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Metabolomics for Plant Improvement: Status and Prospects

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Post-genomics era has witnessed the development of cutting-edge technologies that have offered cost-efficient and high-throughput ways for molecular characterization of the function of a cell or organism. Large-scale metabolite profiling assays have allowed researchers to access the global data sets of metabolites and the corresponding metabolic pathways in an unprecedented way. Recent efforts in metabolomics have been directed to improve the quality along with a major focus on yield related traits. Importantly, an integration of metabolomics with other approaches such as quantitative genetics, transcriptomics and genetic modification has established its immense relevance to plant improvement. An effective combination of these modern approaches guides researchers to pinpoint the functional gene(s) and the characterization of massive metabolites, in order to prioritize the candidate genes for downstream analyses and ultimately, offering trait specific markers to improve commercially important traits. This in turn will improve the ability of a plant breeder by allowing him to make more informed decisions. Given this, the present review captures the significant leads gained in the past decade in the field of plant metabolomics accompanied by a brief discussion on the current contribution and the future scope of metabolomics to accelerate plant improvement.

Keywords: biofortification, crop improvement, metabolomics, phytonutrient, fruit quality

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INTRODUCTION

Recent years have witnessed huge developments in different 'Omics' fields, namely genomics, transcriptomics, epigenomics, proteomics, metabolomics and phenomics. The information generated by these 'Omics' approaches has enhanced precision and speed to the ongoing breeding programs in developing climate smart and nutrition rich germplasm, which is key for ensuring food security (Parry and Hawkesford, 2012). In recent times, the role of phenomics-based breeding has become evident in improving the crop's performance, and similarly, genomics has made notable contribution in achieving higher genetic gains (Khush, 2001; Langridge and Fleury, 2011; Wang et al., 2017; Xavier et al., 2017). Nevertheless, the diverse omics platforms have great potential in improving the current understanding of important traits, enabling us to develop new strategies for plant improvement. Among omics approaches, the metabolomics is the most complex and has received inadequate attention in crop science, particularly for trait mapping and plant selections.

Metabolites are indispensable component of plant metabolism owing to their influence on plant biomass and architecture (Turner et al., 2016). In recent years, metabolomics has established itself as one of the major breakthroughs in science, paving the way for accurate metabolite profiling in microbes, plants and animals (Heyman and Dubery, 2016; van Dam and Bouwmeester, 2016; Wuolikainen et al., 2016). Metabolomics has the ability to detect a vast array of metabolites from a single extract, thus allowing speedy and precise analysis of metabolites. In other words, metabolomics offers a comprehensive view of cellular metabolites like small organic compounds, which participate in different cellular events, thus representing the absolute physiological state of a cell. In view of the rapidly advancing metabolomics, the metabolite investigation of mutants and transgenic lines holds potential to understand the metabolic networks and to pinpoint the underlying candidate gene(s) (Fernie, 2003; Yonekura-Sakakibara and Saito, 2006; Hong et al., 2016). Also, the metabolomics helps to resolve gene's' function: how a particular gene impacts upon the metabolic pathway, and uncovers different layers of regulation and interception between linked pathways (Wen et al., 2015), which otherwise is difficult to achieve by conventional assays like microarray (Kusano and Saito, 2012). An integrated approach accommodating inferences from genomics, transcriptomics, proteomics, and metabolomics will allow researchers for cataloging and prioritizing the genes to improve important traits in crop species. Further, above-mentioned omics studies have been further extended to explore the associated regulatory steps such as epigenetic regulation, post-transcriptional and post-translation modification. To this end, the interactome network studies aiming to reveal molecular interactions between biomolecules (nucleic acid, proteins, amino acids, carbohydrates, lipids, etc.) deepen our knowledge about the genotype–phenotype relationship (Vidal et al., 2011; Vadivel, 2015).

Metabolomics is being increasingly used in many crop species irrespective of the availability of transgenic system (Oikawa et al., 2008; Fernie and Schauer, 2009; Daygon and Fitzgerald, 2013; Simó et al., 2014). The metabolomics has the potential to facilitate selection of superior traits and improvement of breeding materials (Zivy et al., 2015). In conjunction with the advances in metabolomics, the availability of whole genome sequence, genome-wide genetic variants and cost-effective genotyping assays opens exciting opportunity to effectively integrate metabolomics in crop breeding programs (Hall et al., 2002; Fernie and Schauer, 2009).

The methods and tools employed in metabolomics study, including the mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy have witnessed substantial improvement. The currently available metabolomics platforms have the capacity to allow large-scale metabolite surveys covering both known as well as unknown metabolites. The deluge of such data, however, makes annotation of metabolites a considerable challenge (Matsuda et al., 2010; Lei et al., 2011). In this context, the ever growing strength of bioinformatics tools coupled with the establishment of metabolomics databases such as the one for model plant Arabidopsis[1], and others for various plant species[2] have greater implications for metabolite annotation (Tohge and Fernie, 2009; Afendi et al., 2012). A considerable amount of data have resulted from metabolic surveys, which might support plant improvement schemes focusing on the traits of agricultural importance such as yield and stress tolerance. Further, rapid generation of genome scale data by sequencing of DNA and RNA, and by MS quantification of proteins and metabolites necessitates integration of these information in order to devise a holistic way of improving traits of interests (Pandey et al., 2016). Although, most of the current studies are coming in well-established model organisms, such studies may be of common occurrence in other plant species as well. Scientific community currently faces a herculean challenge of dealing with massive multi-omics data for conducting systems-level analyses (Suravajhala et al., 2016). In such scenario, improved statistical and bioinformatics tools will be required to analyze these data sets together for better consolidation, which can eventually be translated for improving plant performance. In this review, we briefly describe about the latest investigations on plant metabolites and the application of metabolomics including metabolic engineering for plant improvement.

