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Review

The applications of network analysis in fruit ripening

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ABSTRACT

Fruit ripening is a complex process that involves the coordination of genes, hormones, and environmental factors. Understanding the mechanism of fruit ripening is important to improve shelf life and storage duration. Our current understanding of the fruit ripening mechanism is limited to model organisms such as tomatoes for climacteric fruits and grapes for non-climacteric fruits. Studies on the fruit ripening mechanism for other non-model fruits such as mangosteen, orange, and papaya are still limited. Recently, high-throughput sequencing and mass spectrometry technologies have generated abundant omics-based data from various fruits. While it is important to perform differential expression analysis to identify molecular changes, network analysis gives an added value by integrating all the omics data to infer the interactions between molecules. This provides a more comprehensive understanding of gene function, regulation, and mechanism to improve fruit shelf life. This review illustrates different types of network analysis and their applications in the identification of hub genes, proposing regulatory network models, metabolic shift detection, and guilt-by-association prediction of unannotated gene functions. The fruit ripening mechanism is also reviewed by integrating results from network analysis to fill in the gaps of knowledge. Lastly, the perspectives of network analysis in fruit ripening are discussed.

1. Introduction

Fruit ripening is a complex process that involves the coordination of gene expression, cell-cell signaling, and various biochemical pathways (Giovannoni et al., 2017). At the molecular level, it is a network of genome, transcriptome, proteome, and metabolome that gives rise to a concerted effect in fruit ripening. Regardless of whether climacteric or non-climacteric fruits, fruit ripening eventually led to changes such as cell wall softening, sugar accumulation, and color changes with the production of aroma and volatiles (Giovannoni, 2004). It also leads to senescence, increased pathogen invasion, and consequently decreased fruit shelf life. Hence, understanding the molecular mechanisms of fruit ripening is key to extending fruit shelf life and improving fruit quality.

With the advent of affordable high-throughput sequencing and analytical chemistry technologies, large amounts of data are generated at an unprecedented scale. These have resulted in the development of omics research (Ko and Brandizzi, 2020). Omics profiling and comparative analyses such as differential expression analysis enable large-scale identification of molecular changes through studies of phenotypic variation, environmental factors, and the effects of various treatments on fruit ripening (Costa-Silva et al., 2017). However, differential expression analysis alone could not resolve the long-standing challenge of deciphering the regulatory mechanism of fruit ripening (Horvath and Langfelder, 2011).

Gene-gene interaction network is defined as the functional interaction between pairs of genes that results in the phenotype observed in an organism. Network analysis could be a powerful bioinformatics tool for deciphering fruit ripening at the molecular level. It shortens the lengthy and tedious screening or identification of different molecular components for resolving their interactions, as well as holistically addresses the biological questions regarding regulatory mechanisms of fruit ripening as a whole (Higashi and Saito, 2013; Jordán et al., 2012; Ko and Brandizzi, 2020).

To date, reviews on plant network analysis are limited, especially for fruit ripening (Aoki et al., 2007; Higashi and Saito, 2013; Ko and Brandizzi, 2020; Usadel et al., 2009; Wong and Matus, 2017; Yixiang et al., 2010). In this review, we aim to provide an overview of the network analysis performed on both climacteric and non-climacteric

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fruits reported since 2016 and discuss the applications of network analysis in elucidating molecular processes of fruit ripening.

2. Types of network analysis

There are different types of biological networks (Fig. 1), which can be distinguished by the molecular elements and the edge properties (directed, undirected, and weighted), such as gene co-expression networks (GCNs), gene regulatory networks (GRNs), protein-protein interaction networks (PPINs), metabolic networks, signaling networks, and integrated networks (Tieri et al., 2018).

2.1. Gene co-expression networks

Gene co-expression networks (GCNs) are undirected graph that consists of interacting genes represented by nodes (genes) and edges (interactions between genes) (Tieri et al., 2018). This approach uses transcriptomic data generated from microarray or RNA-Sequencing (RNA-Seq) (Table 1). GCNs are constructed using gene pairs that exceed a predefined threshold of calculated co-expression measures, such as Pearson's or Spearman's rank correlation coefficients (Lee et al., 2015; Serin et al., 2016). There are several tools available for GCNs, such as CoExpNetViz (Tzfadia et al., 2016), Weighted Gene Co-expression Network Analysis (WGCNA) (Langfelder and Horvath, 2008), LeMoNe (Michoel et al., 2007), Consensus Coexpression Network Analysis (CCNA) (Shahan et al., 2018), and Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNe) (Margolin et al., 2006). WGCNA is the most popular R software used for such analysis (Tables 1 and 3) and the gene interactions are commonly visualized with Cytoscape. In general, WGCNA clusters highly correlated or co-expressed genes together into modules (Langfelder and Horvath, 2008). A gene within the module with the highest connection with other genes in the network is defined as a hub gene (Hollender et al., 2014). CCNA, on the other hand, is computed using Euclidian distance. The frequency of co-clustering between gene pairs in 1,000 runs of WGCNA with randomized parameters and sampling is used to calculate the bootstrap confidence intervals (Shahan et al., 2018). The tutorial of WGCNA can be referred for detailed guidelines (Horvath and Langfelder, 2011).

2.2. Gene regulatory networks

Gene regulatory networks (GRNs) are also known as transcriptional regulatory networks (Tieri et al., 2018). It is usually represented by a directed graph that shows the linkage between regulators and their targets. *Cis*-regulatory element (CRE) is the non-coding DNA region (usually 100–1,000 bp) that regulates the transcription of its targets in the vicinity (Davidson, 2010). Meanwhile, the *trans*-regulatory element regulates the transcription of its targets distantly. The primary gene expression data used to generate GCNs are from both microarray and RNA-seq. There are several methods used to infer GRNs (Hecker et al., 2009; Liu et al., 2019) and the most popular method is based on mutual information (MI), which is a measure of the mutual dependence between the two variables and quantifying one variable given knowledge of another (Tieri et al., 2018).

