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PHYTOCHEMICALS, ANTIMICROBIALS, AND GREEN DRUG DEVELOPMENT

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PREFACE

This volume brings together a collection of scholarly contributions that explore the growing significance of natural products and sustainable approaches in pharmaceutical sciences. As global health challenges intensify and the demand for safer, more efficient therapies increases, the integration of plant-based compounds and environmentally responsible drug development strategies has become increasingly important.

The chapters in this book address key themes related to phytochemistry, antimicrobial research, and green pharmaceutical technologies. The detailed examination of *Centella asiatica* highlights the pharmacological potential of plant-derived bioactive compounds in modern therapeutics. The discussion on green drug delivery systems emphasizes innovative approaches that align pharmaceutical development with environmental sustainability. In addition, the investigation of antimicrobial properties of natural plant extracts reflects the ongoing search for effective alternatives in combating resistant pathogens.

By adopting an interdisciplinary perspective, this volume integrates insights from pharmacology, natural product chemistry, microbiology, and pharmaceutical sciences. It contributes to academic discourse while also offering practical implications for researchers and professionals seeking sustainable and innovative solutions in drug development.

It is hoped that this book will serve as a valuable resource for scholars, practitioners, and students interested in natural therapeutics and pharmaceutical innovation, while encouraging further research at the intersection of nature, science, and sustainable healthcare.

Editorial Team
May, 2026
Türkiye

CHAPTER 1
PHYTOCHEMICAL AND PHARMACOLOGICAL INSIGHTS INTO *CENTELLA ASIATICA*

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INTRODUCTION

Centella asiatica (L.) Urban also called Indian pennywart, or gotu kala, is a perennial herb that is a member of the family Apiaceae (Arribas-Lopez et al., 2022). It is commonly found in tropical and subtropical environments especially in swampy areas in Asia (such as China, India, Indonesia, Malaysia and Sri Lanka). It is a plant that prefers wet climate and also inhabits the Himalayan and sub-Himalayan areas because of the favorable climate (Singh et al., 2022).

Traditionally, Centella asiatica has been widely used in the traditional medicinal systems, including Ayurveda, Traditional Chinese Medicine (TCM), and Unani medicine. It has been used in the treatment of various conditions, such as memory impairment, anxiety disorder, wound care, and cognitive disorders (Diniz et al., 2023).

In the recent years, scientific studies have been done to discover the bioactive compounds that cause its medicinal properties. The triterpenoids found in the plant are asiaticoside, madecassoside, asiatic acid and madecassic acid that can be termed as the main pharmacologically active constituents. All these compounds have a diverse biological activity that includes antioxidant, anti-inflammatory, neuroprotective and antimicrobial. Moreover, Centella asiatica is a source of flavonoids, phenolic acids, and essential oils, which also play a role in the therapeutic potential of this plant (Gray et al., 2018).

Centella asiatica is commonly known to have neuroprotective properties, especially in terms of cognitive improvement and neurodegenerative diseases like Alzheimer disease. It has been demonstrated to enhance memory and learning via modulation of neurotransmitter levels, plasticity of synapses, and inhibition of oxidative stress in brain tissues. Moreover, its anxiolytic and antidepressant effects can be attributed to its capability to modulate the hypothalamic-pituitary-adrenal (HPA) axis as well as decrease the amounts of cortisol (Jiang et al., 2025).

1. PHYTOCHEMICAL STRUCTURE AND MEDICAL IMPORTANCE

Centella asiatica has a high phytochemical content, comprising of triterpenes, flavonoids, polyphenols, and essential oils, which explain its therapeutic potential (Sabaragamuwa and Perera, 2022). Of these, triterpenoid saponins, including asiaticoside, madecassoside, asiatic acid, and madecassic acid, can be regarded as the main bioactive components (Tripathy and Srivastav 2025). These phytochemicals have a broad spectrum of biological activities, such as antioxidant, cytotoxic, antibacterial, and thrombolytic activities (Rashid et al., 2023). It is primarily the scavenging of reactive oxygen species and stimulation of endogenous defense mechanisms that are attributed to the antioxidant potential, which protects cells against oxidative damage. Moreover, the cytotoxic action of these compounds has been linked to control the cell cycle development and triggering the process of apoptosis of abnormal cells. The mechanism of action of the antibacterial effect is the destabilization of microbial membranes and the inhibition of the most vital metabolic activities, and the thrombolytic effect plays a role in the dissolution of fibrin clots and an increase in the work of the vessels. Together, these pharmacological actions underscore the synergistic action of Centella asiatica phytoconstituents in its widespread use in both traditional and contemporary therapeutic practices (Rashid et al., 2023).

2. NEUROPROTECTIVE AND COGNITIVE EFFECTS

The positive impact on the central nervous system has been extensively researched with Centella asiatica. It has shown the possibility of improving the memory, improving cognitive performance, and treating neurological disorders (Samuel et al., 2022). Empirical evidence shows that Centella asiatica extracts have the potential to slow age-related cognitive impairment and anxiety through promotion of mitochondrial activity and NRF2-mediated antioxidant activities (Gray et al., 2024). The antioxidant effects of it are also important in the prevention of oxidative stress and neurodegeneration (Hein et al., 2025).

Quercetin, chlorogenic acid, and kaempferol are several examples of bioactive compounds with neuroprotective properties by inhibiting the formation of amyloid aggregates and cytotoxicity in neuronal cells (Chatterjee et al., 2024; Chamberlin et al., 2024; Eze et al., 2024). Moreover, the plant is acetylcholinesterase inhibitory, and it is applicable in the treatment of the Alzheimer disease (Reubun et al., 2021).

The use of thiolated chitosan-Centella asiatica nanocomposites is another advanced formulation that has been investigated as a delivery method to the brain, specifically via the nasal route (Haroon et al., 2021). These innovative delivery systems increase bioavailability, enhance penetration of active compounds into the blood-brain barrier, and provide prolonged release of active compounds, which increase therapeutic efficacy in neurodegenerative diseases. In sum, the combination of the traditional knowledge and modern nanotechnology underlines the potential of Centella asiatica as a promising drug development candidate in terms of neuroprotection.

3. CYTOPROTECTIVE AND ANTIOXIDANT POTENTIAL

Centella asiatica possesses cytoprotective actions, which are closely associated with its high antioxidant activities. The plant also has numerous phenolic compounds such as flavonoids, tannins, polyphenols, which neutralize free radicals and prevent oxidative damage to cells (Hossain et al., 2024). Research has shown that extracts of Centella asiatica increase the action of native antioxidant enzymes which include superoxide dismutase (SOD) and glutathione peroxidase (Pillai et al., 2024). Caffeic acid, gallic acid, sinapic acid, and oxalic acid are some compounds that make it an anti-inflammatory and antioxidant agent (Hambali et al., 2024; Buraphaka et al., 2024).

Besides enzymatic modulation, these phytochemicals assist in maintaining cellular redox balance, stabilizing membrane lipids, and reducing lipid peroxidation as well as preventing protein oxidation, thus preserving cellular integrity in general, during stress conditions. The use of modern extraction methods such as ultrasonic-assisted extraction and microwave-assisted extraction has been used to extract bioactive compounds to the maximum extent out of Centella asiatica leaves (Bhuyar et al., 2021).

These novel techniques are proven to not only enhance the extraction efficiency, but also increase the capture of heat-sensitive phenolics and flavonoids to produce extracts that have high biological activity. These extracts have also been shown to exhibit antimicrobial, antifungal and antioxidant effects and this further justifies their therapeutic efficacy in preventive and curative treatment.

Also, synergistic effects of phytochemicals on succinic acid or oxalic acid can increase the overall antioxidant and anti-inflammatory activity of the plant (Syahputri et al., 2024). This synergism is thought to enhance the overall cytoprotective activity, and Centella asiatica is a promising source of natural agents in combating oxidative stress-related cell damage and related pathological conditions.

4. CARDIOPROTECTIVE EFFECTS

There is also emerging evidence that Centella asiatica is also involved in cardiovascular health. Glicic acid among other compounds has been reported to enhance endothelial function and cardioprotective effects (Eff et al., 2025). The plant contains organic acids that help in the regulation of cardiovascular and neurological functions, such as citric acid, malic acid, and tartaric acid (Kaur, 2025). Also, phenolic acids like p-coumaric acid have high antioxidative activity that can alleviate vascular damage caused by oxidative stress and inhibit the occurrence of atherosclerosis and other cardiovascular diseases (Legiawati, 2021). All these bioactive compounds aid in vasodilation, enhancing blood circulation, and lipid homeostasis by regulating cholesterol metabolism and LDL oxidation, respectively. Moreover, the general antioxidant atmosphere formed by these phytochemicals helps in protecting cardiac tissues against ischemia–reperfusion injury, which explains the prospects of Centella asiatica as an adjuvant in the prevention and treatment of cardiovascular diseases.

5. ANTIMICROBIAL ACTIVITY

The protective effect against microorganisms of Centella asiatica is explained by its complex phytochemical structure, especially phenolic acids, flavonoids.

Gallic acid and kaempferol have proven to be effective antibacterial and antifungal agents (Kauser-Ul-Alam et al., 2025; Lim et al., 2021). The effect of these bioactive compounds on microbes is mainly these compounds interfere with cell membrane integrity, activity of enzymes and disrupts vital metabolic processes, resulting in the inhibition of growth or death of the cell. The compounds have a wide spectrum of wound-related pathogens and this makes the plant especially useful in topical formulations to hasten wound healing and prevent infection. They have also been investigated as preservatives in food systems, where they assist in increasing the shelf life of perishable foods like poultry by decreasing microbial load and oxidative rancidity. Moreover, succinic acid and other secondary metabolites have a synergistic effect on the antimicrobial action of plants by increasing membrane permeability and complementing the overall bioactivity of phenolic constituents (Bunse et al., 2022). These results, taken altogether, suggest Centella asiatica as a promising natural source of antimicrobial agents both in pharmaceutical and food industry.

