Biotechnology and Bioprocess Engineering
https://doi.org/10.1007/s12257-025-00234-6

REVIEW PAPER

From gene to green product: an integrated pipeline of biotechnology and green chemistry for sustainable phytochemical production

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Received: 12 July 2025 / Revised: 18 October 2025 / Accepted: 20 October 2025

Abstract
Phytochemicals are indispensable to medicine and nutrition, yet their conventional production faces a sustainability crisis due to intensive resource consumption and environmental degradation. This review introduces a holistic "gene-to-final-product" pipeline, a paradigm shift that synergistically integrating upstream biotechnological tools, including metabolic engineering and synthetic biology, with downstream green processing technologies. In contrast to previous studies that have treated these fields as separate disciplines, this work provides a timely and integrative synthesis of their synergy by framing a complete value chain from genetic design to the final product. The review evaluates key strategies for enhancing biosynthetic pathways, designing novel production routes in microbial cell factories, and implementing sustainable extraction methods. The power of this integrated model is demonstrated through compelling synergistic effects; for example, higher phytochemical yields achieved via metabolic engineering can make milder, greener extraction methods economically viable. Practical case studies, including the industrial-scale production of paclitaxel and artemisinin and the valorization of waste streams into polyphenols, validate the feasibility and potential of these integrated systems. By framing these advancements within Green Chemistry principles and the UN Sustainable Development Goals, this review provides actionable insights for a necessary transition toward a circular bioeconomy and sustainable industrial biomanufacturing.

Keywords Green chemistry · Metabolic engineering · Phytochemicals · Sustainable production · Synthetic biology

1 Introduction

Historically essential for human health, phytochemicals—a diverse spectrum of non-nutritive substances including flavonoids, phenolic acids, and glucosinolates found in fruits, vegetables, and grains—are instrumental in disease prevention and overall health promotion. Additionally, phytochemicals have a substantial impact beyond health, significantly affecting the economy. They are vital to major industries, including pharmaceutical sciences, agriculture, and food, demonstrating their crucial role in supporting both health and economic prosperity. For instance, lavender, known for its essential oils, holds substantial economic value, finding applications in pharmaceuticals, cosmeceuticals, agriculture, and the food industry due to its range of biologically active compounds [1]. Similarly, the candelilla plant (*Euphorbia antisyphilitica*) is crucial in desert regions, offering valuable phytochemicals for use in diverse industries, emphasizing the need for sustainable production methods [2]. Moreover, certain wild species native to biodiversity hotspots are gaining attention for their unique compounds beneficial for health, adaptable for climate change scenarios, and valuable for the food and pharmaceutical sciences industries [3].

The nutritional importance of phytochemicals is well-documented, with extensive research correlating their intake with reduced risk of chronic diseases, including cancer, cardiovascular diseases, and neurodegenerative conditions. They contribute to essential biological functions, such as antioxidant activity, modulation of detoxification enzymes, stimulation of the immune system, and regulation of cell proliferation. These findings have sparked public interest and increased demand for phytochemicals, which are now used in pharmaceuticals, nutraceuticals, and cosmetics, beyond just food and beverages. Moreover, the contemporary dietary shift towards plant-based nutrition underscores

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Published online: 28 October 2025

the relevance of phytochemicals in daily diet regimens, necessitating a deeper exploration of their health-promoting properties [4–6].

Phytochemicals form an economic foundation in multiple industries, witnessing rapid market expansion. Propelled by rising consumer awareness and a preference for natural products, this market expansion profoundly impacts sectors such as nutraceuticals, pharmaceuticals, and agriculture. Their use in enriched foods, supplements, and medicinal products underscores their adaptability and healing promise. Additionally, growing crops rich in phytochemicals provides economic advantages, especially in developing countries, promoting stability and expansion [7].

The growing interest underscores the need for sustainable, innovative, and ethically responsible methods in phytochemical extraction and production—a central tenet of sustainable pharmacy—ensuring environmental preservation and resource efficiency. Present production methods, typically demanding high resource use, present environmental issues, such as high-water use, deforestation, and chemical contamination from agrochemicals. Additionally, the industrial extraction and processing of phytochemicals frequently employ environmentally detrimental solvents and conditions. Furthermore, there are intrinsic constraints in the production of phytochemicals. Aspects like restricted bioavailability, breakdown during handling, and variations from farming methods and seasonal shifts impede steady phytochemical production. Traditional cultivation and extraction methods further strain sustainability, given their extensive land, water, and energy requirements, leading to environmental degradation [8].

To tackle these challenges, the bioeconomy concept encourages a shift from fossil-based systems to those relying on renewable biological resources. This includes the sustainable production of food, health products, and bioenergy [9]. This transition is crucial, considering climate change and biodiversity loss, requiring environmentally responsible solutions in phytochemical production.

In summary, although phytochemicals are economically important, current production methods face significant sustainability challenges. Innovative, eco-friendly approaches in cultivation, extraction, and processing are essential to meet growing demand without compromising environmental integrity. However, while numerous reviews have expertly detailed progress within these individual disciplines—focusing either on metabolic engineering or on green extraction technologies—a critical, integrative analysis of their synergy remains a significant gap in the literature. The rapid and parallel evolution of these fields necessitates a new, holistic overview. Therefore, this review is both fundamental and timely as it aims to provide a comprehensive synthesis that uniquely evaluates the integration of upstream biotechnological innovations with downstream green processing. Its original contribution is to offer a 'gene-to-final-product' pipeline framework by critically assessing the potential and challenges of this combined approach. To achieve this, this review will specifically address three key questions: (1) How can the powerful tools of metabolic engineering and synthetic biology be most effectively integrated with eco-friendly extraction and purification processes to create a seamless and sustainable value chain? (2) What are the primary scientific, economic, and regulatory bottlenecks that currently hinder the industrial-scale adoption of these integrated systems? (3) What future research directions hold the most promise for aligning phytochemical production with the principles of a circular bioeconomy? By addressing these questions, this review seeks to provide a strategic roadmap for researchers and industry stakeholders, justifying why an integrated approach is not just beneficial, but crucial for the future of sustainable phytochemical production, aligning scientific innovation with the global imperatives outlined in the 2030 Agenda for Sustainable Development [10].

2 Phytochemical basics

Plants produce a vast array of secondary metabolites (alkaloids, phenolics, terpenoids, etc.) not directly for growth, but as a crucial defense arsenal against biotic and abiotic stress. These compounds, which include the nitrogenous alkaloids, structurally reinforcing phenolics, and the vast class of terpenoids, deter herbivores, inhibit pathogens, and mitigate environmental damage. This chemical diversity is not only vital for the plant's survival but also represents a rich reservoir of phytochemicals with significant pharmacological value.

Many of these secondary metabolites found in medicinal and aromatic plants possess therapeutic effects. Compounds such as alkaloids, phenolics, and flavonoids display a wide range of functions, including antioxidant, anti-inflammatory, anticancer, and antimicrobial actions. These properties make them invaluable for the prevention and management of chronic diseases and as candidates for new drug development. Furthermore, some compounds can modulate the immune system, offering potential as safer alternatives to traditional drugs, while others exhibit antidiabetic, neuroprotective, and cardioprotective benefits.

The ability to produce these valuable compounds sustainably and efficiently hinges on a deep understanding of their biochemical origins. The major biosynthetic pathways are not merely academic concepts; they represent the molecular roadmaps that must be understood to be re-engineered for targeted, high-yield production. Therefore, a concise overview of these core pathways is essential to contextualize the innovative strategies discussed later in this review. A foundational grasp of how plants naturally synthesize these molecules is the critical first step in designing metabolic engineering approaches aimed at sustainable goals.

The main biosynthetic pathways of key phytochemicals are summarized below (Figs. 1, 2 and 3), highlighting their significance as targets for biotechnological intervention.

3 Current challenges in phytochemical production

Traditional farming methods, crucial for worldwide food supply, encounter difficulties in contemporary production of phytochemicals. These techniques, relying on human labor and natural processes, are challenged to meet modern needs for high productivity, expansion capability, and eco-friendly operations. A major issue is their susceptibility to climate change, as changes in weather and severe occurrences disturb the steadiness these methods traditionally relied on, impacting crop production and the uniformity of the resulting phytochemicals [11, 12].

These agricultural systems face significant operational and structural challenges. The intensive consumption of resources—including water, arable land, and energy—and a heavy reliance on synthetic agrochemicals are well-documented problems in traditional cultivation [13]. Concurrently, structural issues such as small-scale landholdings and land ownership disputes often deter long-term investment in more sustainable and innovative farming methods [14].

From the perspective of Green Chemistry, these agricultural practices are fundamentally unsustainable. The high resource and energy inputs directly conflict with Principle 6 (Design for Energy Efficiency) and Principle 7 (Use of Renewable Feedstocks). Similarly, the reliance on agrochemicals violates Principle 3 (Less Hazardous Chemical Syntheses) and Principle 4 (Designing Safer Chemicals). Furthermore, the underutilization of agricultural by-products represents a significant inefficiency [15], a practice that contradicts the foundational Principle 1 (Prevention), which prioritizes avoiding waste generation over its subsequent treatment.

