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Review

Biotechnologies and Strategies for Grapevine Improvement

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Abstract: Grapevine (*Vitis vinifera* subsp. *Vinifera*) is one of the most widespread and economically important perennial fruit crops in the world. Viticulture has changed over the years in response to changing environmental conditions and market demands, triggering the development of new and improved varieties to ensure the crop's sustainability. The aim of this review is to provide a perspective on the recent developments in biotechnology and molecular biology and to establish the potential of these technologies for the genetic improvement of grapevine. The following aspects are discussed: (i) the importance of molecular marker-based methods for proper cultivar identification and how NGS-based high-throughput technologies have greatly benefited the development of genotyping techniques, trait mapping, and genomic selection; (ii) the recent advances in grapevine regeneration, genetic transformation, and genome editing, such as new breeding technology approaches for enhanced grapevine yield, quality improvement, and the selection of valuable varieties and cultivars. The specific problems and challenges linked to grapevine biotechnology, along with the importance of integrating classical and new technologies, are highlighted.

Keywords: biotechnology; crop improvement; genome editing; germplasm management; molecular markers; organogenesis; somatic embryogenesis

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1. Introduction

Domesticated grapevine (*Vitis vinifera* subsp. *vinifera*), one of the most economically important perennial fruit crops in the world [1,2], had a worldwide production of approximately 78 million tons in 2020 [3]. In 2020, the International Organization of Vine and Wine (OIV) estimated the world area under vines at 7.3 million ha [4]. The European Union (EU) had 3.2 million hectares of vines in 2020, equivalent to approximately 44 % of the world's total wine-growing areas [5]. Over half of these areas were cultivated with red wine varieties. Most of the harvested grapes are used for wine production but also for consumption as fresh fruit, raisins, juices, vinegar, seed oils, and spirit drinks [6,7]. Grape extracts are also used as food additives, in cosmetics, and in the pharmaceutical industry, while some species are grown for ornamental purposes [8,9].

Grapevine cultivars are susceptible to biotic (bacteria, fungi, viruses, and insects) and abiotic stressors (drought, extreme temperatures, and salinity) that reduce both the yield and lifespan of vineyards, causing substantial economic losses to grape production and the wine industry [10]. Vegetative propagation and growth on rootstocks ensure the grapevine tolerance to phylloxera, an insect pest that almost destroyed European viticulture in the late nineteenth century [11]. Other pathogens, such as gray mold, downy, and powdery mildew, as well as bacterial diseases (e.g. black rot and Pierce's disease), cause serious yield losses [11,12]. Due to continuous climate change, viticulture faces outbreaks

of these diseases, while thermal stress and severe dryness registered during the last decade harmfully impacted the whole winemaking sector, especially in southern European winemaking regions [13–15]. Thus, a reduction in table quality vines and wine grape production was anticipated [13]. All these threats triggered the need to improve viticulture's sustainability by imposing new varieties versus traditional varieties [15–17].

Conventional breeding, based on the hybridization of valuable grapevine genotypes, is difficult due to the long life cycle and heterozygosity [18]. Moreover, numerous diseases require specific solutions found in the natural variations of the *Vitis* genus [19] but also in genetic improvements via molecular manipulation. Thus, in recent years, biotechnology research proved to be a powerful complement to conventional breeding methods playing an increasing role in the improvement of the existing grapevine varieties and rootstocks. The novel approaches include the development of molecular markers for fingerprinting, genetic mapping, genetic diversity assessments in populations, gene tagging for breeding purposes (marker-assisted selection), and gene cloning; these technologiesaim to improve on the current plant transformation strategies and genetic editing to enhance disease tolerance and improve berry quality [9,17].

In the precision breeding of grapevine, only genetic elements encoding desirable traits are used; thus, the results are more predictable than conventional breeding. In the last decades, whole genome sequencing by next-generation sequencing (NGS) platforms and bioinformatics have allowed the rapid selection of plants for propagation and manipulation for different purposes.

Although modern techniques of precision breeding have taken a large scale and numerous valuable varieties have been obtained, genetically modified plants, however, are not easily accepted on the market. Edited plants were considered a solution to genetically transformed plants, mostly because the edited plants did not contain a transgene; thus, these plants were not subject to legal restrictions. Depending on the specific legislations in different countries, such as the USA, Argentina, Australia, and Brazil, even genetically modified organisms (GMOs) are accepted on the market because it is considered that edited plants do not contain foreign genes; thus, risk assessments are unnecessary. On the other hand, the European Union also considers that organisms obtained via mutagenesis, as well as those obtained via genome editing, are GMOs, as stated in the GMO European Directive 2001/18/EC [20] and should pass through the regulatory process of classical GMOs [21,22]. It is important to mention that point mutations induced by gene editing are practically impossible to distinguish from the natural ones or those induced by mutagenesis. This uncertainty could have negative consequences not only for agriculture but also for the economy; most researchers claim that organisms with only small genetic modifications without any foreign genetic material should not be considered GMOs [21,22]. Nevertheless, the latest technologies, i.e., genetic transformation and genome editing, are currently developing, the main limitation in grapevine being related to the complexity of some important agronomic traits [23].

In this review, we discuss the most recent achievements, specific problems, and challenges linked to grapevine biotechnology, along with the importance of integrating classical and new technologies for the genetic improvement of grapevine.

2. Grapevine Genetic Diversity and Molecular Markers Used in the Identification of Cultivars

Archaeological and archaeobotanical data showed that grapevine domestication began 6000–8000 years ago in the Transcaucasian region [24]. The dispersal of cultivated varieties from this primary center throughout the Near East and Europe relied upon (i) cultivars, the later clonal selection, and (ii) vegetative propagation [6]. In addition, secondary domestication events in other areas were also reported [25–28].

The genus *Vitis* [2n = 38] exhibits significant genetic diversity among cultivars, wild subspecies, and hybrids [29,30]. This is mainly due to their asexual reproduction, wide range of suitable planting, and frequent communication among grape accessions [31].