ANALYTICAL TOOLS FOR METABOLOMIC STUDIES

The modern metabolomics platforms involve generation of metabolome data using two important techniques, namely NMR and MS (**Figure 1**). The NMR based metabolite detection relies upon the utilization of magnetic properties of nuclei of atoms under magnetic field. The NMR is a non-destructive method extensively used to identify metabolites with smaller molecular weight (<50 kDa) for diverse applications like metabolite fingerprinting, profiling, metabolic flux and extracting the atomic structural information of compound present in the biological samples (Winning et al., 2009). However, the poor sensitivity of this technique owing to a limited coverage of low-abundance biomarkers poses a major limitation that in turn restricts its extensive use. Unlike NMR, greater sensitivity of MS allows researchers to attain a wide coverage of metabolome data. This led researchers to identify novel metabolic biomarker, and molecules that can facilitate the reconstruction of metabolic pathways and networks. Recently, MS has achieved greater accuracy with the advances in the ionization methods such as atmospheric pressure chemical ionization (APCI), electrospray ionization (ESI) and MALDI-TOF (Issaq et al., 2009). For enhancing the throughput, MS is usually combined with chromatography techniques such as gas chromatography (GC), liquid chromatography (LC), capillary electrophoresis (CE), fourier transform ion-cyclotron resonance (FT-ICR) and field asymmetric waveform ion mobility spectrometry (FAIMS). Notwithstanding the low sensitivity and large sample requirement of NMR, its capacity of identifying physical properties of ligands, binding sites on

[1]https://www.arabidopsis.org/biocyc/

[2]http://www.plantcyc.org/

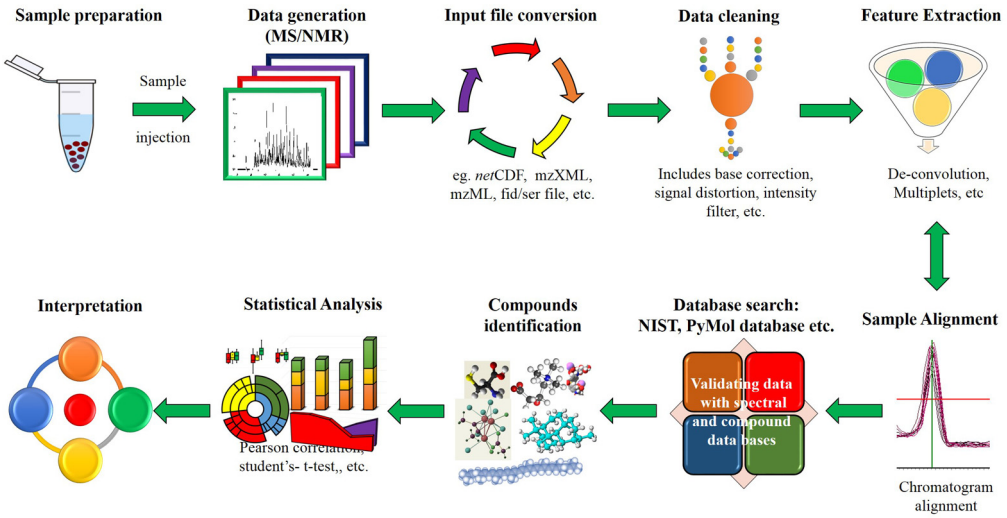

FIGURE 1 | Schematic representation of high throughput data analysis process. A set of raw data files is read after file conversion to desired formats. Data cleaning involves cleaning input file to remove false positives through noise reduction and background correction. Feature extraction is used to differentiate individual peaks from overlapped or closely aligned ones. Additionally, compounds can be identified by analyzing spectra and chemical compound structures available in the metabolomics library or databases.

protein, uncovering structures of protein ligand complexes and direct binding of target protein retains its use over MS.

The GC-MS platform is widely used for non-targeted analysis (Dutta et al., 2012). GC-MS approach involves derivatization of samples which makes the compounds volatile; however, this leaves underivatized compounds (except hydrocarbon) unnoticed during analysis. Introduction of GC X GC-TOF-MS has notably improved the separation of co-eluting peaks (deconvoluted peak) and also facilitated higher sample throughput (Ralston-Hooper et al., 2008). LC-MS mostly uses ESI and APCI; it has been widely used for targeted and non-targeted approach to detect both primary and secondary metabolites of higher mass i.e., <1500 Da (Turner et al., 2016). Additionally, the combination of UPLC with QTOF-MS has increased the peak resolution, mass accuracy and rapid identification of hundreds of metabolites in a short span of time (Chawla and Ranjan, 2016). In addition to these platforms, CE-MS provides high-resolution separation of different groups of analytes (charged, neutral, polar and hydrophobic) in both targeted and untargeted metabolomics studies (Ramautar and de Jong, 2014). FT-ICR-MS driven by high-resolution mass analysis facilitates detection of large-scale metabolite species with high accuracy (Brown et al., 2005), which could also be combined with separation techniques in order to resolve "very complex matrices" (Schrader and Klein, 2004) and to tackle other issues including ion separation (Lopes et al., 2017). Additionally, FAIMS or differential mobility spectrometry (DMS) an ion mobility based electrophoretic technique coupled with MS. The FAIMS technology was used for the detection of biological samples like volatile compounds formed during bacterial growth (Zrodnikov and Davis, 2012).

Exhaustive data set generated from above high throughput tools are processed through data processing platforms like MET-COFEA, Met-Align, ChromaTOF, MET-XAlign, etc., (Pegasus, 2007; Lommen et al., 2012; Kessler et al., 2014; Zhang et al., 2014, 2015; Ma et al., 2016; Misra and van der Hooft, 2016; de Souza et al., 2017). This basically includes baseline correction, alignment, separation of co-eluting peaks (deconvolution), normalization, etc. (**Figure 1**) prior to identification of compounds. Metabolome databases like METLIN, NIST, GOLM etc., can be used for identification of metabolites (Johnson and Lange, 2015). Further, the identified metabolites data are subject to statistical analysis such as correlation map, principal component analysis (PCA), partial least squares (PLS), K-means clustering, boxplot, heatmap, reconstructing metabolic pathways etc., by using web tool and softwares such as MetaboAnalyst, Cytoscape, Statistical analysis tool etc., (Tsugawa et al., 2015; Xie et al., 2015). These analyses are useful to monitor and identify metabolic markers associated with several agronomic traits.