The challenges extend into the post-harvest phase with traditional methods of phytochemical extraction, which, despite their historical significance, are fraught with limitations from a sustainability perspective (Fig. 4). Processes like maceration and percolation are notoriously slow and demand large volumes of organic solvents, leading to high

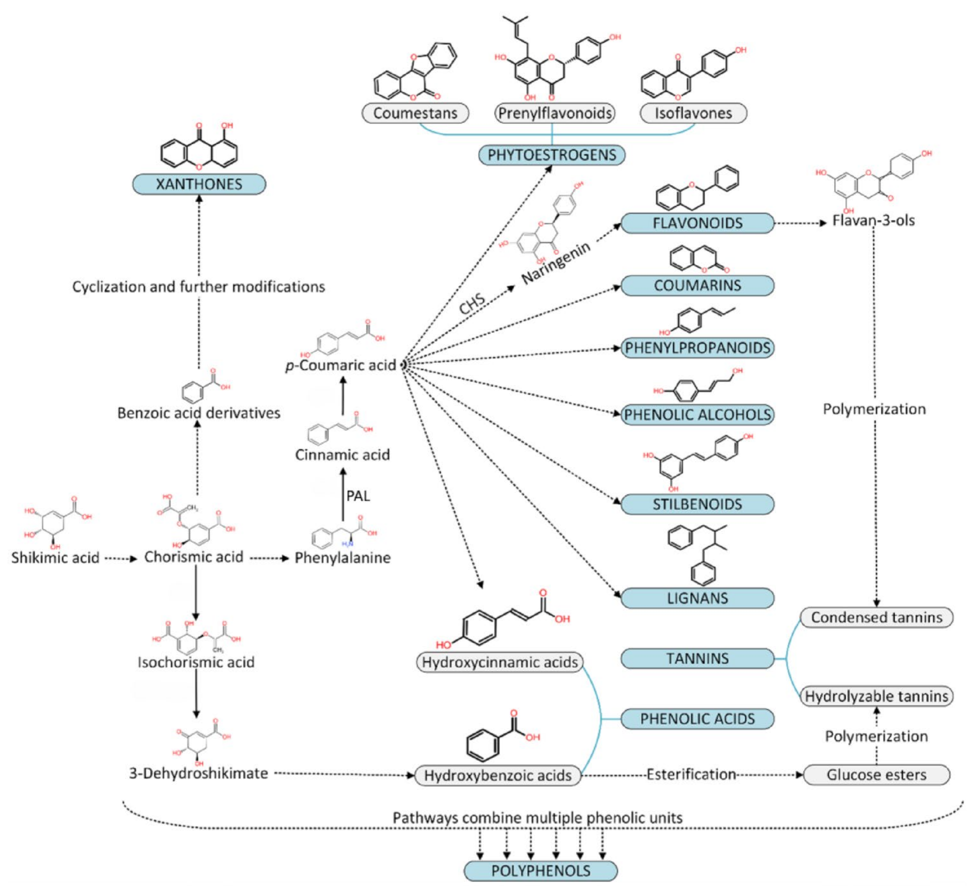


Fig. 1 The phenylpropanoid pathway and its derivatives. Originating from the amino acid phenylalanine, this pathway is a factory for a vast range of phenolic compounds, including flavonoids, stilbenes (e.g., resveratrol), coumarins, and lignans. These compounds are highly sought after for their antioxidant, anti-inflammatory, and cardioprotective properties. Rather than a simple linear process, it is a complex network with key enzymes like phenylalanine ammonia-lyase (PAL) and chalcone synthase (CHS) acting as critical control points. Targeting these enzymatic gateways through metabolic engineering is a primary strategy for sustainably increasing the yield of high-value phenolics for the pharmaceutical and nutraceutical industries. In this diagram, solid arrows indicate single-step enzymatic reactions, whereas dashed arrows represent reaction sequences that involve multiple enzymatic steps

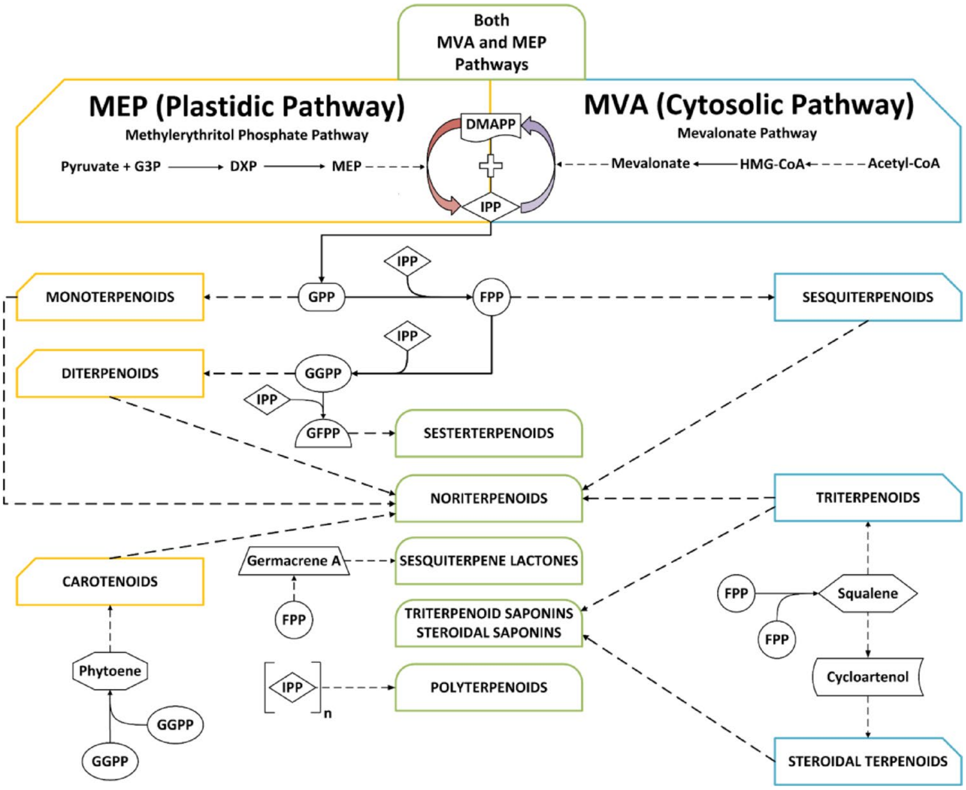


Fig. 2 Overview of terpenoid biosynthetic pathways. Terpenoids, the largest class of secondary metabolites, are synthesized via the cytosolic mevalonate (MVA) and plastidial methylerythritol phosphate (MEP) pathways. These routes provide the fundamental building blocks (IPP and DMAPP) for an enormous diversity of molecules, from monoterpenoids like menthol to vital anticancer drugs like paclitaxel (Taxol) and antimalarials like artemisinin. In this diagram, the cytosolic MVA pathway and its associated products are shown in blue, the plastidial MEP pathway and its associated products are shown in orange, and products derived from both pathways are shown in green. The solid arrows indicate single-step enzymatic reactions, whereas dashed arrows represent reaction sequences that involve multiple enzymatic steps. The modular nature of terpenoid biosynthesis makes these pathways prime candidates for engineering in microbial hosts, allowing for scalable and sustainable production independent of agricultural constraints and complex plant extraction. HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A, DXP: 1-Deoxy-D-xylulose 5-phosphate, G3P: glyceraldehyde 3-phosphate, IPP: isopentenyl pyrophosphate, DMAPP: dimethylallyl pyrophosphate, GPP: geranyl pyrophosphate, FPP: farnesyl pyrophosphate, GGPP: geranylgeranyl pyrophosphate, GFPP: geranylfarnesyl pyrophosphate

energy consumption and significant environmental waste. Techniques such as reflux and Soxhlet extraction, while faster, exacerbate these issues by requiring even more solvent and high temperatures, which can thermally degrade sensitive target compounds. These conventional extraction practices are in direct conflict with several core principles of Green Chemistry [16]. The heavy reliance on volatile and often toxic organic solvents violates Principle 5 (Safer Solvents and Auxiliaries). The high energy inputs required for heating and long processing times disregard Principle 6 (Design for Energy Efficiency). Finally, the degradation of target compounds reduces overall process efficiency, undermining Principle 2 (Atom Economy), which seeks to maximize the incorporation of all materials used in the process into the final product.

Collectively, these limitations in both cultivation and extraction underscore a fundamental unsustainability in the traditional phytochemical supply chain. The reliance on methods that are resource-intensive, environmentally damaging, and inefficient establishes a clear and urgent need for a paradigm shift. Therefore, the following sections of this review will examine how upstream innovations, particularly direct plant host engineering, are being developed to specifically address these agricultural and processing bottlenecks, offering a path toward a more sustainable future for phytochemical production.

4 Upstream innovations: engineering the genetic blueprint

To overcome the agricultural and environmental limitations outlined in the previous section, the production of sustainable phytochemicals is increasingly driven by advanced genetic engineering methods designed to enhance plant biosynthetic capabilities directly within the host. To accurately evaluate the advancements in upstream innovations, it is critical to first establish a clear distinction between the primary production platforms and the engineering tools applied to them. Production platforms represent the biological 'chassis' used for phytochemical synthesis: whole-plant engineering involves the genetic modification of the entire plant in an agricultural context; plant tissue (or cell) culture utilizes undifferentiated plant cells or tissues grown in vitro in sterile and controlled bioreactors; and microbial engineering employs microorganisms such as yeast (*Saccharomyces cerevisiae*) or bacteria (*Escherichia coli*) as heterologous hosts. Each platform offers a distinct profile of advantages and disadvantages in terms of scalability, complexity, and biological containment.

