

Original Article

SMART-HERBALOMICS: An innovative multi-omics approach to studying medicinal plants grown in controlled systems such as phytotrons

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ARTICLE INFO

Keywords:

In vitro propagation

Multi-omics

Pharmacology

Phytomedicine

phytotron

Smart-Herbalomics

ABSTRACT

Background: Traditional medicine has supported human health for centuries. However, its dependence on wild-sourced medicinal plants now poses serious threats to biodiversity, with over 90 % of these species harvested directly from their natural habitat. Overexploitation and increasing global demand have accelerated the depletion of medicinal plant genetic resources, raising concerns about extinction and long-term sustainability.

Purpose: This review introduces “Smart-Herbalomics (SH),” a novel interdisciplinary approach that merges traditional herbal knowledge with modern scientific methods. This review aims to ensure a sustainable use and conservation of medicinal plants while enhancing their therapeutic efficacy and safety. SH integrates advanced plant identification, propagation in controlled environments (e.g., phytotron and smart farms), and standardization protocols to maintain genetic integrity and bioactive compound consistency. Additionally, this novel approach incorporates cell-based assays for cytotoxicity and mechanistic evaluation, animal models for pre-clinical safety and efficacy assessment, and clinical trials for human validation. Additionally, multi-omics tools, including genomics, transcriptomics, metabolomics, and proteomics, help uncover the molecular basis of herbal actions.

Method: Data were collected through a comprehensive literature review using electronic databases such as PubMed, Google Scholar, Scopus, AMED, and the Cochrane Library. Key search terms included “Herbalomics,” “Pharmacology,” “Pharmacognosy,” “Multi-Omics,” “Botany,” “Safety and Toxicity,” “Herb Formulation,” and “Medicinal Plant Species.”

Abbreviations: ABA, Absciscic acid; ANOVA, Analysis of variance; BAP, Benzylaminopurine; BPH, Benign Prostatic Hyperplasia; CE, Controlled environment; CHE, Chee and Pool; CHU, CHU N6; CMCs, Cambial meristematic cells; CO₂, Carbon dioxide; COX, Cyclooxygenase; CyTOF, Mass cytometry; DJ, DE GREET & JACOBS; DNA, Deoxyribonucleic acid; DTG, Differential thermogravimetric analysis; FL, Follicular lymphoma; FT-NIR, Fourier Transform Near-Infrared; GA, Gibberellin; GB5, Gamborg's B-5; GC-MS, Gas chromatography-mass spectrometer; GMP, Good Manufacturing practices; GPE, Genotype phenotype environment; HPLC, High-Performance Liquid Chromatography; HPLF, Human lung fibroblasts; IAA, Indole-3-acetic acid; IBA, Indole-3-butyric acid; ICBN, International Code of Botanical Nomenclature; IMC, Imaging mass cytometry; IOT, Internet of Things; Kn, Kinetin; LC-MS, Liquid chromatography-mass spectrometry; LD₅₀, Lethal Dose 50 %; LS, Linsmaier and Skoog; LSC, Large single-copy; LOX, Lipoxygenase; ITCL, Longitudinal thin cell layer; MAPK, Mitogen-activated protein kinase; MoA, Mechanism of action; MS, Murashige and Skoog's; NAA, Naphthaleneacetic acid; NAD, Nicotinamide adenine dinucleotide; NN, Nitsch and Nitsch; PSK, Phytosulphokine-α; NMRS, Nuclear magnetic resonance spectroscopy; PGRs, Plant growth regulators; POD, Peroxidase; PT-PCR, Reverse transcription polymerase chain reaction; QL, Quoirin & Lepoivre; RNA-seq, RNA sequencing; rRNA, ribosomal RNA; SA, Sodium alginate; SH, Smart-Herbalomics; SELEX, Systematic Evolution of Ligands by Exponential Enrichment; SEM, Scanning Electron microscopy; SPSS, Statistical Package for the Social Sciences; SSC, Small single-copy; TCL, Thin Cell Layer; TCM, Tradition Chinese Medicine; tTCL, Transverse thin cell layer; TDZ, Thidiazuron; Tfh, Follicular Helper; TM, Traditional medicine; TME, Tumor microenvironment; TGA, Thermal gravimetric analysis; UV, Ultraviolet; VW, Vacin and Went; WPM, Woody Plant Medium.

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<https://doi.org/10.1016/j.phymed.2025.157303>

Received 25 May 2025; Received in revised form 12 August 2025; Accepted 15 September 2025

Available online 24 September 2025

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Conclusion: This article introduces SH for the first time as an integrative approach that offers a comprehensive and sustainable pathway to develop standardized, safe, and evidence-based herbal therapies. It bridges the fields of ethnopharmacology and pharmaceutical innovation, supporting the future of personalized, eco-conscious healthcare.

Introduction

Despite technological advancements in pharmacological medicine, ancient methods such as herbology, pharmacognosy, application of “Yin” and “Yang,” the five element theories, Sasang Constitutional theory, and various other approaches have been fundamental in the discovery and transformation of herbal medicine and the understanding of disease etiology (Zhang et al., 2023a; Luo et al., 2022). Herbology, “the lore of medicinal plants,” has long been an integral part of human culture, influencing religion, medicinal remedies, food, and behaviors (Hesam Shahrajabian, 2019). Pharmacognosy, which integrates art and science in traditional medicine (TM), has been used to identify medicinal plants, extracts, and prepare herbal remedies; evaluate biological activities; discover new herbal medicines; formulate and standardize herbal preparations; and integrate these practices with spiritual and cultural aspects (Alamgir, 2017c). The “Yin” and “Yang” theory, along with the five element theory, employs dualism to demonstrate how opposing forces such as cold, damp, heat, deficiency, and “Qi” are complementary, interconnected, and interdependent in the natural world during disease identification and management (Cheng, 2000). In contrast, the Sasang constitutional theory focuses on four human constitutions: (i) sensitivity of certain groups of herbs and medicine, (ii) equilibrium among internal organ function, (iii) physical features, and (iv) physiological characteristics of humans (Yoo et al., 2012). The application of the above mechanisms aligns with the holism theory in traditional Chinese medicine, which emphasizes the unity of body and mind, the interaction of humans, and the natural environment (Lozano, 2014). Based on the traditional methods of herbal medicine, it is likely that the profound knowledge of herbal remedies in ancient cultures developed through trial and error over centuries, with most materials collected from the wild or natural environment. Over time, humans have identified medicinal plants using organoleptic assessment, relying on the physical senses of taste, smell, and appearance (Fitzgerald et al., 2019). However, the invention of basic analytical techniques such as paper chromatography, microscopy, spectrometry, spectroscopy, and deoxyribonucleic acid (DNA) barcoding has greatly advanced the identification of medicinal plants. These innovations have shifted the focus from sensory assessment to the use of pharmacogenetics and pharma-omics approaches, which explore the physical, chemical, biochemical, and biological properties of natural drugs (Siddiqui et al., 2017). The invention has paved the way for integrated omics approaches, including genomics, metabolomics, transcriptomics, proteomics, food omics, lipidomics, microbiomics, ionomics, phenomics, etc. These techniques have played a significant role in the discovery of varied chemical compounds in plants, supporting research on the pharmacological effects, toxicity, and the target diseases of these compounds and establishing knowledge of the quality of medicinal plants and their suitability for clinical research (Aborode, 2022; Dhami, 2013; Nayak et al., 2021). Application of various omics in pharmacogenetic approaches has led to the production of drugs that are safe to both humans and the environment, which has contributed to the increasing recognition and popularity of herbal healing systems as an alternative modern medicine (Pandey et al., 2016). As the interest in nature as a source of potential chemotherapeutic agents grows, a large volume of plant-based natural resources is being used to produce safe drugs to meet the growing population and an increasing demand for herbal remedies, hence driving the need for sophisticated technologies. Consequently, the ongoing applications of these technologies have increased the volume of medicinal plants used in herbal medicine production, aiming to meet

global demand. However, this has also led to overexploitation of medicinal plant resources, with some species facing extinction due to their medicinal value (Chanda, 2014; Patil et al., 2022). According to Cragg and Newman (2013) and Ahmad Khan and Ahmad (2019), natural products and their derivatives accounts for over 50 % of all the drugs in clinical use worldwide, and an estimated 60 % of global population relies primarily on traditional, largely herbal medicine to meet their primary health care needs. Since the cultivation of medicinal plants is far less widespread than the harvesting of wild plants for herbal medicine extraction, and the demand for herbal medicine increases annually (Astutik et al., 2019), overharvesting from the wild has posed a threat to wild herbs, which are the primary source of diverse raw material. Chen et al. (2016) has reported that over 90 % of medicinal plants in Europe are harvested from the wild. This overharvesting, coupled with other challenges such as climate change, loss of genetic diversity, and habitat destruction, has led to significant concerns. To ensure the sustainable production of medicinal plants and their application in herbal medicine practices, Smart-Herbalomics (SH) offers a viable alternative. This novel approach provides solutions to common issues in herbal medicine, including misidentification of medicinal plants, genetic erosion, phenotypic variability, extract inconsistency, toxic contamination during processing, and standardization of dosage. SH, an advanced evolution of the herbalomics concept, represents a holistic, modern, and integrated approach to herbal medicine by merging traditional knowledge with cutting-edge scientific and technological advancements. It bridges multiple disciplines, including identification and propagation of medicinal plants, and their cultivation under controlled conditions such as phytotrons, laboratories, smart farms, plant growth chambers, hydroponics, biotrons, climatron systems, mist chambers, and precision farm setups. This approach also incorporates chemical profiling, cellular assays, animal model testing, and clinical trials, with the aim of optimizing the discovery, validation, and therapeutic application of medicinal plants. Central to this approach is the incorporation of multi-omics studies, including genomics, transcriptomics, proteomics, phenomics, metabolomics, microbiomics etc, which provide comprehensive, system-level insights into plant biology and human physiological responses to herbal treatments. By leveraging multi-omics data, SH enables a deeper understanding of the molecular mechanisms, synergistic effects, and personalized responses associated with plant-based therapies. The overarching goal of SH is to enhance the efficacy, safety, sustainability, and personalization of herbal medicine, aligning with the global shift toward evidence-based, precision, and holistic healthcare. As illustrated in (Fig. 1), SH can be summarized in three key concepts: “Smart,” “Herbal,” and “Omics”.

The term “Smart” represents the application of intelligent technologies such as sensors, Internet of Things (IOT), and analytics in herb cultivation. Additionally, under SH, “Smart” represents the use of cutting-edge technologies and computational tools to collect, analyze, and interpret large-scale biological data from cultivated herbs. “Herbal” represents the identification, propagation of herbs, cultivation of herbs using advanced technologies, processing of herbs, and application of omics studies on the herbs, while “Omics” represents the application of multi-omics studies such as genomics, metabolomics, transcriptomics, and epigenomics on cultivated herbs. SH, an integrative approach, tackles key challenges in the conservation, cultivation, and therapeutic use of vulnerable, threatened, and endangered medicinal plant species. By incorporating controlled environments (CE) for propagation and growth, SH offers solutions to cultivation-related obstacles, including the management of phenotypic variability in bioactive compounds and

toxins.

Notably, traditional herbal medicine systems and modern pharmacognosy have both played vital roles in medicinal plant management and drug discovery, however, there remains significant gaps in standardization, sustainable cultivation, and precision application of herbal remedies due to issues like overharvesting, species misidentification, extract inconsistency, and loss of genetic diversity. Nevertheless, SH bridges these gaps by combining tissue culture techniques (such as *In vitro* propagation), controlled-environment cultivation, and multi-omics technologies (genomics, metabolomics, proteomics, etc.) with smart farming tools such as IoT, AI, and sensor-based monitoring, enabling precise control over growth condition, enhancing consistency in phytochemical production, reducing variability and contamination, and ensuring traceability of medicinal plant resources. This integrated approach not only improves the efficiency of medicinal plant cultivation and utilization but also supports evidence based validation of their therapeutic efficacy, safety, and quality. This manuscript aims to introduce SH not only as a theoretical concept but as a practical, data-driven framework that ensures the sustainable, safe, and scientifically validated use of medicinal plants in modern healthcare. Beyond medicinal plants, the SH approach can also be applied in the production of functional foods as well as plants used in cosmeceutical and nutraceutical development.

Literature review method

The literature review was conducted by searching for information from original peer reviewed article published in scientific journals ranging from 1924 to 2025, and collection of information from the smart herbalomics lab. The smart herbalomics lab provided information on: *In vitro* propagation protocols of specific medicinal plants, literature on chemical analysis, and biological activities of some medicinal plants, protocol of conducting chemical analysis. Other data search process used were modified to obtain information from the original peer reviewed articles published in scientific journals with focus on propagated (*In vitro* propagated) medicinal plants, tissue culture, pharmacognosy, herbology, pharmacology, common formulation, treatment intoxication, enzyme assays, animal models, and clinical trials. To

obtain the relevant data, the authors carefully obtained the literature via electronic search using Google scholar electronic literature data base, Scopus, Pubmed, AMED, Cochrane library data bases. The following key research terms were used to extract relevant literature: “Herbalomics” “Pharmacology” “Botany” “pharmacognosy” “Herbology” “Safety and Toxicity” “Formulation” “Species”, “Multi-Omics”. The information was got from only peer reviewed paper. The obtained data was summarized, analyzed and conclusions were drawn accordingly.

Discussion

The origin and evolution of the SH approach

SH originates from the herbalomics concept, which itself is based on the holistic theory of Traditional Chinese Medicine (TCM). According to Haiyan et al. (2010), herbalomics was developed by integrating the holistic theory of TCM with interdisciplinary and multitarget approaches of TCM. This integration applied scientific principles to modernize herbal medicine, resulting in modern dosage forms (e.g., oral solutions, capsules, and tablets) derived from traditional ones (e.g., powders, boluses, and ointments). In 1982, the industrialization of TCM enabled it to compete equally with modern medicine. The advent of the genomic era led to the “omics” revolution, described as “pharmacognosy in the digital era,” expanding into genomics, transcriptomics, proteomics, and other omics fields (Allard et al., 2018). The development of high-throughput screening technologies and integrated omics further transformed herbalomics, incorporating bioinformatics, systems biology, and synthetic biology into herbal medicine research (Aizat et al., 2018). Thus, through thorough research and novelties, SH was established, growing into a multidisciplinary field encompassing the identification and propagation of medicinal plants (*In vitro*, *ex vivo*, and *in vivo*), and their cultivation under controlled conditions such as phytotrons, laboratories, smart farms, plant growth chambers, hydroponics, biotrons, climatrons, mist chambers, and precision farm setups. This approach also incorporates chemical profiling, cellular assays, animal model testing, and clinical trials, with the aim of optimizing the discovery, validation, and therapeutic application of medicinal plants. The key difference between SH and the original herbalomics concept lies

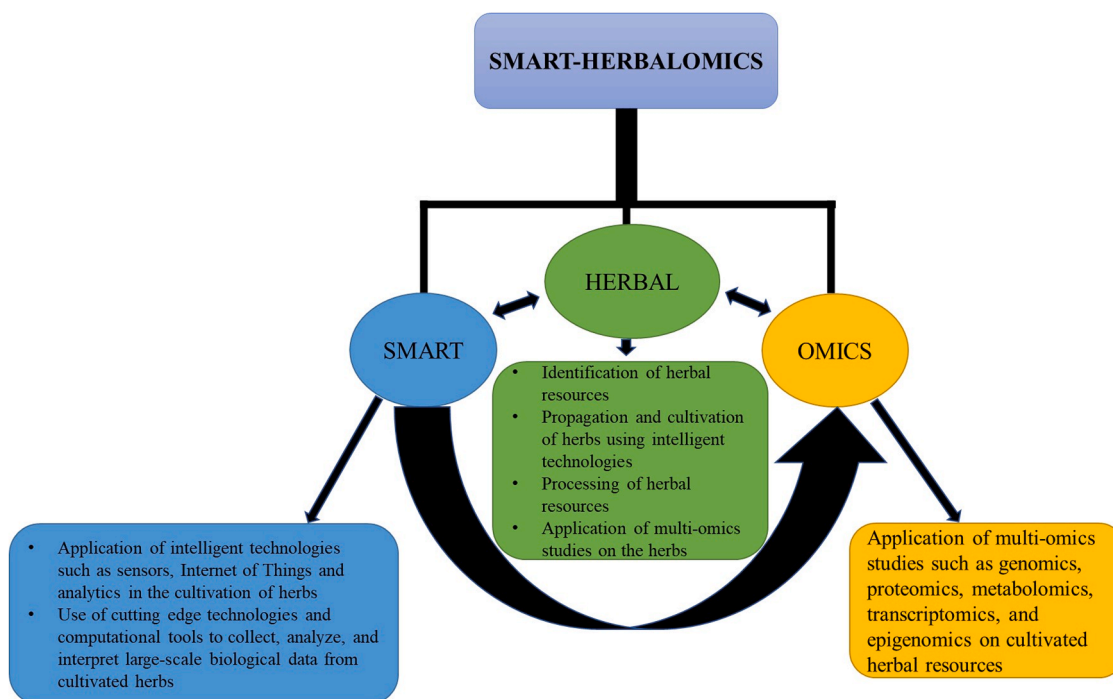


Fig. 1. Conceptual framework of SH: Integrating smart technologies, herbal resources, and omics approaches.

in technological advancement, integration depth, and practical application scope, which together justify the need for SH. SH evolves herbalomics into a fully data-driven, precision-based, and technologically empowered framework, making it not only more effective in research but also more applicable, scalable, and trustworthy in clinical and commercial settings. Additionally, SH is poised to enhance the value of many lesser-known and under-researched medicinal plants, playing a significant role in drug discovery and development.

With the evolution of the SH approach, several medicinal plants from different parts of the world have been accurately identified, authenticated, and propagated for therapeutic use. Table 2 presents the profile of medicinal plants identified, cultivated, and studied under the SH lab framework. The identification process integrates both traditional knowledge systems and advanced modern science techniques, ensuring precise species classification, bioactivity validation, and quality control. Traditional herbal medicine system classify and identify herbs based on energetic properties (e.g. *hot/cold, dry/wet, and Yin/Yang*), therapeutic functions (such as *adaptogens, tonics, diuretic, expectorants,*

antispasmodics, stimulants, and sedatives), organ system support (including *digestive system herbs, cardiovascular herbs, respiratory herbs, nervous system herbs, immune system herbs, skin and integumentary herbs, and liver and detox herbs*), safety and toxicity levels (*safe herb, moderate herbs, and toxic herbs*), plant parts used (root, leaf, flower, bark, fruit, etc), and cultural or philosophical principles of their healing practices such as the “Five Elements in TCM” or the doshas in Ayurveda (Che et al., 2024; Happy et al., 2025b; Ormsby, 2021; Zhang et al., 2024). These classifications aim to ensure synergy between herbs and the body’s natural healing processes, tailoring remedies to individual constitutions and imbalances (Abate et al., 2022). Zhang et al. (2024) highlights the application of phenomics in developing a modern TCM diagnosis and treatment system for diabetes. The modern mechanism of the SH approach builds upon traditional insights by applying scientific precision and digital technologies to improve accuracy and reproducibility as indicated in Table 1. This approach can significantly expand the scope of herbal pharmacology, offering alternative treatment options for various health conditions and enriching the global medicinal

Table 1
The use of Smart-Herbalomics approach to improve traditional methods.

Major term	Description	Application	Integration outcome	Reference
“Smart” (Digitizing and Optimizing Herbal Practices)	Brings technology and data intelligence into herbal medicine, enabling the transition of traditional practices into standardized, evidence-based systems.	IoT sensors and smart farming tools to monitor and control environmental conditions for optimized herb cultivation (e. g., soil health, light, temperature, moisture). AI and machine learning to predict optimal growth conditions, harvest timing, and yield of medicinal compounds based on real-time data.	Digitizing traditional herb cultivation and usage, modern systems can standardize and validate traditional formulations, ensuring consistency, safety, and efficacy.	(Joshi et al., 2024; Happy et al., 2024)
		Blockchain and traceability systems for ensuring the quality, authenticity, and ethical sourcing of herbal raw materials.		(Joshi et al., 2024)
		<i>In vitro</i> propagation and tissue culture for conserving threatened, endangered and most demanded herbs used in traditional medicine and enabling mass production (e. g., adventitious root culture, synthetic seeds).		(Li et al., 2022b; Tripathi, 2025) (Komakech et al., 2022b)
“Herbal” (Bridging Cultural Practices with Scientific Cultivation and Use)	Emphasizes the identification, propagation, processing, and application of herbs from traditional systems using advanced techniques.	Smart cultivation techniques such as phytotrons, hydroponics, and bioreactor-based systems to produce clean, potent, and sustainable herbal biomass.	Traditional herbs are cultivated and processed using modern agricultural and pharmaceutical practices, making them suitable for clinical use and commercialization under modern regulatory frameworks.	(Rahmat et al., 2021)
		Standardized herbal extraction and processing methods that retain traditional value while aligning with modern GMP standards.		(Wang et al., 2023)
		Standardizations of traditional formulations into clinical by producing dosage-consistent herbal products through clinical trials.		(Awasthi et al., 2014)
		Raw material evaluation using parameters (botanical identity, purity and authenticity, plant part, primary geographic origin, moisture content, foreign matter, chemical composition, microbial contamination, heavy metal content and residual solvents).		(Upton et al., 2020; Alamgir, 2017b)
“Omics” (Scientific Validation and Mechanistic Understanding).	Provides the biological and chemical evidence needed to bridge traditional claims with modern medical science	Genomics to Identify and characterize medicinal plant species and detect adulteration or genetic variation in traditionally used herbs.	Traditional medicines gain scientific credibility and regulatory acceptance through omics-based validation, enabling their incorporation into modern pharmacotherapy.	(Wang et al., 2025)
		Transcriptomics and metabolomics to understand the biosynthetic pathways of active compounds used in traditional medicine.		(Crispin and Wurtele, 2013)
		Phytochemical profiling and fingerprinting to establish chemical markers for quality control and batch-to-batch consistency.		(Noviana et al., 2022)
		Clinical omics studies to understand how traditional herbal formulations interact at the molecular level in human systems (e.g., immune modulation, inflammation pathways).		(Zhu et al., 2022)

Table 2

Profile of medicinal plants managed in the Smart-Herbalomics Lab.

