Bioculture
Bioculture Journal
Bioculture 3(2): 105–125
ISSN 3025-3632

Institute for Advanced Science, Social and Sustainable Future
MORALITY BEFORE KNOWLEDGE

Bridging agronomy and pharmacology the antidiabetic promise of *Oldenlandia*

Nor Isnaeni Dwi Arista[1]*, Yochidamai Akhsanitaqwim[2]
[1] *Department of Agrotechnology, Faculty of Agriculture, Universitas Jenderal Soedirman, Purwokerto, Central Java, 53122, Indonesia;*
[2] *Applied Natural Medicine Study Program, School of Pharma-Medical Science, Toyama University, Toyama City, Toyama Prefecture, 9300151, Japan.*
*Correspondence: nor.isnaeni@unsoed.ac.id

Received Date: November 20, 2025 Revised Date: January 6, 2026 Accepted Date: January 22, 2026

ABSTRACT
Background: The growing global burden of diabetes and the limitations of current treatments require sustainable alternatives. This study aims to evaluate the potential of the weedy genus *Oldenlandia* as a novel, sustainable resource for diabetes management by synthesizing evidence from agronomy, phytochemistry, and pharmacology. **Methods:** A systematic literature review was conducted using major scientific databases. A multidisciplinary search strategy was employed, and the collected data were integrated using narrative synthesis. **Findings:** The analysis shows that *Oldenlandia* species are resilient plants requiring low agricultural inputs. They are rich in bioactive compounds like iridoids and flavonoids, and preclinical studies confirm significant antidiabetic effects, including lowered blood glucose and reduced inflammation via mechanisms such as AMPK-NF-κB pathway modulation. **Conclusion:** *Oldenlandia* presents a promising and sustainable candidate for developing new antidiabetic therapies, bridging traditional use with scientific validation. **Novelty/Originality:** This review offers a novel, integrated perspective that simultaneously evaluates the agronomic feasibility and pharmacological potential of a weed for diabetes treatment, a unique approach not commonly found in existing literature.

KEYWORDS: diabetes mellitus; herbal diabetes therapy; medicinal weeds; natural products; sustainable sourcing.

1. Introduction

Diabetes mellitus (DM) has arisen as a serious public health issue, sometimes referred to as a global epidemic, affecting over 589 million adults worldwide in 2024, with projections indicating a rise to 853 million by 2050 (Magliano & Boyko, 2025). This chronic metabolic disorder, characterized by sustained hyperglycemia, poses a significant threat to global health due to its severe macrovascular and microvascular complications, which include amputation, kidney disease, and heart disease (Abdel-Rahman et al., 2020; Omale et al., 2023). The escalating healthcare burden, estimated at 1 trillion globally in 2024, represents one of the most pressing public health challenges of this time (Magliano & Boyko, 2025).

This illness is characterized by persistent hyperglycemia caused by insufficient insulin production, impaired insulin action, or a combination of the two, and it is associated with long-term consequences such as neuropathy, nephropathy, retinopathy, cardiovascular

Cite This Article:
Arista, N. I. D., & Akhsanitaqwim, Y. (2026). Bridging agronomy and pharmacology the antidiabetic promise of *Oldenlandia*. *Bioculture Journal. 3*(2), 105-125. https://doi.org/10.61511/bioculture.v3i2.2026.2459

disease, and an elevated mortality rate. Despite substantial progress in the development of synthetic antidiabetic drugs, diabetes treatment remains a significant challenge. Numerous existing therapeutic alternatives are expensive, often inaccessible for patients residing in low- and middle-income nations, and are commonly associated with adverse side effects such as hypoglycemia, gastrointestinal issues, and weight gain. Furthermore, in many cases, conventional allopathic treatments fail to provide lasting glycemic control or prevent complications, highlighting the necessity for novel and complementary therapeutic strategies.

There is an urgent need to explore alternative therapeutic strategies, particularly those derived from traditional medicinal plants (Katrolia et al., 2023; Yahaya et al., 2018). Current therapeutic approaches face significant limitations including high costs, adverse effects, and declining efficacy over time, necessitating the urgent exploration of alternative therapeutic sources that are both sustainable and accessible to global populations. Traditional medicine, particularly plant-derived remedies, offers a rich and largely untapped resource of potential anti-diabetic agents, with numerous phytochemicals exhibiting significant therapeutic promise (Roy et al., 2016).

While most discussions of medicinal plants focus on cultivated species, weeds represent an underappreciated but highly promising source of therapeutic compounds. Weeds are often overlooked as nuisance plants due to their invasive growth and competition with crops. However, weeds are a desirable, sustainable resource for natural product research because of their resilience, availability, and flexibility. Weeds are a cheap and sustainable source of phytochemicals because they can grow in marginal habitats, unlike cultivated medicinal species that need extensive agronomic inputs. Therefore, using weeds for medicinal purposes is a novel approach that supports both ecological sustainability and the availability of healthcare.

Among the many weedy genera with ethnomedicinal value, *Oldenlandia* (syn. Hedyotis) has received increased attention. The Rubiaceae family includes around 700 species that are extensively spread in tropical and subtropical regions such as China, Japan, Vietnam, India, Indonesia, and Thailand. *Oldenlandia* species have traditionally been utilized in a wide range of medical systems, including Traditional Chinese Medicine, Ayurveda, Unani, and Siddha. *Oldenlandia* has been used in these traditions to treat a variety of diseases, including appendicitis, hepatitis, tonsillitis, and urethritis, as well as gastrointestinal and gynecological issues (Sahu et al., 2020; Das et al., 2019). Depending on the condition and cultural context, the plants are produced in a variety of ways such as decoctions, tinctures, poultices, powders, and pastes (Das et al., 2019; De Zoysa et al., 2017).

This study is about the comprehensive evaluation of *Oldenlandia* species as sustainable antidiabetic resources, integrating agronomic cultivation practices with phytochemical characterization and pharmacological validation for diabetes management. The subject of this research is particularly important because it addresses the critical intersection of healthcare accessibility, environmental sustainability, and therapeutic efficacy in diabetes treatment. As healthcare systems worldwide struggle with the increasing diabetes burden, there is a compelling need to explore underutilized natural resources that can provide cost-effective and environmentally responsible therapeutic alternatives. Despite the availability of synthetic antidiabetic drugs, there remains a crucial need for novel therapeutic agents due to issues such as drug resistance and adverse side effects associated with long-term use (Alam et al., 2022).

Researchers who have looked at medicinal plants for diabetes management include numerous investigators across different geographical regions, with recent comprehensive reviews highlighting the therapeutic potential of ethnomedicinal plants. Current literature argues that medicinal plants represent a promising frontier for diabetes management due to their multi-target mechanisms of action and relatively lower side effect profiles compared to synthetic drugs (Sindhu et al., 2021). However, researchers also argue that the translation of traditional knowledge into evidence-based medicine requires rigorous scientific validation through standardized phytochemical analysis and controlled pharmacological studies(Pelkonen et al., 2014). They suggest that the integration of

ethnobotanical knowledge with modern pharmaceutical research methodologies is essential for developing reliable plant-based antidiabetic therapeutics.

Debate centers on several critical issues in plant-based diabetes research. Some researchers emphasize the need for isolated bioactive compounds while others advocate for whole plant extracts that may exhibit synergistic effects (Mahankali et al., 2022). Additionally, there is ongoing discussion regarding the most appropriate models for evaluating antidiabetic efficacy and the translation of preclinical findings to clinical applications. Furthermore, questions persist about standardization and quality control of plant-based medicines, highlighting the complexity of developing consistent therapeutic protocols from natural sources.

Despite extensive research on medicinal plants for diabetes, there is still significant work to be done on systematically evaluating underutilized plant species, particularly those classified as weeds, which may harbor substantial therapeutic potential. What has not been adequately addressed is a comprehensive integration of agronomic practices with pharmacological validation for promising species. This gap is particularly evident in the case of *Oldenlandia* species, widespread weeds that have been traditionally used across various cultures for diabetes management but lack systematic scientific evaluation from both agricultural and pharmaceutical perspectives.

Although *Oldenlandia* species have demonstrated promising antidiabetic properties, the absence of research frameworks that quantitatively connect agronomic stress management with phytochemical optimization and pharmacodynamic outcomes constitutes a major barrier to their standardization and clinical translation. This research question therefore focuses on: What is the current state of knowledge regarding the agronomic potential, phytochemical composition, and antidiabetic properties of *Oldenlandia* species, and how can this information be synthesized to support their development as sustainable therapeutic resources? This study presents an examination of the multidisciplinary literature encompassing agronomy, phytochemistry, and pharmacology of *Oldenlandia* species to evaluate their comprehensive potential as antidiabetic agents.