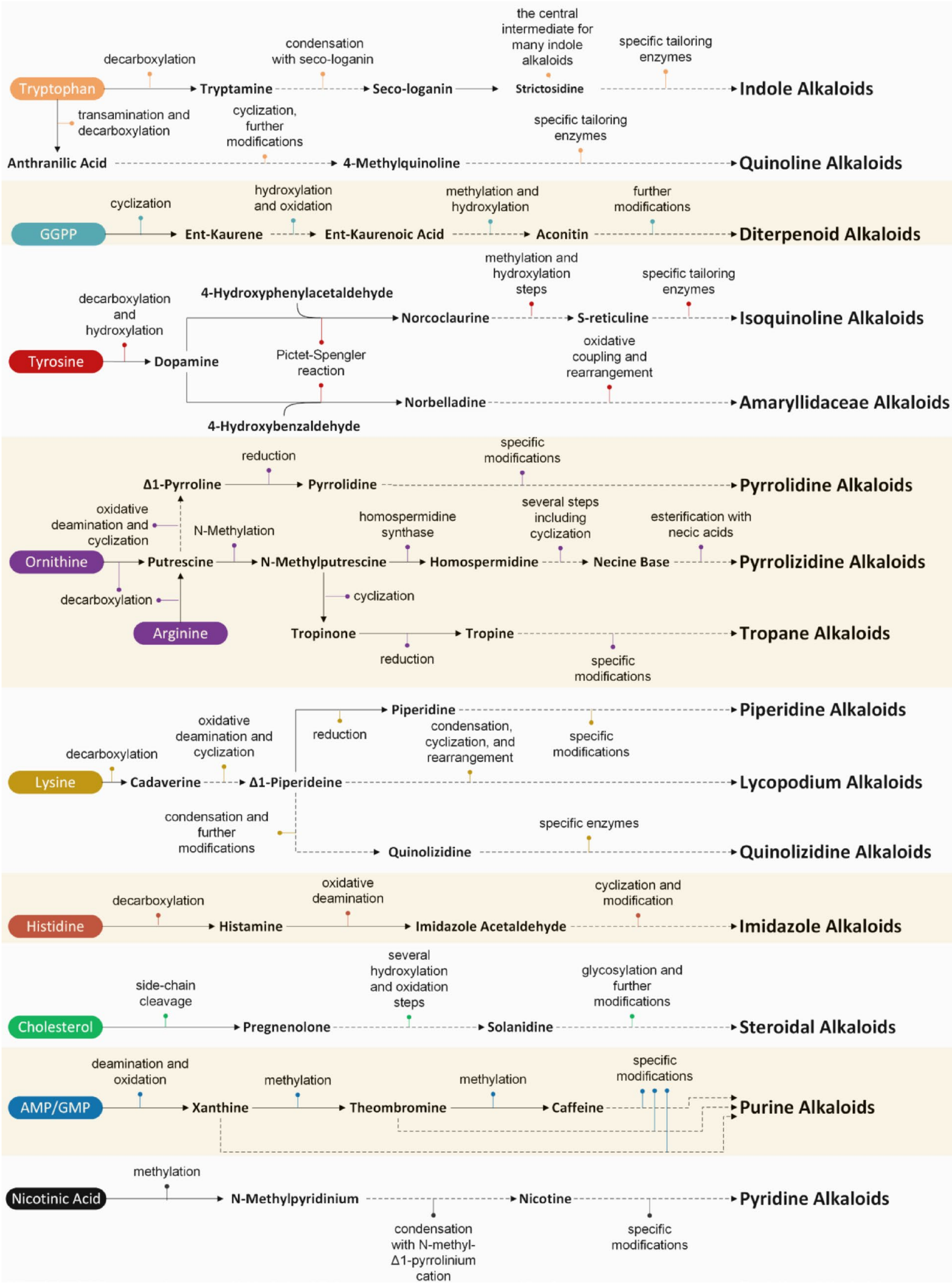
Applied to these platforms are powerful molecular tools: Metabolic engineering refers to the targeted modification of metabolic pathways to enhance the production of a desired compound. Synthetic biology adopts a more holistic 'design-build-test' approach to construct new pathways or redesign entire regulatory networks with greater predictability, often using standardized genetic parts. A key component of both is host engineering, which involves modifying the host organism itself to better support the engineered pathway (*e.g.*, by increasing precursor supply). Finally, and most critically, gene editing, enabled by systems like CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9), is a specific technique that allows for precise, targeted changes to an organism's DNA, serving as a foundational tool for all the aforementioned strategies.

The pursuit of sustainable phytochemicals is increasingly driven by advanced genetic engineering methods designed to enhance plant biosynthetic capabilities. These techniques range from optimizing entire metabolic pathways to precise gene editing, all aimed at boosting the yield of valuable compounds. A key strategic advance in this domain is the direct metabolic engineering of the plant host itself. While microbial platforms are powerful, engineering in planta circumvents common challenges such as the improper folding of complex, plant-specific enzymes (e.g., P450s) or the host's limited tolerance to potent phytochemical products, which can lead to suboptimal yields in engineered microbes. By leveraging the plant's native cellular machinery and pre-existing pathways, direct engineering offers a more robust and direct route to obtaining the final, correctly modified phytochemicals [17]. This core strategy is further enhanced by innovations like epigenetic modifications, which provide nuanced control over gene expression, and the integration of metabolomics and genomics to create a more predictive and effective engineering workflow. Together, these integrated biotechnological efforts are unlocking the potential to sustainably produce valuable phytochemicals for medicine, agriculture, and bioenergy.

However, *in planta* engineering has considerable limitations compared to microbial systems. While microbial fermentation offers rapid growth cycles, facile genetic manipulation, and highly controllable production environments ideal for industrial scaling, plant-based systems are inherently more complex. Challenges in plant engineering include long development and regeneration times, the intricate and often incompletely understood regulation of plant metabolic networks, and the potential for engineered pathways to cause metabolic burden or toxicity to the host plant [18]. Moreover, many high-value phytochemicals are produced in non-model plant species that are recalcitrant to genetic transformation [19]. Finally, the agricultural use of whole genetically modified plants is subject to stringent regulatory hurdles and public perception issues that are less prominent for contained microbial fermentation systems. Therefore, the choice of production platform represents a critical strategic decision, balancing the benefits of a plant's native cellular machinery against the speed and control afforded by microbial cell factories.

Synthetic biology plays a crucial role by applying advanced molecular tools to engineer these biological systems with greater precision and predictability. It enables a deeper understanding of the signaling processes and metabolic networks involved in phytochemical production, from the subcellular to the whole-plant level. This knowledge is then used to rationally design and optimize biosynthetic pathways, redirecting metabolic flux towards target compounds in various organisms, including microalgae, Streptomycetes, and cyanobacteria [20–22]. The use of synthetic biology tools, particularly CRISPR/Cas systems, allows for precise genome editing to introduce desired traits. This precision is a key sustainability benefit, as it minimizes off-target effects, thereby reducing waste in the development pipeline, and accelerates the creation of high-yield, resource-efficient plant varieties. Furthermore, these approaches facilitate the development of sustainable production methods by enabling the discovery of novel biosynthetic gene clusters and reducing reliance on resource-intensive agricultural and extraction processes, offering powerful and sustainable strategies for producing phytochemicals [21].

In summary, the advances detailed within this section, from direct metabolic engineering in planta to the precision afforded by synthetic biology tools like CRISPR/Cas, constitute a powerful and integrated toolkit. The synergy between targeted genetic modification and multi-omics data analysis is enhancing the efficiency and specificity of phytochemical biosynthesis. This approach moves beyond simply increasing yield; it directly contributes to sustainability by enabling the rapid development of resource-efficient



Tryptophan
decarboxylation
Tryptamine
condensation with seco-loganin
Seco-loganin
Strictosidine
the central intermediate for many indole alkaloids
specific tailoring enzymes
Indole Alkaloids
transamination and decarboxylation
Anthranilic Acid
cyclization, further modifications
4-Methylquinoline
specific tailoring enzymes
Quinoline Alkaloids
GGPP
cyclization
Ent-Kaurene
hydroxylation and oxidation
Ent-Kaurenoic Acid
methylation and hydroxylation
Aconitin
further modifications
Diterpenoid Alkaloids
Tyrosine
decarboxylation and hydroxylation
Dopamine
4-Hydroxyphenylacetaldehyde
Pictet-Spengler reaction
Norcoclaurine
methylation and hydroxylation steps
S-reticuline
specific tailoring enzymes
Isoquinoline Alkaloids
4-Hydroxybenzaldehyde
Norbelladine
oxidative coupling and rearrangement
Amaryllidaceae Alkaloids
Ornithine
Arginine
decarboxylation
oxidative deamination and cyclization
Δ1-Pyrroline
reduction
Pyrrolidine
specific modifications
Pyrrolidine Alkaloids
Putrescine
N-Methylation
N-Methylputrescine
homospermidine synthase
Homospermidine
several steps including cyclization
Necine Base
esterification with necic acids
Pyrrolizidine Alkaloids
cyclization
Tropinone
reduction
Tropine
specific modifications
Tropane Alkaloids
Lysine
decarboxylation
Cadaverine
oxidative deamination and cyclization
Δ1-Piperideine
reduction
Piperidine
specific modifications
Piperidine Alkaloids
condensation, cyclization, and rearrangement
Lycopodium Alkaloids
condensation and further modifications
Quinolizidine
specific enzymes
Quinolizidine Alkaloids
Histidine
decarboxylation
Histamine
oxidative deamination
Imidazole Acetaldehyde
cyclization and modification
Imidazole Alkaloids
Cholesterol
side-chain cleavage
Pregnenolone
several hydroxylation and oxidation steps
Solanidine
glycosylation and further modifications
Steroidal Alkaloids
AMP/GMP
deamination and oxidation
Xanthine
methylation
Theombromine
methylation
Caffeine
specific modifications
Purine Alkaloids
Nicotinic Acid
methylation
N-Methylpyridinium
condensation with N-methyl-Δ1-pyrrolinium cation
Nicotine
specific modifications
Pyridine Alkaloids

Fig. 3 An overview of the major alkaloid biosynthetic pathways. Alkaloids are structurally diverse, nitrogen-containing compounds derived from various amino acids. Their biosynthetic pathways are often complex and species-specific, yielding some of the most potent pharmaceuticals known, including the analgesic morphine and the anticancer agents vinblastine and vincristine. Due to their complexity and often low concentration in plants, understanding and reconstructing these pathways in engineered microbial systems (synthetic biology) represents a frontier in sustainable chemistry, promising a reliable and environmentally friendly supply of essential medicines. In this diagram, solid arrows indicate single-step enzymatic reactions, whereas dashed arrows represent reaction sequences that involve multiple enzymatic steps. GGPP: geranylgeranyl pyrophosphate, AMP: adenosine monophosphate, GMP: guanosine monophosphate

production systems and minimizing waste. These foundational biotechnological strategies now provide the basis for the tangible successes and real-world applications that will be explored in the subsequent sections of this review.

