaloids, alongside triterpenoids, flavonoids, glycosides, phenols, steroids, lactones, sterols, sugars and lignans. Between 1919 and 2021, over 160 steroidal alkaloids were identified, although only a select number of genera (approximately 10 of 410) produce these compounds, reflecting the chemotaxonomic specificity within the family [7]. Cardiac glycosides derived from these plants have been investigated extensively, revealing beneficial effects on heart muscle contractility and potential in heart failure treatment, albeit with toxicity concerns dependent on dosage and compound [8].

Among lesser-utilized members of the family, species such as *Marsdenia edulis*, *Vincetoxicum rossicum* and *Gongronema latifolium* display high content of terpenoids, steroids and flavonoids respectively, suggesting important reservoirs of bioactivity yet to be fully exploited. The dual nature of some species bearing toxic as well as therapeutic qualities, necessitates precise species identification and quality assurance. Challenges increasingly met through DNA barcoding innovations, which afford stability, universality, and reproducibility in species authentication [9].

Historically and contemporarily, Apocynaceae species have been integral to traditional medicine and modern pharmacotherapy, with scientific corroboration of their use in combating infectious diseases, cardiovascular ailments and various chronic conditions. The family's significance is epitomized by widely used drugs such as vincristine and vinblastine from *C. roseus* and the antihypertensive reserpine from *R. serpentina*, highlighting the continuum from ethnomedicine to life-saving pharmaceuticals [10].

Ongoing global interest in plant-derived pharmaceuticals is driven by increasing burdens of synthetic drug resistance, adverse side effects of conventional medicines and the pursuit of sustainable, effective therapeutic alternatives. Due to their complex chemical matrices, Apocynaceae plants offer synergistic bioactivities and tend to present reduced toxicity compared to isolated synthetic compounds. Their potent allelopathic and bioactive properties also propose expanded applications beyond medicine including environmentally friendly pest control, underscoring their multidisciplinary value [11].

This review aims to provide a comprehensive and updated synthesis of the bioactive properties of major Apocynaceae crops by examining their phytochemical constituents, biological activities, therapeutic applications and potential for future drug development. By including both well-studied species and emerging candidates, the review underscores the family's continued relevance in modern medicine and sustainable agriculture.

MAJOR PHYTOCHEMICALS AND BIOLOGICAL ACTIVITIES OF SELECTED APOCYNACEAE SPECIES

Adenium

Adenium obesum, commonly known as the Desert Rose and indigenous to African regions, is a medicinal plant recognized for its rich phytochemical composition and broad-spectrum biological activities [12]. Phytochemical analyses including gas chromatography-mass spectrometry (GC-MS) have identified over 26 bioactive compounds within its ethanolic leaf extracts encompassing steroids, glycosides, alkaloids, pregnanes, flavonoids, cardiac glycosides, terpenoids and sugars [13]. Key metabolites identified include benzofuran, benzoic acid, vitamin E, alpha-amyrin, stigmasterol and gamma-sitosterol, each contributing to the therapeutic potential of the plant [14].

Pharmacological research underscores significant anticancer properties of *A. obesum*, where methanolic seed extracts induce cytotoxicity in human breast cancer cells, enhancing DNA damage as revealed by the alkaline comet assay [15]. The ethanolic leaf extract demonstrates potent anti-inflammatory, antioxidant and anticancer effects reducing viability of A549 lung cancer cells through mechanisms involving free radical scavenging and inhibition of cell proliferation [14]. Among solvent fractions, ethyl acetate extracts exhibit superior antioxidant and antibacterial activities while chloroform extracts show comparatively diminished effects. Beyond anticancer applications, *A. obesum* exhibits antidiabetic, antiviral, larvicidal, piscicidal and molluscicidal activities, indicating extensive pharmacological versatility [16].

Mechanistically, the diverse phytochemicals exert synergistic impacts. Cardiac glycosides from *A. obesum* modulate cardiovascular functions by influencing ion transport in cardiac cells. Flavonoids act as antioxidants by scavenging reactive oxygen species and modulating inflammatory signaling pathways, thereby mitigating oxidative stress. Terpenoids contribute to antimicrobial activities by disrupting microbial membranes and inhibiting pathogen growth [17].

