



REVIEW ARTICLE

A review on metabolomics for quality improvement of fruit crops

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Abstract

The field of metabolomics is gaining ground in plant biology, and its potential uses in agricultural biotechnology are expanding. Metabolomics is the study of metabolites, which are extremely small molecules. The phenotype correlates more strongly with the metabolomic profile than with the genomic, transcriptomic, or proteomic profiles. Plant metabolic profiling is another application of metabolomics that has been used to identify previously uncharacterized genes and their roles. The use of metabolomics to evaluate mutants and transgenic plants, track fruit development, determine quality, detect disease resistance, determine abiotic stress tolerance, etc., has become increasingly important. Metabolomics has also been applied to plant studies, which have become increasingly important in efforts to improve fruit quality. We first assess the profound influence metabolomics has had over the past decade, then provide an introduction to the field, its current contribution, and the hope it holds for enhancing fruit production.

Keywords

metabolomics; stress; quality; improvement; fruit crops; metabolites

Introduction

"Omics" has seen substantial advances in genomics, transcriptomics, epigenetics as well as in protein-level analysis, metabolomic and phenomics research in the last few years. All of an organism's metabolites are analysed, detected, and quantified in a systematic manner using metabolomics (1). As a result of these methodologies, ongoing breeding programs for climate-smart and nutrition-rich germplasm have been improved in terms of precision and speed (2). In order to better understand the metabolic changes that occur when plants are under stress, metabolite fingerprinting and metabolite profiling can be used. Analysing the biochemistry of several situations in the same organism can be done using metabolomics in order to better understand the complicated shifts of metabolism through changes in the concentration of metabolites (3). Screening phenotypic reactions to abiotic and biotic stresses requires the rapid, high-quality quantitative analysis of plant metabolic responses to environmental perturbation. (4). Plant metabolites contribute to the colour, flavour, taste, and odor of flowers and fruits, as well as to various resistance and stress response activities (5).

Metabolomics is the most complicated omics technique, although it

has gotten very little attention in the field of agricultural science (6). In metabolomics, also known as metabolite profiling, all of a biological system's metabolites are examined at the same time for any significant changes (5). Transcriptomic, metabolic, and genomic advances in recent years have made it possible to discover new genes and pathways that are responsible for the extraordinary variety of plant metabolomes (7). Metabolic profiling measures low-molecular-weight metabolites and their intermediates to better comprehend the dynamic response of biological systems to genetic modification, physiological, pathological, and developmental stimuli.

Metabolite associations with relevant phenotypes can be discovered using plant metabolomics technology (8), allowing for the development of more rational models that link specific metabolites or pathways to yields or quality-related traits (5, 7). Since the 1970s and 1980s there has been an increasing focus on the metabolome, which plays a vital role in crop growth by developing the phenotypic trait (9). Because of the global population, plant quality trait development has become a global concern (7). Metabolomics-assisted breeding may be effective in generating more resilient crops because of ongoing efforts to understand the metabolic responses to different stresses (10). Metabolomics will play a larger role in crop development in the future (5). This would result in the creation of climate-smart and nutrient-rich bio-enhanced cultivars in a more efficient and expedient manner so as to achieve the desired sustainable food production and security (9).

Aside from its abundance of metabolites, the fruit is a good model for metabolomics studies. Some fruit crops, such as *Citrus spp.*, *Mangifera indica*, *Malus spp.*, *Fragaria ananassa*, *Pyrus communis*, and *Vitis vinifera*, have metabolome data that may be accessed (6,9). It can be explored from Plant Metabolome Library (PMDB) is a database of plant secondary metabolites in three-dimensional structures that are available in biological data banks and databases. The metabolite sets in the described technique are defined using the KEGG databases (10, 11). The MSAN (Metabolite Sets Association Network) assessed the associations between pairs of metabolite sets based on their mutual information by employing metabolite sets as vertexes. Users may access data from a variety of databases, including Plant Metabolic Network (plantcyc.org), Plant Metabolites [CSIR - Central Drug Research Institute, India] (cdri.res.in), and <http://scbt.sastra.edu/>. Citrus EST database obtained from the University of California at Davis genomics facility (<http://cgf.ucdavis.edu>) and the University of California at Riverside (HarvEST Citrus, <http://harvest.ucr.edu>) and similarly MMHub database for mulberry metabolome search can be explored. Currently, the majority of fruit metabolomics research focuses on just a few fruit cultivars, with recent emphasis on quality, environmental stress, mutant analysis and transgene analysis, modified pathway performance, germplasm diversity, and developmental characteristics, among other fruit metabolomics-related topics (12). It is crucial to expand the study of

metabolomics to previously unstudied fruit species. Fruit metabolomics data could also be used for network modelling to better comprehend the relationships between attributes (13). A brief overview of metabolomics' current and prospective contributions to the improvement of fruit quality is included in this review of the past decade in fruit metabolomics, which summarises the most notable advancements in this field.