5 Current innovative techniques and case studies

The quest to enhance the sustainable production of valuable phytochemicals has spurred a range of innovative strategies, moving beyond traditional cultivation. These techniques, broadly categorized, aim to either improve the plant's inherent capabilities or optimize its interaction with the environment (Fig. 5).

One major avenue involves direct genetic and breeding interventions. Molecular breeding, for instance, leverages natural genetic variation and targeted cross-breeding to select for plant lines with inherently higher phytochemical content. Complementing this, gene editing technologies, most notably CRISPR/Cas9, offer unprecedented precision in modifying plant genomes to directly influence phytochemical synthesis pathways, aiming for enhanced production of specific target compounds.

Another powerful set of approaches focuses on manipulating the plant's biochemical machinery. Metabolic engineering seeks to re-wire plant biochemistry by, for example, elevating the levels of key enzymes or creating new metabolite storage capacities to boost the yield of desired phytochemicals. This is often closely linked with pathway engineering, which meticulously optimizes individual enzymatic steps, and host engineering, which modifies the host organism (plant or microbial) to better support the engineered pathways.

Underpinning many of these targeted interventions are 'omics' technologies and an understanding of gene regulation. Metabolomics and genomics provide a comprehensive view of the plant's metabolic and genetic landscape, revealing the blueprint for phytochemical biosynthesis and guiding more effective engineering efforts. Alongside these, epigenetic modifications offer a nuanced yet powerful tool to influence phytochemical levels by altering gene expression without changing the underlying DNA sequence. A striking example of this is the epigenetic regulation of glucosinolate biosynthesis in *Arabidopsis thaliana* [23]. The fact that this regulation can be triggered by external stimuli, such as sound vibrations, provides novel insight into how environmental cues can modulate plant immunity and secondary metabolism.

Finally, strategies that harness external stimuli or beneficial biological interactions are also gaining prominence. Elicitation techniques use biotic or abiotic stressors to trigger the plant's natural defense mechanisms, often leading to an increased accumulation of protective phytochemicals. Similarly, symbiotic enhancements, such as leveraging mycorrhizal fungi or endophytic microorganisms, can improve nutrient uptake and stimulate secondary metabolite production in the host plant.

These diverse approaches, often used in combination, are significantly advancing our ability to produce phytochemicals more sustainably and efficiently. The following Table 1 provides a detailed look at recent research, showcasing specific examples of how these techniques—including epigenetic modifications (EM), gene editing (GE), metabolomics and genomics (MG), molecular breeding (MB), metabolic engineering (ME), host engineering (HE), pathway engineering (PE), symbiotic enhancement (SE), and elicitation (E)—are being applied to a variety of plant species and microbial systems to achieve these goals.

The case studies presented in Table 1 collectively illustrate a vibrant and rapidly evolving landscape of research aimed at sustainable phytochemical production. A clear trend is the increasing sophistication and integration of techniques. For instance, metabolic engineering (ME) is often coupled with elicitation (E) or underpinned by insights from metabolomics and genomics (MG) to achieve targeted outcomes, as seen in *Amaranthus palmeri* and *Artemisia annua*. Gene editing (GE), particularly CRISPR/Cas9, emerges as a powerful tool for creating non-transgenic improvements, enhancing nutritional value in *Brassica cretica* or altering fatty acid profiles in *Camelina microcarpa*. Host engineering (HE) in microbial systems like *S. cerevisiae* and *E. coli* demonstrates significant promise for scalable production of complex plant compounds, such as noscapine and salidroside, thereby reducing reliance on plant biomass.

A meta-analysis of the case studies in Table 1 reveals distinct strategic patterns. For instance, in established plant systems, elicitation (E) and symbiotic enhancement (SE) are frequently employed to boost the yield of existing pathways (e.g., *Berberis lycium*, *Andrographis paniculata*). In contrast, for the *de novo* production of complex molecules, host engineering (HE) in microbial platforms like *S. cerevisiae*

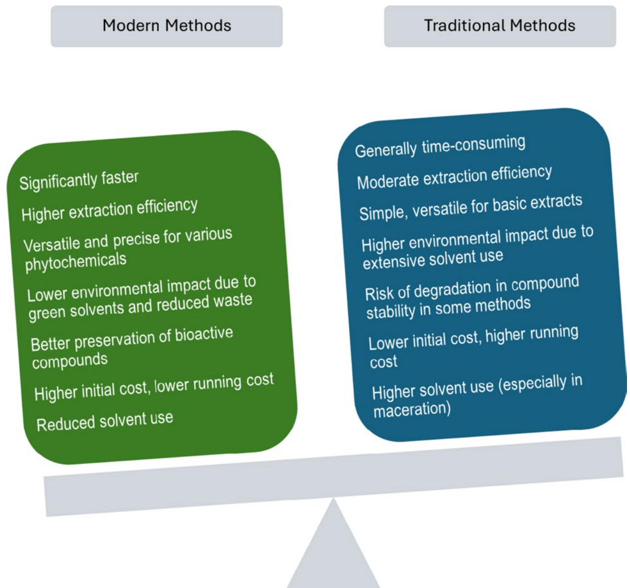


Fig. 4 A comparative overview of modern versus traditional techniques for natural product extraction

and *E. coli* is the dominant strategy, enabling the complete biosynthesis of compounds like noscapine and salidroside, thereby bypassing agriculture entirely.

Common successes include significant increases in target phytochemical yields (e.g., andrographolide in *(A) paniculata* via SE, catharanthine in *Catharanthus roseus* via ME) and the elucidation of complex regulatory networks (e.g., in *Astragalus membranaceus* via PE). However, challenges remain, particularly in translating laboratory successes to industrial-scale production and navigating the regulatory landscape for genetically engineered organisms. While techniques like elicitation can boost phytochemicals (e.g., in *(B) lycium*), the responses can be species-specific and require careful optimization. Overall, the most promising approaches often involve a multi-pronged strategy, combining precise genetic tools with a deep understanding of plant and microbial physiology to achieve sustainable and economically viable phytochemical production.

6 Validating the pipeline: integrated systems in practice

The industrial application of phytochemical production from plants has seen numerous success stories, demonstrating the efficacy of biotechnological advances in harnessing plant secondary metabolites. One such example is the large-scale production of the anti-cancer drug paclitaxel, originally sourced from the bark of the Pacific yew tree (*Taxus brevifolia*) [24]. Due to sustainability concerns, methods like plant cell culture technology have been employed, leading to a more sustainable and scalable production process. This shift has critically reduced the reliance on wild harvesting, directly contributing to the conservation of *T. brevifolia* populations and aligning with UN SDG 15 (Life on Land) by protecting terrestrial ecosystems.

Metabolic engineering has been pivotal in enhancing the production of plant secondary metabolites. By manipulating biosynthetic pathways, researchers have increased the yield of desired compounds in plant cell cultures. This approach has been particularly successful in producing complex pharmaceuticals like paclitaxel and tropane alkaloids, which are challenging to synthesize chemically. Phytochemicals such as vinca alkaloids (vinblastine and vincristine), podophyllotoxin, paclitaxel, and camptothecin derivatives are

Fig. 5 Overview of plant enhancement techniques for phytochemical production

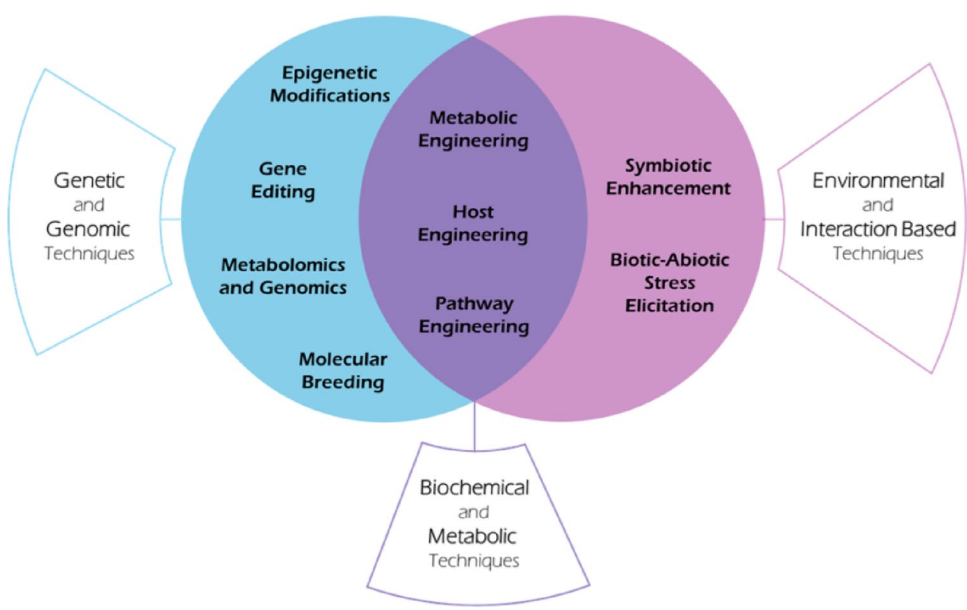


Table 1 Recent research on sustainable biosynthesis of essential phytochemicals of plants

