



MEDICINAL PROPERTIES OF PERIWINKLE [*CATHARANTHUS ROSEUS* (L.) G. DON]

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ABSTRACT

Madagascar periwinkle [(*Catharanthus roseus* (L.) G. Don], also known as the "Madagascar vinca," is a plant native to Madagascar that has significant commercial prospects in agriculture and industry, particularly in the pharmaceutical industries. It can grow and thrive as an invasive species in certain conditions, impacting local indigenous flora. Originally native to Madagascar, this plant has been widely cultivated as an ornamental and medicinal plant. It is hardy and adaptable to various climates, particularly tropical and subtropical regions. Grown for its attractive flowers in gardens and landscapes; with proper care and adherence to these agronomic conditions, Madagascar periwinkle can be a profitable crop for both medicinal and ornamental purposes. Extracts are used to produce anticancer drugs. Madagascar periwinkle contains over 100 alkaloids, several of which are pharmacologically active. The two most notable alkaloids are vincristine and vinblastine, which are used in modern cancer treatments. However, its invasive potential in non-native ecosystems warrants careful management.

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INTRODUCTION

The periwinkle plant [(*Catharanthus roseus* (L.) G. Don], also known as Madagascar periwinkle (Ghannam et al., 2024), is a small flowering plant native to Madagascar (Ehrenworth and Peralta-Yahya, 2017). It is a small, evergreen shrub that typically grows up to 1 meter tall (Fig. 1) and is known for its attractive, glossy green leaves (Fig. 2). The plant is widely grown as an ornamental plant due to its beautiful flowers that are bright, star-shaped and can be pink, white, or purple in colour (Sreevalli et al., 2002) (Fig. 3). It thrives in tropical and subtropical climates and is also grown in many parts of the world for its medicinal properties (El-Tanbouly et al., 2024).



Fig 1: Variation among habits of different Madagascar periwinkle cultivars. Photo credit: Saikat Kumar Basu.

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The periwinkle plant is renowned for its alkaloids, particularly vincristine and vinblastine (Fig. 4), which are used in cancer treatment (Faraouk et al., 2022). These compounds are effective in treating various cancers, including leukaemia, Hodgkin's lymphoma, and breast cancer (Baskara and Jhang, 2016). Traditional medicine systems use periwinkle for treating diabetes, high blood pressure, and microbial infections (Ehrenworth and Peralta-Yahya, 2017). Vincristine and vinblastine are vital components of chemotherapy regimens (Faraouk et al., 2022). Other alkaloids from the plant are being studied for potential therapeutic applications (El-Sheikh et al., 2019). The plant is popular in landscaping and gardening because of its hardiness and ability to bloom continuously in different environments (Sreevalli et al., 2002). In some cultures, it is used in rituals or symbolic contexts (Ghannam et al., 2024).



Fig 2: The diversity of leaf shape, size, texture and phyllotaxy among different cultivars of periwinkle. Photo credit: Saikat Kumar Basu.

Distribution and Adaptability

The Madagascar periwinkle is native to Madagascar, where it evolved in the island's tropical and subtropical ecosystems (El-Sheikh et al., 2019). Within its native range, it primarily occurs in dry forests and sandy or well-drained areas along the coast (Sreevalli et al., 2003). However, due to its ornamental value, medicinal properties, and adaptability, Madagascar periwinkle has been widely introduced and naturalized in tropical and subtropical regions worldwide (Baskara and Jhang, 2016; Ehrenworth and Peralta-Yahya, 2017). Its current distribution includes parts of Asia (e.g., India, Sri Lanka, the Philippines),

Africa (beyond Madagascar), Central and South America, the Caribbeans, Australia and the Pacific islands (Baskara and Jhang, 2016; El-Tanbouly et al., 2024). It thrives in a variety of environments, including disturbed areas, roadsides, and gardens, making it an invasive species in some regions (El-Tantaway et al., 2023). Despite its wide distribution, it remains closely associated with its origins in Madagascar (Das et al., 2020).



Fig 3: Diversity of Madagascar periwinkle cultivars with diverse colour of petals across various biogeographic regions. Photo credit: Saikat Kumar Basu.

