Unravelling the Genetic Enigma: Exploring the Molecular Basis of Heterosis

ABSTRACT

Heterosis, the phenomenon where hybrid offspring exhibit superior traits compared to their inbred parents, has captivated scientists for decades due to its immense potential for crop improvement. Unravelling the molecular basis of heterosis has remained a challenge, but recent advancements in genomic and molecular techniques have shed new light on this intriguing phenomenon. This review paper provides a comprehensive overview of the current understanding of the molecular mechanisms underlying heterosis. We delve into the intricate interplay of genetic factors and regulatory networks that contribute to the manifestation of heterosis. Genomic studies have revealed structural variations, such as rearrangements and copy number variations, which may play a crucial role in hybrid vigour. Furthermore, we explore the dynamic nature of gene expression patterns during hybridization, highlighting the activation of novel gene networks and the modulation of epigenetic mechanisms. Transcriptomic analyses have identified key genes and pathways associated with heterosis, shedding light on the intricate molecular interactions that drive the superior performance of hybrids. Additionally, we discuss the emerging role of small RNAs, transcription factors, and regulatory elements in orchestrating heterosis. These molecular players act as conductors in the genetic symphony of hybrid vigour, fine-tuning gene expression and facilitating the coordinated functioning of diverse biological processes. Understanding the molecular basis of heterosis holds immense promise for crop improvement and sustainable agriculture. By leveraging this knowledge, breeders can harness the full potential of hybrid breeding to develop high-yielding and resilient crop varieties. This review aims to inspire further research and collaboration in unravelling the mysteries of heterosis, paving the way for innovative strategies to enhance global food security and agricultural productivity.

Keywords: *Crop Improvement, Heterosis, Hybrid Vigour, Hybrid Breeding, Resilient Crop, Transcription.*

1. INTRODUCTION

Heterosis, also known as hybrid vigour, is a phenomenon that has fascinated scientists and breeders for over a century [1]. It refers to the superior performance of hybrid offspring compared to their inbred parental lines in various traits, such as yield, growth rate, disease resistance, and stress tolerance. The exploitation of heterosis has revolutionized agriculture by significantly improving crop productivity and quality. Shull [2] discovered and initially introduced the idea of heterosis by observing its occurrence in hybrid offspring of maize. He later officially coined the term "heterosis" to describe this phenomenon. The concept of heterosis was first implemented in genetic breeding of maize, leading to the production of numerous high-quality maize hybrids starting from the 1930s [3]. Notably, since 2011, the cultivation of hybrids has contributed significantly to an eightfold increase in maize yield in America [4]. Despite the practical importance of heterosis, its underlying genetic and molecular mechanisms have remained elusive. Understanding the molecular basis of heterosis is crucial for unravelling the secrets behind this phenomenon and harnessing its

potential for crop improvement. Koelreuter [5] presented the initial empirical evidence demonstrating that the growth of hybrid tobacco surpasses that of its parental plants.

Over the years, numerous studies have attempted to decipher the intricate genetic and molecular interactions that contribute to heterosis. Recent advancements in genomics, transcriptomic and molecular techniques have provided unprecedented insights into the molecular underpinnings of this phenomenon. F1-hybrid plants exhibit various advantageous characteristics compared to their homozygous parental inbred lines, such as increased biomass, size, yield, development speed, fertility, disease resistance, resistance to insect pests, and tolerance to challenging climates [6]. However, if hybrids are self-pollinated over multiple generations, the level of heterozygosity and vigour gradually decreases, leading to a phenomenon known as inbreeding depression (refer to Glossary). Therefore, heterosis and inbreeding depression are two distinct aspects of the same phenomenon [3]. Charles Darwin first described heterosis in 1876 when he noticed that cross-pollinated maize (*Zea mays*) progeny were 25% taller than inbred maize progeny [8].

At the genomic level, researchers have discovered structural variations, such as chromosomal rearrangements, copy number variations, and transposable element mobilizations, which are associated with heterosis. These alterations can lead to changes in gene dosage, gene expression, and regulatory networks, ultimately influencing the phenotypic traits observed in hybrid offspring.