This study is closest to recent comprehensive reviews of medicinal plants for diabetes management, particularly those focusing on underexplored species and traditional remedies(Bhattacharya et al., 2024). However, it differs significantly by specifically addressing the agricultural sustainability aspect alongside pharmacological validation, recognizing that therapeutic plants must also be environmentally and economically viable for large-scale implementation. The contribution of this study is to provide the integrated analysis combining agronomic feasibility, phytochemical characterization, and pharmacological evidence for *Oldenlandia* species as antidiabetic agents, offering a holistic framework for evaluating plant-based therapeutics.

This study is important for several interconnected reasons. Firstly, it addresses the critical need for sustainable and accessible antidiabetic treatments by focusing on widely distributed weed species that require minimal agricultural input and can potentially be cultivated in diverse environmental conditions. Secondly, it provides a comprehensive knowledge synthesis that can guide future research directions and inform evidence-based policy decisions regarding plant-based diabetes management strategies. Thirdly, it contributes to the broader understanding of how agricultural sustainability can be integrated with pharmaceutical development to create environmentally responsible therapeutic solutions that align with global sustainability goals.

This paper presents a systematic review and critical analysis of *Oldenlandia* species, examining their traditional uses, agronomic characteristics, phytochemical diversity, and demonstrated pharmacological activities relevant to diabetes management. The analysis aims to synthesize agronomic, phytochemical, and pharmacological literature on *Oldenlandia* species and discuss their potential as sustainable antidiabetic resources, while identifying critical knowledge gaps and establishing a roadmap for future research opportunities in developing these widespread weeds into standardized, evidence-based antidiabetic therapeutics.

2. Methods

2.1 Database selection and search protocol

Four major electronic databases were systematically searched to ensure comprehensive coverage of relevant literature: PubMed (for biomedical and life sciences literature), Scopus (for multidisciplinary peer-reviewed literature), Web of Science (for high-impact scientific publications), and Google Scholar (for broader academic content including grey literature and regional publications). The search strategy employed a combination of controlled vocabulary terms and free-text keywords designed to capture all relevant aspects of *Oldenlandia* research. Primary search terms included "*Oldenlandia*" and its taxonomic synonym "Hedyotis", and therapeutic applications ("antidiabetic", "hypoglycemic"). Additional phytochemical terms ("phytochemistry", "bioactive compounds", "secondary metabolites").

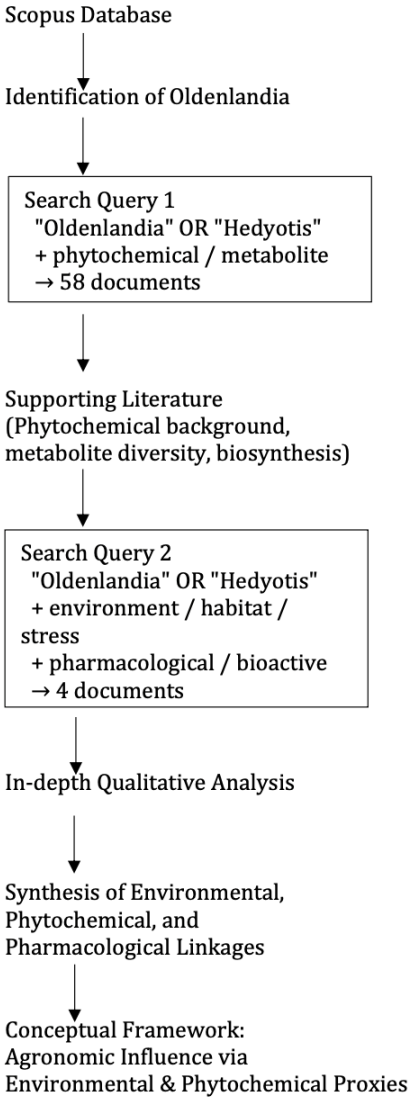

Fig. 1. Database selection framework

A structured literature review for specific was conducted using the Scopus database to examine studies related to *Oldenlandia* spp. (syn. Hedyotis) with particular emphasis on phytochemical, environmental, and pharmacological dimensions. Due to the scarcity of studies explicitly addressing agronomic practices in *Oldenlandia*, agronomic influence was assessed indirectly through environmental and phytochemical proxies, which are widely

recognized determinants of secondary metabolite production in medicinal plants. By integrating insights from both datasets, this review synthesizes indirect agronomic evidence and pharmacological findings to construct a conceptual framework bridging environmental influence and pharmacological potential in *Oldenlandia* spp. This approach acknowledges current limitations in direct agronomic research while providing a scientifically grounded basis for future cultivation-oriented investigations.

2.2 Data synthesis and analysis approach

The extracted data were synthesized using a narrative synthesis approach organized into thematic subsections corresponding to the major research domains: agronomic potential, phytochemical diversity, and pharmacological activities. This approach was selected to accommodate the heterogeneous nature of the evidence base, which spans multiple disciplines with varying methodological approaches and outcome measures. To enhance clarity and accessibility of findings, the synthesized information is presented through a combination of narrative discussion supported by comprehensive tables summarizing key findings and figures illustrating important relationships and trends. This mixed presentation approach allows for both detailed examination of specific aspects and broader pattern recognition across the research domain.

This review will synthesize existing literature on the genus *Oldenlandia*, focusing on species documented for their traditional antidiabetic uses, cultivated properties, and phytochemical profiles, particularly those with reported hypoglycemic activities. The systematic analysis will encompass studies detailing their mechanisms of action at the cellular and molecular levels, including effects on insulin signaling pathways. The methodological approach will also involve a comparative analysis with established antidiabetic agents to ascertain the relative potency and therapeutic advantages of *Oldenlandia* species. This comparative analysis will help identify whether *Oldenlandia* species offer novel mechanisms of action or improved safety profiles compared to current synthetic antidiabetic drugs. This holistic approach will bridge the gap between traditional ethnomedicinal claims and modern scientific validation. Furthermore, the review will consider the potential of bio-affinity ultrafiltration liquid chromatography/mass spectrometry to identify active antidiabetic compounds within *Oldenlandia* extracts, thereby accelerating the isolation of bioactive molecules targeting enzymes like α-glucosidase.

3. Results and Discussion

3.1 Agronomic and ecological perspectives

Oldenlandia is a genus of flowering plants in the family Rubiaceae that is pantropical in distribution. The genus demonstrates remarkable taxonomic diversity, with both *Oldenlandia* and Hedyotis, two of the largest genera within the Rubiaceae, occurring throughout tropical and subtropical regions worldwide and grouped in the Hedyotis-*Oldenlandia* complex, comprising more than 500 species. This taxonomic complexity reflects the genus's evolutionary success across diverse ecological niches.

The morphological characteristics of key *Oldenlandia* species reveal adaptations well-suited to their weedy nature (Guo et al., 2013). *Oldenlandia* herbacea is characterized as an erect annual or perennial herb with much-branched wiry stems, while *Oldenlandia* corymbosa presents as an erect plant, slightly branched, with leaves that are opposite and decussate, linear and sessile, with a serrated stipular collar, and white, axillary flowers. These morphological features contribute to their resilience and competitive advantage in disturbed habitats.

The distribution patterns of *Oldenlandia* species demonstrate their remarkable ecological plasticity and adaptability to diverse environmental conditions. *Oldenlandia*

herbacea is identified as a common weed found throughout the warmer parts of Asia and Africa and in some parts of tropical America, while its native range extends from Africa to the Indian Subcontinent and Andaman Islands, growing primarily in the seasonally dry tropical biome (Guo et al., 2013). This widespread distribution pattern indicates the genus's ability to colonize and establish in varied climatic conditions.

The ecological success of *Oldenlandia* species in agricultural systems is particularly noteworthy. Although reported in cowpea, maize, rice and oil palm fields, it is not known to cause problems, suggesting their role as non-invasive weeds that can coexist with agricultural crops without significant competitive interference (Salaudeen et al., 2022). This characteristic positions *Oldenlandia* species as potentially valuable resources that can be cultivated or harvested from existing agricultural landscapes without disrupting primary crop production.

The adaptability of these species to low-input environments represents a critical advantage for sustainable resource development. Their ability to thrive in marginal lands, roadsides, and disturbed habitats without intensive agricultural inputs makes them attractive candidates for sustainable medicinal plant production (Osewa et al., 2013). This ecological resilience translates directly into economic advantages, as cultivation costs remain minimal while resource availability remains high through their natural proliferation patterns. The ethnobotanical significance of *Oldenlandia* species spans multiple traditional medicine systems and geographical regions, reflecting their broad therapeutic potential. *Oldenlandia* diffusa, prevalent in East Asia and Southern China, is used in traditional Chinese medicine to clear "heat" and to eliminate "toxins", and is used in combination with other herbs for the treatment of hepatitis, snake bites, and tumors of the liver, lung, and stomach (Liang et al., 2008). This traditional use pattern demonstrates the species' integration into sophisticated medical systems with established therapeutic protocols.