Periwinkle is a low-maintenance plant that can thrive in poor soils and is often used for erosion control (El-Tanbouly et al., 2024). Despite its benefits, periwinkle can become invasive in some areas, outcompeting native vegetation (Sharma et al., 2020). Careful management is required when cultivating it in non-native regions (Baskara and Jhang, 2016). The plant has widely adapted to habitats outside its natural range due to several biological and ecological traits, as well as human intervention (Faraouk et al., 2022; El-Tanbouly et al., 2024). Here are the key factors contributing to its adaptability:

Hardiness and Tolerance: The plant is highly drought-tolerant and can thrive in poor soils, allowing it to grow in a wide range of climates (Sreevalli et al., 2003). It can grow in sandy, loamy, or rocky soils, tolerating conditions that many plants cannot (Ghannam et al., 2024). It has natural alkaloids that deter pests and herbivores, helping it survive in unfamiliar environments (Ehrenworth and Peralta-Yahya, 2017).

Reproductive Success: The plant produces numerous seeds, increasing its chances of spreading. Although it is capable of cross-pollination, it can also self-pollinate, ensuring reproduction even when isolated from other plants (Ghannam et al., 2024). The plant matures quickly, allowing it to colonize new areas efficiently (Ehrenworth and Peralta-Yahya, 2017).

Medicinal and Ornamental Value: Humans have spread the plant globally because of its ornamental beauty and its use in traditional and modern medicine (e.g., for producing alkaloids like vincristine and vinblastine, used in cancer treatment) (Sharma et al., 2020). Its ease of cultivation and low maintenance make it a popular choice in gardens and landscaping (Ehrenworth and Peralta-Yahya, 2017).

Invasive Potential: In non-native areas, the Madagascar periwinkle often outcompetes local vegetation due to its robust growth and ability to tolerate stress (Das et al., 2020). Its ability to naturalize and spread in disturbed habitats, roadsides, and urban areas has made it an invasive species in some regions (Sreevalli et al., 2003; Sharma et al., 2020).

Climatic Compatibility: Originally native to Madagascar's tropical climate, the plant's ability to adapt to both tropical and subtropical conditions has allowed it to establish itself in similar climates worldwide (Sreevalli et al., 2003; Sharma et al., 2020).

This combination of ecological versatility, human dissemination, and competitive advantages has made the Madagascar periwinkle a globally widespread plant (El-Tanbouly et al., 2024).

Phytochemical compounds

Madagascar periwinkle is a well-known medicinal plant valued for its diverse array of phytochemicals (Wang et al., 2011). These compounds, particularly alkaloids, have significant pharmacological activities (El-Tanbouly et al., 2024). Madagascar periwinkle is a phytochemical reservoir, with its alkaloids, flavonoids, tannins, and terpenoids contributing to its pharmacological importance (Sreevalli et al., 2002). A detailed discussion of the primary phytochemicals found in Madagascar periwinkle is presented below:

Alkaloids: The plant is particularly famous for its alkaloids, which are nitrogen-containing organic compounds with complex chemical structures (Ghannam et al., 2024). The discovery and synthesis of compounds like vincristine and vinblastine underscore the plant's value in modern medicine (Gawade et al., 2023). Over 130 alkaloids have been isolated from this species (El-Tanbouly et al., 2024).

The key alkaloids are Vincristine ($C_{46}H_{56}N_4O_{10}$) and Vinblastine ($C_{46}H_{56}N_4O_9$) (Sharma et al., 2022) (Fig. 4). Both are complex dimeric indole alkaloids derived from tryptophan and terpenoid pathways (Tang et al., 2022). Vincristine and vinblastine are anti-mitotic agents, disrupting cell division by binding to tubulin and inhibiting microtubule formation (Sharma et al., 2022). These are widely used as chemotherapeutic agents to treat cancers, such as leukaemia, lymphoma, and breast cancer (Sharma et al., 2022). Another important alkaloids found in this plant is ajmalicine ($C_{21}H_{24}N_2O_3$), a monomeric alkaloid that acts as a vasodilator and antihypertensive agent that improves cerebral blood flow and is used to treat circulatory disorders (Sharma et al., 2022). Serpentine ($C_{21}H_{20}N_2O_3$) is another indole alkaloid that exhibits hypotensive and sedative effects that is investigated for use in traditional and modern medicine for cardiovascular diseases (Talaat et al., 2005).

