



Review

Genomic Potential and Climate Resilience of *Agave angustifolia* Haworth in Raicilla Production

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Abstract

Agave angustifolia Haw. is one of the primary sources for the production of mezcals such as raicilla and tuxca, in western Mexico. In Jalisco, *Agave angustifolia* evolved from being a pre-Hispanic ritual and food resource (200–1500 CE) to becoming the primary basis for 16th-century vino mezcal, the precursor to all modern mezcals, including raicilla and tequila. This review synthesizes current genomic, epigenetic, and metabolic evidence to elucidate the species' evolutionary and adaptive potential. Our analysis suggests that the domestication of *A. angustifolia* is characterized by a “domestication paradox,” where intensive clonal management ensures short-term productivity but creates genetic bottlenecks that limit long-term adaptive capacity. We synthesize empirical evidence to show that adaptive plasticity is driven by the integration of Crassulacean Acid Metabolism (CAM) flexibility and dynamic global DNA methylation (GDM) profiles, which, while currently correlative, suggest an environmental response mechanism. We conclude that securing the socio-economic viability of *Agave* spirits requires a transition from intensive monocultures to regenerative agroforestry, incorporating sexual propagation to maintain evolutionary potential. Furthermore, we outline a roadmap for Genomics-Assisted Breeding (GAB 4.0), integrating marker-assisted selection for juvenile traits to accelerate the release of resilient biotypes, and precision diagnostic tools to reduce the ecological footprint of *Agave* production. This framework secures the genomic integrity of traditional spirits within a circular, climate-resilient bioeconomy.

Keywords: genetic diversity; epigenomics; CAM metabolism; chloroplast genome; transcriptomics; micropropagation; tequila; *Agave angustifolia*; raicilla; domestication syndrome



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1. Introduction

The genus *Agave* L. represents one of the most remarkable examples of biological and cultural evolution in the Americas [1–3]. With Mexico as its primary center of origin and diversification, these plants have been utilized for over 9000 years as sources of food, fiber, and fermented beverages [4,5]. Archeological evidence demonstrates that *Agave* species, specifically *A. angustifolia* and *A. maximiliana*, were integral to the dietary, economic, and ceremonial frameworks of the populations in Colima and Jalisco from 200 to 1500 Common Era (CE) [6].

The primary use of agave lies in the production of spirituous beverages. Etymologically and historically, all distillates derived from cooked agave are classified as mezcals (a term rooted in the Nahuatl *mexcalli*, from *metl*, ‘maguey,’ and *ixcalli*, ‘cooked’) and originated in western Mexico during the colonial period [4,7]. Consequently, mezcal serves as a

generic descriptor for all Mexican-produced agave spirits, encompassing diverse regional products such as tequila, bacanora, raicilla, mezcal, sisal, and tuxca, among others [4,8–12].

Zizumbo and Colunga [13], aligning with the findings of Bruman [14], documented that *Agave* distillation in Western Mexico commenced between 1580 and 1600 [7]. This chronology is corroborated by other researchers [15–17]. As the ancestral precursor to all modern agave spirits, vino mezcal (also referred to as vino del cerro or mountain wine) was distilled as early as the 16th century in artisanal distilleries called tabernas (taverns), located across the coastal and mountainous regions of Jalisco [7,18,19]. During the colonial era in New Spain (modern-day Mexico), alcoholic beverages in general were called wine, including distilled spirits [7]. This development was catalyzed by the arrival of Filipino migrants in New Galicia aboard the Manila Galleon, who introduced Asian distillation technology to the region. This trans-Pacific corridor, historically known as the *Nao de China*, served as the primary maritime link connecting New Spain with the Philippines and Southeast Asia from 1565 to 1821 [20].

In the historical territory of New Galicia, which currently encompasses the modern-day state of Jalisco, and the province of Colima, indigenous and colonial groups distilled coconut wine using Asian technology, which was subsequently adapted for *Agave* in New Spain [13,14,19,20]. The nomenclature of raicilla originated in San Sebastián del Oeste in 1621, when chronicler Lázaro de Arregui documented that wine obtained by distillation is produced from the roots and stems of the maguey. This record identifies raicilla as the oldest documented agave distillate in Mexico [7,21]. The historical and evolutionary trajectory of *Agave* distillates in western Mexico is illustrated in Figure 1.

16TH-CENTURY EMERGENCE OF “VINO MEZCAL” IN WESTERN MEXICO, THE COMMON ANCESTOR OF ALL MEZCALS

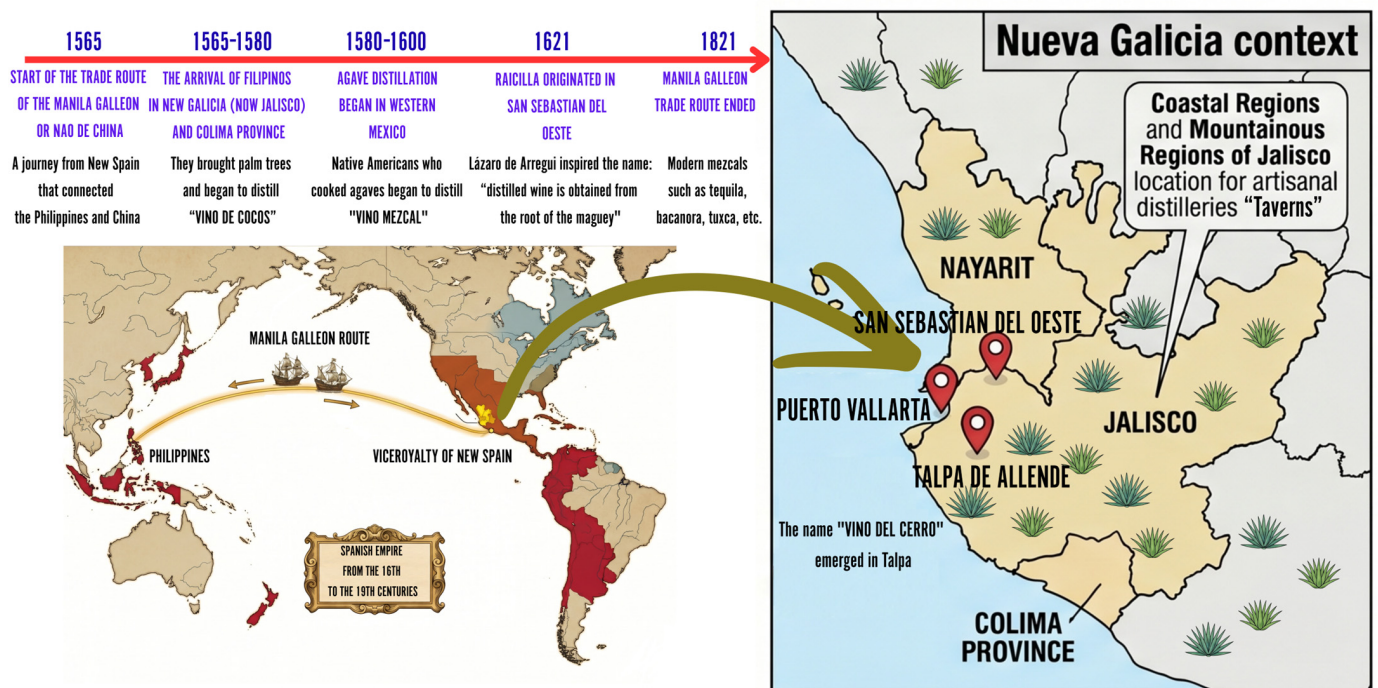


Figure 1. Historical foundations and the emergence of mezcal wine in 16th-century Western Mexico. The illustration depicts the ancestral origins of raicilla following the arrival of the Manila Galleon. The introduction of Asian distillation technology to the coasts of Colima and Nueva Galicia facilitated the processing of endemic *Agave* varieties into proto-mezcals, such as the wine of the hill “vino del cerro” originating in Talpa de Allende. From these common ancestors arose the modern raicilla, tuxca, bacanora, mezcal, and tequila industries [7,13,14,18].

Agave angustifolia Haw. constitutes a fundamental biological resource owing to its extensive geographic distribution and its role as a putative wild ancestor for several agronomically significant taxa. These include the fiber-producing *A. fourcroydes* and various local landraces utilized for mezcal production [22,23]. *Agave angustifolia* is the second most utilized species in the raicilla industry with a 31.6% adoption rate, following *Agave maximiliana* [24,25]. The biological potential of this species is not only of botanical interest, but is a socio-economic necessity for the thousands of families whose livelihood depends on its sustainable exploitation [26].

The current state of research into *A. angustifolia* has transitioned from classical morphological descriptions to a holistic framework integrating high-throughput genomic data, metabolic profiling, and environmental adaptability [27–31]. The chloroplast (cp) is a semi-autonomous organelle of cyanobacterial origin, found in plants and algae, that contains its own genome and performs photosynthesis by converting sunlight into chemical energy [32,33]. Recent studies have successfully assembled its cp genome (plastome), providing critical data for phylogenetic resolution within the *Agave* genus [34]. Furthermore, the species' remarkable climate resilience is attributed to its water-conserving CAM and a significant degree of photosynthetic plasticity, allowing flexible CO₂ uptake under varying environmental stresses [23,35–38]. At the molecular level, this adaptation is supported by complex epigenetic mechanisms, such as global Deoxyribonucleic acid (DNA) methylation, which regulates physiological responses to light intensity and helps maintain plant vigor during in vitro propagation and environmental transitions [39,40].