Metabolite database and equipment's used for metabolomic analysis

Emerging metabolomic approaches offer realistic tools for monitoring overall metabolic variations in plants throughout various physiological activities (14). Metabolomic databases are continuously evolving, which will make metabolite annotation easier in the future. Different metabolomic techniques, such as targeted metabolomics, non-targeted metabolomics, pseudo-targeted metabolomics, and extensively targeted metabolomics, might be used depending on the experimental goal. Metabolomics will drive fruit tree research forward by improving equipment, analytical platforms, and metabolite databases, as well as lowering the cost of the experiment (12). Although QTL (Quantitative Trait Loci) mapping is beneficial for deciphering particular pathways, it is insufficient for dissecting metabolism in its whole due to its complexity (15). As a result, metabolite correlation network analysis has been proposed as another tool for uncovering new relationships in plant metabolism (16, 17).

Through accurate and high throughput correlative peak annotation through snapshotting the plant metabolome, metabolomics is utilized to gain a huge quantity of relevant information for the discovery of genes and pathways (18). It appears that there is a complex regulatory network among these small molecules in plants, and metabolomic research helps greatly to the knowledge of the relationship between genotype and metabolic outputs by addressing critical network components (19). Integrating metabolomic and transcriptome analysis has been used effectively to examine the coordinated rules of metabolic fluxes and metabolite concentrations in plants (19, 20). Nonetheless, plant metabolomics has evolved into a powerful tool for investigating various aspects of plant physiology and biology, significantly expanding our understanding of the metabolic and molecular regulatory mechanisms governing plant growth, development, and stress responses, as well as improving crop productivity and quality. Knowledge-based metabolic engineering solutions, such as big datasets and rational models of metabolic pathways generated by wide-scale collecting and mining of diverse omics data, will assist to continually modify the input and output of engineering plants (21).

Metabolomic databases are rapidly developing, which in the future will make metabolite annotation easier (23). Metabolomics in plants relies heavily on its methods and equipment to accurately identify and quantify every molecule (5). Non-destructive nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS)-based

methods, including gas chromatography-MS (GC-MS), liquid chromatography-MS (LC-MS), and capillary electrophoresis-MS (CE-MS) are currently available for large scale analysis of highly complex mixtures (24, 25). Using various sampling techniques, metabolomics can be performed in a single cell or even at a subcellular level (26).

GC-MS is the technique of choice for assessing tiny polar metabolites that are thermally stable and may be rendered volatile by a derivatization procedure (27). GC-MS is primarily employed in plant metabolomic investigations to explore central primary metabolism, which comprises sugars, sugar alcohols, amino acids, organic acids, and polyamines (28). Furthermore, GC-MS can be used with headspace solid-phase microextraction (HS-SPME) to identify particular volatiles in a sample (29). Because volatile and main metabolite changes occur during fruit postharvest storage, they have been intensively researched. LC-MS is widely used to identify a larger range of metabolites than GC-MS, which is limited to volatile and thermally stable compounds. Because of its adaptability, LC-MS is mostly used to study the large diversity of plant secondary metabolites, which contains tens of thousands of distinct chemicals (30). Although rare, capillary electrophoresis (CE)-MS is another approach used to research plant metabolomics. This method detects a wide spectrum of highly polar or charged metabolites by sorting them according to their mass-to-charge ratio (31). In this regard, this technique has been advocated as a beneficial supplementary strategy for samples that are difficult to resolve using the more established GC- and LC-MS platforms (32). Even though NMR has a lower sensitivity than MS techniques, it offers a number of advantages over the previously described methodologies, including structural information, non-destructive sample preparation, and quick metabolite screening (33). Integrated NMR systems that can monitor changes in both primary and secondary metabolites have been created and may be beneficial for studying metabolic alterations in senescent fruits throughout postharvest (34).