Among other indole alkaloids (Fig. 4) are catharanthine ($C_{21}H_{24}N_2O_2$) serving as a precursor for vincristine and vinblastine synthesis; and vindoline ($C_{25}H_{32}N_2O_2$) acting as a building block for vincristine and vinblastine biosynthesis (Sharma et al., 2020; Huang et al., 2024). The alkaloids in Madagascar periwinkle are synthesized via the monoterpenoid indole alkaloid pathway, which involves: tryptophan metabolism for indole synthesis, geraniol and iridoid pathways for terpenoid synthesis, coupling of the indole and terpenoid moieties to produce monomeric alkaloids (e.g., vindoline, catharanthine), and dimerization of monomeric alkaloids to form vincristine and vinblastine (Pandey-Rai et al., 2006; Sharma et al., 2020).

Flavonoids: Flavonoids are phenolic compounds known for their antioxidant properties. In *Catharanthus roseus*, the flavonoids include: kaempferol ($C_{15}H_{10}O_6$), a flavonol with antioxidant and anti-inflammatory properties; and quercetin ($C_{15}H_{10}O_7$) (Fig. 4), another flavonol that acts as an anti-inflammatory, antihypertensive, and antidiabetic agent. Rutin ($C_{27}H_{30}O_{16}$) is a glycosylated flavonoid with vasoprotective and anti-inflammatory effects (Pandey-Rai et al., 2006; Sharma et al., 2020) (Fig. 4).

Tannins: Polyphenolic compounds (Fig. 4) present in the plant with astringent and antimicrobial properties. These compounds contribute to wound healing and protection against microbial infections (Pandey-Rai et al., 2006; Sharma et al., 2020).

Phenolic Acids: Gallic acid and caffeic acid (Fig. 4) are commonly present in Madagascar periwinkle. These

compounds have antioxidant and anti-inflammatory activities, protecting the plant and its consumers from oxidative stress (Huang et al., 2024).

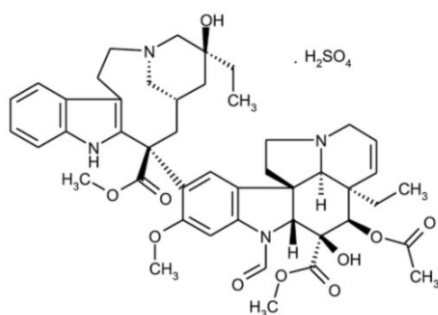
Terpenoids: Include monoterpenes, sesquiterpenes (Fig. 4), and diterpenes. These compounds often function as precursors for alkaloid biosynthesis and contribute to the plant's aroma and insect-repellent properties (Renjini et al., 2017).

Steroids: Stigmasterol and β -sitosterol are common phytosterols in the plant. They exhibit anti-inflammatory and cholesterol-lowering effects.

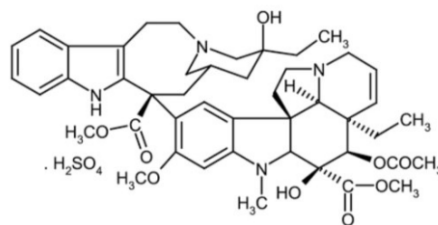
Glycosides: Cardiac glycosides (Fig. 4) are present, contributing to the plant's traditional use in treating heart conditions (Huang et al., 2024).

Saponins: Saponins are glycosides with foaming properties (Fig. 4). They have antimicrobial, antifungal, and immune-modulatory activities (Kumar et al., 2012).

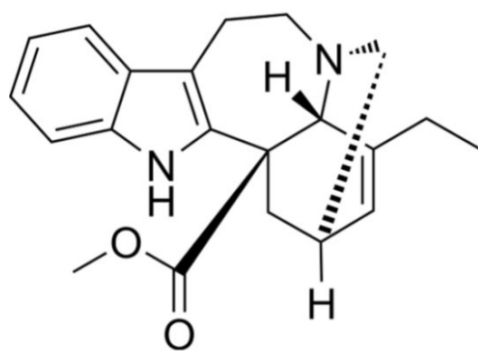
Essential Oils: Contain terpenes, sesquiterpenes, and volatile phenols. These oils have antimicrobial and insecticidal properties (Yokoyama and Inomata, 1998).