6. REGENERATIVE AND WOUND HEALING APPLICATIONS

The wound healing and tissue regeneration are one of the most developed applications of Centella asiatica. Trierpenoids like asiaticoside and asiatic acid induce collagen production, stimulate angiogenesis, and speed up tissue repair (Diniz et al., 2023). These substances promote fibroblast growth and the formation of extra cellular matrix that all leads to tightening of the wound and faster rate of re-epithelialization. Consequently, Centella asiatica is generally known as effective in enhancing structural and functional healing of destroyed skin tissues.

Additional bioactive agents, such as quercetin and fumaric acid, play a role in wound healing by regulating inflammatory responses and promoting cell regeneration (Ariani et al., 2023; Dhawal et al., 2023). Along with decreasing unwanted inflammation, the compounds assist in balancing cytokine generation and oxidative damage within the wound area, thus providing optimal conditions to repair tissues and reducing scarring.

Moreover, the phenolic acids, including p-coumaric acid, are useful in the prevention and treatment of skin disorders because of their high antioxidant and photoprotective effects, which prevent the damage and early aging of skin cells caused by UV light (Banerjee et al., 2025).

The occurrence of various organic acids, such as citric, malic, oxalic, and quinic acids, also confirms the therapeutic potential of Centella asiatica in use in dermatological treatments (Tahsin, 2025). These compounds help skin to remain hydrated, maintain pH, and provide metabolic support to skin cells, thus contributing to the overall skin barrier functioning. Together, these synergistic phytochemicals have rendered Centella asiatica a very powerful natural wound healing, scarring reducing and skin regeneration agent.

7. TOXICOLOGICAL PROFILE AND SAFETY CONSIDERATIONS

The toxicology of Centella asiatica has been thoroughly studied in preclinical and limited clinical research and tends to suggest a good safety margin when used in the recommended dosages. The animal models of acute and sub-chronic toxicity have indicated that standardized extracts of C. asiatica lack any significant organ toxicity or behavioral abnormalities in therapeutic doses, with no-observed-adverse-effect levels (NOAEL) being reported even with relatively high oral exposures (Deshpande et al., 2015; Songvut et al., 2019). Likewise, water-soluble and triterpenoid-rich extracts like Centell-S have proven to have low toxicity profiles in sub-chronic studies, which prove their safety in the long-term usage under controlled circumstances (Junsai et al., 2024). Topical use Cosmetic safety assessments have also established that ingredients derived C. asiatica are mostly safe with low potential of irritation or sensitization of human skin in topical use (Johnson et al., 2023).

Although it is generally safe, there are a few reports that overdose or when taken in high dosages or non-standardized preparations, excessive use or prolonged use could be linked to mild adverse events, including gastrointestinal discomfort, headache, or hepatotoxicity (Biswas et al., 2021; Prasesti and Kurniati, 2022). Such risks underscore the need to have adequate standardization, control of dosage and quality of herbal preparations.

Moreover, the existing literature highlights the necessity of more rigorous clinical trials to develop the long-term safety, drug-herb interaction profiles and pharmacovigilance data, particularly in vulnerable groups, including pregnant women, children, and those with pre-existing liver problems (Wright et al., 2022; Hein et al., 2025).

8. PHARMACOKINETICS AND BIOAVAILABILITY

The pharmacokinetics and bioavailability of Centella asiatica has received growing scientific focus because of the complex behavior of major triterpenoid constituents within the herb, especially asiaticoside, madecassoside, asiatic acid and madecassic acid. Research has revealed that these compounds have a relatively low oral bioavailability, which is primarily explained by the low aqueous solubility and low intestinal permeability of these compounds, reducing their systemic absorption upon oral administration (Yuan et al., 2015). After ingestion, triterpenoid glycosides are highly bio-transformed in the gastrointestinal tract where they are broken down to their active aglycone forms, which play a major role in their pharmacological effects (Anukunwithaya et al., 2017).

Pharmacokinetic studies in animal models and human clinical trials have found that the absorption characteristics of Centella asiatica constituents tend to follow a delayed and multi-peak (bimodal) plasma concentration model, indicating complicated absorption and enterohepatic recirculation pathways (Wright et al., 2022). Furthermore, the type of formulation, extraction technique, and bioenhancement may also contribute to variability in bioavailability, and thus, may greatly enhance solubility and systemic exposure of active compounds (Songvut et al., 2021).

Moreover, intestinal permeability and transporter interactions have also been proposed in silico pharmacokinetic modeling and machine learning methods to estimate the absorption efficiency of Centella asiatica phytoconstituents (Pumkathin et al., 2025). All these results suggest that despite the promising pharmacological characteristics of the plant, its clinical performance is extremely reliant on the formulation approaches that can increase bioavailability.

Hence, enhanced delivery technology and bioenhancing processes are deemed as important in streamlining the therapeutic activity of Centella asiatica in contemporary pharmacotherapy.

9. MECHANISMS OF ACTION (MOLECULAR AND CELLULAR PATHWAYS)

Centella asiatica has pharmacological impacts mediated by various molecular and cellular mechanisms that are mainly mediated by its triterpenoids that include asiaticoside, asiatic acid and madecassoside. These bioactive substances are known to control essential signaling pathways in inflammation, oxidative stress, apoptosis, and tissue repair. The NF-kB signalling pathway, which involves the suppression of pro-inflammatory cytokines and the inhibition of the production of inflammatory mediators, is one of the key mechanisms, and C. asiatica constituents have strong anti-inflammatory effects (Sun et al., 2020; Wiciński et al., 2024).

Furthermore, Centella asiatica alters PI3K/Akt and MAPK pathways, which play a crucial role in cell survival, proliferation and apoptosis. The stimulation of these routes leads to improved wound healing, neuroprotection, and tissue regeneration through the facilitation of cellular repair pathways and the prevention of programmed cell death in response to stressful situations (Nagoor Meeran et al., 2018; Tan et al., 2021). Moreover, the plant can regulate the Wnt/ 2 -catenin signaling, which is a major factor in skin rejuvenation and fibroblast stimulation that facilitates collagen production and skin remodeling (Choi et al., 2025).

Another key process is oxidative stress regulation, and in this case, Centella asiatica stimulates the Nrf2/ARE antioxidant pathway, resulting in the up-regulation of endogenous antioxidant enzymes including the superoxide dismutase and glutathione peroxidase. This increases cellular resistance to reactive oxygen species and oxidative injury to neuronal, hepatic, and vascular tissues (Gray et al., 2018). Furthermore, asiatic acid has been found to suppress the apoptotic and fibrosis-associated pathways by regulating the TGF-B and RAGE-induced signaling, especially in cardiac and hepatic tissues (Fadhillah et al., 2025).

10. PHARMACEUTICAL AND COSMETIC APPLICATIONS

Due to the broad range of bioactive compounds, especially triterpenoids, flavonoids, Centella asiatica has become an important plant in the pharmaceutical, cosmetic, and nutraceutical industries today. It is usually used as capsules, tablets, syrups, and standardized extracts in the pharmaceutical industry to assist with cognitive functions, wound healing, and anti-inflammatory processes (Shah et al., 2025; Hein et al., 2025). The use of standardized oral formulations is especially appreciated to provide consistency in dosing and improved therapeutic effect, particularly in neuroprotective and vascular health care.

Centella asiatica has been widely applied in the topical formulations including creams, gels, lotions, and wound ointments in dermatological and cosmetic industries because of its high wound-healing, collagen-stimulating, and anti-inflammatory activities (Pandey & Gupta, 2025). These preparations have extensively been used in products aimed at skin regeneration, scar reduction, acne treatment and managing eczema. In addition, its collagen-stimulating properties and skin-elasticity have made it an essential component in anti-aging skincare, sunscreens and dermal repair formula (Suvedi et al., 2025; Hein et al., 2025).

In addition to topical and oral pharmaceutical applications, Centella asiatica is also known in the nutraceutical and functional food sectors. It is added to dietary supplements, health drinks, and herbal functional foods designed to boost the cognitive performance, stress reduction, and overall wellness (Sarkar et al., 2024). C. asiatica has been incorporated into cosmeceuticals and functional nutrition products as a result of the increasing consumer preference to plant-based and natural health products. It has also been enhanced with sophisticated delivery vehicles including phytosomes and nanoformulations that have enhanced its stability, absorption, and skin penetration, hence increasing its commercial and therapeutic uses (Dwivedi et al., 2025).

11. AGRICULTURAL, INDUSTRIAL, AND ECONOMIC IMPORTANCE

Centella asiatica is a commercially-important medicinal plant and is commonly grown to be used as a pharmaceutical and other commercial purposes. It has an agricultural significance because it is adaptable to a broad spectrum of climatic conditions, especially in humid and semi-shaded areas, and can be harvested in the wild, as well as in commercial farming. Research revealed that the practices of cultivation, such as soil fertility control, phosphate application, and post-harvest treatment, have a significant effect on the yield of biomass and the concentration of bioactive compounds, including centellosides (Singh et al., 2023; Vinolina and Sigalingging, 2022). In addition, ecological modeling studies suggest that climate change and environmental factors can affect its distribution and productivity, highlighting the need for optimized agronomic strategies for sustainable production (Lin et al., 2024).

Industrialatically, Centella asiatica is an important raw material in the production of standardized phytochemicals that find application in pharmaceuticals, cosmetics and nutraceuticals. The development of green extraction and purification systems has provided the possibility to produce high-quality bioactive fractions on a large scale and use them in industrial applications (Razzaq et al., 2026). In addition, plant tissue culture and in vitro propagation methods are under investigation to address the growing demand of the herbal industry, and to provide uniformity in the phytochemical composition (Gbolahan et al., 2016).

In herbal medicine and cosmetical industries, Centella asiatica is a high-value cash crop in various Asian economies because of the high demand of this plant world-wide. It offers considerable livelihoods to small scale farmers, particularly in rural and semi-arid areas where it is grown as a commercial medicinal crop (Suryanarayana et al., 2022). Nonetheless, exploitation of the natural stocks has caused sustainability challenges and regulated production and preservation measures are necessary that would ensure the economic security in the long-term (Singh et al., 2010).