METABOLOMICS FOR IMPROVEMENT OF FRUITS

Metabolomics studies have provided greater insights in fruit biology specially related to ripening and quality. Tomato (*Solanum lycopersicum*) is a rich source of carotenoids, anti-oxidants and flavonoids (Tohge and Fernie, 2015). Metabolite segregation pattern of 50 tomato cultivars showed close agreement with segregation of fruit's size (Moco et al., 2008). Metabolome is useful to dissect the ripening event by plotting a correlation with fruit transcriptome (Carrari et al., 2006; Osorio et al., 2011). Metabolome can be used to elucidate diverse and

differential biochemical pathways exist in the fruits of tomato ILs and Ecotypes (Toubiana et al., 2012; Upadhyaya et al., 2017), and the ancestral species through genome wide metabolic survey (Perez-Fons et al., 2014).

Apple (*Malus* spp.) contains beneficial nutrients in the peel and flesh, including antioxidants that reduce the risk of chronic diseases such as asthma, cancer, cardiovascular disease, and diabetes (Boyer and Liu, 2004). The metabolite contents of the apple fruits are used to differentiate commercially important cultivars (Cuthbertson et al., 2012). For example, the cultivar 'Golden Delicious' contains a high load of myo-inositol, sugars and succinic acid; whereas, the cultivars 'Red Delicious' and 'Fuji' show relatively higher abundance of triterpene/sterols, flavonoids, phenolic acids, stearic acid, anthocyanins, and carbohydrates. The fruit peel extract of 'Fuji' contained high levels of carbohydrate including glucose and sorbitol, and was significantly differentiated from 'Red Delicious' and 'Granny Smith' which contain high levels of unsaturated fatty acids (oleic and linoleic acid). Spatial distribution of sugars and organic acids between fruit layers has been elucidated in a recent study on metabolic profiling of apple fruit (Cebulj et al., 2017). The browning of apple fruits during storage renders them unmarketable, thus exerting an adverse impact on the apple industry. The metabolomics study on stored apple fruits showed a difference in the level of primary metabolites with different time duration (Hatoum et al., 2014). The increased levels of mannose and xylose during post-harvest indicated a breakdown of cell wall hemicellulose, which enhances fruit senescence. The study by Hatoum et al. (2016) established a relation between metabolic regulation during post-harvest storage and cellular respiration and stress.

In recent years, the Kiwifruit (*Actinidia Lindl.* spp.) has gained popularity in international markets due to its distinct appearance and the health benefiting nutrients such as vitamin C and fiber (Ward and Courtney, 2013). A total of 51 metabolites were detected during kiwifruit development and ripening (Nardozza et al., 2013). The content of soluble sugars and ascorbate significantly changes during ripening, which eventually determines the fruit quality and taste (Nardozza et al., 2013). Hence, the quality and flavor of Kiwifruit can be improved by targeting the metabolites that can render consumer acceptance. In Kiwifruit, application of synthetic cytokinin *N*-(2-chloro-4-pyridyl)-*N*′-phenylurea significantly increases fruit size, and affects the ripening processes by altering the accumulation pattern of metabolites such as amino acids, sugars, organic acids etc., (Ainalidou et al., 2015).

The quality and taste of orange (*Citrus* spp.) fruit depend on the composition of metabolites such as organic acids, sugars, vitamins, flavonoids, and carotenoids. The metabolomics study of orange bud mutant 'Hong Anliu' (accumulates higher levels of lycopene and sweeter than wild type) led to the identification of 130 metabolites that include acids, sugars, flavonoids, alkaloids, limonoids, coumarins, amino acids, and plant hormones (Liu et al., 2007; Pan et al., 2014). The flavor and the taste of 'Hong Anliu' sweet orange was determined by the higher levels of soluble sugars and lower levels of organic acids along with differential levels of flavonoids at ripe stage.

The infection of *Candidatus* Liberibacter asiaticus, causal agent of Citrus Huanglongbing disease, deteriorates juice quality (Slisz et al., 2012). The infection leads to severe decrease in glucose, fructose, sucrose and amino acids such as alanine, arginine, isoleucine, leucine, proline, threonine, and valine; whereas, it enhances the levels of citrate and phenylalanine. Heat treatment of fruit is widely used as a means to avoid fruit infection during post-harvest storage, which is well supported by metabolomics study. In a study, the heat treatment significantly decreased the content of organic acids and amino acid; however, it promoted the accumulation of metabolites such as 2-keto-D-gluconic acid, tetradecanoic acid, oleic acid, ornithine, succinic acid, myo-inositol, glucose, fructose, sucrose, and turanose, which reduces the risk of post-harvest infection (Yun et al., 2013). Recently, ABA is reported to serve as a regulator of citrus cuticular wax biosynthesis during fruit development (Wang et al., 2016).

In grape (*Vitis vinifera*), the fruit setting relies upon the abundance of metabolites, and is regulated by the reprograming of hormones and sugar metabolism pathways (Domingos et al., 2016). The effect of geographical distribution on grape metabolite content is well documented (Son et al., 2009). The grapes grown in the regions perceiving high sun light-low rainfall show enhanced content of sugars and amino acids, Na and Ca, along with low levels of organic acids, suggesting the role of extrinsic factors on grape fruit qualities. The metabolite abundance in grapes berry that is reported to be stage specific and cultivar dependent, regulates the ripening processes (Cuadros-Inostroza et al., 2016). Stilbenes are the major polyphenols present in the grapes that determine the quality of drinking wine. The MS analysis of grapes allowed the detection of several bioactive stilbenes like ampelopsin H, caraphenol, isohopeaphenol, trans-resveratrol, *Z*- and *E*-astringin, piceatanno, *Z*- and *E*-piceid, B pallidol and pallidol-3-*O*-glucoside and parthenocissin A (Flamini et al., 2015). The study focused on the polyphenolics content of the grape identified upto 450 compounds including anthocyanin, glycoside aroma precursors, flavanols and procyanidins, flavones and flavanones, phenolic acids and stilbenes. Particularly, this study allowed identification of several 100 compounds, which were used to build a new database of putative compounds (Grape Metabolomics).