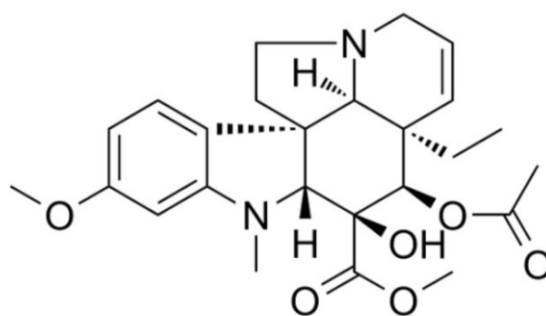
Vincristine



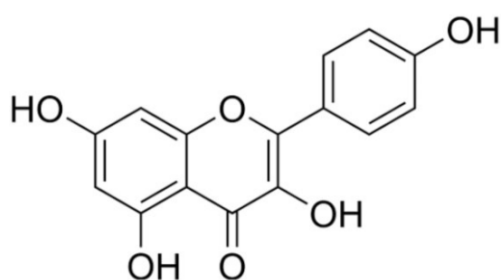
Vinblastine



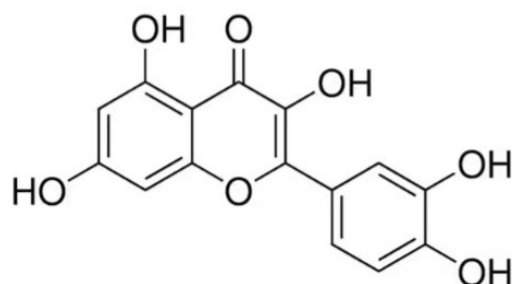
Catharanthine



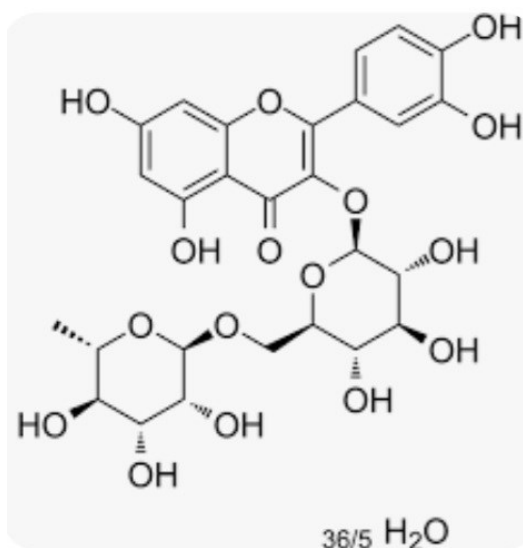
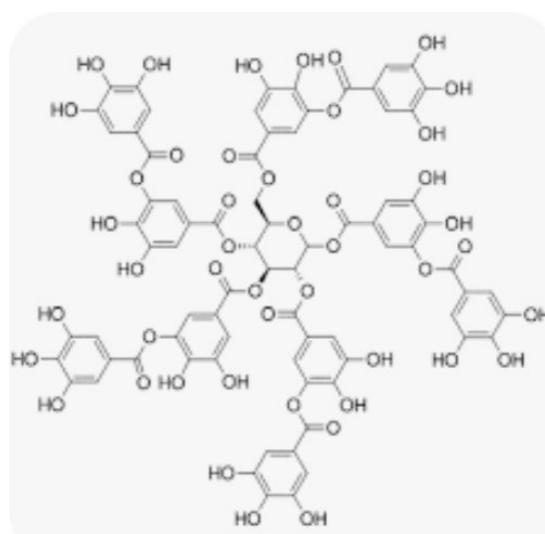
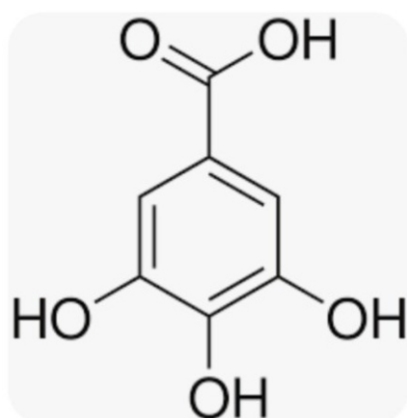
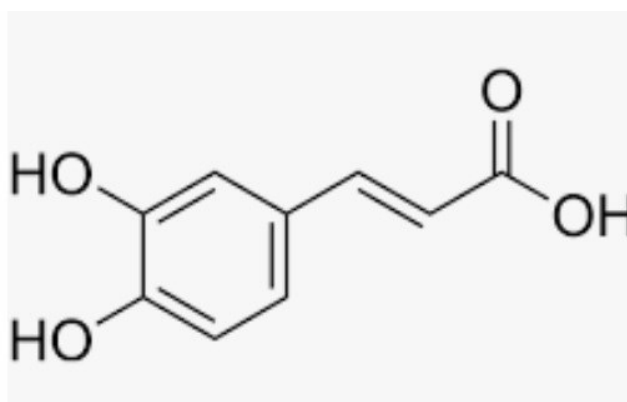
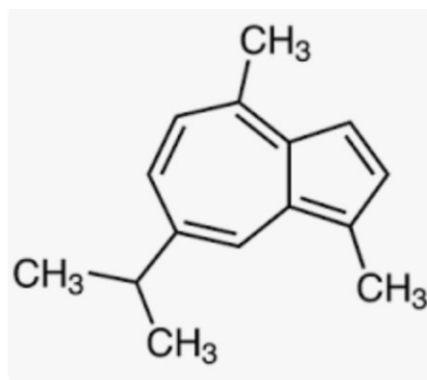
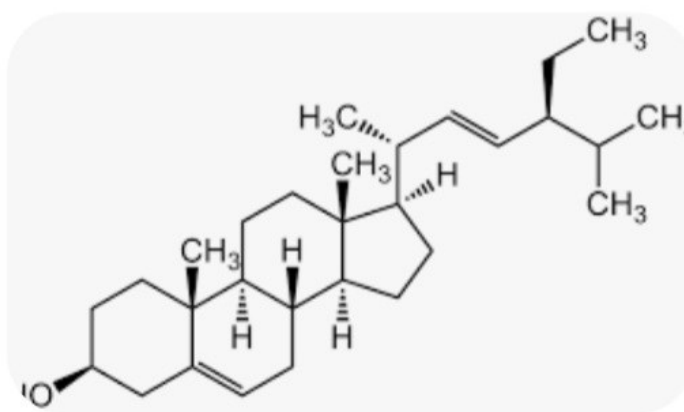
Vindoline