Scientific name	Family	Origin	Habitat type	Complete chloroplast genome sequence	Main plant part used	Mode of processing and preparation	Mode of administration	Major phytochemicals	Bioactivity	Molecular biology mechanism	Main use	Reference
<i>Aconitum kusnezoffii</i>	Ranunculaceae	Siberia, South Korea and China	Grows in moisture-retentive but well drained soils of mountain	440,720 bp, GC content of 46.85 with mitochondrial genome containing 37 protein-coding genes, 29 tRNAs, and 3 rRNAs (<i>rrn18</i> , <i>rrn26</i> and <i>rrn5</i>).	Root, Stems, leaves, flowers	Frying (Stir-frying and sand-frying), Boiling, Dried and powdered, Roasting in ashes, Baking and decorticating, Soaking in water	Oral, Acupuncture	Aconitine, Hypaconitine, Benzoylhypaconine, Benzoylaconine, Mesaconine, Benzoylmesaconine, 10-OH-mesaconitine, 3-acetylmesaconitine, 3-acetylaconitine, Deoxyaconitine	Anti-inflammatory, analgesics, induces tachyarrhythmia, anti-arrhythmic, inhibits respiration, elevates pain thresholds	-	As Herb	(Li et al., 2018; Happy et al., 2025)
<i>Aleovera Liliaceae</i>	Asphodelaceae	Arabian peninsula	Warm, dry climate	152,875 bp, chloroplast genome of 47,185 bp and total GC content of 37.7 %. 131 genes were found that included 85 PCGs, 38 tRNAs and 8 rRNAs.	Leaves, flowers and roots	Dried and powdered, juiced from fresh leaves, concentration	Oral, Smearing, Bathing	Carotene, Lupeol, Barbaloin, Vitamin E, C and A, Folic acid, Phytol	Antimicrobial and probiotic activity, Anti-oxidant, Anti-Lipidemia, Anti-inflammatory, Antidiabetic effects	Aloin – regulation of the PI3K, NF-κB inhibitor alpha, and MAPK signaling pathways as anticancer agent.	As Cosmeceutical and as Herb	(Hiremath et al., 2020; Ren et al., 2020; Xiao et al., 2022)
<i>Apios americana</i>	Fabaceae	Canada, U.S.A	Grows in moist, low-lying areas like wetlands, marshes, wet thickets, stream banks, and bottom land forests	1555,207 bp, and the GC content of 34 %, chloroplast genome o 132 genes, 83 protein-coding genes, 41 rRNA genes and 8 ribosomal RNA (rRNA) genes	Root tubers, Leaves, Flowers, Vines	Steaming, Cooking, Dried, fried, roasted and sipped	Eating	Soluble protein, Saponin, Flavonoids, isoflavone, soluble sugar, amino acid, Vitamins	Anti-inflammatory, Anti-oxidant, Antidiabetic, Anti-tumor, Anti-hypotensive, Anti-atherosclerosis	-	As Herb and as Functional food	(Li et al., 2021c)
<i>Asarum sieboldii</i>	Aristolochiaceae,	South Korea	Grows in rich mesic soils in shady deciduous forests	193,356 bp long chloroplast genome, 78 protein-coding genes, 30 rRNA genes and 4 tRNA genes	Rhizome and Root	Boiling, Dried and powdered	Oral, Acupuncture	Asarinin, 9-methoxyaris-tolactam, Aristololactam, Aristolochic acid d, Methyleugenol, Estragole, 3,4-Dimethox-ycinnamyl alcohol, (–)-asarinin, Epipinoresinol	Treatment of: Cough, headache, acute toothache, fever, sinusitis, chills, asthma, allergies, neuralgia and bronchitis	-	As Herb	(Liu and Wang, 2022; (Li et al., 2021a; Quang et al., 2012)
<i>Asparagus cochinchinensis</i>	Liliaceae	South Korea	Grows in thin forested slopes, roadsides and waste fields	Chloroplast genome of 157,095 bp, 137 genes annotated, 86 protein-coding genes, 8 ribosomal RNAs, 5 pseudo-genes.	Rhizomes and Roots	Dried and powdered, thickening	Acupuncture, Oral, eating, smearing	Saponin, tannins, flavounoids, sterpenoids, sterol, phenolic compounds, alkaloids, glycosides	Used to treat: Constipation, fever, pneumonia, stomachache, tracheitis, rhinitis, cataract, acne, urticaria.	Methylprodioscin – inhibite dproduction of IL-6, IL-8, and TNF- α.	As Herb, as functional food and as Cosmeceutical	(Wang et al., 2022; Kim et al., 2021; Lee et al., 2015)
<i>Aspilia africana</i>	Asteraceae,	Uganda	Grows on grassland, woodland, forest margins and abandoned cultivated areas	NA	Leaves, Roots and Stem	Dried and powdered	Oral	Saponins, α –pinene, Car-3-ene, α -phellandrene, β-Caryophyllene, α -cubebene, α -cedrene, Phenol, Anthraquinones, Linolenic acid.	Anti-inflammatory, Antimicrobial, Antidiabetes	-	As Herb	(Okello et al., 2020; Niyoniziye et al., 2020)

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Table 2 (continued)

Scientific name	Family	Origin	Habitat type	Complete chloroplast genome sequence	Main plant part used	Mode of processing and preparation	Mode of administration	Major phytochemicals	Bioactivity	Molecular biology mechanism	Main use	Reference
<i>Atractylodes macrocephalae</i> Koidzumii	Asteraceae	Korea, China, Vietnam, Japan and Russia	Grassland and forests at elevation of 600-2800 meters	153,208 bp, GC content of 37.7 %, two inverted repeat (IR) regions of 25,147 bp, separated by a LSC region of 84,255 bp and a small single-copy (SSC) region of 18,659 bp. 113 unique genes present in the genome, including 80 protein-coding genes, 29 represented tRNA genes, and four denoted rRNA genes.	Rhizome, Root, Leaves	Cleaning, slicing, roll vacuum. Pulsation drying, and low temperature vacuum drying	Oral, Optical	Minerals, amino acid, fatty acid, volatile flavor compound, Sugar (Sucrose, Fructose, Maltose, Xylose), keton and esters, aldehydes	Anti-inflammatory, antinociceptive, and atractylon (Anti-cancer, antiviral and gastroprotective activities)	-	As Herb	(Wang et al., 2024; Luo et al., 2025)
<i>Codonopsis pilosula</i>	Campanulaceae	Asia	Grows in forests, meadow and scrub	170,672 bp long, containing 108 genes, including 76 protein-coding genes, 28 tRNA, and 4 rRNA	Roots	Dried and powdered	Oral	Luteolin, Oleanolic acid, Echinocystic acid, Albigenic acid, Luteolin-7-galactoside, alpha-Spinaterin, Lobetyolin, Lobetyol, Tangshenoside I	Immune enhancing, anti-tumor and treatment of: bronchitis, obesity, hepatitis, colitis.	-	As Herb	(Gang et al., 2023; Li et al., 2022a; Yue et al., 2022)
<i>Diospyros kaki</i> (Persimmon)	Ebenaceae	South Korea	Subtropical to mild temperate climatic areas with moderate winters and mild summers	Chloroplast genome of 157,773 bp, 131 genes, 86 protein-coding genes, 37 tRNA and 8 rRNA.	Fruit	Drying, Squizing	Eating	Tannins, Carotenoids, Flavonoids (Flavanols Anthocyanidins), Phenolic compounds (Gallic acid, zeaxanthin, lutein, β -carotene, and Ferulic acid)	Treatment of chronic ulcer, cough, internal hemorrhage, hypertension, cerebral arteriosclerosis, colony diseases hematemesis, cardiovascular diseases, reduce blood pressure increasing salivation and slaking thirst.	-	As Functional food	(Xu et al., 2021; Fareed et al., 2022)
<i>Pinellia ternata</i>	Araceae	Korea, China, Japan	Grows is shady and damp grass thickets on mountains	Has Chloroplast genome length of (167,280 bp), contained in SSC region of 23618, one large copy (LSC,92450), two repeat regions (IRs 25,606) bp, 113 genes, 79 PCG, 4 rRNA 30 ribosomal RNAs protein-coding genes	Rhizomes	Dried and powdered	Oral	β -cubeben, Atractylon, Methyleugenol, β -vati renene, Paeonol, a-humulene, δ -cadinene	Used in the management of: Cough, excessive phlehm, airway inflammation, vomiting and cancer.	Polysachharide -induce apoptosis of HepG2 cells as antitumor activity	As Herb	(Kim et al., 2020b; Bai et al., 2022b)
<i>Polygonati Rhizoma</i>	Liliaceae	China	Temperate climates of woodland and shaded areas	Chloroplast genome of small single copy (SSC 26,372 bp), one	Roots, leaves, flowers, fruits,	Steaming, Cooking, Dried, fried, roasted and sipped	Eating, Oral, Smearing	Beta-sitosterol, Baicalein, Diosgenin, Acetic acid, 2-Butanone, Methyl acetate, Butyl butanoate,	Anti-oxidant, anti-diabetes, anti-osteoporosis, anti-cancer, anti-hyperlipidemia,	-	As Herb, as Functional food and as cosmeceutical	(Chen et al., 2021b; Mu et al., 2021;

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Table 2 (continued)

Scientific name	Family	Origin	Habitat type	Complete chloroplast genome sequence	Main plant part used	Mode of processing and preparation	Mode of administration	Major phytochemicals	Bioactivity	Molecular biology mechanism	Main use	Reference
				large copy (LSC,84.438), two repeat regions (IRs 26.372) bp, 86 genes, 86 protein-coding genes, 38 ribosomal RNAs, 8 rRNA	seeds and seedlings			Heptanal, Acetaldehyde, 3-Hydroxy-2-butanone	cardiomyocyte protection, immunomodulatory, treatment of infertility, anti-microorganisms, improving sleep memory, chronic diseases management, antiaging			Zhun et al., 2020)
<i>Polygonum multiflorum</i>	Asparagaceae	China	Grows in temperate climate in the forest in moist loamy soils	Chloroplast genome of 159,015bp – 163,461 bp, 112 genes, 78 protein-coding genes, 30 ribosomal RNAs, 4 rRNA	Roots	Dried and powdered	Oral	Emodin, Rhein, Aloe-emodin, Chrysophanic acid, Physcione, Polygonumoside A -Herbal function Polygonimitin E and Polygonimitin F- Functional food function	Treatment of: Backache, Dizziness, liver disease, graving of hair and constipation	Sargencuneside – inhibited LPS-induced NF-κB activation by inactivating phosphorylation of IKKα/β	As Herb and as Functional food	(Kim et al., 2020b; Teka et al., 2021; Guo et al., 2022; Park et al., 2016)
<i>Prunus Africana</i>	Rosaceae	Uganda	Grows in tropical forests	158,138 bp, 131 genes, 18 protein coding genes, 38 tRNA genes and 8Rrna.	Leaves, Roots and Stem	Dried and powdered, Squeezing	Oral	Lauric acid, n-docosanol, ferulic acid, β-sitostenone, β-sitosterol, Ursolic acid	BPH treatment, cancer treatment, diabetes treatment, malaria treatment, gastrointestinal disease treatment, treatment of chest pain and respiratory conditions, treatment of skin infection, wound healing	-	As Herb	(Komakech et al., 2019; Rubegeta et al., 2023)
<i>Rehmannia glutinosa</i>	Orobanchaceae	China	Grows in temperate climate zones of grass land, cultivate areas and hill sides	Chloroplast genome of 153,678 bp, 149 genes annotated, 104 protein-coding genes, 37 ribosomal RNAs, 8 rRNA pseudo-genes.	Roots	Steaming and soaking with liquor, Dried and Powdered, Extraction	Oral	Pinellic acid, Oleic acid, Stearic acid, Caprylic acid, Indoline, 4-Hydroxyquinoline, Lugustroside, 3,4-Dimethylbenzoic acid, D-Methionine, L-tyrosine	Used in: Decreasing blood glucose, treating diabetes, hematinic deficiencies, adrenal disorder, promoting hematopoiesis, antiaging and antitumor.	Verbacoside - activation of microglia and astrocytes, inhibited IL-1β and IL-6 production, and enhanced IL-4, IL-10, and TGF-β production	As Herb	(Chung et al., 2023; Yang et al., 2021; Chen et al., 2022)
<i>Trichosanthes kirilowii maxim</i>	Cucurbitaceae	China	Worm, moist habitats with well drained sandy soil, particularly in temperate biome	Chloroplast genome of 157,481 bp, 130 genes, 85 protein coding genes, 8 rRNA and 37 tRNA	Seed, Root tubers, Fruits	Steaming, Cooking, Dried, extraction, Juicing	Eating, Oral	Alkaloids, Fatty acids, triacylglycerol, Tocppherol, Easters, Pheolics, aldehydes, ketons, polyphenols and other volatile substances	Anti-oxidant activity, anti-inflammatory activity, antitumor, improve cardiovascular system function, cough expectorant	-	As Herb, and as functional food	(Bharathi et al., 2013; Yang et al., 2019)
<i>Warburgia ugandensis</i>	Canellaceae,	Uganda	Grows in lowland rainforest, grass land and swamp forest.	NA	Back, Roots and leaves	Dried and powdered	Oral	Drimenin, Pereniporin B, Ugandenial A, Bemadienolide, Kaempferol, Myricetin, Quercetin, Quercetin 3-rhamnoside, Quercetin 3-glucoside, Kaempferol 3-rutinoside	Treatment of: Cough, constipation, chest pain, malaria, fever, stomachache, hernia, fatigue, sinuses, ulcers, throat infection, snake bite, intestinal worms, diarrhea, weak joints and so on	-	As Herb	(Okello et al., 2018; Kipanga et al., 2020)

(continued on next page)

Table 2 (continued)

Scientific name	Family	Origin	Habitat type	Complete chloroplast genome sequence	Main plant part used	Mode of processing and preparation	Mode of administration	Major phytochemicals	Bioactivity	Molecular biology mechanism	Main use	Reference
<i>Zingiber officinale</i>	Zingiberaceae	China	Found in humid, partly-shaded tropical to subtropical lowland forests	162,507 bp, 113 genes, 79 protein coding genes, 30 tRNA, 4 rRNA genes.	Rhizomes	Dried and powdered	Oral, Smearing	Phenolic acid-Functional food function, Gingerol, Shogaol, Carboxylic acids, Amino acids (Lysine and Leucine)-Cosmeceutical function	Managing conditions such as arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, constipation, indigestion, vomiting, hypertension, dementia, fever, infectious diseases and helminthiasis	Gingerol: inhibition hERG K ⁺ channel as analgesic agent	As Functional food and as Cosmeceutical	(Jiang et al., 2023; Liu et al., 2022)

LSC large single copy. *MAPK* mitogen activated protein kinase. *NF-κB* Nuclear factor kappa-B. *P13K* phosphatidylinositol-3-hydroxy kinase. *PCGs* protein coding genes. *rRNA* ribosome RNA. *SSC* small single copy. *TNS* tumor necrosis factor. *tRNA* transfer RNA.

plant repertoire.

Techniques used in the integration include DNA-based techniques (molecular marker), chemotaxonomic techniques, morphological and microscopic identification, geographic information system and remote sensing, proteomics and metabolomics, artificial intelligence, and machine learning. Additional tools applied under modern mechanisms in medicinal plants under SH are Blockchain and traceability systems (Ambavane et al., 2024; Kalita et al., 2025; Li et al., 2019; Tharachand et al., 2012). According to Bandara and Katukurunda (2024), these tools ensure authenticity, transparency, and security throughout the entire life cycle of medicinal plants from the wild habitat to management under a controlled system and to other scientific studies and use. By combining these traditional and modern approaches, SH ensures accurate species identification, phytochemical profiling, and holistic understanding of therapeutic actions, making it a robust framework for herbal medicine development in both research and clinical settings. The classification process of the identified medicinal plants gives details in the sequence order of Kingdom, Division, Class, Order, Family, Tribe, Genus, Section, Series, Species, Variety, and Form. This is based on the International Code of Botanical Nomenclature (ICBN) hierarchy ranking (Alamgir, 2017b; Haider, 2018).

Major activities in the SH approach

SH follows a systematic schematic flow, as illustrated in (Fig. 2), beginning with the accurate identification of medicinal plants, followed by *In vitro* propagation and cultivation under CE. The process progresses through harvesting and standardized processing, leading to detailed chemical analysis and comprehensive biological validation studies including *In vitro* assays, in vivo models, and clinical trials. Throughout each stage, the approach integrates multi-omics technologies (such as genomics, metabolomics, and proteomics) to ensure precision, consistency, and scientific rigor. This holistic framework not only bridges traditional knowledge with modern science but also lays a strong foundation for enhancing the efficacy, safety, and sustainability of herbal medicine for future generations.

Identification of medicinal plants

In the “Handbuch de Pharmakognosie” (Handbook of Pharmacognosy), Power (1924) cites a colleague who states: “in its true sense no discovery is really independent, each [discovery] is conditioned and most often also evoked by the actual spirit of its time in any case, however, primed by previous works.” Historically, the knowledge of medicinal herb identification was largely based on the scattered literature embedded in unstructured (natural language) forms (Sharma and Sarkar, 2013). This included traditional knowledge and wisdom from indigenous people and traditional healers, sensory identification (herbalists relying on plant’s shape, size, leaf pattern, flower structure, color, smell, and taste of the plant), traditional classification systems, cultural and ritual uses, symbolic associations, the plant’s relationship with its environment, healing practices based on experience (trial and error), and intuitive observation of effects of plant use (Leonti et al., 2020; Mwaka et al., 2023; Si, 2016). Additionally, the exchange of plant resources among cultures worldwide has contributed to the diversification of medicinal floras and pharmacopoeias (Medeiros et al., 2012). Although these approaches were not scientifically formalized, they formed an essential foundation for identifying herbs in traditional healing systems worldwide and continue to provide valuable insights into plant medicine. Today, the identification of medicinal plants is a complex, multidisciplinary and multi-technological process involving traditional knowledge, integration of omics technologies (genomics, transcriptomics, bioinformatics, proteomics, metabolomics, pharmacogenomics, ionomics, among other omics studies), system biology, automated separation techniques, botanical classification, chemical analysis, biological testing, and modern molecular tools (Pan et al., 2013; Yue et al., 2021; Zhang et al., 2023b). Modern databases such as

NAPRALERT™ and PROCEA series can also aid in identifying candidate specimens that warrant further pharmacological and pharmacogenomic studies (Buenz et al., 2005). Besides these technological advancements, Aziz et al. (2017) indicates that collaboration with traditional healers, local herbalists, and indigenous people remains one of the most relevant methods for identifying potential herbs for novel pharmaceuticals. Additionally, de Medeiros et al. (2015) has demonstrated how the concentration of certain compounds in specific plants can determine their local importance, linking ancient methods with the present medicinal plant identification studies. From ancient times to date, discovering and identifying plant-based drugs has required significant time, labor, and resources. However, the value of the plant often far outweighs the cost associated with the plant-based drug (Kataoka, 2010). Modern approaches to medicinal plant identification and selection consider the historical, ecological, and pharmacological perspectives of the plant. By combining these multidisciplinary approaches, researchers can identify plants with therapeutic potential, validate their medicinal properties, and facilitate the development of natural products for pharmaceutical, functional food, and cosmeceutical applications (Luo et al., 2012). Jamshidi-Kia et al. (2017) highlights how ethnomedicine data reveals that reliance on plants for medicinal purposes dates back to ancient civilizations, which developed early strategies for identifying medicinal plants. This suggests that the modern pharmaceutical industry owes much of its development to the valuable knowledge found in thousands ancient manuscripts, which details the ethnobotanical uses of herbs and systems of plant-based remedies (Vedam et al., 2021), aligning with Power (1924)'s notion that discoveries are shaped by the spirit of the prevailing spirit of the time.

Propagation and cultivation of medicinal plants

Micropropagation of herbs. Micropropagation is a widely used technique in plant biotechnology that is based on the principle of cell totipotency. This principle refers to the ability of a single plant cell to divide and differentiate into a complete plant (Gupta et al., 2020). Essentially, micropropagation is a process of clonal propagation of plants, wherein new plants are produced from small pieces of plant tissue known as explants. The explants can be derived from various plant parts, including shoot tips, root tips, embryos, seeds, ovules, pollen grains, or even a single cell. This process is carried out under sterile laboratory conditions in an environment that mimics the natural conditions required for plant growth. It involves growing explants in nutrient-rich media and providing the optimal light, temperature, and humidity for growth (Shekhawat, 2019). This process is carried out under sterile tissue culture conditions, which involve cultivating plant cells, tissues, or organs on a nutrient-rich medium in a CE that mimics the natural conditions

necessary for plant growth. The medium typically contains essential nutrients, growth regulators (such as auxins and cytokinins), vitamins, and sugars to support the development of the plant tissue. Micropropagation is driven by tissue culture techniques, to revolutionize rapid plant multiplication and clonal propagation. The process of micropropagation begins with the selection of explants, where a suitable plant part such as a shoot tip, root tip, embryo, or even a single cell is chosen. The selected explants are then subjected to sterilization to remove any microbial contamination, ensuring the culture remains free of pathogens. Next, the sterilized explants are placed onto an appropriate culture medium, which provides essential nutrients, growth regulators like auxins and cytokinins, and hormones to support growth and cell division. Depending on the plant species and explant type, the explants undergo organogenesis (formation of shoots or roots) or embryogenesis (formation of embryos), resulting in the development of new plant tissues. Once new plant parts have formed, the explants are subjected to subculture, transferring them to a fresh medium for further growth and multiplication. After multiple shoots have been generated, they are transferred to a medium with auxins to induce root formation. Finally, once the plants have developed roots, they are gradually acclimatized to external environmental conditions, transitioning from *in vitro* to *ex vitro* conditions for growth in natural environments. Micropropagation has a wide range of applications, including the mass production of plants, enabling rapid propagation in a short period, which is particularly valuable in horticulture and forestry. It also ensures disease-free plant production, as plants are grown from tissue explants under sterile conditions, minimizing the risk of pathogens and diseases, leading to healthy and high-quality crops. Additionally, micropropagation plays a key role in the conservation of endangered species by using tissue culture techniques, especially embryogenesis, to preserve and regenerate rare or threatened plants, thereby contributing to biodiversity conservation. In micropropagation experiments, a variety of plant species can be used, depending on the purpose of the research or the desired outcomes. The types of plants selected typically fall into categories such as horticultural crops, medicinal plants, ornamental species, threatened, and endangered or rare species. The basis for their selection often includes factors such as economic importance, ease of propagation, clonal uniformity, growth rate, among others.

Within the SH framework, medicinal plant micropropagation is conducted using *in vitro*, *ex vivo*, and *in vivo* propagation methods. The process involves the growing the identified plants under more hygienic conditions, introducing explants to culture into culture media, conducting media testing for pH and nutrient suitability, performing shoot and root proliferation tests, acclimatizing and eventually transferring the plant to phytotrons, smart farms, or precision systems. The success of micropropagation in the SH concept is based on a well-developed

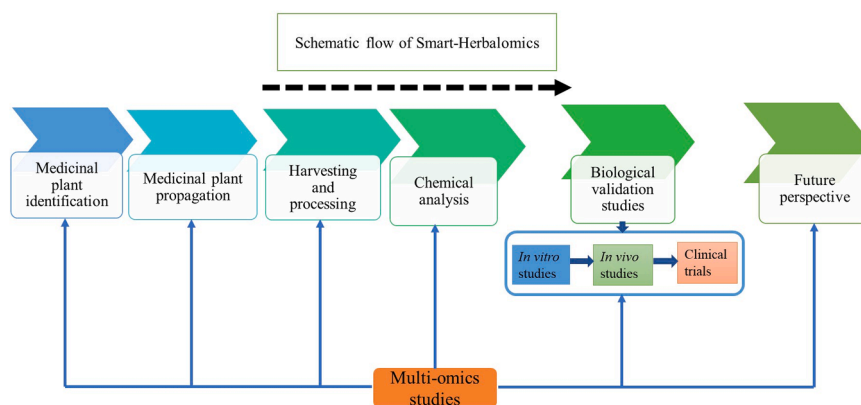


Fig. 2. Schematic flow of SH: Medicinal plant identification, propagation methods (tissue culture and management under CE, harvesting and processing, extraction and phytochemical analysis, biological validation (*In vitro*, *in vivo* and clinical trials), Multi-omics integration, data interpretation and feedback loop, incorporation of advancing technology.

micropropagation protocol specific to each herbal plant, which guides the entire process (Komakech et al., 2020a). Several media including Murashige and Skoog's (MS) basal medium (Classic Murashige and Skoog, 1962; Murashige and Skoog, 1962), Woody Plant Medium (WPM) and, Linsmaier and Skoog (LS) media (Komakech et al., 2020a) are used for plant tissue culture and micropropagation, supplemented with appropriate amounts of plant growth hormones (PGRs) such as cytokinins, auxins, abscisic acid, gibberellins (GA), ethylene, and several other growth regulators (phytohormone) with similar metabolic effects to influence plant growth (Bhatt et al., 2020; de Souza Vandenbergh et al., 2014; Gaspar et al., 1996). In the SH context, medicinal plants are selected based on specific criteria. These include plants that are difficult to propagate using traditional methods, such as those with slow growth rates, specific environmental requirements, or limited seed viability. Such plants include *Warbugia ugandensis* (Kuria et al., 2012) and *Prunus Africana* (Komakech et al., 2020a). Additional criteria include plants that have been valuable in herbal medicine for centuries are prioritized for propagation, given their medicinal properties and economic importance such as *Asarum sieboldii* (Happy et al., 2025a), *Akonitum kusnezoffii* (Happy et al., 2025b), and *Trichosanthes kirilowii* and *Trichothanes rosthornii* (Mudondo et al., 2025b). The selection also focuses on plants that are threatened, endangered and medicinal plants that are nearing extinction such as *Prunus Africana* (Komakech et al., 2020b). This allows for their conservation and sustainable cultivation. Another important criterion is the plant's commercial value in the herbal medicine market, as well as its ability to regenerate efficiently under controlled culture conditions. These include *Atractylodes macrocephala* Koids (Luo et al., 2025) and *Apios americana* Medik (Gang et al., 2024). The selection also emphasizes plants that are homologous, that is those that can serve both medicinal and nutritional purposes. These include *Atractylodes macrocephala* Koids, (Luo et al., 2025) and *Apios americana* Medik (Li et al., 2021b). The homologous plants are particularly valuable because they offer a dual benefit: they can be used for their therapeutic properties while also providing essential nutrients. Such plants play a crucial role in promoting sustainable health solutions, as they contribute to both dietary needs and herbal remedies, making them key assets in traditional and modern wellness practices. Additionally, homologous plants can support biodiversity conservation by diversifying agricultural systems and reducing dependency on single-purpose crops (Mudondo et al., 2025a). Furthermore, the criteria prioritize medicinal plants that have been less researched such as *Asarum sieboldii* (Happy et al., 2025a), and *Aspilia Africana* (Okello et al., 2021c). These plants are of particular importance because they hold the potential to lead to the discovery of novel herbal medicines. By studying and exploring these under-explored species, new bioactive compounds may be identified, contributing to the development of innovative therapeutic agents. Additionally, the criteria are based on priority medicinal plants to specific systems, selected for their significant therapeutic potential and cultural value. Researching these plants is vital as it can reveal novel bioactive compounds, which could lead to the development of new medicines and treatment options for various diseases. Many of these plants, deeply embedded in TM, may possess unique pharmacological properties that have not yet been fully explored or utilized. By studying them, we have the opportunity to advance modern healthcare, preserve indigenous knowledge, and protect biodiversity. Moreover, research on priority medicinal plants can contribute to the sustainable cultivation of these species, reducing the pressure on wild populations and ensuring their availability for future generations. Certain medicinal plants are priorities for specific regions based on local needs and cultural significance. For instance, as noted by (Wamalwa et al., 2006), *Warburgia ugandensis* is among the 10 priority medicinal plant in Kenya, where it is highly valued for its therapeutic uses. Research in such plants is therefore vital as it can support local healthcare systems, offer economic opportunities through sustainable cultivation, and preserve traditional medicinal knowledge. Micropropagation and tissue culture have not only advanced basic research but also impacted the multiplication of economically important plants.

The ability to regenerate plantlets from cultured tissues is a requirement for the successful application of tissue culture technology to SH, horticulture, agriculture, and forestry. By manipulating nutrient media and culture environments, plant tissues can demonstrate their intrinsic ability for organized development, resulting in selective gene activation, which is evident in biochemical, biophysical, biophysiological, and structural changes in the cultured tissues.

Plant tissue culture. Plant tissue culture involves a collection of techniques used to grow or culture plant cells, tissues, and organs under controlled sterile conditions on a nutrient culture medium of known composition (Sudheer et al., 2022). It serves as the foundation step in micropropagation, involving the growing of plant cells and organs on a nutrient medium. The concept of tissue culture originated from the German scientist, Gottlieb Haberlandt, in the early 20th century, whose experiments aimed to sustain mesophyll cells in culture, based on the idea of "totipotency" of plant cells. This laid the ground work numerous publications on tissue culture techniques in biotechnology, soma clonal variation, genetic biodiversity conservation, embryo rescue, *In vitro* propagation, ploidy level management, germplasm conservation, genetic transformation, plants bioreactors, and breeding programs, with ongoing reports emerging annually (Delgado-Paredes et al., 2021; García-Hernández et al., 2022; Weckx et al., 2019). Plant tissue culture plays an important role in the plant development process, enabling the generation of transgenic plants with specific industrial and agronomic traits, gene function analysis, genetic transformation, and micropropagation, which significantly supports pharmaceutical and industrial outcomes (Chandran et al., 2020). In herbal plants, tissue culture creates a potential environment for cost-effective and sustainable production of bioactive compounds (alkaloids, flavonoids, terpenes, steroids, among others) for the pharmaceutical industry and offers an alternative to traditional herbal methods (Zhou and Wu, 2006). Several methods of plant tissue culture for medicinal plants exist (Chadipiralla et al., 2020). The most commonly used methods under the SH approach include organogenesis, somatic embryogenesis, zygotic embryogenesis, callus culture, thin cell layer (TCL) culture, and seed culture. These cultures are used for the mass production of herbal plants through micropropagation and for the production of specific plant organs, such as roots in hair root culture (Rahimi et al., 2023).