The diversity of traditional applications extends beyond the well-documented Chinese medicinal uses. The leaves are used to treat multiple ailments, such as sore eyes, fever, and jaundice, indicating a broad spectrum of therapeutic applications that align with modern understanding of inflammatory and metabolic disorders. *Oldenlandia* corymbosa is also used interchangeably in South China for treating hepatitis and malignant tumors of the liver, lung and stomach, suggesting interspecies therapeutic equivalency within the genus (Archana et al., 2020; Julca et al., 2023; Liang et al., 2008; Wang et al., 2022).

Traditional records also describe the use of *Oldenlandia corymbosa* decoction as a "cold property" plant for fever relief, detoxification, and improved blood circulation (Das et al., 2019; De Zoysa et al., 2017). Its ethnomedicinal use in the treatment of gastrointestinal disorders, jaundice, cough, and infections demonstrates the genus' flexibility (Sahu et al., 2020). The transition from agricultural weed to therapeutic resource represents a paradigm shift that aligns environmental sustainability with healthcare innovation. *Oldenlandia* species exemplify this transformation potential through their unique combination of abundance, accessibility, and bioactive potential. Their status as widespread weeds eliminates the need for dedicated cultivation infrastructure while ensuring consistent supply availability across diverse geographical regions.

The agronomic advantages of utilizing existing weed populations include reduced land competition with food crops, minimal resource investment for production scale-up, and inherent sustainability through natural regeneration cycles. These species contain a wide range of compounds such as iridoids, anthraquinones, triterpenes, phytosterols, and flavonoids, indicating substantial phytochemical diversity that supports their therapeutic potential across multiple biological targets (Zhao et al., 2021). Furthermore, these phytochemical constituents have demonstrated diverse pharmacological activities, including anti-inflammatory, antioxidant, and antidiabetic effects, underscoring their potential for developing novel therapeutic agents for various metabolic and inflammatory conditions.

The agronomic and ecological characteristics of *Oldenlandia* species present compelling arguments for their development as sustainable antidiabetic resources. As

abundant weeds, *Oldenlandia* species offer unprecedented opportunities for low-cost supply chains that can support both research initiatives and eventual therapeutic applications. The agronomy-based approach to resource development provides inherent scalability advantages, as production can expand through natural population management rather than intensive cultivation requirements. This sustainable foundation addresses critical healthcare accessibility challenges while maintaining environmental responsibility. The agronomic perspective thus provides essential scaffolding for the comprehensive evaluation of *Oldenlandia* species as antidiabetic resources, establishing the foundation for detailed phytochemical analysis and pharmacological validation that will determine their ultimate therapeutic potential.

3.2 Pharmacological evidence

More specifically, *Oldenlandia* diffusa has demonstrated significant potential in diabetes management. Experimental studies using gestational diabetes mellitus (GDM) rat models reported that treatment with *Oldenlandia diffusa* reduced blood glucose, improved oral glucose tolerance (OGTT), lowered HbA1c levels, and alleviated pancreatic tissue damage. Histological analysis revealed that therapy reduced pancreatic islet contraction, decreased inflammatory infiltration, and restored insulin secretion, indicating a protective effect in pancreatic architecture and function. Furthermore, *Oldenlandia diffusa* greatly lowered inflammatory cytokines such IL-6, IL-1β, and TNF-α, which are increased in GDM and contribute to insulin resistance. Mechanistic studies suggest that *Oldenlandia diffusa* regulates the AMPK-NF-κB signaling pathway, leading to its beneficial effects on glucose metabolism and inflammation. *Oldenlandia diffusa*'s ability to regulate AMPK, a metabolic enzyme that regulates glucose uptake and utilization, and NF-κB, a key regulator of inflammatory responses, indicates its therapeutic potential in diabetes (Xie et al., 2022).

Clinicians should be cognizant that herbal product use may alter treatment responses, underscoring the necessity for transparent patient communication. Empirical validation of these traditional approaches through phytochemical and clinical studies is vital, particularly for rural communities where reliance on medicinal herbs is considerable. However, existing literature contains significant gaps. Most published papers are fragmented, focused on either pharmacological examination of extracts or ethnobotanical documentation of their applications. As such, herbal medicine is once again attracting renewed attention as a source of new innovative, efficient, and affordable remedies to treat insulin-dependent (IDDM) as well as non-insulin-dependent diabetes mellitus (NIDDM).

Oldenlandia corymbosa was found to contain tannins, phlobatannins, saponins, and flavonoids as its major phytochemical constituents and has demonstrated antioxidant activity. Numerous studies have indicated that medicinal plants possess antidiabetic potential with minimal side effects, making them promising alternatives for diabetes management. Accordingly, the present study aimed to evaluate the antidiabetic effects of *Oldenlandia corymbosa* in alloxan-induced diabetic rats.

Following alloxan administration, diabetic rats exhibited a marked increase in blood glucose levels along with a reduction in body weight. This weight loss may be attributed to enhanced catabolism of fats and proteins, as well as metabolic disturbances and stress that can lead to anorexia and impaired digestion. Treatment with the aqueous extract of *Oldenlandia corymbosa* resulted in a significant increase in body weight compared to untreated diabetic controls. This improvement suggests that the plant may help prevent the degradation of structural proteins and potentially reduce muscle wasting.

The elevation in blood glucose levels observed after alloxan induction may result from decreased insulin secretion by pancreatic β-cells or increased insulin resistance in peripheral tissues. In this study, administration of *Oldenlandia corymbosa* aqueous extract significantly lowered blood glucose levels in diabetic rats while having no effect on normoglycaemic animals. The hypoglycaemic activity of *Oldenlandia corymbosa* may be associated with enhanced activity of enzymes involved in insulin-dependent glucose

utilization or the regeneration of damaged pancreatic β-cells. These effects are likely attributable to the bioactive compounds present in the plant, which may contribute to the restoration of pancreatic tissue function and improved glucose homeostasis (Elwon et al., 2020)

3.3 Integrating agronomy and pharmacology

At the same time, the relationship between its phytochemistry and pharmacological activity has not been fully synthesized across investigations. This lack of integration impedes the creation of a full understanding of how *Oldenlandia* might be transitioned from folk use to evidence-based application. As a result, an integrated assessment encompassing agronomic, phytochemical, and medicinal aspects is urgently required. Such a synthesis would provide light not only on the medicinal potential of *Oldenlandia* spp. in diabetes care, but also on its viability as a long-term, underutilized resource. This study seeks to bridge the gap between traditional knowledge and current science by bringing together findings from agronomy, phytochemistry, and pharmacology, opening the way for the creation of affordable and environmentally sustainable diabetes therapies.

The ecological strategy of *Oldenlandia* species as successful colonizers of disturbed habitats has inadvertently optimized their phytochemical profiles for medicinal applications. As ruderal species, *Oldenlandia* have evolved enhanced secondary metabolite production as defense mechanisms against herbivores, pathogens, and environmental stressors (Divekar et al., 2022). Consequently, this evolutionary pressure has resulted in the accumulation of structurally diverse compounds including iridoid glycosides, anthraquinones, flavonoids, and triterpenoids, the very molecules responsible for their documented anticancer, antimicrobial, hepatoprotective, and immunomodulatory effects. (Kim & Choi, 2021)

The relationship between environmental stress and phytochemical abundance in *Oldenlandia* follows established principles of plant defense theory, whereby plants growing in marginal habitats typically upregulate biosynthetic pathways for secondary metabolites, thereby enhancing their chemical arsenal. This phenomenon explains why wild-collected *Oldenlandia* specimens often exhibit higher concentrations of bioactive compounds compared to plants cultivated under optimal conditions (Sheikh et al., 2024). Recent metabolomic studies have confirmed that plant subjected to moderate drought stress demonstrates elevated levels of ursolic acid and oleanolic acid, both recognized for their anticancer properties (Caser et al., 2018). Similarly, UV-B exposure has been shown to increase flavonoid content, particularly apigenin and luteolin derivatives, which contribute significantly to antioxidant and anti-inflammatory activities (Vanhaelewyn et al., 2020).

This ecological-phytochemical relationship presents important considerations for cultivation strategies. Unlike many medicinal plants wherein domestication leads to diminished potency through genetic bottlenecks and reduced stress exposure, *Oldenlandia* species maintain pharmacological activity even under cultivation, provided that moderate stress conditions are incorporated into growing protocols. This resilience positions them as exceptionally suitable candidates for controlled agricultural production.