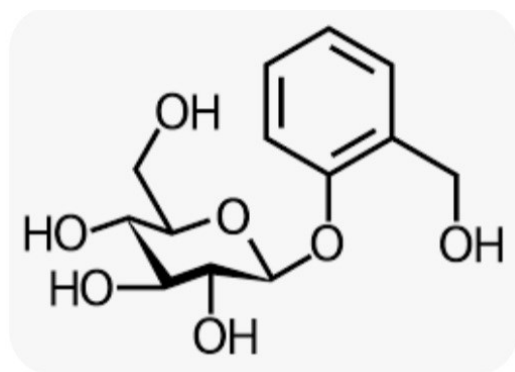


Kaempferol

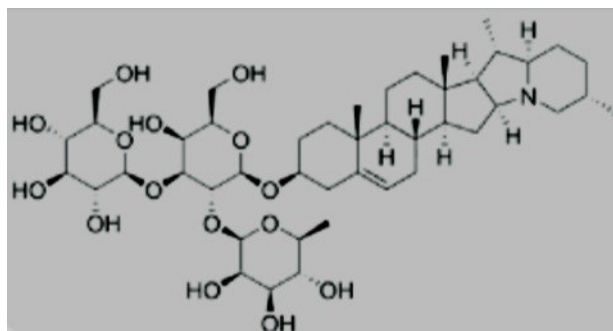


Quercetin

**Rutin****Tanin****Gallic Acid****Caffeic Acid****Sesquiterpene****Stigmasterol**



Glycoside



Saponin

Fig 4: Important phytochemicals present in Madagascar periwinkle.

Medicinal Properties

The Madagascar periwinkle is renowned for its medicinal properties (Pandey-Rai et al., 2006). It contains alkaloids like vincristine and vinblastine, which are widely used in modern medicine (Nejat et al., 2015). While Madagascar periwinkle has potent medicinal properties, it is highly toxic if not used correctly (Rani et al., 2023). Direct consumption of raw plant parts is not advised due to the risk of poisoning, and pharmaceutical formulations should only be used under medical supervision (Kumar et al., 2012). Here are some diseases and conditions where it has applications or potential remedies:

Cancer Treatment: Vincristine and vinblastine are derived from the plant and are crucial in chemotherapy for leukaemia (especially childhood acute lymphoblastic leukaemia), lymphoma (Hodgkin's and non-Hodgkin's), breast cancer, lung cancer and testicular cancer (Bhaskar and Jhang, 2016). These alkaloids inhibit cell division by interfering with the microtubule formation, making them effective anticancer agents (Pandey-Rai et al., 2006; Gawade et al., 2023).