12. LIMITATIONS AND RESEARCH GAPS

Although there is a wealth of evidence on the pharmacological potential of Centella asiatica, a number of limitations and gaps in the field of research continue to impede its complete clinical translation. The absence of standardized extracts and the variation in the phytochemical composition as a result of geographical origin, cultivation conditions, harvesting time, and post-harvest processing procedures is one of the biggest issues. This heterogeneity results in unreliable biological activity and restricts reproducibility of experimental and clinical research (Hein et al., 2025; Oyenihi et al., 2023).

The other notable limitation is the lack of large-scale and well-controlled clinical trials. The majority of existing studies are either preclinical or are based on small samples, which limits the possibility of making conclusive findings about efficacy, optimal dose, and long-term safety in humans (Arribas-López et al., 2022).

Moreover, despite the large number of pharmacological effects that have been reported, the exact molecular pathways of many bioactive compounds are not completely understood. Such pathways have been preliminarily studied by network pharmacology and in silico, and there is still limited experimental validation of such pathways, especially in complex disease models (Hein et al., 2025).

13. FUTURE PERSPECTIVES

The future of Centella asiatica study is very bright owing to the growing uses of the plant in pharmacology, nutraceutical, cosmetic and biotechnology. Among the most important future directions, the establishment of standardized extracts and the standard phytochemical profiles to guarantee the reproducible therapeutic effects should be noted. Further analytical tools, such as metabolomics and systems biology methods, will likely be instrumental in the discovery of new bioactive compounds, as well as synergies between them (Hein et al., 2025; Oyenihi et al., 2023). The other perspective of significance is the optimization of cultivation strategies in the changing climatic conditions.

According to the ecological niche modeling studies, climate change could have a strong impact on the geographical distribution and productivity of C. asiatica, and adaptive agricultural strategies and regulated cultivation systems could be crucial to guarantee sustainable production (Lin et al., 2024). Also, the use of biotechnological strategies like the plant tissue culture, genetic enhancement, and elicitor-based enhancement of secondary metabolites is under consideration to enhance the production of bioactive constituents, especially centellosides (Gbolahan et al., 2016).

On a pharmaceutical note, improved bioavailability by way of novel drug delivery systems such as nanoparticles, phytosomes, and nanoemulsions is likely to be the subject of future study and to improve absorption and targeted delivery of triterpenoids. To incorporate C. asiatica into clinical practice, there will be a need to conduct large-scale randomized controlled trials to confirm the effectiveness, safety, and optimization of its dosage in various disease situations (Biswas et al., 2021).

CONCLUSION

Centella asiatica is a multifunctional medicinal plant with a broad spectrum of pharmacological effects, such as neuroprotective, antioxidative, cardioprotective, antimicrobial, and regenerative effects. Its therapeutic effect is based on its rich phytochemical composition, especially triterpenoids, and phenolic compounds.

Its potential in clinical applications has also been increased recently by the development of new methods of extraction and delivery systems of drugs. Nevertheless, the clinical trials and mechanistic studies should be more standardized to completely clarify its therapeutic potential and guarantee safe and effective use in modern medicine.

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CHAPTER 2
GREEN DRUG DELIVERY SYSTEMS FOR CLIMATE-SMART HEALTHCARE

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INTRODUCTION

Worldwide pharmaceutical industry is at revolutionary point aiming to overcome the challenges for environmental responsibility and bring new advancements in therapeutic strategies. Generally, drug development scientist concerns with the safety and efficacy of the drug used with its side effects but, now the term "GREEN PHARMACY" is receiving a globally attention. Nowadays, pharmaceutical businesses all over the world are adopting the standards of sustainable drug delivery technologies. Regulatory requirements, customer demand, and a sincere realization that the long-term health of the earth is inherently connected to the health of the living population (Shah, Chauhan et al. 2023).

Modifying dosage forms and delivery systems to minimize waste production and environmental toxicity without compromising efficacy, safety, and quality of the pharmaceutically used material is the main intent of green drug delivery systems. This modern perspective unites pharmaceutical innovation with climate-smart healthcare, which can be described as enduring, low-carbon, and eco-friendly sustainable healthcare (Salem 2025).

1. CLIMATE-SMART HEALTHCARE: CONCEPT AND RELEVANCE

Climate-smart healthcare in pharmaceutical industry, is an effective strategy that incorporates environmental responsibility during drug development and throughout life cycle of a drug.

Climate-smart healthcare defines health related benefits, adaptation and planning strategies which are less harmful for the environment and delivery of healthcare (Agrawal, Bansal et al. 2024).

1.1 Key Principles

Reduction of Greenhouse Gas Emissions

Global greenhouse gas (GHG) emissions hit a record 60.63 billion tons in 2025 up 0.5% from 2024, according to the Climate TRACE February 2026 report. Additionally, methane emissions reversed a 2024 drop and reached a new record of 412.59 million tons (Mt) (Buizza 2026).

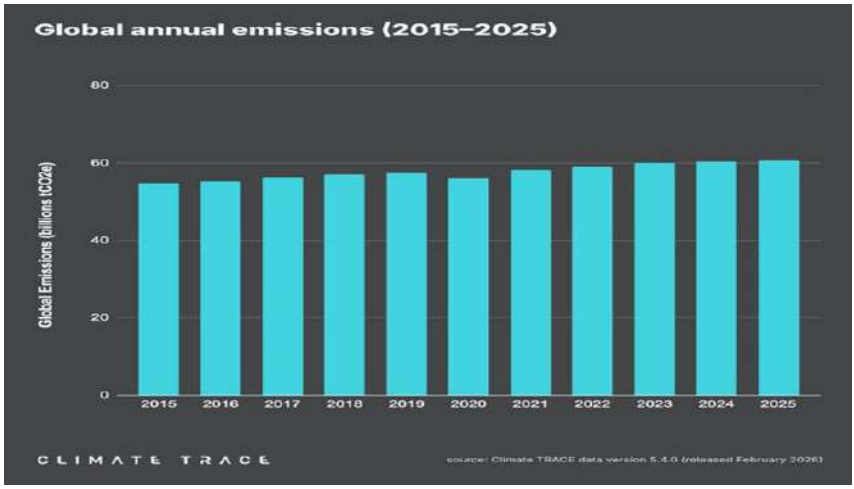

Figure 1. Global annual emissions(2015-2025)

Efficient Use of Energy and Resources

Reducing waste by using fewer inputs to produce the better or quality services is known as efficient use of energy and resources. This can be achieving by adopting energy-efficient appliances, sustainable, and renewable materials. It encourages long-term environmental sustainability, lowers expenses, and reduces emissions (Rani, Yadav et al. 2026).

Waste Minimization and Circular Economy Practices

By establishing a Circular Pharmacy Supply Chain in the pharmaceutical industry focuses on moving from a conventional concept to a modified system that minimize the medical waste. By managing & optimizing inventory data stock outs and overstocking of medicines can be avoided. An eco-friendly and biodegradable packaging may also reduce plastic waste and by adopting a setting up take-back programs, in which pharmacies collect used inhalers, blister packs, or medicines not used by the patients for safe recycling or energy recovery. Applying these practices in pharmaceutical sector can reduce its ecological footprint, lower raw material prices, and ensure that valuable resources can be recycled (Farrukh and Sajjad 2025).

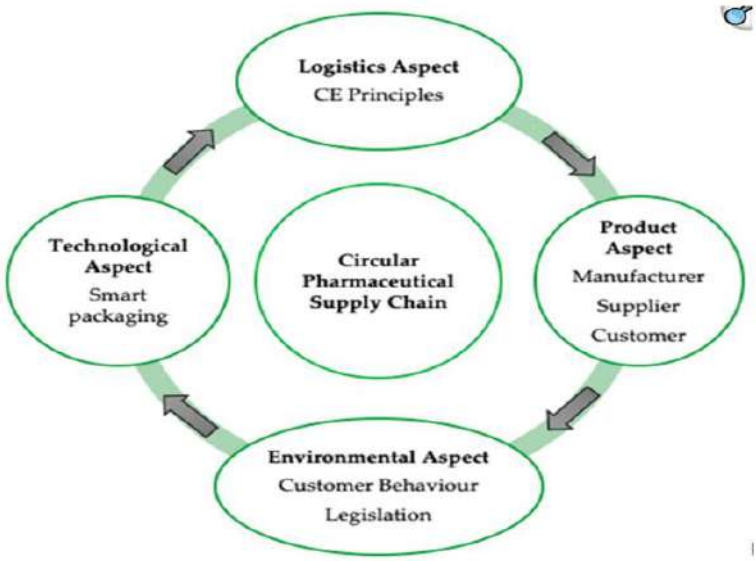

Figure 2. Framework of the Circular Pharmaceutical Supply Chain and Its Key Aspects

Resilient Healthcare Infrastructure and Supply Chains

Developing a resilient healthcare facilities and supply chain to the pharmaceutical industry is intended to create a strong, adaptable system that is both ecofriendly and assures continuous delivery even during critical situations.

A collaborative relationship amongst the pharmaceutical industries might be helpful in fuel savings and substantially reducing carbon emissions (CO2). Additionally, recyclables from one can be used as a raw material for another, this increases the effectiveness and economy of waste management.

The system can be further protected by incorporating digital tools and solar-powered storage from problems brought upon by power failure and climate change. Eventually, by promoting regional production and united collaboration, we can establish a supply chain that ensures a resilient healthcare framework with continuous delivery & reduced carbon footprint involved with worldwide shipping. Supply chains in a health care system requires a fundamental re-evaluation of how products are designed, used, and reused in the sector, based on the following principles (García-Navarro and Poltronieri 2024).

1.2 Role of Pharmaceutical Sciences

Pharmaceutical scientists in the modern era are playing their crucial role in developing an eco-friendly healthcare framework by adopting a sustainable Cradle-Cradle design, this practice helps pharmacists in modernizing the pharmaceutical industry from traditional polluting practices to a Circular Economy.

Reducing Dosing Frequency and Medicine Wastage

Pharmacist can play a vital role in developing such dosage forms that reduces dose frequency. Many research suggests that nanotechnology has shown significant contribution to an ecofriendly healthcare system because functionally, nanoparticles act as long acting reservoirs keeping the drug within the therapeutic range for a prolonged duration of time, thus providing a controlled and sustained release of drug. By enhancing absorption, avoiding rapid degradation and improving bioavailability nanoparticles ultimately facilitate reduction in dose frequency (Yadav, Rathore et al. 2025).