Despite ongoing progress, the domestication status and genomic health of *A. angustifolia* remain subject to conflicting hypotheses [41]. Certain researchers classify it as a wild or partially domesticated taxon, while others identify distinct domestication syndromes, including elevated carbohydrate concentrations and diminished leaf dentition within landraces managed under traditional agricultural frameworks [26]. A significant controversy involves the genomic consequences of human intervention. Intensive clonal management has paradoxically induced an unexpected excess of heterozygosity in specific regions, whereas wild populations exploited for regional spirits like bacanora reveal concerning levels of inbreeding and weak genetic structuring [42,43]. These divergent evolutionary paths highlight the decisive role that socioeconomic policies play in shaping the *Agave* genome [44].

While this review focuses primarily on *A. angustifolia* Haw., data from *A. tequilana* Weber, *A. maximiliana* Baker, and other congeners are included as essential comparative proxies to address specific knowledge gaps where *A. angustifolia*-specific empirical data remain limited. These inclusions are necessary to validate broader evolutionary hypotheses regarding CAM metabolic flexibility, fructan biosynthetic pathways, and the genomic consequences of human-mediated selection within the *Agave* genus. To systematically address the critical knowledge gaps, this review is structured to: (1) synthesize the current landscape of *A. angustifolia* genomics [45,46]; (2) critically evaluate the empirical evidence linking molecular mechanisms, such as epigenetic regulation and metabolic profiling, to climate resilience and industrial performance [47]; and (3) formulate a hierarchical data framework that distinguishes between published research findings in *A. angustifolia*, evidence extrapolated from other *Agave* species, and emerging research hypotheses, thereby providing a robust foundation for future germplasm conservation and precision breeding strategies [25,48].

We conclude that securing the socio-economic viability of *Agave* spirits requires a transition from intensive monocultures to regenerative agroforestry, incorporating sexual propagation to maintain evolutionary potential. Furthermore, we outline a roadmap for GAB 4.0, which serves as a promising prospective framework integrating marker-

assisted selection for juvenile traits to accelerate the release of resilient biotypes, and precision diagnostic tools to reduce the ecological footprint of *Agave* production. This framework secures the genomic integrity of traditional spirits within a circular, climate-resilient bioeconomy.

2. Scope and Literature Synthesis Approach

This study provides an integrative narrative review of the genomic architecture and climate resilience of *A. angustifolia* [7,19,49]. While not a systematic review, as it does not employ PRISMA protocols, it utilizes a structured, comprehensive search strategy across leading repositories to synthesize current knowledge and address knowledge gaps between molecular research and artisanal production [44,50].

To ensure the rigor of this synthesis, a systematic screening procedure was implemented [51,52]. A comprehensive search was executed across leading academic repositories, namely PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, utilizing Boolean operators and specific keyword strings, such as “*Agave angustifolia* genomics”, “raicilla production sustainability”, “Crassulacean Acid Metabolism resilience”, “SNP population structure *Agave*”, and “DNA methylation abiotic stress” [53–56]. The literature search encompassed eight decades, from foundational botanical descriptions in 1944 to 2026 advancements in high-throughput sequencing and Artificial Intelligence (AI) for *Agave* classification [57]. Preference was given to peer-reviewed studies in English and Spanish published between 2010 and 2024 to prioritize modern genomic methodologies [44,45]. Inclusion criteria focused on studies providing primary genomic data, identifying biosynthetic pathways, such as Cinnamyl Alcohol Dehydrogenase (*AaCAD*) genes or evaluating physiological responses to environmental stressors in *A. angustifolia* [46]. Conversely, studies were excluded if they lacked primary empirical data, were restricted to non-spirit-producing varieties, or were published outside the specified date range, thereby ensuring the review focuses on modern genomic methodologies and their practical applications [23,34,39,40].

Findings were synthesized through a comparative narrative analysis to resolve conflicting hypotheses regarding the impact of clonal propagation on genetic variability [38,44,58,59]. The review acknowledges inherent regional research biases, as the majority of *A. angustifolia* studies remain concentrated in Mexico [60,61].

3. Taxonomy and Genomic Diversity of Genus *Agave*

The genus *Agave* L. (Asparagaceae, Agavoideae) constitutes a monophyletic lineage of recent origin currently undergoing rapid diversification centered in Mexico, which hosts approximately 75 percent of the more than 200 recognized species [22,62]. Intra-generic classification identifies two primary subgenera based on inflorescence morphology: *Agave*, characterized by paniculate forms, and *Littaea*, defined by spicate or thyrsoid structures [63–65]. However, this reliance on classical morphological descriptors often fails to capture the high levels of intraspecific variation, particularly within the *A. angustifolia* complex, historically obscuring the evolutionary relationships among wild, managed, and fully domesticated populations.

Within this framework, the *Agave angustifolia* Haw. complex exhibits significant taxonomic complexity, encompassing a gradient of wild, managed, and fully domesticated populations across Mesoamerica [5,50]. In specific regions such as Oaxaca, this complex includes wild varieties like *A. angustifolia* var. *angustifolia* and var. *rubescens*, alongside the extensively cultivated ‘Espadín’ and partially cultivated taxa like *A. rhodacantha* [22,66]. Recent genomic and ethnobotanical evidence suggests that *Agave tequilana* Weber is a domesticated cultivar derived from its closest wild relative, *Agave angustifolia* [67,68].

Recent population genomics utilizing Single Nucleotide Polymorphisms (SNPs) highlights how human management profoundly impacts *Agave* genomic health. A pivotal finding within the *A. angustifolia* complex involves the marked disparity between genetic variability and heterozygosity levels [44]. Intensively managed cultivars like ‘Espadín’ exhibit reduced total genetic variability relative to wild counterparts, yet paradoxically maintain a significantly higher proportion of heterozygotic genotypes (Table 1) [44,69].

Table 1. Genomic Diversity and Management Metrics of *Agave* Populations in the Raicilla Denomination of Origin.

Taxon	Ploidy Level	Genetic Diversity (Nei's H_E)	Polymorphic Loci (%)	Marker Type (RAD-seq/AFLP/ISSR)	Nuclear Genome Size (pg/Mb)
<i>Agave angustifolia</i> Haw. Wild	Diploid ($2n = 60$); $2x$, $3x$, $4x$, $6x$	0.13–0.404 (H_E , H_B)	65.16–97.2%	RADseq (SNPs), AFLP, ISSR	5.4 pg/5281 Mb; $2C = 8.499$ pg
<i>Agave angustifolia</i> Haw. (Traditional landraces)	Diploid ($2n = 2x = 60$)	0.141–0.336 (H_B)	18.8–92.8%	ISSR	Not reported
<i>Agave angustifolia</i> ‘Espadín’	Diploid ($2n = 60$); Triploid ($2n = 3x = 90$)	0.07 (Expected)/0.12 (Observed) 0.31034	95.8%	RADseq (SNPs), AFLP	5.4 pg/5281 Mb
<i>Agave angustifolia</i> var. <i>pacifica</i>	Diploid ($2n = 60$)	0.25 (H_E)	Not reported	RADseq (SNPs)	Not reported
<i>Agave angustifolia</i> ‘Cimarrón’/‘Lineño’	Diploid ($2n = 2x = 60$)	Not reported	Not reported	AFLP, RAPD, FISH	8.179–8.217 pg/4002–4013 Mb
<i>Agave tequilana</i> Weber var. ‘Azul’	Diploid ($2n = 2x = 60$)	0.118 (H_B); 0.20550	0.8–79.9%	RADseq, AFLP, ISSR, RAPD	5.0 pg/4890 Mb; 8.304–8.517 pg
<i>Agave rhodacantha</i> Wild/Managed	Diploid ($2n = 2x = 60$)	0.21–0.330 (82.4% H_B); 0.20550	82.4%	AFLP, ISSR	Not reported
<i>Agave maximiliana</i> Wild/Managed	Diploid ($2n = 60$)	0.418 (Similar to wild)	Not reported	RADseq (SNPs), Microsatellites, ISTR	5.1 pg/4988 Mb
<i>Agave inaequidens</i> Wild/Managed	Not reported	Not reported	Not reported	Not reported	Not reported

Genomic data indicate that agricultural intensity plays a central role in shaping the evolutionary trajectory of *Agave* populations. Traditional polycultures effectively preserve genetic diversity at the wild level and essential private alleles. H_B = Bayesian Heterozygosity/genetic diversity; H_E = Nei’s Expected Heterozygosity; AFLP = Amplified Fragment Length Polymorphism; RADseq = Restriction Site-Associated DNA sequencing; ISSR = Inter-Simple Sequence Repeat; FISH = Fluorescence in situ hybridization. Data compiled and adapted from [5,42,44,50,69–71].

This dichotomy suggests that traditional management preserves agrobiodiversity through diverse landraces [5,43,44]. Consequently, facilitating gene flow between wild and managed pools is essential to prevent the accumulation of deleterious mutations and safeguard the adaptive potential of *A. angustifolia* within raicilla production systems [10,49,50]. Future studies must move beyond descriptive population genetics to prioritize functional genomic assays that can distinguish between plastic, environmentally driven phenotypes and fixed, selection-driven traits.