For *Adenium obesum*, ethanol-based leaf and seed extractions are commonly used with GC-MS analysis revealing a rich mix of steroids, glycosides and cardiac glycosides; ethyl acetate extracts yield superior antioxidant and antibacterial fractions while methanolic seed extracts demonstrate pronounced cytotoxicity [18]. However, despite these promising bioactivities demonstrated in *in vitro* and small-scale *in vivo* models, there are notable research gaps in compound isolation, detailed mechanistic studies, pharmacokinetics and clinical evaluations.

Future research efforts should prioritize the isolation and structural characterization of active compounds, evaluation of their molecular targets, dose-response relationships and toxicity profiles in relevant animal models and human clinical trials. Additionally, standardization of extraction protocols and optimization for bioavailability and safety will be critical for advancing *A. obesum* derived therapeutics to clinical and commercial applications.

Allamanda

Allamanda cathartica, a prominent member of the Apocynaceae family, stands out for its remarkable phytochemical diversity and broad ethnomedicinal applications. The plant is rich in secondary metabolites such as alkaloids, flavonoids, terpenoids, steroids, glycosides, organic acids, phenolic compounds, saponins, tannins and carbohydrates with nearly every tissue leaves, stems, roots and flowers demonstrating abundance in bioactive compounds. Notable among these constituents is plumericin, isoplumericin, allamandin, plumieride, ursolic acid, beta-amyrin, beta-sitosterol, lupeol and several flavonoids (quercetin, kaempferol, naringenin), each associated with specific therapeutic effects [19].

Pharmacological investigations have validated a spectrum of biological activities for *A. cathartica*. Extracts from different plant parts exhibit antioxidant, antibacterial, antifungal, cytotoxic, anti-inflammatory, thrombolytic, nematicidal and wound-healing effects in both *in vitro* and *in vivo* settings. Compounds such as plumericin and allamandin induce programmed cell death (apoptosis) in cancer cell lines by inhibiting cell proliferation and modulating key signaling cascades [20]. Flavonoids like quercetin and kaempferol show potent free radical scavenging via direct neutralization of reactive oxygen species and indirect modulation of inflammatory pathways. Agricultural studies demonstrate that *Allamanda blanchetii* leaf

extracts suppress fungal pathogens in crops, highlighting a plausible role as biopesticide and resistance-inducing agent [21].

Tissue-specific extracts and solvent selection are critical; ethanol-based extracts of stems and roots generally display higher antioxidant and antimicrobial activity compared to aqueous extracts, attributing efficacy to the concentration and solubility of key phytochemicals. Some animal studies and clinical derivatives propose hepatoprotective, wound-healing and antifertility applications further expanding the therapeutical canvas of the genus [22]. *Allamanda cathartica* utilizes ethanol, methanol and aqueous extractions across stems, roots, and flowers; ethanol-based stem and root extracts present higher antioxidant and membrane-stabilizing effects attributed to concentrated flavonoids, saponins and steroids [23].

Despite these promising bioactivities, the translation from laboratory discovery to clinical application faces notable challenges. Current studies predominantly rely on crude extracts and small-scale assays leaving pharmacokinetics, toxicity, and dosage optimization underexplored. More research is needed to isolate, purify and characterize the active compounds, followed by robust animal testing and human trials to confirm efficacy and safety. Standardized extraction methods and in-depth mechanistic investigations will facilitate reproducible and effective therapeutic uses.

In summary, *Allamanda cathartica* emerges as a pharmacologically versatile and chemically rich tropical medicinal plant, serving as a potential source for drug development and sustainable biopesticides. Rigorous future research, focusing on compound isolation, mechanism elucidation and clinical validation is essential to unlock and realize its full medical and agricultural potential.