Pear (*Pyrus communis*), a member of Rosaceae, is grown worldwide for its unique 'melting' texture. Japan is one of the largest producers of pears. The metabolomics analysis of pear fruit confirmed differential accumulation of ∼250 metabolites during fruit development and ripening (Oikawa et al., 2015). Ripening of pear fruit manifested accumulation of sugars (e.g., sucrose), sulphur-containing amino acids, phytohormone such as ABA and brassinosteroids. This study reported detection of 15 phytohormones including abscisic acid, auxin, brassinosteroids, gibberellins, jasmonic acid and salicylic acid. The blooming stage shows a substantial increase of the metabolites (amino acids and organic acids), which further decreases during fruit development.

Like pears, strawberry (*Fragaria* × *ananassa*) is rich in secondary metabolites such as flavonoids. The process of gain and loss of strawberry fruit flavors during evolution

and domestication was illustrated by Aharoni et al. (2004). The cultivated species of strawberry predominantly contain terpenoids such as monoterpene linalool and the sesquiterpene nerolidol. Whereas, the wild species were rich in the olefinic monoterpenes and myrtenyl acetate. Surprisingly, these were absent in the cultivated species (Aharoni et al., 2004). The untargeted (GC-MS) and targeted (HPLC) based studies of strawberry fruits were employed at seven different stages of fruit development. The metabolic study revealed a shift in the metabolite content during fruit development and ripening. The strawberry ripening involved rise of free amino acid content, with change in sugar content, including substantial changes in other major metabolic pathways such as ester biosynthesis, shikimate, and tricarboxylic acid (Zhang et al., 2011).

The effect of biotic stress and the fungicide (to avoid biotic stress) on strawberry quality was evaluated by quantitative estimation of primary and secondary metabolites accumulated in the infected and non-infected fruits (Mikulic-Petkovsek et al., 2013). The *Colletotrichum nymphaeae* infection induces accumulation of sugars and reduces the organic acid content. The infected fruits displayed altered content of metabolites such as ellagic acid derivatives, flanonols, flavan-3-ols, oligomeric procyanidins and total phenolics. Recent work by Nagpala et al. (2016) revealed an increase in the polyphenol levels in white-fruited species of strawberry as a result of infection from fungal pathogens *viz*. *Botrytis cinerea* and *Colletotrichum acutatum*.

METABOLOMICS FOR IMPROVEMENT OF LEGUME CROPS

Forage and grain legumes contribute 27% of the world gross primary crop. The grain legumes alone cater 33% of required human dietary protein, contribute to food security and environmental sustainability (Graham and Vance, 2003; Ramalingam et al., 2015). Notwithstanding the extensively investigated model legumes, metabolomics studies in other legumes remain limited. Concerning model legume, investigation of the effect of rhizobial node factor (Nod) in Medicago revealed a decrease in oxylipins (Zhang et al., 2012). In another study, metabolic profiling of salt tolerant *Lotus* species uncovered a series of changes involving metabolic adjustments of shoot constituent for survival (Sanchez et al., 2011).

Stress conditions such as salinity and anoxia result in an accumulation of alanine, and its biosynthesis co-substrates such as glutamate and GABA, and succinate in soybean (Rocha et al., 2010b). Differential expression was also obtained for genes involved in nitrogen fixation and fermentation in root. Interestingly, a negative correlation was observed for the amino acid derived from glycolysis and the TCA cycle during water logging, and several TCA cycle enzymes were induced upon exposure to water logging (Rocha et al., 2010a). Likewise, an attempt to elucidate the metabolic changes associated with flooding stress in soybean led authors to identify a set of 81 mitochondria associated metabolites, thus suggesting a boost in concentrations of metabolites involved in respiration and glycolysis such as, amino acids, NAD and NADH coupled with the depletion of free ATP (Komatsu et al., 2011). Under drought and salinity conditions, metabolite phenotyping of four different Mediterranean accessions of lentil suggested a decrease in intermediates of the TCA cycle and glycolytic pathway (Muscolo et al., 2015). Importantly, this study yielded metabolite markers for specific stress; such as threonate, asparagine/ornithine and alanine/homoserine for NaCl, drought and salinity, respectively. Another study that aimed to assess the impact of water deficiency on *Lupinus albus* demonstrated plant stem serving as a storage organ for sugars and amino acids (Pinheiro et al., 2004). Importantly, tolerant plant accumulated significantly higher level of metabolites such as asparagine, proline, sucrose and glucose in the stem stelar region (Pinheiro et al., 2004). The authors proposed reorganization of nitrogen and carbon metabolism pathways in plants in order to tolerate salinity stress. In soybean, consistent increase in pinitol (sugar alcohol, osmoprotectant) was reported in the tolerant plant at both normal and drought-stressed conditions (Silvente et al., 2012). Similarly, accumulation of sucrose, free amino acids and soluble proteins was observed in tolerant soybean in response to water stress (Tripathi et al., 2015).