4. *Agave angustifolia* Haw. Biology and Socioeconomic Importance

4.1. Geographical and Ecological Distribution

The English botanist Adrian Hardy Haworth formally described *Agave angustifolia* Haw. in 1812, publishing it on page 72 of his Synopsis Plantarum Succulentarum [72,73]. This taxon possesses the widest distribution within the genus, ranging from Sonora and Tamaulipas, Mexico, south to Panama [74–77]. This remarkable distribution allows the species to thrive in diverse ecosystems, ranging from coastal dunes at sea level to oak-pine forests at elevations of 2200 m [23,43].

Historically, this plant has been a cornerstone of Mesoamerican cultures, utilized for food, fiber, medicine, and the production of traditional fermented and distilled beverages [42].

4.2. Reproductive Biology and Propagation Strategies

Agave angustifolia employs a mixed reproductive strategy encompassing one sexual and two distinct asexual pathways, which collectively ensure its ecological resilience and agricultural viability [41,78]. As a monocarpic perennial, the species flowers once at the conclusion of its 6 to 10 year life cycle, generating a massive panicle inflorescence between 3 and 8 m in height [7]. The hermaphroditic flowers are protandrous and strictly self-incompatible, with anthers releasing pollen before stigmas reach receptivity. This mechanism necessitates cross-pollination, primarily by nectar-feeding bats such as *Leptonycteris* spp., alongside diurnal birds and insects, to produce dehiscent capsules containing flat, black seeds (Figure 2) [68].



Figure 2. Sexual reproduction pathways and ontogenetic development of *Agave angustifolia* Haw. (a) Reproductive units illustrating green and dry bulbils collected from the floral scape. (b) Morphological characteristics of viable seeds. (c,d) Early germination phase and seedling emergence within specialized seedbeds. (e) Nursery stage transplantation. (f) Acclimatized specimens exhibiting optimized vigor prior to field integration. (g) A one-year-old agave specimen showing well-developed rosette architecture. All stages illustrated correspond exclusively to sexual reproduction lineages. Photographs courtesy of 42 Tavern “Ruta del Peregrino,” an establishment part of the raicilla route of the “Consejo Mexicano Promotor de la Raicilla” (CMPR), Talpa de Allende, Jalisco, Mexico.

Asexual reproduction occurs via two primary vegetative mechanisms. The first involves the continuous production of subterranean rhizomatous offshoots, locally termed ‘hijuelos’ (suckers), which emerge from the base of the maternal plant (Figure 3) [4,79].

A. angustifolia employs a robust strategy for asexual propagation through vegetative apomixis, primarily utilizing rhizomatous offshoots and the formation of aerial bulbils from axillary meristems on the inflorescence, which serve as a critical survival mechanism when sexual reproduction or floral development is compromised following floral abscission or injury [79,80]. Clonal propagation is widely leveraged in agricultural practice to maintain phenotypic uniformity and accelerate crop establishment [81]. Within the *A. angustifolia* complex, apomixis serves as a critical evolutionary mechanism to preserve polyploid lineages and bypass meiotic instability (Figure 4) [28].

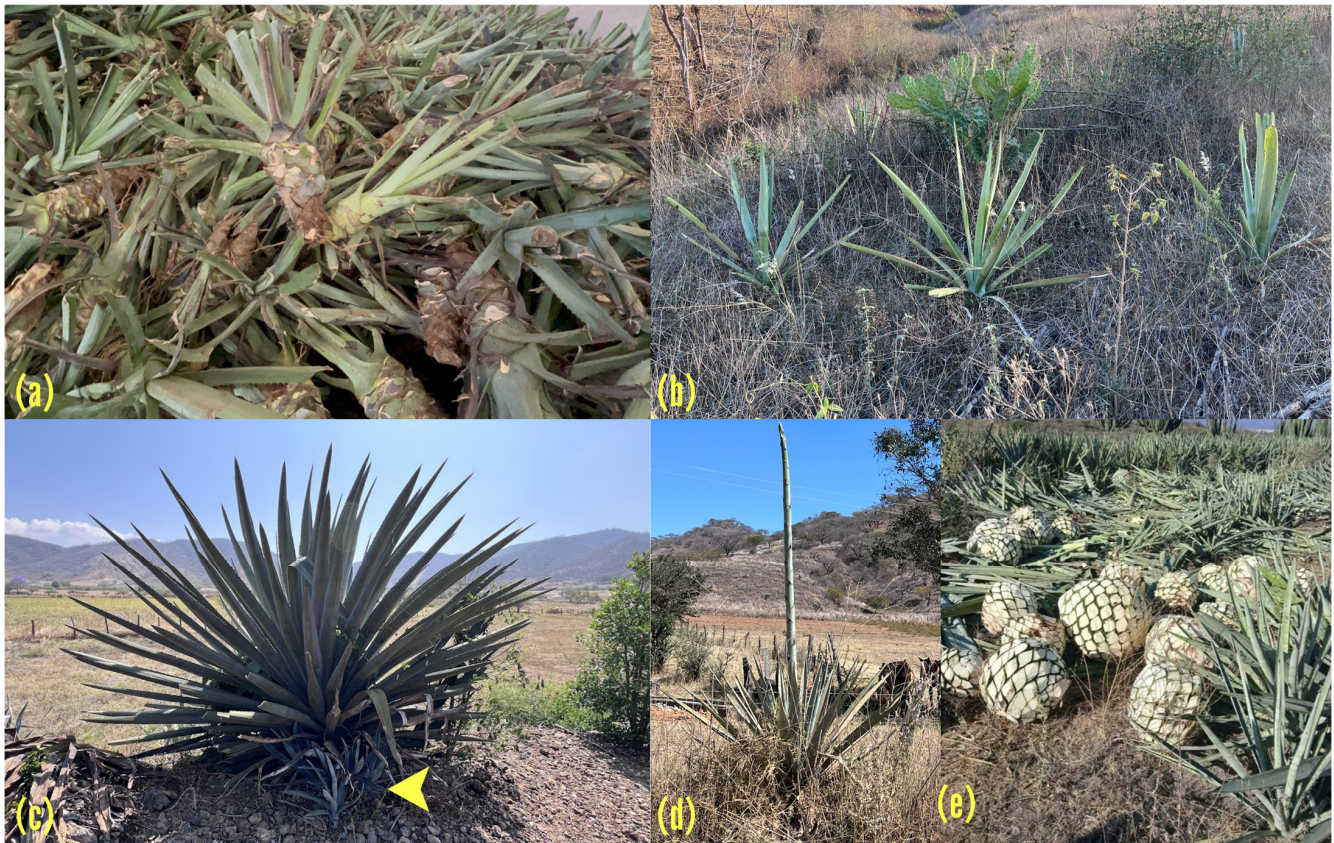


Figure 3. Vegetative propagation pathways and ontogenetic development of *Agave angustifolia* Haw. var. Chico Aguiar via rhizome offshoots. (a) Rhizome derived offshoot or hijuelo optimized for field establishment and transplantation. (b) One-year-old specimens established on hillside grazing lands within regenerative agriculture systems. (c) Six-year-old agave with 5 rhizomes (arrow). (d) Mature individual integrated into living fences displaying a fully developed floral scape or quite. (e) Traditional harvesting or jima of mature stems or piñas for raicilla production. All illustrated stages correspond exclusively to asexual reproduction lineages from the municipalities of Cabo Corrientes and Mascota, Jalisco. Photographs courtesy of Benito Spirits and Hacienda el Divisadero taverns.

4.3. Phytochemical Reservoir and Industrial Versatility

A. angustifolia serves as the primary biological substrate for distilled spirits, including mezcal in Oaxaca (>86% of state output), bacanora in Sonora and raicilla in Jalisco. This species defines the characteristic flavor and organoleptic profile of these spirits; consequently, the vast majority of globally consumed mezcal is a distillate of this specific taxon [43]. The stem or piña is harvested after 6 to 10 years, roasted, fermented, and distilled to produce these culturally and economically vital mezcals [28,82].

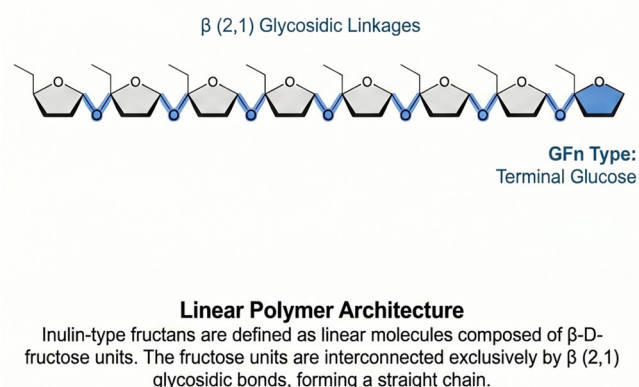
Beyond distillates, the species represents a diverse reservoir of bioactive compounds and raw materials. While historically utilized for construction and ixtle fiber, contemporary research emphasizes the utility of agro-industrial by-products like leaves and bagasse [83,84]. Bagasse is currently evaluated as a feedstock for biofuels, biodegradable packaging, and the extraction of high-value phytosterols like β -sitosterol (BSS), a potent bioactive sterol used as a therapeutic agent and nutritional supplement [85,86]. Furthermore, the branched neo-fructans identified as agavins within the plant exhibit significant prebiotic potential, while various extracts have long been employed in traditional medicine to treat sprains, bone fractures, and digestive ailments due to their inherent anti-inflammatory properties (Figure 5) [84,87].