2.3. Protein-protein interaction networks

Similarly, protein-protein interaction networks (PPINs) also comprise nodes that represent proteins with an edge that connects two interacting proteins (Tieri et al., 2018; Vidal et al., 2011). PPINs refer to physical interactions among proteins and each has undirected edges (Yixiang et al., 2010). Several plant protein databases are available for protein-protein interaction network analysis such as BioGRID (Biological General Repository for Interaction Datasets) (https://thebiogrid.org/) (Oughtred et al., 2021), PlaPPISite (http://zzdlab.com/plappisite/index.php) (Yang et al., 2020), TAIR (The Arabidopsis Information Resource) (https://www.arabidopsis.org/) (Berardini et al., 2015), and Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) (https://string-db.org/) (Szklarczyk et al., 2019). STRING is the most popular database used for PPINs (Table 2). It consists of both known and predicted protein-protein interactions and information on gene co-expression. The data sources are derived from experimental data, computational predictions, as well as known protein-protein interactions from public sources (Szklarczyk et al., 2019). PPINs are useful in determining a novel function and specificity of a protein in addition to pathway prediction (Hawkins and Kihara, 2007; Khan et al., 2019).

2.4. Integration of multi-omics data in networks

Multi-omics approaches in studying fruit ripening favor the integration and incorporation of the various types of omics data through different approaches (Jamil et al., 2020) for network analysis (Table 3). The integrated co-expression analysis combining transcriptome and metabolome helps to predict gene functions associated with the accumulation of specific metabolites. As such, the datasets used for integrated network analysis were generated from different experimental conditions such as fruit development and ripening (Arhondakis et al., 2016; Zhang et al., 2019a; Zhang et al., 2019b), or in combination with other factors such as temperature or exogenous hormone treatments (Luo et al., 2020; Mou et al., 2016; Tang et al., 2020), differences in cultivars or mutants (Bodanapu et al., 2016; Feng et al., 2021; Leng et al., 2021; Wu et al., 2016), and environmental factors (Karagiannis et al., 2020; Sun et al., 2019). Furthermore, integrated networks linked to CRE (Kuang et al., 2021; Loyola et al., 2016; Nicolas et al., 2014; Savoi et al., 2016; Wong et al., 2017Wong et al., 2018) have been used for investigating the regulatory role on target genes.

3. Network conditions and approaches

3.1. Condition-independent versus condition-dependent experimental design

Network analysis can be divided into two categories (Fig. 2), namely condition-independent and condition-dependent (Aoki et al., 2007; Usadel et al., 2009). The condition-independent approach is conducted by using different data sources from multiple tissues and conditions to provide a global overview of gene co-expression patterns (Usadel et al., 2009). Therefore, this approach is more suitable to investigate the interacting genes with the gene of interest without considering tissues and conditions. AppleMDO (Da et al., 2019), Melonet-DB (Yano et al., 2017), and TomExpress (Zouine et al., 2017) are examples of web-based

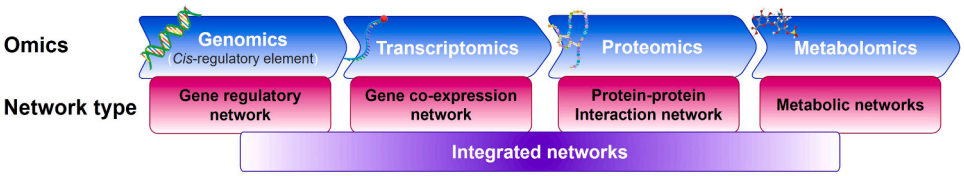

Fig. 1. Different types of network analysis using different omics data.

Table 1
Applications of gene co-expression networks using transcriptome data to study the ripening mechanism of climacteric and non-climacteric fruits.