METABOLOMICS FOR IMPROVEMENT OF CEREAL CROPS

Cereals remain the prime source of nutrition worldwide owing to their grains rich in vitamins, minerals, carbohydrates and fats (Sarwar et al., 2013). Cereals have been widely studied in order to quantity variation in metabolites and their association with sequence variation (Chen et al., 2014, 2016). In rice, different research groups have harnessed the potential of metabolomics in order to explore the metabolites diversity between different varieties and natural variants (Kusano et al., 2007; Redestig et al., 2011; Gong et al., 2013; Hu et al., 2014, 2016; Kusano et al., 2015; Chen et al., 2016; Okazaki and Saito, 2016). Similarly, metabolomics studies in maize have allowed researchers to differentiate and subsequently select the superior genotypes with enhanced nutritional composition (Matsuda et al., 2012; Wen et al., 2014; Venkatesh et al., 2016). Recently, metabolomic approach has been utilized to survey chemical diversity between different maize and rice variety and its natural variants (Chen et al., 2016). In maize, drought stress is reported to be regulated by amino acid metabolism (Obata et al., 2015). Photorespiration is tightly regulated under drought as the two amino acids involved in this pathway, glycine and serine are rendered up-regulated. Further, accumulation of glycine and myo-inositol was reported to relate with grain size of maize under drought, implicating these metabolites as potential markers for identifying drought tolerant maize (Obata et al., 2015). Similar work in rice demonstrated drastic induction of certain compounds in tolerant plants such as allantoin, galactaric acid, glucose, gluconic acid, glucopyranoside and salicylic acid, which could be considered as metabolite markers to address drought stress in rice (Degenkolbe et al., 2013). As demonstrated in sorghum by Ogbaga et al. (2016), the plant's ability to acquire and reorganize its metabolic status in order to cope with drought shows considerable variation within species. Under drought condition, sorghum variety having a

greater tolerance to drought (Samsorg 17) accumulated sugars and sugar alcohols in comparison with less drought tolerant variety (Samsorg 40) that accumulated free amino acids. Marked abundance of soluble sugars with amino acids was also observed in the roots of tolerant barley plants under salinity stress (Shelden et al., 2016). Like drought, chilling stress is also known to induce accumulation of amino acids and carbohydrates. For example, chilling stress caused substantial changes in metabolic profiles of rice varieties *viz.* Nipponbare (*Japonica*) and 19-11 (*Indica*) (Zhang et al., 2016). The chilling tolerance of Nipponbare involved metabolic adjustment to activate antioxidation pathway by modulating key metabolites such as γ-glutamylisoleucine, γ-glutamylglutamine, 5-oxoproline, glycine, glutamate, adenine dinucleotide and putrescine (Zhang et al., 2016). Further, chilling stress activates glycolytic pathway, however, normal activity is resumed during recovery phase. In both wheat and barley, cold stress expedites the amino acid pool and induces the GABA-shunt genes to promote conversion of glutamate to GABA (Sutka and Snape, 1989; Mazzucotelli et al., 2006). It is well established that cereal grains accumulate flavones/flavone-glycosides, which protects plants from various stresses (Caasi-Lit et al., 2007). For example, rice produces plenty of flavone-glycosides to protect it from abiotic stress and herbivores (Adjei-Afriyie et al., 2000; Matsuda et al., 2012). However, examination of herbivore-induced defense system in maize showed an increase in azealic acid, *N*-hydroxycinnamoyl tyramines, phospholipids, tryptophan, and 1,3-benzoxazin-4-ones (Marti et al., 2013). Accumulation of resistance related metabolites is also reported during plant–pathogen interaction. For instance, a tolerant variety of wheat can accumulate a wide range of metabolites conferring tolerance such as coumaroylputrescine and coumaroylagmatine during fusarium head blight (Kage et al., 2016). Further, evaluation of these hydroxycinnamic acid amide compounds and their placement on metabolic pathways has led to the identification of an important gene *agmatine coumaroyl transferase* (*ACT*).

IMPACT OF HIGH CO_2 STRESS ON THE METABOLOME AND ITS ATTRIBUTES TOWARD QUALITY AND YIELD

According to a report of the intergovernmental panel on climate change (IPCC), anthropogenic activity, deforestation and combustion of fossil fuel could boost CO_2 level upto 700 ppm by 2100 (IPCC, 2013)[3]. The CO_2 uptake and water availability are directly connected to photosynthesis and plant growth, and CO_2 sequestration by plants helps in maintaining terrestrial ecosystems (Weltzin et al., 2003; Reich et al., 2006; Arora and Boer, 2014). A recent study by Liu et al. (2016) has shown the impacts of elevated atmospheric CO_2 on plant growth rate, biomass and leaf area. Terrestrial plants and phytoplankton significantly utilize increased atmospheric CO_2 to increase their biomass (Lawlor and Mitchell, 1991; Schippers et al., 2004; Forkel et al., 2016). However, enhanced CO_2 levels might promote grass species in the long term (Smith et al., 2000), which is an encouraging finding concerning food crops such as cereal. Sustaining crop performance in the face of growing CO_2 levels remains a key challenge of 21st century agriculture. Therefore, studies are required to understand the metabolic composition and the relevant alterations on metabolome due to high CO_2 stress.

Effect on Quantity

Fruit, grain and tuber are the ultimate sink organs of the plant. The growth of these sink organs is directly depends on the partitioning of photosynthate from source organ to sink (Marcelis, 1996; Osorio et al., 2014). The sink organs store variety of metabolites which depends on species, source strength, composition of allocated photosynthate and plant requirement (Edson et al., 1995; Heuvelink, 1997; Cuzzuol et al., 2005; Kanai et al., 2007; Albacete et al., 2014; Li et al., 2015). To date several reports have been published that have focused on the correlation of high CO_2 with yield (harvesting sink organ) in commercial crop species (Schippers et al., 2004). For instance, high CO_2 was reported to cause a significant increase in productivity due to the increased level of photosynthesis in rice, wheat and soybean (Teramura et al., 1990). More recent studies in wheat and rice validated stimulation of yield under greater amount of atmospheric CO_2 (Cai et al., 2016; Fitzgerald et al., 2016). Though, the increase in soybean was quite consistent, it was not as significant and high as reported in the case of rice and wheat (Morgan et al., 2005; Ziska and Bunce, 2007). Coupling enrichment of CO_2 with drought stress in barley to examine yield loss rescue ability of elevated CO_2 suggested that modern barley cultivar could perform better under climate change (Schmid et al., 2016). Similar result was obtained earlier in potato in which enriched CO_2 farming led a 54% increase of tuber yield (Miglietta et al., 1998). Likewise, enhanced CO_2 level registered higher yield in cotton, however, it was lower than the yield obtained under elevated temperature (Osanai et al., 2017).