Diabetes: Traditionally, extracts from Madagascar periwinkle have been used to lower blood sugar levels. It is used in folk medicine for managing type 2 diabetes. However, clinical use for diabetes requires caution due to potential toxicity (Yokoyama and Inomata, 1998).

Hypertension: Alkaloids in the plant have shown potential in regulating blood pressure, making it useful in traditional remedies for high blood pressure (Rai and Upadhyay, 2024).

Malaria: In traditional medicine, the plant has been used to treat malaria in some regions. Its antimalarial

properties are linked to its alkaloid content (Pandey-Rai et al., 2006).

Infections and Wounds: The leaves and flowers are used as antiseptic poultices for treating wounds, skin infections, and ulcers in traditional medicine (Renjini et al., 2017).

Immune Modulation: Some studies suggest the plant has immune-modulatory effects, which may aid in conditions where immune function is compromised (Rady, 2019).

Other Traditional Uses: The plant has been used in folk remedies for treating fevers, and used to regulate menstruation in traditional medicine. Decoctions are commonly used to manage digestive issues like dysentery and diarrhoea (Gawade et al., 2023).

Uses in Alternative Medicine

The plant is globally recognized for its alkaloids, vincristine and vinblastine, which are used in modern medicine to treat cancers such as leukaemia and Hodgkin's lymphoma (El-Sheikh et al., 2019). While traditional uses are widespread, its therapeutic applications in alternative systems are often backed by anecdotal evidence or localized practices, rather than rigorous scientific studies (Yokoyama and Inomata, 1998). Care must be taken due to its potential toxicity in high doses (Kumar et al., 2012). The plant is used in various traditional and alternative health systems like Ayurveda, Siddha, and Unani, though its applications vary (Singh, 2016).

Ayurveda: Known as Sadapushpa or Nityakalyani, it is used to treat conditions like diabetes, fever, skin diseases, and inflammation (Singh, 2016). The plant's extracts are sometimes applied to wounds for their antiseptic properties (Kulkarni, 1999).

Siddha: It is valued for its ability to control high blood sugar levels (anti-diabetic). It is also used for treating hypertension, ulcers, and as a blood purifier (Bhaskar and Jhang, 2016).

Unani: Unani practitioners use Madagascar periwinkle primarily for its anti-cancer, blood-purifying, and diuretic properties. It is considered useful in addressing chronic diseases like diabetes and some skin disorders (El-Tanbouly et al., 2024).

Homeopathy: Madagascar periwinkle is used in diluted forms to treat conditions like excessive menstrual bleeding, skin ailments, and ulcers (El-Sheikh et al., 2019).

Agronomic Practices

Madagascar periwinkle can be grown commercially, primarily for ornamental purposes or for its medicinal properties (Dagar et al., 2005; Hassan et al., 2009). It is a source of alkaloids like vincristine and vinblastine, which are used in cancer treatment (Abdolzadeh et al., 2006; Hassan et al., 2009). The crop prefers warm climates; optimal temperature is 20–30°C. It cannot tolerate frost, so it should be grown in frost-free areas (Dagar et al., 2005). The crop thrives in areas with moderate rainfall (750-2,000 mm annually). However, it can tolerate drought conditions due to its hardy nature (Hassan et al., 2009). Well-drained sandy loam or loamy soils are ideal; with pH: preference for slightly acidic to neutral soil (pH 5.5-7.5) (Ghannam et al., 2024). Moderately fertile soil is sufficient, but organic matter can improve growth; and requires full sunlight, though it can tolerate partial shade (Ghannam et al., 2024). The plant is primarily propagated through seeds or stem cuttings (Abdolzadeh et al., 2006).

Seeds should be sown directly in the field or raised in nurseries before transplantation (Dagar et al., 2005). Planting should be typically done during the early monsoon or spring season (Ghannam et al., 2024). Maintaining a spacing of 30-40 cm between plants and 40-60 cm between rows is essential for optimum growth (Abdolzadeh et al., 2006; Hassan et al., 2009). The crop requires moderate irrigation. Overwatering should be avoided to prevent root rot. Irrigate every 7-10 days in dry conditions, but allow the soil to dry between watering. Applying a balanced fertilizer like NPK (10:10:10) (Ghannam et al., 2024). Incorporate organic manures (e.g., compost) before planting (Hashemabadi et al., 2015).