Calotropis

Calotropis procera and *Calotropis gigantea*, two notable xerophytic shrubs of the Apocynaceae family, possess extensive ethnomedicinal applications supported by their rich phytochemical repertoire. Gas chromatography-mass spectrometry (GC-MS) and phytochemical screenings reveal a diverse set of bioactive constituents spread across plant parts like leaves, roots, flowers, stems and latex. The compositions include alkaloids, flavonoids, terpenoids, steroids, glycosides, oxypregnanes, tannins, saponins, phenolic compounds, anthraquinones and cardiac glycosides [24].

GC-MS studies on methanolic extracts of *C. procera* flowers identified 30 constituents with γ-sitosterol (15.39%) being the predominant compound. Both species harbor cardioactive glycosides such as calactin, calotoxin, usharin and vouscharin implicated in their known insecticidal, molluscicidal and nematicidal activities crucial for traditional and agricultural pests control [25]. Notably, the latex of these plants contains complex mixtures with potent irritant, neurotoxic and anticholinergic properties accounting for both therapeutic actions and toxicity risks emphasizing the need for cautious handling [26].

Antibacterial activity assays utilizing the disc diffusion method demonstrate that *C. procera* leaf extracts exhibit significant inhibitory effects on *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Bacillus cereus* whereas inhibition against *Salmonella typhi*, *Escherichia coli*, *Klebsiella pneumonia* and *Enterococcus faecalis* is comparatively limited [27]. The essential oils of *C. procera* display pronounced phytotoxicity against weed species such as *Digitaria aegyptium*, suggesting these oils' application as environmentally benign bioherbicides [28]. Furthermore, ethanolic leaf extracts of *C. procera* harbor potent anticancer activity against human MCF-7 breast and HCT-116 colon cancer lines attributed to constituents like luteolin, kaempferol, ferulic acid and caffeic acid exhibiting dose-dependent inhibition and strong antioxidant efficacy outperforming ascorbic acid controls [29].

Additional pharmacological properties include antioxidant, anti-inflammatory, antidiabetic, antifungal, anthelmintic, gastroprotective, wound-healing, anti-analgesic, antimalarial, neuroprotective, antiulcer and hepatoprotective effects expanding the therapeutic spectrum of Calotropis species [30]. The presence of proteolytic enzymes and volatile fatty acids in *C. gigantea* further contributes to its wound healing and enzyme-inhibiting capacity [31]. Extracts from *C. procera* leaves also promote growth and enhance the production of bioactive compounds like flavonoids and anthocyanins in medicinal plants such as *C. roseus*, indicating potential as a biostimulant [32]. Calotropis extraction generally targets leaves, latex and flowers employing methanol and ethanol for GC-MS profiling and disc diffusion antibacterial testing. Latex is often collected directly highlighting the plant's proteases and volatile compounds though caution is warranted due to potent irritancy and toxicity [33].

Despite compelling pharmacological profiles, the clinical translation of Calotropis extracts is constrained by limited isolation studies, inconsistent extraction protocols, and a paucity of comprehensive toxicological profiling. Particularly, the toxic effects related to the plant's latex necessitate stringent safety evaluations. Future research should focus on pure compound characterization, molecular mechanism elucidation, controlled animal studies and human clinical trials to fully harness Calotropis species' medicinal and agricultural potential.

Nerium

Nerium oleander, a globally cultivated ornamental shrub belonging to the Apocynaceae family, accumulates a spectrum of phytochemicals including phenols, tannins, flavonoids, coumarins, sterols, triterpenes, alkaloids, phlobatannins, cardiac glycosides and saponins widely distributed in leaves, flowers, seeds and stems [34]. Quantitative phytochemical analysis shows that alcoholic extracts of oleander flowers and aqueous extracts of leaves possess the highest concentrations of phenolic compounds and flavonoids respectively, correlating with their potent antioxidant capacities. GC-MS studies identified 34 chemicals from flowers representing approximately 1.76% essential oil encompassing bioactive cardiac glycosides like oleandrin which is predominantly abundant in roots but also present in other parts [35].