Effect on Quality

Obtaining crop produce with high quality also remains a global concern, especially at a time when a substantial proportion of the population worldwide is affected with nutrition related disorders (Bohra and Singh, 2015). Though enhanced yield was witnessed as a result of elevated CO_2, will this be able to meet the demand concerning nutritional quality and food security as most of these studies are being conducted in cereals that are rich in carbohydrate. Also, though elevated CO_2 in atmosphere increases yield, it affects the C/N ration in C_3 and C_4 plants by altering nitrate assimilation (Taub and Wang, 2008; Bloom et al., 2012). For instance, as shown by Bloom et al. (2014), wheat grown in the elevated CO_2 open field condition manifests slower nitrate metabolism. The reduced nitrogen in cereal results from increased levels of carbohydrates (Idso and Idso, 2001). Metabolomics studies of wheat grown under CO_2 enriched atmosphere have shown a substandard accumulation of amino acids, and a significant

[3]https://www.ipcc.ch/pdf/assessment-report/ar5/wg1/WGIAR5_SPM_brochure_en.pdf

increase in fructose, fructan and lipidic content in grains (Högy et al., 2009, 2010b). In soybean leaves, ureide (derived from urea) and total amino acid levels were increased at the early season, but, later it resumed to initial level (Rogers et al., 2006). Similarly, a combination of temperature and elevated CO_2 efficiently decreases the levels of amino acids in root of Chinese cabbage (Reich et al., 2016). In the strawberry fruit, elevated CO_2 and high temperature increase the sugar and sweetness index along with a reduction in the antioxidant and nitrogen content (Sun et al., 2012b). CO_2 enrichment has also shown encouraging results in other crops, such as increase of vitamin A and C in tomato, and vitamin C in orange fruit (Idso and Idso, 2001). Taken together, it becomes evident that crop grown in elevated CO_2 obtains higher yield to a certain extent; however, this may drastically affect the nutritional content, especially nitrogenous amino acids.

Elevated CO_2 was reported to exert a huge impact on mustard seed oil quality due to an increase in starch and oil content of seed at the expense of protein. The excess of carbohydrate affects the lipid composition of mustard seed, thus causing an increase in the concentration of oleic acid, and a simultaneous decrease in the content of linolenic acid and nervonic acid (Högy et al., 2010a). The CO_2 enrichment is reported to reduce the erucic acid (undesired factor) while improving mustard seed quality (Uprety et al., 2010). In groundnut, elevated CO_2 directed storage of high-quality oil in seeds of two varieties JL 24 and ICGV 91114 (Yadav et al., 2011) corroborated with the results reported in mustard. Similarly, sunflower seed showed a decrease in amino acids, proteins and minerals at high CO_2 concentration, however, oil load with health-benefiting unsaturated acids was increased (Pal et al., 2014).

EFFECT OF BIOTIC AND ABIOTIC STRESS ON PLANT LIPIDOME

Lipids are an important constituent of cell membrane enclosing organelles and suborganelles, in which various biochemical reactions occur. Modern lipidomics has facilitated profiling of lipids to understand lipid dynamics and biosynthesis on exposure to a range of stresses (Kosma et al., 2010; Burgos et al., 2011; Szymanski et al., 2014; Hou et al., 2016; Li et al., 2016; Tenenboim et al., 2016).

Plants adjust their lipid structure according to varying environmental conditions (Tenenboim et al., 2016). For instance, cold tolerant plants increase the levels of desaturated glycerolipids to maintenance membrane fluidity (Sakamoto et al., 2004; De Palma et al., 2008; Degenkolbe et al., 2012). Freezing plants up to a sublethal temperature can induce the level of lysophospholipids, phosphatidic acid, and phosphatidylglycerol (Welti et al., 2002; Zhang et al., 2013a). In contrast, tolerance to heat stress involves an increase in saturated glycerolipids (Larkindale and Huang, 2004). Recently, MS based analysis revealed remodeling of lipids, antioxidants and galactolipids in tomato plant during high temperature stress (Spicher et al., 2016). A combined glycerolipidomic and transcriptomics study provided insight on lipid remodeling, and regulatory genes involved in lipid biosynthesis and heat stress management (Burgos et al., 2011; Szymanski et al., 2014; Higashi et al., 2015; Légeret et al., 2016; Narayanan et al., 2016a,b). Most strikingly, high temperature can induce dramatic increase of lipid antioxidant such as α-tocopherol and plastoquinone/-ol, and saturation of membrane lipids like galactolipids and phosphatidyl ethanolamine (Spicher et al., 2016).

Hypoxia represents another important type of abiotic stress that plant faces due to excessive watering or flood and leads to limited O_2 availability and increased salinity for a submerged plant (Rajapakse et al., 2009). According to Xie et al. (2015), plant cell synthesizes and accumulates unsaturated ceramides, a class of sphingolipids under hypoxia. More recently, root lipidic content of two barley genotypes was examined to understand the mechanism underlying their tolerance to salinity stress (Natera et al., 2016). Phosphorus availability during stress is known to directly affect the membrane lipid texture. For instance, Arabidopsis grown in phosphorus-deficient condition can induce replacement of phospholipids with non-phosphorus SQDG class lipids (galactolipids) (Essigmann et al., 1998; Härtel et al., 2000). These galactolipids are mostly associated with plastic thylakoid membrane, and phosphorus deprivation causes its enrichment in the roots extraplastidic membrane for survival.