Table 1. Agronomic factors influencing phytochemical composition and diabetes-related bioactivities of *Oldenlandia* species

Agronomic actor	Phytochemical Compound(s)	Diabetes-Related Activity	Proposed Mechanism and Relevance
Moderate Drought Stress (Julca et al., 2023)	Ursolic acid	Antidiabetic	Ursolic acid demonstrates potential in enhancing insulin sensitivity and regulating glucose metabolism through modulation of metabolic pathways

Moderate Drought Stress (Julca et al., 2023)	Oleanolic acid	Hypoglycemic	Oleanolic acid exhibits capacity to enhance insulin secretion and reduce insulin resistance, contributing to glycemic control
UV-B Exposure (Chen et al., 2022; Yulizar et al., 2018)	Flavonoids (apigenin and luteolin derivatives)	Antioxidant & Anti-inflammatory	Flavonoids attenuate oxidative stress and inflammation, both recognized as critical pathogenic factors in type 2 diabetes mellitus development and progression
Growth in Marginal Habitats (Huang, 1981; Zhang et al., 2020)	Iridoid glycosides	Hepatoprotective & Immunomodulatory	Iridoids support hepatic function and immune regulation, indirectly contributing to metabolic homeostasis relevant to diabetes management
Environmental Stress (Julca et al., 2023; Mahajan et al., 2020)	Triterpenoids	Anti-inflammatory & Metabolic regulation	Triterpenoids demonstrate capacity to modulate inflammatory pathways and metabolic processes implicated in insulin resistance and diabetic complications
Controlled Cultivation with Moderate Stress	Enhanced secondary metabolite profile (cumulative effect)	Comprehensive antidiabetic potential	Balanced stress conditions optimize the biosynthesis of multiple bioactive compounds, yielding synergistic effects on glucose homeostasis and diabetic complication prevention

Oldenlandia species possess several agronomic characteristics that position them as ideal candidates for large-scale cultivation within pharmaceutical supply chains. Unlike many high-value medicinal plants requiring specific soil conditions, complex nutrient regimens, or intensive management, *Oldenlandia* as a weed thrives in poor soils with minimal inputs (Ripoche et al., 2024). This low-maintenance profile translates directly into reduced production costs and environmental footprints, thereby enhancing economic and ecological sustainability.

Furthermore, these plants demonstrate remarkable adaptability to various cultivation systems, ranging from traditional field production to containerized greenhouse cultivation. Water requirements remain modest compared to conventional crops, with *Oldenlandia corymbosa* and *Oldenlandia diffusa* exhibiting drought tolerance that reduces irrigation demands to leafy vegetable crops cultivated under similar conditions. This resilience to water stress further underscores their potential for sustainable cultivation in regions facing water scarcity. The inherent hardiness and minimal input requirements of *Oldenlandia* species also reduce the reliance on synthetic fertilizers and pesticides, aligning with organic farming practices and further diminishing environmental impact. Such controlled systems can further optimize the production of valuable plant secondary metabolites by precisely managing environmental factors and nutrient delivery (Julca et al., 2023). This controlled cultivation also mitigates the risk of contamination from environmental pollutants and agricultural runoff, ensuring a purer product suitable for pharmaceutical applications (Bączek et al., 2019). The cultivation of *Oldenlandia* species, therefore, presents a compelling model for sustainable agricultural practices, aligning with the growing global demand for natural products that are both environmentally friendly and cost-effective (Marcelino et al., 2023).

The ease of propagation further enhances agronomic feasibility. While seed production and germination rates vary among species, vegetative propagation through stem cuttings provides a reliable alternative that maintains genetic uniformity—a characteristic critical for standardizing phytochemical content. Stem cuttings root readily within 7-10 days under humid conditions, thereby enabling rapid multiplication of elite germplasm selected for elevated bioactive compound content. This allows for the rapid scale-up of promising cultivars, a significant advantage for commercial production where consistent quality and

quantity are paramount (Amissah et al., 2024). This inherent clonality minimizes variability in pharmaceutical precursors, ensuring a predictable and reproducible active pharmaceutical ingredient yield (Munguía-Rosas, 2021).

The transition from wild harvesting to systematic cultivation represents a crucial step in establishing *Oldenlandia* within formalized pharmaceutical value chains. Current domestication initiatives in China have identified *Oldenlandia diffusa* accessions exhibiting higher iridoid content compared to wild populations, thereby demonstrating the genetic variability available for improvement through selective breeding (Liang et al., 2008). These efforts mirror successful domestication programs for other medicinal plants such as Panax ginseng and Catharanthus roseus, wherein targeted selection dramatically increased commercially valuable compound concentrations over successive generations (Wang et al., 2024) (Rojas-Sandoval, 2022). For *Oldenlandia*, marker-assisted selection techniques could accelerate this process by identifying genetic markers associated with high-yielding secondary metabolite pathways.

3.4 Challenges and future directions

Agronomic issues, such as the ecological distribution, abundant potential for sustainable exploration of *Oldenlandia* as a weedy resource, remain underexplored. Pharmacological challenges: Extract standardization, dosage, toxicity, clinical validation. However, existing literature contains significant gaps. Most published papers are fragmented, focused on either pharmacological examination of extracts or ethnobotanical documentation of their applications. Agronomic issues, such as the ecological distribution, abundant potential for sustainable exploration of *Oldenlandia* as a weedy resource, remain underexplored. At the same time, the relationship between its phytochemistry and pharmacological activity has not been fully synthesized across investigations. This lack of integration impedes the creation of a full understanding of how *Oldenlandia* might be transitioned from folk use to evidence-based application.

As a result, an integrated assessment encompassing agronomic, phytochemical, and medicinal aspects is urgently required. Such a synthesis would provide light not only on the medicinal potential of *Oldenlandia* spp. in diabetes care, but also on its viability as a long-term, underutilized resource. This study seeks to bridge the gap between traditional knowledge and current science by bringing together findings from agronomy, phytochemistry, and pharmacology, opening the way for the creation of affordable and environmentally sustainable diabetes therapies.

3.4.1 Challenges

The domestication of *Oldenlandia* species remains in its nascent stages, presenting both opportunities for genetic improvement and risks of genetic erosion. Unlike fully domesticated medicinal plants such as Panax ginseng, for which centuries of selection have established distinct cultivated varieties (Wang et al., 2024), *Oldenlandia* cultivation relies predominantly on wild-collected germplasm with minimal breeding intervention. This situation necessitates urgent implementation of comprehensive germplasm collection programs to capture the genetic diversity present across the genus's broad geographic distribution before habitat destruction and climate change irreversibly diminish this resource. While this diversity represents valuable genetic material for breeding programs, it simultaneously complicates efforts to develop uniform cultivars suitable for standardized pharmaceutical production. Molecular marker-assisted selection offers a potential solution by enabling identification of genotypes possessing desirable allelic combinations for both agronomic traits and biosynthetic pathway genes controlling production of key bioactive compounds.

Furthermore, the reproductive biology of different *Oldenlandia* species requires careful consideration in domestication strategies (Archana et al., 2020; Florentín et al., 2016;

Neupane et al., 2009, 2015). While some species produce abundant viable seeds facilitating seed-based propagation systems, others exhibit low seed set or poor germination rates, necessitating reliance on vegetative propagation. Although vegetative propagation through stem cuttings maintains genetic uniformity—advantageous for standardization—it limits opportunities for genetic recombination and improvement through conventional breeding approaches. Consequently, comprehensive studies of reproductive biology, breeding systems, and genetic architecture are essential prerequisites for developing effective domestication strategies tailored to individual species.

The establishment of dedicated germplasm repositories and field gene banks represents a critical infrastructure requirement for long-term *Oldenlandia* improvement. These repositories should encompass geographically diverse accessions representing the full range of genetic variation within target species, particularly *Oldenlandia diffusa*, *Oldenlandia corymbosa*, and *Oldenlandia umbellata*—the most extensively utilized species in traditional medicine. Ex situ conservation in botanical gardens and research institutions should be complemented by in situ conservation measures protecting wild populations in their natural habitats, thereby preserving the ecological contexts that have shaped their phytochemical profiles.

Yield optimization and agronomic performance, optimizing biomass yield while maintaining or enhancing phytochemical content represents a central challenge in *Oldenlandia* cultivation. As with many medicinal plants, an inverse relationship frequently exists between rapid vegetative growth and secondary metabolite accumulation—a consequence of resource allocation trade-offs between primary and secondary metabolism. This challenge necessitates development of cultivation protocols that strategically incorporate moderate stress conditions to stimulate secondary metabolite biosynthesis without severely compromising overall productivity. For instance, controlled drought or nutrient limitation could potentially enhance the production of desired bioactive compounds, mimicking natural environmental stressors (Azizah et al., 2023). Further research into specific physiological responses of *Oldenlandia* species to various abiotic stresses is crucial for developing optimized cultivation regimes that balance biomass accumulation with secondary metabolite production. Developing improved cultivation strategies for *Oldenlandia* species, including in vitro propagation techniques, could significantly enhance propagation efficiency and contribute to better breeding programs (Ezema et al., 2023).