Fruit	Tool/Method	Target(s)	Main Findings	Refs.
Apple	WGCNA	–	1-Methylcyclopropene (1-MCP) treatment could activate the transcription of genes involved in the anabolic pathway.	Storch et al., 2017
Apricot	Cytoscape	Phenylpropanoid biosynthetic genes	Transcription factor (TF) NAC secondary wall thickening promoting factor 1 (NST1) could regulate the expression of a cinnamyl alcohol dehydrogenase (*CAD*) gene for lignification.	Zhang et al., 2019c
Banana	CoExpNetViz	*ERS2*	Identification of two-component system (TCS) members that directly interact with *MaERS2*.	Dhar et al., 2019
Banana	Cytoscape	*MADS24* and *MADS49*	*MaMADS24* interacts with hormone-responsive TFs, starch biosynthesis, and transportation. *MaMADS49* interacts with enzymes in ethylene biosynthesis and the conversion of starch to sugar.	Liu et al., 2017
Banana	Cytoscape	*OFP1*	Identification of TFs and auxin response proteins that interact with ovate family protein 1 (*MaOFP1*).	Zhang et al., 2020b
Citrus*	WGCNA	Sugar/acid ratio-associated genes	Identification of sugar/acid ratio-related hub genes (*Cs1g24590* and *Cs5g05940*) with unknown function.	Qiao et al., 2017
Durian	Correlation network	Ripening-associated *ERF*s with ripening-related genes	Ethylene response factor (ERF) gene family, *Dz*ERF6 and *Dz*ERF9, are negative and positive regulators of ethylene biosynthesis, respectively.	Khaksar and Sirikantaramas, 2021
Durian	Expression Correlation Network	*CAMTA3* and *CAMTA8*	Identification of co-expressed genes that are positively and negatively correlated with calmodulin-binding transcription activator (CAMTA) gene family, *DzCAMTA3* and *DzCAMTA8*, during fruit ripening.	Iqbal et al., 2021
Grape*	WGCNA	*bHLH075* and *WRKY19*	The hierarchical cascade of gene activation involving basic helix-loop-helix075 (*VvbHLH075*) and *VvWRKY19* at the onset of fruit ripening was proposed.	Fasoli et al., 2018
Grape*	SWItchMiner	–	Identification of switch genes that act as master regulators in white and red-skinned grapes during the transition from herbaceous to maturation phase.	Massonnet et al., 2017
Grape*	WGCNA	–	*GDSL* and xyloglucan endotransglucosylase/hydrolase 30 (*XTH30*) were identified as the hub genes in the modules related to hydrogen peroxide treatment with involvement in the fruit ripening mechanism.	Guo et al., 2020
Kiwi	WGCNA	–	Identification of *GRAS13* as a hub gene related to fruit ripening.	Brian et al., 2021
Kiwi	CCNA	–	TF zinc transporter (*Ad*ZAT5) trans-activated the expression of pectate lyase (*AdPL5*) and *β*-galactosidase (*Adβ-Gal5*) in the pectin degradation pathway.	Zhang et al., 2021b
Lychee*	WGCNA	*MYB, GST4, SGR, ABI5*	Identification of novel candidate genes (*LcbHLH, zinc finger, LcWRKY*) that may be involved in peel coloration.	Ding et al., 2021
Melon*▪	WGCNA	–	Development of an online database (Melonet-DB; https://melonet-db.dna.affrc.go.jp/ap/top) for functional genomics study of muskmelon. Targeted approach network analysis can be done using the 'co-expression viewer' feature in the database.	Yano et al., 2017
Melon*▪	WGCNA	Fruit ripening-related genes	Identification of tomato *AGAMOUS-like* gene homolog, *MELO3C019694.jh1*, in Harukei-3 fruit, which co-expressed with ethylene-related genes.	Yano et al., 2020
Papaya	WGCNA	–	Pulp softening is coordinated by increasing the expression of polygalacturonase (*PG*) and decreasing the expression of pectinesterase (*PME*) and *PL*.	Soares et al., 2021
Pear	WGCNA	Ethylene-related genes	There was direct interaction between the ethylene synthesis gene, S-adomet synthetase (SAMS), ethylene receptor, and laccase during pear fruit development.	Zhang et al., 2016
Pepper*	ARACNe-AP	*ARP9* and *MED25*	*MED25* (*cis*-regulated gene) interacted with TFs (e.g., AG and WRKY) that play an important role in fruit ripening.	Díaz-Valenzuela et al., 2020
Pepper*	WGCNA	–	Identification of several TRs such as F-box protein SKIP23, GATA, U-box domain-containing protein 52, FYVE/PHD-type, RING/FYVE/PHD-type, and CONSTANS-LIKE 9 that may involve in the regulation of capsanthin-capsorubin synthase gene.	Li et al., 2021a
Pepper*	WGCNA	*R2R3-MYB* and *CBGs*	*CaR2R3-MYB* genes play important roles in regulating capsaicin and dihydrocapsaicin biosynthesis.	Wang et al., 2020a
Strawberry*	WGCNA	–	*Fve*ERF might regulate the expression of *AAT* (acyltransferase) and subsequently influence ester accumulation.	Li et al., 2020
Tomato▪	TomExpress co-expression tool	–	Development of tomato RNA-seq online database (TomExpress; http://gbf.toulouse.inra.fr/tomexpress) comprising transcriptome data generated from different organs and development, mutants, biotic interactions, and hormone treatment. The database is useful for expression, clustering, and network analysis.	Zouine et al., 2017
Tomato	WGCNA	–	TF *Sl*GRAS38 might regulate carotenoid and ethylene metabolism.	Shinozaki et al., 2018
Tomato	Correlation network	Auxin- and ethylene-related genes	A fruit ripening inhibition model was established. Exogenous auxin application altered the expression of auxin- and ethylene-related genes via the inhibition of demethylation.	Li et al., 2016
Tomato	Correlation network	*GGPPS* isoforms	Two isoforms of geranylgeranyl diphosphate synthase (GGPPS), *SIG2* and *SIG3* function in GGPP production were highly co-expressed with most of the genes involved in isoprenoid pathways compared with *SIG1*.	Barja et al., 2021

▪ Condition independent.
* non-climacteric fruit.

co-expression network databases constructed by using a condition-independent approach using 'Golden Delicious' apple, 'Harukei-3' melon, and tomato, respectively. Hence, these databases could serve as a valuable reference for predicting the putative functions of homologous genes from other plants.

Condition-dependent studies are more commonly performed in fruit ripening studies by using specific datasets of different cultivars, abiotic stress conditions, or developmental stages. This approach pinpoints the differences between physiological conditions from which gene functions are inferred (Obayashi et al., 2011). For instance, it enables the identification of unique switch genes in white-skinned and red-skinned grapes during the transition from the herbaceous to the maturation phases,

Table 2
Applications of protein-protein interaction networks to study the ripening mechanism of climacteric and non-climacteric fruits.

Fruit	Tool/Method	Target(s)	Main Findings	Refs.
Akebia trifoliata	STRING	–	PL, pectinesterase (PME), β-GAL, and peroxidase (PRX), were identified as the hub proteins that might participate in fruit softening.	Niu et al., 2021
Banana	STRING	–	PPIN Construction of 1,988 upregulated genes or proteins in the banana peel during ripening. The key proteins identified are acetyl-coenzyme A carboxylase, receptor protein kinase, inactive leucine-rich repeat receptor-like protein kinase, glutamate dehydrogenase, ATP-citrate synthase, glycine dehydrogenase, and glucose-6-phosphate isomerase.	Yun et al., 2019
Grape*■	NetworkAnalyst	–	Identification of key proteins related to fruit development such as RAN1, cytochrome P450 51, the family of CBL interacting protein kinases, ubiquitin-related reactions, and heat shock protein 70 (HSP70).	Benny et al., 2019
Grape*■	STRING	BBX18 and BBX19	B-BOX (BBX) gene family, *Vv*BBX18 and *Vv*BBX19, play roles in anthocyanin accumulation through the *Vv*HY5-mediated signal transduction network.	Wei et al., 2020
Jujube*■	STRING	bHLHs	*Zj*bHLH15 affects anthocyanin synthesis.	Li et al., 2019b
Kiwi	STRING	–	Energy-related proteins formed the main cluster amongst the ethylene and/or chilling-responsive proteins and interacted with proteins related to disease/defense, protein destination/storage, protein synthesis, and metabolism.	Minas et al., 2016
Kiwi	STRING	–	Ripening inhibitors affected proteins related to energy, protein destination/storage, and disease/defense without ethylene treatment; while perturbed proteins related to disease/defense, energy, transporters, protein destination/storage, signal transduction, and secondary metabolism with ethylene treatment.	Minas et al., 2018
Kiwi	STRING	–	Exogenous ethylene treatment affected proteins related to allergens/fruit ripening, defense response, and protein biosynthesis.	Shin et al., 2020
Kiwi	STRING	–	Ethylene mainly regulates sugar catabolism and chlorophyll degradation during fruit ripening.	Salazar et al., 2021
Mango■	STRING	Rab proteins and cell wall softening proteins	Rab GTPases influence fruit softening through interactions with cell wall softening-related proteins and vesicle trafficking proteins.	Lawson et al., 2020
Melon*	STRING	Sugar metabolism proteins	Auxin response factor (AUXRF) gene family, *Cm*AUXRF1, *Cm*AUXRF2, and *Cm*AUXRS interact with sucrose synthase 1 (*Cm*SUS1), trehalose-6-phosphate synthase 7 (*Cm*TPS7), and *Cm*TPS5 through hexosyltransferase and argonaute proteins in the sugar pathway.	Schemberger et al., 2020
Strawberry*	STRING	bHLH	*Fv*bHLH25, *Fv*bHLH29, *Fv*bHLH80, and *Fv*bHLH98 interact with each other and participate in strawberry anthocyanin biosynthesis during ripening.	Zhao et al., 2018
Tomato■	STRING	BAG	B-cell lymphoma2 (Bcl-2)-associated athanogene (BAG) interacts with HSP70 in fruit ripening.	Irfan et al., 2021
Wax apple	STRING	–	The differentially expressed proteins were involved in amino acid synthesis, glycolysis, carbon metabolism, and carbon fixation.	Al-Obaidi et al., 2018