Research material	Technique	Key findings/Outcomes	Reference
Allium sativum L.	MB	Garlic traits (organosulfur, phenolics, solids) vary significantly by genotype and environment; certain cultivars consistently high in phytochemicals.	[96]
Amaranthus palmeri S.Watson	ME, E	Glyphosate resistance in *Amaranthus palmeri* induces specific metabolic changes, distinct from general stress responses like drought.	[97]
Andrographis paniculate (Burm.f.) Wall.	MB	Enhanced andrographolide content and highlighted the advancements in phytochemical enhancement.	[98]
Andrographis paniculate (Burm.f.) Wall.	SE	Identified bacterial endophytes, particularly *Micrococcus luteus*, which significantly increased the biomass and andrographolide content in *Andrographis paniculata*.	[99]
Arabidopsis thaliana (L.) Heynh.	EM	Elucidated the epigenetic regulation of glucosinolate biosynthesis in plants triggered by sound vibration, providing insights into the epigenetic modulation of plant root immunity.	[23]
Arctostaphylos uva-ursi (L.) Spreng.	MB	Highlighted genetic influences on varying arbutin, catechin, and myricetin levels in populations, affected by geographic and climatic factors.	[100]
Artemisia annua L.	ME	Discovery of AabHLH2 and AabHLH3 as negative regulators in artemisinin biosynthesis offers potential CRISPR/Cas9 targets for enhanced artemisinin production.	[101]
Astragalus membranaceus var. mongholicus (Bunge) P.K.Hsiao	PE	Merged metabolomic and transcriptomic analyses to elucidate the biosynthesis pathways of key phytochemicals, offering detailed molecular regulatory insights.	[102]
Azadirachta indica A.Juss.	E	Increased salinity in *Azadirachta indica* root cultures slightly enhanced azadirachtin production, particularly under higher salinity in the 4th incubation week.	[103]
Azospirillum brasilense	HE	Engineered *Azospirillum brasilense* Car-1 to overproduce carotenoids and heterologously produce geraniol and amorphadiene, showcasing its metabolic engineering potential.	[104]
Bacillus subtilis	HE	Developed a *Bacillus subtilis* system producing α-L-arabinofuranosidase, a key enzyme for the bioprocessing and valorization of phytochemical-rich biomass (e.g., wheat bran) by degrading complex arabinoxylans to release valuable compounds.	[105]
Berberis lyceum Royle	E	Elicitation with methyl jasmonate and salicylic acid significantly increased berberine, palmatine, and polyphenols in *Berberis lycium* callus cultures.	[106]
Bidens pilosa L.	ME	Manipulation of *Bidens pilosa* callus metabolome with PGRs, particularly 2,4-D and BAP, led to distinct profiles dominated by chlorogenic acids.	[107]
Brassica oleracea L.	EM	Explored UVA-radiation's impact on growth, phytochemicals, and glucosinolate biosynthesis in Chinese kale, linking photoreceptors to glucosinolate gene expression.	[108]
Brassica cretica Lam.	GE	CRISPR/Cas9 editing of *MYB28* in broccoli protoplasts yielded glucoraphanin-rich cultivars, enhancing nutritional value without typical transgenic GMO issues.	[109]
Brassica rapa L.	ME	Optimized protoplast isolation and transfection in Chinese cabbage using a binary vector enhanced metabolic engineering, yielding high efficiency for gene analysis and genome editing.	[110]
Camelina microcarpa Andrz. ex DC.	GE	Knocking out *FAE1* genes in the seeds significantly reduced VLCFAs to less than 2%, increasing C18 unsaturated fatty acids for industrial and food/feed uses.	[111]
Camellia sinensis (L.) Kuntze	EM	Increased expression of ABA biosynthesis genes under dehydration stress in postharvest tea processing, underlining epigenetic regulation in phytohormone accumulation.	[112]
Catharanthus roseus (L.) G.Don	ME	Explored metabolic changes in *C. roseus* cell cultures with geraniol synthase overexpressed, indicating the need for omics analysis in understanding metabolic engineering effects.	[113]
Catharanthus roseus (L.) G.Don	ME	Overexpression of *CrTPT2* transporters in *C. roseus* hairy roots increased catharanthine accumulation fivefold.	[33]
Citrus aurantium L.	SE	Endophytic bacteria, particularly *Bacilluscereus* and *Pseudomonasaeruginosa*, improve sour orange seedlings' growth, offering biofertilizer alternatives to enhance crop yield and health.	[114]
Corynebacterium glutamicum	PE	Utilized synthetic biology to adjust metabolic pathways and manipulate host enzymes, significantly boosting essential compounds for phytochemical biosynthesis.	[115]
Dioscorea alata L.	MB	Selection and hybridization of parental lines from diverse heterotic groups can maximize genetic diversity and exploit population heterosis, enhancing winged yam breeding programs.	[116]
Duboisia leichhardtii (F.Muell.) F.Muell.	ME	Aimed to boost scopolamine in *Duboisialeichhardtii* by silencing the *QPT* gene, enhancing yields for pharmaceuticals through gene silencing techniques.	[117]
Escherichia coli	PE	Optimized a microbial co-culture system for indigo production, offering flexible pathway balancing and reduced metabolic burden, enhancing phytochemical synthesis.	[118]

Table 1 (continued)

Research material	Technique	Key findings/Outcomes	Reference
Escherichia coli	HE	Tested genetically engineered *E. coli*-produced salidroside for safety; found non-mutagenic with a NOAEL of 2,000 mg/kg in rats, suitable for supplements and pharmaceuticals.	[119]
Fragaria x ananassa (Duchesne ex Weston) Duchesne ex Rozier	E	Preharvest leaf wounding on *Fragaria* x *ananassa* significantly raised phenolics (up to 137%) and sugars in strawberries, overexpressing phenylpropanoid and sugar transport genes, demonstrating phytochemical enhancement from distant stress.	[120]
Gloriosa superba L.	SE	Endophytic *Bacillus* bacteria, especially strains NBRI HYL5 and NBRI HYL8, significantly enhanced *Gloriosasuperba'*s growth and colchicine, gloriosine levels.	[121]
Isatis tinctoria L.	E	Blue LED light exposure in *Isatis tinctoria* L. hairy root cultures significantly increased flavonoids (up to 9.31-fold) and biomass, suggesting CRY-mediated light signaling enhances flavonoid biosynthesis.	[122]
Juniperus procera Hochst ex Endl.	E	Biogenic silver nanoparticles (AgNPs) applied to *Juniperus procera* callus cultures notably increased biomass, antioxidants, and phytochemicals like coumarin, tannic acid, quercetin, rutin, gallic acid, and hesperidin.	[123]
Lallemantia iberica Fisch. & C.A.Mey.	E, SE	Cs-NPs and Myco-Root application under 60% FC irrigation notably increased *Lallemantiaiberica*'s essential oil content, especially germacrene D and (E)-caryophyllene, enhancing oil quality and plant physiology under water deficit.	[124]
Lathyrus oleraceus Lam.	GE	CRISPR/Cas9 editing of the *PsLOX2* gene in peas significantly reduced lipoxygenase activity, cutting beany flavored volatiles and boosting essential polyunsaturated fatty acids, enhancing seed nutritional quality.	[125]
Malus toringo (Siebold) Siebold ex de Vriese	EM	Analyzed the expression of genes related to flavonoid and anthocyanin biosynthesis, revealing the mechanism of petal color fading.	[126]
Malus Mill.spp.	MB	Genome-wide association studies (GWAS) were used to explore the genetics of phytochemical production and red skin color in apples, revealing the complexity of fruit quality traits influenced by genetic and environmental factors.	[127]
Microbial consortium	PE	Developed a microbial co-culture converting simple sugars to phenylpropenes like ferulic acid, eugenol, using enzyme promiscuity and pathway modularization, enabling scalable plant compound synthesis.	[128]
Musa acuminata Colla	PE	Elucidated the interplay between R2R3 MYB-type activators and repressors in regulating proanthocyanidin biosynthesis in banana.	[129]
Nicotiana benthamiana Domin	ME	Metabolic engineering of *Nicotianabenthamiana* chloroplasts to overexpress certain enzymes significantly boosted taxane production, including Taxol, providing a sustainable alternative to traditional extraction methods.	[130]
Nicotiana benthamiana Domin	GE	Used CRISPR/Cas9 to create a glyco-engineered *Nicotianabenthamiana* platform for producing glycoprotein-based phytochemicals with tailored glycosylation patterns designed to enhance bioactivity and reduce potential immunogenicity.	[131]
Ocimum basilicum L.	E	Application of abiotic elicitors, including drought, calcium, salicylic acid, and varying light intensities, increased the yield and altered the composition of essential oils in *O. basilicum* L.	[132]
Ocimum basilicum L.	E	Vermicompost application significantly alters phenylpropene biosynthesis in different chemotypes of basil (*Ocimumbasilicum* L.), in turn affecting the plant's aroma and antimicrobial properties. A consistent pattern revealed that solid vermicompost decreased the concentration of methylated phenylpropenes and related gene expression, whereas vermicompost tea increased the production of these compounds and enhanced gene activity. This indicates that the application method is a critical factor in shaping the chemical profile of basil.	[133, 134]
Ocimum tenuiflorum L.	SE	Arbuscular mycorrhiza notably improved essential oil composition and antioxidant properties in *Ocimumtenuiflorum* L., enhancing its pharmaceutical and therapeutic value.	[135]
Ophiorrhiza pumila Champ. ex Benth.	ME	Targeted metabolic engineering in *Ophiorrhizapumila* hairy roots effectively increased anti-cancer drug camptothecin production, demonstrating the potential of manipulating metabolic pathways for enhanced phytochemical synthesis.	[136]
Oryza sativa L.	EM	Demonstrated the extensive activation of multiple rice diterpenoid phytoalexin biosynthesis genes by OsWRKY10, emphasizing the role of transcription factors in mediating the effects of epigenetic modifications on phytochemical production.	[137]
Pinus koraiensis Siebold & Zucc.	MG	The study emphasizes the importance of natural genetic variation across different geographical provenances for the genetic improvement of *Pinuskoraiensis* in China, underscoring its significance in breeding programs aimed at enhancing phytochemical content.	[138]
Platycodon grandifloras A.DC.	EM	Conducted whole-genome, transcriptome, and methylome analyses to provide insights into the evolution of platycoside biosynthesis in *Platycodon grandiflorus*, highlighting the impact of epigenetic modification on gene families affecting platycoside biosynthesis.	[139]