The pharmacological profile of *N. oleander* includes notable cytotoxic, antioxidant, antibacterial, anti-inflammatory, antiparasitic, analgesic, dermatological, hypolipidemic, antidiabetic, cardiovascular and neuroprotective activities. The plant has traditional uses for managing ailments such as hemorrhoids, epilepsy, skin disorders, ulcers and sexually transmitted infections with each plant part contributing varied bioactivities [36,37]. The alkaloid and cardiac glycoside oleandrin act by inhibiting the Na+/K+-ATPase pump in cell membranes, conferring cardiac effects but also posing risks of severe cardiotoxicity. Other cardenolides like nerin, digitoxigenin and olinerin synergize these actions but require careful dosing due to a narrow therapeutic index [38].

Nerium oleander exhibits significant antibacterial activity mainly against gram-positive bacteria with both ethanolic and aqueous extracts demonstrating moderate effects by inhibiting bacterial growth and decreasing pro-inflammatory cytokine production as shown in *in vivo* models [39]. The antioxidant efficacy assessed through peroxide radical scavenging and β-carotene bleaching assays reveals a robust ability to neutralize oxidative stress supporting anti-inflammatory and cytoprotective roles [35,37]. For Nerium, alcoholic flower extracts and aqueous leaf extracts are standard, as they confer high yields of phenolics and flavonoids. GC-MS is used for root profiling to isolate cardiac glycosides like oleandrin, with additional attention to toxicity management throughout extraction and downstream use [40].

Despite promising therapeutic properties, oleander's utilization is constrained by potent toxicity manifested as cardiac arrhythmias, inflammatory cell infiltration and gastrointestinal symptoms due to its frequency of lethal overdoses and lack of standardized safe dosing. This necessitates extensive toxicological profiling, development of safer derivatives and well-designed clinical studies to translate traditional use into modern medicine safely.

In conclusion, *N. oleander* represents a double-edged medicinal resource with a rich chemical diversity underpinning its broad pharmacological spectrum. Comprehensive future research should prioritize isolation of bioactive constituents, mechanistic elucidation, targeted toxicity mitigation and clinical validation to optimize its therapeutic applications while minimizing adverse effects.

Plumeria

The genus Plumeria, encompassing species such as *Plumeria obtusa*, *P. alba*, *P. rubra* and *P. pudica* has attracted substantial ethnomedicinal interest due to its diverse bioactive chemical constituents and broad pharmacological effects. Phytochemical analyses reveal a complex composition of over 130 chemical components in *P. obtusa* alone including flavonoids, terpenoids, phenolic acids, iridoids, cardiac glycosides, pentacyclic triterpenoids (e.g., kaneroside, oleandrin, α-amyrin), steroids, saponins, tannins, coumarins, anthraquinones, alkaloids, glycosides, volatile oils and fatty acid esters [41,42]. These bioactives are distributed throughout the plant's leaves, flowers, stem bark and roots as confirmed by GC-MS, chromatographic and spectroscopic techniques. Major volatile constituents of *P. alba* essential oils include linalool (23.91%), α-terpineol (10.97%), geraniol (10.47%) and phenyl ethyl alcohol (8.65%), which demonstrate significant antibacterial and antibiofilm functions [44].

Pharmacological investigations demonstrate *Plumeria* spp.'s pronounced antimicrobial activity against a range of pathogenic bacteria. For instance, *P. obtusa* leaf extracts inhibit *Pseudomonas aeruginosa* more effectively than *Staphylococcus aureus* with methanolic extracts generating the largest inhibition zones in agar diffusion assays [41]. Frangipani flower extracts exhibit antibacterial properties comparable to broad-spectrum antibiotics against uro-gastropathogens such as *Shigella fexneri*, *Salmonella typhi*, *Bacillus cereus*, *Bacillus subtilis* and *Staphylococcus aureus*. Moreover, innovative applications including frangipani-based silver nanoparticles have shown promise in suppressing these pathogens, indicating potential for novel antimicrobial formulations [45]. The antibacterial efficacy extends to *P. rubra* and *P. alba* extracts where a broad spectrum of gram-positive and gram-negative bacteria are inhibited, highlighting the genus' wide therapeutic applicability [46].