As a result, to better understand the various applications and classifications of metabolomic approaches like targeted metabolomics, untargeted metabolomics, metabolite fingerprinting (untargeted analytics in which changes occurring in the biological sample are characterized), and metabolomics-based

metabolomics (targeted metabolomics in which a hypothesis is already formulated) (more focused kind of analysis compared to fingerprinting, as it identifies the metabolites). These methods are therefore meant to describe a metabolome's collection of metabolites in various ways. Fig. 1 represents the general pathway of metabolomic analysis. The graphic depicts a typical metabolomics study procedure. To begin, samples are taken from different plant tissue, cells, and so on. Following that, metabolites are frequently extracted with the addition of internal standards and derivatization (46). Metabolites are measured during sample analysis (liquid chromatography or gas chromatography combined with MS and/or NMR spectroscopy). The raw output data can be utilized to extract metabolite features and further processed prior to statistical analysis (such as PCA). There are several bioinformatic methods and software available to detect relationships with specific traits and outcomes, establish meaningful correlations, and define metabolic profiles in reference to known biological information. Recent advances in high-throughput metabolome analysis methods have made it possible to discover new metabolite forms and metabolic pathways while also gaining a more complete understanding of already known pathways (9).

The application of metabolomics in fruit quality improvement

It is possible to monitor a large number of substances using metabolomics, making it an ideal technique for studying metabolism in fruit. To improve fruit quality, metabolic networks and key regulatory enzymes can be investigated during development utilising metabolomics. Additionally, the fruit contains a high concentration of nutrients that are helpful to health. Among the distinctive metabolites found in rosaceous plants are flavonoids, anthocyanins, and phenolics, all of which contribute to the fruit's nutritional value (35). During fruit growth and ripening, the metabolic network has been considerably altered. Strawberry development has been studied using metabolic profiling (36), grape development (37, 38), apple development (39), citrus development (40), and more. In contrast, just a few research have been published on fruit metabolic networks (41). Using metabolomics, we want to improve fruit quality in the following areas: (Fig. 2).

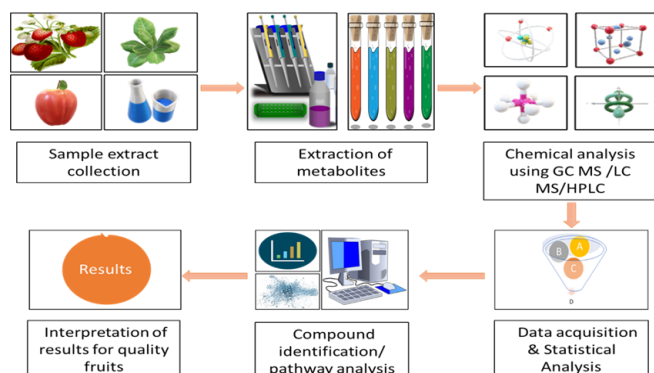


Fig. 1. General steps of metabolomic analysis of fruit crops.



Fig. 2. Metabolomics study targets for quality improvement in fruit crops.

Developmental stages of fruit crops

The complete data set at various phases highlights particular metabolic processes for fruit growth and may enable the identification of critical variables associated with desirable characteristics of important species. From early to late development, the metabolism of the peach mesocarp changes, and ripening after harvest is reflected by metabolic networks. During the early stages of stone hardening, the levels of bioactive polyphenols and amino acids decreased significantly. Sucrose levels significantly increased throughout development, indicating transfer from the leaf (41). In order to determine the precise chemical composition of the fruit, including polar and non-polar metabolites at different stages of strawberry growth, examined the metabolic profiles using GC-MS analysis. It was discovered by combining LC-MS data that amino acids are essential for giving red-ripe strawberry fruit its flavour and can enhance fruit quality (42). Similar findings from studies on pears showed that during the growth and ripening stages, there were differences in the accumulation of about 250 metabolites. As pear fruit ripened, sugars and amino acids containing sulphur were collected. The formation of fruit results in a large decrease in the metabolites (amino acids and organic acids), which increase during the blooming stage (43). Using MS analysis of grapes, several bioactive stilbenes (polyphenols) that affect wine quality were identified (44). The metabolite abundance in grape berries regulates the ripening processes and affects quality by being stage- and cultivar-dependent (45). The fruit's metabolite composition affects the fruit's quality at various phases of production. When fruits are developing, the physiological factors alter, which affects the composition of metabolites and hence manipulate the quality of fruit crops (41).