Table 1 (continued)

Research material	Technique	Key findings/Outcomes	Reference
Prunus persica (L.) Batsch	PE	Demonstrated the fine-tuning regulatory loop induced by activator-type *R2R3-MYB* genes, which balance the accumulation of anthocyanin and proanthocyanidin in *Prunus persica* by competing with MYB activators for binding to basic Helix Loop Helixes (bHLHs).	[140]
Saccharomyces cerevisiae	HE	Achieved the complete biosynthesis of noscapine and halogenated alkaloids in yeast by introducing and optimizing the expression of genes involved in the biosynthetic pathway.	[141]
Saccharomyces cerevisiae	HE	A specialized engineering framework was used to increase daidzein production by 94-fold to 85.4 mg/L and to synthesize bioactive puerarin (72.8 mg/L) and daidzin (73.2 mg/L) using plant glycosyl-transferases, setting the stage for synthetic yeast cell factories to produce valuable isoflavonoids.	[142]
Solanum lycopersicum L.	GE	CRISPR-based gene editing targeted genes for pectin-degrading enzymes, notably pectate lyase (PL), polygalacturonase 2a (PG2a), and β-galactanase (TBG4), affecting fruit firmness and possibly altering phytochemical composition related to ripening.	[143]
Solanum esuriale Lindl.	E	The study on *Solanumxanthocarpum* callus cultures under varied monochromatic lights showed light as a key elicitor influencing biomass, secondary metabolites, and properties like antioxidant, anti-diabetic, and anti-inflammatory activities.	[144]
Syzygium aromaticum (L.) Merr. & L.M.Perry	MG	The research provided a 370-Mb high-quality clove genome assembly, showing genome conservation with *Eucalyptusgrandis* and identifying eugenol biosynthesis genes, alongside a hypothesis for eugenol acetate's role in eugenol accumulation in clove leaves and buds.	[145]
Trifolium pratense L.	GE	CRISPR/Cas9-mediated knockout of the isoflavone synthase (*IFS1*) gene *Trifolium pratense* resulted in lower isoflavone levels, unaffected nodulation, but increased expression of biotic stress response genes, suggesting a defensive role for isoflavones in the rhizosphere.	[146]
Taxus chinensis (Rehder & E.H.Wilson) Rehder	ME, GE	Repression of the *PAL* gene via CRISPR-mediated targeted DNA methylation resulted in an approximately 25-fold increase in paclitaxel accumulation (from 0.76 µg/g DW to 24.5 µg/g DW).	[34]

ABA: Abscisic acid, AgNPs: silver nanoparticles, BAP: 6-Benzylaminopurine, bHLHs: basic Helix-Loop-Helix transcription factors, C18: fatty acids with an 18-carbon backbone, CrTPT2: *Catharanthusroseus* pleiotropic drug resistance transporter 2, CRY: Pesticidal crystal protein, Cs-NPs: Chitosan Nanoparticles, DW: dry weight, FAE1: Fatty Acid Elongation 1, FC: Field capacity, GMO: genetically modified organism, GWAS: Genome-Wide Association Studies, IFS1: isoflavone synthase 1, MYB28: myb domain protein 28, NOAEL: No-Observed-Adverse-Effect Level, PAL: Phenylalanine Ammonia-Lyase, PG2a: polygalacturonase 2a, PGRs: Plant Growth Regulators, PL: pectate lyase, PsLOX2: *Pisumsativum* lipoxygenase-2, QPT: quinolinic acid phosphoribosyl transferase, R2R3-MYB: a class of transcription factors containing two repeats of the MYB DNA-binding domain, TBG4: tomato β-galactosidase 4, VLCFAs: very long-chain fatty acids.

produced using plant cell biofactories. These compounds are crucial in cancer therapy and are produced through biotechnological methods to ensure sustainability [25, 26]. To achieve industrial-scale camptothecin production, a shift in bioprocess engineering is essential, moving beyond traditional methods to a holistic strategy. This involves optimizing upstream fermentation parameters and implementing high-cell-density cultivation, alongside innovative bioreactor designs like the sequencing batch reactor. Such an integrated approach enhances yield, ensures process stability by mitigating production attenuation, and paves the way for the economically viable and scalable manufacturing of camptothecin [27]. For vinca alkaloids, traditionally requiring vast amounts of *C. roseus* plant material, plant cell culture offers a significant sustainability gain by reducing land and water footprint, aligning with Green Chemistry Principle 7 (Use of Renewable Feedstocks) when cell cultures are considered as such.

The integration of plant cell culture with bioreactor technology has been crucial for scaling up the production of phytochemicals. Bioreactors offer a controlled environment that enhances the growth and productivity of plant cells, making it feasible to produce large quantities of secondary metabolites [28]. Despite the slow growth of the plant bioreactor industry, there have been notable successes. For instance, the production of shikonin in stirred tank reactors and other secondary metabolites in various bioreactor systems has demonstrated the potential of this technology for industrial applications [29]. Moreover, the production of saponins, used in a wide range of applications from pharmaceuticals to cosmetics, has been optimized through in vitro plant tissue cultures, notably in species like *Panax ginseng*, enhancing yield and purity [30], thereby potentially reducing pressure on wild or slow-growing plant populations. Another breakthrough has been in the production of curcumin from turmeric (*Curcuma longa*). Through tissue culture and metabolic engineering, curcumin yield has been significantly increased, making its use more feasible in various industries, especially in food and medicine [31, 32], reflecting a more efficient use of plant material.

The five-fold increase in catharanthine accumulation in *C. roseus* hairy roots, as achieved by Wang et al. [33]. serves as a prime example of how upstream engineering can be a critical enabler for downstream sustainability. This is not merely an incremental improvement; such a significant increase in titer can cross a critical economic viability threshold. This, in turn, renders greener yet often more capital-intensive extraction techniques, such as supercritical fluid extraction, commercially competitive against traditional, solvent-intensive methods. Similarly, the reported ~25-fold increase in paclitaxel accumulation following CRISPR-mediated gene suppression by Brzycki Newton et al. [34]. powerfully demonstrates this principle. At naturally low concentrations, the cost of green purification methods would be prohibitive. However, at these engineered high titers, the entire downstream process can be redesigned around sustainability principles, thus completing the 'gene-to-final-product' pipeline in a manner that is both economically and environmentally robust.

Another significant achievement is the production of artemisinin, a key compound in anti-malarial treatments. Originally derived from the plant *A. annua*, its production has been revolutionized by synthetic biology approaches, particularly through the work of AMYRIS and SANOFI, to produce semi-synthetic artemisinin, thereby meeting global demands more effectively [35, 36]. This innovation ensures a scalable and consistent supply, independent of agricultural volatilities, and utilizes simple sugars as a feedstock via fermentation, aligning with Green Chemistry Principle 7 (Use of Renewable Feedstocks) and directly supporting UN SDG 3 (Good Health and Well-being).

Derived from *Cannabis sativa*, cannabinoids are increasingly used in the cosmeceutical industry. Advances in plant biotechnology, such as tissue culture, have facilitated the large-scale production of these compounds, which are valued for their therapeutic properties [37]. Additionally, alternative biotechnological platforms are emerging for cannabinoid production. Genetic engineering of fungi, such as *Penicillium chrysogenum*, has been explored for the biosynthesis of Δ9-tetrahydrocannabinolic acid (Δ9-THC), offering a sustainable and high-yield alternative to plant extraction [38]. Engineered *S. cerevisiae* systems allow for the production of cannabinoids like cannabigerolic acid and cannabidiolic acid from simple sugars, providing scalable and controlled production methods [39, 40]. Advances in synthetic biology have further enabled cannabinoid production through heterologous systems, bypassing the need for cannabis plants and utilizing engineered microorganisms for compounds like Δ9-THC and cannabidiol [41, 42]. These microbial fermentation routes offer sustainability benefits by potentially reducing the high energy and water consumption associated with traditional cannabis cultivation, aligning with Green Chemistry Principle 6 (Design for Energy Efficiency).