Several human diseases may benefit from Plumeria's bioactivities. In diabetic rat models, oral administration of *P. obtusa* leaf extracts significantly improved serum glucose, glycosylated hemoglobin, insulin and lipid profiles supported further by histological and ultrastructural tissue analyses emphasizing the plant's antidiabetic potential [47]. Additionally, *P. species* possess anti-inflammatory, wound-healing, anti-mutagenic, antiallergic, carminative, cytotoxic, laxative, diuretic, anti-ulcer, anti-leprosy and anti-ascitic activities ascertained through both traditional and experimental investigations [43]. The chemoprotective and antiproliferative potential is highlighted by the isolation of novel compounds such as plumercine, isoplumericine and 13-O-p-coumaroyl plumieride from *P. alba* exhibiting promising anti-leukemic activity validated via *in vitro* cytotoxicity assays and *in silico* molecular docking approaches [43].

Morphoanatomical studies have further corroborated the plant's pharmacological relevance and chemical biosynthesis capabilities. The biochemical repertoire includes cardiac glycosides known for their critical role in modulating cardiovascular function as well as lignins, steroids and polyphenols widely distributed particularly in the leaves, contributing to antioxidant and antimicrobial functions [48]. Essential oils extracted from the genus show not only antibacterial but also antibiofilm capabilities making them candidates for addressing biofilm-associated infections resistant to conventional antimicrobials [44]. Plumeria spp. extraction encompasses leaves, flowers, stems and roots, utilizing methanolic extracts for cytotoxicity and antimicrobial evaluation while essential oil distillation (notably from *P. alba*) efficiently isolates volatile terpenoids and antibiofilm constituents [49].

Despite promising pharmacological profiles, challenges persist regarding the characterization of toxicity, bioavailability and mechanisms of action alongside a notable lack of clinical studies. Varied extraction methodologies warrant standardization to enable reproducibility and comparability of research findings. Future research must focus on isolation of active principles, elucidation of molecular targets, detailed pharmacokinetics, toxicology and well-controlled clinical trials to ultimately translate Plumeria's ethnopharmacological significance into validated therapeutic interventions.

Sarpagandha

R. serpentina, commonly known as Sarpagandha, has been a cornerstone of traditional medicine for centuries particularly in treating hypertension and various neurological disorders. Its principal bioactive alkaloid, reserpine was extensively studied over the past 75 years and predominantly accumulates in the root (72%) with lesser concentrations in the stem (25%) and leaves (3%) [50]. Reserpine exerts its antihypertensive effect primarily through the irreversible inhibition of the vesicular monoamine transporter (VMAT), leading to depletion of catecholamines and serotonin in adrenergic nerve terminals, which results in vasodilation and lowering of blood pressure. This pharmacological action underpins Rauvolfia's long-standing use in managing essential hypertension, a role further validated by recent studies standardizing Sarpagandha formulations and confirming efficacy in animal models [51].

The phytochemical landscape of *R. serpentina* is rich and diverse comprising a spectrum of indole alkaloids such as ajmaline, ajmalicine, deserpidine, indobine, reserpine, rescinnamine and yohimbine, alongside a suite of flavonoids, tannins, phenols and cardiac glycosides [52]. Each alkaloid exhibits unique biological activities like ajmaline serves as an antiarrhythmic agent, yohimbine is employed clinically to treat erectile dysfunction and multiple compounds display antifungal, anti-inflammatory, antiproliferative, antidiabetic and neuroprotective properties. Reserpine, notably, has demonstrated antiviral activity against SARS-CoV-2 *in vitro*, suggesting emerging therapeutic applications [53].