There are approximately 60–70 inter-fertile wild *Vitis* species widespread throughout Eurasia and Northern America [32]. *Vitis vinifera* subsp. *sylvestris*, the only wild *Vitis* taxon native to Europe and the Near East, is considered the ancestor of almost 10,000 domesticated grapevine cultivars [31]. Moreover, approximately 1200 commercial grapevine cultivars are interspecific hybrids of the domesticated grapevines and other wild *Vitis* species [33]. Consequently, there is a huge number of named cultivars (15,000), including several synonyms (identical genotypes but different names) and homonyms (same names but different genotypes) [34]. The working group on Vitis, referring to the European cooperative programme for plant genetic resources (ECPGR), reports 27,000 accessions of grapes held only in European collections [35]. In spite of the passport data available for approximately 35,000 accessions from European countries, the problem of cultivar synonyms and the presence of duplications need to be solved [35]. Therefore, a proper identification system, cultivar registration and protection, seed certification, and plant variety rights are essential in grapevine germplasm management for breeding programs but also for economic interests, trade, and scientific knowledge [30,36].

2.1. Morphological Markers

Grapevine cultivars have traditionally been identified based on their morphological characteristics (ampelography) jointly provided by the International Organization of Vine and Wine (OIV), the International Union for the Protection of New Varieties of Plants (UPOV), and the International Plant Genetic Resources Institute (IPGRI) [37]. Although efficient for the assessment of qualitative traits, the application of morphological markers is limited in the evaluation of quantitative traits. Moreover, this method is time-consuming, requiring extensive field trials and the identification of closely related cultivars is difficult [38].

To complement the morphological identification of grapevine varieties and overcome classification errors and double designations, cytogenetic, biochemical, as well as DNA and RNA-based technologies were developed for the analysis of the existing grape germplasm diversity [30].

2.2. Cytological Markers

In earlier studies, following morphological markers, cytological markers (karyotypes, banding patterns, deletions, repeats, translocations, and inversions) were developed. The chromosome number and morphology, and the DNA amount and composition, are characterized with Giemsa staining, fluorochrome banding, silver staining, and fluorescence in situ hybridisation (FISH) [39]. However, only a few cytogenetic studies are available in grapevine, mainly due to the large number of small chromosomes and the difficulty of obtaining good chromosome preparations from the roots or anthers [30]. Sequential silver nitrate staining and FISH were used to study ribosomal DNA (rDNA) loci [39–41] to localize the retrotransposon Gret1 [40], BAC clones [42], and telomeric sequences [43]. However, FISH is considered a niche technique because it allows the analysis of only a few samples at a time, and its accuracy is highly dependent on excellent quality confocal microscopy and image analysis procedures [30]. However, with the advent of sequencing technologies (next-generation sequencing (NGS)) and the availability of high-quality de novo reference genomes for grapes, new horizons were opened for modern cytogenomics [30]. Thus, the physical mapping of DNA sequences on chromosomes facilitated comparative plant genomics, improving the genome and chromosome assemblies.

2.3. Molecular Markers

Molecular markers include protein-based markers (products of gene expression) and DNA-based markers derived from the direct analysis of polymorphisms in DNA sequences [44]. Depending on the detection method used, DNA markers are categorized as

hybridization-based markers and polymerase chain reaction (PCR) and DNA sequence-dependent molecular markers.

Since their discovery, different molecular markers, such as restriction fragment length polymorphisms (RFLPs) [45], random amplified polymorphic DNA (RAPD) [46], sequence characterized amplified regions (SCARs) [47,48], simple sequence repeats (SSRs) [31,49], inter-simple sequence repeats (ISSRs) [50,51], amplified fragment length polymorphisms (AFLPs) [52], single nucleotide polymorphisms (SNPs) [53], expressed sequence tags (ESTs) [54,55], and random amplified microsatellite polymorphisms (RAMPs) [56] have been widely used for the genetic diversity characterization of grapevine cultivars, molecular mapping, parentage analysis, clone's identification, and the detection of synonymies.

Among these, SSRs and SNPs have become the preferred markers for the characterization of grapevine genetic resources and varietal identification in germplasm collections [30]. Several studies reported nuclear and chloroplastidial SSR loci (nSSR and cpSSR) as useful to demonstrate the multiple origins of *V. vinifera* spp. *sativa* (cultivated grapevine), to reveal synonymies, homonymies, as well as inter and intra-specific genetic variations and phylogenetic relationships among wild and cultivated grapevines [27,57–62]. In recent years, SNP markers have also gained high popularity for evaluating allelic variations throughout grapevine genomes and dissecting complex traits via QTL (quantitative trait loci) for breeding programs [63,64]. SNPs are highly abundant across plant genomes and offer higher reproducibility than microsatellite data, facilitating the integration and interpretation of genotyping data throughout grape gene banks and databases [65,66]. The rise of NGS and resequencing techniques have facilitated the release of an extensive number of SNPs [31,67] and the development of reliable platforms, such as VitisGDB (the multifunctional database for grapevine breeding and genetics), for comparing and mining *Vitis* genomic information [68]. There are currently many reference Vitis databases, including simple genetic information or only descriptive information (i. e., the species name, country of origin, cultivar names, usage, etc.) Among these, we mention the International Variety Catalogue (VIVC) [69], Instituto de Ciencias de la Vid y del Vino [70], the European Vitis database [71], the Greek Vitis database [72], the Italian Vitis database [49], the molecular pathway database, the transcriptome database, grape sRNA atlas [68], etc.

In the last years, DNA marker systems used in grapevine characterization have evolved from interrogating small numbers of loci and individuals to tens of thousands of loci in studies of large populations [73]. Moreover, *Vitis* spp. genome sequencing has led to significant progress in the development of large-scale high-throughput DNA markers and the identification of QTL, allowing the confirmation of candidate genes and the development of breeding programs based on marker-assisted selection (MAS). The earliest method, restriction site-associated DNA [RAD] sequencing, was successfully applied to identify significant traits in elite grape cultivars [74,75]. Other sequencing-based methods, such as whole genome resequencing approaches, have been applied for the characterization of somaclonal variations within cultivars [76,77]. Moreover, RNA-seq has been widely applied in *Vitis vinifera* to study different aspects such as bud development [78], berry development and ripening [79], and the response to disease or pathogens [80]. Recently, a set of 2000 DNA low-cost marker panels transferrable across the entire *Vitis* genus was designed and implemented using rhAmpSeq (RNase H2 enzyme-dependent amplicon sequencing), which could be easily adapted for other taxa for ecological and evolutionary studies, QTL mapping, a genome-wide association study (GWAS), and molecular breeding [81].