The concepts of midparent heterosis (MPH) and best parent heterosis (BPH) quantify the extent of phenotypic difference exhibited by a trait in a hybrid (F_1) compared to its parental inbred lines (P_1, P_2) [9]. MPH denotes a trait that demonstrates a hybrid performance significantly superior to the average value (midparent) calculated from the two parental inbred lines ($MPH = F_1 * [(P_1 + P_2)/2]$). On the other hand, BPH indicates a hybrid trait that performs significantly better than the superior does (BP) of the two homozygous parental inbred lines ($BPH = F_1 * BP$) [10]. In addition, studies on gene expression patterns have revealed the presence of unique transcriptomic profiles in hybrid plants compared to their parental lines. Complex regulatory networks, involving transcription factors, small RNAs, epigenetic modifications, and hormone signaling pathways, have been implicated in orchestrating the differential gene expression patterns that contribute to hybrid vigour [11].

The molecular basis of heterosis is a multifaceted puzzle that requires an integrative approach, combining genetics, genomics, epigenetics, and systems biology. By unravelling the genetic and molecular factors underlying heterosis, scientists aim to develop strategies for predicting hybrid performance, optimizing parental combinations, and manipulating key genes and pathways to enhance desired traits. In this review, we aim to provide a comprehensive overview of the current understanding of the molecular basis of heterosis. We will explore the latest research findings, discuss the key genetic and molecular players involved, and highlight the challenges and future directions in this exciting field of study. By gaining a deeper understanding of the molecular mechanisms driving heterosis, we can unlock its full potential for sustainable agriculture and meet the challenges of global food security [12].

Recently, several laboratories have commenced examining various molecular aspects of heterosis utilizing newly available molecular tools. In the past, the analysis of quantitative trait loci (QTLs) served as an initial step in comprehending the molecular underpinnings of heterosis [21]. While these studies demonstrated that heterosis is determined by a limited number of individual genes inherited in a complex manner, none of the QTLs associated with heterotic traits have been successfully cloned thus far. However, with the advent of innovative molecular tools enabling comprehensive phenotyping based on QTL analysis, followed by map-based cloning, there is a potential for identifying the loci responsible for controlling heterotic traits in the foreseeable future [27].

2. STRATEGIES FOR HETEROSIS BREEDING

Conducting extensive hybridization tests to obtain hybrid F_1 lines exhibiting heterosis is not recommended due to the significant resources, time, and unreliable results it entails [13]. Melchinger and Gumber [14] proposed an alternative approach of utilizing heterotic groups as a foundation for crossbreeding. Heterotic groups are populations classified based on their breeding requirements, possessing abundant genetic variation and high combining ability. In a genome-wide association study (GWAS) conducted by Chen *et al.* [15] on yield traits, general combining ability (GCA), and specific combining ability (SCA) in rice, the use of combining ability as a basis for classifying heterotic groups was strongly supported, providing valuable insights for studying combining ability in vegetables (Figure. 1). Other studies have also demonstrated that combining ability, genetic distance, and molecular markers can serve as the foundation for evaluating parental inbred lines and predicting heterosis in F1 hybrids of vegetables [16-17].

General combining ability (GCA) represents the average performance of a specific set of hybrid combinations and is primarily influenced by additive gene effects and additive × additive interactions. On the other hand, specific combining ability (SCA) assesses the average performance of particular hybrid combinations in relation to the parental lines and arises from dominance, epistatic deviations, and genotype × environmental interactions [18]. Parents with a high GCA effect exhibit greater adaptability and are less influenced by environmental factors [19]. It is important to note that superior traits in parents do not always guarantee their inheritance in offspring [20]. Hence, evaluating combining ability provides more reliable information than solely assessing the performance of individual lines. Various types of combining ability tests can be employed to identify superior parental lines for developing heterotic hybrids, such as line × tester analysis, topcross tests, single-cross tests, poly-cross tests, and diallel mating [21]. Singh *et al*. [22] conducted a complete diallel cross test on seven diverse bitter gourd lines and observed that combinations with high × high GCA often produced substantial SCA effects, making them potential candidates for developing superior variants through the pedigree method. Combinations involving high/low × low GCA can also exhibit high but less stable SCA effects, which are suitable for heterosis breeding. This finding aligns with the results reported by Chaudhary *et al*. [23] in okra and Franco *et al*. [24] in common bean, genetic variability in mung bean by Thonta *et al*. [7].