Clinical experience and ethnomedical practices endorse R. serpentina's efficacy in diverse indications including hypertension, psychiatric and neurological conditions, gastrointestinal ailments and reproductive health, where the root extract stimulates uterine contractions facilitating childbirth [54]. The multifaceted pharmacodynamics stem from synergistic action of its complex phytoconstituents acting on cardiovascular, immunological and neural pathways. However, the therapeutic use of Rauvolfia is tempered by well-documented adverse effects, including sedation, depression, bradycardia and potential toxicity from overdose, necessitating judicious application and rigorous safety profiling. In *R. serpentina*, roots serve as the principal tissue for indole alkaloid recovery, predominantly via ethanol or methanol extraction followed by HPLC, GC-MS, or NMR quantification and structural elucidation; standardization for reserpine content is a clinical priority [55].

Progress in analytical techniques such as HPLC, GC-MS56 and NMR has facilitated precise quantification and structural elucidation of *R. serpentina's* compounds, advancing quality control and formulation development [56]. Nonetheless, challenges remain in standardizing alkaloid concentrations, optimizing delivery systems and conducting robust clinical trials. Future research must prioritize isolation of less

toxic analogs, enhanced drug delivery and translational studies to harness *R. serpentina's* medicinal potential while mitigating risks.

Tabernaemontana

The genus *Tabernaemontana*, notably *Tabernaemontana catharinensis* and *Tabernaemontana divaricata*, harbors a wealth of bioactive secondary metabolites conferring a multitude of pharmacological effects. Traditional medicine harnesses *T. catharinensis* leaves for skin conditions and inflammatory diseases due to their potent topical anti-inflammatory properties. Experimental studies have demonstrated that leaf extracts inhibit edema and modulate inflammatory cytokine expression by elevating myeloperoxidase (MPO) activity. This bioactivity is attributed to a complex mixture of phenolic compounds, terpenes, and monoterpene indole alkaloids [57].

Alkaloid diversity within this genus is remarkable, encompassing monoterpene neuro-active compounds such as catharanthine, coronaridine, voacangine, voacamine, ibogamine and apparicine manifesting pharmacodynamic actions including antitumor, antimicrobial, analgesic, CNS stimulation, vasodilation, anticonvulsant, cardiotonic, bradycardic and hypotensive effects [58,59].

Specifically, alkaloids like 12-hydroxy akuammicine induce uterotonic activity, while coronaridine and voacamine exhibit anti-inflammatory and antimicrobial properties, respectively. These compounds collectively contribute to the botanical's ethnopharmacological use against a broad spectrum of ailments including tumors, epilepsy, asthma, fever, infections and rheumatic pain [60].

Phytochemical screening confirms the presence of not only alkaloids but also terpenoids, steroids, flavonoids, phenolic acids, glycosides, saponins, tannins and carbohydrates with quantifications indicating significant levels of total phenols, flavonoids, alkaloids, chlorophyll and ascorbic acid highlighting the plant's antioxidant and therapeutic potential [61]. The presence of vitamin derivatives (vitamins A, D and E) and phytol further augment its antioxidant and wound-healing attributes [62].

The genus demonstrates notable antibacterial actions, with extracts showing activity against *Streptococcus mutans*, *Lactobacillus acidophilus*, *Staphylococcus aureus*, *Enterococcus faecalis* and drug-resistant *Mycobacterium* strains [63-65]. Cytotoxicity assays reveal antiproliferative effects against multiple cancer cell lines including colorectal and melanoma attributed mainly to quinoline and indole alkaloids such as voacangine and coronaridine [66].

Recent phytochemical investigations using HPLC and mass spectrometry reveal novel indole alkaloids from *T. corymbosa* and *T. cymosa* with some displaying potent antibacterial and antifungal effects offering new avenues for antimicrobial drug discovery [67]. Moreover, molecular docking studies have supported the efficacy of key indole alkaloids as anticancer agents, underscoring their potential in overcoming multidrug resistance in cancer treatment [68]. Tabernaemontana spp. extraction commonly employs ethanol or methanol for leaves, efficiently isolating antioxidant and anti-inflammatory phenolics, terpenoids and monoterpene indole alkaloids. Specialized methods such as column chromatography and molecular docking studies, enable high-purity isolation of alkaloids for bioactivity assays [69].