Improving Drug Stability Under Variable Climate Conditions

The stability and efficacy of drugs can be compromised by climatic change. For many pharmaceutical drugs particular temperature and humidity ranges are needed to be maintained within specific range. Elevated humidity and temperature can reduce efficacy of many thermo labile drugs such as vaccines. Even extreme weather conditions, such as storms & floods may cause delays in supply chains and even exposing drugs to ideal conditions. These challenges emphasize the need of a sustainable climate-resilient drug management strategies (Shashiashvili 2025).

Utilizing temperature-controlled storage devices. By adopting real-time monitoring systems to monitor and educate staff to alert from specified conditions.

Regular monitoring of stability profiles regular assessment of stability profiles of drugs specifically sensitive to heat and humidity to determine appropriate storage requirements.

Creating Backup Plans: Creating standard procedures for preserving the integrity of medications in the disruption of power outages or HVAC system breakdowns, including backup power options and other storage arrangements.

Enhancing Distribution Systems for Climate Resilience. Eco-friendly logistics techniques are vital for alleviating the effects of climate change on drug distribution. Pharmacists and distributors can adopt AI-driven route planning to cut fuel emissions and avert weather-related delays. By using biodegradable insulation and electric transportation, a sustainable cold chain is maintained, ensuring that temperature-sensitive drugs continue to be effective with a low carbon impact. Additionally, by using IoT-enabled real-time tracking and strategic stockpiling, pharmaceutical waste and medicine deterioration are avoided, resulting in a robust, environmentally friendly supply chain that protects patient health and the environment (Sahu 2024).

Education and Stakeholder Engagement Training and Awareness. Educating and training personnel working in the pharmaceutical sector on sustainable development standards, green chemistry concepts, and environmentally responsible methods. Involving Stakeholders Working together to exchange best practices, encourage innovation in sustainable pharmaceutical procedures, and promote eco-consciousness with healthcare professionals, regulators, researchers, and community stakeholders (Smale, Egberts et al. 2021)

2. GREEN DRUG DELIVERY SYSTEMS: DEFINITION AND SCOPE

Green drug delivery system refers to design, develop and implement a pharmaceutical delivery system that combine the concepts of green engineering and green chemistry to limit toxic waste & produce a benevolent environment.

2.1 Core Objectives

In the field of pharmaceutical “green chemistry" offers a framework for developing a sustainable and eco- friendly chemical processes which promotes using renewable resources, reducing waste, enhancing atom economy, and creating safer reaction conditions.

The concepts of green chemistry are described in the given table with their description &their pharmaceutical applications.

Green chemistry principle	Description	Pharmaceutical application
Waste prevention	Avoid the generation of waste at the source.	Use of one-pot synthesis to minimize purification steps and reduce by-products. For example, Pfizer has reduced waste in its production of sertraline by redesigning the synthesis pathway, lowering solvent use, and improving process yield.
Atom economy	Maximize the incorporation of all materials used into the final product.	Cycloaddition and rearrangement reactions that minimize side products. For example, Johnson & Johnson reported improved atom economy by switching to catalytic hydrogenation in the synthesis of certain APIs, reducing waste by 25%.
Safer solvents and auxiliaries	Use of less hazardous solvents and reaction media.	Replacement of toxic organic solvents with water or supercritical CO_2. For example, BASFs switch to supercritical CO_2 for extracting pharmaceutical intermediates reduced VOC emissions and solvent disposal costs
Catalysis	Use of catalytic reagents over stoichiometric reagents.	Biocatalysts and metal catalysts for selective and efficient transformations. For example, Novartis uses biocatalysis for chiral amine synthesis, improving selectivity and cutting reaction steps.
Use of renewable feedstocks	Employ renewable raw materials instead of depleting ones.	Utilization of plant-based biomass or fermentation products for API synthesis.

Figure 3. Green Chemistry Principles and Their Pharmaceutical Applications

Minimize Environmental Toxicity

Green medication delivery, which combines clinical efficacy and sustainability, is a revolutionary change in the pharmaceutical industry. Fundamentally, this method seeks to minimize ecological damage by using safer, bio-based substitutes for toxic solvents and hazardous reagents during the synthesis process (Salahvarzi, Fathi-karkan et al. 2025).

Enhance Biodegradability and Recyclability

By using carriers that spontaneously break into non-toxic byproducts are made from materials like poly (lactic-co-glycolic acid) (PLGA) and natural polymers like chitosan and alginate. This reduces the environmental impact of medical waste and eradicates of long-term systemic accumulation. By utilizing Nanotechnology & Smart Carriers drugs can be precisely delivered to targeted cells, including tumors, while protecting healthy tissue by engineering nano-sized systems (1–100 nm) with active targeting ligands. "Smart" carriers only release their payload at the intended area in response to internal triggers like pH shifts (El-Tanani, Satyam et al. 2025).

Reduce Energy and Solvent Consumption

By replacing eco- friendly substitutes like water, supercritical CO2, and ionic liquids for toxic volatile organic chemicals, green drug delivery methods are redefining the pharmaceutical industry. In certain applications, the incorporation of energy-efficient techniques, such as microwave-assisted and ultrasound-mediated processes, lowers energy usage by more than 70% while coordinating production with environmental sustainability. An example of how green chemistry principles have been successfully applied in pharmaceutical manufacture is the antiepileptic drug rufinamide. The initial synthesis was a multi-step process that used harmful reagents and produced a lot of waste. In order to reduce the number of unit activities and do away with intermediary isolation, a new technique used continuous flow chemistry with in-line separation. The ingenious method has boosted volumetric productivity tenfold while reducing waste production by half. Reactions at elevated temperatures under regulated conditions were made possible by replacing flow reactors with batch reactors, which increased reaction yields and speeds. This example demonstrates how increasing process intensity using the green chemistry method can simultaneously enhance economic and environmental indicators (Stefanache, Marcinschi et al. 2025).

Financial Benefits

A comprehensive cost-benefit analysis is necessary for the pharmaceutical sector to use green polymers in order to rationalize the transformation from traditional petroleum-based products. Incorporating eco-friendly polymers such as PLA (Polylactic Acid) and PHA Poly hydroxyal kanoates) lowers waste management expenses and financial concerns related to environmental compliance. Additionally, using green products proactively enhances an organization's CSR reputation, which could result in a rise in the market share of customers who care about the environment. Macro economically interpreted, as economies of scale are realized and the financial costs of carbon emissions from traditional plastics increase due to international taxation, the cost-benefit analysis is progressively moving in favor of biopolymers (Basem, Ata et al. 2026).

A high degree of circumambulation used in solvent recovery is made possible by modern techniques such distillation, membrane separation, evaporation, and adsorption have explored a high degree of a high of circumambulation insolvent recovery Pharmaceutical processes require a higher level of purity (usually over 99.5 percent in a reassurance of solvent reuse in drug substance manufacturing), which varies significantly depending on the probability that recovered solvents will be reused in the same operation or elsewhere. Advanced case studies also demonstrate how on-site solvent recycling can recover up to 70% of solvents on an industrial scale and reduce greenhouse gas emissions by roughly 48% over the course of the solvent lifespan According to economic impact studies, solvent recovery systems save pharmaceutical manufacturing facilities between 30% and 50% of their expenditures. They also lower the costs associated with disposal and regulatory compliance. Membrane-based separation technologies are becoming more popular in green manufacturing workflows because, according to environmental quantification, none of them require more energy than traditional distillation and must meet comparable purity standards (Nair, Maity et al. 2025).

2.2 Life-Cycle Perspective

Green Drug Delivery Systems (GDDS) integrate sustainability throughout the whole product lifetime, from the procurement of raw materials to the environmental impact after use. Biodegradable and sustainable polymers like PLGA are preferred (Michael 2025). Green chemistry techniques, such as one-pot synthesis, are employed during formulation and manufacture to reduce waste, solvent use, and energy consumption (Sheldon 2017). Sustainable materials like recyclable or biodegradable packaging are used in the packing and distribution phase to reduce the carbon impact. (NAIR) Additionally GDD-like targeted nanoparticles help lower drug dosage and restrict pharmaceutical residues in the environment in terms of usage, disposal, and post-use environmental effect. When combined, these strategies show how GDDS incorporates environmental responsibility at every stage of drug lifecycle.

3. GREEN MANUFACTURING AND PROCESSING TECHNOLOGIES

3.1 Solvent-Free and Low-Solvent Techniques

Hot-melt extrusion is a green manufacturing method of drug that process the drug in molten state thus reducing need of organic solvent. This technique also reduces environmental risks related to solvent disposal, increases drug solubility, and improves content homogeneity. Furthermore, compared to traditional batch processing, HME is a continuous process that uses less energy and produces less waste. Many research indicates that hot-melt extrusion is widely acknowledged as an effective and environmentally sustainable method for creating regulated drug delivery systems and solid dispersions (Roychowdhury 2020).

3.2 Continuous Manufacturing

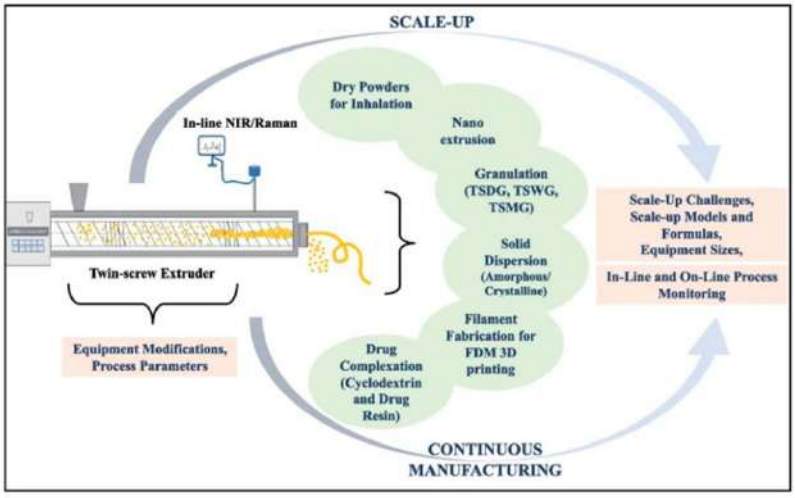

Figure 4. Scale-Up Strategies in Continuous Pharmaceutical Manufacturing

Even though many pharmaceutical manufacturing processes like tablet compression, encapsulation, roller compaction, and extrusion are basically continuous, they are usually used separately as batch processing equipment.