■ Condition independent.
* non-climacteric fruit.

through comparative transcriptomics and integrated network analysis (Massonnet et al., 2017; Palumbo et al., 2014). This helps to identify the genes that are responsible for the differential accumulations of anthocyanin in these varieties.

3.2. Non-targeted versus targeted approaches

Meanwhile, network analysis can be divided into non-targeted or targeted approaches regardless of conditions (Fig. 2) but depends on the measurement methods or data used for analysis (Aoki et al., 2007). The non-targeted or global approach uses all molecules in the omics data for network analysis. For instance, WGCNA can be used to correlate transcriptome data with the content of organic acids and soluble sugars (malic acid, citric acid, quinic acid, fructose, glucose, sucrose, and abscisic acid) in citrus (Wu et al., 2016). This approach was applied to determine modules that were highly correlated with total soluble sugar and anthocyanin content in grape (Leng et al., 2021). Whereas, the targeted approach depends on the selected "guide gene" based on experimental knowledge and literature review (Lisso et al., 2005). The guide gene approach is useful for studying the cross-talk between ethylene and ABA in regulating climacteric tomato fruit ripening (Mou et al., 2016) and screening co-expressed genes that are directly related to the gene of interest (Dhar et al., 2019; Liu et al., 2017; Zhang et al., 2020b; Zhang et al., 2016). Additionally, databases such as AppleMDO, Melonet-DB, and TomExpress (Da et al., 2019; Yano et al., 2017; Zouine et al., 2017), are useful for searching co-expressed genes of a targeted gene by submitting the locus/gene ID (guide gene) in the "Co-expression" and "Coexpression viewer"' tools.

4. Applications of network analysis in fruit ripening

In general, there are five applications of network analysis in fruit ripening, namely (1) identification of the hub gene that controls certain molecular mechanisms; (2) construction of regulatory network models; (3) detection of metabolic shift; (4) finding a new role of known or unknown genes; and (5) predicting the gene function via guilt-by-association, which are discussed in the following section.

4.1. Identification of hub genes

A hub gene is defined as a "highly connected gene" with other genes in the same module or a gene with high module membership (kME) (Horvath and Langfelder, 2011). For example, a single TF may act upstream of ethylene biosynthesis and hence regulates multiple fruit ripening traits, or it acts downstream of ethylene biosynthesis and regulates specific fruit ripening traits. On the other hand, a key gene could be a structural gene that is regulated by the TF or TR. Both play an important role in a specific metabolic pathway as their expressions are highly correlated with fruit characteristics. The identification of hub and key genes is well-reported. For instance, hub genes related to fruit ripening (Brian et al., 2021), lignin content (Feng et al., 2021; Zhang et al., 2019c), ester content (Li et al., 2020), capsanthin-capsorubin synthase (CCS) gene expression (Li et al., 2021a), °Brix level, and cultivars in red versus white grape berries (Ghan et al., 2017) have been identified.

Nonetheless, some of the reported hub genes related to certain fruit ripening pathways/traits are not functionally validated by downstream experiments. Predicted hub genes and structural genes should be verified for assured understanding of fruit ripening metabolic pathways. Functional analysis such as the generation of mutants is exemplified by

Table 3
Application of integrated networks to study the ripening mechanism of climacteric and non-climacteric fruits.