In general, each technology provides results with a different resolution and accuracy, and the degree of detected genetic divergence depends on the marker system applied and the scope and type of plant samples used. The different applications of molecular markers in grapevine are presented in Table 1.

Although high-throughput sequencing technologies provide enormous potential to improve our way of understanding and accessing grapevine biodiversity, downstream

bioinformatic analysis requires reliability to be ensured. There is not just one perfect array for all different research questions; therefore, the choice of the genotyping tool should be based on the purpose, sample size, resolution, accuracy, and budget available.

Table 1. Application of the most widely used molecular markers in grapevine.

Application	Molecular Marker *	References
Genetic diversity population structure	RAPD, ISSR, SSR, retrotransposon-based markers, SRAP, SNP, RAMP, REMAP, and IRAP	[49,50,82–88]
Cultivars, rootstocks, and clone identification	RAPD, cpSSR; SCAR; RFLP, SSR, SNP, AFLP, SAMPL, M-AFLP, MSAP, CAPS, IRAP, REMAP, SSAP, EST, and retrotransposon-based markers	[31,38,45,47,89–98]
Synonymies and homonymies clarification	RAPD and SSR	[99–101]
Origins of cultivated grapevine/phylogeographic patterns	cpSSR, SSR, and SNP	[27,53,57,60,62,102–104]
Genetic linkage maps	RFLP, SRAP, and SNP	[105,106]
Disease diagnostics	RFLP, SCAR, SSR, SSCP, ITS, and RNA sequencing	[48,80,107–110]
Transcriptome analysis and new gene discovery	EST	[54,55,111]
Genetic stability and somaclonal variation	RAPD, AFLP, SSR, CDDP, ISSR, and MSAP	[112–117]
QTL mapping	RAPD, CAPS, AFLP, SCAR, SSR, SNP, RAD sequencing, rhAmpSeq markers, SLAF-seq, and sequencing	[70,74,75,81,118–127]

* RFLP, restriction fragment length polymorphism; RAPD, randomly amplified polymorphic DNA; SCAR, sequence characterized amplified region; AFLP, amplified fragment length polymorphism; M-AFLP, microsatellite-amplified fragment length polymorphism; SSR, simple sequence repeat; cpSSR, chloroplast simple sequence repeat microsatellite; ISSR, inter simple sequence repeat; SAMPL, selectively amplified microsatellite polymorphic loci; SRAP, sequence-related amplified polymorphism; SSCP, single strand conformational polymorphism; S-SAP, sequence-specific amplification polymorphism; CAPS, cleaved amplified polymorphic sequence; SNP, single nucleotide polymorphism; EST, expressed sequence tag; RAMP, randomly amplified microsatellite polymorphism; REMAP, retrotransposon-microsatellite amplified polymorphism; IRAP, interretrotransposon amplified polymorphism; SSAP, sequence-specific amplified polymorphism; ITS region sequences- ribosomal DNA internal transcribed spacer; CDDP, conserved DNA derived polymorphism; RAD sequencing, restriction site-associated DNA sequencing; rhAmpSeq, RNase H2 enzyme-dependent amplicon sequencing; SLAF-seq, specific length amplified fragment sequencing.

3. Grapevine Plant Regeneration Methods

Biotechnology research offers the potential to improve the yield and quality of grapes. The development of in vitro plant regeneration methods is essential to overcome the difficulties in conventional breeding studies, preserve and propagate valuable genotypes, as well as to increase genetic variability through genetic engineering (transgenic, cisgenic, and gene-edited plants) [128,129]. In addition, in vitro mass multiplication represents an alternative to the current greenhouses or outdoor repositories and allows the exposure of genotypes to in vitro-induced stresses (i.e., biotic and abiotic risks) [82].

To date, grapevine regeneration has been obtained with two fundamental pathways of propagation and regeneration through organogenesis and somatic embryogenesis

[7,128]. Organogenesis is based on the ability of competent tissues to form whole plants directly from the meristematic regions of explants (direct organogenesis) or intervened with callus formation (indirect organogenesis). Indirect organogenesis induces somaclonal variation involving both genetic and epigenetic changes in in vitro regenerated plants. In applied studies involving commercial scale multiplication or transgenic plants, the plants must be "true to type", meaning high genetic uniformity of the regenerated plants [130,131]. Therefore, to demonstrate the genetic fidelity as well as the somaclonal variation of the in vitro plants, molecular marker approaches were applied. Somaclonal variation is an alternative source of genetic variability in horticultural crops with a narrow genetic base or difficult breeding [132].

Grapevine, similar to other woody species, has revealed a genotype and explant type dependent recalcitrance to in vitro regeneration techniques [17,129]. Many studies have reported that rootstock varieties reveal higher organogenesis and somatic embryogenesis potential than hybrids and varieties belonging to the *V. vinifera* species [133]. However, several other factors were reported to influence the efficiency of grapevine in vitro plant regeneration, such as culture medium composition, especially the type and concentrations of plant growth regulators (PGRs) [134,135]; explants' developmental stage [136] and phyllotactic position [137]; light regime [138]; pH value [139], etc. Therefore, over the years, numerous studies were focused mainly on optimizing protocols for efficient regeneration across different grapevine genotypes. A thorough review of successful reports via organogenesis and somatic embryogenesis in several grapevine cultivars and rootstock species using different explants was published by Zhang et al. [17]. Further on, we briefly discuss some aspects related to the applications of in vitro regeneration systems in grapevine improvements.

The first attempts in grapevine biotechnologies started in the 1960s with in vitro propagation for mass production and healthy plant regeneration [23]. Over the years, different studies have focused on inflorescence culture [140,141] to study the mechanisms of floral induction [44], hairy root cultures [142–144] to study plant-pathogen interactions, the efficiency against nematodes [145,146], or phylloxera [147,148], and shoot tip culture combined with thermotherapy, chemotherapy, or cryotherapy to eliminate viruses [149–151].

Nowadays, the rapid technological advancements in molecular and cell biology include a wide range of new plant breeding technologies (NPBTs), which in association with the new genomic data available, offer the opportunity: (i) to develop new grapevine varieties with enhanced yields, quality, stress tolerance, and disease resistance through genetic manipulation [17] and (ii) to have a clearer picture of the molecular regulation of plant cells, tissue culture, and regeneration processes [128].