Plant regeneration *In vitro* occurs through two developmental pathways: organogenesis and embryogenesis. These pathways differ in the initial formation of either bipolar or unipolar structures.

Organogenesis. Organogenesis involves inducing the vegetative tissue to form organs such as roots, shoots, flowers, and tubers, which eventually develop into a complete plantlet (a small, fully formed plant). When a plant organ is used *In vitro* to generate a new plant, the process is referred to as organogenesis (Desai et al., 2022). Organogenesis can be categorized into two types, i.e., direct and indirect organogenesis, as demonstrated in Fig. 2. Direct organogenesis involves the direct formation of organs from the explant tissue, while indirect organogenesis requires an intermediate callus stage before the formation of organs (Singh and Kundu, 2024). Common stages of organogenesis include explant selection, medium selection, cytokinin optimized conditions, auxin optimized conditions, and acclimatization of the *In vitro* regenerated plant, as illustrated in (Fig. 3). To promote the conservation and large-scale production of *Apios americana* Medik under the SH approach, (Gang et al., 2024) developed an organogenesis-based *In vitro* propagation protocol using the stem segment as an explant. The explants were cultured in various basal media, which included Quoirin & Lepoivre (QL), WPM, DE GRETT & JACOBS (DJ), WPM, LC, and CHU N6 (CHU). After the media optimization test, the explants were subjected to different cytokinin (benzylaminopurine (BAP), kinetin (Kn), thidiazuron (TDZ), zeatin, and 2ip) for shoot proliferation as well as different auxins (indole-3-butyric acid (IBA), naphthaleneacetic acid (NAA), and

indole-3-acetic acid (IAA) for root proliferations, all tested at multiple concentrations. Among the tested, QL yielded the highest shoot growth, showing a statistically significant difference ($p < 0.05$) compared with other media. The optimal shoot proliferation was achieved with QL supplemented with 2.0 mg/L BAP, while the best root development occurred on QL containing 1.0 mg/L IBA. The combination produced the highest number of roots (2.80 ± 0.30), length (85.80 ± 7.49 mm), and surface area (10.40 ± 0.82 cm²). Following the acclimatization, the survival rate of regenerated and acclimatized plants reached 92.7 %, indicating the high efficiency and reliability of the protocol for sustainable propagation of *Apios americana* Medik. Explants under organogenesis go through a development process that leads to shoot and root formation in the process of organogenesis (Table 3).

Although the process leading to shoot and root formation in most medicinal plants is not entirely synchronous, the key physiological changes and histogenic events leading to shoot formation occur within a 6 to 14-day culture period. During days 6 to 12, high metabolic activity occurs as shoot primordia are being formed (Ahmad et al., 2021; Valerio et al., 2022).

One of the key characteristics of organogenesis is the ability of the whole plant (shoot and root) to maintain its apical meristem function even after a part of the meristem has been removed. Through organogenesis, new plant and lateral roots are successfully produced when the entire meristems are excised, along with plant cells from differentiated tissues or organs (Lal, 2019). However, there exist two patterns of organogenesis, “indirect organogenesis” and “direct organogenesis” (Liu et al., 2023), as shown in Fig. 3. In “indirect organogenesis,” plant organs are derived from unorganized tissue (callus mass) or tissue formation occurring on a plant wound or cut in the explant. Stages of indirect organogenesis include callus induction, callus proliferation, differentiation, plant regeneration, and acclimatization (Islam and Alam, 2018). The formation of shoots and roots in indirect organogenesis requires a callus phase (García-Hernández et al., 2022). In contrast, “direct organogenesis” allows explants to develop shoots and roots directly through the manipulation of plant growth regulators (PGRs) and culture conditions, bypassing the need for a callus phase. Direct organogenesis involves several steps: initiation of explant (shoot bud, root, leaf, and stem), shoot proliferation, shoot elongation, rooting proliferation, and acclimatization of regenerated plant (Lalthafamkimi et al., 2021).

Thin cell layer culture. TCL culture is another organogenesis-based *In vitro* propagation technique. The technique has been successfully applied to numerous medicinal plants for mass propagation, preservation, and genetic transformation. It serves as an experimental model for controlling organogenesis potential and for studying and understanding processes such as totipotency and differentiation in plant cells, tissues, and organs (Bhattacharyya et al., 2018). TCL has been used in the *In vitro* propagation of various plants, including *Bacopa monnieri* (Croom et al., 2016), *Dendrobium aphyllum* (Bhattacharyya et al., 2018), and *Withania coagulans* (Tripathi et al., 2018). This method uses small explants of approximately 0.5–2 mm in thickness excised either longitudinally (ITCL) or transversely (tTCL) from different plant organs, such as stem (hypocotyl), flower primordium, rhizome, leaf (petiole, lamina, midrib, etc.), root (primary and secondary), floral inflorescence, cotyledon, axillary, apical zone, and embryo. (Nhut et al., 2003), as indicated in (Fig. 4). The use of TCL for various explants has emerged as a promising approach for research in cellular processes, bioreactor applications, biochemistry, genetic transformation, molecular studies, and nanotechnology (microtome-based explanation) that control *In vitro* morphogenesis in plants (Iannicelli et al., 2018). TCL was initiated by Tran Thanh Van in 1973 using *Nicotiana tabacum* as a model plant in his work, benchmarking on the central dogma of plant tissue culture. Over time, TCL has presented overwhelming evidence in the mass propagation of herbs, ornamentals, fruits, functional foods, forest species, and

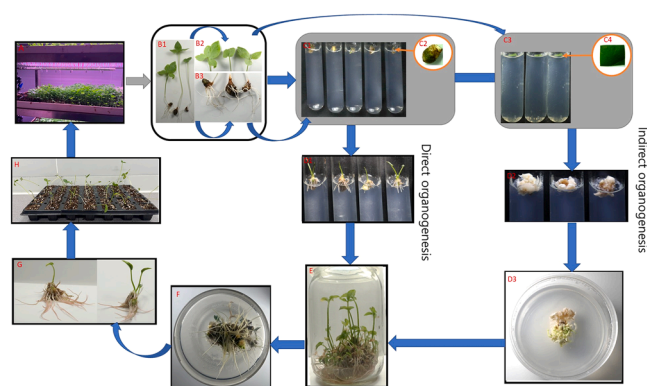


Fig. 3. Summary of organogenesis (direct and Indirect organogenesis) of *P. ternate* herb using two explants [egg-shaped micro tubers (direct organogenesis (Kim et al., 2020a)) and leaf explant (indirect organogenesis (Ahn and Lee, 2021))]. (A) *P. ternate* plants managed in the phytotron. (B1) Fourth-month-old maternal plant of *P. ternate*. (B2) Leaves of the maternal plant. (B3) Egg-shaped micro tubers with roots. (C1) Egg-shaped microtubers inoculated in LS medium under direct organogenesis. (C2) Morphology of egg-shaped micro tubers. (C3) Leaves inoculated in MS medium containing 2.0 mg/L 2,4-D and 0.2 mg/L BA under indirect organogenesis. (C4) Morphology of leaf induced. (D1) Proliferated shoots in LS medium. (D2) Callus formed after four weeks on leaf inoculation. (D3) Proliferated shoots from callus after three weeks of callus formation. (E) Proliferated shoots after adding cytokinin. (F) Proliferated roots after adding auxin. (G) Plantlets removed from the medium, and roots washed. (H) Regenerated *P. ternate* plantlets transferred to soil and acclimatized.

vegetables, including species that are considered difficult to propagate, such as bamboo [82] and pine (Ramírez-Mosqueda et al., 2019). As illustrated in (Fig. 3), the TCL process involves stages such as explant preparation, explant induction, shoot induction and elongation, root induction and elongation, and acclimatization (Bravo-Ruiz et al., 2022). Wild medicinal plants, which are rich in biologically active compounds, have traditionally been used in TM; however, ecological factors pose a significant threat to their survival. The SH approach could enhance their mass propagation through TCL, thereby increasing the potential of extracting a large volume of raw materials for formulating herbal medicine.

Embryogenesis. Embryogenesis begins with the formation of a zygote and ends with the development of a mature embryo, capable of germinating and developing into a sporophyte (Kruglova et al., 2022).

Somatic embryogenesis. Somatic embryogenesis is a process in which somatic plant cells (non-reproductive cells) or tissues or organs develop into differentiated (bipolar) embryos. The developed tissue or organs typically include shoots and/or roots (Neumann et al., 2020). This process can be directly initiated from the explant or indirectly through the formation of a mass of unorganized cells called a callus. Somatic embryogenesis can occur from any type of somatic cells, such as juvenile leaves, stems, or roots. It is not a natural process since somatic cells do not typically form embryos on their own. In plant regeneration, somatic embryogenesis has become a valuable biotechnological tool for clonal regeneration, genetic improvement, and germplasm conservation (Martínez et al., 2019). Somatic embryos are characterized by their large numbers, the presence of bipolar structures, rapid production, relatively stable genetic traits, the presence of shoot and root apices, high efficiency in seedling formation, and minimal variation in regenerated plants (Nascimento et al., 2020). Somatic embryogenesis has been instrumental in micropropagation, conservation, secondary metabolites production, and genetic transformation of several endangered and vulnerable medicinal plants, including *Annona muricata*, *Chinchona pubescens/officinalis*, *Theobroma cacao*, *Juglans neotropica*, *Bixa Orellana*, *Mycianthes pungens*, *Swietenia macrophylla*, etc (Mihai et al., 2023). The

Table 3
Development sequence of explants in the formation of the shoot and root.

Day	Characteristics	Reference
0 to 6	Formation of cell clusters surrounding the inoculum, development of some tracheary elements in the areas between the cell files and the inoculant, and high respiration rate associated with wounding response in the plants	(Maeda and Thorpe, 1979; Ahmad et al., 2021)
6 to 8	Observation of zones of preferential cell division activity near the tracheary element Start accumulation peak in the lower or SF portion of the callus	(Maeda and Thorpe, 1979; Ahmad et al., 2021)
9	Meristemoids and or meristem-like cell masses start to form of cells in the lower half of the callus, the beginning of accumulation peak in the upper portion of the whole callus, increased glucose oxidation	(Maeda and Thorpe, 1979; Tripathi et al., 2022)
10 to 12	Cell division stops, cell elongation progresses Meristemoids becoming shoot primordia are more noticeable on broad protrusions in callus surface in contact with the medium	(Campanoni et al., 2003; Tripathi et al., 2022)
14	Emerging and appearance of bud from the lower half of the callus	(Okello et al., 2021c)
15	No primordia observed Development of numerous roots	(Valletta et al., 2016)
18 to 21	Appearance of recognizable leafy vegetative shoot and roots	(Komakech et al., 2020a),
25 to 28	Re-appearance and fast rate growing of primordia in some tissues More shoots and better-quality physiological tissues	(Smith et al., 1992; Aguilar et al., 2022)

seedlings derived from somatic embryos are widely applied in smart farming systems (Mohammed et al., 2022). Somatic embryogenesis includes direct somatic and indirect somatic embryogenesis, as these are the only methods documented to date (Bhusare et al., 2020). Fig. 4 illustrates both direct and indirect somatic organogenesis. In indirect organogenesis, the formation of shoots and roots requires a callus phase, whereas in direct somatic embryogenesis, embryonic cell formation occurs directly from the surface of the explant (Śliwińska et al., 2021). Although Okafor et al. (2023) indicates that adult medicinal plants are reported to provide suitable zygotic embryos that can be induced to form somatic embryos, inducing somatic embryos from older tissues, particularly in many woody medicinal plants, remains a challenging process (Arora et al., 2022).

Zygotic embryogenesis. Zygotic embryogenesis is a natural *In vitro*

process that involves the formation of an embryo through the double fertilization of the ovule. The zygote undergoes a series of differentiation stages that result in the production of a mature embryo, as illustrated in Fig. 5. The embryo, a product of fertilization, is the most important component of the seed, with other components serving to support the embryo by providing nutrition and protection. It acts as a foundation for the future plant's life (Armenta-Medina et al., 2021). Plant development in zygotic embryogenesis begins inside the embryo sac (female gametophyte), where two male gametes are transported via siphonogamy into the egg cell and/or the embryo sac nuclei, involving complex processes. The ovule undergoes two rounds of fertilization, creating the zygotic embryo, which contains both the endosperm and the plant embryo that eventually grows into a seed. The development of major embryonic organs, as well as shoot and root apical meristems, is influenced by the hormone auxin, occurring through partitioning events along the apical-basal axis (Chen et al., 2021). Seeds can also grow without fertilization through an apomixis-related process (Fiaz et al., 2021). The application of zygotic embryogenesis includes the production of herbal plants, haploid (gametophytic) production, shortening of the breeding cycle (through double haploid production), rapid seed viability testing, and propagation of medical plants. During zygotic embryogenesis, different phases of rapid cell division and morphogenesis occur, beginning with a single-cell zygote. These stages include pre-globular, globular, heart, torpedo, and cotyledon stages (Li et al., 2023). As the embryo matures, the requirements for food, energy, and embryo protection increase. Therefore, both the production and storage of macromolecules, such as carbohydrates, lipids, oils, and proteins, by the cells and the hardening of the seed coat occur during the maturation stage (Savassa et al., 2021). These macromolecules act as food and energy supply during germination and seedling growth, while the hardened seed coat helps to safeguard the embryo and preserve available nutrients (Rogo et al., 2023). Dormancy, which results from conditions outside the embryo, marks the end of embryogenesis. The mature zygotic embryo enters the state of developmental arrest, becoming metabolically quiescent (dormant) and surrounded by the seed's maternal tissues. The dormancy enables the embryo to persist for a long time, providing a significant survival advantage (Bhatla and Lal, 2023). Through the process of zygotic embryogenesis, the SH concept develops an *In vitro* embryogenesis system, which can be cultured in the laboratory and either transferred to the recipient immediately or cryopreserved for transfer.

Winkelmann (2016) indicates the similarities and differences between somatic and zygotic embryogenesis regarding the morphological, histological, biochemical, and physiological aspects.

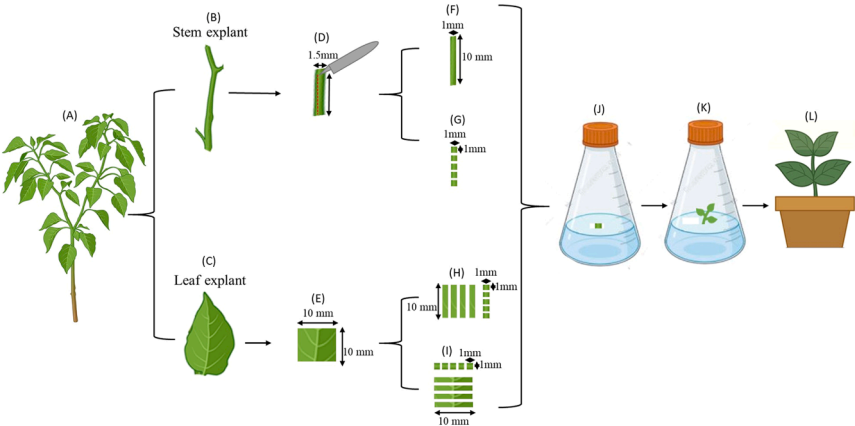


Fig. 4. Schematic flow diagram of the preparation of a transverse thin cell layer (tTCL) and a longitudinal thin cell layer (lTCL) from explants (stem internode and leaf). (A) The donor plant. (B) Internode explant. (C) Leaf explant. (D) The excising process of the stem internode explant. (E) Excised leaf explant ready for making thin cell layers. (F) Prepared explant 1 mm x 10 mm. (G) 1 mm thick rings are excised from the prepared explant cut from the internode. (H) Thin cell layers from leaf explant excised longitudinally (lTCL-L). (I) Thin cell layers from leaf explant excised transversely (tTCLs). (J) TCL cultured basal side or top side down on culture media. (K) Shoot formed on the thin cell layer explant. (L) Plantlet grown from a TCL explant.

Synthetic seed culture. Synthetic seed culture is a powerful technique in plant biotechnology that offers significant potential for mass propagation, conservation, and research. It merges tissue culture benefits with convenience seed-like properties, enabling year-round production of genetically uniform plants, particularly those difficult to propagate traditionally, like *Prunus africana*. (Gantait et al., 2015). This technique has successfully been applied in mass propagation and short-term storage of various medicinal plants that include *Catharanthus roseus*, *Musa spp.*, *Vitis vinifera*, and *Swertia chirayita* (Ara et al., 2000; Kaur et al., 2019; Lata et al., 2009). The seeds are characterized by having artificial embryos, which are derived from somatic embryogenesis rather than sexual reproduction. Synthetic seeds, also known as artificial seeds, contain somatic embryos, not produced through sexual reproduction, and are encapsulated in protective materials like hydrogels. These encapsulated embryos can be stored and later germinate into whole plants under suitable conditions (Haque and Ghosh, 2016). Baskaran et al. (2017) indicate that embryos can also be derived through other *In vitro* propagation techniques. These embryos are encapsulated in a protective gel or other material, imparting to them the physical properties of a seed. They can be stored for extended periods under controlled conditions, similar to conventional seeds, but with the added benefit of potentially being produced year-round through tissue culture and their somatic embryos' ability to germinate and develop into full-grown plants when planted in suitable growth media (Gantait et al., 2015; Gray Ph.D et al., 1991), as illustrated in (Fig. 6). In a study on synthetic seed production, Baskaran et al. (2015) examined somatic embryos (SEs) at heart, torpedo, and cotyledonary stages, evaluating their viability using various concentrations of sodium alginate (SA) and calcium chloride. The most effective combination was 3 % SA and 100 mM $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, using embryos from media with 0.5 μM mTR and 0.25 μM IAA. This formulation produced uniform, durable beads, achieving the highest survival (95.7 %) and germination (73 %) rates. Higher concentrations of SA and $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ resulted in firmer beads but reduced the viability and germination, likely due to over-absorption, and inhibited embryo development. Synthetic seeds from all embryo stages germinated well, especially when derived from optimized embryo

development media. Viability testing after cold storage at 4°C revealed reduced but still promising germination rates when the seeds were transferred to MS medium supplemented with 30 g/L sucrose and 8 g/L agar. Viability loss during storage was attributed to oxygen deficiency and desiccation. Ultimately, plantlets (70–90 mm) derived from synthetic seeds were successfully acclimatized in a 1:1 vermiculite-soil mix, achieving a greenhouse survival rate of 90 %. This study highlights the importance of medium composition and encapsulation conditions in synthetic seed success.

Despite its potential, challenges remain in optimizing synthetic seed culture protocols across species and improving the consistency of somatic embryo development and germination. Key steps include embryo induction, maturation, encapsulation, desiccation, and planting. Other parts of the plant, such as nodal segments and axillary buds, can also be used in synthetic seed culture (Ghanbarali et al., 2016; Ramírez-Mosqueda et al., 2023). Methods for synthetic seed production include desiccated seeds (for desiccation-tolerant species), hydrated seeds (for sensitive species), and alginate encapsulation using SA and $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ to form stable beads. These advances position synthetic seed culture as a promising approach for large-scale plant production and biodiversity conservation (Kaur et al., 2019; Lata et al., 2009).

***In vitro* callus culture.** Callus refers to an unspecialized, unorganized mass of cells that grow and divide continuously. Callus culture involves the culture of dedifferentiated plant cells induced on media usually containing auxin or a combination of auxin and cytokinin, under controlled *In vitro* conditions, such as in a test tube or Petri dish. This process is a critical step in initiating *In vitro* cultures, which later stimulates the formation of whole plants. It also helps to amplify limited plant materials. Callus can be derived from various plant parts such as leaves, stems, roots, axillary buds, nodal segments, or any part of the plant. The obtained explants are cultured on the appropriate solid medium, with either auxin or a combination of auxin and cytokinin. MS and 2,4-D are media commonly used during callus culture (Babich et al., 2020). In the SH approach, callus formed from the culture of explants has been used in the extraction of bioactive compounds. Callus cultures

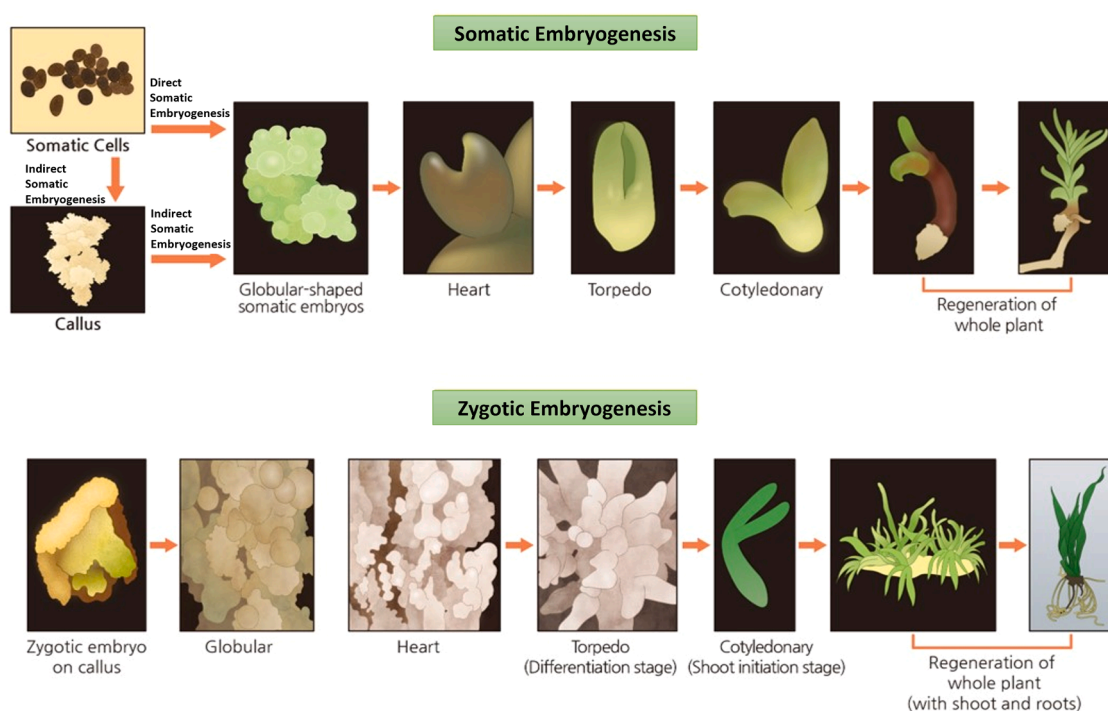


Fig. 5. Morphological and developmental stages (somatic cells, callus formation, globular, heart, torpedo, cotyledonary, regenerated plant) of somatic and zygotic organogenesis.

containing bioactive compounds are harvested at specific stages of callus development (usually during the stationary phase of the callus growth cycle, because greater production of secondary metabolites is always common during the stationary phase. After the harvest, they are dried and extracted, and the extracts are taken for identification and qualification of desired medicinal compounds using Fourier transform near-infrared (FT-NIR), high-performance liquid chromatography (HPLC), etc. To maximize callus production and further scale up the yield enhancement studies of compounds, callus is raised in suspension, first in shake-shake culture, later in a suitably designed bioreactor. During callus formation, there is some degree of dedifferentiation both in morphology and metabolism, resulting in the loss of the ability to photosynthesis. Callus can be divided into two types, i.e., Compact callus (characterized by densely aggregated and tightly packed cells with hard texture) and Friable callus (characterized by loosely associated soft/watery cells that can easily break apart). The processes of callus culture is divided into different stages: (1) Induction where cell in plant dedifferentiate and begin to divide, (2) Proliferative stage where rapid cell division occurs, and (3) morphogenesis stage where differentiation and organized structures are formed, particularly those that lead to plant regeneration from somatic cells (Kruglova et al., 2023). The color and texture of callus can be different depending on the nature of the plant and the nature of the hormones used in callus culture.

Mehta et al. (2022) outlines the steps involved in the callus culture process as follows: (1) Incise explants into small pieces of 8–10 m, (2) transfer the incised explants to media with an appropriate medium with either auxin or a combination of auxin and cytokinin. MS and 2,4-D are media commonly used. Medium for callus culture should contain 3 % sucrose (w/v) and 0.75 % agar (w/v). Before autoclaving the medium (121°C and 1.2 kg.cm⁻² pressure for 20 minutes), it should be adjusted to pH 5.7 to 5.8. (3) Incubate the cultures at 25°C in 16:8 photoperiod under cool white fluorescent tubes, (4) observe the culture after every 10 days for 30 days and record the observation, (5) add an adjuvant (CW) with different percentages (2.5, 5 and 10 %) to initiate the production of green callus, (6) routinely subculture the callus after 15 days into fresh medium for either friable or compact callus production with a high proliferation rate, (7) incubate the sub-cultured callus containing Petri plates with a 16:8 h photoperiod at 25 ± 1°C and record the observation.

