

BOTANY, PHYTOCHEMISTRY, TRADITIONAL USES, PHARMACOLOGY OF APOCYNACEAE FAMILY: A REVIEW

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Abstract

The Apocynaceae family, also known as the dogbane family, consists of a wide variety of flowering plants with important ecological roles and multiple human applications. However, there is still a necessity for a comprehensive study of its botanical characteristics, chemical variability, traditional uses, and potential medical benefits. This review brings together information from a variety of scientific databases, articles, and books to offer a comprehensive look at the Apocynaceae family. The search for relevant literature involved using keywords such as "Apocynaceae," "alkaloids," "pharmacological activity," and "antimicrobial" to identify studies that have investigated the phytochemical constituents, traditional uses, and emerging pharmacological potential of this plant family. The Apocynaceae plant family is known for its wide variety of growth forms, unique flower structures, and the presence of characteristic latex or milky sap. Phytochemically, plants in this family are mainly recognized for alkaloids such as cardiac glycosides and vincamine. These compounds have demonstrated potential for treating cardiovascular diseases and enhancing cerebral blood flow. Traditional medicine has long used these plants for their healing properties to treat wounds and control infections. Recent pharmacological studies suggest promising effects against cancer, hypertension, and neuroprotection. Although significant progress has been made in understanding the Apocynaceae family, gaps in knowledge remain regarding the mechanism of action of many phytochemicals and their clinical applications. Future research is recommended to explore these unknowns to safeguard the biodiversity of Apocynaceae and develop new therapeutic agents.

Keywords: Apocynaceae Family, Traditional Uses, Pharmacology Medicinal , Medicinal Plants, Alkaloids, Cardiac Glycosides, Anticancer.

INTRODUCTION

The family Apocynaceae, also known as the dogbane family, includes a diverse range of flowering plants well-recognized for their production of chemical compounds that offer protection against herbivores and pathogens. [1]. They consist of numerous species with medicinal properties that are traditionally used to treat various ailments. [2] The significance of Apocynaceae is apparent in its influence on both traditional medicine and modern pharmacy.

Many plants in this family contain active compounds such as alkaloids, glycosides, and terpenoids, which have diverse effects, including anti-inflammatory qualities, as well as antimicrobial and antitumor actions. [3] [4] Additionally, the Apocynaceae family encompasses ornamental plants and species utilized for wood production, dyes, and fragrances with varied uses, including cancer treatment applications through *Catharanthus roseus* and cardiac glycosides found in arrow poisons from plants like *Strophanthus*.

Previous research on the Apocynaceae family has identified several species that produce compounds with potential applications in cancer therapy. Notably, some species have been found to contain alkaloids with cytotoxic properties that can be effective against tumor cells. For instance, the use of alkaloids such as vincristine and vinblastine, derived from the *Catharanthus roseus* plant, which belongs to the Apocynaceae family, has been well established in clinical oncology.

These alkaloids disrupt the assembly of microtubules, thereby inhibiting mitosis in cancer cells, which makes them valuable as chemotherapeutic agents for certain types of cancer, such as leukemia and lymphoma.

Additionally, the study titled "Phytochemicals from *Kigelia pinnata* Leaves Show Antioxidant and Anticancer Potential on Human Cancer Cell Line" suggests that extracts from the leaves of the *Kigelia pinnata* plant, which is also part of the Apocynaceae family, possess compounds that exhibit tumor cytotoxic potential. [5]

This indicates that they could potentially be included in drug combinations for future cancer chemotherapy. The accumulated research indicates not only the potential efficacy of plants in the Apocynaceae family for cancer treatment but also the importance of further investigation into their phytochemicals to uncover new, effective anticancer agents.[1]

These findings support the continued exploration of the Apocynaceae family as a source for novel cancer therapies. The association of the Apocynaceae family with anticancer therapy has been documented by various researchers and is broadly supported in the scientific community.[6] Specifically, seminal work on the alkaloids vincristine and vinblastine from *Catharanthus roseus*, a species within the Apocynaceae family, has played a significant role in cancer therapy.[7]

The discovery of these compounds and their development into chemotherapy drugs is attributed to the work of scientists like Robert Nobel, Charles Beer, and colleagues in the 1950s and 1960s. [8] They identified the anticancer properties of these alkaloids through research on plant extracts. Since then, numerous studies have been carried out to further understand the mechanisms of action, efficacy, and potential side effects of these alkaloids when used as chemotherapy agents [9].