Figure 4. Vegetative vivipary and apomixis propagation pathways in *Agave angustifolia* (locally known as maguey de quioite). (a) Floral scape at anthesis phase preceding bulbil formation. (b) Localized mechanical lesion on the inflorescence stalk inducing vegetative vivipary. (c) Mature bulbils or vegetative plantlets developing directly on the quioite. (d) Harvested bulbils optimized for initial nursery establishment. (e) Acclimatized young plantlets in nursery seedbeds optimized for field integration. (f) One-year-old specimens established under standardized nursery conditions. (g) Three-year-old commercial plantation derived exclusively from bulbil propagation. All images illustrate asexual reproduction lineages via vegetative vivipary. Courtesy of CMPR.

Structural Comparison of Fructan Architectures: Linear Inulins vs. Complex Agavins

(a) Inulin-Type Fructans: The Linear Standard



(b) Agavins: The Complex Neo-Fructan Architecture

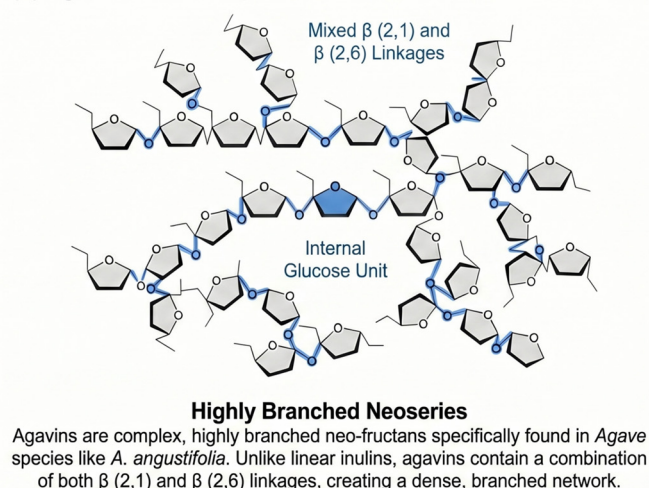


Figure 5. Structural comparison of fructan architectures. (a) Inulin-type fructans: linear polymers with β (2,1) linkages and a terminal glucose residue (GFn type). (b) Agavins: highly branched neo-fructans from *Agave angustifolia*, characterized by an internal glucose unit and mixed β (2,1) and β (2,6) linkages. This complexity underpins the high solubility and fermentative potential of *Agave* landraces used in raicilla production [87–89].

5. Genomic Potential and Molecular Architecture of *Agave angustifolia*

5.1. Genomic Architecture and Population Genetics

The conserved diploid karyotype of *A. angustifolia* ($2n = 2x = 60$), characterized by 10 macrochromosomes and 50 microchromosomes with a nuclear DNA content of 8.17–8.21 pg, provides a structural foundation for metabolic stability in arid environments [80,90,91]. While the macro-structure exhibits evolutionary stasis, microchromosomal rearrangements serve as primary drivers for regional cultivar differentiation [92,93]. Ploidy variability ranging from diploidy in traditional landraces to triploidy in ‘Espadín’ and hexaploidy in specific wild populations, remains a critical, yet under-investigated, factor in ecological fitness [94]. Furthermore, high-throughput genomic data, including Restriction Site-Associated DNA sequencing (RADseq) and Amplified Fragment Length Polymorphism (AFLP), indicate that anthropogenic management intensity is the principal force shaping divergent genetic frameworks within the species [92,95].

Although the conserved chloroplast genome structure facilitates phylogenetic resolution, the functional correlation between micro-structural genomic variations remain poorly understood, representing a significant knowledge gap in our ability to correlate karyotypic diversity with specific adaptive traits and deploy this information in precision breeding pipelines [4,32–34] (Figure 6).

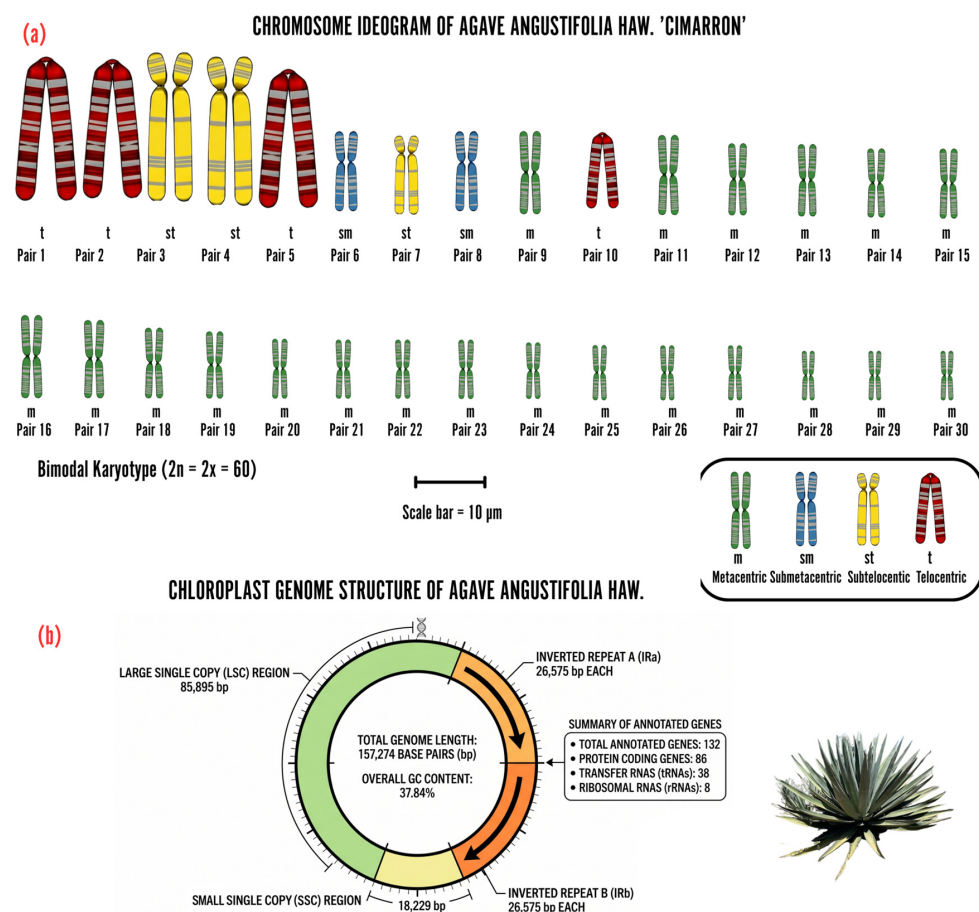


Figure 6. Genomic architecture of the *Agave angustifolia* Haw. complex. (a) Idiogram representing the bimodal diploid karyotype consisting of 5 macrochromosome pairs (L₁–L₅) and 25 microchromosome pairs (S₆–S₃₀). (b) Circular map of the complete chloroplast genome (157,274 bp), exhibiting the classic quadripartite structure of angiosperms: a LSC region of 85,895 bp, a SSC region of 18,229 bp, and a pair of IRs spanning 26,575 bp each. Within this cp architecture, 132 annotated genes are highlighted (86 protein-coding genes, 38 tRNAs, and 8 rRNAs), with functional gene clusters color-coded according to the legend [32,34,94].

5.2. Population Genomics and Anthropogenic Management

Recent population genomics, utilizing over 50,000 SNPs, reveals that intensive anthropogenic management fundamentally alters the evolutionary trajectory of *A. angustifolia* [42,43]. The defining feature of this process is the ‘domestication paradox’. Intensive clonal management, historically employed to maintain desirable agronomic traits, paradoxically preserves individual heterosis while simultaneously eroding population-level allelic richness. This creates a severe genetic bottleneck characterized by high observed heterozygosity ($H_O > H_E$) in cultivated lineages, contrasting sharply with the concerning inbreeding coefficients ($F_{IS} \approx 0.13$) observed in fragmented wild populations. This disparity indicates that while clonal propagation stabilizes the performance of landraces, it limits the genetic reservoir necessary for long-term adaptive responses to environmental stochasticity, necessitating robust conservation strategies [44,69,70].

In contrast, wild populations utilized for spirits such as bacanora (*A. angustifolia* var. *pacifica*) maintain higher total variability but show concerning signs of inbreeding and shallow population structure, likely resulting from overexploitation and restricted gene flow. This underscores the need to integrate data on gene flow with genomic monitoring, as the long-term sustainability of these populations remains vulnerable to unchecked habitat fragmentation [42–44].

5.3. Functional Genomics: Candidate Genes for Industrial and Adaptive Traits

Transcriptomic profiling identifies key regulatory hubs that underpin the commercial and biological potential of *A. angustifolia*. The *AaCAD* family, particularly *AaCAD2* and *AaCAD14*, regulates lignification, providing a structural basis for fiber quality and stem integrity essential for raicilla production [38,46,96]. Simultaneously, the identification of Radical-Induced Cell Death (*SRO*) genes, specifically *AhSRO2* and *AhSRO3*, serves as a molecular diagnostic for abiotic stress, displaying significant up-regulation under thermal and oomycete-induced stress [34,45].

Furthermore, proteomic analysis of somaclonal variants reveals that metabolic reprogramming, specifically the differential accumulation of key enzymes like *AaCM*, *AaALS*, *AaBCAT*, and *AaIPMS1*, is critical for physiological adjustment in chloroplast-deficient lineages. These genomic and proteomic markers provide a robust technical foundation for marker-assisted selection. Transitioning from these correlative associations to predictive breeding requires targeted functional validation, such as CRISPR/Cas9-mediated gene editing (envisioned here as a future direction for functional validation), to explicitly indicate their contribution to climate resilience and industrial performance [32,33].