Due to their morphogenetic competence, embryogenic tissues are mostly preferred in genetic transformation studies for the application of new genomic techniques, such as cisgenesis and intragenesis, genome editing, and RNAi [7], and these could be a possible tool for virus and viroid elimination [152]. Moreover, somatic embryogenesis could prevent the development of chimerism, allowing the regeneration of genetically transformed embryos under selective culture conditions [153]. However, some genotypes have proven to be very recalcitrant to somatic embryogenesis; thus, genetic engineering techniques are difficult to apply [154].

The acquisition of embryogenic competence is related to different patterns of gene expression involving internal cell reprogramming leading to a reversion of the differentiation state [128,155,156]. Somatic embryos may be obtained through the development of an embryogenic callus (indirect embryogenesis) followed by the emergence of pro-embryogenic masses (PEMs), from which new somatic embryos are formed [157], or may occur directly from the explants without the callus developmental phase. In most cases, direct somatic embryogenesis is used for clonal propagation rather than indirect somatic embryogenesis, which is characterized by a high incidence of somaclonal variation [158]. The explants mostly employed for somatic embryogenesis induction are anthers, ovaries,

leaves, petioles, tendrils, and nodal sections [159]. It was demonstrated that, amongst other factors, the type and concentrations of plant growth regulators (PGRs) play a crucial role in the induction of an embryogenic callus [160]. In particular, 2,4-dichlorophenoxyacetic acid (2,4-D) was reported as the most effective compound for the induction of somatic embryos [161,162].

Considering the importance of somatic embryogenesis in the genetic improvement of grapevine and the critical factors affecting its success, the development of efficient and reproducible genotype-specific protocols for all major grapevine, table grape cultivars, and rootstocks is required.

4. Somaclonal Variation

Plants cultivated in vitro could develop different modified characteristics and genetic variability due to somaclonal variation [163]. The genetic bases of somaclonal variation are gene mutations and also the rearrangements of chromosomes, karyotype changes [164–166], or epigenetic modifications driven by hyper or hypo-methylation [167]. Most of these are induced by oxidative stress [168], as shown in Figure 1.

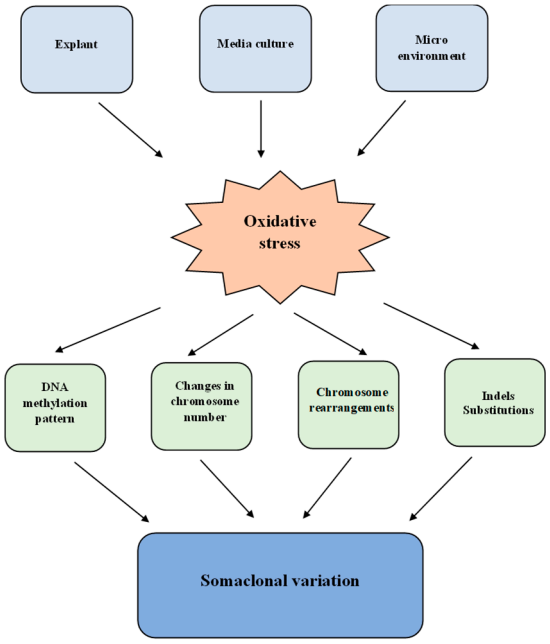

Figure 1. Mechanism of somaclonal variation induced by oxidative stress in plants cultivated in vitro.

The genetic variation of micro-propagated plants is generally considered obstructive, and the loss of genetic fidelity was often observed. However, increased genetic variability has applications in the improvement of horticultural crops. The most important advantage of somaclonal variations is the reduced time and space for the screening of valuable genitors and traits than the crossing of perennial crops. Moreover, different somaclones could be used in breeding applications and genetic improvements with in vitro selection [132].

Several in vitro procedures imposing oxidative stress, such as protoplast culture, callus induction, or somatic embryogenesis, are more frequently followed by somaclonal variation due to the epigenetic changes in plant tissues [169]. Thus, polyploids were obtained with somatic embryogenesis in six Spanish *V. vinifera* cultivars [170]. High methylation was detected in two cultivars during somatic embryogenesis, and the AFLP markers showed higher variability in these plants, but the SSR patterns were similar in plants derived from somatic embryos and control plants [117]. Somaclonal variation in grapevine could also appear by several major genetic changes by the spatial arrangement of

periclinal, mericlinal, and sectorial cell layers that are genetically different [171]. Periclinal chimeras originated from mutations in one of the cell layers, are stable plants producing axillary buds and have the same apical organization as the terminal meristem from which they were generated [172]. Somatic embryos in grapevine derive from a single cell; thus, the clonal characteristics are not transferred to the progeny, as shown with microsatellite markers in Pinot Meunier. Nevertheless, different accessions of Pinot Meunier have three alleles in the VVS2 locus and the accessions of Pinot Noir, Pinot Gris, and Pinot Blanc have two alleles in this locus, explained by a mutation in one of the two alleles in one of the cell layers in Pinot Meunier and its maintenance through the vegetative propagation of a periclinal chimera [173]. A similar variation was also observed in the VVS19 locus in the embryogenic callus induced from the cell layers of anther filaments in Primmitivo ist [173,174].

Other studies showed that the intracultivar variability within Pinot Noir and chardonnay are also due to mutations in the by a mutation in one of the two alleles in one of the cell layers in Pinot Meunier and its maintenance through vegetative propagation of a periclinal chimera[174,175]. Thus, somatic embryogenesis is a valuable tool to understand the origins, genetic structures, and relationships between ancient cultivars and should be considered before using them for Micropropagation, genetic conservation, or transformation [175].