Compared to abiotic stress, lipidomics studies of biotic stress are scanty. During biotic stress, lipid peroxidation occurs due to formation of reactive oxygen species (ROS), ultimately leading to program cell death (PCD) (Zoeller et al., 2012). A recent report suggests *inositol phosphorylceramide synthase* as instrumental to coordinate the PCD, a mechanism acquired by plants for its self-defense to limit biotrophic pathogens (Wang et al., 2008). Lipid peroxidation results in formation of jasmonate and oxylipins, which are signaling molecules during plant immune response (Shah, 2005). Recently, nearly 100 membrane-associated lipids were quantified in response to methyljasmonate and cerium, suggesting increase of lysophosphatidylcholine, phosphatidic acid and phosphatidylcholine associated with PCD (Yang et al., 2008). Plant–pathogen interaction also impacts upon plant cuticle that serves as a first physical barrier limiting pathogen invasion along with protecting plants from other physical damages (Jenks et al., 1994). The cuticle layered over epidermal cells, is mainly composed of wax and cutin (Samuels et al., 2008; Mazurek et al., 2017). The cutin is mainly composed of hydroxylated C_{16} and C_{18} (Cheng and Walden, 2005; Kunst and Samuels, 2009). The permeability of cuticle relies upon its composition, which can restrict the invasion of fungal pathogens such as *Botrytis cinerea* (Saladié et al., 2007; Curvers et al., 2010). The role of cuticle in relation to plant defense against pathogen invasion is well described in the recent articles (Chassot and Métraux, 2005; Bessire et al., 2007; Chassot et al., 2008; Raffaele et al., 2009; Reina-Pinto and Yephremov, 2009; L'Haridon et al., 2011; Buxdorf et al., 2014; Serrano et al., 2014; Lara et al., 2015; Fernández et al., 2016).

INTEGRATING LAYERS OF METABOLOMICS AND OTHER OMICS SCIENCE

Epigenetic Modifications and Plant Metabolites

Epigenetic modification refers to DNA methylation and histone modification, which in turn alters the gene expression in a heritable fashion without causing any change in the underlying DNA sequence (Bird, 2007). For example, deformity of the flower in the toadflax (*Linaria vulgaris*) mutant was created due to extensive methylation and suppression of *cyc*-like gene that controls flower symmetry (Cubas et al., 1999). Research during the last decade has led to a significant gain in the knowledge related to epigenetic influence on metabolism, however, most of the studies were confined to animal system (Kaelin and McKnight, 2013; Petersen et al., 2014; Paul et al., 2015). The reason may be less availability of epigenetic mutants in the plants. In plant breeding, the epialleles can serve as a novel source of trait variation.

In Arabidopsis, disruption of *MSH1* caused altered plant growth phenotypes due to hypermethylation of chromosome segments (Virdi et al., 2015). Hypomethylation of *RAV6* promoter in rice *Epi-rav6* mutant resulted altered leaf size and grain size, via modulating brassinosteroid (BR) homeostasis (Xianwei et al., 2015). In maize, the *IPA* mutation affects the biosynthesis and accumulation of phytic acid in the seed, which influences germination along with affecting plant growth and responses to various environmental conditions (Pilu et al., 2009). The maize epigenetic mutation *lpa1-241* leads to drastic reduction of phytic acid and higher level of free inorganic phosphate in seeds. Similarly, epigenetic regulation of maize *booster1*, *Pericarp color1, purple plant1* and *red1* genes impacting upon anthocyanin and flavonoid biosynthesis is well documented (Della Vedova, 2004; Chandler and Alleman, 2008; Mach, 2012). In tomato, whole genome bisulphite sequencing of fruit revealed methylation of 1% of the total genomic region (Zhong et al., 2013). Further, it was demonstrated that epigenetic modification is not static during tomato fruit development and ripening, instead methylation of the promoter region significantly decreases for ripening specific genes such as *ripening inhibitor* (*RIN*) and *colorless non-ripening* (*CNR)*. In fact, DNA methylation regulates fruit phenotype by altering wide range of primary and secondary metabolites in tomato. For example, methylation of SBP-box promoter of epigenetic mutant *Cnr* results in severe decline of ethylene and carotenoids, thus affecting fruit shelf life (Manning et al., 2006). Additionally, the interaction of CNR with RIN affects the expression of ripening related gene (Oa et al., 2011). The *rin* mutant exhibits reduced levels of carotenoids, downregulation of ethylene, amino acids, organic acids and sugars (Osorio et al., 2011). A recent study in tomato has demonstrated that methylation in the promoter region of the gene *2-methyl-6-phytylquinol methyltransferase* (*VTE3*) affects biosynthesis and accumulation of γ- and α-tocopherols (Quadrana et al., 2014). *VTE3* underlies VTE quantitative trait locus (QTL) that is responsible for the modulation of important metabolic QTL. Domestication of allotetraploid cotton has resulted 12 million differentially methylated cytosines, which includes more than 500 genes contributing to agronomyic traits including seed dormancy and flowering time (Song et al., 2017).