Conventional batch production procedures take a sequential method, introducing the material into a particular unit operation and transforming it into an intermediate product before discharging it and testing it offline. After that, the intermediate product is shifted to the next unit operation for additional processing. Hold time investigations are necessary since the holding time for intermediates can change based on the scale. These processes, including as mixing, hot melt extrusion, milling, compression, and coating, are typically repeated over several unit operations. However, continuous manufacturing (CM) can be used to integrate the same unit processes. Following this manufacturing path, the material is automatically transferred, tracked, and controlled. The finished product is released at the end of the process unit, while the starting material is constantly charged into the first process unit at the start of the line. A real end-to-end continuous solid oral dosage form production process can be established by constantly integrating the twin-screw extruder with downstream tablet making unit activities. A control plan (feed-forward or feed-back) can be established using process analytical technology (PAT). It takes less time to produce a final product in such a continuous process because hold time studies and intermediate testing are not required.

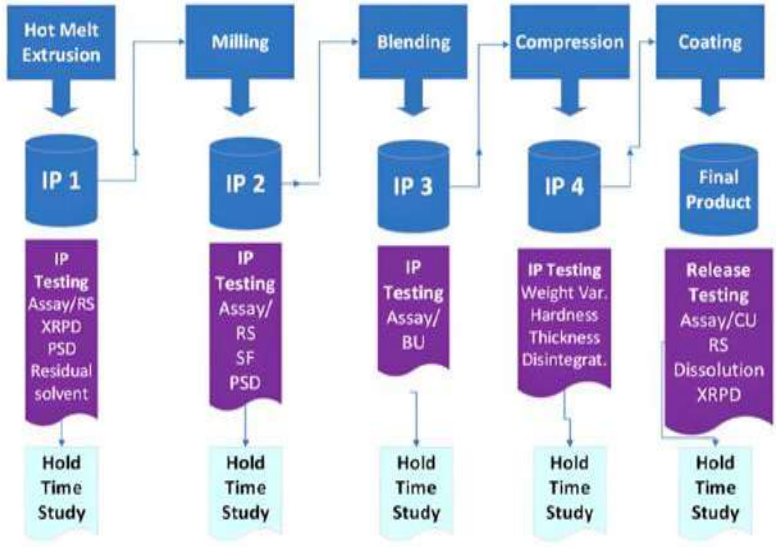

Figure 5. Manufacturing Process Flowchart

3.3 Advantages of Pharmaceutical Continuous Manufacturing

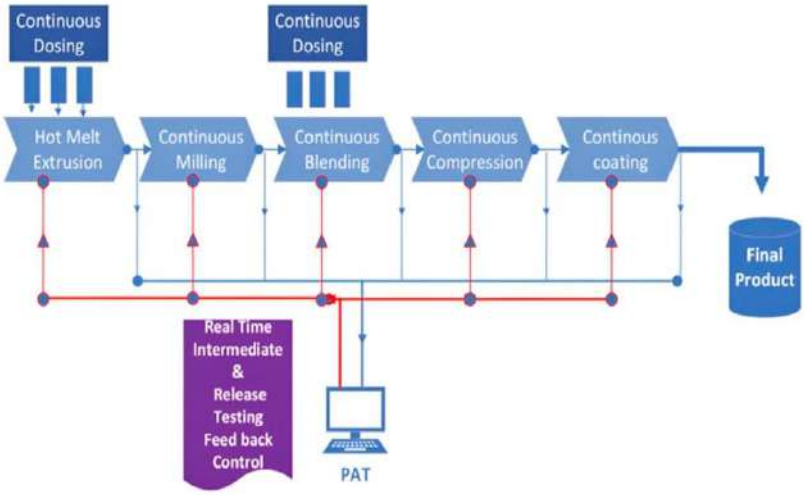

Figure 5. Schematic of a Continuous Manufacturing Process with PAT Integration

Continuous manufacturing shows many advantages like Quality, control, sustainability, and economics. By incorporating quality into the product rather than depending on final product testing, it is a true example of quality by design (QbD). Endpoint testing and total batch rejection can be prevented by putting in place inline in-process monitoring and control mechanisms. This lowers the cost of goods by eliminating the need for costly and time-consuming testing, batch rejection, and QA management activities. Continuous pharmaceutical manufacturing is flexible and economical. Based on the quality by design (QbD) approach, it permits real-time monitoring and control of critical process parameters (CPPs) and critical quality attributes (CQAs) (Patil, Vemula et al. 2024)

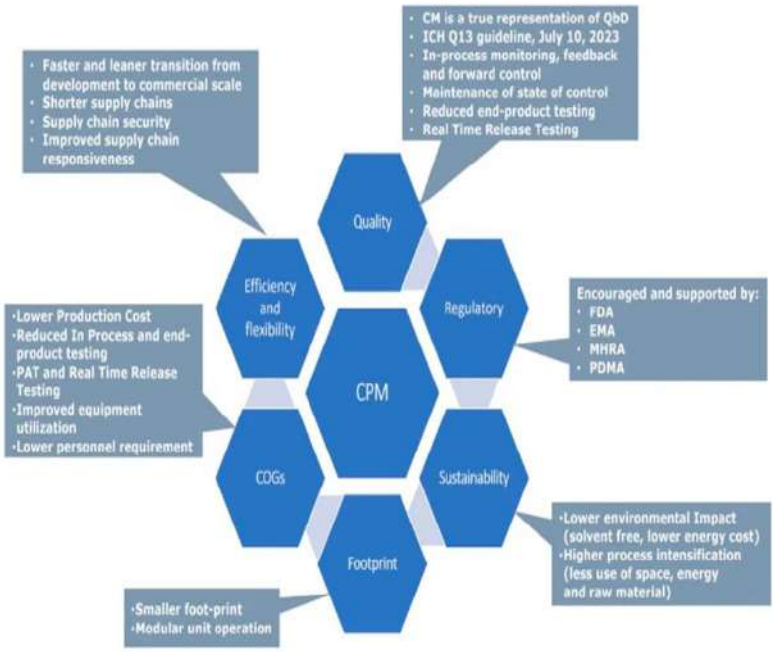

Figure 6. Key Drivers and Benefits of Continuous Pharmaceutical Manufacturing (CPM)

4. GREEN NANOTECHNOLOGY-BASED DRUG DELIVERY

4.1 Nano Carriers

In order to minimize harmful effects on patients and the environment, nanotechnology offers possibility for reducing dose frequency by target drug delivery. In present era environmentally benign nano carriers have become a viable strategy. polymers which are biodegradable like poly lactic acid (PLA), poly glycolic acid (PGA), or their copolymers are used to create polymeric nanoparticles, which offer regulated and prolonged medication release while organically breaking down into non-toxic byproducts. Solid lipid nanoparticles, which are made from natural lipids like triglycerides or stearic acid, provide stability, low toxicity, and biocompatibility while lowering dependency on artificial ingredients.

Furthermore, green-synthesized metallic nanoparticles made with microbes, plant extracts, or other natural reducing agents replace hazardous chemicals with environmentally friendly processes, lessening their negative effects on the environment. When combined, these environmentally friendly nano carriers improve site-specificity and therapeutic efficacy while also supporting cleaner, more sustainable pharmaceutical (Yang, Yin et al. 2024)

A number of nano carriers, including metal/metal oxide nanoparticles (NPs), nonmetal NPs, quantum dots, polymeric NPs, silica NPs, carbon nanomaterials, liposomes, dendrimers, nanostructured lipid carriers, solid lipid nanoparticles, etc., have been developed to deliver a wide range of molecules, including drugs, peptides and proteins, DNA/RNA, antibodies, etc. The figure shows of various Nano vectors and therapeutic components that can be effectively targeted and administered (Kanwar, Rathee et al. 2019).

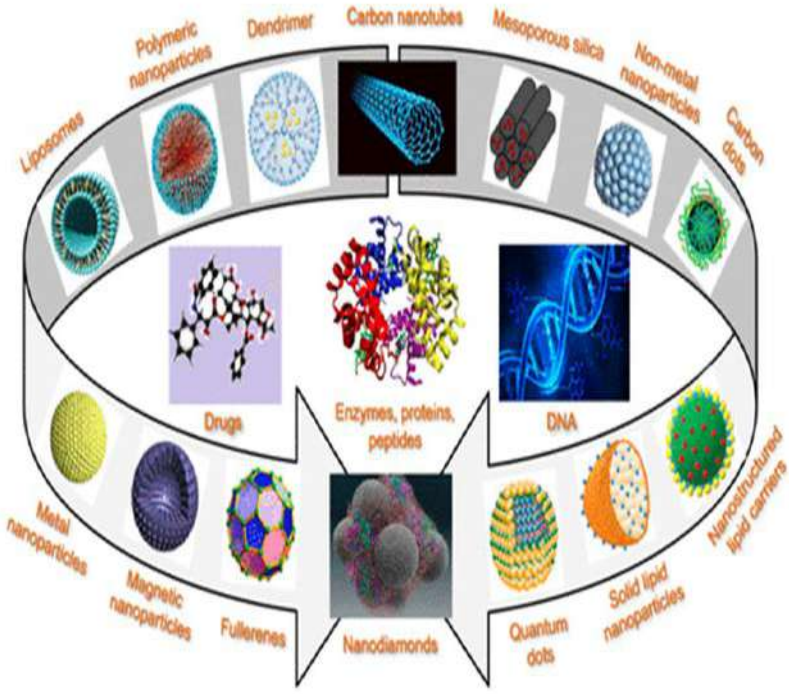

Figure 7. Classification of Nanocarriers for Drug and Biomolecule Delivery

5. PACKAGING INNOVATIONS FOR SUSTAINABLE DRUG DELIVERY

The study of the eco-friendly packaging identified four primary innovative themes that are concerned to the green global pharmaceutical packaging:

Sustainable packaging material: involve use of packaging materials that based on plant, microbial-based, and algae.