Ongoing research continues to investigate other species within the Apocynaceae family for their anticancer properties, with researchers around the world conducting phytochemical screenings and preclinical trials. [10] [11]

The literature review "A review on antimicrobial botanicals, phytochemicals, and natural resistance-modifying agents from the Apocynaceae family: Possible therapeutic approaches against multidrug resistance in pathogenic microorganisms" discusses the potential of Apocynaceae plants in medicinal applications, including anti-cancer therapy (Anand, U. et al., 2020). Additionally, various authors and institutions [12] contribute to the growing body of research that further explores the therapeutic potential of this plant family.

Apocynaceae Family



Figure 1: Graphical Abstract

METHODS

This comprehensive review is based on the latest scientific databases on the families Apocynaceae *Allamanda*, *Alstonia scholaris* (L.) R.Br., *Cerbera*, *Nerium*, *Plumeria*, and *Tabernaemontana*. The database was scanned from March 2004 to March 2024 for animal, in vitro, and clinical studies.. This review brings together information from a variety of scientific databases, articles, and books to offer a comprehensive look at the Apocynaceae family. The search for relevant literature involved using keywords such as "Apocynaceae," "alkaloids," Only published data were included in this study; meanwhile, untitled references in English are not included. An extensive literature search was conducted to collect data, involving the use of scientific reports published in Frontiers, Science Direct, Scopus, Google Scholar, PubMed, Wiley Online Library, Elsevier, and other references over the past two decades. Data collected regarding botany, phytochemistry, traditional uses, and pharmacology of the Apocynaceae family is critically analyzed, and future strategies as well as appropriate perspectives of the plant as a new natural resource are discussed.

Botanical Overview of the Apocynaceae Family

The Apocynaceae family is known for its wide range of diversity and evolutionary adaptation, encompassing about 78 genera with approximately 860 species. [13] The taxonomy of this family involves hierarchical classification, which includes the former Asclepiadaceae family as a subfamily within Apocynaceae, adding an additional 348 genera to it [14]. Several genera in this family hold significant pharmacological, decorative, and economic importance due to their medicinal substances, attractive flowers, swollen stems (referred to as "pachycaul" genera), and contributions to timber production, as well as traditional dyes and aromatic compounds for perfume.

This diverse variety offers opportunities for exploring potential new medications while also contributing to global ornamental and cultural value. Distribution: Geographical spread and ecological adaptability [15]The Apocynaceae family has a broad geographical range, with its members flourishing in different environments ranging from tropical and subtropical regions to temperate zones. [14] [16] They demonstrate adaptability by thriving in diverse habitats such as arid areas, rainforests, and temperate surroundings . [17] Their wide distribution across coastal areas and mountainous terrain contributes significantly to their ecological importance within ecosystems due to their abundance. [18]

Phytochemistry of Apocynaceae

The Apocynaceae family produces a wide variety of chemical compounds that play important roles in plant defense and environmental interaction. These include alkaloids, steroids, flavonoids, terpenoids, and glycosides with significant ecological importance, such as reducing herbivory and providing defense against pathogens. [19] Many of these secondary metabolites have also been used in traditional and modern medicine due to their health benefits [20]. The chemical structures of notable compounds in the Apocynaceae family are diverse and complex, reflecting a wide range of secondary metabolites. Alkaloids, cardiac glycosides, flavonoids, terpenoids, and steroids all have unique structures that determine their biological functions and potential for medicinal use.

Plants in the Apocynaceae family produce secondary metabolites that play essential roles in ecological interactions, including defense against herbivores and microbes, attraction of pollinators, and competitive interactions. [1] These compounds also have potential health benefits such as anticancer properties, cardiovascular health effects, antimalarial activity, anti-inflammatory effects, and neuroprotective and cardioprotective effects.[15] The mechanisms through which these compounds exert their effects involve interactions with enzymes, receptors, and cellular components. Understanding these mechanisms is crucial for developing new drugs based on natural products from this plant family,[21]