Biotic stress management for quality fruits

A study found several primary and secondary metabolites, that are crucial for signalling microbial infection (46). Citrus juice's quality is diminished by Huanglongbing disease, according to a report (47). The substances found in biotically stressed plants help to identify new defence molecules and also act as helpful markers for the defensive condition of plants (48). To evaluate how biotic stress and the fungicide affect strawberry quality, quantitative measurement of primary and secondary metabolites accumulated in infected and non-infected strawberries has been used (49). Researching suitable cultivars before releasing them into disease-prone areas can be modelled using the number of metabolites found in diseased and uninfected plant parts (50; Table 1). Using targeted analysis, the fungal diseases *Botrytis cinerea* and *Colletotrichum acutatum* infection increased the polyphenol levels in white fruited strawberry species (51). In order to clearly understand the resistance mechanism against the pathogen in fruits, a genome-scale metabolic network built using metabolome datasets is created.

Managing post-harvest disease is essential to guaranteeing fruit of enriched quality. According to metabolomics studies, heat treatment (HT) has traditionally been utilised to maintain fruit quality during

postharvest storage. When it comes to fruit stress tolerance during storage and differential metabolite build up, HT provides a comprehensive picture. The ability of fruit to handle stress is increased by the up-accumulation of secondary metabolites in metabolic substrates. According to results that are consistent with earlier findings, citrus fruit exposed to stress responds by producing more lignin and less H₂O₂ in the HT, which may boost the fruit's resistance to infections. Additionally, the HT increases several metabolites that lower the risk of post-harvest infection, such as 2-keto-gluconic acid, tetradecanoic acid, oleic acid, etc (52). Citrus cuticular wax biosynthesis during fruit formation has recently been found to be regulated by ABA which may help increase disease resistance (53). Hence, metabolomics plays an important role in managing pre harvest and post-harvest diseases for managing fruit quality.

Abiotic stress management for quality improvement

Recent research on vine, including transcriptome and metabolome investigations, demonstrated that mechanisms related to osmotic adjustment, photoinhibition protection, and scavenging of reactive oxygen species are triggered by drought (54, 55). Similarly, post-harvest treatments like cold or low oxygen in apples and pears have been successfully evaluated using GC-MS-based metabolomics (56, 57). Few reports suggested the accumulation of sugars, in plant cells when exposed to combinatory stress, presumably protecting plants against oxidative damage induced by most stress conditions through osmotic adjustment (58). The molecular response of stressed plants is successfully characterised by network analysis in various fruits, and metabolites with significant structural and biological activities are categorised. Profiling and metabolite analysis show coordinated changes in the grapevine's reaction to water stress (59).

A finding suggests that nutrients are exported from the flesh to the rind to sustain the activity of the entire fruit when the citrus fruit's skin is directly exposed to the atmosphere, resulting in energy expenditure in reaction to stress (40). Additionally, several physiological adjustments to the cold stress in bananas occurred, including changes in sugar metabolism and the use of reducing agents (60). The integration of omics techniques has greatly improved our understanding of how plants respond to stress conditions and allowed us to rebuild the whole range of cellular activities, enabling quick responses and adaptability to various abiotic stress stimuli (61).

Senescence's metabolism for quality fruits

Senescence has a significant impact on postharvest fruit quality, as well as fruit resistance to disease attack and environmental stress. It is common for fungal infections to accelerate fruit senescence after harvest in senescent fruits (62). Using a mix of omics data sets, researchers were able to uncover the regulatory link or alterations in metabolic pathways in strawberry and peach during the ripening and senescence phase (41). Several omics perspectives have recently been used to study citrus senescence (63, 64). Phytohormone reactions, transcription factor (TF) modulation, and a series of physio

Table 1. Determination of metabolites under different conditions for quality improvement