5.4. Evolutionary Plasticity: Epigenetic Regulation and Meiotic Restitution

The evolutionary plasticity of *Agave angustifolia* Haw. is underpinned by a sophisticated integration of epigenetic regulation and meiotic flexibility. GDM levels, ranging from 13% to 22%, appear to constitute a dynamic regulatory layer governing physiological vigor. However, following the direct evidence versus hypothesis hierarchy, these current data remain correlative and require longitudinal, bisulfite-sequencing-based validation to verify transgenerational memory. Within this epigenetic stress-memory framework, hypomethylation events triggered by low-light conditions correlate directly with phenotypic transitions in somaclonal lineages. Simultaneously, specific chromatin modifications, including H3K4me3 and H3K27me3, enable the plant to precisely reprogram CAM regulation in response to microclimatic stressors [46,51,83]. Nevertheless, characterizing these epigenetic patterns as a memory mechanism necessitates further longitudinal evidence to confirm their persistence and transgenerational stability.

Complementing these mechanisms, the species exhibits genomic flexibility through meiotic restitution, characterized by the formation of unreduced diploid number ($2n$) pollen grains via Second Division Restitution (SDR) and abnormal spindle formations resulting in triads [79]. Although genetically determined, these events are significantly modulated by environmental factors such as temperature and water deficit. This process provides the fundamental raw material for polyploidization, a common evolutionary strategy within the *Agave* genus used to enhance adaptive potential and biomass production in fluctuating environments [5,97,98].

5.5. Future Perspectives: Genomics-Assisted Breeding 4.0 (GAB 4.0) and the Agavinome

The transition in *Agave angustifolia* Haw. research from descriptive botany to a comprehensive genomics framework is driven by the high-resolution characterization of the agavinome, which comprises the conceptual space and molecular infrastructure of all genomic, transcriptomic, and epigenetic resources within the genus *Agave*. This framework is now accessible through high-resolution tools like the chromatin immunoprecipitation (ChIP) assay [39,40,99].

Complementarily, integrating metabolomics via Fourier-Transform Mid-Infrared (FT-MIR) and Gas Chromatography-Mass Spectrometry (GC-MS) has enabled rapid agavinome profiling [89,100,101]. These analyses indicate a metabolic superiority in *A. angustifolia*, with fructan concentrations approximately 100 mg/g higher than regional averages [37,83,102]. This metabolic foundation dictates raicilla yield and quality through molecular signatures varying by plant age and environmental terroir, providing the data necessary to synergize genomics, transcriptomics, and epigenomics within the GAB 4.0 frontier, which represents the latest paradigm shift in crop improvement that integrates multi-omics data with AI, deep learning, and automated high-throughput phenotyping for precise predictive breeding [5,42,103].

Integrating multi-omics with high-throughput phenotyping, Clustered Regularly Interspaced Short Palindromic Repeats/Cas (CRISPR/Cas) genome editing, and AI-driven predictive modeling, constitutes a promising prospective framework for future crop improvement. While the long generation time of *Agave* (6–10 years) inherently limits the speed of traditional breeding, GAB 4.0 provides immediate, near-term applications that bypass this temporal bottleneck. By leveraging genomic prediction models, we can perform marker-assisted selection for critical juvenile traits, such as early sugar accumulation patterns, stress-responsive gene expression (e.g., the *AhSRO* gene family), and fiber quality markers, as early as the seedling stage. This allows for the selection of superior phenotypes within the first 12–18 months of development. Compared to traditional long-term breeding timelines in other CAM crops, which often rely on slow, labor-intensive field phenotyping, the integration of GAB 4.0 enables a high-throughput, predictive pipeline that significantly compresses the selection cycle and accelerates the release of climate-resilient biotypes (Table 2) [104,105].

Table 2. Integrated Genomic and Metabolic Landscape of *Agave angustifolia*: Evidence Hierarchy.

Biological Variant	Transcriptomic/ Functional Markers	Epigenetic Indicators	Metabolomic Markers	Phenotypic and Physiological Characteristics	Industrial Relevance and Evidence Hierarchy
General Species	67,314 unigenes; <i>AhSRO2/3</i>	13–22% GDM; stress memory	Agavin superiority; BSS presence	CAM plasticity; microclimate adaptation	High raicilla yield (Direct Evidence)
Traditional Landraces	67,175 SNPs	Methylation shifts	High sugar content	Bimodal karyotype; variable leaf morph	Highest yielder (Direct Evidence)
Cultivated ‘Espadín’	WRKY defense markers	Chromatin remodeling	High fructan content	Morphological homogeneity	>80% Oaxaca mezcal (Direct Evidence)

Table 2. Cont.

Biological Variant	Transcriptomic/ Functional Markers	Epigenetic Indicators	Metabolomic Markers	Phenotypic and Physiological Characteristics	Industrial Relevance and Evidence Hierarchy
Cultivated ‘Lineño’	<i>AhSRO1a/b/c</i> ; <i>AhSRO2/3</i>	Not reported	Agavins; BSS; steroidal saponins	Cold/drought tolerant	Raicilla/Bacanora; high cellulose (Direct Evidence)
Wild ‘Cimarrón’	Reference transcriptome	Not reported	Levan/Inulin moieties	High meiotic abnormality	Bacanora production (Direct Evidence)
Somaclonal Variants	<i>PHYA</i> ; RuBisCo genes	30.5–40% GDM levels	Chlorophyll/Carotenoid profiles	Heterotrophic vs. CAM phenotypes	Ornamental AI models (Hypothesis)

This table synthesizes the multi-layered molecular architecture of *A. angustifolia* Haw., bridging foundational structural genomics with functional transcriptomic, epigenetic, and metabolomic regulatory data. Evidence hierarchy distinguishes between empirical findings obtained directly from *A. angustifolia* (Direct Evidence) and research pathways requiring further validation (Hypothesis). Functional insights from 67,314 unigenes and stress-responsive loci (e.g., *AhSRO2*, *AhSRO3*) elucidate the genomic basis for climate resilience. Furthermore, dynamic GDM levels and chromatin remodeling suggest an “epigenetic stress memory” facilitating rapid adaptation to Jalisco’s diverse microclimates. The metabolomic superiority in agavin biosynthesis (~100 mg/g above regional averages) directly correlates with raicilla yield and quality. Data compiled and adapted from [5,34,39,40,44–46,50,94,99,104,105]. Abbreviations include Agave hybrid Radical-Induced Cell Death gene family (*AhSRO*), Artificial Intelligence (AI), β -sitosterol (BSS), Crassulacean Acid Metabolism (CAM), Global DNA Methylation (GDM), Phytochrome A light sensor protein (*PHYA*), Ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCo), Single Nucleotide Polymorphisms (SNPs), and the WRKY transcription factor family (*WRKY*).

6. Mechanisms of Climate Resilience and Adaptation

6.1. Metabolic and Physiological Plasticity

The exceptional climate resilience of *Agave angustifolia* Haw. within arid and semi-arid environments is anchored in the plasticity and efficiency of its CAM. This water-conserving pathway minimizes transpirational loss by restricting stomatal opening to nocturnal hours. Under standard conditions, nocturnal CO₂ fixation contributes approximately 75% of the total daily carbon gain [5,23,106].

However, the species retains significant metabolic flexibility under extreme environmental shifts. For instance, withholding nocturnal CO₂ while providing elevated concentrations during the day can trigger a transition toward C₃-like light-only uptake. This enables optimized carbon assimilation during transient fluctuations in gas availability or atmospheric pressure [41]. These synergistic traits, alongside specialized architectural adaptations, position *A. angustifolia* as a premier climate-ready crop for marginal lands facing severe drought and a warming global climate. While these metabolic responses confer superior drought resilience, extrapolating laboratory findings to field conditions requires caution, as real-world interactions with soil microbiomes and extreme hydric variability may significantly modulate these assimilation rates [83].

6.2. Respiratory Metabolism and Thermal Limits

Isothermal microcalorimetry across clonal lines identifies 35 °C as the physiological optimum for growth-related metabolic activity in *A. angustifolia* [23,41]. Beyond the 45 °C threshold, most clonal lines exhibit a marked decrease in metabolic heat rates and CO₂ production, coupled with reduced substrate-to-carbon conversion efficiency and increased enthalpy loss. However, intraspecific variation persists; the *Agave angustifolia* clonal line CL24b, derived from bulbils, functions as a high-performance biotype characterized by exceptional respiratory efficiency and thermal resilience. Comparative metabolic assessments identify CL24b as the most productive genotype, exhibiting superior biomass conversion and leaf-mass accumulation under extreme thermal stress. Although the CL24b biotype exhibits superior efficiency under controlled settings, broader comparative studies encompassing diverse clonal lines and variable edaphoclimatic conditions are necessary to determine whether this trait is stable or a niche-specific genotypic response [23,41].