The phytochemistry of the Apocynaceae family has identified a diverse array of pure chemical compounds, which include: Alkaloids: These nitrogen-containing compounds are found in many plants and are known for their pharmacological effects.[1] They can have a variety of biological activities, including analgesic, antiarrhythmic, antibacterial, and antimalarial effects. Cardiac Glycosides: These compounds have a specific action on the heart, increasing its force of contraction, and are used in the treatment of certain heart diseases. Flavonoids: These are polyphenolic compounds with potential health benefits due to their antioxidant properties [22]. They can also influence various cellular processes and have been studied for their anti-inflammatory, anti-cancer, and neuroprotective effects. Terpenoids: Also known as isoprenoids, these diverse organic chemicals are derived from five-carbon isoprene units constructed in multiple ways. Terpenoids have a wide range of biological functions and uses, including as anti-inflammatory, antimicrobial, and antineoplastic agents. Steroids: A type of terpenoid, steroids are important components of cell membranes and precursors to significant hormones and vitamins. [23]

They have numerous biological activities and are critical to the functioning of various physiological systems. These phytochemicals play essential roles in plant defense against herbivores and pathogens, as well as in attracting pollinators. [24] Many of them are of interest for their therapeutic properties and are used in traditional and conventional medicine [25]. allows abnormal cells to survive and grow in an ectopic pelvic cavity. However, little progress has been made in identifying the genetic variants that play a role in endometriosis [26]

Traditional Uses of Apocynaceae Plants

The Apocynaceae family has a rich tradition of being used across various cultures for medicinal purposes. Some traditional uses include the following: Anti-inflammatory and Pain Relief: Plants from this family have been used in traditional medicine for their anti-inflammatory properties and to relieve pain. For instance, extracts from certain

species are applied to wounds to reduce swelling and alleviate pain. Additionally, some plants are used orally or topically to treat conditions such as arthritis, rheumatism, and muscle pain. Cardiovascular Treatments: Cardiac glycosides found in some Apocynaceae plants have been utilized in treating heart conditions. They work by increasing the force of the heart's contractions, helping to manage symptoms of heart failure.

Antimicrobial and antiparasitic: Several Apocynaceae species have been employed for their antimicrobial properties to treat infections. Some are used against parasitic infections, such as malaria, due to the presence of compounds like alkaloids. [11]. Cancer Treatment: The potential anticancer properties of Apocynaceae plants have been explored in various traditional practices, where extracts are used in an attempt to control or treat certain types of cancer. [27] Neuroprotective and cardioprotective: The various secondary metabolites, such as flavonoids and steroids, have been implicated in neuroprotection and cardioprotection, leading to their use in improving cognitive functions and protecting the heart muscle in traditional medicinal systems. [28]

Digestive Health: Some plants in the Apocynaceae family are used for digestive health, treating issues like dysentery and diarrhea, or as purgatives. [2] External Uses: External applications include using plant extracts for skin diseases, as insecticides, or for dental care. [2] It is important to note that, while these traditional uses are part of ethnomedical practices, scientific research is necessary to confirm their efficacy and safety. Moreover, some plants in this family may contain toxic compounds and should be used with caution. Indigenous communities have traditionally depended on plants from the Apocynaceae family for various purposes, drawing on extensive knowledge in ethnobotany to understand how different cultures and regions utilize these indigenous plants. [13]

The use of Apocynaceae plants encompasses their medicinal properties and nutritional advantages: Many species are utilized to treat conditions such as gastrointestinal issues, fever, malaria, pain, skin diseases, diabetes, hypertension, and cancer. For example, *Catharanthus roseus* is employed in cancer treatment due to its alkaloids like vincristine and vinblastine [7]. Additionally, some Apocynaceae plants provide sustenance for these communities, enabling dietary variety and improved nutrition [29] The medicinal applications of Apocynaceae plants are wide-ranging, providing remedies for cancer, cardiovascular diseases, diabetes, hypertension, asthma, urinary problems, gastrointestinal issues, skin diseases, malaria, and pain relief and anti-inflammatory effects. These traditional uses continue to be the subject of pharmacological research for potential integration into modern medicine. [30] The Apocynaceae plant family has a wide variety of applications aside from their medicinal qualities. For instance, certain species are eaten as food by tribal and indigenous communities, bringing diversity to their diet and offering nutritional advantages. [29] Additionally, these plants hold cultural importance and are featured in traditional rituals. Some ornamental varieties with striking flowers adorn societies, enriching them culturally and aesthetically [31]. Due to the potent secondary metabolites they contain, some Apocynaceae plants are used to create poison.