5. Genome Sequencing and Applications

Grapevine is not only an important fruit crop but also a plant model for genetic studies due to its small genome size of 475–500 Mb and 38 chromosomes (n = 19). Most of the *Vitis* species are diploids, but there are also fertile interspecies hybrids [9]. The international grape genome program (IGGP) generated the first genome sequence for the Pinot Noir clone ENTAV 115 with Sanger and shotgun sequencing, which was important to understand the genome organization and the 19 linkage groups of *Vitis vinifera*. The genomic sequences of Pinot Noir clone ENTAV 115 (477.1 Mb) were assembled in 2093 metacontigs (approximately 28,352 genes and pseudogenes), of which 96.1% were assigned to linkage groups and candidate genes encoding relevant traits were predicted. In the NCBI taxonomy web portal for *V. vinifera*, there are 29,971 listed unique coding genes, and the information about these genes and the metabolic pathways in which they are involved are available at the TIGR site [176]. A consensus map was developed based on the genetic maps [177–181] and physical maps [182] previously developed. Other facilities are also available for different genomic and transcriptomic analyses, such as the grape BAC library from the French national resources center for plant genomics [183]; 14,000 transcripts from *V. vinifera* and 1700 transcripts from other *Vitis* species were released by The GeneChip® *Vitis vinifera* genome array (Affymetrix). An array-ready oligo set contains 14,562 probes of 70-mers representing grape gene transcripts released by Qiagen (http://www1.qiagen.com). The design of the grape oligo set was based on the sequence information from TIGR's grape gene index (http://www.tigr.org/tdb/tgi) [9].

Advancements in NGS technology allowed the development of genome-wide approaches for the genetic characterization of complex traits or for marker-assisted selection, such as genome-wide association studies (GWAS) or genomic selection (GS).

GWAS was used to understand the genetic bases of the important traits and to identify the polymorphic molecular markers associated with these traits [184] that could be further used in marker-assisted selection programs.

In contrast to the GWAS method, which identifies polymorphisms linked to the variations for selected traits, GS allows the prediction of a breeding value for the genotypes tested [185] based on large sets of markers. Thus, GS could significantly reduce costs for the marker-assisted selection of valuable variants by limiting the size and number of field experiments. Genotype-based prediction also allows selection in breeding schemes when the phenotyping of breeding candidates is impossible or difficult [186,187].

Unfortunately, GWAS and GS methods, which use genome-wide marker data for phenotype prediction, are difficult to use in highly heterozygous species such as grapevine [188]. Moreover, the efficiency of GWAS also depends on the genetic architecture of the trait; thus, the detection of molecular markers associated with polygenic traits depends on the size of the sample and the density of the molecular marker used [189]. In grapevine, there are no available valuable lines from complex breeding schemes; the breeders use highly diverse and heterozygous parental genotypes (H = 0.76) [190]. This is the result of strong inbreeding depression and vegetative propagation [190,191]. In addition, this panel of parental genotypes is also characterized by a low level of linkage disequilibrium (LD) between marker loci (r^2~0.2 at 5–10 Kb) [67,191]; most cultivars are interconnected by a series of first-degree relationships (i.e., Pinot noir – Chardonnay – Gouais blanc, Cabernet franc – Merlot [192,193]), but the number of connected generations is relatively low [194,195]. However, GWAS and GS have become more relevant in grapevine since the number of molecular tools is constantly increasing due to the high demand for new grapevine cultivars adapted to climate change [196,197].

6. Genetic Transformation

As conventional culture and the selection of new valuable varieties are time and resource-consuming, genetic transformation provided an alternative for developing new varieties with increased productivity, higher quality, and tolerance to different stress factors. Conventional breeding cannot provide resistance to diseases or pests to elite cultivars of *Vitis* [198]; thus, these cultivars are currently maintained through vegetative propagation [199] and require the frequent use of pesticides to control diseases [200]. To overcome these concerns, modern biotechnology proposed so-called precision breeding [201] and the genetic improvement of elite cultivars, which was previously known as cisgenic or intragenic improvements [202].

Unfortunately, the grapevine is considered a recalcitrant species in terms of genetic transformation due to several aspects, including (i) genes involved in grapevine transformation, (ii) vectors used for gene delivery and protocols for grapevine transformation, and (iii) protocols for transgenic plant regeneration [7].

The insertion of specific genes into plants with different methods and vectors was developed for over thirty years in perennial crops. In grapevine, physical and chemical delivery methods were tested over the years, and transgene delivery was mediated by *Agrobacterium* and viruses [23,203-206] Several grapevine varieties were transformed with biolistic bombardment [203] and *Agrobacterium*-mediated transformation [204]. There are also several other methods of transformation, such as electroporation or protoplast transfection [23,205]. Viral vectors were used for the heterologous gene expression or the silencing of host genes (i.e., virus-induced gene silencing -VIGS) [206]. Cloning strategies and tools for the genetic engineering of grapevine were detailed and reviewed by [17,23].

Several grapevine infectious viruses, such as Vitivirus Grapevine Virus A (GVA) [207], the Closterovirus Grapevine leafroll-associated virus-2 (GLRaV-2) [208], and the Foveavirus Grapevine rupestris stem pitting-associated virus (GRSPaV) [209] were used for the silencing of PDS (phytoene desaturase) or ChlI (subunit I of magnesium protoporphyrin IX chelatase), which was observed with the development of the albino phenotype [207,208]. A diagram showing the most important steps in genetic manipulation with transformation or editing of grapevine is shown in Figure 2.