Fruit	Tool/Method	Target(s)	Elements	Main Findings	Refs.
Apple■	Global co-expression network	–	E, G, T	Development of a multi-omics online database (AppleMDO; http://bioinformatics.cau.edu.cn/AppleMDO/) with functional gene annotation, co-expression network (global and conditional networks), protein-protein interaction, gene ontology (GO) enrichment analysis tool, and chromatin states.	Da et al., 2019
Apple	STITCH	–	M, P	Protein-metabolite network associated with low- and high-altitudes in peel ripening.	Karagiannis et al., 2020
Apricot	WGCNA	–	M, T	Identification of TF *Pa*MYB10 as the hub gene that works with seven structural genes to regulate anthocyanin biosynthesis.	Xi et al., 2019
Apricot	WGCNA	–	M, T	TFs related to light signaling (phytochrome interacting factor: PIF3/4 and long hypocotyl 5: HY5), phytohormones (ERF4/5/12, AP2, AP2-like, and BZR1), and development factors (MADS14, NAC2/25, MYB1R1/44, Golden 2-Like: GLK1/2, and WRKY6/31/69) might be involved in the regulation of carotenoid metabolism.	Zhang et al., 2019a
Apricot	WGCNA	–	M, T	Flavor production particularly sucrose, malate, lactones, and apocarotenoids is controlled by the combination of a regulatory network consisting of ethylene and ABA signaling, ripening factors, and stress transduction.	Zhang et al., 2019b
Banana	WGCNA	–	CRE, T	*Ma*ZFP46/48, *Ma*TALE1/2, and *Ma*G2–1/2 in fruit ripening.	Kuang et al., 2021
Blueberry	Regularized canonical correlation analysis	Phenolic pathway genes	M, T	MYBA, MYBPA1, bHLH2, and MYBC2 TFs regulate anthocyanin biosynthesis.	Günther et al., 2020
Citrus*	Correlation network	–	M, T	*TAT1* and *VTE4* affect tocopherol content.	Rey et al., 2021
Citrus*	WGCNA	–	M, T	TFs RD26, WRKY42, and MYB21/77 influence glucose and fructose content.	Wu et al., 2016
Citrus*	WGCNA	–	M, T	Identification of hub gene, *Cs*ERF74, related to lignification.	Feng et al., 2021
Grape*	WGCNA	–	M, T	Light-responsive TFs (bHLH, MYB, WRKY, NAC, and MADS-box) affect the content of phenolic content.	Sun et al., 2019
Grape*	WGCNA	–	M, T	Identification of novel CREs (AuxRE/ETT) in the promoters of gene modules responsive to water deficit.	Savoi et al., 2017
Grape*	WGCNA	–	M, T	GATA26 regulates norisoprenoid accumulation by up-regulating *VvCCD4a, VvPSY2, VvPSY3*, and two *VvZEP*s, while down-regulating *VvPSY1* and *VvZDS*.	He et al., 2021
Grape*	WGCNA	–	M, T	Two hub genes, 4-coumarate-CoA ligase (*4CL*) and copper amine oxidase (*CuAO*), regulate the total soluble solid and total anthocyanin content in cultivar 'Nantaihutezao'.	Leng et al., 2021
Grape*	WGCNA	–	M, T	Identification of hub and key genes related to anthocyanins and soluble sugars and proposed a fruit quality model under red and blue light treatments.	Zhang et al., 2021a
Grape*	Mutual Rank (MR)-based coexpression analysis	–	CRE, T	Identification of CRE-driven modules in stress- and development-specific GCNs.	Wong et al., 2017
Grape*■	MR gene co-expression network (GCN)	Major intrinsic protein (MIP)	CRE, T	Promoter analysis of the major intrinsic protein (MPI) and their co-expressed genes showed the enrichment of different types of CRE such as AP2/ERFs and NACs.	Wong et al., 2018
Grape*	MR and PCC as co-expression similarity indices	*HY5* and *HYH*	CRE, T	Construction of a HY5 and HYH co-expression network by integrating data sets from gene expression atlas (microarray) and stress-related data (RNA-seq and VTCdb) with the identification of CREs in the co-expressed genes.	Loyola et al., 2016
Grape*	Global metabolite-transcript network	Linalool, nerol, and α-terpineol	M, T	Construction of a monoterpene gene-metabolite network and identification of drought-responsive and MYB recognition sites through promoter enrichment analysis.	Savoi et al., 2016
Kiwi	WGCNA	–	M, T	TFs *Ad*NAC5 and *Ad*Dof4 activate and suppress the expression of *AdFAD1*, respectively.	Zhang et al., 2020a
Kiwi	Correlation analysis	β-carotene, chlorophyll b, and chlorophyll a	M, T	Three ethylene response factors (ERFs), *Acc*29730, *Acc*25620, and *Acc*23763, regulate the expression of carotenoid and chlorophyll-related genes (*AcPAO2, AcLCY-β*, and *AcCCD1*).	Liu et al., 2021
Mango	WGCNA	–	M, T	TFs *Mi*bZIP66 and *Mi*bHLH45 activate the key gene (*MiPSY1*) that regulates β-carotene biosynthesis	Ma et al., 2021
Peach	Cytoscape	–	M, T	Identification of key anthocyanin compounds and transcripts contributing to the different fresh colors in different cultivars.	Ying et al., 2019
Peach	WGCNA	–	M, P, T	Construction of a comprehensive ethylene biosynthesis model by filling in the role of auxin in the fruit ripening pathway.	Zeng et al., 2020
Plum	WGCNA	–	M, T	UDP-galactose metabolism in climacteric plum (Santa Rosa) and non-climacteric plum (Sweet Miriam) produces galactose and raffinose, respectively.	Farcuh et al., 2017
Tomato	Linear correlation network analysis	–	M, T	Organic acids (citric acid, malic acid, butanedioic acid, cis-aconitic acid) were highly correlated with plants hormones (ethylene and ABA), TFs (MYB, AP2/ERF, WRKY, NAC), and genes (*IDH3, PDHA, MDH, PEPC3, PEPCK1*) involved in primary metabolic pathways.	Tang et al., 2020
Tomato	LeMoNe		CRE, T	Six calcium related-genes [calcium-binding EF (*CBEF*), calmodulin-like protein 1 (*CLP1*), calmodulin-like protein (*CLP*), CBL-interacting protein kinase 18 (*CBLPK18*), calcium-dependent protein kinase 3 (*CDPK3*), and calmodulin-binding heat-shock protein (*CBHSP*)] have the W-box CRE that is recognized by WRKY22 TF.	Arhondakis et al., 2016
Tomato	Correlation network	ABA and ethylene	M, T	ABA network involves fruit ripening TFs, such as NAC—NOR, TDR4, AP2A, HB-1, RIN, TAGL1, CNR, and ethylene-biosynthesis-related genes.	Diretto et al., 2020
Tomato	Correlation network	ABA and ethylene	M, T	ABA acted upstream of ethylene biosynthesis and signaling, while ethylene is the hub in the tomato fruit ripening network.	Mou et al., 2016

(*continued on next page*)

Table 3 (*continued*)

Fruit	Tool/Method	Target(s)	Elements	Main Findings	Refs.
Tomato	WGCNA	–	M, T	TFs zinc finger proteins, FAR1, and B3 were associated with the ascorbic acid content while TFs bHLH, NAC, and MADS-box, were associated with phenylpropanoid accumulation.	Sacco et al., 2019
Tomato -mutant	Correlation network	–	H, M	ABA was not detected in the *shr* mutant metabolite and hormone networks.	Bodanapu et al., 2016
Strawberry*	WGCNA	–	M, T	ABA and sucrose treatments inhibit glycolysis but accelerate fruit ripening.	Luo et al., 2020

CRE: *Cis*-regulatory element; E: epigenomic; G; genomics; H: hormones; M: metabolomics; P: proteomics; T: transcriptomics.
▪ Condition independent.
* non-climacteric fruit.