For example, certain species have been historically used to make arrow and dart poisons for hunting and warfare. In addition to these roles, other species in the Apocynaceae family are used for utilitarian purposes, such as fodder for animals,

wood for construction and craft, and plants like *Rauvolfia* spp. [13], which have been used for dyes and perfume. The versatile uses of Apocynaceae plants highlight their importance in various aspects of human life across different cultures and geographies. [17]

Pharmacology of Apocynaceae

Bioactive components in Apocynaceae plants, as well as in other plant families, represent a variety of chemically active compounds known for their potential pharmacological effects. Below are descriptions of common pharmacologically active compounds. [32] 1. Alkaloids: Alkaloids are nitrogen-containing compounds with diverse chemical structures. They are known for their pronounced pharmacological effects on the human body. [33] These effects can range from stimulatory to inhibitory, and alkaloids are often used for their medicinal properties. For example, alkaloids like vincristine and vinblastine from *Catharanthus roseus* have been used in cancer chemotherapy [34]. 2. Cardiac Glycosides: These are molecules that combine sugar residues with a steroidal aglycone. Cardiac glycosides are particularly known for their effects on heart tissue, as they can increase the force of the heart's contraction without necessarily increasing the oxygen demand. They are useful in treating certain heart conditions [35]. 3. Flavonoids: A large group of polyphenolic compounds found in plants, flavonoids act as antioxidants, mop up free radicals, and may reduce the risk of chronic diseases such as heart disease and cancer.

They also exhibit anti-inflammatory, antiviral, and antimicrobial properties [36]. 4. Terpenoids, including steroids: Terpenoids are the largest class of plant secondary metabolites. They are based on the isoprene structure and affect numerous physiological functions of the organisms that consume them. They have been associated with anti-inflammatory, anti-cancer, and antimicrobial activities. Steroids, a subclass of terpenoids, are involved in structural functions in cell membranes and as signaling molecules [37]. 5. Phenolic Acids: Phenolic acids are known for their antioxidant properties. They effectively neutralize harmful free radicals that can damage cells and lead to chronic diseases, including cardiovascular diseases and cancer, [38]. These compounds mediate their effects through various biological pathways, such as inhibiting enzymes, modulating receptors and ion channels, interfering with DNA synthesis in cancerous or microbial cells, and neutralizing oxidative agents. Due to these interactions, these bioactive components contribute significantly to the therapeutic potential of plants, which is why they are of great interest for drug discovery and development in pharmacology. [39] Additionally, the traditional uses of plants from the Apocynaceae family further highlight their pharmaceutical potential.

The therapeutic effects of compounds found in the Apocynaceae family and other medicinal plants have been extensively studied due to their potential to treat various health conditions. [13] Here's an overview of the evidence for their anticancer, antimalarial, anti-inflammatory, and other properties: Anticancer Properties: Several compounds, especially certain alkaloids such as vincristine and vinblastine, have been clinically used in chemotherapy for their ability to inhibit cell division by binding to tubulin and preventing microtubule formation, which is essential for cell mitosis. The anticancer properties of these compounds have been supported by both laboratory studies and clinical use. [40]

Antimalarial Properties: Some plant-derived alkaloids are known to exhibit antimalarial activity. For example, quinine, historically derived from the bark of the Cinchona tree (not in the Apocynaceae family), has been used for the treatment of malaria due to its ability to interrupt the life cycle of the malaria-causing Plasmodium parasite.[41]

Anti-inflammatory Properties: Various compounds, such as terpenoids and flavonoids, exhibit anti-inflammatory properties by inhibiting the production of inflammatory mediators. For instance, many flavonoids can downregulate the activity of enzymes involved in inflammation, such as cyclooxygenases and lipoxygenases, thereby reducing inflammation. **Cardioprotective Effects:** Cardiac glycosides, found in some Apocynaceae plants, have a long history of use in treating heart conditions. They achieve a cardioprotective effect by increasing the force of cardiac muscle contraction, which can help in cases of heart failure, and by regulating heart rate and rhythm. **Antimicrobial Properties:** Plant compounds such as alkaloids, terpenoids, and polyphenols have shown antimicrobial activity against a range of bacteria, fungi, and viruses. These compounds often interfere with microbial cell walls or inhibit key enzymes necessary for their growth and reproduction. [42] **Neuroprotective Properties:** Flavonoids, among other compounds, are being studied for their neuroprotective effects, potentially applicable in the treatment of neurodegenerative diseases. The antioxidant properties of flavonoids protect neuronal cells from oxidative stress and inflammation, which can contribute to neurodegeneration. **Other Properties:** Many bioactive compounds also exhibit additional therapeutic effects, such as anti-diabetic, anti-hypertensive, antiviral, antifungal, and antioxidant activity. Aside from their medicinal applications, plants from the Apocynaceae family and their bioactive compounds play various roles in diet, culture, and even as poisons due to their diverse pharmacologically active constituents. [2]