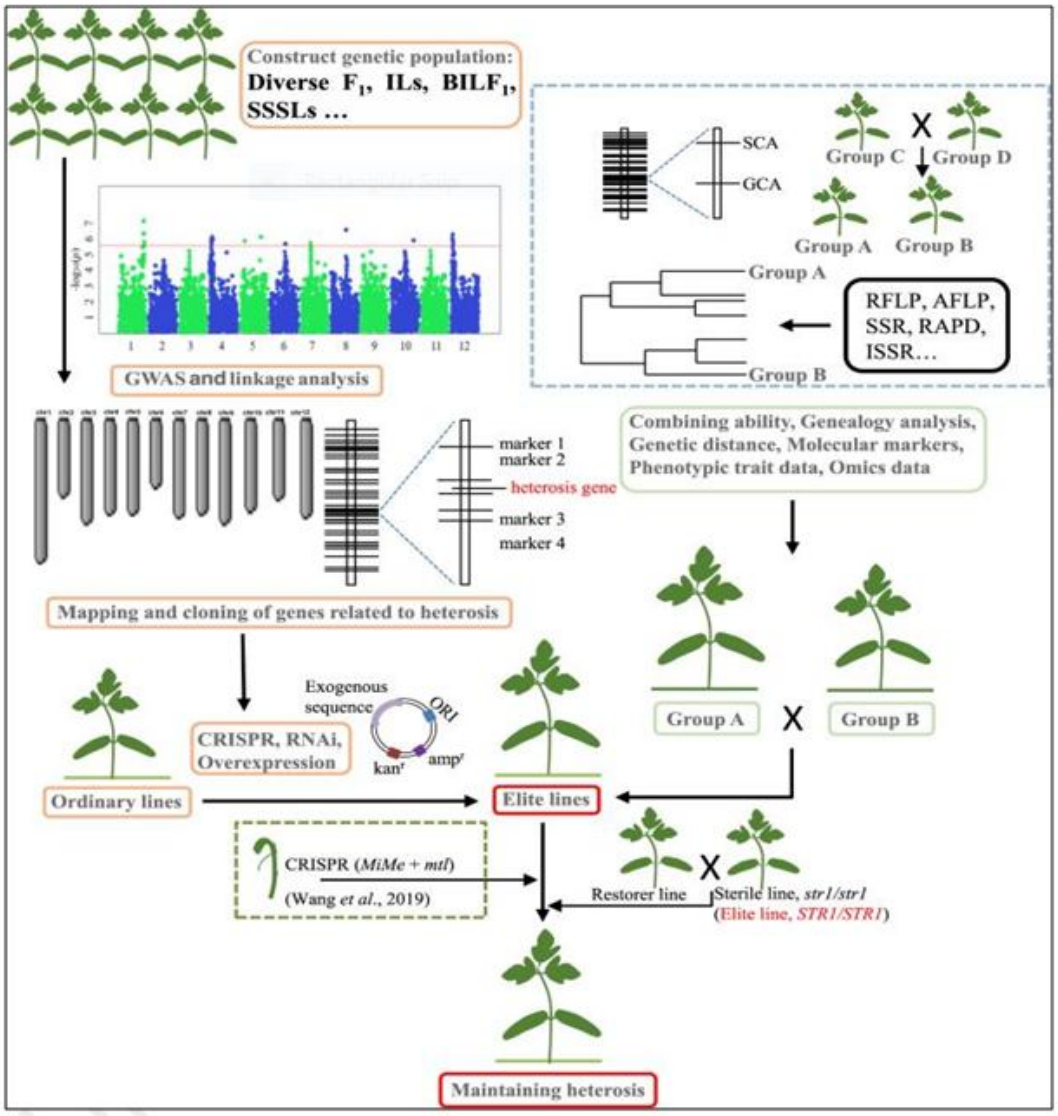

Figure 1. *Factors involved in applying heterosis-breeding strategies: obtaining heterotic lines and maintaining heterosis in the elite lines in the offspring.* ***Source: Yu et al. [26].***

HETEROSIS-ASSOCIATED GENE EXPRESSION IN RICE & MAIZE

In maize, the presence of small gene families contributes to the complexity of understanding the quantitative effects of gene deletions in inbred lines. It is likely that these genes are functionally compensated by duplicate copies located elsewhere in the genome, resulting in only minor effects on plant performance [58]. In recent years, several studies have focused on analyzing gene expression associated with heterosis in maize and rice. These studies have employed different approaches, such as comparing gene expression patterns between inbred lines and hybrids using selected genes or conducting high-throughput gene expression analyses through microarray profiling or Gene Calling [31]. Various stages of plant development have been investigated, including embryos, endosperm, seedlings, shoot

apical meristems, ear tissue, leaves, and rice panicles, using different genetic backgrounds [31,33] (Table 1).