In vitro plant cell culture. Plant cell cultures is a technology that

promotes dedifferentiated plant cells by growing them under strictly controlled environmental conditions. These techniques enable the production of various biologically active compounds, such as podophylotoxin and ribosome-inactivating protein, for biotransformation. Plant cells are considered totipotent, meaning they possess the ability to express the full genetic information in the nucleus, which allows them to produce a wide range of secondary metabolites, typically found in mother plants. In the SH approach, plant cells are cultured and multiplied with nutrient media in an aseptic and CE to produce a large amount of uniform, mature and contamination-free herbal, aromatic and medicinal plants in a short period of time. This system supports the production of rare bioactive compounds such as resveratrol and terpenoids, which are usually found in low yield from natural resources whose isolation and purification require the processing of large amount of plant biomass (Loyola-Vargas and Vázquez-Flota, 2006). Plant cell culture explores conditions that promote cell division and genetic programming *In vitro*. The SH approach practices different plant cell culture technologies that include: (1) Plant cell elicitation, (2) Cell suspension, (3) Meristematic stem cell (cambial meristematic cells culture), (4) Callus culture, and (5) Hair root culture. Additionally, plant cell culture contributes to the production of recombinant protein expressed by cell culture, as well as emulsification of cells, powdered leaf cells, and glycerin-based leaf cells used in drug development, phytochemical profiling, nutrition, and cosmetic formulation. In the cosmetic industry, differentiated plant cell cultures are used to generate active cosmetic ingredients that include “plant stem cells,” “leaf stem cell,” “fruit stem cell,” “root stem cells,” “meristem stem cells,” “flower stem cells,” and “rhizome stem cells” (Georgiev et al., 2018). Additionally, two primary techniques for cell culture, i.e., single-cell culture in indirect somatic embryogenesis and the bioreactor cell culture technique, are commonly used. Elucidation approach is applied in the bioreactor to boost the accumulation of plant active compounds. The use of plant cell culture in *In vitro* propagation is illustrated in (Fig. 7). Okello et al. (2021b) describes indirect *In vitro* regeneration of medicinal plants through plant cell culture, while Rahmat et al. (2021) describes the steps involved in the bioreactor cell culture technique as in Fig. 6. Both studies were conducted in the SH lab in Naju, Korea. According to Rahmat et al. (2021), the steps involved in the bioreactor cell culture technique include: (1) Adventitious root culture. (2) Elicitor preparation and treatment of cultured roots that have been supplemented with sucrose

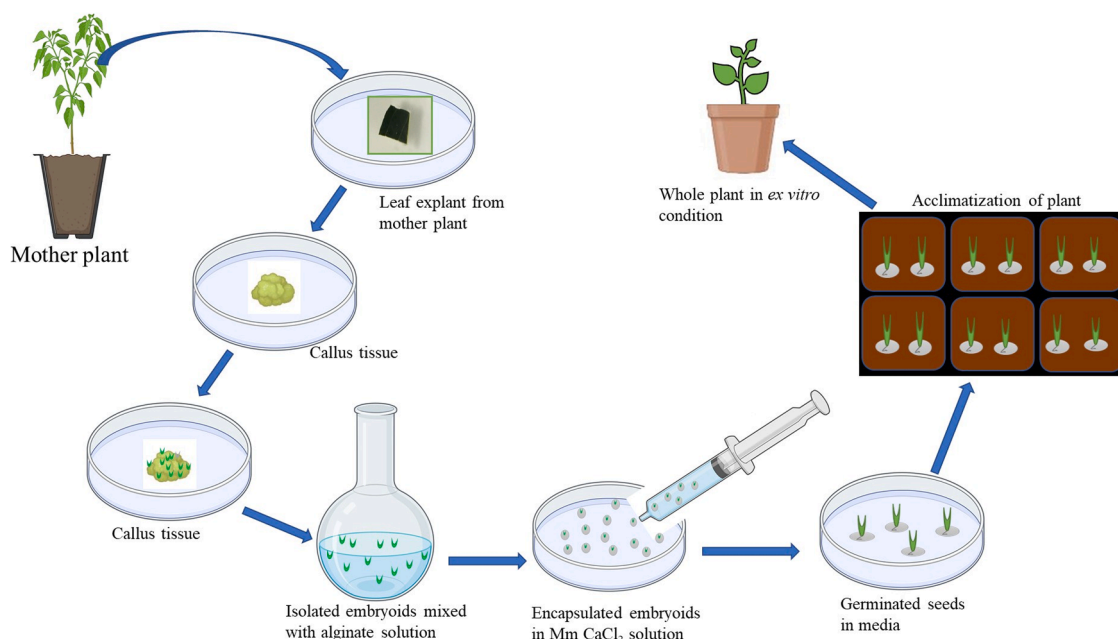


Fig. 6. Stepwise procedure for synthetic seed production using encapsulation techniques.

and hormones. (3) culturing the adventitious roots in balloon type (air lift) bubble bioreactor. (4) Determination of the root biomass. (5) Determination of compounds using HPLC and FT-NIR spectrometer analysis, among other studies.

Other *In vitro* propagation techniques include cambial meristematic cell culture, suspension culture (which involves cells or cell aggregates grown in agitated liquid media derived from callus tissue), protoplast culture, endosperm culture (used for triploid production), somatic hybrids, and cybrids.

Media and PGRs commonly used; Several media and plant regulators have been used in *In vitro*, *in vivo*, and *ex vitro* propagation of medicinal plants under the SH approach. These include (1) Media [MS, WPM, LS, DJ, CHU, QL, Chee and Pool (CHE), Gamborg's B-5 (GB5), Vacin and Went (VW), Nitsch and Nitsch (NN), Schenk and Hildebrandt, and White's medium], for culturing a wide range of plant cells, tissues, and development of a wide range of plants, (2) Auxin (IAA, IBA, NAA, and 2,4-dichlorophenoxyacetic acid) encouraging root formation, (3) Cytokinins [BAP, Kn, zeatin, GA, ABA, TDZ also known as 1-phenyl-3-(1,2,3-thiadiazol-5-yl)-urea, ethylene, polyamines (putrescine, spermidine, and spermine)] shoot initiation, shoot proliferation, organogenesis, formation of callus, embryogenesis, involved in stem elongation, flowering, and seed germination, promote shoot elongation, overcome dormancy, and induce flowering or fruit set in some species, (4) Sucrose to provide the necessary carbohydrates for the plant tissue or cell to grow and develop, (5) Agar/agarose to solidify the medium, creating a stable surface for explants to grow on in culture (Gang et al., 2023; Gang et al., 2024; Komakech et al., 2020b; Okello et al., 2021d; Olaitan et al., 2022; Rakesh et al., 2021; Rathore et al., 2022), (6) Activated charcoal is added to media to improve the growth and viability of the explants (Thomas, 2008), (7) Bee honey aids in enhancing whole plant growth, promoting rooting and shoot regeneration, protecting against oxidative stress, providing nutritional support to plant tissues, useful additive in plant tissue culture media and improvement of plantlet acclimatization (El-Banna et al., 2024; Mantovani and Pivetta, 2015), (8) Myo-inositol promotes healthy cell division, embryogenesis, and shoot formation (El Sharabasy, 2019), (9) Vitamins (thiamine, pyridoxine, nicotinic acid, etc.) support optimal growth and development of the cultured plant material (Mansour and Bana), (10) Amino acids (glutamine and glycine) improve the growth rate, shoot formation, and somatic embryogenesis in plant cultures (El-Sharabasy et al., 2012), (11) Coconut water inducing organogenesis, improving plantlet acclimatization, reducing

oxidative stress, and supporting overall healthy growth in plant tissue cultures (Prando et al., 2014), (12) Sea weed extracts, *In vitro* regeneration of root and shoot growth (Loconsole et al., 2024; Prando et al., 2014), (13) Phloroglucinol stimulates the formation and elongation of shoot and roots in *In vitro*, *in vivo*, and *ex vivo* propagation of medicinal plants (Deltalab et al., 2023), (14) Silver nitrate (AgNO₃) and silver nanoparticles (Ag NPs) enhance plant growth and development (Mahendran et al., 2019; Shalima Sihag et al., 2018), (15) Phytosulphokine-alpha, a versatile and powerful growth regulator in plant tissue culture, particularly useful for promoting growth, differentiation, and regeneration in *In vitro* propagation (Mestinšek Mubi et al., 2024), (16) Adenosine 5-monophosphate supporting role in *In vitro* propagation by enhancing nucleotides and energy metabolism, which are essential for cell division, shoot multiplication, and overall growth in tissue culture (Min et al., 2018), (17) Nicotinamide adenine dinucleotide, involvement in energy production, redox balance, and cellular processes like division, differentiation, and embryogenesis makes it an essential coenzyme for the successful regeneration of plant tissues in culture (Ashihara et al., 2008), (18) methyl jasmonate, aids in stress responses, defense mechanisms, secondary metabolite production, and growth processes. Commonly used in abiotic elicitors on adventitious roots biomass, (19) Salicylic acid, used in rooting, embryogenesis, growth regulation, and secondary metabolite production. Both methyl jasmonate and salicylic acid are commonly used in abiotic elicitors on adventitious roots biomass (Rahmat et al., 2021), (20) Alginate solution, aids in encapsulation of plant cells and embryos during synthetic seed formation, (21) calcium chloride, used in the process of encapsulation of plant tissues, particularly in the formation of alginate beads that serve as the synthetic seed (Iqbal et al., 2019), (22) Aleo vera gel, used in inducing roots in plants (Mirihagalla and Fernando, 2020), and (23) Cinnamon powder, used as an antifungal and a plant growth promoting agent (Kowalska et al., 2020). To enhance a successful *In vitro* propagation protocol for optimizing the plants' growth, auxins and cytokinin are combined. Their combination is commonly used to control callus formation, shoot proliferation, and root induction (Okello et al., 2021c), in some propagation studies, auxins are used to promote root growth. (Haissig, 1974) indicates the use of a synergetic combination of auxins (IAA and NAA) in adventitious root primordia initiating and developing, while a study by (Kumlay, 2014) indicates a combination of auxins (IBA and IAA) to improve the commercial tuber production of Potato (*Solanum tuberosum* L.) under *In vitro* conditions. In some *In vitro* propagation

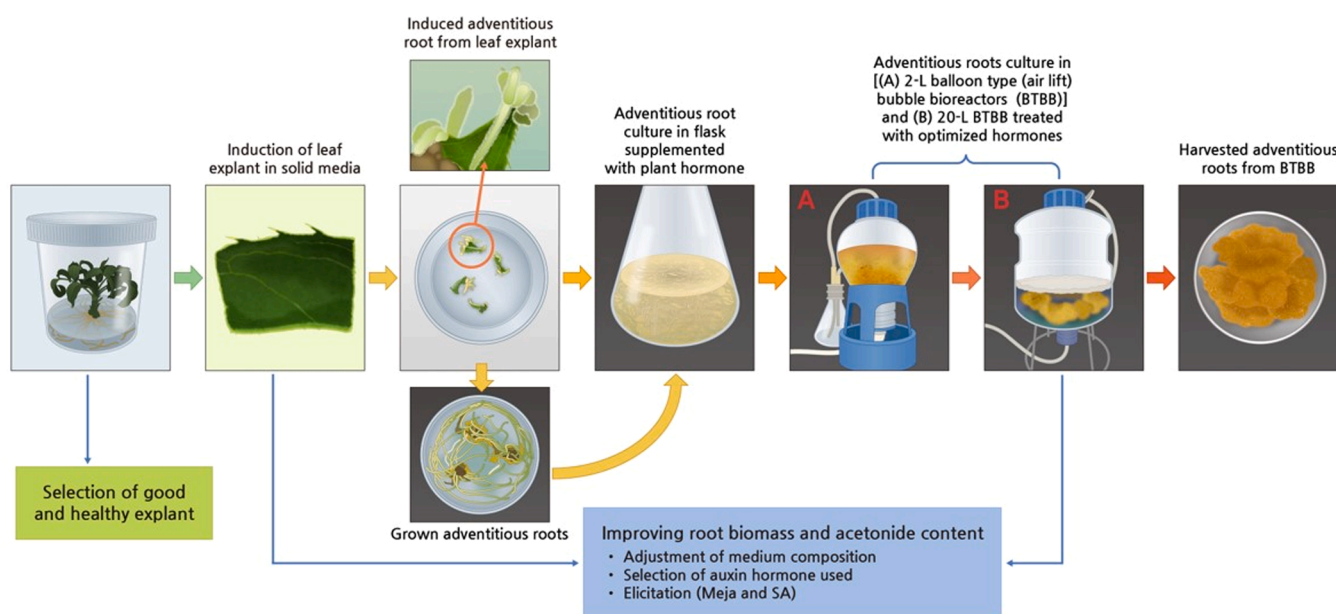


Fig. 7. Schematic representation of the adventitious cell culture process for enhanced metabolite production.

studies, cytokinin and cytokinin combinations are commonly used to aid in the proliferation of shoot growth. A study by (Ara et al., 2010) indicates the combination two cytokinin (BAP and Kn) in the *In vitro* propagation of Fever Tea (*Lippia javanica*), a medicinal shrub. Depending on the propagation objective, all other PGRs are used accordingly.

Acclimatization of *In vitro* propagated plants

Gradual acclimatization of *In vitro* propagated plantlets to different environments, such as phytotron, greenhouse, smart farm, and open field, is essential due to their unique physiological and anatomical characteristics (Chandra et al., 2010). Media used during *In vitro* propagation lack symbiotic propagules and environmental stressors; therefore, plantlets obtained from these media are not associated with any symbiotic fungi or bacteria and other environmental stress *In vitro* but often develop a negative association with a pathogenic organism and other factors when they are being managed under other systems, such as phytotron, smart farms, and/or open fields. Studies by Akula and Ravishankar (2011) and Janská et al. (2010) have shown that stress during acclimatization (such as water deficit, pathogens, low temperature, and inadequate light.) affects alkaloid metabolism, which eventually affects the herb formulation, leading to limited compound production in medicinal plants. Therefore, successful acclimatization requires carefully managing environmental conditions, including lower relative humidity, higher light level, autotrophic growth, and aseptic environment that are characteristics of phytotron, greenhouse, or field (Tisarum et al., 2018). However, Velásquez et al. (2018) note that some plants struggle with acclimatization due to rapid desiccation or susceptibility to diseases and humidity. As a result, acclimatization may vary depending on plant species, although some general principles can be applied. In the SH context, the process of acclimatization occurs both *In vitro* (using abiotic approaches for acclimatization) and *ex vitro*. Under the abiotic approach, acclimatization focuses on substantially changing from *In vitro* environment, particularly during the later stages of propagation, to induce the phenotype with better storage capacity, photosynthetic ability, water conservation, and improved transpiration once the plant is *ex vitro*. Grout and Millam (1985) suggest that larger persistent leaves, packed with storage compounds, could contribute more effectively after transpiration. Tichá et al. (1998) found that plant growth, dry matter accumulation, and total leaf area were higher under protomorphic compared with photoautotrophic conditions and that exogenous sucrose significantly affect photo synthesis and biomass production. To support leaf persistence, sugar concentrations in leaves are increased, optimizing the leaves' nutrient functions, as reported by Hazarika (2006). For *ex vitro* acclimatization, plants are put in pots filled with garden soil, compost, and sand (substrates) in a 1:1:1 ratio, respectively (depending on the plant). According to da Silva et al. (2017), the substrate composition can vary for different plants during acclimatization. The plants are kept in a surface chamber for initial periods, and later, in a greenhouse with 80 % humidity and 31°C for 10 days, depending on the plant species. Afterward, the plants are moved to a shade house with less humidity, and after five days, they are transferred to the soil. Proper acclimatization plays an important role in sustainability, increasing the survival rate and reducing the mortality rate of *In vitro* propagated plants (Hazarika et al., 2006). The acclimatization process of *Codonopsis pilosula* is as indicated by (Gang et al., 2023).

Comparative studies between *In vitro* propagated plants and maternal plants

During *In vitro* propagation, there is a possibility of genetic changes such as somaclonal variation, which can affect various traits, including plant height, flower color, and disease resistance (Israeli et al., 1991). Bhojwani and Dantu (2013) describe somaclonal variation as both a “boon and a bane”. These variations can reduce the commercial value of the propagules. Similarly, genetically engineered plants undergo thorough screening to prevent unwanted and unintended somaclonal variations, ensuring that only clones with the desired traits from the transgene are commercially released. However, somaclonal variation

can also lead to the emergence of desirable genotypes, which may result in the development of novel cell lines or plants with agronomic and commercial benefits. Thus, comparing somaclonal variation between *In vitro* propagated and maternal plants is important as indicated in (Fig. 8). Various studies have been conducted to assess the similarity between the two, including evaluation of genetic and clonal fidelity, ploidy level comparison, and morphological and phenotypic comparison, through flow cytometry analysis, biochemical, and physio local studies (Gang et al., 2024; Tikendra et al., 2022). These studies are as indicated in Table 4.

NB. SH integrates advanced technologies such as *In vitro* propagation, precision farming, multi-omics analysis, and sensor-based monitoring to enhance the efficacy, safety, and sustainability of medicinal plant use. Importantly, these practices do not involve genetic modification. *In vitro* propagation, a central component of SH, is used to clonally multiply high-quality plant material under sterile, controlled conditions. While this method allows for rapid and uniform plant production, it does not involve altering the plant's genetic code or inserting foreign genes, as is done in genetic modification. Instead, it replicates the existing genetic material of a selected mother plant. Although occasional somaclonal variation may occur due to tissue culture stress, this is unintentional and can be monitored using molecular tools to ensure genetic stability. Likewise, the integration of omics tools (genomics, metabolomics, transcriptomics, etc.) and smart farming technologies (e.g., IoT, AI, and environmental controls) in SH is focused on monitoring, analyzing, and optimizing plant growth, compound production, and therapeutic quality not altering DNA. Therefore, SH presents a non-GMO, science-based solution that respects traditional herbal knowledge while leveraging modern tools to ensure consistency, safety, and traceability in herbal medicine production.

The *In vitro* propagation protocol is meant to present a reproducible technique that is efficient in producing a high number of plantlets that are similar to the maternal plant (Longchar and Deb, 2022). (Fig. 8) presents comparative studies between maternal plants and *In vitro* regenerated *Polygonum multiflorum*.

Cultivation of medicinal plants in a controlled room. Cultivating medicinal plants under CE offers a sustainable approach to meet the growing demand for herbal products while ensuring consistent quality and conservation. Recent studies have demonstrated the efficacy of CE systems in enhancing the production of bioactive compounds in medicinal plants (Alamgir, 2017a; Dsouza et al., 2025). In an experiment by Aldarkazali (2020) in a smart greenhouse facility equipped with Internet of Things-based environment control, a randomized block design with three replicates of *Ocimum basilicum* (Sweet Basil) medicinal plant was established under smart farm conditions. The objective of the study was to evaluate how controlled environmental variables (light intensity, temperature, humidity, and nutrient levels) affect the growth performance and essential oil yield of *O. basilicum*, a widely used medicinal plant. Four treatments were applied in the experiments, i.e., (1) Light: White LED vs. Red-Blue LED (16-hour photoperiod), (2) Temperature: 22°C vs. 28°C, (3) Humidity: 50 % vs. 70 %, (4) Nutrient delivery: Standard vs. Enriched hydroponic solution. The parameters monitored were: Plant height, leaf area, biomass accumulation, chlorophyll content (SPAD values), and essential oil composition (analyzed via GC-MS). The results showed that plants under red-blue LED light and moderate temperature (22°C) showed the highest growth rate and biomass, 70 % humidity and enriched nutrient solution significantly improved leaf size and chlorophyll content, and essential oil yield increased by 30 %, with higher concentrations of key compounds like linalool and eugenol under optimized conditions. The study has demonstrated that managing medicinal plants under CE, like smart farms, allows precise manipulation of growing conditions, resulting in improved yield and standardized quality of bioactive compounds. This experiment supports the SH approach by emphasizing reproducibility, traceability, and enhanced

therapeutic efficacy. Various systems, such as phytotrons, have been used to promote the growth of medicinal plants (Saleem et al., 2023). Phytotron, as illustrated in (Fig. 9), is a set of sophisticated growth chambers, equipped with precise means of simultaneously and independently controlling environmental conditions such as lighting (the energy level, quality of light, duration of illumination, and so on), temperature, and humidity, enabling research into plant response environmental changes. The integration of automation and computing technology in these systems improves plant biomass production by optimizing environmental conditions (Munns, 2015). The SH approach used a phytotron for short, medium, and long-term studies within ecological systems, requiring careful management to prevent failure. The phytotron farming system embraces computing and high-tech sensing to manage plants indoors. Key management practices include (1) Automated and optimized nutrient delivery and flow: In hydroponic phytotrons, nutrients, fertilizers, and pesticides are delivered through irrigation systems. Sensors monitor the temperature and pH of the media to ensure proper nutrient absorption. In soil-based phytotrons, nutrients are delivered via irrigation or nanostructured materials such as nanoparticles, nanohydrogel, and nanoemulsions to enhance nutrient delivery and absorption (Hadavi and Ghazijahani, 2018). (2) Environmental management: Sensor systems help control temperature, humidity, light, and carbon dioxide (CO₂) levels within the phytotron as indicated in Fig. 8. Light management uses energy-efficient, self-automated LED lighting to regulate plant growth based on their specific needs (e.g., short-day, long-day, or day-neutral plants). Temperature is carefully managed using sensors that eliminate fluctuations, ensuring stable growth conditions. Humidity is also regulated using sensors to maintain optimal levels for plant health (Roy et al., 2021). (3) Pest/disease control and pesticide delivery. The commonly applied pesticides in the phytotron are insecticides to kill insects, herbicides to kill weeds, rodenticides to kill rodents, and fungicides to control fungi, mold, and mildew. In eco-friendly systems, biodegradable smart nanocarriers are

used in soil-based phytotrons for pesticide delivery, promoting green practice (M.J. Romer, 2000; Ma et al., 2023).

Harvesting, processing, extraction, separation, isolation, and characterization of bioactive compounds

The chemical diversity found in medicinal plants continues to play a significant role in the discovery of new drugs through either pure compounds or standardized extracts. Global interest in therapeutic drugs from natural drugs has increased, as secondary metabolites from natural sources are often perceived to have greater likeness and biological compatibility than fully synthetic molecules. This has led to higher demand for chemicals from natural products. As a result, medicinal plants cultivated in a phytotron contain various bioactive compounds and secondary metabolites, which are extracted, isolated, and characterized for further development of drugs. The analysis of these compounds typically involves phytochemical screening assays and chromatographical techniques such as HPLC, thin-layer chromatography, as well as non-chromatographic techniques such as FT-IR (Baetz et al., 2022; Dr Arun Bhardwa, 2022; Sytar et al., 2018).

Harvesting. In a controlled system, medicinal plants must be harvested at the optimal time to ensure the best possible quality of both source materials and the final products. It is well known that the quantitative concentration of biologically active phytoconstituents varies with the stage of the plant's growth and development. Different medicinal plants have varying maturity periods (Jayasundara and Arampath, 2021), and the specific plant parts, are used in herbal medicine processing also differ, e.g., plants used for roots (e.g., *Panax ginseng*, *Aconitum kusnezoffii* Reichb., *Asarum sieboldii*, and *Apios americana*) (Gang et al., 2024; Govindaraghavan and Sucher, 2015; Singhuber et al., 2009) bulb (e.g., *Allium sativum*) (Sasi et al., 2021) leaves (e.g., *Aleovera barbandesia* Miller, and *Ginkgo biloba*), berries/fruits (e.g., *Diospyros kaki* and *Crataegus monogyna*), fruit covers (e.g., *Punica granatum* Linn) (Lima Bezerra

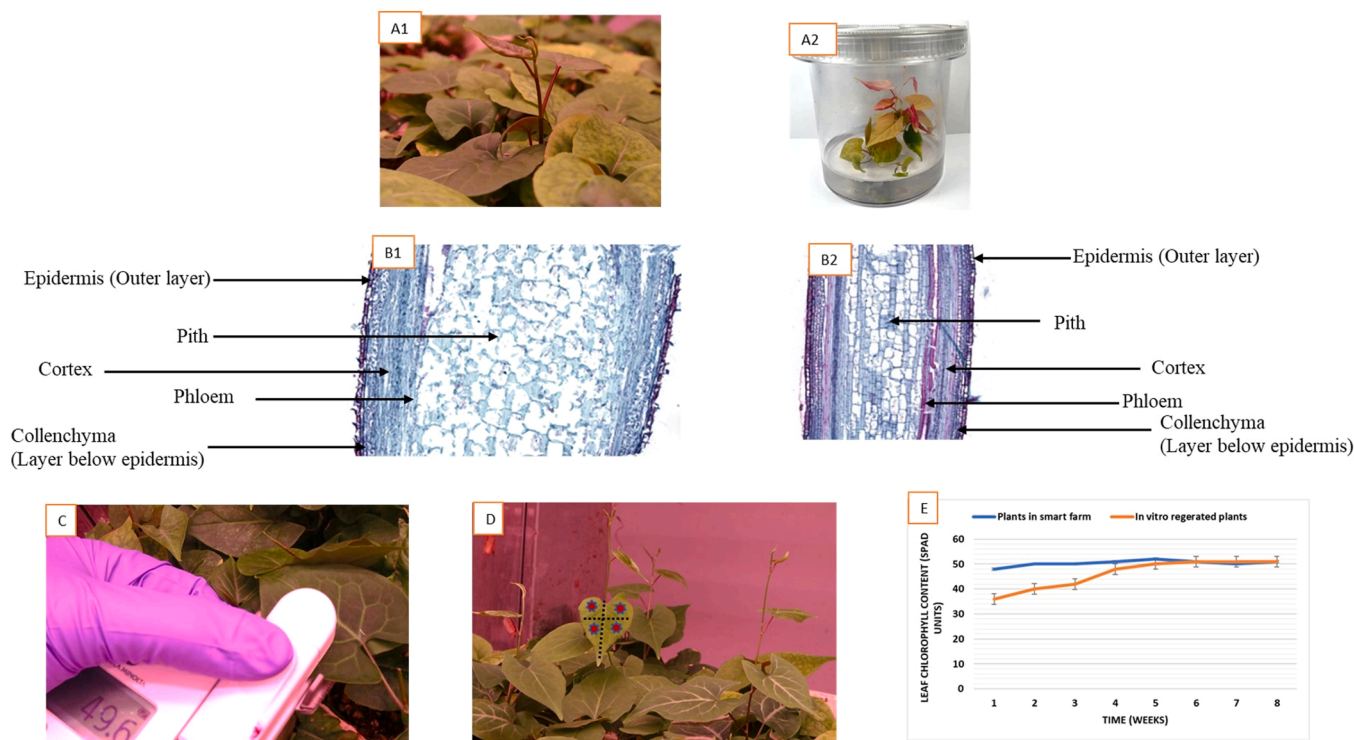


Fig. 8. Comparative studies between the maternal plant and the *In vitro* regenerated *Polygonum multiflorum* plant. (A1) *P. multiflorum* mother plant from phytotron, (A2) *In vitro* regenerated *P. multiflorum* plant. Histological similarities. (B1) Histological features of the maternal plant. (B2) Histological features of *In vitro* regenerated *P. multiflorum* plant. (C) Chlorophyll content of *P. multiflorum* leaf being measured with SPAD meter. (D) Various points on a leaf are considered for the average chlorophyll content of each leaf. (E) Chlorophyll contents of the maternal plant in comparison to those of the *In vitro* regenerated plant across eight weeks.