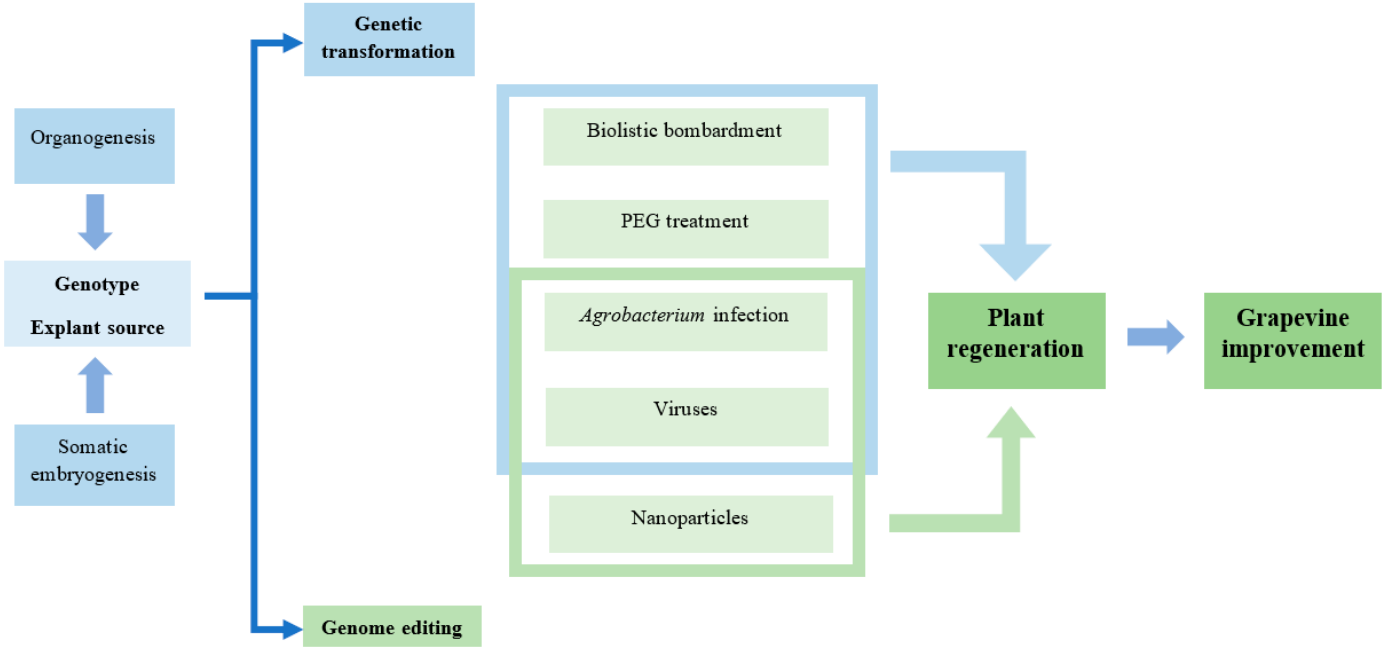

Figure 2. Diagram of grapevine genetic manipulation with transformation or editing.

The success of a transformation is facilitated by the marker genes as selectable marker genes and reporter genes that ensure the rapid and accurate selection of modified cells from non-modified cells [210]. Some of the marker genes encode resistance to antibiotics or herbicides, and the reporter genes encode proteins such as green fluorescence protein (GFP) or glucuronidase (GUS) [211]. Previously, most transgenic plants were obtained with vectors containing the *NPTII* gene as a selectable marker gene and GFP as a reporter gene, ensuring the visual selection of transformed plants [210]. For the elimination of the marker gene from transgenic plants, a complex system is used, which consists of two strains of *Agrobacterium*, one of them carrying a binary vector which contains the target gene, and another containing a binary vector with the selection marker genes as *codA*/*nptII*. The cells containing the target gene and the *codA*/*nptII* genes grow on the media with kanamycin, and then the cells containing the marker gene are eliminated with negative selection based on the *codA* function [212].

The analysis of the gene expression was performed using the *VvMybA1* gene involved in the anthocyanin biosynthesis pathway [213]. This gene allows the visual identification of transformed cells without kanamycin selection [210]. Unfortunately, the transformed plants of grapevines (Thompson Seedless) containing this visual reporter gene were not vigorous due to the intense pigmentation and curly and highly brittle leaves [213], and the viability was reduced. These inconveniences were mitigated by placing the *VvMybA1* gene under the control of tissue-specific and developmentally regulated promoters, for example, the promoter of the *Dc3* gene, expressed in late embryogenesis in carrots (*Daucus carota*), followed by the production of anthocyanin exclusively in embryos [214]. Moreover, being a visible marker, *VvMybA1* could be used for monitoring transgene expression in the whole plant. Transgene expression could also be monitored by reporter genes such as GUS and GFP [215]. Anthocyanin has a pink-to-red color which is easily discerned, and it is suitable for the analysis of gene expression in experiments involving the selection of hundreds of transgenic plants. [216]. The marker gene *VvMybA1*, placed under the control of the ubiquitin gene promoter, was used for the high-throughput analysis of genes and promoters [217].

The employment of appropriate promoters highly influences the development of valuable traits. Unfortunately, the progress of functional analyses in grapevine is reduced in comparison with *Arabidopsis* and rice, mainly due to the limited ability to obtain enough

explants and difficulties in the analysis of the gene expression. The functional annotation of at least 18,725 genes in the grapevine allowed the evaluation of their promoters, as well as the gene expression under developmental and environmental factors. For proper uses, a detailed characterization of these promoters is required regarding their sequences and activation. First, constitutive viral promoters were used for most of the transgenes in grapevines [218] and then after, these promoters were replaced by ubiquitin gene promoters. The gene expression was monitored with an anthocyanin-based assay mentioned previously [214].

Precision breeding requires appropriate promoters for gene expression in particular tissues or certain stages of plant development. Thus, the discovery and characterization of potential promoters are extremely important for precision breeding in grapevine [218].

Successful genetic transformation also depends on the efficient regeneration of transgenic plants. Factors such as genotype, explant source, acceptor material, culture medium, bacterial strains, selectable markers, and selection methods affect the efficiency of plant transformation and regeneration. The genetic transformation of several grapevine cultivars, such as Thompson Seedless, Silcora, and Chardonnay, was obtained with shoot organogenesis from meristematic tissue [219–221]. The in vitro organogenesis of some grapevine cultivars and rootstocks was obtained from different types of explants, such as petioles, leaf internodes, and shoot apices [137,138,220–222]. One limitation of direct organogenesis is the regeneration of chimeras explained by the induction of adventitious buds from multiple cells [223]. Plant regeneration from somatic embryos induced from a single cell could be used to avoid such chimeras. Somatic embryogenesis was also used for grapevine micropropagationand genetic transformation. Unfortunately, the induction of somatic embryogenesis is generally low and dependent on the type of explants [224]. Moreover, the maintenance of embryogenic masses on calluses and somatic embryos is also very important [225]. Therefore, transgenesis in grapevine is mostly based on the *Agrobacterium* system, and the regeneration of transformants is generally achieved with somatic embryogenesis. Improved *Agrobacterium*-mediated transformation protocols were published to enhance the fruit quality and tolerance to different stress factors [226,227].

Several factors influence the regeneration of transformants via somatic embryogenesis, such as the grapevine genotype [228], explant source [137,138,229], and culture medium [222,224,230]. All of these factors were reviewed by Zhang et al. [17].

Important achievements in grapevine using direct transformation methods and *Agrobacterium*-mediated transformations are shown in Table 2. Several experiments were also carried out in order to develop an efficient transformation method; these were reviewed by Zhang et al. [17].