The industrial production of polyphenols is expanding due to rising demand in sectors like food, pharmaceuticals, and cosmetics. Key polyphenols such as lignins, tannins, and cashew nutshell liquid are widely used in industrial applications, particularly in biobased additives and materials [43]. Phenolic acids, valued for their antioxidant properties, are increasingly produced via microbial biosynthesis as a sustainable alternative to chemical synthesis [44]. Agricultural waste from *Olea europaea* and *Vitis vinifera* is also being utilized for polyphenol recovery, promoting a circular economy approach [45]. This valorization of waste streams is a direct application of Green Chemistry Principle 1 (Prevention) and Principle 7 (Use of Renewable Feedstocks). Advances in microbial engineering and synthetic biology have enabled the eco-friendly production of flavonoids, stilbenes, and anthocyanins, though yield optimization is still needed for commercial success [46, 47]. Additionally, base-catalyzed depolymerization of lignin and technologies like reverse osmosis and cavitational reactors provide scalable, energy-efficient methods for polyphenol extraction [48–50].

Microbial production of flavonoids has advanced significantly, offering sustainable alternatives to plant-based methods. Flavanones like naringenin, pinocembrin, and eriodyctiol serve as precursors for a variety of flavonoids, with engineered microorganisms enabling cost-effective production [51]. Metabolic engineering strategies have optimized microbial cell factories to efficiently produce flavonoids such as flavones, isoflavones, and anthocyanins, improving yields and titers [52, 53]. Nonconventional yeasts, including *Yarrowia lipolytica* and *Pichia pastoris*, are emerging as robust hosts for flavonoid synthesis due to their metabolic versatility [54]. Synthetic biology approaches, such as genetically encoded biosensors, further enhance production pathways. Co-culture systems, using multiple engineered microbial strains, enable the reconstruction of complex biosynthetic pathways, leading to higher production of specific bioactive flavonoids [55, 56]. These microbial routes represent a significant step towards sustainability by reducing reliance on agricultural land and resources.

The large-scale synthesis of resveratrol serves as a prominent example. Resveratrol, a compound found in grapes and berries with significant health benefits, is now produced industrially through biotechnological methods. Advances in genetic engineering have enabled enhanced production of resveratrol in yeast and bacteria, thereby facilitating its use in pharmaceuticals and nutraceuticals [57–59]. This microbial fermentation approach, utilizing renewable sugar feedstocks, aligns with Green Chemistry Principle 7 (Use of Renewable Feedstocks) and offers enhanced energy efficiency compared to extensive agricultural extraction.

Several carotenoids are produced on an industrial scale due to their wide-ranging applications. Astaxanthin, commonly used in aquaculture, is primarily sourced from microalgae like *Haematococcus pluvialis* and yeast such as

Phaffia rhodozyma, with natural production favored over synthetic. β-Carotene, used as a colorant and vitamin A precursor, is produced from *Dunaliella salina* and *Blakeslea trispora*. Lutein, essential for eye health, is extracted mainly from marigold flowers (*Tagetes erecta*), while microbial production remains under development. Canthaxanthin, used in poultry feed, is produced synthetically and via microbial fermentation. Lycopene, valued for its antioxidant properties, is sourced from tomatoes and microbial fermentation [60]. Zeaxanthin, another eye health carotenoid, is derived from both synthetic and natural microbial sources [61]. Lastly, fucoxanthin, produced from marine microalgae like *Phaeodactylum tricornutum*, is gaining popularity for its health benefits [62]. The shift towards microbial and algal production for many of these carotenoids represents a significant sustainability gain by reducing reliance on petrochemical-derived synthetic routes or resource-intensive extraction, aligning with Green Chemistry Principle 7 (Use of Renewable Feedstocks).

Collectively, these case studies validate the "gene-to-final-product" pipeline by illustrating distinct models of synergistic integration. In the first model, "Upstream-Enables-Downstream," significant titer increases from upstream metabolic engineering, as seen with paclitaxel and catharanthine, cross a critical economic threshold that makes greener, more capital-intensive downstream extraction methods commercially viable. A second model, "Downstream-Feeds-Upstream," is evident in the valorization of agricultural wastes for polyphenol recovery, where downstream processing of by-products generates sustainable feedstocks for upstream microbial platforms, creating a circular bioeconomy. The most transformative model is "Upstream-Replaces-Downstream," where heterologous production in engineered microbes—exemplified by artemisinin, cannabinoids, and various flavonoids—obviates the need for resource-intensive agriculture and subsequent extraction entirely. These models are not merely theoretical; they represent proven strategies where biotechnological innovation does not just optimize a single step but reconfigures the entire value chain for phytochemical production, driving it towards genuine sustainability.

7 The impact of the advancements on agriculture, economy, and nutrition

The advancements in the industrial production of phytochemicals from plants have had a profound impact on agriculture, the economy, and nutrition. In agriculture, these biotechnological innovations have led to more sustainable and efficient farming practices. For instance, the development of tissue culture and genetic engineering techniques for high-yield crops reduces the need for extensive land use and lowers the environmental impact. Economically, the biotechnological production of phytochemicals represents a burgeoning market. The global demand for natural products and their derivatives has led to significant economic growth in this sector, creating new job opportunities and revenue streams, particularly in the pharmaceutical and nutraceutical industries [63, 64]. Nutritionally, the increased availability of phytochemicals like resveratrol, curcumin, and saponins, known for their health-promoting properties, has enhanced the nutritional value of food products. This availability has also led to the development of functional foods and dietary supplements that cater to health-conscious consumers, thereby contributing to public health and wellness.

Building on these impacts, the influence of phytochemical production on global agriculture extends to crop protection as well. The utilization of phytochemicals in biopesticides offers an eco-friendly alternative to synthetic chemicals, reducing the environmental footprint of agriculture [65]. Prominent examples include neem oil, containing the active compound azadirachtin which functions as an antifeedant and growth inhibitor for numerous insect species [66–68], and microbial biopesticides such as *Bacillus thuringiensis*, which produces proteins that are specifically toxic to certain insect larvae [69, 70]. This shift not only promotes sustainable farming practices but also helps in maintaining soil health and biodiversity. Economically, the biotech-driven phytochemical industry is a significant contributor to the bioeconomy, fostering innovation and competitiveness in agricultural sectors worldwide. This contribution is particularly notable in developing countries, where cultivation and processing of medicinal plants provide an important source of income [71, 72]. Moreover, the enhanced production of phytochemicals has implications for global nutrition security. By improving the nutritional profile of food crops through biofortification, these advances address micronutrient deficiencies prevalent in many parts of the world, thereby contributing to the fight against malnutrition [73]. These advancements in phytochemical production from plants have facilitated the discovery of new phytochemicals, enhancing opportunities for nutritional research and innovation. For instance, intensive research on the bioactive components of ginseng, driven by the need to standardize and enhance their production via biotechnological means, has enabled the detailed characterization of compounds like gintonin. Subsequent studies revealed this compound's potential to suppress cancer metastasis by targeting the TGF-β signaling pathway, opening previously unknown avenues for pharmaceutical development [74]. Similarly, the application of synthetic biology to solve an ecological problem—bee malnutrition—required the precise identification and subsequent production in engineered yeast of six essential sterol compounds critical for bee health [75]. This process resulted in the creation of a novel, nutritionally complete supplement that was not previously available. Such progress highlights the extensive impact on various sectors, including agriculture, health, and nutrition, presenting a significant stride towards a sustainable, economically feasible, and nutritionally rich future.

In conclusion, the advancements in the industrial production of phytochemicals have significantly impacted agriculture, the economy, and nutrition. In agriculture, these biotechnological innovations have enabled more sustainable and efficient farming practices by reducing land use and environmental impact through high-yield crops developed via tissue culture and genetic engineering. Economically, the expanding market for natural products and their derivatives has fostered economic growth, generated new jobs, and created revenue streams, particularly in the pharmaceutical and nutraceutical industries. Nutritionally, the increased availability of health-promoting phytochemicals such as resveratrol, curcumin, and saponins has enriched food products, promoting the development of functional foods and dietary supplements that enhance public health and well-being.

Furthermore, phytochemical production has advanced crop protection by providing eco-friendly biopesticides that reduce the need for synthetic chemicals, thereby supporting soil health and biodiversity. The biotechnological phytochemical industry also plays a key role in the bioeconomy, especially in developing countries where cultivating medicinal plants offers valuable income opportunities. In terms of nutrition, these advancements contribute to addressing micronutrient deficiencies by improving the nutritional content of crops through biofortification. Overall, the impact of phytochemical production extends across multiple sectors, paving the way for a sustainable, economically viable, and nutritionally rich future that enhances global health and agricultural resilience.

8 Regulatory and ethical considerations

The rapid evolution of plant biotechnology, while offering substantial promises for sustainable phytochemical production, is inextricably linked to a complex landscape of regulatory and ethical challenges. These domains are frequently intertwined, profoundly influencing public acceptance, market authorization, and the equitable deployment of novel technologies. A nuanced understanding of this landscape is essential for responsible innovation.

8.1 The global regulatory dichotomy: process-based vs. product-based frameworks

The international regulatory environment for genetically modified organisms (GMOs) is characterized by significant divergence, primarily rooted in two contrasting philosophical approaches. The process-based framework, notably adopted by the European Union, regulates an organism based on the method of its creation. Under this paradigm, if an organism's genome has been altered using genetic engineering techniques, it is classified as a GMO and subjected to stringent oversight, irrespective of the final product's characteristics [76, 77]. This approach prioritizes the precautionary principle, focusing on potential risks associated with technology itself.