Table 4
Comparative studies between *In vitro* propagated plants and maternal plants.

SN	Studies	Focus	Methods	Reference
1	Genetic stability and clonal fidelity	Assess whether the <i>In vitro</i> propagated plants are genetically identical (or nearly identical) to the maternal plant. This is essential for confirming that the propagation process has not caused genetic changes, such as soma clonal variation.	Flow Cytometry Molecular markers Chromosomal counting (Karyotyping) Random Amplified Polymorphic DNA (RAPD) or Microsatellite Markers Comparative Genomic Hybridization (CGH) Flow cytometry	(Gang et al., 2024; Okello et al., 2021d)
2	Ploidy level comparison	Asses change in ploidy levels		(Gang et al., 2024)
3	Morphological and phenotypic comparison	Compares the external traits of <i>In vitro</i> propagated plants and maternal plants, such as plant size, leaf shape, flowering time, and overall growth patterns. Any significant differences might indicate that the <i>In vitro</i> propagation process has caused phenotypic changes, even if the plants are genetically stable.	Visual observation (Measuring physical characteristics like height, leaf size, flower development, and overall plant form). Statistical analysis (Using parameters such as growth rate and leaf area to compare the phenotypic traits of both plant groups).	(Jogam et al., 2020)
4	Biological and Physiological studies	Compare the biochemical and physiological characteristics of <i>In vitro</i> propagated plants with maternal plants. It focuses on factors like photosynthesis efficiency, stomatal conductance, chlorophyll content, and stress resistance.	Chlorophyll content analysis (Using instruments like a chlorophyll meter to compare chlorophyll levels). Photosynthetic rate measurements (To assess the plant's ability to perform photosynthesis). Biochemical assay (Analyzing key metabolic markers, such as antioxidant levels or enzyme activities, to assess plant health and stress responses) Stress tolerance tests (Assessing resistance to environmental stressors like drought, salinity, or temperature fluctuations).	(Gang et al., 2024)
5	Genetic and Epigenetic studies	Investigate whether <i>In vitro</i> propagation induces epigenetic changes in the plants. This can include modifications in gene expression without changes to the DNA sequence itself. These changes might not be detected by genetic markers but can affect plant behavior or growth.	Gene expression analysis RT-PCR or RNA-seq to examine any differences in gene expression between <i>In vitro</i> propagated plants and maternal plants). DNA methylation studies (To explore epigenetic modifications that could occur due to <i>In vitro</i> culture conditions).	(Jogam et al., 2020)
6	Metabolic profiling	Investigates whether the metabolic profile (e.g., production of secondary metabolites, vitamins, or sugars) of <i>In vitro</i> propagated plants differs from that of the maternal plant.	Gas chromatography-mass spectrometer (GC-MS) analyze volatile compounds. HPLC (identify and quantify secondary metabolites such as alkaloids, flavonoids, or terpenoids). Enzyme activity assay (assess any differences in metabolic enzyme activity, which can influence growth and plant productivity).	(Abdelsalam et al., 2021; Ban et al., 2024)
7	Histological studies	Cellular structure indicating cell size, shape, and arrangement. For example, differences in the organization of vascular tissues, epidermal cells, or mesophyll cells between <i>In vitro</i> and maternal plants can be observed. Other focuses include: Tissue development and differentiation, somaclonal variation identification, growth patterns, root and shoot morphological evaluation, chloroplast and stomatal development and development timing.	Fixation and tissue preparation, staining techniques (make cellular structures visible under a microscope), microscopic examination (light microscopy and electron microscopy), cell division and growth analysis, tissue localization studies (used to localize specific genes or proteins within tissues. These methods can help identify any genetic or biochemical changes in <i>In vitro</i> propagated plants compared to maternal plants), SEM (used to investigate the surface characteristics of plant organs like leaves, roots, or stems. It is particularly useful for examining stomatal density, trichome formation, and surface texture, which can provide insights into how <i>In vitro</i> propagation affects plant development), quantitative analysis of tissue differentiation used to quantify the differences in tissue structure, such as cell size, tissue thickness, and vascular bundle arrangements).	(Banciu and Aiftimie-Păunescu, 2012; Okello et al., 2021a)

GC-MS Gas Chromatography and Mass Spectrometry, HPLC High performance liquid chromatography, RNA-seq. RNA sequencing, RT-PCR Reverse transcription polymerase chain reaction, SEM Scanning electron microscopy

and Domingos da Silva, 2025), bark (e.g., *Wabugia ugandensis* and *P. africana*) (Karani et al., 2013; Komakech et al., 2022; Okello et al., 2021a), Latex (e.g *Ficus insipid* wild) (Mahapatra and Panda, 2012), flowers (e.g., *Aconitum kusnezoffii*, *Lavandula angustifolia*, and *Hibiscus syriacus*) (Coyago-Cruz et al., 2023; Singhuber et al., 2009), seeds and husks (e.g., *Cajanus cajan*, and *Plantago ovata*) (Govindaraghavan and Sucher, 2015; Yang et al., 2020) or derived products such as gum/resins (e.g., *Ferula assafoetida* Linn, and *Boswellia serrata*), (Govindaraghavan and Sucher, 2015; Ravindran, 2024). Harvesting *In vitro* propagated medicinal plants involves several critical steps to ensure minimal damage and maximum preservation of their bioactive compounds. The steps include: (1) timing the harvests at a specific growth stage, when the plant is sufficiently developed but has not fully matured. This is vital for maintaining the stability of bioactive compounds, which may change during different growth phases. Proper timing of harvest ensures the

optimal concentration of the desired compounds. (2) Carefully harvesting the plant materials, whether small plants or those grown from tissue cultures, individual plantlets or parts (such as shoots, roots, or leaves) are gently removed. In the case where the plant has developed in a bioreactor or a flask, the material is extracted carefully without disturbing the growth medium (Alamgir, 2017a; Mehalaine and Chen-chouni, 2021). For *ex vivo*-propagated plants managed in phytotrons and smart farm systems, the harvesting process is more sophisticated and integrates advanced technologies to optimize plant growth, preserve bioactive compounds, and increase yield. These steps include: (1) data-driven harvesting timing, where the ideal time for harvesting is determined not just by the plant's physical appearance but also by analyzing growth data and the expected concentration of bioactive compounds. This data ensures that the plant is harvested at the peak of its medicinal value, (2) harvesting specific plant parts, where precise

algorithms guide which plant part is most productive at the time of harvest. For instance, if roots contain the highest concentration of bioactive compounds, they will be prioritized for harvesting (Alamgir, 2017a; Eguchi et al., 2022; Paul et al., 2022; Zade et al., 2024).

Processing. The processing of medicinal plants involves a series of techniques aimed at extracting, preserving, and enhancing the medicinal properties of plant materials. These processes, rooted in ancient tradition, are important for preparing plant-based remedies in both traditional and modern herbal medicine (Alamgir, 2017d; Liu et al., 2019). A synergistic approach that integrates traditional herbal knowledge with modern processing techniques has the potential to optimize the therapeutic value of the herbs, maximize ingredient yield, and enhance the efficacy, standardization, and scientific validation of plant-based treatments (Jain and Venkatasubramanian, 2014; Manousi et al., 2019). Modern processing techniques that integrate traditional processing methods include steaming, drying, infusion and decoction, fermentation, maceration and percolation, cold processing (for essential oils), enzyme-assisted extraction, ultrasonication, and cryogenic grinding. These techniques are commonly used in scientific research related to herbal medicine (Jha and Sit, 2022). Fong (2012) suggests that combining scientific research in herbal processing with traditional knowledge offers an evidence-based approach of health care, helping to mitigate potential side effects of natural medicine, thereby making herbal remedies safer and widely accepted by patients. This integration enhances the scientific, cultural, educational, and legal aspects of herbal medicine. The processing of herbal medicine involves several stages, including harvesting, sourcing, and post-harvest handling. Post-harvest processing focuses on preserving the physical, chemical, organoleptic, and pharmacological properties of the herbal plant (Addo et al., 2021). Poor post-harvest processing can lead to low-quality raw material, loss of active ingredients, increased microbial load, and undesirable commercial presentation. Ingredient loss can occur through various processes such as metabolite degradation, hydrolysis of active compounds, light-induced decomposition, enzymatic breakdown, heat degradation of thermolabile substances, essential oil volatilization, and microbial contamination by bacterial and fungi (Al Ubeed et al., 2022). The next recommended step after harvesting is washing the herbal raw materials with running water. It is essential to remove soil from rhizomes and roots; only clean, uncontaminated water should be used. Special care should be taken when washing more delicate parts such as seeds. After washing, ensure that all excess water is drained from the herbs before drying. Additional steps in post-harvest handling include garbling (which involves sorting, cleaning, and removing impurities, done before washing), milling and re-milling, sieving, storing, and labeling

(including name of plant, part used, and harvesting date) (Alamgir, 2017b; Ur-Rahman et al., 2019).

Storage. Despite careful harvesting and drying, medicinal plants can still experience a loss of active ingredients due to degradation during storage (Dhulipalla et al., 2023). While the recommended storage duration for leaves and shoot tips is 12 to 18 months, for bark and roots it is 12 to 36 months; some plants may begin to lose their active compounds much sooner (Martinazzo et al., 2009). The longevity of medicinal plant raw materials largely depends on the storage conditions. Proper storage prevents exposure to sunlight, dust, rodents, insects, and other factors that could cause degradation, thereby aiding in the preservation of volatile compounds. The materials should be stored in clean, dry, and undamaged containers. These containers, such as glass jars, should be sealed in a manner that does not react with the plant material or alter its quality. Additionally, containers should be clearly labeled with information such as the scientific name of the plant, the part used, the storage date, and the origin (Ravikumar et al., 2024).

Drying. Drying is a vital step in the post-harvest processing of medicinal raw materials, following the washing process. Plants, particularly herbs, are dried to eliminate moisture and prevent spoilage. Additionally, proper drying helps preserve the plant's medicinal properties, although the method and duration can influence the potency of the bioactive compounds. While some plants, such as those used for essential oils, homeopathic tinctures, or certain extracts like artichoke (*Cynara scolymus*), are processed fresh; most herbal medicine uses dried plant materials (Frutos et al., 2019; Zhang et al., 2022). When drying indoors, factors such as drying time, temperature, humidity, and other conditions need to be adjusted and tailored to the specific plant part (root, leaf, stem, bark, flower, etc.) and the presence of volatile compounds like essential oils. Fresh plant moisture content typically ranges from 60 to 80 %, and drying reduces this to between 5 % and 12 %. The weight loss during drying varies by plant part: leaves lose 20 to 85 %, bark 40 to 65 %, wood 30 to 70 %, roots 25 to 80 %, and flowers 15 to 80 % (Amrutanand et al., 2021; Azizi et al., 2017; Babu et al., 2018; Havlík et al., 2022; Zhang and Davies, 1989). The drying process prevents degradation caused by yeasts, enzymes, and microorganisms, preventing oxidation and hydrolysis reactions. However, drying with heat can lead to the loss of essential oils and other volatile substances as well as degradation of heat-sensitive compounds. Most medicinal plants can be dried at temperatures between 30°C and 60°C, but plants with essential oils or volatile components should be dried at temperatures below 40°C because essential oils and volatile components are heat-sensitive and can easily evaporate or degrade when exposed to high temperatures. Proper air circulation is essential to promote efficient drying (Ebadi et al., 2015; Rocha et al., 2011). The drying method should be determined experimentally for each medicinal plant, as slow drying may lead to undesirable changes from enzymes, fungi, and bacteria, while overly rapid drying could cause the superficial layer to harden, negatively impacting the plant's quality (Tunan, 2012). Chua et al. (2019) describes several drying methods, as outlined below:

1. Open-air drying (in the shade, out of direct sunlight).
2. Drying on frames or in wire-screened rooms.
3. Sun drying (appropriate for fleshy materials).
4. Drying in ovens or solar dryers.
5. Indirect heat drying (e.g., baking, lyophilization, microwave, or infrared drying).
6. Vacuum drying.
7. Spray drying (e.g., for papaya latex and pectin)

Temperature and humidity should be carefully controlled to prevent damage to active chemical constituents. The drying method and temperature choice significantly impact the quality of the final herbal

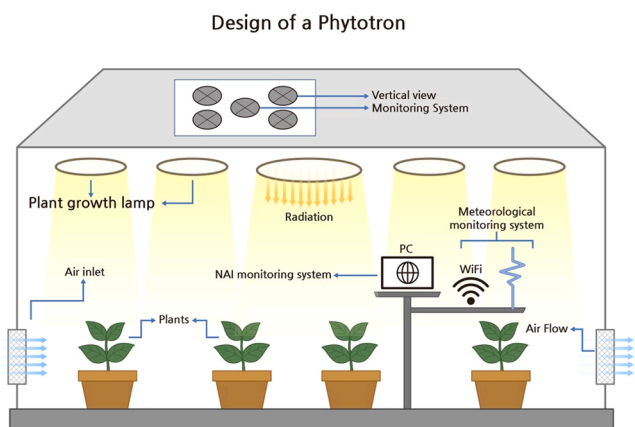


Fig. 9. Innovative phytotron design for optimized growth, research, and sustainable management of medicinal plant species. The basic concept was developed with reference to (Saravitz and Chiera, 2019) and (Thiel et al., 1996).

product. For example, shade drying is ideal for preserving the color of leaves and flowers, and lower temperatures are recommended for materials containing volatile compounds. It is important to record the drying conditions for consistency and quality control (Chua et al., 2019).

Steaming. Steaming is a technique used to soften plant materials and activate specific bioactive compounds. It is commonly used in the preparation of leaves, roots, barks, and tubers. In modern research, controlled steaming is applied to optimize the release and stabilization of bioactive compounds such as saponins, flavonoids, and alkaloids (Ammendola et al., 2020; Wu et al., 2022). For example, in the preparation of ginseng, steaming is used to convert the ginsenoside compounds into more bioactive forms (Xu et al., 2018).

Steam and water blanching. Several blanching techniques have been employed for various purposes with herbs. These include inactivation of enzymes, enhancing drying rates and product quality, expelling air from plant tissue, reducing browning reactions, cleaning plant surfaces, increasing the extraction of bioactive compounds, decreasing oil absorption, removing toxic residues, decreasing microbial load, and eliminating damaged seeds and foreign materials (Dwivedy and Rayaguru, 2013; Xiao et al., 2017). Steam blanching involves exposing herbs to steam for a short period. The steam helps to preserve volatile compounds and prevent degradation of certain active ingredients. For example, red ginseng (*Panax ginseng*) is often steam blanched to preserve its ginsenosides while making it more palatable and stable (Koh et al., 2015). In water blanching, herbs are briefly immersed in hot water (usually boiling) and then rapidly cooled. This method is commonly used for herbs with higher water content or softer textures, such as Chrysanthemum (*Chrysanthemum morifolium*), to preserve its beneficial compounds and ensure the quality of the final product (Xie et al., 2023). The effectiveness of water blanching on bioactive compounds depends on the blanching temperature and time (Qin et al., 2011). Both methods enhance the medicinal properties and shelf life of herbs by preventing enzymatic browning or spoilage during storage. Other blanching technologies include ohmic blanching, infrared blanching, microwave and radio frequency blanching, and high humidity hot air impingement blanching (Xiao et al., 2017).

Steaming and co-steaming with adjuvants and additives. Steaming and co-steaming with adjuvants and additives involves subjecting herbs to steam while incorporating various substances to enhance their properties or extract beneficial compounds. The use of adjuvants and additives in steaming and co-steaming with herbs serves key purposes, depending on the desired outcome. Common objectives include enhancing therapeutic effects, improving aroma, boosting nutrient extraction, preserving and stabilizing compounds, and detoxification of toxic herbs (Ban et al., 2024; Chen et al., 2018; Tiwari et al., 2018). Various processing adjuvants and additives have been applied in the steaming and co-steaming of herbs. These include rice wine, honey, clam powder, sand kernel, wheat bran, brine and wine, black beans, ginger juice, soy beans, turmeric, milk, lemon juice, urine, mint, salt solution, and vinegar (Li et al., 2024b). A study by Meng (2016) has demonstrated that the use of adjuvants during the processing of Rehmanniae Radix enhanced its chemical composition. Additionally, Chen et al. (2018) noted that herbs are usually fried with honey to improve their qi-nourishing and lung-moistening effects. Honey itself may also have antitussive properties, which likely contribute to the synergistic increase of therapeutic properties in herbs, beyond its impact on volatile oil composition. Moreover, research by (Ban et al., 2024) indicates the effectiveness of co-steaming process of *P. multiflorum* with additives. Thus, adjuvants and additives are commonly used to balance the therapeutic efficacy, maximize the effectiveness of the herbs, and target specific therapeutic goals, for overall wellness (Chen et al., 2018).

Boiling. Boiling herbs, a common practice in herbal medicine, involves immersing plant parts, such as roots, bark, or stems, in water and heating them to extract their active compounds. This process, known as decoction, is particularly effective for tougher plant materials that require prolonged exposure to heat to release their medicinal properties. Boiling helps break down the plant's fibrous components and extract both water-soluble and heat-stable compounds, making it ideal for treating conditions such as digestive issues, colds, and inflammation. The resulting liquid can be consumed as a tea or tonic for therapeutic purposes (Hlatshwayo et al., 2025). Additionally, boiling aids in detoxifying toxic plants. Happy et al. (2025b) notes that various ancient dynasties in East Asia have used boiling methods to detoxify *A. kusnezoffii* Reichb, a toxic yet highly valuable medicinal plant, making it safe for human use.

Herb plus herb/spices combinations

The combined application of herbs is a key characteristic of TCM. In TCM, a formula is divided into four categories: monarch (main) drugs, minister drugs, assistant drugs, and guide drugs. Moreover, in the TCM theory, every herbal medicine in formula is ascribed a property, such as "cold," "cool," "neutral," "warm," or "hot." "Cool" and "cold" herbs are used to treat heat-related conditions such as high fever, strong sweating, and strong thirsty, while "warm" and "hot" herbs are used for cold related conditions such as cold limbs, aversion to cold, and watery diarrhea (Ergil and Ergil, 2009; Wang et al., 2013). The SH approach integrates TM into the modern process by combining herbs with other herbs and herbs with spices during processing. This involves carefully drying, grinding, and sometimes fermenting the herbs together to preserve their flavor, aroma, and medicinal properties. Unique combinations of herbs are often used to achieve mutual reinforcement, assistance, restraint, and detoxification. Zou et al. (2023) demonstrates that combining *Paeonia lactiflora* Pall. 9 g, *Asarum sieboldii* Miq 6 g, *Zingiber officinale* Rosc. 6 g, *Glycyrrhiza uralensis* Fisch processing with honey 6 g, *Cinnamomum cassia* Presl 9 g, *Schisandra chinensis* (Turcz.) Bail. 6 g, with 9 g of *Pinellia ternate* (Thumb.) Breit. help in dispersing cold from the exterior of the body, warming the lungs, and dissolving fluid. Additionally, combining *P. ternate* with *Zingiberis* (Ginger) enhances the overall efficacy of herbal formulations and improves nerve activity (Nijima et al., 1998). Furthermore, combining *Aconitum* species with other herbs such as *Radix Glycyrrhizae* (Shen et al., 2011), *Rhizome atracylodes* (Xin et al., 2011), *diammonium glycyrrhizinate* (Chen et al., 2009), and *paeoniflorin* (Fan et al., 2012) improves the pharmacokinetics and reduce the toxicity of *Aconiti* alkaloids, hence improving its efficacy. Herb combination, also referred to as "herb couple," describes the compatibility between two or more herbs. However, some herb combinations are regarded as "combination taboo" due to their potential adverse interactions between their active compounds. These interactions can reduce the efficacy of the herbs, increase toxicity, and cause unexpected side effects (Happy et al., 2025b; Jin'ao et al., 2012). For example, Singhuber et al. (2009) notes that a combination of *Radix Aconiti* with *Rhizoma Pinelliae* (Banxia), *Fructus trichosanthis* (Tianhuafen), *Bulbus Fritillariae* (Beimu), *Radix Ampelosis* (Bailian), and *Rhizoma Bletillae* (Baiji) is considered a combination taboo. In addition to herb-to-herb combinations, several studies emphasize the benefits of combining herbs and spices during processing. Van Hecke et al. (2017) highlights how such combinations can help reduce lipid oxidation.

Grinding

Grinding is used to reduce the particle size of medicinal plant raw materials, enhancing their suitability for extraction. When raw materials are processed in their whole form or large fragments, extraction is often incomplete owing to the poor penetration of the solvent into the plant tissues. This inefficiency arises because cell membranes act as barriers hindering solvent penetration (Ngo et al., 2018; Ravikumar et al., 2024). By grinding or partially breaking down the raw materials, the cell

membranes are disrupted, facilitating easier and more efficient dissolution of the cellular components into the solvent. However, excessive grinding that results in fine powder can pose challenges during extraction. In the percolation process, the powder may compact, obstructing solvent flow and leading to incomplete extraction. In maceration, fine particles may pass into the extract, causing it to appear cloudy. Typically, milling is preceded by screening to remove impurities, such as large wood particles or metal fragments, ensuring the raw materials are free from foreign matter (Gao et al., 2020; Lomovsky and Lomovsky, 2011).

Extraction, separation, and characterization

Extraction and separation serve as the foundation step in the discovery of compounds from natural resources. These processes provide the basis for subsequent stages, such as further separation and characterization (Vuorela et al., 2004). noted by Rasul (2018), the extraction process involves isolating natural products from a mixture, commonly using solvents to separate the desired components based on differences in solubility, volatility, or affinity. This process follows selective and standard procedures. In the SH approach, various steps are involved in extracting source materials to provide samples suitable for HPLC analysis. These steps include harvesting medicinal plant parts (such as roots, rhizomes, leaves, and flowers) from the phytotron, washing, drying, or freezing the raw materials, grinding, and finally extracting. Kumari and Kotecha (2016) emphasize that these processes aid in obtaining a homogenous sample, increasing the surface area in contact with the solvent, hence improving the kinetics of analytic extraction. Specific solvents are used in the extraction of medicinal raw materials. Green extraction (eco-friendly) solvents (Chemat et al., 2019) and organic solvents (Lefebvre et al., 2021) are commonly used to extract secondary metabolites from plant materials. While organic solvents are often effective in dissolving a wide range of substances, their potential negative effects raise concerns (Roy, 2014). Therefore, green extraction solvents are preferred for extracting a wide range of secondary metabolites, as they do not harm human health and the environment. According to Hashemi et al. (2022), green extraction solvents are characterized by low toxicity, minimal environmental impact, high extraction efficiency, and biodegradability, making them an ideal choice.

Use of green-extraction (eco-friendly) solvents. Green extraction refers to techniques of extracting compounds from plant materials using natural solvents. It focuses on developing extraction processes that minimize or eliminate the use of energy-intensive and petroleum-based solvents, while maintaining the safety and quality of the extracts (Chemat et al., 2019). According to Putra Nicky et al. (2023), green extraction, often described as eco-friendly extraction by Shrivastav et al. (2024), addresses contemporary environmental challenges of the 21st century by protecting the ecosystem, ensuring consumer safety. It also encourages academia and industry to adopt more sustainable, eco-friendly, and innovative practices. Common green-extraction techniques include supercritical fluid extraction (SFE), which uses CO₂ and water, microwave-assisted extraction (MAE), and ultrasound-assisted extraction (Picot-Allain et al., 2021). Hashemi et al. (2022) highlights that the green extraction process, rooted in green chemistry, focuses on preventing harm, improving atom efficiency, reducing the use of hazardous chemicals, designing safer solvents, enhancing energy efficiency, utilizing renewable feedstocks, reducing chemical derivatives, and preventing pollution. Key green extraction solvents include green solvent water, supercritical fluids (CO₂ and water), solvents based on organic salts (ionic liquids and deep eutectic solvents), and agro-solvents (e.g., ethanol, glycerol, methyl esters of fatty acids of vegetable oil, and terpenes) (Castro-Puyana et al., 2017; Viñas-Ospino et al., 2023). The green extraction process involves various techniques, including SFE, pressurized liquid extraction, and MAE. Factors influencing the yield and

recovery of natural plants and herb extracts include the solvent-to-sample ratio, extraction time, temperature, pH, additives such as salts and acids, solvent flow rate, pressure, and CO₂ flow rate. The major compounds that are extracted using green extraction include alkaloids, flavonoids, terpenoids, polysaccharides, phenolic compounds, natural pigments, fatty acids, and essential oils (Abdul Aziz et al., 2020; Dandekar and Gaikar, 2002; de Moraes et al., 2020).