However, it is important to note that these studies exhibited significant variations in their experimental designs, statistical procedures, and tissues and genotypes analyzed. Consequently, no consistent global expression patterns were observed across all the gene expression studies. Some studies highlighted non-additive gene expression as prevalent between inbred lines and hybrids, while others observed predominantly additive gene expression for most genes. Additionally, one study reported an equal number of genes exhibiting additive and non-additive expression [31, 33] **(Table 1).** The discrepancies in these findings may stem from the differences in genotypes, plant materials, experimental designs, and statistical procedures employed in the respective studies.

In summary, the analysis of gene expression associated with heterosis has yielded diverse and sometimes conflicting results. The variations in experimental approaches and genetic backgrounds utilized by different studies contribute to the lack of uniformity in global expression patterns. Future research should aim to address these discrepancies by employing standardized experimental designs and statistical procedures, as well as conducting comparative analyses across multiple genetic backgrounds, to gain a more comprehensive understanding of heterosis-related gene expression.

Table 1. Heterosis-associated gene expression in Rice and maize.

Plant organ	Developmental stage	Approach	Genetic background	Global expression trend	Refs
Rice					
Panicle	Stage III, IV, V	9K cDNA microarrays	Zhenshan97 Minghui63	Additivity	[29]
Maize					
Embryo	6 DAP	12K cDNA microarrays SSH qRT-PCR	UH005 UH301	Additivity	[30]
Endosperm	10, 14, 21 DAP	Gene Calling	7 Pioneer inbred lines	Non-additivity	[31]
Endosperm	18 DAP	RT-PCR	B73 BSSS53	Non-additivity	[32]
Embryo	19 DAP	13.5K microarrays	Mo17	Additivity	[33]
Seedling Immature ear	11 DAG		B73		
Seedling	14 DAG	14K cDNA microarrays qRT-PCR	Mo17 B73	Additivity	[34]
Shoot apical meristem	21–23 DAP	12K cDNA microarrays qRT-PCR	UH002 UH005 UH250 UH301	Non-additivity	[35]
Adult leaves of diploids and triploids		Quantitative Northern	Mo17	Non-additivity	[36]

		blotting			
Immature ear		Gene Calling	B73 17 Pioneer inbred lines	Additivity and Non-additivity	[37]

Abbreviations: *DAP, days after pollination; DAG, days after germination; SSH, suppressive subtractive hybridization.* ***Source: Hochholdinger and Hoecker [28]***

VARIOUS MODELS FOR UNDERSTANDING THE MOLECULAR BASIS OF HETEROSIS

Exploring heterosis at the molecular level involves various approaches, such as genome organization studies, transcriptome-wide gene expression profiling, and investigating allele-specific contributions to gene expression [38]. These molecular investigations ultimately converge on fundamental and widely accepted models of heterosis, which include the combined expression of alleles and diverse interactions between alleles in a hybrid [39]. Despite ongoing research efforts, heterosis remains a captivating and intriguing subject, prompting continuous exploration and the acquisition of additional knowledge. Recent advancements in epigenetics, genomics, proteomics, and metabolomics have played a crucial role in unravelling the mysteries of this phenomenon. In this context, we present a summary and comprehension of the current perspectives that shed light on the existence of hybrid vigour in plant species. Several models have been proposed, represented in (Figure 2) to understand the molecular basis of heterosis. Here are some of the prominent models:-

1. Dominance Model: This classical model suggests that heterosis arises from the dominance of advantageous alleles in hybrids [40]. The superior performance of hybrids is attributed to the masking of deleterious recessive alleles by dominant alleles [41-42].