3.4.2 Pharmacological challenges: From crude extracts to standardized medicines

The translation of traditional *Oldenlandia* preparations into pharmaceutical products necessitates rigorous standardization to ensure consistent composition, potency, and therapeutic efficacy. Unlike synthetic drugs with defined molecular structures and purities, botanical extracts comprise complex mixtures of hundreds of compounds whose relative abundances vary with plant genetics, growing conditions, harvest timing, and processing methods. This inherent variability presents formidable challenges for quality control and regulatory compliance. Moreover, the multi-component nature of herbal extracts means that their biological activity is often not attributable to a single compound, but rather to the synergistic or additive effects of several constituents, further complicating standardization efforts (Heinrich et al., 2022).

Current standardization approaches for *Oldenlandia* products remain inadequate. While some commercial preparations specify total iridoid content or individual marker compounds such as asperulosidic acid, these specifications often lack validation demonstrating that marker compound levels reliably predict overall pharmacological activity. This lack of comprehensive chemical characterization often leads to irreproducible research results and difficulties in interpreting biological activities (Kellogg et al., 2019).

The establishment of authenticated reference standards for key *Oldenlandia* bioactive compounds remains incomplete. While commercial standards are available for common

flavonoids and triterpenoids, many species-characteristic iridoids and anthraquinones lack readily available authenticated reference materials, thereby hindering quantitative analysis. Analytical methodology represents another critical standardization challenge. While high-performance liquid chromatography (HPLC) has become the standard technique for quantifying major *Oldenlandia* constituents. However, variability in extraction techniques and parameters across different studies contributes to discrepancies in reported chemical profiles and biological activities, underscoring the need for harmonized protocols (Wang et al., 2023).

Traditional *Oldenlandia* preparations typically employ crude decoctions or powders at dosages derived from empirical experience rather than systematic dose-response studies. While these traditional dosages provide useful starting points, translating them into standardized extract preparations with defined bioactive compound concentrations requires rigorous pharmacological investigation. This involves establishing robust methods to quantify active compounds and developing reference standards for consistent quality control across batches (Wang et al., 2023).

Preclinical dose-response studies have identified effective dosage ranges for specific *Oldenlandia* extracts and isolated compounds in animal models. *Oldenlandia* diffusa improved glucose metabolism and attenuated inflammation in a streptozotocin-induced gestational diabetes mellitus rat model, mechanisms potentially mediated through the modulation of the activated protein kinase pathway. These findings suggest that *Oldenlandia* could represent a promising therapeutic agent for the treatment of diabetes (Xie et al., 2022).

3.4.3 Future directions

Traditional disciplinary boundaries between agricultural sciences and pharmaceutical research have historically impeded optimal development of medicinal plants. Agronomists typically prioritize yield maximization with secondary consideration for phytochemical quality, while pharmacologists focus on bioactivity with limited understanding of agronomic constraints affecting raw material production. Such integrated approaches would generate data sets linking specific agronomic interventions to downstream pharmaceutical quality attributes, thereby enabling evidence-based cultivation protocols tailored to pharmaceutical requirements. (Marcelino et al., 2023; Marchev et al., 2021). Advanced analytical techniques, particularly metabolomics and systems biology approaches, offer powerful tools for this integrative research. Metabolomic profiling can rapidly characterize the complete small-molecule composition of *Oldenlandia* samples, revealing how genetic variation, environmental factors, and agronomic practices influence the biosynthesis of both target compounds and the broader metabolome (Julca et al., 2023). Furthermore, molecular biology tools enable investigation of the genetic and biochemical mechanisms underlying secondary metabolite production in *Oldenlandia*.

Table 2. Evidence linking agronomic resources to pharmacological applications in plant-based therapeutics

No	Author	Findings	Relationship Between Agronomy and Pharmacy
1	Essa et al. (2012)	Natural compounds derived from diverse plant sources exhibit neuroprotective effects against Alzheimer's disease.	Cultivated plants (agronomy) serve as direct sources of chemical compounds (phytonutrients) that possess pharmacological activity.
2	Zhang et al. (2020)	Traditional Chinese Medicine (TCM) herbs and their active monomeric compounds can be used to treat liver cancer by targeting the Tumor Microenvironment (TME).	Medicinal plants (products of agronomy) provide active compounds for the development of modern anticancer drugs (pharmacy).

3	Smithies et al. (2020)	Engineering of cyclotides) to generate scaffolds compatible with enzymatic cyclization (AEP), enabling large-scale production for pharmaceutical applications.	Agronomy provides biological resources (*Oldenlandia affinis*) containing molecular "blueprints" (cyclotide structures and AEP enzymes). Pharmacy exploits these blueprints for the engineering and production of next-generation peptide therapeutics, establishing a development cycle from natural sources to clinical applications.
4	Ansari et al. (2011)	The potential of several herbs as natural hepatoprotective agents for the treatment of liver disorders.	Medicinal plants (products of agronomy) represent promising raw material candidates for the development of hepatoprotective pharmaceutical agents.

Based on the table, the integral role of agronomy as the foundational source of bioactive compounds that drive pharmaceutical innovation. Across diverse therapeutic areas—including neurodegenerative diseases, cancer, and liver disorders—cultivated and medicinal plants consistently provide phytonutrients, phytochemicals, and complex biomolecules with demonstrable pharmacological activities. The reviewed literature illustrates a continuum from traditional and conventional plant cultivation to advanced pharmaceutical applications, ranging from the identification of natural neuroprotective and hepatoprotective agents to the sophisticated engineering of plant-derived cyclotides as next-generation drug scaffolds. This synergy underscores the importance of integrating agronomic practices with pharmaceutical research to ensure sustainable, high-quality, and scalable production of medicinal plant resources. Future directions should focus on optimizing crop management and breeding strategies to enhance the yield and consistency of bioactive compounds, advancing biotechnological and enzymatic approaches for efficient drug development, and strengthening interdisciplinary collaboration between agronomy, pharmacology, and biotechnology to accelerate the translation of plant-based resources into clinically effective and sustainable therapeutics.

3.4.3.1 Sustainable biorefinery concepts

Initial extraction of high-value pharmaceutical compounds from *Oldenlandia* biomass typically leaves substantial residual material. Rather than treating this as waste, it might be evaluated for secondary applications such as animal feed supplements, biopesticide production (given the documented antimicrobial properties), or even bioenergy production (Jørgensen et al., 2022). Such integrated utilization would improve the overall economics of *Oldenlandia* cultivation while reducing environmental impacts through enhanced resource efficiency. The development of cascading extraction schemes optimized for sequential recovery of different compound classes represents a technical challenge requiring chemical engineering expertise in addition to botanical and pharmaceutical knowledge. However, successful implementation could substantially improve the economic competitiveness of *Oldenlandia*-based products, particularly important for botanical pharmaceuticals competing against synthetic alternatives.

3.4.3.2 Participatory approaches and traditional knowledge integration

Effective *Oldenlandia* development cannot proceed solely through top-down research and development models but must integrate the traditional knowledge and practical expertise of communities with long histories of utilizing these plants medicinally. Traditional knowledge offers invaluable insights often overlooked in conventional pharmaceutical research (Domingo-Fernández et al., 2023). For instance, traditional combination formulas incorporating *Oldenlandia*with complementary herbs may reflect

empirical understanding of synergistic interactions that could inform modern formulation development.

Table 3. Strategic framework for integrating agronomy and pharmacology in the development of antidiabetic herbal medicines

Focus Area	Key Approach	Herbal Medicine Potential	Specific Link to Diabetes
1. Agronomy-Pharmacy Integration	Link cultivation practices directly chemical and pharmacological analysis.	Standardized, potent raw material.	Maximize yield of proven anti-diabetic compounds (e.g., ursolic acid).
2. Advanced Analytical Techniques	Use metabolomics & molecular biology to map chemical composition & pathways.	Quality control based on full phytochemical profile; understand synergy.	Discover novel anti-diabetic metabolites and synergistic combinations.
3. Sustainable Biorefinery	Develop cascading extraction to fully utilize biomass after primary extraction.	Improve economic viability; create co-products (e.g., supplements).	Use residues for diabetic-friendly animal feed or nutraceuticals.
4. Participatory Research & Traditional Knowledge	Integrate indigenous knowledge & practices into R&D, ensuring ethical benefit-sharing.	Discover synergistic formulas & effective processing methods.	Validate traditional combination therapies and preparations for diabetes management.