Design innovations: Emphasizing on reducing packaging volume and weight, and employing life-cycle assessments to improve sustainability.

Smart technology innovations: Incorporating technologies such as electronic patient information leaflets (e-PIL), QR codes, and computer-centered tools for eco-proposal.

Waste management innovations: Introducing novel processes for separating aluminum and plastic in waste pharmaceutical blister packs.

Many researchers are addressing more these themes, highlighting the interconnected nature of innovations in this field.

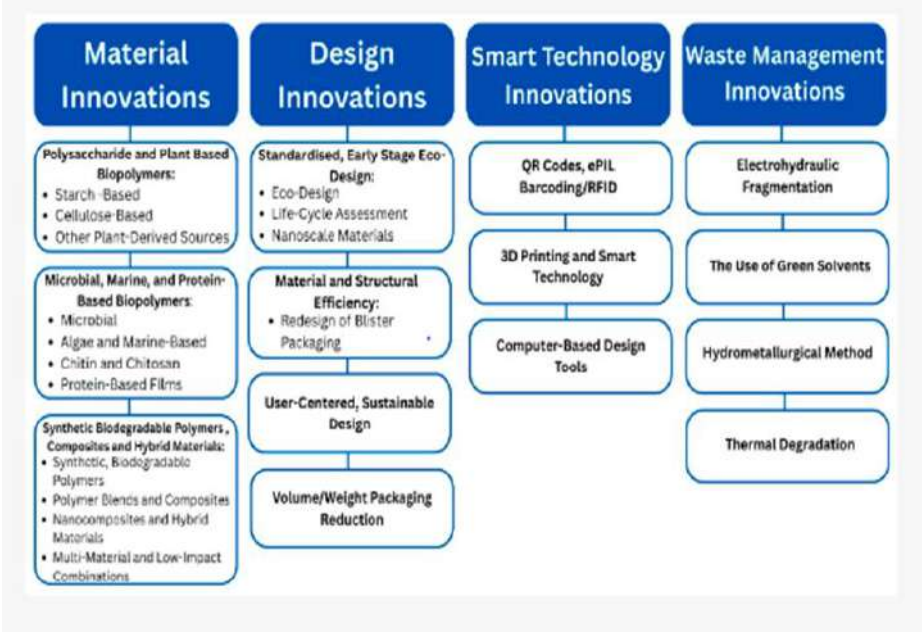

Figure 8. Framework for Sustainable Innovations in Packaging

Material Innovations

Material used for sustainable packaging are defined as biodegradable substances designed to substitute petroleum-based plastics in pharmaceutical packaging. These material innovations were categorized into three subthemes based on their sources: plant-based, microbial-based, and algae-based packaging matters.

Plant-Based Packaging Materials

Materials derived by plant basis have been the top extensive studied among sustainable packaging options. An active biodegradable film combining rosmarinic acid and gelatin have been developed which offers antioxidant and antibacterial properties suitable for both foodstuff and pharmaceutical packing (Ge, Zhu et al. 2018).

Another study enlightened several types of cellulose as promising bioplastics for pharmaceutical packaging. Notably, three studies focused on cellulose-chitin films as potential bioplastic materials for this purpose (Yu, Ji et al. 2020). Advancement in the field of packaging by improving the oxygen barrier, mechanical strength, and optical characteristics of nano cellulose and nano chitin films, transferring these plant-based sustainable materials closer to meeting the stringent requirements of pharmaceutical packaging.

Algae-Based Packaging Materials

Algae-Based Packaging Materials are another the beneficial characteristics of seaweed-derived polysaccharides for the development of sustainable pharmaceutical packaging materials, such as biocompatibility, non-cytotoxicity and antimicrobial properties, highlight-ing that sustainable algae-based food packaging has already been tested by consumer (Khalil, Saurabh et al. 2017). Similarly, (Rane, Savadekar et al. 2014) developed a biocomposite film by blendingk-carageenan from red seaweed with nanosilica. This biopolymer showed improved bar-rier properties, enhanced flexibility and mechanical strength compared to the carageenanbiofilm alone, increasing its suitability for the packaging of pharmaceuticals.

Design Innovations

Design innovations are defined as innovative design approaches to diminish the ecological influence of pharmaceutical packages during its lifespan.

Two subthemes were analysed: packaging volume-weight reduction and the use of life

Cycle assessment (LCA) mechanism.

Packaging Volume/Weight Reduction

It has been suggested from many research studies that by incorporating simple alterations to packaging scheme and method incredibly lessen the quantity of material used, thus packaging weight and/or volume will decrease and improving whole viability.

A study conducted by (Falconnier-Williams, Taeschner et al. 2024) reducing the sealing area around each alveolus to 2 mm and assembling the dosages in two rows can decrease primary packaging material usage by 37%. Another study showed that by replacing old traditional syringes by pre-filled versions eliminates the need for secondary packaging, reducing weight by 30%, volume by 50%, and reducing emissions related to storage and transport (Okereke 2021)

.

Use of Lifecycle Assessment Tools for Eco Design (LCA)

LCA is defined as an innovative device to permit pharmaceutical sector to design a knowledgeable and effective decision to develop ecofriendly changes in pharmaceutical packaging(Shah, Singh et al. 2025). Life Cycle Assessment (LCA) methodology was implemented following the international standards (ISO 14040, 2006, ISO 14044, 2006), defining objective and scope of life cycle models and inventories for pharmaceutical packaging to assess ecological impacts for thirteen categories (global warming, abiotic depletion – fossil fuel, acidification, ozone depletion, abiotic depletion – mineral and metal, particulate matter, eutrophication freshwater, eutrophication marine, eutrophication terrestrial, ionizing radiation, photochemical ozone formation, land use and water use), selected based on European recommendations (European Commission, 2021).

In a study the life cycle impact assessment has been performed for five categories global warming, abiotic depletion-fossil fuels, acidification, ozone depletion, and eutrophication (Bassani, Rodrigues et al. 2024). The sustainability tool helps pharma sector to determine which sustainability interventions, such as material reduction approaches, are needed during the product lifecycle. It also helps confirm the ecological impact of these changes over all the entire product lifespan.

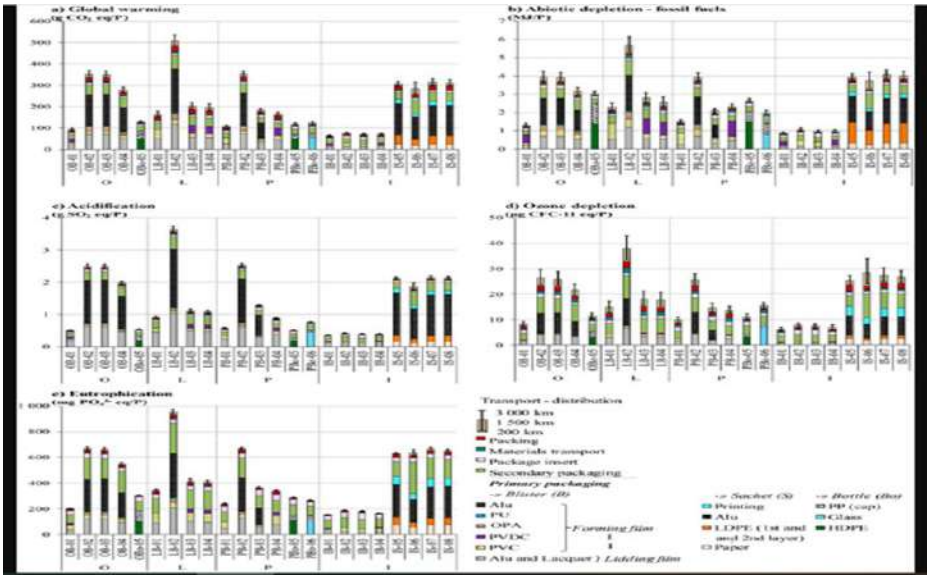

Figure 9. Life Cycle Assessment (LCA) Results for Various Packaging Scenarios

Smart Technology Innovations

By applying advanced digital technology in pharmaceutical packaging greatly increase sustainability by causing a markable decrease in material waste and improving design efficiency. The shift from physical Paper Information Leaflets (PILs) to electronic versions (e-PILs) accessed via QR codes already mandated in Brazil—has the potential to eliminate over 6,110 tons of paper waste and 5,760 tons of emissions annually in the US and Europe alone. This digital change not only lowers the environmental impact associated with cutting down tree and the disposal challenges of glossy papers but also improves patient access by addressing issues like small font sizes and complex language.

Additionally, computer-based eco-design tools, including user-centered frameworks and Green Lean Six Sigma support systems, help manufacturers identify production inefficiencies and embed sustainability principles into the design process. By incorporating these digital innovations a well-informed delivery, optimize packaging design, extensively reduced carbon foot-print and an green sustainable the pharmaceutical packaging can be obtained (Jackman, Brennan et al. 2025).

Regulatory and Quality Considerations

The World Health Organization (WHO), via its Department of Regulation and Prequalification, has launched an initiative called "Greener pharmaceuticals' regulatory highway." This demands highlights the intensive need to implement innovative regulatory approaches that minimize the environmental impact of medical products while ensuring their safety & efficacy (Organization 2024).

Quality by Design (QbD)

Quality by Design (QbD) is a concept introduced by Joseph M. Juran, a pioneer in quality management, introduced a concept of Quality by Design (QbD), emphasized that quality should be incorporate into the product from the design stage, most of the product faces quality problems during this initial phase (Duarte, Duarte et al. 2025)

QbD has five central components which are comprehensively explained in the literature & regulatory guidelines. These components can be summarized as:

- Establishment of a Quality Target Product Profile (QTPP) to identify the appropriate Critical Quality Attributes (CQAs).
- Design a drug and understanding via risk assessment to link CQAs with clinical safety and efficacy of drug.
- Designing and understanding the manufacturing process by defining Critical Process Parameters (CPPs), including knowledge of scale-up and how variations in CPPs and Critical Material Attributes (CMAs) affect CQAs.