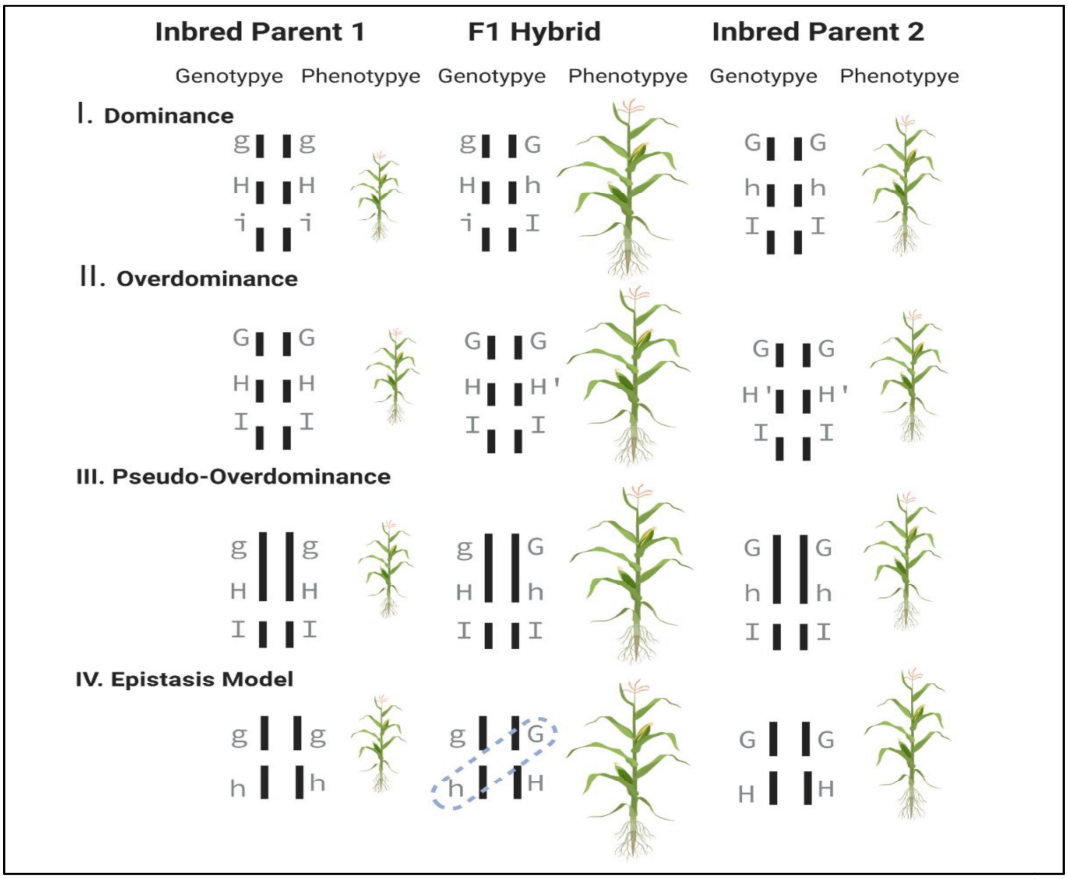

Figure 2. *Genetic models for heterosis for dominance, overdominance, pseudodominance and epistasis model.* ***Source: Rehman et al. [59].***

2. Over dominance/Epistasis Model: This model proposes that heterosis is driven by the interaction between different alleles at multiple loci [43]. The combined effect of these alleles in hybrids leads to a superior phenotype that exceeds the performance of both parents [44-46].

3. Additive Model: According to this model, heterosis results from the accumulation of additive genetic effects across multiple loci. The interaction between additive alleles leads to enhanced performance in hybrids [47].

4. Combinatorial/Network Model: This model emphasizes the importance of gene regulatory networks and interactions between genes. Heterosis is thought to arise from the combinatorial effects of genes and their interactions within these networks [48].

5. Metabolic Model: This model focuses on the metabolic pathways and biochemical processes involved in heterosis. It suggests that the increased metabolic activity and efficiency in hybrids contribute to their superior performance [49].

6. Epigenetic Model: Epigenetic modifications, such as DNA methylation and histone modifications, have been proposed to play a role in heterosis. This model suggests that changes in the epigenetic landscape contribute to the altered gene expression patterns and phenotypic superiority observed in hybrids [50].