Use of organic extractors for the extraction process. Organic solvents are commonly used in the extraction of secondary metabolites from medicinal plants, playing an important role in the evaluation of bioactive compounds and functional properties (Lefebvre et al., 2021). Common organic solvents used in plant extraction include ethanol, methanol, acetone, chloroform, hexane, diethyl ether, ethyl acetate, acetonitrile, toluene, isopropyl alcohol, and dichloromethane. These solvents help in breaking down plant cell walls, facilitating the release of bioactive compounds into the solvent. Solvents are selected based on their ability to dissolve the target compounds while avoiding the extraction of undesirable substances. The choice of solvent and extraction technique significantly affects the efficiency and selectivity of the extraction process, influencing the solubility of plant metabolites, such as alkaloids, flavonoids, terpenes, and phenolic compounds. The extraction yield, extract purity, and extract quality depend on factors such as solvent type, plant material, extraction technique, solvent-to-sample ratio, pH of the extraction medium, agitating or stirring, polarity of compounds, concentration of active compounds, types of extraction vessels, and presence of co-solvents (Joshi and Adhikari, 2019; Lefebvre et al., 2021; Yolci Omeroglu et al., 2019). Extraction is based on the polarity of solvents. Polar solvent (ethanol, water, and methanol) extract alkaloids, flavonoids, polyphenols (Lefebvre et al., 2021; Takla et al., 2018; Yang et al., 1997), non-polar solvents (hexane, chloroform, and diethyl ether) extract, essential oils, fatty acids, terpenes, (Joshi and Adhikari, 2019; Lefebvre et al., 2021; Logan and Lutcavage, 2008), and moderately polar solvents (acetone, ethyl acetate, and acetonitrile) (Joshi and Adhikari, 2019; Lefebvre et al., 2021). Extraction techniques include MAE, maceration, ultrasound-assisted extraction, pressurized liquid extraction, Soxhlet extraction, and SFE (Lefebvre et al., 2021). When extracting thermally sensitive or non-polar compounds, additional methods such as sonication, heating under reflux, and Soxhlet extraction are employed (Jha and Sit, 2022). After extraction, purification of extracts follows, starting with the removal of solvent through evaporating under reduced pressure using a rotary evaporator, which leaves behind a concentrated extract. Filtration is conducted to remove traces of residual solid particles, followed by crystallization, where the extract is dissolved in suitable solvents and slowly evaporated to allow the desired compounds to crystallize. Finally, the extracts are dried, either under vacuum or with desiccant, to eliminate any residual solvents. The purification process ensures that the extract is free from solvent residues and impurities. After extraction, the filtrate is then concentrated in a vial before being injected into the HPLC for separation. (Papadoyannis and Samanidou, 2004). A Guard column is essential during analysis of crude extracts to protect the lifespan of the analytical column from strongly binding components in natural products such as chlorophyll, which can negatively affect the column's performance Qiao et al. (2006).

Another extraction mechanism is acid extraction, used in herbal medicine and chemistry to extract specific compounds from plant materials using an acidic solution (Ngo et al., 2018). This process dissolves or breaks down specific chemical components from raw material into an acidic solvent, which facilitates the release of certain active compounds that may not be soluble in neutral or alkaline conditions. Acid extraction methods include maceration, maceration with continuous stirring, percolation, hydro-distillation, heat reflux extraction, Soxhlet solvent extraction, ionic solvent-based heating extraction, ultrasound-assisted extraction, ionic liquid-based ultrasound-assisted extraction, microwave-assisted extraction, microwave-assisted extraction under

nitrogen pressure, microwave-assisted extraction under vapor pressure, microwave-ultrasound-assisted extraction, SFE, pressurized liquid extraction, enzyme-assisted extraction, and accelerated solvent extraction (Arceusz et al., 2013; Ngo et al., 2018).

Chemical analysis and characterization of bioactive compounds

Phytochemical analysis is conducted using various chromatographic techniques such as paper chromatography, thin-layer chromatography, gas chromatography-mass spectrometry, HPLC, and FT-IR. The compounds obtained are then characterized through various identification techniques such as mass spectroscopy, infrared spectroscopy, ultraviolet spectroscopy, nuclear magnetic resonance spectroscopy (NMRS), thermal gravimetric analysis/differential thermogravimetric analysis, and liquid chromatography-mass spectrometry (LC-MS) (Loconsole et al., 2024; Trivedi et al., 2020).

The use of HPLC. HPLC is a powerful and versatile analytical technique widely used for the identification, quantification, and purification of compounds from complex natural mixtures (Kanu, 2021). In the chemical analysis of herbal extracts, HPLC plays a central role in ensuring quality control by separating components based on their chemical properties and interactions with the chosen stationary and mobile phases. The efficiency of separation is influenced by factors such as the type of column, solvent system, and elution method. For samples with diverse phytochemicals, gradient elution, where the ratio of organic solvent to water is gradually adjusted, improves resolution, increases detection sensitivity, and shortens analysis time (Govindarajan et al., 2019). Following this approach, the leaf extracts of *In vitro* regenerated *Polygonum multiflorum* cultivated under a controlled system, were analyzed using HPLC, offering a precise and detailed approach for identifying and quantifying key bioactive compounds within the plant's roots. HPLC chromatogram (Fig. 10) revealed the separation of five major compounds: (1) Polygoacetophenoside, a unique polyphenolic glycoside with antioxidant and anti-inflammatory properties; (2) Tetrahydroxy Stilbene Glucoside (THSG), known for its anti-aging and neuroprotective effects; (3) Quercetin, a flavonoid with antioxidant, anti-inflammatory, and antimicrobial properties; (4) Emodin, an anthraquinone compound associated with laxative, anticancer, and anti-inflammatory effects; and (5) Physcion, another anthraquinone derivative with antibacterial, anti-inflammatory, and antioxidant properties. The quantification of these compounds was carried out using external standards, employing reference compounds to generate calibration curves for accurate analysis based on peak retention times and areas. While Polygoacetophenoside could not be quantified using a pure reference standard, its presence was confirmed qualitatively by comparing its retention time, peak intensity, and UV-Vis absorption spectrum to those reported in prior studies (Queiroz et al., 2024). The findings were consistent with previous studies by (Rui et al., 2019), who analyzed leaf extracts of *Polygonum multiflorum*, harvested from the natural habitat, utilizing UPLC/ESI-Q-TOF-MS and Multivariate Statistical Analysis, the study successfully isolated several key bioactive compounds, including Polygoacetophenoside, THSG, Quercetin, Emodin, Physcion, among other compounds from the medicinal plant. This validates the consistent presence of these compounds in *Polygonum multiflorum* leaf extracts cultivated under controlled conditions compared to the plants from the natural environment.

A similar study was conducted by (Ban et al., 2024), who analyzed root extracts of *In vitro* regenerated *Polygonum multiflorum*, cultivated under a controlled system of smart farm, utilizing a range of advanced analytical tools, including FT-NIR, HPLC, GC-MS, and UPLC-TOF. The study successfully isolated several key bioactive compounds, including elaidamide, Polygoacetophenoside, phenol, THSG, Quercetin, Emodin, Physcion, among other many compounds. Similarly, several studies have been conducted using HPLC, GC-MS, UPLC-TOF, among other equipment to identify and quantify key bioactive compounds within the

plant roots of *Polygonum multiflorum* harvested from the natural habitat and others cultivated from open fields, and the results have shown the presence of elaidamide, Polygoacetophenoside, phenol, THSG, Quercetin, Emodin, Physcion, among other many compounds (Liang et al., 2010; Liu et al., 2020; Thiruvengadam et al., 2014). This validates the consistent presence of these compounds in *Polygonum multiflorum* root extracts since they appear in plants cultivated under controlled conditions, plants cultivated under open fields and plants harvested from the wild.

The study presented in (Fig. 10) and the research by Ban et al. (2024) not only emphasizes the pharmacological potential of *P. multiflorum*, but also underscores the importance of using advanced analytical techniques like HPLC to explore its medicinal properties. A key takeaway from this research is the confirmation of the role of managing medicinal plants under controlled systems, as these plants can continue to produce their secondary metabolites consistently. This highlights the critical value of controlled cultivation methods in ensuring the sustainable production of medicinal plants, thus safeguarding the ongoing availability of their bioactive compounds for therapeutic use. The integration of such practices could significantly improve the quality and consistency of plant-based medicines, aligning with the SH approaches.

Identification of known compounds and structural elucidation of unknown compounds. Identifying known compounds involves verifying their identity by comparing their physical and chemical properties, such as melting point, boiling point, and spectroscopic data, with known standards or reference materials. In contrast, the structural elucidation of unknown compounds focuses on determining the molecular structure of substances that have not been previously characterized. This process uses techniques such as mass spectroscopy, NMRS, IR spectroscopy, UV/Vis spectra, and X-ray crystallography. These methods provide valuable information on molecular weight, functional groups, connectivity, and the arrangement of atoms within the compounds (Hermann et al., 2023; Molyneux et al., 2019). Chemical structure of medicinal plants managed under the phytotron is as indicated in (Fig. 11).

Integrated biological activities

Yeast and Fungi activities for plant health in the phytotron. In both *In vitro* propagation and the growing of medicinal plants under CE, yeast and fungi contribute significantly to plant health and productivity. Their roles include promoting root growth, enhancing nutrient absorption, supporting disease resistance, and improving stress tolerance. By integrating these microorganisms into precision farming practices, smart farms can optimize conditions for growing medicinal plants while minimizing the need for chemical interventions (Al-Khayri and Naik, 2016; Haniffadli et al., 2024). The use of fungal and yeast-based products in tissue culture and smart farming systems provides a more sustainable and efficient approach to cultivating high-quality medicinal plants. Additionally, yeast and fungi can enhance the production of secondary metabolites in various *In vitro* propagation techniques. Zaker et al. (2015) demonstrates that yeast extracts, acting as a biotic elicitor, promoted the production of cryptotanshinone and tanshinone IIA compounds in adventitious root culture of *Perovskia abrotanoides*. In another study, Silja et al. (2014) has shown that yeast extracts enhanced the accumulation of plumbagin compound in the embryogenic cell suspension cultures of *Plumbago rosea*. Tonk et al. (2016) has found that the elicitation by the *Aspergillus flavus* fungus increased the yield of vincristine and vinblastine compounds through callus biomass growth in *Catharanthus roseus*. Yeast also produces phytohormones such as IAA, which stimulates plant growth by enhancing root development and general plant vigor under *In vitro* and *ex vitro* conditions (Kachalkin et al., 2022). Furthermore, Keswani et al. (2019) noted that many secondary metabolites produced by yeast have antifungal properties that can inhibit the growth of pathogenic fungi, reducing the incidence of

fungal diseases in plants managed under controlled systems. Rahmat et al. (2024) illustrates how *Metschnikowia persimmonesis*, a yeast isolated from Persimmon fruits, inhibited the growth of *Fusarium oxysporum*, a soil-borne pathogen that affects plant growth by causing diseases such as wilt and root rot.

Enzyme inhibition assays. Enzyme assays are instrumental in evaluating the pharmacological effects of herbal extracts by enabling the identification of bioactive compounds and understanding their mechanisms of action. Through the assessment of specific enzyme activities, researchers can gain insight into how plant-derived compounds interact at the molecular level. Commonly targeted include α -amylase, polyphenol oxidase, peroxidase, lipoxygenase, cyclooxygenase (COX), phospholipase, catalase, laccase, peroxidase (POD), lysozyme, and reporter enzymes alkaline phosphate and luciferase (Bisswanger, 2014). Within the SH framework, many *In vitro* propagated medicinal plants have been studied for their enzyme-modulating properties. Approach has been researched for their enzyme activities. The application of enzyme activity assays to *In vitro* propagated medicinal plants acts as a powerful tool in the screening and development of pharmaceuticals, functional foods, and nutraceuticals derived from plants with well-documented antioxidant, anti-inflammatory, anticancer, antibacterial, and antidiabetic properties (Conforti et al., 2008). By understanding enzyme activity at the molecular level, researchers can optimize cultivation and extraction processes to maximize the health benefits derived from medicinal plants (Puri et al., 2012). One such example is a study of COX inhibition by *Codonopsis pilosula*. The study by Yoo and Kim (2013) assessed the impact of a methanol extract of *Codonopsis pilosula* on COX-2 expression in lipopolysaccharide-stimulated RAW 264.7 macrophage cells. The results indicated that the extract inhibited COX-2 expression by approximately 60 %, suggesting a potential anti-inflammatory effect through COX-2 modulation. However, the extract did not significantly inhibit COX-1 expression in the same model. The selective inhibition of COX-2 by *Codonopsis pilosula* extract implies its potential as a therapeutic agent for conditions characterized by inflammation, such as arthritis and other inflammatory disorders. By

targeting COX-2, *C. pilosula* may offer anti-inflammatory benefits with a reduced risk of gastrointestinal side effects commonly associated with non-selective COX inhibitors. Another enzyme inhibition assay was conducted on *P. multiflorum*. One of the medicinal plants managed under the SH system, *P. multiflorum* is a traditional Chinese medicinal plant renowned for its diverse pharmacological properties. Extensive research has been conducted to evaluate its enzyme-inhibitory activities, particularly concerning α -glucosidase, α -amylase, and other enzymes relevant to metabolic disorders. A study by Yang et al. (2014) used ultrafiltration combined with liquid chromatography-tandem mass spectrometry (LC-ESI-MS²) to identify potential α -glucosidase inhibitors from *P. multiflorum* extract. The extract demonstrated a 50 % inhibition concentration (IC₅₀) of 0.0032 mg/mL. Additionally, nine active compounds were identified, including anthraquinones (emodin, aloe-emodin, physcion, and rhein) and stilbene derivatives (resveratrol and 2,3,5,4'-tetrahydroxystilbene-2-O-glucoside). Among these, emodin exhibited the strongest inhibitory activity with an IC₅₀ value of 4.12 Mm. To support its sustainable large-scale production, an *In vitro* propagation protocol for *Polygonum multiflorum* was developed by Kang et al. (2018). Given the plant's significant therapeutic value, this protocol plays a crucial role in promoting its conservation and enabling mass propagation to meet the growing demand for the plant.

Cell *In vitro* assays. Cell *In vitro* assays are laboratory-based experimental techniques used to evaluate the biological and pharmacological effects of substances on cultured cells outside their natural biological context, typically in Petri dishes or multi-well plates. These assays are essential tools in preclinical research, allowing scientists to investigate the cellular responses to various compounds in a CE. In the context of herbal medicine, cell *In vitro* assays are widely used to: Screen herbal extracts for bioactivity (e.g., anti-inflammatory, anticancer, and antioxidant), Assess cytotoxicity and safety of herbal preparations, explore mechanisms of action at the molecular level, Identify bioactive constituents responsible for therapeutic effects (Nag et al., 2012; Siriwatanametanon et al., 2010). *In vitro* studies have demonstrated the potential of *P. africana* (African cherry) in managing benign prostatic

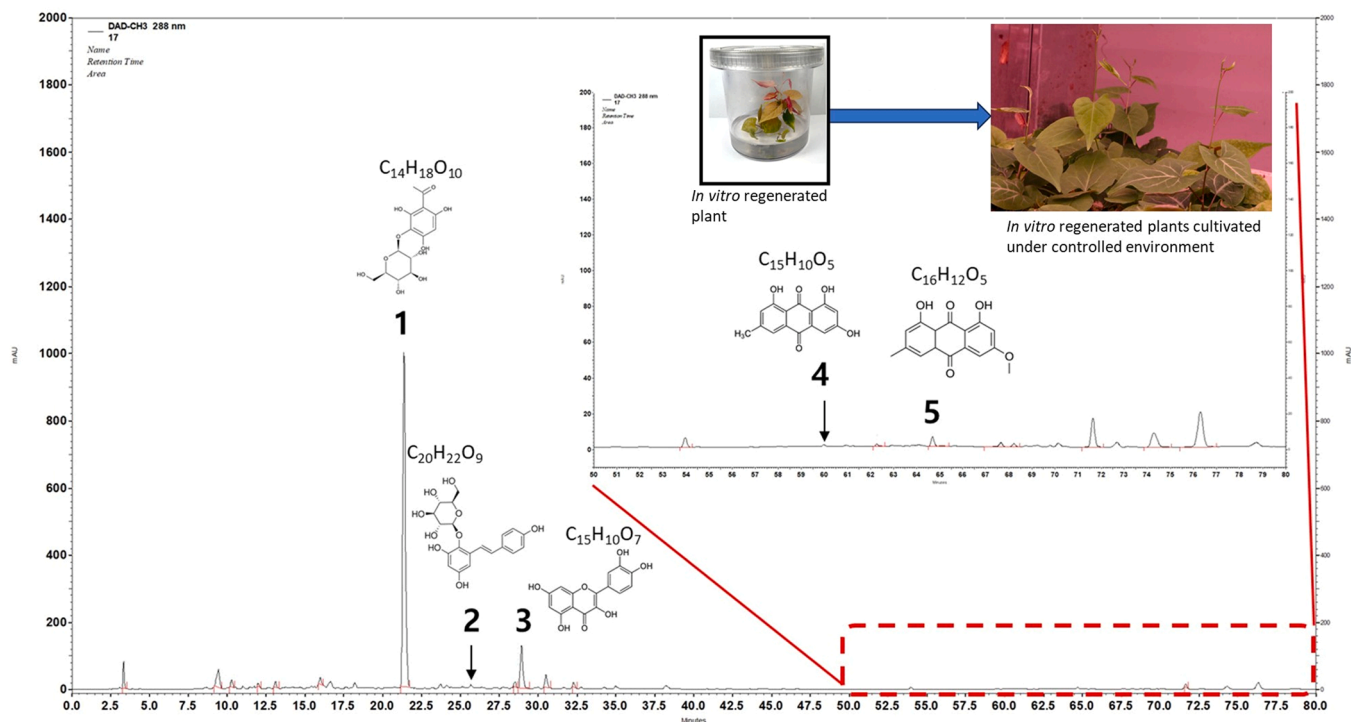


Fig. 10. HPLC chromatogram from *In vitro* regenerated *Polygonum multiflorum* leaves and major compound peaks. (1) Polygoacetophenoside (2) THSG, (3) quercetin, (4) emodin, and (5) physcion.

hyperplasia (BPH) through various mechanisms, including anti-inflammatory effects, apoptosis induction, androgen receptor modulation, etc (Villar et al., 2024b). Various mechanisms have been applied in evaluating the effectiveness of *P. africana* in managing BPH; these include anti-inflammatory effects, apoptosis induction, and androgen receptor modulation (Komakech and Kang, 2019). A study by Villar et al. (2024a) illustrates the use of *P. africana* to inhibit the release of pro-inflammatory cytokines in lipopolysaccharide-stimulated human peripheral blood mononuclear cells. This suggests that the extract may reduce inflammation associated with BPH, while (Komakech et al., 2022) used the apoptosis mechanism, where *P. africana* extracts were observed to induce apoptosis in human prostate cancer cells (PC-3) via

caspase-3 activation. This apoptotic effect may contribute to the reduction of hyperplastic prostate tissue. A study by Namboozee et al. (2022) used the mechanism of androgen receptor modulation, where atraric acid, a compound found in *P. africana*, has demonstrated strong antiandrogenic activity. It decreased cell proliferation in androgen receptor-positive prostate cancer cells (PC-3-AR) and repressed androgen receptor-mediated transactivation, indicating potential for modulating androgen signaling pathways involved in BPH. *In vitro* studies support the therapeutic potential of *P. africana* in managing BPH. Its anti-inflammatory, pro-apoptotic, and androgen receptor-modulating properties suggest that it could be a valuable component in the development of treatments for BPH. *In vitro* studies

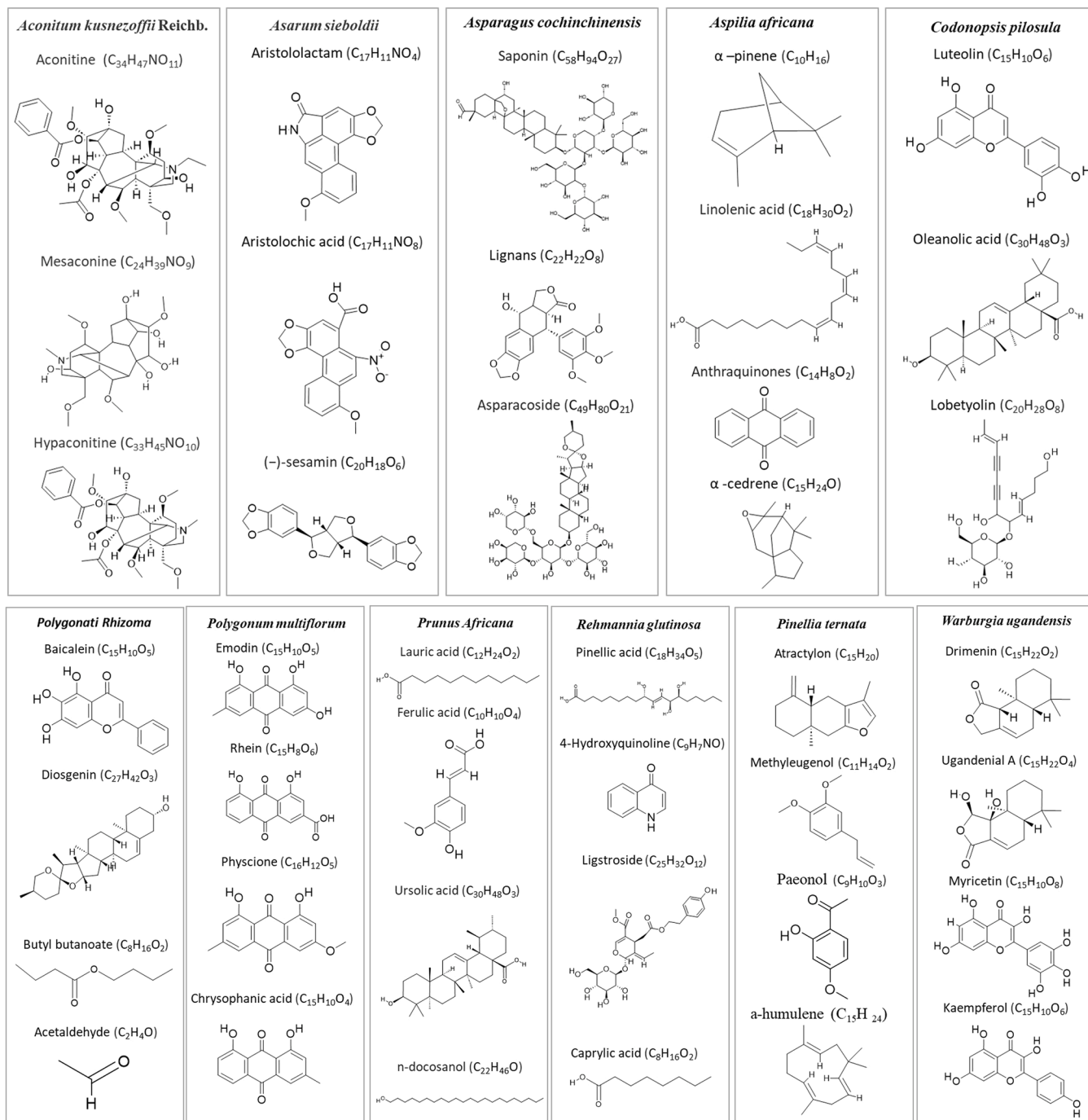


Fig. 11. Major phytochemical structures present in medicinal plants (*Aconitum kusnezoffii*, *Asarum sieboldii*, *Asparagus cochinchinensis*, *Aspilia Africana*, *Codonopsis pilosula*, *Pinellia ternate*, *Polygonati Rhizoma*, *Polygonum multiflorum*, *Prunus Africana*, *Rehmannia glutinosa*, *Warburgia ugandensis*,) managed under the SH.

have highlighted the potential of *P. ternata* in managing peptic ulcers through various mechanisms, including antioxidant activity, anti-inflammatory effects, and enhancement of gastric mucosal protection (Bai et al., 2022). Various *In vitro* mechanisms of action have been applied in identifying the potential of *P. ternata* in managing peptic ulcers. A study by Zhao et al. (2024) presents the antioxidant activities. In this study, polysaccharides extracted from *P. ternata*, such as PTC, PTH, and PTB, have demonstrated significant free radical scavenging abilities. PTC exhibited the highest antioxidant activity, with IC₅₀ values of 1004.1 µg/mL for DPPH, 1584.1 µg/mL for superoxide anion, and 1584.1 µg/mL for hydroxyl radicals. While a study by Yu et al. (2022) presents the *In vitro* assay anti-inflammatory effects of *P. ternate*. This study has shown that *P. ternata* extracts can modulate inflammatory pathways. For instance, the combination of *P. ternata* with other herbs has been reported to reduce levels of pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin (IL)-1β, in cell cultures. *In vitro* studies support the therapeutic potential of *P. ternata* in managing peptic ulcers. Its antioxidant and anti-inflammatory protective properties indicate that it could be a valuable component in the development of treatments for peptic ulcer disease.

In vivo studies. The application of *in vivo* studies significantly contributes to drug discovery in herbal medicine. These studies help to bridge traditional use and modern drug development, supporting evidence-based application of herbal medicine (Zhang et al., 2012). *In vivo* studies have demonstrated the potential of *P. africana* in managing BPH through various animal models, particularly using testosterone-induced BPH in rats. In a testosterone-induced BPH rat model by Jena et al. (2016), 28 male Wistar rats (200 ± 50 g) were used and divided into four groups. Group 1: Negative control (olive oil and saline), Group 2: BPH induction via subcutaneous testosterone propionate (3 mg/kg/day) for 28 days, Group 3: Positive control treated with finasteride (5 mg/kg/day), Group 4: experiment group treated with *P. africana* extract (400 mg/kg/day). Both finasteride and *P. africana* extract significantly ameliorated histopathological changes induced by testosterone, such as epithelial hyperplasia and stromal expansion. Histomorphometric analysis revealed that *P. africana* extract restored prostate architecture, reducing epithelial height and luminal area, and increasing stromal area, comparable to the negative control group. Biochemical assays indicated that *P. africana* extract administration led to decreased serum testosterone levels, reduced prostate weight, enhanced antioxidant enzyme activities, and lowered inflammatory markers. Histological examinations showed a reduction in prostatic epithelial cell proliferation and an increase in apoptotic cell counts, suggesting that *P. africana* extract may exert its effects through anti-inflammatory and pro-apoptotic mechanisms. Phytochemical analysis of *P. africana* bark has identified bioactive compounds such as β-sitosterol, ursolic acid, and ferulic acid, which are believed to contribute to its therapeutic effects in BPH management. These compounds may inhibit 5α-reductase activity, reduce oxidative stress, and modulate inflammatory pathways, thereby alleviating BPH symptoms (Komakech and Kang, 2019). The *in vivo* studies Jena et al. (2016) support the efficacy of *P. africana* in managing BPH, demonstrating improvements in histological and biochemical parameters in testosterone-induced rat models. These findings align with traditional uses and suggest that *P. africana* could be a valuable phytotherapeutic agent for BPH management. (Komakech et al., 2020a) outlines a micropropagation protocol for *P. africana* that enables rapid and large-scale production of this valuable medicinal plant. Given that *P. africana* is endangered and increasingly threatened by overharvesting for its therapeutic benefits, this highlights the importance of adopting an SH approach to promote its sustainable utilization and long-term conservation. In an ethanol-induced gastric ulcer rat model by Izhar et al. (2021), male Wistar rats were divided into four groups: Group 1: Control (normal saline), Group 2: Ethanol-induced gastric ulcer model, Group 3: Positive control treated with omeprazole (20 mg/kg/day). Group 4:

Experimental group treated with *P. ternate* extract (5 g/kg/day). The study has found that *P. ternata* extract significantly reduced the ulcer index compared with the ethanol-induced group. Histopathological examination revealed that the extract promoted mucosal healing and reduced inflammatory cell infiltration. Biochemical assays showed that *P. ternata* extract increased the levels of gastric mucus and enhanced antioxidant enzyme activities, indicating its protective effect on the gastric mucosa. The therapeutic effects of *P. ternata* in peptic ulcer management are attributed to its multifaceted mechanisms: Enhancement of gastric mucus production, antioxidant activity, anti-inflammatory effects, and promotion of mucosal healing (Zou et al., 2023). The *in vivo* studies by Izhar et al. (2021) support the efficacy of *P. ternata* in managing peptic ulcers, demonstrating improvements in histological and biochemical parameters in ethanol-induced rat models. These findings suggest that *P. ternata* could be a valuable phytotherapeutic agent for peptic ulcer management. Likewise, the mass production protocol for *P. ternata* established by (Kim et al., 2020) through the SH approach plays a vital role in securing a sustainable supply of the plant, especially given its demonstrated effectiveness in treating peptic ulcers.