Role in Diet: While not as prominent in dietary uses due to the presence of toxic substances in many Apocynaceae species, some plants may still be utilized for their nutritional and health-promoting benefits. [2] For example, certain non-toxic parts of plants or extracts containing flavonoids and antioxidants might be incorporated into the diet to leverage their health benefits [13]. **(1) Cultural Significance:** Apocynaceae plants often have a strong cultural impact, especially in traditional medicines across the world. They are used in various rituals and traditional healthcare practices. For instance, some cultures use these plants for their psychoactive effects in religious or spiritual ceremonies. [43]

Use as Poisons: Many Apocynaceae plants contain potent alkaloids and other compounds that can be toxic. Historically, some of these toxic compounds have been used in hunting and warfare as poisons. In certain parts of the world, the sap or other parts of Apocynaceae plants have been used to lace arrows or darts for hunting.[29] The cardiac glycosides, while therapeutic in controlled doses, can be lethal if misused, hence their historical use as poisons. [13] It's crucial to approach the use of Apocynaceae plants with an understanding of their potent biological activities, being mindful of both their potential therapeutic applications and their toxicity. [13] The dual nature of these compounds as both medicine and poison highlights the importance of dosage and context in their use [44].

Biotechnological Advances and Pharmacological Applications

Modern extraction techniques have significantly advanced, offering more efficient and environmentally friendly methods compared to traditional extraction. [45] Some of these modern techniques include supercritical fluid extraction, pressurized liquid extraction, microwave-assisted extraction, ultrasound-assisted extraction, enzyme-assisted extraction, and matrix solid-phase dispersion. [46] These methods aim to enhance yield while following green chemistry principles. [47]

Drug development involving the translation of traditional knowledge into modern therapeutics follows a specific process, including ethnopharmacological studies, bioactive compound identification, pharmacological screening, lead compound optimization, clinical trials, and regulatory approval.[48] Throughout this process, challenges such as identifying active components in complex mixtures and scaling up production while maintaining efficacy are addressed to integrate ancient wisdom with modern medical science. The difficulties and future paths in utilizing Apocynaceae plants include the need for conservation, sustainable harvesting, analysis of plant compounds, and assessment of medicinal properties; ensuring standardization for quality control is crucial due to variability within species; identifying and isolating active components can be complex; Addressing side effects and toxicity is essential for safe usage [49].

Further advancements in extraction techniques are necessary to improve efficiency and minimize environmental impact. Rigorous clinical trials are required to validate effectiveness. [50]. Regulatory approvals involve extensive testing while considering ethical dimensions, respecting traditional knowledge, and fair benefit sharing efforts. Collaborating across disciplines, cultural sensitivity, and commitment to sustainability are key to overcoming these obstacles while harnessing the potential of Apocynaceae plants. [51]

CONCLUSIONS

The Apocynaceae family comprises a diverse group of plants that include tropical trees, shrubs, and vines. These plants are characterized by their production of milky sap, which is almost universal across species within the family. They are widely distributed and known for their complex chemical makeup, which includes a variety of bioactive compounds such as alkaloids, terpenoids, steroids, and flavonoids. The purpose of a review of the Apocynaceae family would be to consolidate and discuss the extensive ethnobotanical knowledge, phytochemical content, traditional medicinal uses, and pharmacological activities associated with this family of plants. Moreover, the review would address the role of these plants in traditional medicine for treating various ailments and explore their potential in the development of new drugs, especially in the face of challenges such as the rise of multidrug-resistant pathogens.

A review with such a scope would aim not only to highlight the traditional knowledge regarding the uses of Apocynaceae plants but also to connect this knowledge with modern scientific research, thereby validating traditional claims and possibly discovering novel therapeutic agents. A review was conducted, with database searches, study selection criteria, and approaches used in analyzing the literature. The main findings from the literature reviewed, such as identified phytochemical compounds, traditional uses of plants, and pharmacological. Things that need to be

discussed are their significance, comparing them with existing literature, and perhaps suggesting directions for future research.

Supplementary Materials

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