Despite extensive *in vitro* and *in vivo* data, further research is essential to isolate stable bioactive compounds fully elucidate molecular mechanisms evaluate pharmacokinetics, safety and establish clinical efficacy. The genus *Tabernaemontana* stands as a promising phytotherapeutic resource supporting development of novel antimicrobial, anti-inflammatory, neuroprotective and anticancer drugs.

Periwinkle

C. roseus, also known as *Vinca rosea* or Madagascar periwinkle is a medicinally vital plant renowned for its complex secondary metabolite profile particularly its rich diversity of indole alkaloids. Over 130 alkaloids have been identified including therapeutically significant compounds such as vincristine, vinblastine, ajmalicine, serpentine and reserpine which have greatly advanced cancer chemotherapy and cardiovascular treatments [70,71]. These *vinca* alkaloids are particularly effective due to their potent ability to disrupt microtubule formation during mitosis, leading to cell cycle arrest and apoptosis in rapidly dividing cancer cells. Vincristine and vinblastine were among the first plant-derived anticancer agents to undergo clinical trials revolutionizing lymphoma and leukemia treatments [72,73].

The biosynthesis of these alkaloids is primarily localized in the leaves and flowers which accumulate precursors such as catharanthine and vindoline while roots store bioactives like ajmalicine and serpentine notable for their antihypertensive activities [74,75]. Additional bioactive constituents include flavonoids like quercetin and kaempferol, phenolics, steroids, terpenes and tannins contributing antioxidant, anti-inflammatory and antimicrobial actions [76]. The plant's ability to scavenge free radicals is demonstrated by robust *in vitro* assays involving DPPH, nitric oxide and superoxide radicals underlining its potential in managing oxidative stress-related diseases including neurodegeneration and cancer [77].

Beyond oncology, *C. roseus* exhibits hypolipidemic, hypoglycemic, gastroprotective, antiulcer and wound healing properties supporting traditional uses for diabetes, hypertension and chronic wounds. The alkaloid vincamine garners attention for cerebrovascular benefits improving cerebral blood flow and offering neuroprotection making it valuable in cognitive disorders and memory enhancement therapies [78].

Recent advances leverage green nanotechnology to biosynthesize manganese and copper nanoparticles using *C. roseus* extracts harnessing its phytochemicals as reducing and capping agents. Such nanoparticles have exhibited potent antimicrobial activity innovating biomedical applications [79]. However, therapeutic use of *vinca* alkaloids is limited by neurotoxicity underscoring the need for novel analogues with improved efficacy and safety profiles [77]. *C. roseus* protocols include ethanol/methanol extraction of leaves and flowers for *vinca* alkaloids with biosynthetic studies and green nanotechnology approaches also exploiting leaf extracts for nanoparticle synthesis and antimicrobial testing. Roots may be extracted separately for ajmalicine and serpentine [80].

Given its versatile phytochemical pool, major therapeutic relevance and ongoing research into biosynthetic pathways and biotechnological production *C. roseus* remains a pivotal species in phytopharmaceutical development. Future studies should focus on clinical translation optimized extraction methods and mechanistic elucidation fostering the development of novel anticancer, cardiovascular and neuroprotective drugs from this botanical treasure.

DISCUSSION

The Apocynaceae family represents a rich and multifaceted source of secondary metabolites with enormous pharmacological and therapeutic potential yet its full biochemical diversity and clinical utility remain incompletely explored. This review highlights the exceptional variety of bioactive compounds across major genera including *Catharanthus*, *Rauvolfia*, *Nerium*, *Plumeria*, *Tabernaemontana* and *Vinca*. Each contributing unique alkaloids, terpenoids, flavonoids, steroids and glycosides that underpin their diverse medicinal activities.

Each major genus within the Apocynaceae family is driven by the dominance of specific phytochemical groups which underpin their major pharmacological activities and therapeutic relevance. Indole

alkaloids are especially significant in genera such as Catharanthus, Rauvolfia and Tabernaemontana providing the basis for their potent anticancer, antihypertensive and neuroprotective effects exemplified by vincristine and vinblastine in Catharanthus for cancer therapy and reserpine in Rauvolfia for blood pressure control [81,82]. The monoterpene indole alkaloids in Tabernaemontana including voacangine and coronaridine offer antitumor, antimicrobial and CNS stimulant properties, thus shaping its application in both traditional and contemporary medicine.