Madagascar periwinkle is highly drought-tolerant and can colonize disturbed areas, roadsides, and open spaces. It competes with native plants for resources

like sunlight, water, and nutrients (Ghannam et al., 2024). The plant may release chemicals into the soil that inhibit the growth of nearby native plants (allelopathy), further reducing biodiversity. Its ability to produce numerous seeds and grow in poor soils allows it to establish quickly in new areas, displacing indigenous flora (Hashemabadi et al., 2015). To mitigate its impact, it's essential to: monitor its spread in sensitive ecosystems, removing it from areas where it threatens native plants, promoting the growth of native species to outcompete it, and regular weeding is essential, especially during the early stages of growth (Ghannam et al., 2024). Pests such as aphids, whiteflies, and caterpillars may attack the plants (Dagar et al., 2005). Use organic or chemical pesticides as needed. The plant is susceptible to leaf blight, root rot, and powdery mildew (Ghannam et al., 2024). Maintaining proper drainage and use of fungicides are important as preventive measures (Dagar et al., 2005). For medicinal use, leaves and stems are harvested 3-4 months after planting (Hashemabadi et al., 2015). Seeds can be collected after the pods mature if propagation is desired (Abdolzadeh et al., 2006).

Ethnobotany and Ethnomedicine

The Madagascar periwinkle has significant ethnobotanical uses and has been widely valued in traditional medicine and modern pharmacology and Pharmacognosy (Ehrenworth and Peralta-Yahya, 2017). It is an essential plant in ethnobotany, valued for its traditional uses and revolutionary contributions to modern medicine. Its dual role in traditional practices and pharmaceutical development highlights the importance of preserving and studying ethnobotanical knowledge (Sharma, 2016). Madagascar periwinkle has been used in various traditional healing systems, including in Africa, India, China, and the Caribbean (Abdolzadeh et al., 2006; Hassan et al., 2009). In traditional Indian medicine (Ayurveda), periwinkle leaves have been used to control blood sugar levels. Decoctions made from its leaves or roots are consumed for managing diabetes (Bhaskar and Jhang, 2016).

In many cultures, crushed leaves are applied topically to treat wounds, insect bites, and skin infections due to their antimicrobial and anti-inflammatory properties (Sharma et al., 2022). Infusions from the plant are used to treat diarrhoea, dysentery, and other gastrointestinal issues (Abdolzadeh et al., 2006; Hassan et al., 2009). The plant has been used traditionally to reduce fevers and as a remedy for malaria in African and tropical regions (Kulkarni, 1999). It has been used for treating respiratory problems, menstrual irregularities, and hypertension in different cultural

practices (Wang et al., 2011). In addition to its medicinal uses, Madagascar periwinkle has been used symbolically in rituals (Tang et al., 2022).

It is sometimes associated with protection and is planted around homes in some cultures to ward off evil spirits (Abdolzadeh et al., 2006; Hassan et al., 2009). The plant is occasionally used in ceremonial offerings in regions where it holds spiritual significance (Yokoyama and Inomata, 1998). While Madagascar periwinkle has therapeutic benefits, it is also toxic if consumed in large quantities or prepared improperly. This toxicity is due to its potent alkaloids, which can cause adverse effects like nausea, vomiting, and organ damage (Tang et al., 2022). Traditional use often relies on expert knowledge to avoid harmful effects (Kulkarni et al., 2001).

Although widely cultivated, Madagascar periwinkle's wild populations in its native range face threats due to habitat destruction (Ehrenworth and Peralta-Yahya, 2017). Sustainable harvesting and cultivation practices are necessary to preserve its biodiversity (Kulkarni, 1999). Modern science has leveraged the plant's properties to produce synthetic analogs of its alkaloids, which are used in chemotherapy drugs. Its extensive use in research underscores its value both traditionally and in contemporary medicine (Acharjee and Kumar, 2022).