Similarly, traditional processing methods, such as fermentation, heat treatment, or preparation with specific adjuvants, may alter bioavailability or biological activity in ways not captured by standard extraction protocols. Implementing access and benefit-sharing agreements consistent with international frameworks such as the Nagoya Protocol ensures that *Oldenlandia* development proceeds on ethically sound foundations while incentivizing conservation of both genetic resources and associated traditional knowledge. Furthermore, figure 2 in below illustrated a causal and translational continuum in which agronomic interventions act as upstream determinants of the phytochemical profile of *Oldenlandia*, ultimately shaping its pharmacological efficacy in diabetes management. Environmental and cultivation factors such as moderate drought stress, UV-B exposure, growth in marginal habitats, and controlled cultivation systems are shown to selectively enhance the biosynthesis of key secondary metabolites, including ursolic acid, oleanolic acid, flavonoids (apigenin and luteolin), iridoid glycosides, and triterpenoids. These phytochemical enhancements are mechanistically linked to downstream antidiabetic, antioxidant, anti-inflammatory, and hepatoprotective effects, reflecting improved therapeutic potential. From a future-oriented and actionable perspective, this framework underscores the need to transition from passive plant collection to evidence-based cultivation strategies in which agronomic variables are deliberately optimized to maximize pharmacologically relevant compounds. The future directions include the development of stress-calibrated cultivation protocols, integration of metabolomic profiling to identify agronomy–phytochemical–bioactivity correlations, and the establishment of standardized cultivation guidelines aligned with pharmaceutical quality requirements. Such an approach enables the rational design of agro-pharmaceutical production systems, ensuring consistent bioactive compound yield, supporting clinical translation, and positioning *Oldenlandia* as a scalable, sustainable medicinal crop rather than an opportunistic wild resource.

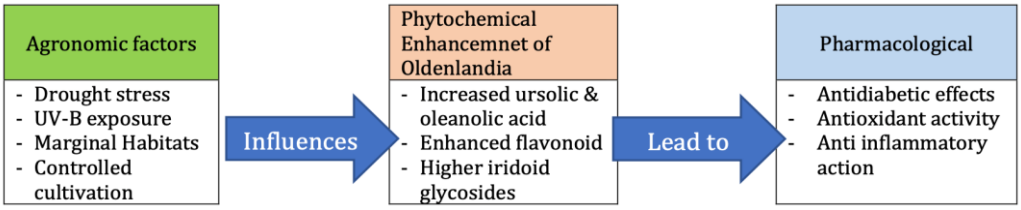

Fig. 2. Agronomy–phytochemistry–pharmacology in *Oldenlandia* spp. for antidiabetic applications

4. Conclusions

Oldenlandia spp. is undervalued weeds with strong potential for diabetes management. The ethnomedicinal relevance, phytochemical richness, and pharmacological data all point to *Oldenlandia* as a good option for further study in diabetes therapy. Agronomy perspective highlights sustainability, accessibility, and scalability. Such a synthesis would provide light not only on the medicinal potential of *Oldenlandia* spp. in diabetes care, but also on its viability as a long-term, underutilized resource. Pharmacological evidence supports traditional claims but needs more validation. *Oldenlandia* could be repositioned from nuisance weed to medicinal crop through interdisciplinary research.

Oldenlandia species possess substantial potential as sustainable antidiabetic resources, thereby addressing the central research question concerning their feasibility for therapeutic development. The findings indicate that the weedy ecological nature of *Oldenlandia* confers significant agronomic advantages, including resilience to environmental stress, low input requirements, and adaptability to marginal habitats, which collectively support scalable and environmentally responsible production. These agronomic conditions are closely linked to enhanced phytochemical accumulation, particularly of iridoid glycosides, flavonoids, triterpenoids, and phenolic compounds, whose biosynthesis is stimulated under moderate environmental stress. Pharmacological evidence from preclinical studies further corroborates that these bioactive constituents exert antidiabetic effects through multiple mechanisms, including improvement of glucose homeostasis, enhancement of insulin sensitivity, attenuation of oxidative stress, and modulation of inflammatory pathways such as AMPK–NF-κB signaling. Although clinical validation remains limited, the convergence of traditional use, phytochemical richness, and mechanistic pharmacological data supports the repositioning of *Oldenlandia* from an underutilized weed to a promising medicinal resource. Overall, this synthesis confirms that integrating agronomic feasibility with phytochemical and pharmacological validation provides a robust framework for developing *Oldenlandia* species as accessible, cost-effective, and sustainable candidates for future antidiabetic therapies.

Acknowledgement
The authors sincerely thanks the reviewers for their constructive feedback that significantly enchanched the manuscript, and also expresses to colleagues and mentors for their guidance and support during the research.

Author Contribution
The authors was involved in formulating the research idea, designing the study, collecting and analyzing the data, and preparing the manuscript. All authors took part in writing, revising, and giving final approval for the manuscript to be published.

Funding
This research received no external funding.

Ethical Review Board Statement
Not available.

Informed Consent Statement
Not available.

Data Availability Statement
Not available.

Conflicts of Interest
The authors declare no conflict of interest.

Declaration of Generative AI Use

During the preparation of this work, the author used Grammarly to assist in improving grammar, clarity, and academic tone of the manuscript. After using this tool, the author reviewed and edited the content as needed and took full responsibility for the content of the publication.

Open Access

References

Abdel-Rahman, R. F., Ezzat, S. M., Ogaly, H. A., Abd-Elsalam, R. M., Hessin, A. F., Fekry, M. I., Mansour, D. F., & Mohamed, S. O. (2020). *Ficus deltoidea* extract down-regulates protein tyrosine phosphatase 1B expression in a rat model of type 2 diabetes mellitus: a new insight into its antidiabetic mechanism. *Journal of Nutritional Science, 9,* e2. https://doi.org/10.1017/jns.2019.40

Alam, S., Sarker, Md. M. R., Sultana, T. N., Chowdhury, Md. N. R., Rashid, M. A., Chaity, N. I., Zhao, C., Xiao, J., Hafez, E. S. E., Khan, S. A., & Mohamed, I. N. (2022). Antidiabetic Phytochemicals From Medicinal Plants: Prospective Candidates for New Drug Discovery and Development [Review of Antidiabetic Phytochemicals From Medicinal Plants: Prospective Candidates for New Drug Discovery and Development]. *Frontiers in Endocrinology, 13.* https://doi.org/10.3389/fendo.2022.800714

Amissah, J. N., Opoku-Agyemang, F., Asem, F. E., Osei-Safo, D., & Addae-Mensah, I. (2024). Increasing the planting density of Cryptolepis sanguinolenta (Lindl.) Schlt increased root biomass and cryptolepine yield. *Heliyon, 10*(10). https://doi.org/10.1016/j.heliyon.2024.e30932

Ansari, J. A., Ali, S., & Ansari, M. A. (2011). A brief focus on hepatoprotective leads from herbal origin. *International Journal of Pharmacology, 7*(2), 212–216. https://doi.org/10.3923/ijp.2011.212.216

Archana, V., Thomas, N. N., Lakshmi, S., Rauf, A. A., & Edwin, B. T. (2020). Pharmaceutical properties of *Oldenlandia* corymbosa Linn. *Materials Today Proceedings, 41*, 698. https://doi.org/10.1016/j.matpr.2020.05.585

Azizah, N. S., Irawan, B., Kusmoro, J., Safriansyah, W., Farabi, K., Oktavia, D., Doni, F., & Miranti, M. (2023). Sweet Basil (Ocimum basilicum L.)—A Review of Its Botany, Phytochemistry, Pharmacological Activities, and Biotechnological Development. *Plants, 12*(24), 4148. https://doi.org/10.3390/plants12244148

Bączek, K., Kosakowska, O., Gniewosz, M., Gientka, I., & Węglarz, Z. (2019). Sweet Basil (Ocimum basilicum L.) Productivity and Raw Material Quality from Organic Cultivation. *Agronomy, 9*(6), 279. https://doi.org/10.3390/agronomy9060279

Bhattacharya, S., Gupta, N., Flekalová, A., Gordillo-Alarcón, S., Espinel-Jara, V., & Fernández-Cusimamani, E. (2024). Exploring Folklore Ecuadorian Medicinal Plants and Their Bioactive Components Focusing on Antidiabetic Potential: An Overview. *Plants, 13*(11), 1436. https://doi.org/10.3390/plants13111436

Caser, M., Chitarra, W., D'Angiolillo, F., Perrone, I., Demasi, S., Lovisolo, C., Pistelli, L., Pistelli, L., & Scariot, V. (2018). Drought stress adaptation modulates plant secondary

metabolite production in Salvia dolomitica Codd. *Industrial Crops and Products, 129,* 85. https://doi.org/10.1016/j.indcrop.2018.11.068

Chen, H., Shang, X., Yuan, H., Niu, Q., Chen, J., Luo, S., Li, W., & Li, X. (2022). Total flavonoids of *Oldenlandia* diffusa (Willd.) Roxb. suppresses the growth of hepatocellular carcinoma through endoplasmic reticulum stress-mediated autophagy and apoptosis. *Frontiers in Pharmacology, 13*. https://doi.org/10.3389/fphar.2022.1019670

Divekar, P. A., Srinivasa, N., Divekar, B. A., Kumar, R., Gowda, G. B., Ray, A., Singh, A. K., Rani, V., Singh, V., Singh, A. K., Kumar, A., Singh, R. P., Meena, R. S., & Behera, T. K. (2022). Plant Secondary Metabolites as Defense Tools against Herbivores for Sustainable Crop Protection [Review of Plant Secondary Metabolites as Defense Tools against Herbivores for Sustainable Crop Protection]. *International Journal of Molecular Sciences, 23*(5), 2690. https://doi.org/10.3390/ijms23052690