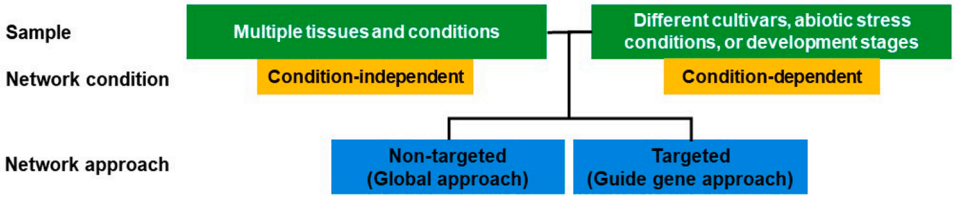

Fig. 2. Different types of network conditions and approaches in network analysis.

RNAi-silenced *SlGRAS38* tomato fruits that showed a lower content of ethylene and lycopene (Shinozaki et al., 2018). Dual luciferase and yeast one-hybrid assays verified that β-carotene biosynthesis in mango was regulated by *Mi*bZIP66 and *Mi*bHLH45 TFs (Ma et al., 2021) while dual-luciferase system and electrophoretic mobility shift assays validated that TF *Ad*ZAT5 trans-activated the expression of *AdPL5* and *Adb-Gal5* during pectin degradation (Zhang et al., 2021b) in kiwi. Transient gene overexpression (for instance, *PaMYB10*) in the non-blushed skin cultivar 'Luntaixiaobaixing' resulted in blushed skin observed during the maturation stage (Xi et al., 2019). Furthermore, bagging significantly decreased the gene expression of *PaMYB10* and subsequently reduced anthocyanin accumulation in apricot "Jianali' (Xi et al., 2019). RT-qPCR experiments ascertain the relative gene expression level of differentially expressed genes (Sacco et al., 2019; Sun et al., 2019).

While expression studies help to identify differentially expressed genes in different fruit developmental stages and cultivars, network analysis narrows down the screening of thousands of genes by identifying key genes that play a central role in the metabolic pathway associated with specific traits. Although the general regulators and structural genes that are involved in the specific mechanism of the fruit ripening pathways are known, the orthologs of these genes in other species remain to be determined. Hence, network analysis can be applied to discover genes from the same families associated with specific metabolic pathways. These genes could then serve as useful molecular markers for selecting fruits with better quality and prolonged shelf life through crop breeding or genetic improvement.

4.2. Construction of regulatory network models

Although the general fruit ripening metabolic pathway is well established and conserved across species, our knowledge of the fruit ripening mechanism is still incomplete. Each species has its specialized metabolisms that are affected by different factors. Hence, hub genes and structural genes identified through network analysis could help elucidate the regulatory network.

Network analysis was applied to identify factors that influenced carotenoid metabolism and flavor compounds in the apricot cultivar 'Luntaixiaobaixing' (Zhang et al., 2019a) and 'Jianali' (Zhang et al., 2019b), respectively. Likewise, fruit quality trait and fruit ripening model were proposed as a consequence of red/blue light treatment (Zhang et al., 2021a), hydrogen peroxide treatment (Guo et al., 2020), auxin treatment (Li et al., 2016), and low versus high altitudes (Karagiannis et al., 2020). Furthermore, a comprehensive peach ethylene biosynthesis network involving auxin in the fruit ripening pathway (Zeng et al., 2020) was constructed. In peach, the anthocyanin regulatory network of cultivars with different flesh colors (milk-white, yellow, and blood) comprises several key anthocyanin compounds and transcripts (Ying et al., 2019). The hierarchical cascade of gene activation during grape fruit ripening was proposed in which TF bHLH075 activates *WRKY19* and cell wall softening genes, followed by the activation of other ripening-related genes (Fasoli et al., 2018).

Hence, the proposed network based on network analysis helps to give a better understanding of all factors that affect the metabolic mechanisms and the hierarchical transcription of genes during fruit ripening. In addition, it also explains the phenotypic differences observed due to different treatments and cultivars as well as provides a framework for future functional studies.

4.3. Detection of metabolic shift

With the development of targeted and non-targeted metabolomics approaches, network analysis is useful to detect the metabolic shift. For instance, the Japanese plum cultivar Sweet Miriam (SM) exhibited a non-climacteric ripening pattern due to the sugar metabolic shift in the UDP-galactose metabolism with higher contents of sorbitol, galactinol, and raffinose (Farcuh et al., 2017). Additionally, sucrose and ABA treatment led to the inhibition of glycolysis and accelerated strawberry ripening (Luo et al., 2020). In contrast, 1-MCP treatment led to anabolic pathway activation and delayed apple fruit ripening (Storch et al., 2017). Nitric oxide (NO) overproduction in the tomato *shr* mutant resulted in fruit growth and ripening suppression as there were changes in metabolites, especially those involved in the tricarboxylic acid (TCA) cycle, as compared to the wild-type (Bodanapu et al., 2016). Thus, understanding the metabolic shift during fruit ripening or due to certain treatments, such as 1-MCP treatment or NO production helps improve the fruit shelf life.

4.4. Finding a new role of known or unknown genes

There are many genes with multiple roles in biological processes or molecular functions. Some of them are yet to be explored and determined. By studying the co-expressed genes/molecules in a network, the role of known and unknown genes can be uncovered.

Network analysis revealed that CCCH-type zinc finger TFs are potential regulators of ascorbic acid and phenolic accumulation in tomato

(Sacco et al., 2019) and participated in peel coloration in lychee (Ding et al., 2021). Three TFs, *Ma*ZFP46/48, *Ma*TALE1/2, and *Ma*G2–1/2, were reported for the first time involved in fruit ripening (Kuang et al., 2021). Similarly, both *Ad*NAC5 and *Ad*Dof4 were suggested to be involved in fruit aroma and volatile metabolism (Zhang et al., 2020a). In addition, homeobox genes (*MELO3C022921* and *MELO3C018088*) were identified as highly associated with the volatile-related genes, *CmAAT1* and *CmAAT2* (Yano et al., 2017). Network analysis also identified two hub genes (*Cs1g24590* and *Cs5g05940*) of unknown functions without *Arabidopsis* homolog that might determine the sugar/acid ratio in four citrus varieties, namely Succari (acidless), Bingtang (low acid), and Newhall with Xinhui (normal acid) (Qiao et al., 2017).