Clinical trials. To gain public trust and bring herbal products into the mainstream of today's health care system, the researchers, the manufacturers, and the regulatory agencies must apply rigorous scientific methodologies and clinical trials to ensure the quality and lot-to-lot consistency of the traditional herbal products. One of the medicinal plants that has undergone clinical trials is *P. africana*. *P. africana*, also known as the African plum tree, is primarily used for treating BPH. Clinical studies by Curtis Nickel et al. (2008) have reported significant improvements in urinary symptoms and flow measures among patients using standardized extracts of *P. africana*. For instance, a meta-analysis of 18 trials involving 1,500 men indicated that *P. africana* moderately improved symptoms and flow rate, especially nocturia, compared with placebo. Another study by Pane et al. (2024) involving 92 male patients found that a combination of *P. africana*, *Urtica dioica*, and *Epilobium angustifolium* extracts, when administered alongside standard alpha-blocker therapy, led to significantly reduced International Prostate Symptom Score (IPSS), increased urinary flow, and improved erectile function. These findings suggest that *P. africana* extracts can be effective in managing BPH symptoms, offering a potential alternative or complementary treatment to conventional therapies. Therefore, the clinical promise of *P. africana*, especially in managing BPH, makes its *In vitro* propagation protocols indispensable. They not only ensure sustainable and ethical supply but also support standardization, drug development, and conservation, aligning ecological health with human therapeutic needs. (Komakech et al., 2020a) presents the micropropagation protocol of *P. africana* with WPM + BAP 1.0 mg L⁻¹ + IAA 1.5 mg L⁻¹ being the optimized media-hormone combination to massively produce the medicinal plant within a short time. As an endangered medicinal plant, *P. africana* continues to face depletion from its natural habitat due to excessive harvesting for its therapeutic properties. This underscores the need for an SH approach to ensure its sustainable use and conservation. In another clinical trial, Feng et al. (2024) compared the effects of Anweiyang Capsule and *P. ternate* decoction to standard therapy for eradicating *Helicobacter pylori* and healing peptic ulcers. The observation group, which received the herbal treatment, demonstrated a total effective rate of 96 %, with 41 patients cured, five showing remarkable improvement, two classified as effective, and two as ineffective. In contrast, the control group had a total effective rate of 80 %, with 28 patients cured, four with remarkable improvement, eight effective, and 10 ineffective. Additionally, the observation group exhibited significant improvements in serum levels of procalcitonin, prostaglandin E2, and C-reactive protein, indicating enhanced therapeutic effects. The herbal treatment also resulted in a higher eradication rate of *H. pylori* (94 % vs. 64 %) and a higher ulcer healing rate (82 % vs.

56 %) compared with the control group. The incidence of adverse reactions was lower in the observation group (4 %) than in the control group (18 %). Similarly, the mass production protocol for *P. ternata* developed by Kim et al. (2020) under the SH approach is essential for ensuring a sustainable supply of the plant, given its proven therapeutic value in treating peptic ulcers. Clinical trials indicate that both *P. africana* and *P. ternata* have therapeutic potential for managing conditions like BPH and peptic ulcers, respectively. However, their use should be approached with caution, ensuring proper dosing and monitoring to minimize potential adverse effects. Further research is needed to establish standardized protocols and long-term safety profiles for these herbal medicines.

In the SH framework illustrated in (Fig. 12), a trusted and comprehensive approach to herbal extract preparation and its integration into biological validation studies is emphasized to enhance efficacy and functional understanding. For systematic research, it is vital to follow a well-defined chronological sequence including harvesting, sample preparation, extraction, and compound analysis with precision and critical attention at each stage.

Toxicology

Despite their clinical and pharmacological potential, many medicinal plants are associated with adverse effects and toxicities. Traditionally, the efficacy and safety of these plants have been evaluated through empirical use and clinical experience, rather than rigorous laboratory-based studies (Singh et al., 2022). Notably, several toxic medicinal plants, such as species of *Aconitum*, have long been recognized within TCM for both their potent effects and their risks. *Aconitum* is always referred to as “the queen of poison” (Chan et al., 2021). Historical documentation from various Chinese dynasties including Song dynasty, Jin Yuan dynasty, Qing dynasty, Ming dynasty, and within other ancient theories like “Yin” and “Yang,” and the five elements and Sasang constitutions theory, highlight the toxicity profile of numerous herbs (Kim et al., 2020; Lee, 2022). Both the Chinese and Korean pharmacopoeias clarify herbs for their toxicity levels ranging from mildly to highly toxic. In traditional categorization, herbs are ranked as superior (least toxic), average, and inferior (most toxic) herbs. (Roy Upton, 2015). To ensure safe use, classical literature and pharmacopoeia provide detailed guidelines for proper processing techniques. *A. kusnezoffii* for example is traditionally used to manage inflammation, arrhythmia, analgesia, and to modulate respiration and pain thresholds. However, its improper use remains a leading cause of herbal toxicity (Kakkar et al., 2023). A study by Lu et al. (2022) investigated the hematological and histological effects of aconitine, a principal toxic compound in *Aconitum*, using 120 mice over 30 days. Mice were grouped into control, low (0.14 $\mu\text{mol/L}$), middle (0.28 $\mu\text{mol/L}$), and high-dose (0.56 $\mu\text{mol/L}$) groups and administered aconitine orally. The results revealed that Organ weights (liver, spleen, lungs, brain) significantly increased in the high-dose group ($p < 0.05$ or $p < 0.01$). White blood cells and granulocytes initially decreased then increased, especially in the high-dose group. Red blood cells, hemoglobin, hematocrit, and blood platelets continuously declined, notably in mid- and high-dose groups. Liver and kidney markers (alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine) increased, indicating organ damage. Histopathological changes were observed in all treated groups, particularly degeneration and necrosis in the heart and cerebellum. The results confirmed a clear dose- and time-dependent toxic effect of aconitine on blood parameters and organ tissues. Although the Chinese and Korean pharmacopoeia specifies the roots of *A. kusnezoffii* as the official source of drugs. Numerous studies have indicated that all parts of the plant contain highly toxic cardiotoxins, such as aconitine, mesaconitine, and hypaconitine, which are C_{19} diterpenoid alkaloids. These alkaloids activate voltage-sensitive sodium channels in the heart and nervous tissues, causing them to become refractory to further stimulation (Happy et al., 2025b; Shen et al., 2020). This mechanism underlies a range of toxicity symptoms, as detailed in Table 5. Poisoning from *A. kusnezoffii*

is often results from improper processing or incorrect doing leading to alkaloid overdose. To address this, various detoxification methods for *A. kusnezoffii* have been extensively studied. For example, boiling the roots hydrolyzes the toxic alkaloids, significantly reducing their concentration. Raw *A. kusnezoffii* contains approximately 0.199 % aconitine, which can be reduced to between 0.0084 % and 0.034 % after proper processing (Li et al., 2022). Another medicinal plant that is known for its therapeutic benefits as well as recognized for its toxic potential is *P. ternata* due to the presence of needle-like calcium oxalate crystals (raphides), lectins, and alkaloids that can cause severe irritation to the mouth, throat, and gastrointestinal tract (Bai et al., 2022; Peng et al., 2022). Its toxic effects include local irritation (raw forms can cause oral and throat burning, swelling, and numbness) (Peng et al., 2022), cardiotoxicity (animal studies have shown that unprocessed *P. ternata* can cause myocardial injury) (Su et al., 2016), systemic symptoms: Prolonged exposure may lead to vomiting, diarrhea, and difficulty breathing (Bai et al., 2022).. Table 5 outlines various medicinal plants, associated side effects, toxicity symptoms, and their respective detoxification mechanisms (Table 6).

The SH approach offers an advanced and systematic framework for detoxifying toxic medicinal plants like *A. kusnezoffii* and *P. ternata*. In the context of *A. kusnezoffii*, SH, can Identify and monitor toxic alkaloid profiles (e.g., aconitine, mesaconitine) through real-time metabolomics during various stages of plant growth and processing, standardize processing techniques (like boiling) by integrating biochemical assays with AI-guided quality control to ensure consistent reduction in toxic compounds, apply transcriptomic and proteomic analysis to understand gene and protein expressions involved in alkaloid biosynthesis and their degradation pathways during detoxification, and validate detoxification outcomes via *In vitro* and *in vivo* toxicity studies, supported by high-throughput biological assays and clinical-grade analytics. Overall, SH transforms traditional detoxification practices into evidence-based, reproducible, and safer processes, supporting the modernization of herbal medicine without compromising its traditional roots.

Various pharmacopoeia have documented poisonous herbs, along with procedures for their processing and detoxification (Shan et al., 2024). A common approach in detoxification involves combining processed toxic herbs with non-toxic herbs, where the latter neutralize or reduce the toxicity of the former. The method can be classified into different categories, including mutual reinforcement, mutual assistance, mutual restraint or mutual counteraction, mutual suppression, and mutual antagonism (Che et al., 2013). In addition to the toxic compounds present in herbs, other potential toxins may arise from factors such as the environment and conditions under which medicinal plants are grown or collected, as well as the storage and transportation conditions and processing methods used. Furthermore, herbal products may be contaminated by biological agents, such as bacteria and fungi, or chemical agents, such as metals, mycotoxins, pesticides, and residual solvents (van Wyk and Prinsloo, 2020).

Application of multi-omics in SH

SH, a next-generation evolution of herbalomics, seeks to bridge traditional herbal medicine with advanced technologies to improve the discovery, standardization, and application of medicinal plants. One of the foundational pillars of this approach is the application of multi-omics studies that include genomics, transcriptomics, proteomics, metabolomics, phenomics, and beyond to gain deep insights into the biological, chemical, and therapeutic properties of herbs and their application for human wellness (Duke et al., 2013; Veenstra, 2021). Medicinal plants are chemically diverse, often composed of complex mixtures of largely “unknown components.” Traditional single-compound analysis is insufficient to fully capture their therapeutic potential. Multi-omics addresses this by simultaneously investigating multiple biological layers, thereby revealing how various components interact with each other and with biological targets.

Multi-omics can be applied across a wide spectrum of medicinal plant research (Liu et al., 2014; Pandita et al., 2021).

Multi-omics application in medicinal plant identification

Incorporating multi-omics analysis into medicinal plant identification enables a more precise and molecularly grounded classification system than traditional morphological or chemical methods alone (Wang et al., 2025). Using genomic and transcriptomic profiling, SH can distinguish between closely related plant species, identify cryptic species, and ensure genetic authenticity, critical for ensuring the safety and effectiveness of herbal products. Through genotype-to-phenotype models (bottom-up) and phenotype-to-genotype strategies (top-down), researchers can map genetic traits associated with therapeutic properties, stress tolerance, or the production of secondary metabolites. For instance, genome-wide association studies combined with transcriptomics and metabolomics have already proven effective in identifying key genes involved in biochemical processes in crop species. These same approaches are now being adapted for medicinal plants to unlock unknown therapeutic traits and novel bioactive compounds (Luo, 2015; Miglani and Kaur, 2025).

Multi-omics in application in tissue culture and *In vitro* propagation

SH integrates functional genomics and proteomics to optimize *In vitro* tissue culture techniques, such as somatic embryogenesis, micro-propagation, and callus induction. These techniques benefit from the identification of regulatory genes and proteins involved in plant growth, differentiation, and stress response pathways (Chin and Tan, 2018). By employing high-throughput omics platforms, SH enables the selection of elite genotypes with desired traits (e.g., high metabolite yield and stress resistance), monitoring of gene expression changes during tissue culture stages, and the identification of key transcription factors and metabolic enzymes to improve regeneration efficiency. This multi-layered data contributes to the development of robust and reproducible propagation protocols that conserve endangered medicinal species while maintaining their bioactive profiles (Komakech et al., 2020b; Reshi et al., 2025).

Multi-omics application in the management of medicinal plants under a controlled system

SH also incorporates phenomics, metabolomics, and ionomics to

enhance the cultivation of medicinal plants in controlled systems such as smart farms, phytotrons, biotrons, and hydroponic units. Multi-omics enables the real-time tracking and modeling of plant physiological responses to environmental variables, such as light, humidity, temperature, and nutrient composition (Satrio et al., 2024). For instance, metabolomic profiling helps optimize environmental conditions for maximum secondary metabolite production. The ionomic studies guide nutrient formulation for hydroponics to support metabolic pathways, and phenomics platforms (using sensors and AI-driven analytics) evaluate plant health, stress symptoms, and growth traits, allowing dynamic management of cultivation environments (Angidi et al., 2025; Buitrago-Villanueva et al., 2025; Satrio et al., 2024). Through systems biology modeling, multi-omics data are integrated to build predictive frameworks that support precision cultivation, a core component of SH. These models enable researchers to simulate how medicinal plants will respond to various conditions, allowing for proactive control and optimized yield and compound consistency. As illustrated in (Fig. 13), several other omics studies have been conducted to explore medicinal plants and herbal medicine approaches, these include flavoromics analysis, phenomics, hormonomics, ionomics, lipidomics, agro-chemomics, glycomics, foodomics, metagenomics, interactomics, toxicogenomics, exposomics, pharmacogenomics, spatial omics, single-cell omics, immunophenomics, computational omics, translationalomics, fungeomics, viromics, and phenomics (Baruah et al., 2022; Dragut et al., 2012; Happy et al., 2025b; Jauhari et al., 2024; Li et al., 2024c; Merra et al., 2024; Mostaffa et al., 2023; Patten et al., 2023; Zavafer et al., 2023; Zhu et al., 2021). By leveraging a panomics platform, SH integrates omics technologies into every stage of medicinal plant research from genetic identification and tissue propagation to controlled cultivation and metabolic enhancement. This fusion of omics and systems biology enhances our understanding of genotype phenotype environment (GPE) interactions, facilitating the development of resilient, high-quality medicinal plants that meet modern standards of efficacy, safety, and sustainability (Li et al., 2024a).

Multi-omics application in processing and chemical characterization

One of the critical domains within SH is the processing and chemical analysis (or characterization) of medicinal plants, which is being revolutionized through the integration of multi-omics studies and synthetic

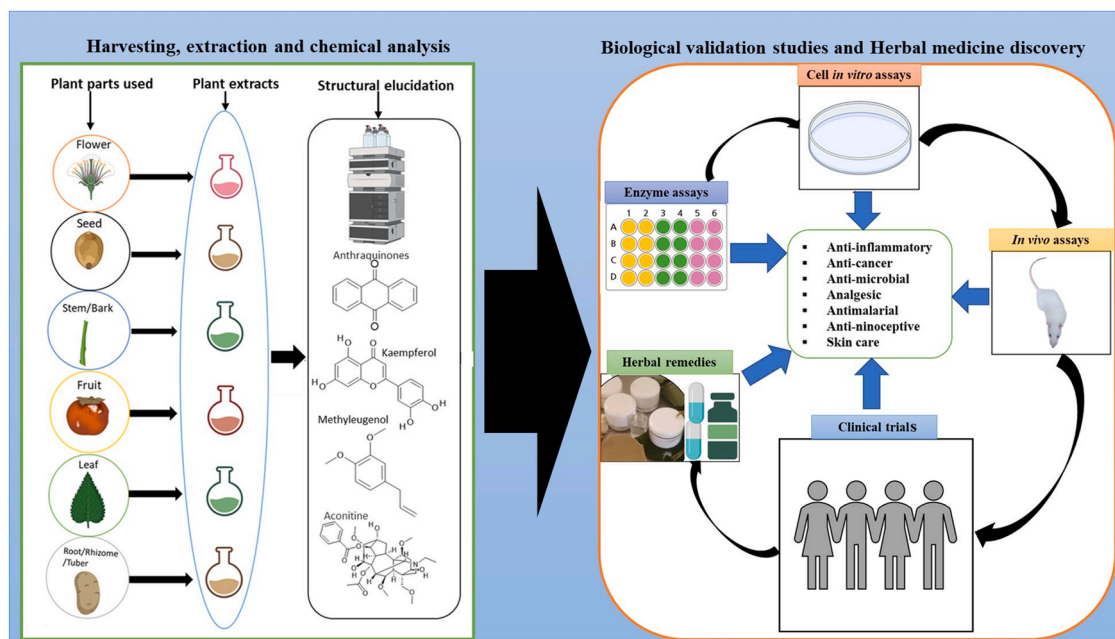
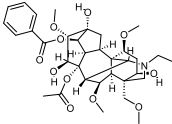
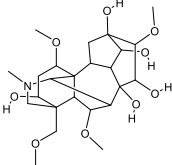
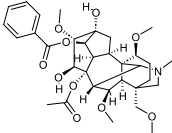
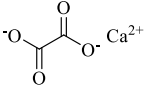
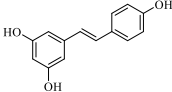


Fig. 12. Comprehensive process of herbal extract preparations and its application in biological validation studies within the framework of SH for enhanced efficacy and functional insights.

Table 5
The Toxicity and Detoxification of toxic herbs.

Herb/Medicinal plant	Toxic compound			Category of toxicity	Side effect/Toxicity symptoms	Detoxification by processing	Statistical analysis /dose-effect relationship	Reference
	Name	Formular	Structure					
	Aconitine	C ₃₄ H ₄₇ NO ₁₁		Highly toxic	Gastrointestinal disturbances, cardiovascular toxicity and arrhythmia, causing toxicity to nervous system, respiratory system, cardiac system, and digestive system. Rapid tingling of hands and feet, vomiting, dizziness, hypotension.	Boiling <i>Aconitum kusnezoffii</i> Reichb. Samples for 2 hours. Steaming or autoclaving <i>Aconitum kusnezoffii</i> Reichb. Crude herbs at 127°C under 0.15 mPa high pressure for 60 to 9 minutes.	Study type: Prescription database Statistical method: SPSS-based dose pattern analysis Findings: 90% of prescriptions ≤ 3.14 g/day dose from historical texts Study type: Animal acute toxicity Statistical method: Dose-tier administration, LD ₅₀ estimation Findings: LD ₅₀ > 1.77 mL/kg via pharmacopuncture in rats	(Chan et al., 2021; Happy et al., 2025b; Kim et al., 2012; Zhang et al., 2018)
	Mesaconine	C ₂₄ H ₃₉ NO ₉						
	Hypaconitine	C ₃₃ H ₄₅ NO ₁₀						
	Calcium oxalate	CaC ₂ O ₄		Highly toxic	Abortion, Tongue numbing, salivating, mucosal irritation, slurred speech, hoarseness and induction of vomiting	Soaking with water until the center of the cut surface is devoid of dry core, decocting with ginger and alum, dried and cutting in slices. Soaking or decocting with 8% alum water to remove the numb-taste, cleaning, cutting in slices and dried. Soaking in water for 7 days to clean the mucus, cutting in slices and stir-frying with ginger juice Processing through boiling, steaming and drying	Study type: <i>In vivo</i> acute toxicity study (ICR mice) Statistical method: Descriptive statistics Findings: LD ₅₀ > 2000 mg/kg; hepatotoxicity at doses ≥ 1000 mg/kg Study type: Metabolomics study in rats Statistical method: Principal Component Analysis (PCA) and Partial Least Squares Discriminant Analysis (PLS-DA) Findings: LD ₅₀ values from ~15.94 mg/kg (crystal) to 5.38 g/kg (powder); shows dose-dependent toxicity	(Lim et al., 2009; Peng et al., 2022; Zhang et al., 2013)
<i>Polygonum multiflorum</i> (He-Shou-Wu)	Resveratrol	C ₁₄ H ₁₂ O ₃		Potentially toxic	Gastrointestinal irritation, diarrhea, electrolyte imbalances, Kidney toxicity, Liver injury (Hepatotoxicity or toxic hepatitis)	Steaming <i>Polygonum multiflorum</i> raw materials for long time between 48 and 72 hours at 100°C to 120°C.	Study type: Single-Dose Toxicity Study Statistical method: Probit analysis (LD ₅₀ estimation) Findings: No mortality observed at doses up to 5000 mg/kg.	(Li et al., 2020; Liu et al., 2019; Min et al., 2025; Yang et al., 2018)

(continued on next page)

Table 5 (continued)

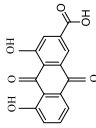
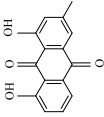
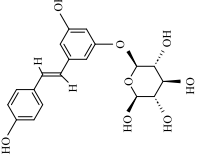
Herb/Medicinal plant	Toxic compound		Category of toxicity	Side effect/Toxicity symptoms	Detoxification by processing	Statistical analysis /dose-effect relationship	Reference
	Name	Formula	Structure				
	Rhein	$C_{15}H_8O_6$		Increased heart defects, tail malformations, and edema at higher concentrations	Study type: Acute Toxicity Study (Zebrafish Embryos) Statistical method: ANOVA (Analysis of Variance)Findings: No mortality observed at doses up to 5000 mg/kg.Findings: Survival Rate: Decreased with increasing concentration.	LD ₅₀ : Estimated for aqueous extract at 2000 µg/mL, ethanol extract at 1500 µg/mL, and emodin at 100 µM.	Developmental Defects: Increased heart defects, tail malformations, and edema at higher concentrations Swimming Behavior: Decreased swimming distance with increasing doses.
	Chrysophanol	$C_{15}H_{10}O_4$					
	Polygatin	$(C_{22}H_{22}O_2)_m(C_{30}H_{40}O_2)_n$					

Table 6
Proposed operational roadmap of integrating Aptamer SELEX, serum pharmacochemistry, molecular docking, in silico modeling, network pharmacology, and nanotechnology in the Smart-Herbalomics approach.

SN	Phase	Key technology	Primary output
1	Medicinal plant identification, sourcing, and propagation	Smart farming, chemical profiling	High-quality raw materials
2	Compound targeting	Aptamer SELEX	Identification of bioactive compounds and binding targets
3	Pharmacokinetics	Serum-pharmacochemistry	Absorption, distribution, metabolism and excretion profiling and compound validation
4	Computational screening	Molecular docking and In-silico modeling	Compound optimization, toxicity prediction, personalization
5	Mechanistic studies	Network pharmacology	Multi-target action maps, synergetic pathway identification
6	Formulation development	Nanotechnology	Stable, bioactivable, targeted herbal formulation
7	Clinical integration	Trial and validation	Evidence-based, patient-specific herbal therapeutics

This SH roadmap provides a structural pathway from plant to patient, integrating traditional knowledge with modern science to accelerate the development of safe, effective, and personalized herbal medicine.

biology. Multi-omics that encompasses genomics, transcriptomics, proteomics, metabolomics, phenomics, and ionomics offers a comprehensive analytical platform to investigate the biosynthesis of specialized metabolites, which are responsible for the therapeutic efficacy of medicinal plants (Zhang et al., 2023b). These techniques allow scientists to map biosynthetic pathways for key bioactive compounds, identify regulatory genes, enzymes, and metabolites involved in secondary metabolism, understand environmental effects on metabolic flux and compound variability, standardize extracts by defining unique chemical fingerprints and quality control markers, and predict pharmacological and toxicological behavior through omics-based modeling (Palazzotto and Weber, 2018; Pandita et al., 2021; Sharma, 2023). In SH, these tools are used to optimize the chemical profiling and quality assurance of herbal products, enabling consistent therapeutic results and ensuring safety compliance (Zhu et al., 2022). Under this domain, in the SH framework, the integration of multi-omics studies offers several advantages, including processing consistency, sustainability, scalability, biosynthesis discovery, etc (Hayes et al., 2024). Moreover, omics-enabled chemical characterization supports standardization protocols, ensures traceability, and helps define the chemical quality benchmarks for herbal products vital for regulatory approval and clinical translation (Sindelar, 2024). Therefore, the integration of multi-omics studies in SH transforms how medicinal plants are processed and chemically analyzed. From identifying key biosynthetic genes and enzymes to reengineering entire pathways in microbial systems, omics tools enable the standardized, scalable, and sustainable production of high-value herbal metabolites (Zhang et al., 2025). Combined with system biology, this approach represents a significant leap toward modernizing traditional herbal medicine for global healthcare systems (Molla and Bitew, 2024).