Table 2. Grapevine improvements with genetic transformations.

Method	Cultivar	Target Gene	Trait	References
Transient expression assays using direct transformation methods, modified from Jelly et al. [231]				
Biolistics	Cabernet sauvignon	VvAdh1, VvAdh2 VvAdh2	Abiotic stress	[232,233]
Biolistics	Chardonnay	VvMYBA1, -F1, -PA1, -PA2 and VvCHS1,VvCHS2, VvCHS3 promoters	Flavonoid synthesis	[234]
Biolistics	Chardonnay	VvMYB5a,-5b and VvANR, VvANS,VvCHI, VvF30 50 H, VvLAR1 promoters	Flavonoid synthesis	[235]

Biolistics	Chardonnay	VvMYBA1, -A2 and VvUFGT promoter Flavonoids GFP, dual Luc Walker et al. [225] Flavonoid VvMYBF1 and synthesis VvANR, VvCHI, VvFLS1, VvLDOX promoters		[236]
Biolistics	Chardonnay	VvMYBF1 and VvANR, VvCHI, Flavonoid VvFLS1, VvLDOX synthesis promoters		[237]
Biolistics	Chardonnay	VvMYBPA1 and VvANR, VvCHI, Flavonoid VvF30 50 H, VvLAR1, synthesis VvLDOX promoters		[238]
Biolistics	Chardonnay	VvMYC1 and VvMYB5a, -5b, -A1, -A2, -PA1 and Flavonoid VvANR, VvCHI, synthesis VvMYC1, VvUFGT promoters		[239]
Biolistics	Chardonnay Pinot Noir	VvMYB14, -15 and VvSTS29, -41 promoters	Stilbene synthesis	[240]
Biolistics	Chardonnay	VvPGIP1 promoter	Resistance to *B. cinerea*	[241]
Biolistics	Thompson Seedless	VvPGIP1 promoter	Resistance to *B. cinerea*	[241]
PEG treatment	Cabernet Sauvignon	VvMSA	Abiotic stress	[242]
PEG treatment	Cabernet Sauvignon	VvWRKY1 and VvJAZ1.1, VvLOX promoters	JA defence pathway	[243]
PEG treatment	Cabernet Sauvignon	VvMYC1	Flavonoid synthesis	[239]
PEG treatment	Cabernet Sauvignon	VvMSA	Abiotic stress	[244]
Transient expression assays using *Agrobacterium*-mediated transformation, modified from Jelly et al. [220]; Zhang et al. [17]				
Agrobacterium	Superior Seedless	hpRNA against VvPDS	Gene silencing	[245]
Agrobacterium	Cabernet Franc, Syrah, Zinfandel	GLRaV-2 cDNA	-	[208]
Agrobacterium	Thompson Seedless	D4E1 (synthetic AMP)	Resistance to *A. vitis*, *X. ampelinus*	[246]
Agrobacterium	Cabernet Franc	hpRNA against VvPGIP1	Resistance to *B. cinerea*	[247]

Agrobacterium	Cabernet Sauvignon, Cinsault, Muscat Ottonel, Syrah	VvVST1	Resistance to *P. viticola*	[248]
Agrobacterium	Carignane	VpGLOX	Resistance to *E. necator*	[249]
Agrobacterium		VpPR10.2	Resistance to *P. viticola*	[250]
Agrobacterium		VpSTS	Resistance to *E. necator*	[251]
Agrobacterium		VpPR10.1	Resistance to *P. viticola*	[252]
Agrobacterium	Syrah	VvNPR1	Resistance to *P. viticola*	[253]
Agrobacterium	Grenache	GLRaV-2 cDNA	-	[254]
Agrobacterium	Prime	GVA cDNA	-	[207]
Agrobacterium	Prime, Thompson Seedless	GRSPaV cDNA	-	[209]
Agrobacterium	Gamay Red	VvDFR	Flavonoid synthesis	[255]
Agrobacterium	Chardonnay	amiRNAs against Grapevine fanleaf virus and GUS sensor	Resistance to GFLV	[256]
Agrobacterium	Thompson Seedless	CaMV35S, CsVMV, *Arabidopsis* ACT2-promoters	-	[257]
Agrobacterium	Thompson Seedless	BDDPs with CaMV35S, CsVMV promoters and enhancers	-	[213]
Agrobacterium	Thompson Seedless	31 grapevine promoters (PR1, PAL, Ubiquitin etc.)	-	[217]
Agrobacterium	Russalka and Rupestris du lot	GFLV CP (grape fanleaf virus coat protein) and four encoding antifreeze proteins (Atf11, Atf62, Atf78, B5) for Russalka, GUS (β-glucuronidase gene) for Rupestris du Lot	Fan Leaf Virus resistance and cold resistance	[258]
Agrobacterium	Chancellor	tfdA gene (a 2,4- D α-ketoglutarate dioxygenase)	Tolerance to 2,4-D	[259]

Agrobacterium	Pusa seedless	A rice chitinase gene	Resistance to powdery mildew	[260]
Agrobacterium	Thompson seedless	vvtl–1 (a thaumatin-like protein)	Broad spectrum fungal disease resistance	[261]
Agrobacterium	Thompson seedless	VvMybA1 (regulatory gene for the last metabolic step of anthocyanin biosynthesis)	Development of an anthocyanin-based quantitative reporter system	[213]
Agrobacterium	Crimson seedless	Chitinase and β–1,3-glucanase genes	Tolerance to downy mildew	[262]
Agrobacterium	Thompson Seedless	VpPUB23 (a ubiquitin ligase gene)	Overexpression of VpPUB23 decreased powdery mildew resistance	[225]
Agrobacterium	Chardonnay	VpSTSgDNA2	Developed a protocol and increased powdery mildew resistance	[263]
Agrobacterium	Thompson seedless and Freedom	LIMA-A (a synthetic gene encoding lytic peptide)	Durable Pierce's disease resistance	[264]
Agrobacterium	Thompson seedless; Red Globe	VqSTS6 in Thompson Seedless; VpPR4–1 (pathogenesis-related proteins) in Red globe	Resistance to powdery mildew	[265,266]
Agrobacterium	Brachetto	Knockdown through RNA interference of VvMLO6, 7, 11 and 13 (mildew locus O)	Reduced susceptibility to powdery mildew	[267]
Agrobacterium	Thompson seedless	Overexpression of VaTLP (thaumatin-like protein)	Resistance to downy mildew	[268]
Agrobacterium	Thompson seedless	Overexpression of VaPUB (a stress-responsive U-box protein gene)	Disease resistance	[269]
Agrobacterium	Thompson seedless	Overexpression of VpPR10.1	Resistance to downy mildew	[270,271]
Agrobacterium	Thompson seedless	Overexpression of AgNHX1 (Na+/H+	Increased salt tolerance	[272]