6.3. Epigenetic Regulation and Environmental Signaling

Beyond physiological responses, *A. angustifolia* utilizes complex epigenetic mechanisms to modulate environmental stress. GDM acts as a dynamic switch regulating phenotypic variation and physiological vigor [39,40]. In environments with fluctuating light intensity, the species modulates these methylation levels; for instance, exposure to total darkness or low light triggers hypomethylation events correlating with phenotypic transitions, such as the emergence of variegated or albino shoots in micropropagated lines. This epigenetic stress-memory is crucial for survival, allowing the plant to reprogram its chromatin state in response to abiotic stressors [39,40]. Furthermore, the identification of Radical-Induced Cell Death (SRO) genes, specifically *AhSRO3*, which are significantly up-regulated under low-temperature stress, suggests an integrated genomic-epigenetic network that protects the plant against thermal and oxidative damage in arid landscapes. In line with our evidence hierarchy framework, the precise mechanism of this epigenetic regulation and its heritability in populations managed under traditional asexual propagation systems remains a hypothesis requiring further empirical evidence before being integrated as a practical selection tool in breeding programs [45].

6.4. Osmoprotection and Secondary Metabolites

Agavins function in both carbon storage and osmotic adjustment. During drought, these carbohydrates serve as osmoprotectants that maintain cellular turgor [87,88]. The concentration and degree of polymerization of these fructans are dynamic and species-specific. *A. angustifolia* exhibits a higher accumulation of high-degree polymerization (HDP) fructans upon maturation, enhancing structural and metabolic resilience against progressive aridization in traditional cultivation zones. Despite these observations, further research is required to ascertain whether the accumulation of HDP fructans is a direct adaptive response to water stress or a secondary phenological trait that may fluctuate significantly across different terroirs [5,7,29,88].

7. Bioeconomy and Phytochemical Potential in Raicilla

7.1. The Raicilla Bioeconomy and Regional Value Chains

Raicilla production has evolved into a cornerstone of Western Mexico's regional bioeconomy, significantly bolstered by its 2019 Denomination of Origin (DO) status [7,107,108]. This industry operates through complex value chains where ancestral knowledge and community-governed decision-making ensure distillate authenticity. Raicilla production utilizes a diverse range of taxa, primarily exploiting *Agave angustifolia* Haw. and *Agave rhodacantha* Trel. in coastal regions, while *Agave maximiliana* Baker and *Agave inaequidens* Koch predominate in the sierra, where they are locally known as 'lechuguillas' [109–111]. Raicilla is defined as a shade-grown spirit (Mezcal de sombra) because *Agave maximiliana* and *Agave inaequidens* populations occur naturally within mountainous ecosystems where they develop beneath the forest canopy [49].

The protected region for the raicilla DO comprises 17 municipalities, with 16 located in Jalisco and the municipality of Bahía de Banderas in Nayarit. In Jalisco, the established territory covers Talpa de Allende, Mascota, San Sebastián del Oeste, Guachinango, Mixtlán, Atenguillo, Cuautla, Ayutla, Atengo, Tecolotlán, Tenamaxtlán, Juchitán, Chiquilistlán, Tomatlán, Cabo Corrientes, and Puerto Vallarta [7,49]. In municipalities like Mascota and Talpa de Allende, Jalisco, the raicilla industry has catalyzed social innovation, linking artisanal production with emerging sectors such as agrotourism [108,112,113]. This socio-economic framework depends on the biological performance of *A. angustifolia* and *A. maximiliana*, as their growth rates and carbohydrate yields determine distillery scalability (Figure 7) [25,114,115].

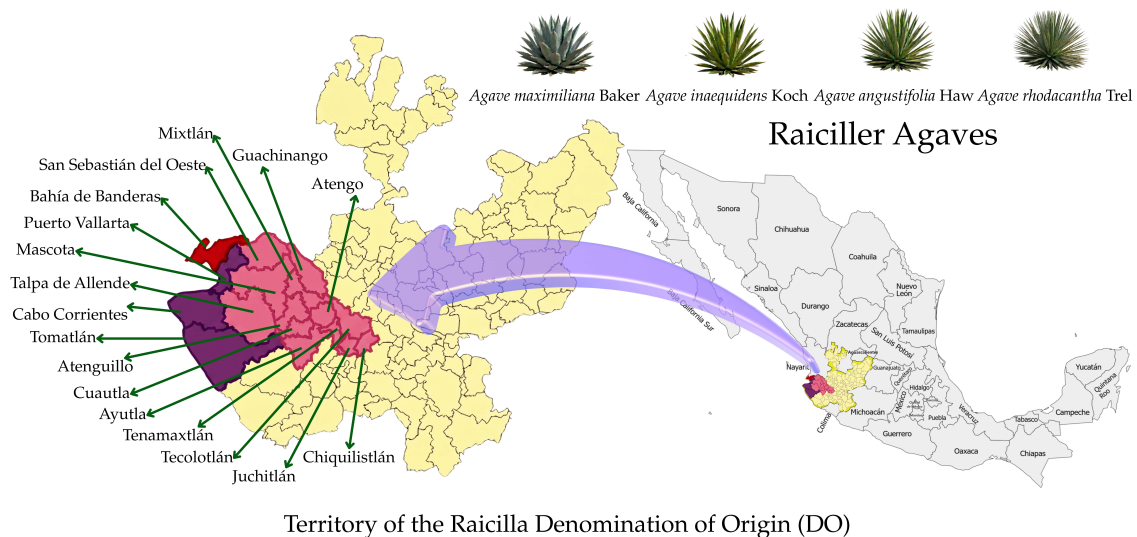


Figure 7. Geographic distribution of the Raicilla Denomination of Origin protection zone. The Sierra Madre Occidental municipalities of Jalisco are indicated in pink, the North Coast municipalities of Jalisco are highlighted in purple, and Bahía de Banderas, Nayarit, is shown in red [7,49].

In the fermentation process, *Saccharomyces cerevisiae* and *Kluyveromyces marxianus* drive ethanol production and the metabolic generation of secondary metabolites responsible for the agave spirit's organoleptic complexity [116,117]. Raicilla production involves the thermal hydrolysis of fructans into fermentable sugars, followed by spontaneous fermentation and double distillation in artisanal stills, a process that generates a distinctive volatile profile [118]. Analytically, the Electrochemical Color Index (ECI) monitors wood-spirit interactions during the first 60 days of maturation, identifying four kinetic phases essential for stabilizing polyphenol and flavonoid extraction [119].

7.2. Phytochemical Reservoir and Bioactive Potential

The phytochemical profile of *A. angustifolia* and its sympatric relatives represents a vast, untapped resource for the pharmaceutical and nutraceutical sectors. These species function as multifunctional sources of bioactive compounds, including steroidal saponinins, saponins, and various phenolic acids [2,112,120,121]. Notably, the leaves, often treated as agro-waste, contain significant antioxidant and hypoglycemic metabolites [122,123]. Recent extraction protocols have demonstrated the feasibility of recovering BSS and its derivatives from agave bagasse through microwave-assisted processes, providing a pathway for the valorization of industrial by-products [38,85]. While traditional ethnopharmacological records suggest efficacy in treating gastrointestinal ailments and wound healing, these properties require further validation through rigorous molecular characterization to confirm their therapeutic potential. Consequently, these medicinal claims should be regarded as preliminary until clinical or well-controlled in vitro studies elucidate specific dose-response relationships [2,112,120,121].

7.3. Valorization of Agavins and Prebiotic Potential

The metabolic dynamics of agavins constitute a core component of the agave bioeconomy, serving as both the primary fermentable sugars for spirit production and as potent prebiotics. This biochemical framework is exemplified in pulque, a viscous, slightly acidic fermented beverage (4–7% ABV) derived from fresh agave sap, or aguamiel. Pulque remains distinct from mezcal because its fermentation utilizes unroasted must, bypassing the thermal hydrolysis of fructans required for traditional distilled spirits [89,100,124,125]. During the development of *A. angustifolia*, the synthesis and storage of these branched

neo-fructans in the piña are influenced by age and environmental stressors, reaching optimal concentrations for distillation between 6 and 8 years of growth [48]. These agavins exhibit functional properties that facilitate glucose and lipid homeostasis in experimental models, positioning them as candidates for high-value food additives. However, given the complexity of the human gut microbiome, these metabolic effects in experimental models must be extrapolated with caution, and human clinical trials are essential to determine the efficacy and safety of these agavins as prebiotics [2,88,89,101,126]. Consequently, identifying specific ecotypes with superior sugar content and biomass is critical for selecting elite biotypes capable of sustaining the high-demand raicilla market while maintaining biological integrity [49,115].

7.4. Industrial Biorefineries and Sustainable Feedstocks

Transitioning to sustainable biorefinery models is essential to mitigate the environmental footprint of raicilla production [59,127,128]. It is estimated that every liter of distillate generates approximately 15 to 20 kg of wet bagasse, posing a significant waste management challenge. However, this fibrous residue possesses a high cellulose content of up to 67%, making it an ideal feedstock for biofuels, bioplastics, and sustainable fiber-based materials [36,128,129]. Integrating advanced biotechnological tools, such as deep learning for high-resolution biomass estimation and automated shredding optimization, enables more efficient utilization of the entire plant [24,50,130]. By shifting focus from spirit-only extraction to a circular bioeconomy, the raicilla industry can mitigate the risks of intensive monocultures while enhancing the long-term conservation of *Agave* genetic resources [11,67,114,123].