Domingo-Fernández, D., Gadiya, Y., Mubeen, S., Bollerman, T. J., Healy, M. D., Chanana, S., Sadovsky, R. G., Healey, D., & Colluru, V. (2023). Modern drug discovery using ethnobotany: A large-scale cross-cultural analysis of traditional medicine reveals common therapeutic uses. *iScience, 26*(9), 107729. https://doi.org/10.1016/j.isci.2023.107729

Essa, M. M., Vijayan, R. K., Castellano-Gonzalez, G., Braidy, N., & Guillemin, G. J. (2012). Neuroprotective effect of natural products against Alzheimer's disease. *Neurochemical Research, 37*(9), 1829–1842. https://doi.org/10.1007/s11064-012-0799-9

Elwon, C. A. M., Shah, M. D., & Iqbal, M. (2020). Hypoglycemic and hypolipidemic effects of Oldenlandia corymbosa against alloxan induced diabetes mellitus in rats. *International Journal of Pharmacy and Pharmaceutical Sciences, 12*(10), 34–40. https://doi.org/10.22159/ijpps.2020v12i10.38951

Ezema, C. A., Aguchem, R. N., Aham, E. C., Ezeorba, W. F. C., Okagu, I. U., & Ezeorba, T. P. C. (2023). Salvia africana-lutea L.: a review of ethnobotany, phytochemistry, pharmacology applications and future prospects [Review of Salvia africana-lutea L.: a review of ethnobotany, phytochemistry, pharmacology applications and future prospects]. *Advances in Traditional Medicine, 24*(3), 703. Springer Nature. https://doi.org/10.1007/s13596-023-00726-x

Florentín, M. N., Fader, A., & González, A. M. (2016). Morpho-anatomical and morphometric studies of the floral structures of the distylous *Oldenlandia* salzmannii (Rubiaceae). *Acta Botanica Brasilica, 30*(4), 585. https://doi.org/10.1590/0102-33062016abb0247

Guo, X., Wang, R., Simmons, M. P., But, P. P., & Yu, J. (2013). Phylogeny of the Asian Hedyotis–*Oldenlandia* complex (Spermacoceae, Rubiaceae): Evidence for high levels of polyphyly and the parallel evolution of diplophragmous capsules. *Molecular Phylogenetics and Evolution, 67*(1), 110. https://doi.org/10.1016/j.ympev.2013.01.006

Heinrich, M., Jalil, B., Abdel-Tawab, M., Echeverría, J., Kulić, Ž., McGaw, L. J., Pezzuto, J. M., Potterat, O., & Wang, J.-B. (2022). Best Practice in the chemical characterisation of extracts used in pharmacological and toxicological research—The ConPhyMP—Guidelines12. *Frontiers in Pharmacology, 13*. https://doi.org/10.3389/fphar.2022.953205

Huang, J. (1981). Neue Iridoide aus *Oldenlandia* Diffusa ROXB. *Archiv Der Pharmazie, 314*(10), 831. https://doi.org/10.1002/ardp.19813141004

Jørgensen, U., Jensen, S. K., Ambye-Jensen, M., Delaby, I., Beaumont, R. A., Brocard, V., Lemauviel-Lavenant, S., Plantureux, S., Vertès, F., & Peyraud, J.-L. J.-L. (2022). Coupling the benefits of grassland crops and green biorefining to produce protein, products and services for the green transition. *Research Portal Denmark, 83*. https://local.forskningsportal.dk/local/dki-cgi/ws/cris-link

Julca, I., Mutwil-Anderwald, D., Manoj, V., Khan, Z., Lai, S. K., Yang, L. K., Beh, I. T., Dziekan, J. M., Lim, Y. P., Lim, S. K., Low, Y. W., Lam, Y. I., Tjia, S., Mu, Y., Tan, Q. W., Nuc, P., Choo,

L. M., Khew, G., Loo, S., … Mutwil, M. (2023). Genomic, transcriptomic, and metabolomic analysis of *Oldenlandia* corymbosa reveals the biosynthesis and mode of action of anti-cancer metabolites. *Journal of Integrative Plant Biology, 65*(6), 1442. https://doi.org/10.1111/jipb.13469

Katrolia, A., Pal, V. K., Shukla, V. K., & Singh, R. (2023). Exploring the Therapeutic Potential of Herbal Plants in Managing Blood Sugar Levels: A Comprehensive Evaluation. *Pharmacognosy Research, 16*(1), 10. https://doi.org/10.5530/pres.16.1.2

Kellogg, J. J., Paine, M. F., McCune, J. S., Oberlies, N. H., & Cech, N. B. (2019). Selection and characterization of botanical natural products for research studies: a NaPDI center recommended approach [Review of Selection and characterization of botanical natural products for research studies: a NaPDI center recommended approach]. *Natural Product Reports, 36*(8), 1196.. https://doi.org/10.1039/c8np00065d

Kim, C., & Choi, K. (2021). Potential Roles of Iridoid Glycosides and Their Underlying Mechanisms against Diverse Cancer Growth and Metastasis: Do They Have an Inhibitory Effect on Cancer Progression? [Review of Potential Roles of Iridoid Glycosides and Their Underlying Mechanisms against Diverse Cancer Growth and Metastasis: Do They Have an Inhibitory Effect on Cancer Progression?]. *Nutrients, 13*(9), 2974. https://doi.org/10.3390/nu13092974

Liang, Z., He, M., Fong, W., Jiang, Z., & Zhao, Z. (2008). A comparable, chemical and pharmacological analysis of the traditional Chinese medicinal herbs *Oldenlandia* diffusa and O. corymbosa and a new valuation of their biological potential. *Phytomedicine, 15*(4), 259. https://doi.org/10.1016/j.phymed.2008.01.003

Lok, B. M., Yee, P., Tunku, M., Rahman, A. H. A., Subramaniam, P., Ramachandran, V., Shah, H., Hamid, A., Kandavello, G., Azmi, N. H. M., Hafizah, N., Nur, I., Nabila, S., Buhari, I., Priya, S. L. S., Amrina, M. A., Thilakavathy, K., Mazlyfarin, M., Farhayu, O. N., … Idris, S. (2024). Abstracts from the 2nd International Conference of Science, Technology, Education, and Management (InSTEM 2023). *BMC Proceedings, 18.* https://doi.org/10.1186/s12919-024-00294-1

Magliano, D., & Boyko E. J. (2025). IDF diabetes atlas 11th edition. *International Diabetes Federation.* https://diabetesatlas.org/resources/idf-diabetes-atlas-2025/

Mahajan, M., Kuiry, R., & Pal, P. K. (2020). Understanding the consequence of environmental stress for accumulation of secondary metabolites in medicinal and aromatic plants. *Journal of Applied Research on Medicinal and Aromatic Plants, 18,* 100255. https://doi.org/10.1016/j.jarmap.2020.100255

Mahankali, S., Kalava, J., Garapati, Y., Domathoti, B., Maddumala, V. R., & Sundramurty, V. P. (2022). A Treatment to Cure Diabetes Using Plant-Based Drug Discovery. *Evidence-Based Complementary and Alternative Medicine*, *1*. https://doi.org/10.1155/2022/8621665

Marcelino, S., Hamdane, S., Gaspar, P. D., & Paço, A. (2023). Sustainable Agricultural Practices for the Production of Medicinal and Aromatic Plants: Evidence and Recommendations. *Sustainability, 15*(19), 14095. https://doi.org/10.3390/su151914095

Marchev, A. S., Vasileva, L. V., Amirova, K. M., Savova, M. S., Balcheva-Sivenova, Z. P., & Georgiev, M. I. (2021). Metabolomics and health: from nutritional crops and plant-based pharmaceuticals to profiling of human biofluids [Review of Metabolomics and health: from nutritional crops and plant-based pharmaceuticals to profiling of human biofluids]. *Cellular and Molecular Life Sciences, 78*. https://doi.org/10.1007/s00018-021-03918-3

Muema, F. W., Nanjala, C., Oulo, M. A., & Wangchuk, P. (2023). Phytochemical Content and Antidiabetic Properties of Most Commonly Used Antidiabetic Medicinal Plants of Kenya [Review of Phytochemical Content and Antidiabetic Properties of Most Commonly Used Antidiabetic Medicinal Plants of Kenya]. *Molecules, 28*(20), 7202.. https://doi.org/10.3390/molecules28207202

Munguía-Rosas, M. A. (2021). Artificial selection optimizes clonality in chaya (Cnidoscolus aconitifolius). *Scientific Reports, 11*(1). https://doi.org/10.1038/s41598-021-00592-0