		antiporter gene in *Atriplex gmelini*)		
Agrobacterium	Thompson seedless	Overexpression of VvWRKY8	Repressed VvSTS15/21 expression and resveratrol biosynthesis	[273]
Agrobacterium	Thompson seedless	Overexpression of VpSTS29/STS2	Resistance to powdery mildew	[274]
Agrobacterium	Thompson seedless	Overexpression of VlbZIP30 (a basic region/leucine zipper transcription factor)	Improved drought resistance	[275]

7. Genome Editing

Genome editing consists of precise genetic modifications with different purposes, such as gene inactivation, that allow the possibility to explore the function of a particular gene and the insertion or replacement of genes at specific sites for genetic improvements. Strategies involving genome editing are known as new breeding technologies [23]. Artificially engineered nucleases, such as zinc-finger nucleases (ZFNs) [276], transcription activator-like effector nucleases (TALENs) [277,278] and clustered regularly interspersed short palindromic repeats (CRISPR) in association with the Cas9 nuclease [279] are capable of inducing specific double-stranded breaks (DSBs) of DNA molecules. The DBS are repaired with natural mechanisms present in all cells, such as non-homologous end joining (NHEJ), which is followed by point mutations due to the insertion or deletion of some nucleotides (INDELS) in the target gene, or homologous recombination (HDR) if a DNA sequence is available for recombination. CRISPR-Cas9 technology is considered the most efficient, among the genome editing tools, due to the high specificity and minimal nontarget effects [280]. Gene editing with the CRISPR-Cas9 system requires a guide RNA (gRNA) containing a spacer sequence complementary with the desired DNA sequence. The complex formed by guide RNA and Cas9 scans the genome, searching for complementary double-stranded DNA [281]. The nuclease recognizes the protospacer-adjacent motif (PAM) and generates a DSB in the specific gene sequence. Thus, genome editing through CRISPR-Cas9 technology requires the PAM sequence downstream of the target gene and proper guide RNAs, designed based on the gene sequences encoding important traits [282]. The description of the genome editing technologies based on ZFNs, TALENs and the CRISPR-Cas9 system was provided by Bortesi and Fischer [283] and Butiuc-Keul et al. [284]. Despite the many advantages of CRISPR-Cas9 technology over ZFNs and TALENs, the occurrence of off-target mutations is one of the shortcomings [285,286], being influenced by different parameters, such as the recognition of the target, the design of guide RNAs, the frequency of repair events with homologous recombination, and anti-CRISPR proteins that inactivate Cas9 [280].

Another limitation of using CRISPR-Cas9 technology is related to the delivery of the system in plant tissues. Generally, gRNAs and Cas9 are delivered into plant cells by *Agrobacterium*, viral vectors, PEG-mediated transformation, biolistic methods, and nanoparticles [280]. The CRISPR-Cas9 system could be released in tissues in its DNA, mRNA, or ribonucleoprotein forms and incorporated in different biomaterials for proper delivery [287], but these studies were carried out mostly in animal and human cells for cancer therapies. The structure of the plant cell wall limits the delivery of the system; thus, the most used system for delivery into plant tissues is *Agrobacterium* [288]. Nevertheless, the direct delivery of the purified Cas9 protein and gRNAs was also applied for the editing of the plant genome [289,290].

Most of the studies regarding the genome editing of grapevine were conducted in order to increase the resistance to powdery mildew [136,289,291,292] and *Botrytis cinerea* [227], the production of tartaric acid [293], the manipulation of the carotenoid biosynthesis pathway, and the induction of the albino phenotype [294,295] [Table 3].

Table 3. Grapevine improvements with CRIPSR-Cas9 technology (modified from Zhang et al. [17]; Butiuc-Keul et al. [284]).

Technology	Cultivar	Target Gene	Trait	References
CRISPR/Cas9	Chardonnay	MLO-7	Resistance to powdery mildew	[289]
CRISPR/Cas9	Neo Muscat	VvPDS	Albino phenotype	[294]
CRISPR/Cas9	Chardonnay, 41B	VvPDS	Albino phenotype and dwarf morphology	[295]
CRISPR/Cas9	Chardonnay	L-idonate dehydrogenase gene (IdnDH)	Biosynthesis of tartaric acid	[293]
CRISPR/Cas9	Neo Muscat	VvPDS (phytoene desaturase gene)	CRISPR-Cas9-mediated protocol development	[294]
CRISPR/Cas9	Thompson seedless	VvWRKY52	Resistance to *B. cinerea*	[227]
CRISPR/Cas9	Thompson seedless	VvPR4b	VvPR4b knockout decreased downy mildew resistance	[291]
	Thompson seedless	VvMLO3 and VvMLO4	Resistance to powdery mildew	[293]

8. Conclusions and Perspectives

The selection of grapevine rootstocks and scion varieties with improved fruit qualities, resistance to herbicides, and tolerance to biotic and abiotic stressors requires different biotechnologies, such as in vitro plant regeneration and multiplication, mutagenesis, the induction of somaclonal variability and selection of new valuable genotypes, and genetic transformation and genome editing. The strategies based on genome editing have the advantage of speeding up crop improvement and reducing the cost of the process, but the implementation of these technologies needs government support. Usually, the edited plants are not considered transgenic even though the delivery of the CRISPR-Cas9 system is mediated by *Agrobacterium*. Thus, edited plants could be easily accepted on the market. Improving grapevine tolerance to diseases and pests is the most promising contribution of new breeding technologies because little is known about genes encoding disease resistance and their functions, and the QTLs are not identified. The development of a multiresistant genotype is complicated, and *V. vinifera* is susceptible to different fungi. Thus, new breeding technology could be considered a significant alternative to the classical selection and breeding of grapevine varieties resistant to biotic and abiotic stress.

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