It is important to note that these models are not mutually exclusive, and the molecular basis of heterosis is likely a complex interplay of multiple factors. Advances in genomics, transcriptomics, proteomics, and other molecular techniques continue to shed light on the underlying mechanisms of heterosis and may lead to the development of new models and hypotheses.

FUTURE SCOPE OF MOLECULAR HETEROSIS

The future of molecular heterosis holds promising possibilities for advancing our understanding and utilization of hybrid vigour. Here are some potential aspects to consider:

1. Genomic Selection: Genomic selection techniques can facilitate the identification of genomic regions associated with heterotic traits. By analyzing large-scale genomic data, researchers can predict hybrid performance and select parental lines with higher combining ability more efficiently [51].

2. Gene Editing and Manipulation: Advanced gene editing technologies like CRISPR-Cas9 offer the potential to precisely manipulate specific genes and regulatory elements involved in heterosis [52]. This could enable targeted enhancements of heterotic traits and the creation of custom-designed hybrids with desired characteristics.

3. Transcriptomics and Epigenetics: Investigating gene expression patterns and epigenetic modifications during hybridization can provide insights into the molecular mechanisms underlying heterosis. Transcriptomic studies can identify key gene networks and pathways associated with hybrid vigour, while epigenetic analysis can uncover heritable changes in gene expression patterns that contribute to heterosis [53].

4. Multi-Omics Integration: Integrating data from multiple omics levels, such as genomics, transcriptomics, proteomics, and metabolomics, can provide a comprehensive understanding of the molecular basis of heterosis. This holistic approach allows for a more detailed characterization of the complex interactions and regulatory networks involved in hybrid vigour [54].

5. Machine Learning and Artificial Intelligence: The application of machine learning algorithms and artificial intelligence techniques can help analyses vast amounts of molecular data and extract meaningful patterns and predictive models related to heterosis. These methods can assist in identifying genetic factors, biomarkers, and molecular signatures associated with hybrid performance [55].

6. Hybrid Breeding Strategies: Incorporating molecular markers and genomic information into traditional breeding programs can optimize hybrid-breeding strategies. Utilizing marker-assisted selection and genomic prediction can enhance the efficiency and precision of hybrid development, leading to the production of superior hybrids with improved performance [56].

7. Systems Biology Approaches: Adopting systems biology approaches can provide a holistic understanding of the complex interactions among genes, proteins, and metabolites that contribute to heterosis. Integrating data from different biological levels can unravel emergent properties and regulatory networks that drive hybrid vigour [57].

By integrating these future aspects of molecular heterosis, researchers can deepen our understanding of the underlying molecular mechanisms, accelerate the development of improved hybrids, and ultimately enhance agricultural productivity and sustainability.

CONCLUSION

In conclusion, the study of heterosis at the molecular level has provided valuable insights into the mechanisms underlying this complex phenomenon. Various models, including the dominance model, over dominance/epistasis model, additive model, combinatorial/network model, metabolic model, and epigenetic model, have been proposed to explain the molecular basis of heterosis. These models highlight the importance of gene expression, allelic interactions, metabolic processes, and epigenetic modifications in driving hybrid vigour. While classical genetic models based on dominance and additive effects remain popular among plant breeders, it is becoming increasingly evident that the understanding of heterosis requires a broader perspective. The context of genome dynamics, particularly in polyploid species, adds complexity to the interpretation of hybrid vigour. The use of molecular markers, allozymes, and sequencing plant genomes has been suggested as valuable tools for unravelling the genetic basis of hybrid vigour and understanding the impact of self-pollination on this phenomenon. Furthermore, the application of modern molecular techniques, such as genomics, transcriptomics, proteomics, and metabolomics, holds great potential for advancing our knowledge of heterosis. These techniques enable the exploration of genome-wide changes in gene and protein expression, as well as the investigation of epigenomic and metabolic alterations in hybrids. In summary, the study of heterosis has evolved beyond classical genetic models, with increasing emphasis on molecular approaches. The integration of various models and the utilization of advanced molecular techniques have the potential to provide a more comprehensive understanding of heterosis and its underlying molecular mechanisms. This knowledge can contribute to the

development of new breeding strategies and the enhancement of crop productivity by harnessing the power of hybrid vigour.

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