Neupane, S., Dessein, S., & Motley, T. J. (2009). The Hedyotis–*Oldenlandia*–Kohautia Complex (Rubiaceae) In Nepal: A Study of Fruit, Seed and Pollen Characters and Their Taxonomic Significance. *Edinburgh Journal of Botany, 66*(3), 371. https://doi.org/10.1017/s0960428609990035

Neupane, S., Dessein, S., Wikström, N., Lewis, P. O., Long, C., Bremer, B., & Motley, T. J. (2015). The Hedyotis-*Oldenlandia* complex (Rubiaceae: Spermacoceae) in Asia and the Pacific: Phylogeny revisited with new generic delimitations. *Taxon, 64*(2), 299. https://doi.org/10.12705/642.8

Omale, S., Amagon, K. I., Johnson, T. O., Bremner, S., & Gould, G. W. (2023). A systematic analysis of anti-diabetic medicinal plants from cells to clinical trials [Review of A systematic analysis of anti-diabetic medicinal plants from cells to clinical trials]. *PeerJ, 11*. https://doi.org/10.7717/peerj.14639

Osewa, S. O., Alamu, O., Adetiloye, I. S., Olubiyi, M. R., & Abidogun, E. A. (2013). Use of some Neglected and Underutilized Plant Species among Rural Dwellers in Akinyele Local Government Area of Oyo State. *Greener Journal of Agricultural Sciences, 3*(12), 817. https://doi.org/10.15580/gjas.2013.3.060913821

Pelkonen, O., Xu, Q., & Fan, T.-P. (2014). Why is Research on Herbal Medicinal Products Important and How Can We Improve Its Quality? *Journal of Traditional and Complementary Medicine, 4*(1), 1. https://doi.org/10.4103/2225-4110.124323

Ripoche, A., Barkaoui, K., Allouch, N., Christina, M., Heuclin, B., Rafenomanjato, A., Moonen, A., Autfray, P., & Marnotte, P. (2024). Do rotation and fertilization practices shape weed communities and affect rice yield in low input rainfed agroecosystems in the Malagasy highlands? *Agriculture Ecosystems & Environment, 373*. https://doi.org/10.1016/j.agee.2024.109136

Rojas-Sandoval, J. (2022). *Catharanthus roseus (Madagascar periwinkle) [Data set].* In CABI Compendium. CAB International Publishing. https://doi.org/10.1079/cabicompendium.16884

Roy, D. N., Ferdiousi, N., Khatun, T., & Moral, Md. R. A. (2016). Phytochemical screening, nutritional profile and anti-diabetic effect of ethanolic leaf extract of Cnidoscolus aconitifolius in streptozotocin induce diabetic mice. *International Journal of Basic & Clinical Pharmacology, 5*(5), 2244–2250. https://doi.org/10.18203/2319-2003.ijbcp20163269.

Salaudeen, M. T., Daniya, E., Olaniyi, O. M., Folorunso, T. A., Bala, J. A., Abdullahi, I. M., Nuhu, B. K., Adedigba, A. P., Oluwole, B. I., Bankole, A. O., & Macarthy, O. M. (2022). Phytosociological survey of weeds in irrigated maize fields in a Southern Guinea Savanna of Nigeria. *Frontiers in Agronomy, 4.* https://doi.org/10.3389/fagro.2022.985067

Sheikh, Z. N., Sharma, N., Sharma, V., Bakshi, P., Raina, S., & Ataya, F. S. (2024). Comparative Analysis of Bioactive Compounds and Health Benefits of Wild and Cultivated Ficus carica Accessions from the Northern Himalayas. *Research Square.* https://doi.org/10.21203/rs.3.rs-5334005/v1

Sindhu, R. K., Saini, B., Kaur, P., & Batiha, G. E. (2021). The Role of Ethnomedicinal Plants for Treatment and Management of Diabetes Mellitus: An Updated Review. *Journal of University of Shanghai for Science and Technology, 23*(7), 1014. https://doi.org/10.51201/jusst/21/07213

Smithies, B. J., Huang, Y.-H., Jackson, M. A., Anderson, M. A., & Craik, D. J. (2020). Circular Permutation of the Native Enzyme-Mediated Cyclization Position in Cyclotides. *ACS Chemical Biology, 15*(4), 962–969. https://doi.org/10.1021/acschembio.0c00052

Vanhaelewyn, L., Straeten, D. V. D., Coninck, B. D., & Vandenbussche, F. (2020). Ultraviolet Radiation From a Plant Perspective: The Plant-Microorganism Context [Review of

Ultraviolet Radiation From a Plant Perspective: The Plant-Microorganism Context]. *Frontiers in Plant Science, 11*. https://doi.org/10.3389/fpls.2020.597642

Wang, H., Chen, Y., Wang, L., Liu, Q., Yang, S., & Wang, C.-Q. (2023). Advancing herbal medicine: enhancing product quality and safety through robust quality control practices [Review of Advancing herbal medicine: enhancing product quality and safety through robust quality control practices]. *Frontiers in Pharmacology, 14*. https://doi.org/10.3389/fphar.2023.1265178

Wang, Z., Wang, T., Hu, J., Jiao, H., Jin, Y., Sun, J., Nan, T., Zhao, Y., Liu, Y., Huang, L., & Yuan, Y. (2024, March 6). Comparisons of wild and cultivated American ginseng (Panax quinquefolius L.) genomes provide insights into changes in root growth and metabolism during domestication. *Plant Biotechnology Journal*, *22*(7). https://doi.org/10.1111/pbi.14316

Wang, Z., Zhang, Y., Zhang, Q., Ao, Q., Luo, C., Wang, B., Bai, C., Ge, X., Wang, Y., Wang, J., Ying, Q., Yu, H., & Gu, X. (2022). On the Core Prescriptions and Their Mechanisms of Traditional Chinese Medicine in Hepatitis B, Liver Cirrhosis, and Liver Cancer Treatment. *Journal of Oncology*, (1). https://doi.org/10.1155/2022/5300523

Xie, F., Wang, H., Cao, Q., Chen, Q., & Lin, F. (2022). The effects of *Oldenlandia* diffusa water extract on glucose metabolism and inflammation level in rats with streptozotocin-induced gestational diabetes mellitus. *Quality Assurance and Safety of Crops & Foods, 14*(1), 24. https://doi.org/10.15586/qas.v14i1.970

Yahaya, N., Dom, N. S. M., Adam, Z., & Hamid, M. (2018). Insulinotropic Activity of Standardized Methanolic Extracts of Ficus deltoidea from Seven Varieties. *Evidence-Based Complementary and Alternative Medicine,* 1. https://doi.org/10.1155/2018/3769874

Yulizar, Y., Latifah, I., Bakri, R., & Apriandanu, D. O. B. (2018). Plants extract mediated synthesis of copper (II) oxide nanoparticles using *Oldenlandia* corymbosa L. leaf. *AIP Conference Proceedings,* 20097. https://doi.org/10.1063/1.5064094

Zhao, C., Wei, M., Zheng, Y., Tao, W., Lv, Q., Wang, Q., Wang, S., & Chen, Y. (2021). The Analyses of Chemical Components From *Oldenlandia* hedyotidea (DC.) Hand.-Mazz and Anticancer Effects in vitro. *Frontiers in Pharmacology, 12*. https://doi.org/10.3389/fphar.2021.624296

Zhang, L.-Y., Zhang, J.-G., Yang, X., Zhang, C.-W., & Hu, Z.-M. (2020). Targeting tumor immunosuppressive microenvironment for the prevention of hepatic cancer: Applications of traditional chinese medicines in targeted delivery. Current Topics in *Medicinal Chemistry,* *20*(30), 2789–2800. https://doi.org/10.2174/1568026620666200908165218

Zhang, Y., Hu, H., & Jia-bo, L. (2020). Diffusosides C and D, two new iridoid glucosides from *Oldenlandia* diffusa. Natural Product Research, *36*(9), 2300. https://doi.org/10.1080/14786419.2020.1830397

Biographies of Authors

Nor Isnaeni Dwi Arista, Department of Agrotechnology, Faculty of Agriculture, Universitas Jenderal Soedirman, Purwokerto, Central Java, 53122, Indonesia

- Email: nor.isnaeni@unsoed.ac.id
- ORCID: 0000-0001-7196-2838
- Web of Science ResearcherID: N/A
- Scopus Author ID: 58185882900
- Homepage: https://sinta.kemdiktisaintek.go.id/authors/profile/6963023

Yochidamai Akhsanitaqwim, Applied Natural Medicine Study Program, School of Pharma-Medical Science, Toyama University, Toyama City, Toyama Prefecture, 9300151, Japan

- Email: m23e8101@ems.u-toyama.ac.jp
- ORCID: 0000-0002-8093-0632
  Web of Science ResearcherID: N/A
- Scopus Author ID: N/A
- Homepage: N/A