Such findings refine our current knowledge of the TFs and structural genes involved in specific metabolic pathways of different species. However, functional characterization is required to ascertain the roles of species-specific genes in the fruit-ripening pathway.

4.5. Predicting the gene function via guilt-by-association

Network analysis is also useful for predicting the function of uncharacterized genes based on the gene ontology (GO) enrichment analysis on the same group of co-expressed genes with known functions (Da et al., 2019) or through a protein-protein interaction database (e.g., STRING). For instance, *Fv*bHLH25, *Fv*bHLH29, *Fv*bHLH80, *Fv*bHLH98, *Vv*BBX18, and *Vv*BBX19 are predicted to participate in anthocyanin biosynthesis pathway (Bai et al., 2014; Chang et al., 2008; Wei et al., 2020; Zhao et al., 2018), while Rab GTPases are involved in fruit softening (Lawson et al., 2020) due to their interactions with proteins involved in anthocyanin biosynthesis/accumulation and cell wall softening-related proteins, respectively.

Most of the fruit ripening studies focused on the molecular regulation of ethylene or ABA synthesis. The post-translational studies of the fruit-ripening proteins are still scarce. The recent increase in proteomics data helps deepen our understanding of biological processes during fruit ripening. In kiwi, studies were performed on protein network clusters from exogenous ethylene treatment (Shin et al., 2020), ethylene and/or chilling treatments (Minas et al., 2016), and ripening inhibitor treatment with or without exogenous ethylene exposure (Minas et al., 2018). Further analysis of the protein clusters identified several proteins that play important role in fruit ripening, such as kiwellin, actinidain, metallothionine, ethylene-related regulated enzymes (Shin et al., 2020), and enolase (Minas et al., 2016; Minas et al., 2018). Enolase (also known as phosphopyruvate hydratase) was also identified as the key protein in wax apple fruit ripening (Al-Obaidi et al., 2018). Enolase converts phosphoglycerate to phosphoenolpyruvate during glycolysis and is known to play an important role in tomato fruit ripening (Srivastava et al., 2010) and grape (Giribaldi and Giuffrida, 2010). Therefore, PPIN broadens our understanding of fruit ripening pathways involved in fruit ripening by implicating the roles of interacting proteins.

5. Fruit ripening mechanism

The findings from the network analysis help to complete the picture of fruit ripening mechanism as depicted in Fig. 3.

For climacteric fruits, ethylene (C_2H_4) is the main phytohormone that regulates fruit ripening. During climacteric fruit ripening, there is an elevated level of ethylene detected. However, this pattern is not observed in non-climacteric fruit during the ripening stage and ethylene

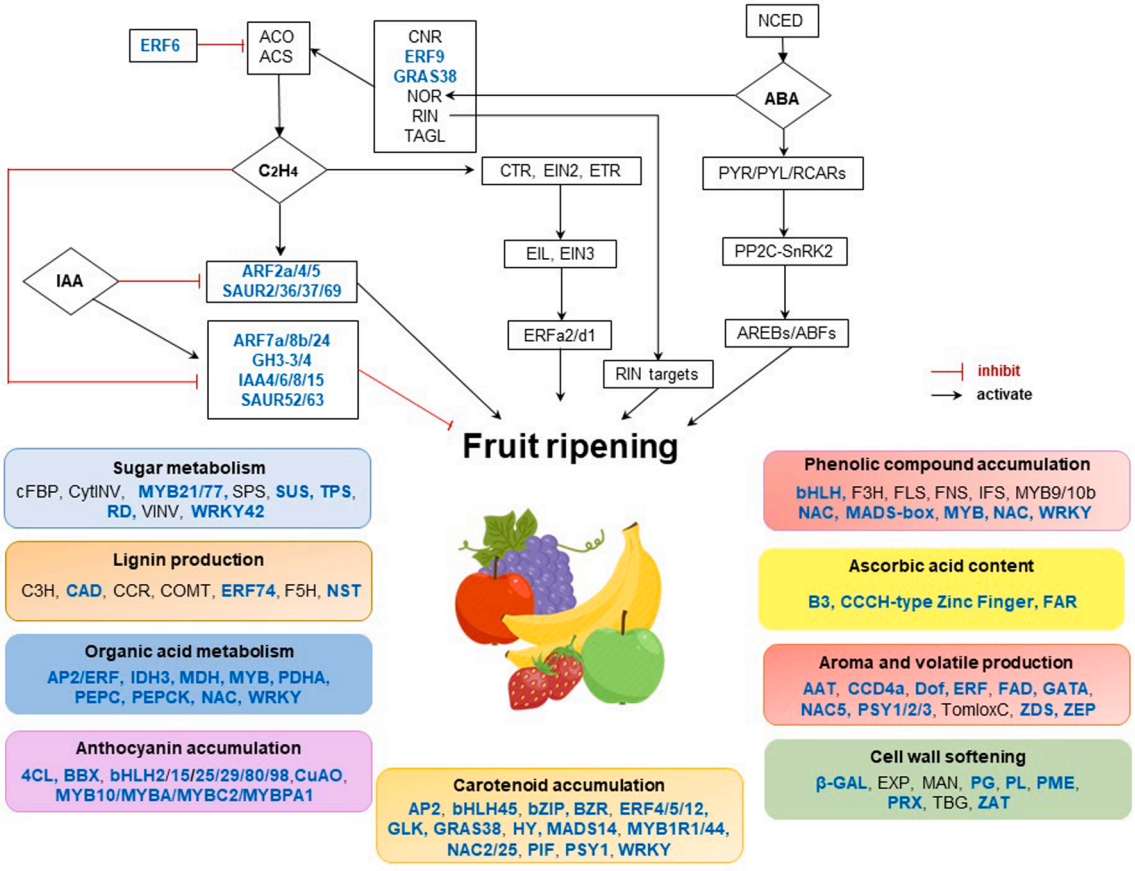

Fig. 3. A schematic illustration of fruit ripening mechanism showing the coordination between phytohormones and transcription factors (TFs). Blue fonts indicate the TFs and structural genes discovered in network analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