In contrast, the product-based approach, pioneered in the United States, centers on the characteristics of the final product. According to this framework, if a genetically modified plant exhibits traits that could also be achieved through conventional breeding, it may be exempted from GMO regulations [78, 79]. This perspective emphasizes risk assessment based on the novelty and potential hazard of the organism's traits rather than the technology used to introduce them. This fundamental dichotomy in regulatory philosophy creates a complex and often unpredictable global landscape for technology developers and agricultural producers.

8.2 The impact of novel technologies: gene editing versus heterologous gene expression

The tension between these two regulatory philosophies has been significantly amplified by the advent of novel biotechnologies. Heterologous gene expression, which involves the transfer of genetic material from a foreign species into a host organism (e.g., a bacterial gene into a plant), is almost universally classified as creating a GMO under both systems due to the introduction of exogenous DNA. The principal point of contention, however, arises from precision gene-editing technologies such as CRISPR.

CRISPR enables the creation of specific modifications within a plant's own genome—such as minor deletions or gene knockouts—that are often indistinguishable from changes that could arise through natural mutation or conventional breeding [80]. Within the EU's process-based system, the use of a genetic engineering process renders the resulting plant a regulated GMO [81]. Conversely, under the product-based framework of the US, if the final modification yields a trait that is familiar and could have been conventionally bred, the plant may be exempt from regulatory oversight [82]. This illustrates a critical dynamic where the pace of technological innovation fundamentally challenges

Table 2 A comparative summary of regulatory approaches for engineered phytochemical production platforms

Feature	Whole-plant engineering (e.g., GM maize)	Plant tissue culture (in bioreactor)	Microbial fermentation (e.g., engineered yeast)
Primary regulatory focus	Environmental release, gene flow, food/feed safety	Biological containment, prevention of release	Contained use, worker safety, waste management
Typical U.S. approach (product-based)	Regulated by USDA, EPA, FDA. Exemption possible for some gene edits if outcome is similar to conventional breeding [82].	Lower regulatory burden if contained. FDA approval may be required if product is for food/feed.	GRAS (Generally Recognized as Safe) pathway is often available for food ingredients. Regulated under contained-use frameworks.
Typical EU approach (process-based)	Regulated as a strict GMO requiring comprehensive risk assessment and labeling, regardless of the specific modification [78].	Regulated as a contained-use GMO.	Regulated as a contained-use GMO.
Key challenge	Public acceptance, lengthy deregulation process, potential for gene flow.	Scaling up production while maintaining sterility and containment.	Process optimization, yield, downstream purification.

USDA: U.S. Department of Agriculture, EPA: Environmental Protection Agency, FDA: Food and Drug Administration, GMO: genetically modified organism

and compels the re-evaluation of established, decades-old legal frameworks.

8.3 Platform-specific regulatory considerations

The regulatory scrutiny applied to engineered organisms is further differentiated by the production platform employed, as summarized in Table 2.

Whole-plant engineering: Genetically modified plants intended for cultivation in agricultural fields are subject to the most rigorous regulatory oversight. This is primarily due to their direct release into the environment, which necessitates comprehensive assessments of potential gene flow to wild relatives, impacts on non-target organisms, and overall food and feed safety [83, 84]. In the United States, this process is managed by a coordinated framework involving the USDA, EPA, and FDA [85].

Plant tissue culture: When phytochemical production is conducted using plant tissue cultures within contained systems, such as bioreactors, the regulatory framework shifts to a focus on 'contained use'. The principal objective of these regulations is to prevent the accidental release of genetically modified material into the environment. As long as the material remains within the contained facility, the regulatory burden is typically substantially lower than that for whole plants intended for environmental release.

Microbial engineering: Engineered microorganisms (e.g., yeast, *E. coli*) used in industrial fermentation also fall under contained-use regulations. This field benefits from a long history of industrial application, resulting in well-established regulatory pathways. Processes utilizing engineered microbes are generally considered to pose a lower environmental risk compared to the open-field release of GM plants, and pathways such as the Generally Recognized as Safe (GRAS) designation are often available for food ingredients produced via this method.

8.4 Multifaceted ethical dimensions

Parallel to these regulatory hurdles are complex ethical considerations that shape public discourse and policy. Concerns regarding human health, particularly potential allergenicity and the long-term effects of consuming GM foods, remain prominent in public debate [86]. Environmental ethics prompt critical questions about ecological risks, including the potential for gene flow to non-GM species, adverse impacts on non-target organisms, and the accelerated evolution of resistant pests [84, 87]. Furthermore, socio-economic ethics are of critical importance, focusing on issues of intellectual property rights, the consolidation of corporate control over the food supply, and the economic marginalization of small-scale farmers [88]. Broader moral questions, including deontological arguments about manipulating life ("playing God") and the imperative for a just and equitable distribution of the benefits and risks of these technologies, are central to ensuring that innovation aligns with societal values [89–92]. Navigating this intricate web of issues necessitates transparent scientific assessment, robust public engagement, and a steadfast commitment to responsible governance.

9 Future directions and opportunities

The future of phytochemical production is poised for a transformative shift, driven by the intersection of advanced biotechnologies and a deepening commitment to sustainability. The path forward lies in integrating different fields to create holistic and intelligent production systems.

9.1 Frontier 1: predictive biosynthesis with artificial intelligence (AI) and machine learning

While current metabolic engineering can optimize known pathways, the fusion of AI with synthetic biology offers the predictive power to design biosynthetic routes entirely *de novo*. This leads to a fundamental, testable hypothesis: Can generative AI models, trained on multi-omics data and enzyme functional databases, design non-natural, 'novel' pathways to produce complex phytochemicals that exceed their natural counterparts in yield and specificity? Future work should focus on the development and validation of these AI-designed pathways in microbial hosts. A critical, underexplored area is the use of genome-scale metabolic models to predict how these novel pathways will interact with the host's metabolism, allowing for proactive host engineering to mitigate metabolic burden and optimize precursor supply [93]. However, the primary obstacle to realizing this vision is not algorithmic but fundamental: the 'data bottleneck.' The predictive accuracy of these models is entirely dependent on large, high-quality, and standardized biological data. Therefore, a major future focus must be the development of automated, high-throughput experimental platforms to generate the necessary training data, effectively building the data infrastructure for the next generation of bio-engineering [94, 95].

9.2 Frontier 2: realizing a fully circular bioeconomy

Moving beyond the current trend of valorizing single waste streams, can we design integrated biorefineries that generate zero waste? The future vision is one of integrated systems that convert entire biomass streams into a portfolio of co-products, including food, feed, energy, and high-value phytochemicals. This approach perfectly embodies the Prevention principle (Principle 1) of Green Chemistry and directly serves UN SDG 12 (Responsible Consumption and Production) by transforming linear, wasteful systems into regenerative ones. The key challenges here are logistical and economic: ensuring that the collection and processing of heterogeneous agricultural waste are economically viable at scale, and the fact that technologies to efficiently deconstruct complex biomass into usable precursors are still maturing.

9.3 Frontier 3: smart agriculture and in-field elicitation

Can we use real-time data to actively manage and maximize phytochemical content on the farm? For phytochemicals where *in planta* production is optimal, the future lies in smart agriculture. This involves the integration of the Internet of Things, remote sensing, and AI. Farmers could deploy targeted stressors, such as specific light wavelengths or controlled drought, as a form of sensor-guided in-field elicitation to maximize the production of desired compounds just before harvest. Such systems would not only increase yield but also enhance agriculture's resilience to climate change, supporting UN SDG 2 (Zero Hunger) and SDG 13 (Climate Action). However, the high upfront costs of these technologies and the global digital divide present significant barriers to their widespread and equitable adoption.

10 Conclusion

The sustainable production of essential phytochemicals is no longer an option but a global necessity. As this review demonstrates, achieving this goal requires a strategic and deep integration of advanced plant biotechnology and green chemistry principles. This review argues that treating metabolic engineering, synthetic biology, and sustainable processing as isolated fields is insufficient. Instead, their convergence creates powerful synergies, enabling a fundamental transition from incremental improvements to a systems-level redesign of the entire production pipeline. The "gene-to-final-product" framework presented herein serves as a transformative conceptual and practical roadmap.

The successful case studies of artemisinin, paclitaxel, and various polyphenols provide compelling proof-of-concept, illustrating how this integrated approach simultaneously enhances efficiency, reduces environmental footprints, and achieves economic viability. These outcomes directly contribute to core tenets of Green Chemistry (e.g., waste prevention, use of renewable feedstocks, safer solvents, energy efficiency) and the UN Sustainable Development Goals, particularly SDG 3 (Good Health and Well-being) and SDG 12 (Responsible Consumption and Production) [10]. For instance, shifting artemisinin production to synthetic biology platforms decouples its supply from agricultural volatility, supporting SDG 3, while converting agro-industrial waste into high-value chemicals embodies Green Chemistry's Prevention (Principle 1) and exemplifies a truly circular biomanufacturing model that advances SDG 12. The microbial biosynthesis of flavonoids or cannabinoids, as an alternative to resource-intensive agriculture or chemical synthesis, presents a particularly potent example of this potential.

Looking forward, the future of phytochemical production lies in an even deeper integration, enhanced by digitalization. The synergy of AI and machine learning with synthetic biology will accelerate the design of novel pathways, while fully circular bioeconomies, realized through integrated biorefineries, will valorize entire biomass streams. This evolution points toward increasingly sophisticated and autonomous sustainable production systems. This review provides a foundational guide for this future, charting a course to revolutionize how the fundamental plant-derived molecules that underpin medicine, nutrition, and industry are sourced and manufactured.

Author contributions İlker Türkay: Conceptualization, Investigation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

Declarations

Conflict of interest The author has no conflicts of interest to declare that are relevant to the content of this article.

Ethical statements Neither ethical approval nor informed consent was required for this study.

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