Multi-omics application in cell In vitro assays

Cell-based assays serve as essential platforms for early-stage screening of herbal extracts and their bioactive constituents (Horvath et al., 2016). Through the application of genomics, transcriptomics, proteomics, and metabolomics, researchers can monitor the global

molecular responses of cultured cells upon exposure to plant-derived compounds. In a study integrating multi-omics approaches Sakagami et al. (2021) investigated the anti-inflammatory properties of the alkaline extract of *Sasa* sp. leaves (SE) using metabolomic analysis and cell-based assays. Methods used included Cell Line [Human lung fibroblasts (HPLF) treated with IL-1 β to induce inflammation], Extract Preparation: [Alkaline extraction of *Sasa* sp. leaves to obtain SE], Metabolomic Analysis: [Quantification of p-coumaric acid levels inside cells using mass spectrometry], Cell-Based Assay: [Measurement of prostaglandin E₂ production as an indicator of inflammation]. Metabolomic Findings: p-Coumaric acid was detected inside HPLF cells at an intracellular concentration of 511 amol/cell, following treatment with IL-1 β . Cell-Based Assay: Treatment with SE significantly inhibited IL-1 β -induced prostaglandin E₂ production in HPLF cells. Comparison with the Pure Compound: The anti-inflammatory activity of p-coumaric acid was less potent than SE, with a chemotherapeutic index (CI) of 0.94–2.9, compared with SE's CI of >96.3. The study demonstrated that the alkaline extract of *Sasa* sp. leaves exhibits notable anti-inflammatory activity, which is likely attributed to the synergistic interactions among its bioactive constituents, including p-coumaric acid. This finding underscores the effectiveness of multi-omics approaches in unraveling the complex biological mechanisms behind the therapeutic effects of herbal extracts. Aligned with the SH approach, this research exemplifies how medicinal plants can be systematically identified, cultivated under CE, and processed through advanced extraction techniques. By integrating multi-omics analyses such as metabolomics to characterize and quantify bioactive compounds, the approach facilitates the discovery of novel therapeutic potentials. Through this comprehensive framework, SH supports the development of safe, development of safe, effective, and personalized herbal medicine.

Multi-omics studies application in in vivo studies

Animal models provide a more integrated biological environment to assess the pharmacological and toxicological outcomes of medicinal

plant extracts. In SH, the application of multi-omics in animal experiments allows for systemic analysis across tissues and organs: Transcriptomic and proteomic analyses in target organs (e.g., liver, kidney, brain) help decode tissue-specific responses and identify biomarkers related to efficacy or toxicity. Metabolomics assesses how plant compounds are absorbed, metabolized, and excreted, offering a deeper understanding of pharmacokinetics and bioavailability. Microbiomics (study of the gut microbiota) has also become integral, especially in understanding how plant compounds interact with the host microbiome to mediate immune or metabolic responses. In an animal model by Li et al. (2021a), *Akebia saponin D* was used to assess its pharmacokinetics, metabolism, and excretion profile and understand the reasons for its low oral bioactivity. The methods that were used included *Quantification*, where a validated LC-MS/MS method was developed for simultaneous quantification of ASD and five key metabolites (m1–m5) in rat plasma, feces, urine, and bile using dextropropofol as internal standard. Metabolite screening, where UPLC-HR/MS (Orbitrap) was used to screen for all possible metabolites in biological samples. Quantification type: Absolute qualification for M0, M3, M4, and M5; semi-quantitative analysis for M1, M2, and other detected metabolites. Animal study design: ASD was administered to rats via intravenous (10 mg/kg) and oral (100 mg/kg) routes, with bio-samples collected at specified intervals. In the results under pharmacokinetics: AUC_{0–t} (exposure): IV (10 mg/kg): 19.05 $\pm$ 8.64 h· μ g/mL, oral (100 mg/kg): 0.047 $\pm$ 0.03 h· μ g/mL. This showed an extremely low oral bioavailability. Under metabolism and absorption, ASD was stable in rat liver microsomes (low hepatic metabolism). Rapid degradation occurred during anaerobic incubation with intestinal contents, suggesting extensive pre-absorption metabolism by gut microbiota. Improved bioavailability was achieved by enhancing lipid solubility and intestinal permeability and inhibiting gut microbiota. P-glycoprotein inhibition had no effect. Under excretion, after IV administration: Urine: 14.79 $\pm$ 1.87 %, Bile: 21.76 $\pm$ 17.61 %, Feces: 0.011 %. These results suggest that urine and bile are primary excretion routes, with extensive gastrointestinal biotransformation. Under

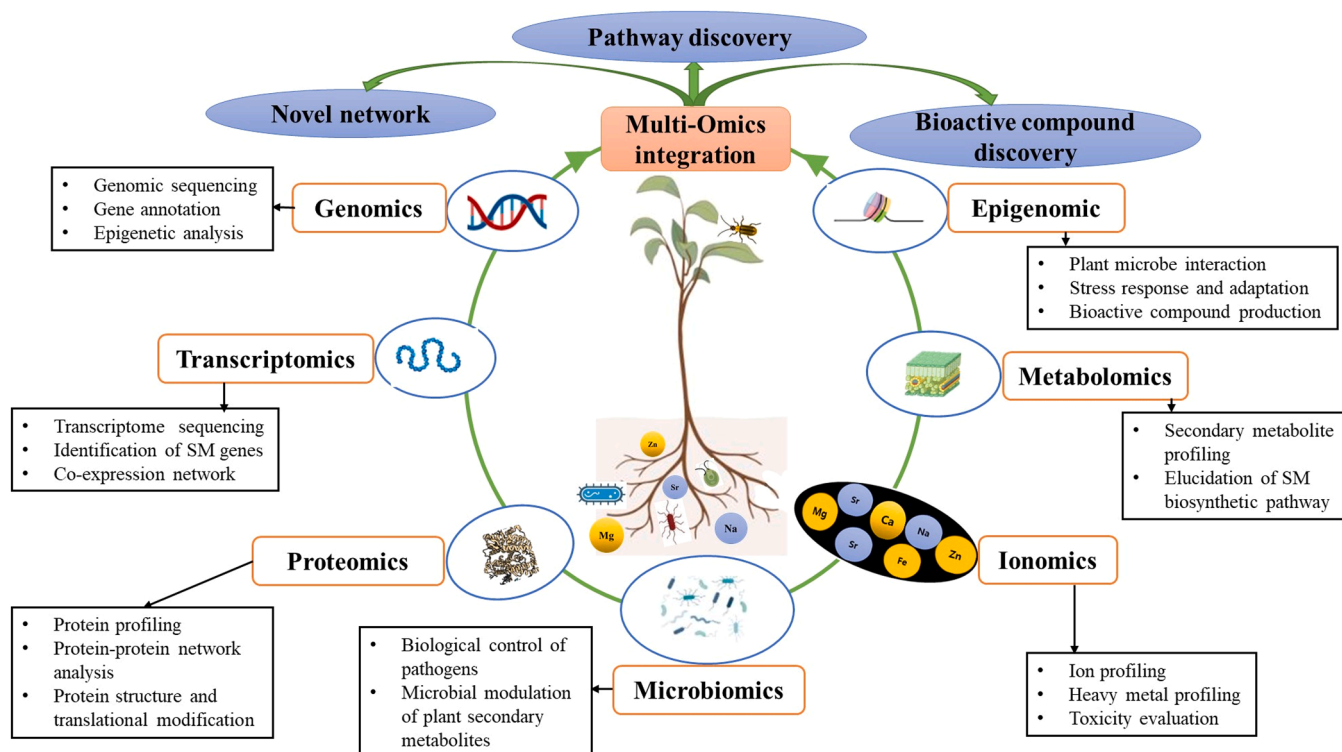


Fig. 13. Integrative multi-omics studies for comprehensive biological analysis and systems-level understanding in medicinal plants.

metabolite identification: 15 possible metabolites detected in bile, feces, and urine. Major biotransformation processes: deglycosylation, demethylation, dehydroxylation, decarboxylation, hydroxylation, and hydrolysis. The study confirms that the very low oral bioavailability of ASD is not due to hepatic metabolism but rather poor intestinal permeability and extensive degradation by intestinal microbiota. Despite its medicinal potential, these pharmacokinetic challenges must be addressed (e.g., via formulation or delivery system improvements) to enhance ASD's therapeutic applicability. This work provides foundational data for further development and standardization of ASD-based plant medicines. This study represents a multi-omics-driven pharmacokinetic investigation, particularly leveraging metabolomics and microbiomics to understand the fate of plant-based bioactive compounds like Akebia saponin D in an animal model. The data generated is crucial for refining drug delivery systems and enhancing the therapeutic applicability of herbal medicines under the SH framework.

Under the SH approach, multi-omics data from cell-based and animal studies feed into a larger pipeline that includes: Identification and propagation of medicinal plants under CE, Chemical characterization and standardization of plant extracts, Predictive modeling of efficacy and safety using bioinformatics and AI, Support for clinical translation by validating molecular biomarkers of action. This integration ensures a seamless progression from laboratory assays to clinical application, helping bridge the gap between traditional knowledge and modern biomedical science. By embedding multi-omics studies into cell-based and animal models, SH enhances the scientific rigor, predictive power, and translational potential of herbal medicine research. These integrated tools not only enable a mechanistic understanding of complex herbal formulations but also drive evidence-based development, quality control, and precision application of plant-derived therapeutics in modern healthcare.

Multi-omics studies in clinical trials

A vital component of SH is the application of multi-omics studies in clinical trials, which enhances our understanding of how medicinal plant extracts interact with the human body at a molecular level. With the evolution of high-throughput single-cell multi-omics platforms, SH now enters a new phase of precision and personalization in evaluating herbal interventions. Clinical trials of medicinal plant extracts benefit significantly from the integration of single-cell multi-omics technologies such as: Mass cytometry (CyTOF), High-dimensional imaging systems (e.g., Hyperion, MIBIScope, CODEX, MACSima), Genomic cytometry platforms (e.g., CITE-seq, REAP-seq), and Single-cell metabolomics and transcriptomics. These technologies allow researchers to analyze immune response, molecular signatures, and cellular phenotypes with unparalleled resolution. They help uncover how plant-based treatments influence immune effector functions, cell-cell interactions, and tissue-specific changes, even at the subcellular level (Hartmann and Bendall, 2020; Yan et al., 2024; Zielinski et al., 2021). By integrating these advanced omics tools, SH enhances clinical research in several ways: Biomarker Discovery and Validation (Multi-omics enables the identification of cellular and molecular biomarkers that predict individual responses to herbal extracts. This improves patient stratification and monitoring during clinical trials, reducing variability and increasing confidence in outcomes. Mechanism of Action (MoA) Elucidation (Multi-omics tools reveal how herbal compounds affect gene expression, metabolic pathways, and protein signaling in real-time, offering a detailed picture of their pharmacodynamics and pharmacokinetics). Personalized and Precision Herbal Therapy (Omics data from patients' immune profiles, metabolomes, and genetic backgrounds can inform customized herbal treatments, aligned with individual health conditions and biological responses). Data-Driven Clinical Trial Design (Omics-guided modeling of biological networks and disease states enables targeted trial designs that are more efficient and statistically robust. These models assist in determining dosage, identifying responsive subpopulations, and avoiding adverse effects. Evaluation of Safety and

Efficacy (Through real-time monitoring of immune cell dynamics, inflammation markers, and metabolic profiles, omics studies improve safety surveillance and efficacy assessments in trials involving plant extracts).

In this study, Patten et al. (2023) used Imaging Mass Cytometry (IMC) to investigate the tumor microenvironment (TME) of untreated patients with follicular lymphoma (FL) enrolled in the Gallium trial (NCT01332968). The study aimed at analyzing the cellular makeup and spatial organization of the FL TME using IMC, focusing on identifying various immune and non-immune cell populations and their interactions within the tissue, in addition to providing insights into disease biology and potential prognostic indicators. Methods used included: *Sample collection*: Formalin-fixed paraffin-embedded biopsies from 100 untreated patients with FL enrolled in the Gallium trial. *IMC Panel*: A 31-plex antibody panel was optimized to identify key cell lineages, including tumor cells, T and NK cells, macrophages, fibroblasts, dendritic cells, endothelial cells, and reticular cells. Functional states such as memory, effector, or regulatory phenotypes were also assessed. *Data Analysis*: 381 high-dimensional images were acquired, with 13 excluded due to suboptimal quality. Over 3.5 million cells across 368 images were analyzed using deep-learning-based cell segmentation and unsupervised clustering algorithms. The results were as follows: Cell Populations Identified 95 distinct cell populations were characterized, including lymphoma subsets with variable expression of CD10, CD11c, and CD80; CD4+ and CD8+ T cell subsets (memory, naïve, exhausted); and various non-lymphoid cells, such as myeloid and stromal cells. T Follicular Helper (Tfh) Cells: A CD4+ CD3+ PD1+ ICOS+ population, indicative of Tfh cells, was identified. On average, Tfh-like cells constituted 1.9 % of cells per image, with considerable variability across samples. Macrophage vs. T Cell Ratios: Significant heterogeneity was observed in the proportions of macrophages and T cells across different samples, suggesting variable immune microenvironments within FL tissues. The study demonstrates the utility of IMC in providing a comprehensive and spatially resolved analysis of the FL TME. The observed heterogeneity in cell phenotypes and their spatial arrangements underscores the complexity of the FL microenvironment and its potential impact on disease progression and treatment response. Ongoing research aims to correlate these findings with clinical outcomes to enhance prognostic capabilities and inform therapeutic strategies. This study exemplifies the integration of advanced imaging technologies in understanding the complex interactions within the TME. By elucidating the spatial distribution and functional states of various cell populations, such research aligns with the principles of SH, which seeks to leverage comprehensive biological data to inform the development and application of herbal-based therapies. Insights gained from such studies can guide the identification of potential herbal compounds that modulate specific immune cell populations or TME characteristics, paving the way for personalized and effective herbal interventions in cancer therapy.

Therefore, multi-omics studies are foundational to the SH framework. They provide a comprehensive, system-level understanding of medicinal plants from genetic identity to clinical efficacy. By incorporating genomics, transcriptomics, proteomics, metabolomics, and other omics, researchers can trace the entire lifecycle of a medicinal plant from identification and propagation to processing, mechanistic evaluation, and therapeutic validation. This integrated approach not only ensures accuracy and reproducibility but also aligns traditional knowledge with modern precision healthcare, ultimately enhancing the efficacy, safety, and sustainability of herbal medicine (Abdullah-Zawawi et al., 2022; Satrio et al., 2024).

Bio-economics of SH

The development of plant-based drugs is considered the next major breakthrough in commercial biotechnologies, with significant potential to deliver affordable, high-quality pharmaceuticals to underserved populations, particularly in developing countries (Chaachouay and Zidane, 2024). The trade in medicinal plants spans three primary levels:

national (within countries), regional (across neighboring borders), and international (global export). At all levels, the value of medicinal plants extends beyond financial gain, contributing to healthcare, cultural identity/preservation, and livelihood security (Hamilton, 2004; He et al., 2018; Hishe et al., 2016). At the core of the SH approach lies a comprehensive research on medicinal plants cultivated under CE, such as smart farms and phytotrons. These cultivated specimens are systematically compared with their wild counterparts to evaluate differences in quality, efficacy, and bioactive compound profiles. The approach integrates both traditional and modern knowledge with cutting-edge technologies, including multi-omics studies (genomics, proteomics, metabolomics, and transcriptomics) to enhance the identification, propagation, and standardization of medicinal plants. Importantly, SH scope extends beyond cultivation and processing by incorporating cell-based assays, animal model studies, and clinical trials into its research pipelines. These experimental stages ensure a scientifically validated understanding of the safety, efficacy, pharmacodynamics, and pharmacokinetics of plant-derived compounds. In cell-based assays, researchers can screen for bioactivity, toxicity, and MoA, while animal studies provide insights into systemic effects, dosage optimization, and therapeutic windows. Clinical trials then validate these findings in human populations, supporting regulatory approval and market integration. From a market and therapeutic perspective, the SH approach merges advanced technology with ethnomedicine to support conservation, sustainable cultivation, mass production, and quality processing of medicinal plants. This creates a more stable supply chain for safer, effective, and standardized herbal therapeutics, aligning both economic and public health outcomes. Extensive research conducted within the SH framework contributes significantly to the discovery of novel plant-based drugs. As noted by Ramawat et al. (2009), medicinal plant research plays an important role in the development of novel medications by uncovering bioactive compounds and therapeutic properties that can be harnessed for new treatments. Additionally, Anand et al. (2019) also document well-known drugs/molecules originating from plant resources, including Aspirin from *Filipendula ulmaria* (L.) Maxim, Codeine from *Papaver somniferum* L., Papaverine from *Papaver somniferum* L., Colchicine from *Colchicum autumnale* L., Digoxin and digitoxin from *Digitalis purpurea* L., Cannabidiol from *Cannabis sativa* L., Tetrahydrocannabinol from *Cannabis sativa* L., Allicin (diallylthiosulfate) from garlic (*Allium sativum* L.), etc. These novel medications derived from in-depth research offer multiple benefits, such as improved therapeutic outcomes, reduction in long-term health care costs, stimulation of biopharmaceutical markets, and enhanced access to effective treatment. Moreover, by integrating cell, animal, and clinical studies with multi-omics technologies, SH promotes cost-effective and evidence-based drug development, reinforcing the pharmaceutical industry's ability to meet global healthcare demand with safe, sustainable, and culturally relevant plants (Alamgir, 2017a).

Future perspective

The future of herbal medicine within the context of SH development lies in the integration of multidisciplinary approaches, merging traditional knowledge with advanced scientific techniques to create more effective, sustainable, and evidence-based therapies (Balkrishna et al., 2024; Gurib-Fakim, 2006). TM systems, such as Ayurveda, Siddha, Uninani, TCM, Japanese traditional herbal medicine (*Kampo*), Korean herbal medicine (Ansari, 2021), Tibetan medicine (*Sowa Rigpa* or *Amchi*) (Samuel, 2023), TM of Uganda (Namuddu et al., 2011), AYUSH in India (Sen and Chakraborty, 2017), Greco-Arab and Islamic medicine (Saad and Said, 2011), Jamu, a TM in Indonesia (Sumarni et al., 2019), naturopathy, osteopathy, homeopathy (Drake and Norman, 2020), Traditional Aboriginal medicine in Australia (Oliver, 2013) and other various indigenous healing medicine practices worldwide have accumulated valuable knowledge regarding the medicinal properties of many plants. However, to gain acceptance, in modern health care, this

traditional knowledge and its remedies must undergo rigorous scientific evaluation. Thus, the integration of innovative techniques such as Aptamer SELEX (Systematic Evolution of Ligands by Exponential Enrichment), serum pharmacology, molecular docking, in silico modeling, network pharmacology, and nanotechnology with TM. This offers a promising pathway for advancing herbal medicine development. The integration of these cutting-edge technologies into SH signifies a transformative shift in herbal medicine. Aptamer SELEX can help personalize treatments (Fang and Tan, 2010; Su et al., 2024) serum pharmacology ensures only bioavailable and effective compounds are used as the technique to elucidate the pharmacokinetics of herbal bioactive compounds, contributing to the optimization of plant-based remedies (Ren et al., 2023). Molecular docking and in silico modeling speed up discovery and improve safety as they are used to predict how small molecules, such as drug compounds, interact with their target proteins or receptors at the molecular level. By simulating the binding of a ligand (usually a potential drug or bioactive compound) to a target protein, molecular docking helps identify the most effective compounds and optimize their binding affinity, selectivity, and overall efficacy. Additionally, molecular docking and in silico modeling simulate interactions between herbal compounds and biological targets (such as proteins, enzymes, and receptors); these models help in identifying the most promising compounds for further testing, thereby reducing the need for extensive experimental work. This speeds up the discovery process, which traditionally relies on time-consuming laboratory trials (Agu et al., 2023; Olğaç et al., 2017; Pinzi and Rastelli, 2019; Yi et al., 2018). Network pharmacology provides a systems-level understanding of efficacy through exploring the complex interactions between drugs, diseases, and targets, considering the diverse components, targets, and pathways involved. This is achieved by integrating key aspects in herbal medicine development that include multitarget drug discovery, systematic understanding of herbal body interaction, identification of active compounds and targets, drug-drug interaction prediction, and pathway enrichment analysis (Zhang et al., 2019; Zhao et al., 2023). Nanotechnology enhances delivery and consistency. Many plant-derived bioactive compounds have low water solubility, which limits their absorption in the body. By using nanotechnology, such bioactive compounds can be encapsulated in nanoparticles (such as liposomes, nanocapsules, or solid lipid nanoparticles), which can enhance their solubility, stability, and controlled release. This makes the herbal compounds more bioavailable, increasing their therapeutic efficacy (Gunasekaran et al., 2014). According to Wang et al. (2014), nanoparticles can improve the solubility and stability of phytochemicals, boost their absorption, shield them from early degradation in the body, and extend their circulation time. These tools enable a comprehensive and precise approach to herbal medicine development. They bridge the gap between traditional healing and modern scientific validation, promoting global acceptance, regulatory approval, and clinical integration of herbal remedies. As these technologies mature and become more accessible, they will play a vital role in creating next-generation herbal medicines that are safe, effective, and tailored to individual needs, thus fulfilling the promise of SH in 21st-century healthcare.

Additionally, the SH looks forward to facilitating drug development. Having conducted enzyme assay, *In vitro* assay, in vivo studies, clinical trials on patients, and integrating Aptamer SELEX, serum pharmacology, molecular docking, in silico modeling, network pharmacology, and nanotechnology in the concept, this will pave the way for drug development since medicinal plants will be sustainably produced using controlled systems.

This SH roadmap provides a structural pathway from plant to patient, integrating traditional knowledge with modern science to accelerate the development of safe, effective, and personalized herbal medicine

Conclusion

Traditional medicine has a long story of serving societies across generations; however, the global interest and demand for herbal remedies now pose a threat to the sustainability of natural biodiversity, as wild plant populations, often the primary source of these medicines, are increasingly overexploited. In response, SH emerges as a forward-looking and sustainable solution to modern challenges in herbal medicine development and conservation. SH represents an advanced, multidisciplinary evolution of the herbalomics concept, offering a comprehensive framework that addresses key limitations in traditional herbal practices, including species misidentification, genetic erosion, phenotypic variability, extract inconsistency, contamination during processing, and a lack of dosage standardization. SH integrates traditional botanical knowledge with cutting-edge technologies in plant science, biotechnology, and systems biology to improve every stage of herbal medicine from plant identification and propagation to drug discovery and therapeutic validation. SH incorporates the use of controlled growing environments, such as phytotrons, smart farms, hydroponics, biotrons, climatron systems, and mist chambers, which enable the mass propagation and cultivation of threatened, endemic, and pharmacologically valuable herbs. These settings support the optimization of plant growth conditions, helping to stabilize genetic and phenotypic traits and improve the yield and consistency of bioactive compounds. Central to this approach is the incorporation of a range of multi-omics technologies, including genomics, transcriptomics, proteomics, metabolomics, epigenomics, microbiomics etc, to deeply characterize both the plant's biology and the body's response to herbal interventions. These technologies offer system-level insights into the molecular mechanisms, synergistic interactions, and personalized therapeutic responses of herbal compounds. Such data are critical for identifying novel biomarkers, validating pharmacological targets, and enhancing the efficacy, safety, and reproducibility of herbal therapies. Furthermore, SH encompasses a robust pipeline of preclinical and clinical evaluation, including cellular assays, enzyme inhibition tests, animal model studies, and clinical trials. This integrated approach enables the transformation of traditional herbal knowledge into evidence-based, standardized, and globally acceptable therapeutic solutions. By adopting this approach, SH can help overcome current bottlenecks in herbal drug development, enhance biodiversity conservation, promote personalized phytomedicine, and align with the global shift toward precision, integrative, and sustainable healthcare. It not only bridges traditional and modern medicine but also ensures long-term accessibility, scientific validation, and consumer trust in plant-derived therapies. Ultimately, SH provides a blueprint for the future of herbal medicine, one that respects its ancient roots while harnessing modern science to meet the needs of a growing global population. While SH offers a groundbreaking and sophisticated framework for the future of herbal medicine, it also faces several important limitations and challenges that must be addressed to ensure its sustainable and equitable implementation across diverse contexts. The implementation of SH requires substantial financial investment due to its reliance on advanced infrastructure such as phytotrons, biotrons, smart farms, and multi-omics platforms, making it potentially challenging in resource-limited settings. High costs associated with equipment, skilled personnel, and ongoing maintenance may hinder scalability, particularly in regions rich in traditional knowledge but economically constrained. Additionally, SH demands interdisciplinary expertise spanning genomics, metabolomics, biotechnology, and bioinformatics which may exceed the capacity of traditional herbal practitioners, creating a knowledge gap that limits broader adoption. Despite the integration of cutting-edge multi-omics tools, our understanding of complex plant synergies and whole-plant interactions remains incomplete. To fully realize its potential, SH must address issues of affordability, accessibility, cultural preservation, and ecological sustainability. A collaborative, inclusive approach bringing together traditional practitioners and modern scientists is essential to ensure SH enhances rather

than displaces traditional herbal knowledge systems. Nevertheless, these challenges can be addressed through strategic investment in capacity-building programs, public-private partnerships, and international collaborations that support infrastructure development and technology transfer in under-resourced areas. Integrating SH training modules into academic and vocational curricula can help bridge the expertise gap, while participatory research and knowledge exchange platforms can ensure active involvement of traditional practitioners. Furthermore, scalable models such as decentralized smart farms and community-based cultivation units can reduce overhead costs and enhance local ownership. By adopting inclusive policies and adaptive frameworks, the scalability and global relevance of the SH concept can be significantly enhanced.

Ethic statement

The current status of smart-herbalomics does not contain any studies with human participants or animal performance.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding statement

This work was supported by Development of Innovative Technologies for the Future Value of Herbal Medicine Resources (KSN2511030) & the National Research Foundation of Korea (NSN2313020: NRF 2023R1A2C3004706, RS-2023-NR077258), Korea Institute of Oriental Medicine through the Ministry of Science and ICT, Republic of Korea. Additionally, its work was also supported by Establishment of Smart Farm Technology Distribution Policy Study for Capacity Enhancement about Functional Plant Resources Production and Processing in Uganda (ERT2311200) Grants from Korea Rural Economic Institute (KREI).

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Kenneth Happy: Writing – original draft, Validation, Conceptualization. **Yeongjun Ban:** Writing – review & editing, Validation. **Joyce Mudondo:** Writing – review & editing, Validation. **Ariranur Haniffadli:** Writing – review & editing. **Roggers Gang:** Writing – review & editing. **Kyeong-OK Choi:** Writing – review & editing. **Endang Rahmat:** Writing – review & editing. **Denis Okello:** Writing – review & editing. **Richard Komakech:** Writing – review & editing. **Youngmin Kang:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Ms EH Kim and Mrs. Mutoni Gloria for helping in illustrations, and Dr. Sungyu Yang for scientific support in

medicinal plant identifications, Ms Subeen Mun and Ms Seyoung Im for the lab work contributions.

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