- Develop a control strategy based on product and process understanding to ensure safety and efficacy.
- Perform process qualification to demonstrate the effectiveness of controls and support continuous improvement as new knowledge emerges (Mustoe, Turner et al. 2025)

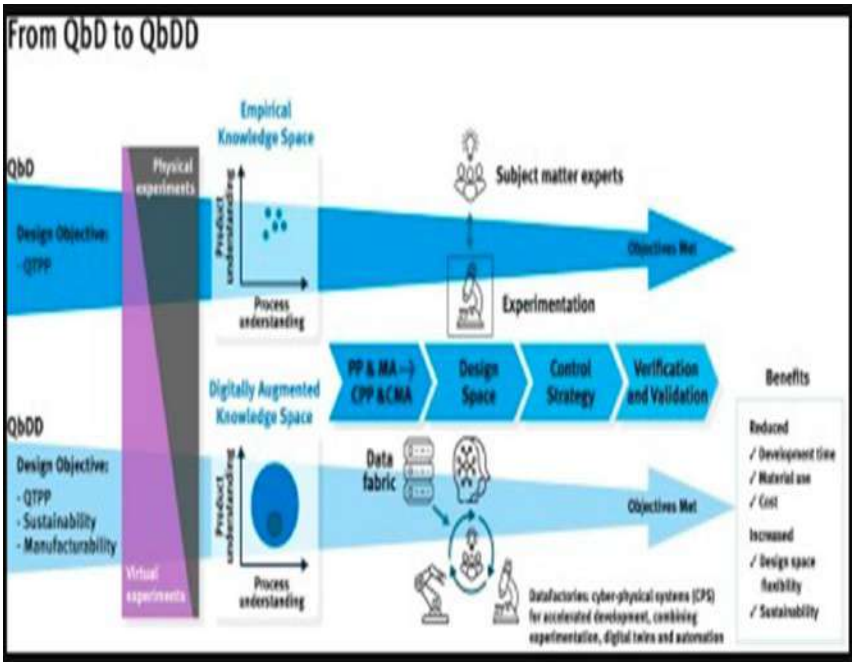

Figure 10. Evolution from Quality by Design (QbD) to Quality by Digital Design (QbDD)

The FDA and (ICH) have published complete guidelines for implementing QbD in accordance with regulatory aspects to drive adoption and promote common practices for regulatory acceptability throughout the pharma sector.

Authority / Guideline	Description
U.S. Food & Drug Administration – Pharmaceutical CGMPs for the 21st Century (2002, final report 2004)	• First mention of QbD • Promotes early adoption of technological innovation and quality systems in manufacturing. • Encourages risk-based approaches
FDA Pilot Program on QbD (CMC), 2005	Companies invited to demonstrate QbD application in CMC to develop a comprehensive quality overview using ICH Q8, Q9, and Q10
Pharmaceutical Quality for the 21st Century – Risk-Based Approach Progress Report (2007)	Focus on improving CGMP processes, quality review, and regulatory systems
ICH Q8 (R2	Pharmaceutical Development
ICH Q9 (R1)	Quality risk management
ICH Q10	Pharmaceutical Quality System
ICH Q11	Development and Manufacture of Drug Substances (Chemical & Biological)

Figure 11. Evolution of Quality by Design (QbD) Guidelines

Regulatory Challenges

The pharmaceutical sector is highly regulated, ensuring safety but makes it complicated to adopt sustainable practices like green chemistry. A major challenge is the lack of defined global standards for sustainability, as GMP and GDP focus on quality but not environmental concerns.

Regulatory authorities such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) require rigorous testing before approving sustainable alternatives this slows down their adoption and implementation.

Another issue comes with sustainability certifications (ISO) that do not meet pharmaceutical regulatory requirements, making approval processes lengthy & expensive (Ogbuagu, Mbata et al. 2024).

Future Directions

Integrating artificial intelligence (AI) into sustainable pharmacy enhances sustainability across the pharmaceutical life cycle by transforming traditional method to eco- friendly sustainable methods. AI performs identification of environmentally friendly compounds in more precise and effective way. In manufacturing process, AI also analyze processes which reduce resource consumption and waste products. Moreover, supply chain management driven by AI improves logistics, minimizing carbon footprints and material waste. Altogether, AI has proven to be smart effective and time resuming tool its application in pharma sector decrease its environmental impact and support global circular economy goals (Brown 2020).

CONCLUSION

The pharmaceutical industry is transforming towards sustainable practices that aims therapeutic innovations with environmental responsibility. Through Green Pharmacy and Climate-Smart Healthcare principles, innovative biodegradable materials, solvent-reducing techniques, continuous manufacturing, and targeted nano delivery are reducing environmental impact across drug lifecycles. Sustainable packaging and circular economy approaches further enhance resource efficiency and reduce waste products. Despite regulatory challenges, frameworks such as Quality by Design facilitate the integration of sustainability without compromising product safety and efficacy. The adoption of artificial intelligence and collaborative supply chain efforts will be crucial in establishing resilient, eco-friendly healthcare systems. Collectively, these strategies enable the pharmaceutical sector to contribute meaningfully to global sustainability goals while maintaining high standards of patient care.

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CHAPTER 3
ANTIMICROBIAL ACTIVITIES OF CHRISTMAS MELON (*Lagenariabreviflora* ROBERT) AGAINST SOME CLINICAL PATHOGEN

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INTRODUCTION

Pathogens are infectious agents that cause illnesses, such as virus, bacterium, fungus, and protozoan. Clinical pathogens are caused by pathogenic microorganisms, and remain a major global health challenge (Bello et al., 2023). Numerous bacterial species, including commensals, which develop on the skin and mucous membranes, are constantly present in the body.

Sufficient nutrients are present in the blood and tissue fluids to sustain the growth of many microorganisms. According to Ryan et al. (2014), the body possesses defense mechanisms that allow it to fend off microbial attack on its tissues and provide it with an intrinsic resistance or natural immunity against a variety of bacteria. Other serious illnesses that affect the world at large, like pneumonia, are caused by pathogenic bacteria, which include Streptococcus, Pseudomonas, and foodborne infections, which can be brought on by bacteria like Salmonella, Campylobacter, and Shigella (Onasanwo et al., 2021).

Antibiotic treatment has grown in importance as a problem-solving tool. Nonetheless, a great number of vaccinations have considerably increased the attack and discrimination of the response (Frieri et al., 2017).

Antimicrobial resistance has emerged as a result of the unrestricted and extensive use of these drugs, which has put bacteria under selective pressure. In addition to saving lives.

According to Oridupa et al. (2025), antibiotics have also contributed to longer lifespans by altering the course of bacterial illnesses. When a novel antibiotic is discovered, doctors frequently reserve this drug rather than immediately prescribing the worst instances out of concern that it would promote drug resistance instead they keep recommending older medications that have demonstrated comparable effectiveness. Accordingly, novel antibiotics are frequently used as last-resort medications to treat severe infections (Cassiret al., 2014).

Many of the medications used in clinical practice today are derived either directly or indirectly, from plants, the use of medicinal plants has a long history of effectiveness in therapy. Over time, medicinal plants have been utilized to heal a variety of illnesses, particularly by those living in rural places without access to facilities and contemporary techniques (Olooto et al., 2018).

These individuals rely entirely on the usage of herbal remedies that are sold by herbalists, folk medicinal healers, and herbal drug dealers. The formulations are occasionally combined with their diverse traditional and cultural customs and beliefs (Rahman et al., 2018). Many plants, particularly in rural areas, have been used to treat and prevent diseases in humans and animals.

1. MATERIALS AND METHODS

1.1 Collection of Plant Sample

The whole fruit of Lagenariabreviflora Robert (Tagiri) was procured from a local herbal market (Bode) in Ibadan, Oyo State Nigeria as shown in figure 1.

Figure 1. *Lagenariabreviflora* fruit

1.2 Preparation of Plant Sample

After thoroughly washing, the Lagenariabreviflora Robert fruit, it was sliced into smaller pieces using a knife and then air-dried until the moisture content decreased to approximately 10%. Subsequently, the dried fruit was ground into a fine powder and taken to the laboratory for extraction using 50g of ethanol to 250ml and 50g of water to 450ml. The mixture was then combined, securely covered, and allowed to stand for 48 hours.

The filtrate was then poured into a sanitized conical flask and heated electrically until it boiled, allowing the ethanol to evaporate and condense back into liquid in a separate tube. The majority of the needed ethanol was obtained by continuing the heating process until the filtrate contained.

1.3 Phytochemical Analysis of Plant Extracts

The Nigerian Forestry Research Institute utilized traditional operational methods to examine the powdered samples for the existence of secondary metabolites. The analysis of plant samples for phytochemicals was conducted in the following manner:

Tannic acid test: Talukdar and Chaudhary (2010): A diluted extract was mixed with three or four drops of 10% FeCl3; the presence of catechol tannin resulted in a green solution, while gallic tannins appeared as a blue color. A small piece of magnesium was heated, and 4 milliliters of extract solution along with 1.5 milliliters of 50% methanol solution were combined.

Upon the addition of five or six drops of concentrated HCl, flavonoids turned crimson. Dil. NH3 test: 5 milliliters of the extract's diluted NH3 solution were taken, and conc. H2 SO4 was added. The presence of yellow-colored precipitation indicated the presence of flavonoids.

Test for terpenoids: Each sample, weighing 0.2 g, was mixed with 2 mL chloroform and 3 mL concentrated H2SO4. The presence of a reddish-brown hue suggested the existence of terpenoids Test for Alkaloids: 3 grams of the powdered material were soaked in 50 centiliters of methanol to produce an extract. Dryness was achieved through evaporation of the extract. A few drops of Hgar's reagent were added to 1cm3 of the filtrate after combining 0.5g of the material with.

1.4 Media and Reagent

The manufacturer's instructions were followed in the preparation of the nutrient agar (NA), nutrient broth, potato dextrose agar (PDA), yeast extract powder, and Mueller Hinton agar, which were then autoclaved for 15 minutes at 121°C.

1.5 Antimicrobial Activity of Lagernariabreviflora Robert Extracts

1.5.1 Test Organisms

Three distinct kinds of test organisms were utilized to ascertain Lagernariabreviflora Robert's antimicrobial activity.