8. Biotechnological Strategies for Sustainable Production

8.1. Advanced Propagation Systems: In Vitro Culture and Micropropagation

The escalating demand for *Agave angustifolia* and *A. maximiliana* within the raicilla industry necessitates high-efficiency mass propagation systems to mitigate wild population overexploitation [131]. Recent biotechnological advancements have established robust protocols, including an indirect somatic embryogenesis system for *A. maximiliana* achieving a 90% embryo-to-plantlet conversion rate. Additionally, axillary shoot proliferation methods provide strategic pathways for ecological restoration and sustainable commercial plantations [38,85]. These micropropagation frameworks utilize a diverse array of plant growth regulators (PGRs), integrating classic agents such as 6-benzylaminopurine (BAP), 2,4-dichlorophenoxyacetic acid (2,4-D), and indole-3-butyric acid (IBA) for shoot multiplication with non-traditional regulators like abscisic acid (ABA) and putrescine to optimize embryo maturation [132]. Specifically for *A. angustifolia*, optimized Murashige and Skoog (MS) media protocols have attained germination rates exceeding 80% and 100% survival during the *ex vitro* transition [48]. Beyond clonal multiplication, these in vitro systems facilitate critical molecular discoveries; for instance, using albino somaclonal variants has elucidated links between GDM and the disruption of CAM machinery, characterized by a failure to accumulate nocturnal malate [7,133,134]. Furthermore, *de novo* transcriptome sequencing within these platforms has identified pivotal gene families, such as *AaCAD*, offering targeted pathways for the genetic improvement of fiber and biomass traits to transform underutilized biomass into value-added products for the food, pharmaceutical, and bioenergy sectors [48,49,59,82].

8.2. Genetic Improvement and Breeding Strategies

The long-life cycles and complex reproductive biology of agaves have historically limited traditional breeding. Genomic insights into polyploidization and meiotic resti-

tution offer new avenues for genetic improvement. The identification of $2n$ pollen grains in *A. angustifolia* provides the biological foundation for sexual polyploidization, which can be harnessed to develop triploid or tetraploid lines with enhanced vigor and biomass [79,102,135]. However, to bridge the gap between genomic potential and artisanal reality, breeding programs must prioritize traits that preserve the unique sensory profiles of raicilla landraces, as increasing biomass yield at the expense of organoleptic quality would undermine the economic value derived from the DO.

8.3. Digital Precision and Sustainable Plantation Management

The modernization of agave cultivation requires digital precision to reconcile industrial yields with the regenerative goals of raicilla production. Integrating advanced deep learning architectures, such as the nano iteration of You Only Look Once (YOLOv8n), provides a critical strategy for sustainable management [57]. This lightweight convolutional neural network (requiring only 2.87 GFLOPs) enables real-time, automated monitoring of plantation health and early disease detection. By implementing this tool, producers can significantly reduce the excessive, blanket application of agrochemicals, replacing them with localized, intervention-based actions [57,81]. Consequently, YOLOv8 serves as a central pillar in our proposal for sustainability, as it optimizes resource use, minimizes chemical leakage into the fragile mountainous ecosystems of the raicilla denomination zone, and improves the economic efficiency of traditional distilleries through data-driven planning [38,48,136–138].

9. Conservation, Challenges, and Future Directions

9.1. Conservation Genomics and Regenerative Agroecology

Regenerative agriculture transitioned from the conceptual frameworks established by Medard Gabel in 1979 and Robert Rodale in 1983 into a rigorous ecological paradigm. A 2019 agronomic study analyzed this genealogy through historical comparative definitions [47]. This progression provided the scientific foundation for California's 2025 official standard prioritizing soil health and ecosystem resilience (<https://www.cdfa.ca.gov/RegenerativeAg/> accessed on 11 July 2026).

Transitioning toward regenerative agroforestry models replaces intensive monocultures with traditional, diversified systems prioritizing intercropping, soil conservation, and microbiome restoration. This paradigm maintains the genetic diversity essential for securing long-term ecological resilience and sustaining spirit production [26,83]. Notably, livestock integration constitutes a definitive feature of Traditional Agroecosystems with Polyculture (ATP), where 60% of producers employ grazing compared to 40% in Conventional Monocultures (ACM). This strategy fulfills three primary ecological functions: facilitating biological soil fertilization, reducing manual weed control expenditures, and decreasing dependence on external commercial feed [139]. Integrating *A. angustifolia* and *A. maximiliana* into raiciller ecosystems preserves agrobiodiversity and fosters eubiosis within associated microbial consortia (Figure 8) [7,26,49].

Genomic monitoring remains essential to maintain gene flow between wild and managed gene pools, preventing the genetic erosion associated with strict clonal propagation [42–44]. By combining ancestral knowledge with high-throughput genomic data, producers can implement management plans that balance industrial productivity with the preservation of the species' evolutionary integrity [10,11,26].

To maintain the evolutionary potential and long-term viability of *A. angustifolia*, management strategies must shift from monocultural clonal systems to diversified approaches. We propose that producers incorporate a minimum threshold of 20% seed-derived (sexual) individuals within new plantations. This integration of sexually propagated lineages is

essential to preserve rare private alleles, disrupt the accumulation of deleterious mutations, and promote the natural genetic recombination required to foster resilience against the shifting environmental stressors of the raiciller landscape.

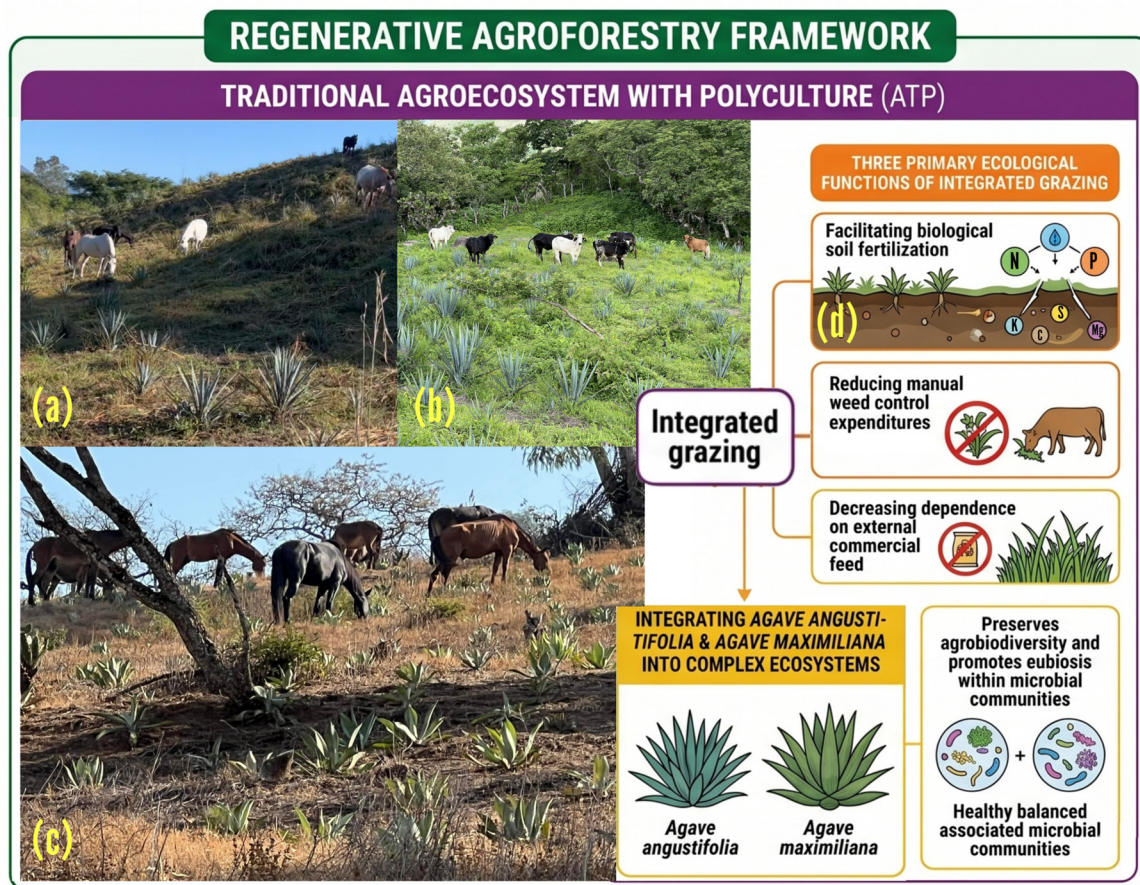


Figure 8. Regenerative agriculture with livestock grazing in the raiciller production area. (a,b) Equine and bovine grazing within *Agave angustifolia* fields. (c) Equine grazing within *Agave maximiliana* fields. (d) Within the framework of the ATP, *Agave angustifolia* and *Agave maximiliana* are integrated into silvopastoral landscapes where grazing facilitates biological soil fertilization and natural weed control. This strategy promotes eubiosis within the associated microbial consortia and ensures genetic diversity, essential for long-term ecological resilience and sustainable raicilla production. Photographs courtesy of Pilgrim’s Route Tavern, Talpa de Allende, Jalisco, Mexico. Abbreviations: N: Nitrogen, P: Phosphorus, K: Potassium, S: Sulfur, C: Carbon, Mg: Magnesium.

9.2. Climate Resilience and Future Biotechnological Innovation

Climate resilience in *A. angustifolia* is not merely a product of constitutive CAM metabolism but is driven by a sophisticated epigenetic switch mediated by GDM. This mechanism allows the plant to reprogram growth and pigment synthesis in response to light and thermal stress [23,40,83]. The identification of stress-responsive genes, such as the *SRO* and *CAD* families, marks a transition toward precision biotechnology in agave cultivation [45,46]. Future research must prioritize the functional validation of these candidate genes through CRISPR/Cas9 or similar gene-editing tools, alongside exploring the agave holobiont, given the vital role of endophytes in mitigating drought and thermal limits [45,106,140,141].