Terpenoids and their derivatives are prominent in Plumeria, Adenium and Allamanda contributing robust antimicrobial, antioxidant and cytoprotective functions through compounds like linalool, stigmasterol and plumericin. Cardiac glycosides dominate genera such as Nerium, Calotropis and Adenium with molecules like oleandrin and calactin modulating ion transport in cardiac cells, thereby conferring powerful cardiotonic and cytotoxic activities allied with both therapeutic promise and potential toxicity. Flavonoids and phenolic compounds found amply in Calotropis, Plumeria, Allamanda and Catharanthus impart antioxidant, anti-inflammatory and wound-healing activities often through free radical scavenging and modulation of inflammatory pathways [83,84].

Steroids and glycosides play complementary roles in several genera, enhancing both the breadth and depth of biological activities, ranging from hormonal activity and membrane stabilization to synergistic effects with other phytochemicals that mitigate toxicity in crude extracts compared to isolated compounds. The complex chemical profiles in Apocynaceae frequently facilitate synergistic bioactivity, reduced side effects and broad-spectrum therapeutic potential substantiating the enduring role of these phytochemical classes in driving the medicinal value and versatility of Apocynaceae plants across diverse health and agricultural applications [85].

One of the critical insights is the prominent role of indole and terpene indole alkaloids (TIAs), such as vincristine, vinblastine, reserpine, oleandrin and voacangine, which have shaped modern medicine through anticancer, antihypertensive and neuroprotective drugs. The complex molecular mechanisms, such as microtubule disruption by *vinca* alkaloids and Na+/K+ ATPase inhibition by cardiac glycosides highlight the sophisticated bioactivity derived from these plants. Nevertheless, toxicity issues narrow therapeutic windows and adverse side effects seen with these compounds necessitate continued research towards safer analogs and targeted delivery systems.

Despite over a century of research many biosynthetic pathways remain partially elucidated, limiting optimization of compound yield and purity. Integrative omics approaches coupled with synthetic biology hold promise to harness the full synthetic potential of Apocynaceae species for scalable production of pharmacologically relevant metabolites.

The ethnopharmacological use of Apocynaceae species across diverse cultures underscores their therapeutic versatility. However, the transition from traditional use to evidence-based medicine requires standardized extraction methods, rigorous pharmacokinetic studies and well-designed clinical trials, areas currently under-addressed in the literature.

Furthermore, environmental factors and genetic variability contribute to significant differences in phytochemical content and bioactivity, emphasizing the need for precise taxonomic authentication using modern molecular tools like DNA barcoding. This is essential not only for quality control but also for conserving botanical diversity, given the dual nature of many species with both therapeutic and toxic potentials.

Beyond human medicine, recent studies uncover promising agro-biotechnological applications of Apocynaceae metabolites as bio-pesticides, allelopathic agents and biochemical stimulants, aligning with sustainable agricultural goals. Expanding research into these ecological roles could open new interdisciplinary avenues.

In conclusion, while current knowledge solidifies Apocynaceae as a pharmacognostic goldmine, critical gaps remain in translating its full chemical and therapeutic potential into clinical and industrial applications. Interdisciplinary, multidisciplinary collaboration spanning phytochemistry, molecular biology, pharmacology and agronomy will be pivotal in overcoming these challenges and unlocking the future of Apocynaceae in health and sustainability.

CONCLUSION

The Apocynaceae family represents a rich source of bioactive phytochemicals with significant therapeutic and agricultural potential. Key species have contributed to the development of important pharmaceuticals, particularly in cancer and hypertension treatment. Despite promising advancements in phytochemistry and molecular studies, challenges such as metabolite variability, toxicity, and limited clinical validation remain. Future research focusing on standardization, safety evaluation, and integrated biotechnological approaches will be crucial to fully harness the potential of this family for sustainable healthcare and agricultural applications.

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