The Department of Microbiology, University College Hospitals, Ibadan, Oyo State, provided the Pseudomonas aeruginosa,Staphylococcus aureus, and Candida albicans.

1.5.2 Preparation of Test Organisms

Test organisms were frozen at -20 ˚C and sub cultured on Nutrient Agar and Potato Dextrose Agar. All strains were pure cultured by sub culturing one colony each onto Nutrient broth and Yeast Extract Powder (Biomerieux, France).

1.5.3 Preparation of 0.5 McFarland Standard

0.5 McFarland standard is made by combining 0.05ml of 1.175% barium chloride dihydrate (Bacl.2H20) with 9.95ml of 1% (H2SO4) sulphuric acid in a test tube.

1.5.4 Determination of Antimicrobial Activities (Agar Well Diffusion Method)

Bacterial cultures were swabbed onto the solidified Muller Hinton agar surface with a sterilized swab stick. The agar wells were created using a sterile cork-borer with a diameter of 1.2mm. The wells were treated with extract doses ranging from 12.5 mg/ml to 100 mg/ml. In addition, a control experiment with 2mg of streptomycin as positive controls will be done. Plates were incubated upright at 37℃ for 18 hours.

1.5.5 Determination of Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration was obtained using the tube dilution method. The inoculums were made with broth from 24-hour-old cultures and adjusted to the 0.5 McFarland standard turbidity. Each test tube received 9mL of sterile nutrient broth, followed by 1mL of extract at four distinct concentrations (12.5 mg/mL, 25 mg/mL, 50 mg/mL, and 100 mg/mL). In addition, 0.1ml of a standardized organism was added, cultivated, and infected for 24 hours at 37oC. The test tube with the lowest extract concentration and no turbidity was selected.

1.5.6 Determination of Minimum Bactericidal Concentration (MBC) and Minimum Fungicidal Concentration (MFC)

The microbial growth was observed on Mueller Hinton agar after transferring the nutrient broth from MIC tests using a sterile wire loop. Incubation at 37oC for 24 hours allowed for the identification of MBCs. The presence of growth indicated a bacteriostatic or fungistatic effect, whereas the absence of growth implied potential bactericidal or fungicidal properties of the extract.

2. RESULTS AND DISCUSSION

2.1 Phytochemicals Screening Results

The phytochemicals found in Lagenariabreviflora Robert's entire fruit are shown in (Table 1). In the entire fruit extract of Lagenariabreviflora Robert, it was found that flavonoids, tannins, saponins, and terpenoid were present but cardic glycosides and alkaloids were not.

Table 1. Phytochemicals Screening of Lagenariabreviflora Robert

Sample test	Phytochemical present
Alkaloid	-
Tanin	+
Flavonoid	++
Saponin	+
Cardiac glycosides	-
Terpenoid	+

- = Negative, + = Positive, ++ = Strongly positive

2.2 Antimicrobial assay of LagenariabreviflouraRobert

The zones of bacterial growth inhibition at different concentrations (100 mg/ml, 50 mg/ml, 25 mg/ml, and 12.5 mg/ml) are displayed in the results of the antimicrobial properties of the ethanol extracts and aqueous extracts of Lagenariabreviflora Robert. The widths of the zone of inhibition (mm) that the plant extract produced were used to express the antibacterial activity. Some of the bacteria were inhibited by the ethanolic extract of Lagenariabreviflora Robert, exhibiting a visible zone of inhibition.

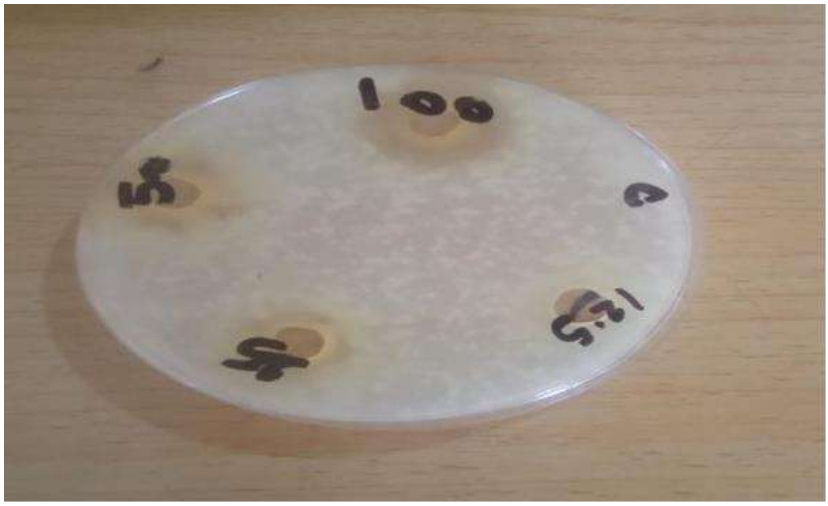

Figure 2. Zone of inhibition concentration of plant extracts on *Candida albicans*

Table 2. Antibacterial Effect of Ethanol Extract of LagenariabrevifloraRobert

Conc. mg/ml	Pseudomonas aeruginosa	Staphylococcus aureus	Candida albicans
100	1.3 mm	1.6 mm	1.5 mm
50	0.8mm	0.3mm	1.0mm
25	0.4mm	0.2mm	0.5mm
12.5	0.0mm	0.0mm	0.0mm

Table 3. Antibacterial Effect of Aqueous Extract of LagenariabrevifloraRobert

Conc. mg/ml	Pseudomonas aeruginosa	Staphylococcus aureus	Candida albicans
100	1.3 mm	0.9 mm	1.3 mm
50	1.1 mm	0.9 mm	0.8 mm
25	0.7 mm	0.5 mm	0.3 mm
12.5	0.0 mm	0.0 mm	0.0 mm

2.2.1 The Effects of the Extracts and Streptomycin on *Staphylococcus aureus*

Lagenariabrevifloraprevented the Staphylococcus aureus colony from growing. The dose that was given had a direct relationship with the clear zone of inhibition.

In comparison to the zone of inhibition created by 12.5 mg/ml of extract, the region of inhibition produced by 100 mg/ml of extract was greater or much larger. In contrast, the extract's (100 mg/mL) degree of inhibition was noticeably less than the streptomycin-induced inhibition.

2.2.2 The Effects of the Extracts and Streptomycin on *Pseudomonas aeruginosa*

The Lagenariabreviflora extract demonstrated the ability to hinder the growth of Pseudomonas aeruginosa. The zone of inhibition resulting from the 100mg/ml concentration of the extract was notably greater than that of the 12.5mg/ml concentration. In general, the zone of inhibition decreased for varying doses of the extract and streptomycin as the concentration varied.

2.2.3 The Effects of the Extracts and Streptomycin on *Candida albicans*

The Lagenariabreviflora extract demonstrated inhibitory effects on the growth of Candida albicans. The extent of inhibition was directly related to the dosage of the extract applied to the culture plate. The bacterial colony exhibited sensitivity to streptomycin, with the zone of inhibition caused by streptomycin being notably larger than that of the area treated with a 100mg/ml extract solution.

2.3 Minimum Inhibitory Concentration (MIC) of *L. breviflora* Extracts

The MICs of the extract on the isolates can be found in (Table 4). The aqueous extract of L. breviflora (tagiri) has a minimum inhibitory concentration ranging from 12.5-50mg/ml against S. aureus, P. aeruginosa, and C. albicans, while the ethanol extract has a minimum inhibitory concentration ranging from 25mg/ml to 50mg/ml against the same isolates.

Table 4. Minimum Inhibitory Concentration (MIC) of *L. breviflora* Extracts

L. breviflora Extracts			
Organism	Conc. mg/ml	A	E
S. aureus	50	-	+
	25	+	-
P. aeruginosa	25	+	-
	12.5	-	+
C. albicans	25	+	-
	12.5	-	+

Key= A= Aqueous, E= Ethanol, + = Turbidity, - = No turbidity

2.3.1 Minimum Bactericidal Concentration (MBC) and Minimum Fungicidal Concentration (MFC) of *L. breviflora* Extracts

The extracts of L. breviflora demonstrated efficacy against S. aureus and P. aeruginosa at a minimum bactericidal concentration (MBC) of 100mg/ml for both ethanol and aqueous extracts. However, the minimum fungicidal concentration (MFC) did not show effectiveness against C. albicans at the same concentration. This finding aligns with previous studies conducted, Bello et al. (2023), and Oridupa et al. (2025), which indicated that higher concentrations of the extract result in a stronger inhibitory effect.

Figure 3. MBC plate of *S. aureus* and *P. aeruginosa*

CONCLUSION

The investigation emphasizes the antimicrobial properties of Lagenariabreviflora extracts against clinical pathogens such as Staphylococcus aureus, Pseudomonas aeruginosa, and Candida albicans. The outcomes indicate that L. breviflora could serve as a promising reservoir of novel antimicrobial substances for combating infections caused by these pathogens. The antimicrobial efficacy of L. breviflora extracts exhibited a stronger impact on both Gram-positive and Gram-negative bacteria as well as yeast, aligning with established antimicrobial susceptibility trends. The minimum inhibitory concentration (MIC) values ranged from 12.5-50mg/ml, comparable to or even lower than certain conventional antibiotics. The minimum bacteriocidal concentration/minimum fungicidal concentration at 100mg/ml demonstrated no growth of Staphylococcus aureus and Pseudomonas aeruginosa for both aqueous and ethanol extracts of tagiri fruit. Conversely, Candida albicans exhibited growth at 100mg/ml on the agar plate for both aqueous and ethanol extracts. Lagenariabreviflora extracts exhibited promising antimicrobial activity against Staphylococcus aureus and Pseudomonas aeruginosa at 100mg/ml, while Candida albicans necessitated a higher concentration for further investigations. These findings validate the traditional medicinal use of L. breviflora and propose its potential as a natural resource for novel antimicrobial agent development. Nonetheless, additional research is imperative to comprehensively elucidate the mechanisms of action and potential interactions with other compounds or microorganisms. In essence, the results of this study underscore the substantial antimicrobial potential of Lagenariabreviflora, warranting further exploration as a prospective reservoir of novel antimicrobial agents.

Conflict of Interest

Authors declare that no conflict of interest exist or competing interest among the authors.

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