Regenerative agriculture and biotechnological tools are essential to ensure the socio-ecological resilience of agave spirits [51,142], facilitating gene flow and scaling production while preserving biological integrity and cultural heritage through community-led

innovation [24,111,143]. Integrating micropropagation and AI monitoring allows for scalable production without compromising biological integrity. This circular bioeconomy must be co-designed with local communities to ensure that genomic innovations remain practical and respectful of cultural heritage [29,88,144].

10. Discussion

The biocultural identity of *Agave angustifolia* Haw. in western Mexico represents a critical evolutionary nexus, marking the ontological transition from a pre-Hispanic ritual staple (200–1500 CE) to the 16th-century ‘vino mezcal,’ the common ancestor for modern agave spirits such as raicilla, mezcal, tuxca, bacanora, sisal, and tequila [7,13]. The genotype and phenotype of *A. angustifolia* reflect a domestication syndrome driven by centuries of management tailored for distilled spirit production. This trajectory underpins the fourth generation of mezcal, tequila, and raicilla, marking a shift toward the technological and genetic integration of traditional agave lineages [7,18,145].

Integrating the complex molecular architecture of *A. angustifolia* requires a holistic agavinome framework that encompasses nuclear and chloroplast structures, LTR-retrotransposon dynamics, and epigenetic networks. This unified paradigm, rather than isolated datasets, clarifies the evolutionary crossroads between wild reservoirs and domesticated landraces [5,50]. Furthermore, the species’ ability to reorganize its chromatin and metabolic state in response to environmental fluctuations reflects fundamental principles of plant cellular organization and signal transduction [146,147]. Consequently, the characterization of the *A. angustifolia* genome provides the definitive framework for elucidating the evolutionary resilience and industrial potential inherent to this species within raicilla production systems [109,110,112,148]. Precision mapping of 18S rDNA loci to the secondary constriction of a specific macrochromosome pair in landraces like ‘Cimarrón’ and ‘Lineño’ provides the necessary cytogenetic resolution to decipher the taxonomic turbulence within the *A. angustifolia* complex [94]. Such structural robustness facilitates the species’ persistence across the heterogeneous agroecological gradients of Jalisco while establishing definitive evolutionary trajectories toward elite industrial hybrids like *A. H11648* [34,46]. *Agave* hybrid (Ah) H11648 is the world’s only commercially exploited Ah, developed in Tanzania (c. 1931) through a strategic backcross, (*A. angustifolia* × *A. amaniensis*) × *A. amaniensis*. This genotype integrates the high cellulose content (67%) of *A. angustifolia* with superior biomass, making it the pillar of the global sisal industry in Africa, Asia, and Brazil [45,90,149].

A significant genomic schism exists between fragmented wild populations and the anthropogenic landraces of the raicilla industry. While wild variants, such as *A. angustifolia* var. *pacifica*, exhibit substantial allelic richness, they are frequently compromised by elevated inbreeding coefficients and homozygosity, a direct consequence of disrupted pollinator networks. In stark contrast, the ‘Espadín’ and coastal raicilla lineages display reduced total polymorphism but maintain a significant excess of observed heterozygosity ($H_O > H_E$) [42,44]. This heterosis fixation is a mechanistic byproduct of multi-decadal clonal propagation and the selective preservation of vigorous individuals by producers, creating a vital genetic buffer against environmental stochasticity in arid habitats [50].

Resilience in *A. angustifolia* is orchestrated by the transcriptomic diversification of 67,314 unigenes, particularly within the *AaCAD* family. Specifically, *AaCAD3*, 5, and 7 dictate tissue-specific lignification, providing a structural shield for the “piña” against high-intensity irradiance [46]. This is augmented by *SRO* genes. Notably *AhSRO2* and *AhSRO3*, which calibrate oxidative responses to thermal stress and oomycete pathogens [45]. Such molecular pathways are intrinsically coupled to the flexibility of CAM, where nocturnal CO₂ uptake provides 75% of carbon gain, ensuring survival under acute water

deficits [23]. Furthermore, the metabolic equilibrium observed at 35 °C in genotypes like the CL24b clone underscores a superior adaptive threshold, positioning these lineages as elite candidates for thermally volatile regions [23,41].

Non-mutational adaptation is further mediated by an epigenetic stress memory, where GDM (13–22%) and meristematic hypomethylation function as rapid physiological responses to environmental fluctuations [39,40]. These light-dependent chromatin remodeling patterns constitute the molecular foundation for terroir in raicilla production [39,40]. Concurrently, meiotic disruptions such as SDR yield $2n$ pollen, serving as a cytogenetic engine for polyploidization and novel genetic combinations [79]. Adopting a GAB 4.0 framework remains imperative to reconcile escalating spirit demand with wild germplasm preservation [103–105,150].

The genomic diversity of *A. angustifolia* shows that management reduces allelic richness while preserving heterozygosity, a balance maintained by high gene flow facilitated by *Leptonycteris curasoae* and dynamic chromatin-based stress memory [50,64,102,135]. To ensure long-term sustainability, we propose a strategic framework that integrates marker-assisted selection of *SRO* genes for climate resilience, industrial valorization of bagasse through microwave-assisted extraction, and the restoration of genomic diversity via sexual propagation and meiotic restitution, thereby securing the species as a foundational biocultural and economic resource [10,19,99].

Strategic Roadmap: Integrated Breeding and Regenerative Conservation

The synthesis of *A. angustifolia* molecular architecture creates a framework for shifting from descriptive botany to a precision bioeconomy. Future research must prioritize three integrated, evidence-based pillars:

1. **GAB 4.0:** While the 6–10 year generation cycle of *Agave* limits traditional breeding, we propose a strategic pivot toward marker-assisted selection for juvenile traits. By implementing genomic prediction models in the first 12–18 months of seedling development, we can compress selection cycles and accelerate the release of climate-resilient biotypes, surpassing the throughput of traditional long-term field trials in other CAM crops.
2. **Regenerative Conservation:** The observed domestication paradox necessitates an immediate shift in management strategies. We advocate for the incorporation of a minimum 20% sexual propagation threshold in new plantations. This is not merely an ecological recommendation but a fundamental requirement to preserve rare private alleles and disrupt the accumulation of deleterious mutations inherent in monoclonal systems.
3. **Precision Agro-Biotechnology:** The implementation of diagnostic tools, such as the YOLOv8n convolutional neural network, must move beyond proof-of-concept. Future efforts should focus on co-designing these tools with local communities to provide actionable, real-time disease detection, thereby minimizing chemical dependency and preserving the eubiosis of the agave holobiont within the fragile ecosystems of the raicilla denomination zone.

In light of recent findings on governance and operational adaptation of microdistilleries of various Mexican mezcals with DO [151], it becomes clear that by reconciling high-resolution molecular predictions with traditional artisanal management, *A. angustifolia* can maintain its role as a foundational resource, ensuring that technological innovation serves to secure, rather than erode, the genomic integrity and socio-economic viability of traditional *Agave* spirits.

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Conflicts of Interest: The author declares no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
2C	Nuclear DNA content
2n	Diploid number/Unreduced pollen grains
2,4-D	2,4-dichlorophenoxyacetic acid
AA	Amino acid residues
AaCAD	Cinnamyl Alcohol Dehydrogenase
ABA	Absciscic acid
AFLP	Amplified fragment length polymorphism
ACM	Conventional Monocultures
AhSRO	<i>Agave hybrid</i> Radical-Induced Cell Death
AI	Artificial Intelligence
ATP	Traditional Agroecosystems with Polyculture
BAP	6-benzylaminopurine
bp	Base pairs
BSS	β -sitosterol
CAM	Crassulacean Acid Metabolism
CE	Common Era
ChIP	Chromatin immunoprecipitation assay
CMPR	Consejo Mexicano Promotor de la Raicilla
CNNs	Convolutional Neural Networks
cp	Chloroplast
CRISPR/Cas9	Clustered Regularly Interspaced Short Palindromic Repeats/Cas9
DNA	Deoxyribonucleic acid
DO	Denomination of Origin
ECI	Electrochemical Color Index
FISH	Fluorescence in situ hybridization
F_{IS}	Inbreeding coefficient
F_{ST}	Genetic differentiation index
FT-MIR	Fourier-Transform Mid-Infrared spectrometry
GAB 4.0	Genomics-Assisted Breeding 4.0
GC-MS	Gas Chromatography-Mass Spectrometry
GDM	Global DNA Methylation
GFLOPs	Giga Floating Point Operations Per Second
H_B	Bayesian heterozygosity
HDP	High-degree polymerization (fructans)
H_E	Nei's Expected Heterozygosity

<i>H_O</i>	Observed Heterozygosity
IBA	Indole-3-butyric acid
IRs	Inverted Repeats
ISSR	Inter-simple sequence repeat
LSC	Large Single-Copy region
MS	Murashige and Skoog (media)
PGRs	Plant Growth Regulators
<i>PHYA</i>	Phytochrome A (light sensor protein)
Put	Putrescine
RADseq	Restriction site-associated DNA sequencing
rRNAs	ribosomal RNAs
RuBisCo	Ribulose-1,5-bisphosphate carboxylase/oxygenase
SDR	Second Division Restitution
SNP	Single Nucleotide Polymorphism
SRO	Similar to RCD One (gene family)
SSC	Small Single-Copy region
tRNAs	transfer RNAs
YOLO	You Only Look Once

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