Crop	Treatment/ Condition	Equipments	Quality improved/ Metabolic traits	Reference
Apple	Prestorage UV-white light irradiation	GC-MS and LC-UV/vis-MS	Metabolic pathways associated with ethylene synthesis, acid metabolism, flavonoid pigment synthesis, and fruit texture, are altered	(39)
Mango	Fusarium	LC-MS	Increased tolerances related to the presence of mangiferin, maclurine and maclurine O-galloyl glucoside in the leaves. High iriflophenone glucoside levels were instead associated with greater risk for infection in cultivars.	(50)
Kiwi fruit	Ethylene	GC/MS	For commercial purposes, ethylene can be applied to 'Jecy green' kiwifruit in order to control ripening.	(87)
Banana	Salicylic acid (SA)	NMR spectrometer	SA enhanced the freezing tolerance through a variety of metabolic pathways.	(61)
Persimmon	AVG than with 1-MCP	MetaboAnalyst 4.0	Treatments of cold-stored persimmons presumably reduced the prevalence of physiological problems, but antioxidant metabolites were less influenced by both regulators.	(88)
Plum	Oil component analysis	GC/MS	Results revealed plum seeds are a good source of naturally occurring secondary metabolites, antidiabetic and antibacterial activity.	(89)
Grape	Antifungal/withering stress response	Untargeted HPLC-MS	taxifolin deoxyhexoside, taxifolin hexoside tetrahydroxyflavanone-Odeoxyhexoside	(90)
Apple	<i>Penicillium expansum</i>	UHPLC-HRAM MSn	procyanidin B1, epicatechin	(91)
Sweet Orange	Part of β , β -xanthophyll pool in mature oranges	HPLC	β -cryptoxanthin	(92)
Strawberry	3 °C, 3 ws supplemented with different CO ₂ concentration	HS-SPME-GC-MS and GC-O	Off-aroma' generation, 'alcohol' aroma	(93)
Mandarin	5 °C, 6 ws + 20 °C, 1 w	HS-SPME-GC-MS and GC-O	Off-aroma' generation, 'alcohol' aroma	(94)
Apple	2.5 °C, 7 d + 1 °C followed by two different low oxygen protocols up to 240 d	HS-SPME-GC-MS	'Off-aroma' generation, 'alcohol' aroma	(95)
Grapefruit	2 °C, 7 w	HS-SPME-GC-MS	Cold-induced responses	(96)
Grapefruit	1 °C, 7 w	HS-SPME-GC-MS	Cold-induced responses	(97)
Lime, mandarin, grapefruit, orange	0 °C up to 12 w, with or without ethylene	GC-MS	Correlation with CI symptom development in 0 °C storage, alpha-farnesene increase	(98)
Citrus	Jasmonic acid (JA) and salicylic acid (SA)	GC/MS	Tryptophan and serine are common biomarker candidates in citrus plants for wound stress.	(99)
Banana	Postharvest senescence	¹ H NMR	the quality of the banana was correlated with the content of a-D-glucose, b-D-glucose, fructose and sucrose.	(100)

-biochemical reactions may play a role in fruit senescence behaviour when internal components are depleted. Citrus fruit senescence is mediated by plant hormones and transcription factors that are comparable, according to the authors (40). Storage is severely impacted by senescence. The field of metabolomics may be employed to learn more about the ageing process in fruits and vegetables. During senescence, it can also be utilised to measure metabolic changes. Increases in post-harvest mannose and xylose levels show that the cell wall hemicellulose is being broken down, which causes fruit senescence (65).

Genetically Modified (GM) crops and mutant's quality examination

Metabolomics can be used to examine the metabolic makeup of GM crops as well as spontaneous or derived mutants. A database of metabolites from GM and traditional crops might be generated using metabolomic technologies (66, 67). GM crops (5) or genetically modified mutants (Mutants) may experience expected and unexpected metabolic impacts as a result of genetic manipulation, according to this study. Fruit crops have been cultivated and bred using natural mutations.

Mutants, on the other hand, have only lately been revealed to have varying gene structure and expression regulation due to their mutations. For example, a study revealed that the combined metabolome and transcriptome study gives us a picture of modulated anthocyanin and flavonoid expression in the "Purple Peel" fig mutant, revealing large-scale changes in nutritionally important compounds and gene expression in a horticultural mutation with a single phenotypic attribute (68).

The "Hong Anliu" orange bud mutant's metabolomic trial also yielded 130 metabolites. Flavonoid levels at the ripe stage of "Hong Anliu" Sweet Orange were assessed by higher amounts of soluble sugars and lower levels of organic acids (69, 70). For the first time, research on the purple-skinned fig mutant has revealed new details about the fig metabolites anthocyanins, flavonoids and procyanidins as well as transcriptional alterations that affect fig colour, secondary metabolism pathways, fruit maturation, and quality development (68). On the other hand, the response to fungal infections by the spontaneous mutant of "Newhall" navel orange (MT) is not wax deficit-dependent and has been linked to jasmonate levels. Improved fruit quality can be attributed to increased JA protection, according to the results of this study (67). Hence, evaluation of GM crops or mutants through metabolomics can provide a positive approach for the assessment of quality fruit crops.