is present only at a basal level. Numerous studies showed that the inhibition of ethylene perception by 1-MCP, an ethylene antagonist, led to a delay in fruit ripening in tomato, mangosteen, kiwi, peach, and banana (Piriyavinit et al., 2011). The ripening regulators for ethylene biosynthesis genes (*ACO* and *ACS*) include TF Colorless Non-Ripening (CNR), Ethylene Response Factor 9 (ERF9), Gibberellic-Acid Insensitive (GAI), Repressor of GAI (RGA) and Scarecrow (SCR) 38 (GRAS38), Non-Ripening (NOR), Ripening Inhibitor (RIN), and TOMATO AGAMOUS-LIKE (TAGL), while ERF6 is the ripening inhibitor. NOR is regulated by ABA as it contains the ABA-responsive element (Zhang et al., 2009b). As auxin is also involved in fruit ripening, the ethylene-auxin (IAA) crosstalk model in regulating fruit ripening was proposed based on the correlation network analysis (Li et al., 2016).

On the other hand, abscisic acid (ABA) is the main phytohormone that regulates non-climacteric fruit ripening. As 9-cis-epoxycarotenoid dioxygenase (NCED) is the key enzyme involved in the biosynthesis of ABA, high levels of NCED and ABA were detected during non-climacteric fruit ripening such as Chinese jujube, strawberry, and grape (Medina-Puche et al., 2016; Zhang et al., 2009a, ; Zhang et al., 2019d). Exogenous ABA treatment on strawberries and grapes was reported to enhance the softening process with increased anthocyanin content (Fuentes et al., 2019). Conversely, exogenous treatment of nordihydroguaiaretic acid (NDGA), which is an inhibitor of ABA synthesis, resulted in decreased ABA content and the absence of red pigment at the strawberry receptacle (Li et al., 2019a).

During the ripening of both climacteric and non-climacteric fruits, there are significant changes in metabolism and physiological traits. The common processes that occur in climacteric and non-climacteric fruits during ripening include cell wall softening, color changes (anthocyanin and carotenoid accumulation), and the productions of lignin, phenolic compounds, aroma, and volatiles, which involve diverse sets of genes (Fig. 3).

6. Conclusion and perspectives

Omics-based network analysis has been adapted to study fruit ripening in the recent decade. Network analysis focuses on the molecular components in fruit ripening-related traits to identify hub and structural genes, functional prediction of unannotated genes, and determining the role of TFs in specific metabolic pathways. Reverse genetic approaches such as RT-qPCR, enzyme activity assays, and functional gene analysis are still needed to verify the predicted gene functions and help to explain the different phenotypes. Nonetheless, network analysis is useful to provide an in-depth and holistic understanding of the molecular mechanisms in fruit ripening. To date, the number of network analysis in fruit ripening remains limited for tropical fruit species. Therefore, it is imperative to encourage more studies using omics approaches integrated with network analysis for a more complete picture of the molecular and metabolic processes in fruit ripening.

Although network analysis is very useful for large-scale data interpretation, there are several limitations and drawbacks. For instance, since GCNs are limited to undirected networks, there might be bias as a result of technical artifacts, assumption of normalized data, and inconsistent results from different co-expression module detection methods (Langfelder et al., 2011; Ovens et al., 2021). In jujube, an ortholog of *Arabidopsis* EGL3 protein, *Zj*bHLH15, did not participate in anthocyanin synthesis as predicted by the PPINs (Li et al., 2019b). Hence, it is important to perform validation experiments for functional characterization, such as mutant analysis, dual luciferase assay or yeast two-hybrid (Y2H) to verify such PPI predictions.

Furthermore, the current findings from network analysis are only limited to regulators that regulate certain metabolic pathways, which act downstream of the well-known master regulators such as RIN, NOR, and CNR. Are there other master regulators besides RIN, NOR, and CNR? This is an open question that may be answered by searching for new hub genes that are well connected to fruit ripening-related genes in network analysis. Transcriptome-wide analysis of hub gene mutants allows screening of the affected genes for verification.

Recently, there are increasing studies that showed the involvement of reactive oxygen and nitrogen species (ROS/RNS) in fruit ripening and fruit quality through post-translational modifications (Corpas et al., 2018; González-Gordo et al., 2019; González-Gordo et al., 2022b; Huan et al., 2016; Zuccarelli et al., 2021). In addition, there is crosstalk between organelles and nucleus through retrograde or anterograde signaling to regulate gene expression (Jan et al., 2022; Koussevitzky et al., 2007; Wang et al., 2020b; Woodson and Chory, 2008). Studies had shown that there are proteome changes in plastids (Barsan et al., 2012; Rödiger et al., 2021), mitochondria (Cai et al., 2018; González-Gordo et al., 2022c; Li et al., 2021b), and peroxisomes (González-Gordo et al., 2022a) during climacteric and non-climacteric fruit ripening. Hence, future network analysis should include both ROS/RNS with a subcellular context of organellar molecules to give a more comprehensive understanding of fruit ripening mechanism.

In the era of artificial intelligence (AI), machine learning (ML) has not only been applied to network analysis to improve precision but also to predict fruit quality and classify fruit ripeness. Instead of exploring the molecules involved in fruit ripening, automation technology evaluates parameters such as duration (time), temperature, relative humidity, color, size, hardness, soluble solids content, and acidity for the development of network analysis based on several classifiers like artificial neural networks, decision trees, support vector machines, and k-nearest neighbors (De-la-Torre et al., 2019). This helps farmers to identify fruit quality and estimate ripeness to avoid fruit spoilage. In the future, both AI and molecular-based network analysis could be combined for an automated phenomics analysis to obtain better quality fruits with a longer storage time.

Author contribution statement

C.C.W. wrote the manuscript. H.H.G. edited the manuscript. V.K.S. and M.A. reviewed the manuscript. All authors read and approved the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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