Nutraceutical and Functional Foods

Madagascar periwinkle has potential applications in the nutraceutical and functional food industries due to its bioactive compounds (Acharjee and Kumar, 2022). This plant is well-known for its rich content of alkaloids, flavonoids, tannins, phenolic acids, and other phytochemicals, many of which have antioxidant, anti-inflammatory, antimicrobial, and anticancer properties with key compounds for potential benefits, such as alkaloids like vincristine, Vinblastine etc (Ehrenworth and Peralta-Yahya, 2017). These are widely used in pharmaceutical applications for their potent anticancer properties. Their potential inclusion in functional foods could support cancer prevention efforts (Yokoyama and Inomata, 1998).

Flavonoids and phenolic compounds have strong antioxidant activity, which can help reduce oxidative stress and support overall health (Acharjee and Kumar, 2022). They may have applications in nutraceutical formulations for heart health and metabolic disorders (Renjini et al., 2017). Extracts from Madagascar periwinkle have shown antimicrobial effects against a range of pathogens. The plant is also traditionally used to manage diabetes, suggesting potential for blood

sugar-regulating functional foods (Acharjee and Kumar, 2022). Compounds in the plant could be used to develop nutraceuticals aimed at reducing chronic inflammation, a root cause of many diseases (El-Tantaway et al., 2023).

Some alkaloids in Madagascar periwinkle, while therapeutic, are highly toxic and must be carefully dosed (Pandey-Rai et al., 2006; Sharma et al., 2020). The inclusion of such bioactive compounds in foods would require rigorous safety evaluations and regulatory approvals (Pandey-Rai et al., 2006). Effective methods to isolate and standardize active compounds for food-grade use would be essential. The plant holds promise for the nutraceutical and functional food industries, but further research, safety assessments, and regulatory clearances are required to unlock its full potential (Sharma et al., 2020).

Conclusion

The Madagascar periwinkle is a source of alkaloids, particularly vincristine and vinblastine, which are used in cancer treatments (e.g., leukaemia, lymphoma, and testicular cancer). This makes the plant valuable for the pharmaceutical industry, with increasing global demand for cancer treatments (Pandey-Rai et al., 2006; Hashemabadi et al., 2015; Sharma et al., 2020; Tang et al., 2022). Expansion of use in drug development: Research is ongoing to discover more potential medicinal uses of the plant, which may lead to further commercial applications in treating diseases like diabetes and hypertension (Pandey-Rai et al., 2006; Sharma et al., 2020). The cultivation of Madagascar periwinkle is growing, particularly in tropical and subtropical climates. Countries with favourable growing conditions are focusing on producing high-quality plants for extraction of alkaloids (Hashemabadi et al., 2015; Sharma et al., 2020). However, the increasing global demand for periwinkle has raised concerns about sustainable harvesting practices, as wild populations are at risk due to overharvesting (Acharjee and Kumar, 2022).

Given the over-exploitation of the plant in the wild, some industries are investing in sustainable farming practices to ensure long-term supply (El-Tantaway et al., 2023). This includes cultivating the plant in controlled environments and enhancing yield through breeding programs (Sharma et al., 2020; El-Tantaway et al., 2023). Herbal medicine and cosmetics: In addition to pharmaceuticals, Madagascar periwinkle is also being explored for use in herbal medicine and cosmetic products, as its extracts are believed to have skin-healing and anti-inflammatory properties (Yokoyama and Inomata, 1998; Hashemabadi et al., 2015).

Future Directions

Madagascar is the primary supplier of the periwinkle plant, and the global market relies heavily on its exports (El-Tantaway et al., 2023). With global awareness of the plant's medicinal benefits increasing, this gives Madagascar significant potential for economic growth if it can maintain sustainable cultivation practices and strengthen its export capacity (Sharma et al., 2020). The overharvesting of wild plants and the challenge of maintaining ecological balance in Madagascar's ecosystems pose a risk to the long-term commercial viability of periwinkle cultivation (Talaat et al., 2005; Hashemabadi et al., 2015). Madagascar's periwinkle exports are highly dependent on the demand for cancer drugs, which can fluctuate with market trends and research advancements (Tang et al., 2022). The global commercial prospects for Madagascar periwinkle are promising, particularly in the pharmaceutical industry (Wang et al., 2019). However, sustainability and the balancing of ecological preservation with economic development will be key factors in determining the long-term success of its cultivation and use (Pandey-Rai et al., 2006; Hashemabadi et al., 2015; Sharma et al., 2020).

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