Metabolite composition to improve fruit quality

An individual fruit's metabolic composition is fundamental to its qualitative characteristics. Sugar and acid quality and quantity, as well as the ratios of individual sugars to each other and the ratios of sugars to acids, have been particularly effective in predicting fruit quality, freshness, maturity, and storability (71). Sweetness, acidity, firmness, colour, carotenoids, and anthocyanins in the peel, and browning of fruit tissue after cutting, for example, are all influenced by the amount and composition of various sugars and sugar alcohols in the fruit. Acidity, on the other hand, is influenced by the amount and composition of organic acids (72, 73). Metabolomics is a new discipline that tries to measure all the metabolites in a cell, tissue, organ, or organism (74). Secondary metabolites in the peel, including as pigments, tannins, and fragrance molecules, have an impact on fruit appearance and quality (75). To explain the difference in colour between the "Green Peel" cultivar and its mutant, researchers discovered that the presence of four cyanidin glucosides in the "Purple Peel" fig cultivar was responsible. Interestingly, the mutant also had a higher concentration of other colourless flavonoids, which suggests an increase in the plant's medicinal qualities (68). Another omics strategy to deciphering carotenoid accumulation in banana pulp (*Musa* spp.) is worth highlighting, integrating metabolite profiling with proteome analysis (76).

The quality of a crop can be determined by cultivars' geographic dispersion, which can represent various metabolite compositions. Research on grape metabolite concentration supports the idea that fruit quality varies geographically, which is in line with the

previous observation. In places where there is a lot of sunlight and low rainfall, grapes have higher quantities of sugars, amino acids, Na and Ca, and lower levels of organic acids (77). Apple quality could be assessed using volatiles emitted by the fruit (78). Using metabolomic analysis, demonstrated that strawberry cultivars could be defined by their primary metabolome and metabolites in response to various agronomic and environmental conditions, which resulted in changes in primary metabolites such as sugars, organic acids, and amino acids (79). It was discovered that the composition of each cultivar of cherry depended more on genetic variability than environmental factors was revealed from a multi-approach metabolomics investigation (80).

The browning of apple fruits while in storage makes them unmarketable, which hurts the apple industry. The study of apple fruit volatile metabolomics has also attempted to correlate quality features and fungus infestation, with mixed results (81). Among commercially significant varieties, the apple's metabolite content distinguished out in terms of quality (82). As the kiwifruit ripens, the amount of soluble sugar and ascorbate increases significantly, affecting the quality and flavour of the fruit. In order to create better variations, it is possible to focus on the metabolites that make kiwifruits more appealing to consumer demands (83). The levels of primary metabolites in preserved apple fruits varied depending on the time period, according to the metabolomics analysis (84). It is possible to change the aggregation patterns of metabolites in kiwi fruit through the use of synthetic cytokinin's, such as amino acids, carbohydrate chains, organic acids, etc (85). The spatial distribution of sugars and organic acids in apple fruit has been discovered by recent metabolic profiling studies (86).

Conclusion

To meet the ever-increasing demand for high-quality food, scientists are continually seeking to increase the availability of superior crop varieties. Metabolomics is a potential strategy for crop improvement because it has provided information on the essential metabolites involved in quality enhancement. Recent advances in plant metabolomics have enabled the precise selection of desirable characteristics and the possibility of creating metabolically modified plants. The transition from single metabolite analysis to high throughput assays that generate fingerprints of multiple compounds simultaneously has paved the way for the development of more accurate models of metabolite networks and the identification of reliable biomarkers. Metabolic profile alterations can be utilised as a marker for stress physiology and metabolic movements and variables can be examined in combination with other "omics" approaches. It has not only found a myriad of recognised as well as new metabolites but has also permitted assessment toward enhancing essential plant qualities such as quality, yield, shelf life, and so on. More research is necessary for the application of metabolomics, and attempts in this area are imminent. To that purpose, NGS

technology has been immensely beneficial as a low-cost, high-throughput technique of understanding the architecture of metabolic characteristics. Metabolite genetic mapping is a key step in establishing which genes are responsible for this variance in metabolite levels. We believe that combining metabolomics and other omics technologies would enable for the quick creation of high-performing crop genotypes capable of solving the demands of fruit improvement.

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Authors contributions

RP designed the outline and wrote the draft of manuscript, KP participated in editing and compiling the final draft, NR participated in the literature search, RP participated in managing the analyses of the study, SS participated in editing. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

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