Correlation Analyses of Transcriptomics and Metabolomics

Researchers increasingly focus on correlating metabolome with genomic segments to discover genetic determinants of regulatory pathways to improve compositional quality of crops species (Riedelsheimer et al., 2012; Gong et al., 2013; Strauch et al., 2015). Metabolome study in Arabidopsis has enriched the understanding of the metabolism and biosynthesis of glucosinolate, oil biosynthesis and oligosaccharides in seed (Bentsink et al., 2000; Kliebenstein et al., 2001; Hobbs et al., 2004). Recent advances have revealed an association of genetic variants with metabolites that could be used for metabolic engineering across various plant species such as Arabidopsis, broccoli, maize, mustard, potato, rice, sesame, tomato, and wheat (Schauer et al., 2005, 2006; Kusano et al., 2007; Yonekura-Sakakibara et al., 2007; Laurentin et al., 2008; Rochfort et al., 2008; Tohge and Fernie, 2012; Khakimov et al., 2014; Cho et al., 2016; Wen et al., 2016). For example, study of Arabidopsis ecotypes *Landsberg erecta* from Cape Verdi Islands revealed a strong correlation of *fatty acid desaturase 3* with the unsaturated fatty acid content (linoleic and linolenic acids) in seeds (Hobbs et al., 2004). The flavonoid biosynthesis in Arabidopsis is regulated by gene *flavonol 7-O-rhamnosyltransferase,* its transcripts accumulate with the flavonoid abundance in floral buds (Yonekura-Sakakibara et al., 2007). Another study revealed induction of eight novel anthocyanins out of 1800 metabolites in an overexpression line of MYB transcription factor encoding *PAP1* gene (Tohge et al., 2005). These approaches in tomato and populus enabled gathering in-depth knowledge about the flavonoid biosynthetic pathway (Spencer et al., 2005; Morreel et al., 2006). Concerning the flavonoid metabolism pathway, a strong correlation between transcripts and metabolites was inferred in potato through combining transcriptomics and metabolomics approaches (Cho et al., 2016). The study captured interaction between 22 metabolites and 119 transcripts, which strongly regulate the anthocyanin content of light-red Hongyoung and dark-purple Jayoung potatoes. Analysis of 210 recombinant inbred lines (RILs) derived from Bay × Sha facilitated detection of more than 400 QTLs for 243 metabolites. Total 11 QTL clusters were obtained, of which five overlapped with expression QTLs reported in earlier studies. Importantly, epistatic interactions were noted in eight QTL clusters (Rowe et al., 2008). In a similar fashion, genetic interactions explained the metabolic variation in maize (Wen et al., 2016). Two RIL populations (B73/By804 and Zong3/Yu87-1) were phenotyped for 155 metabolites and detected > 800 QTLs from both populations, majority of which had smaller effect sizes. This work provided deeper insights on flavonoid pathway, highlighting the significance of the *p* locus. Notably, 32 QTLs were cross validated between the two populations, whereas 57 associations detected in the genomic

regions that overlapped with the QTLs detected earlier in genome-wide association studies (GWAS) performed by Wen et al. (2014). In rice, 2,800 metabolite QTLs (mQTLs) were detected for 900 metabolites showing strong association with 24 candidate genes involved in various metabolic biosynthetic pathways, including *O*-glycosyl flavonols (Gong et al., 2013). Recently, metabolic profiling of leaf and fruits of five wild relatives of tomato (S. *chmielewskii, S. habrochaites, S. neorickii, S. pennellii,* and *S. pimpinellifolium*) showed a wide range of metabolome variability that are important for stress response, and also contribute to nutritional richness (Schauer et al., 2005). Another study that combined transcriptomics and metabolomics of tomato fruits revealed a strong correlation between the ripening-induced transcripts and metabolites specific to the Krebs cycle and sugars (Carrari et al., 2006). A more recent study consolidating profiling patterns of transcripts, proteins, and metabolites of ripening defective mutants *non-ripening* (*NOR*), *never-ripe* (*Nr*) and *ripening-inhibitor* (*RIN*) suggested shifts in the primary metabolites that eventually reduced metabolic activities during ripening (Osorio et al., 2011). Metabolite QTLs analysis based on metabolic profiling of 76 introgression lines (ILs) of tomato has uncovered a strong regulation of seed metabolism during fruit development (Toubiana et al., 2012). Recently, a tomato Eco-TILLING population showed wide variation in the folate content in the fruits (Upadhyaya et al., 2017). Additionally, the genome-wide metabolomic survey of ILs and the ancestral species *Solanum pennellii* led to identification of important compounds such as Vit-E etc. and importantly, this analysis assigned nearly 2,000 compounds to the tomato genome (Perez-Fons et al., 2014). Interestingly, the segments introgressed from *S. pennellii* (Chromosomes 3, 6, 8, and 12) into ILs were reported to alter isoprenoids and tocopherols content at the fruit level and the study led authors to associate the differential expression of metabolites with photosynthesis and photorespiration. Similarly, metabolic profiling of aneuploid wheat highlighted the genes regulating variation in the branched chain amino acids and accumulation of trehalose in mature grain (Francki et al., 2015).

Further, the use of metabolic information in genome wide predictions, as demonstrated by Riedelsheimer et al. (2012) in hybrid maize, opens up novel opportunities to considerably enhance genetic gains. Similarly, modern techniques such as the epigenome wide association studies (EWAS) employed recently in human (Petersen et al., 2014) may also be extended to plants to better capitalize on the potential of trait-associations like "methylome-metabotype association" for accelerating plant improvement. Additionally, recent interactome network studies, which focus on molecular interactions between biomolecules (nucleic acid, proteins, amino acids, carbohydrates, lipids, etc.) provide deeper insights on correlation between genotype and phenotype (Vidal et al., 2011; Vadivel, 2015; Zivy et al., 2015).

Combining Proteome Analysis with Metabolite Profiling

In addition to genomics, proteomics in combination with other modern high throughput approaches such as genomics and transcriptomics has contributed to revolutionize the omics era, and has paved the way to decipher the complex molecular mechanism underlying various commercial traits (Weckwerth, 2008; Barros et al., 2010; Ricroch et al., 2011; Ramalingam et al., 2015). For instance, the effect of pollutant ozone (O_3) was studied in rice because it damages cellular tissue by creating ROS, thus altering photosynthetic ability that severely reflects in yield loss. It was reported that exposure of O_3 to rice leaves significantly induced oligopeptidase-B and proteasome subunit alpha type1, which are involved in the 20S proteasome alpha subunit that mediate ATP dependent protein degradation (Cho et al., 2008). Further, O_3 exposure induced accumulation of stress and metabolism related proteins such as glutathione peroxidase, aconitate hydratase, fumarylacetoacetase hydrolase, dehydrogenase P protein, and thiamine biosynthetic protein. These protein modulations in O_3 exposed leaves were concomitant with dramatically increased levels of free amino acids, nucleotides and glutathione. A combined proteomics and metabolomics approach in response to temperature induced stress in Arabidopsis revealed several important markers (Wienkoop et al., 2008). Cold or heat stress induces production of osmolytes (metabolic markers) proline, glutamine, raffinose and galacinol. In Arabidopsis, these metabolites were identified along with protein markers chloroplastidic glyceraldehyde-3-phosphate dehydrogenase (GAPDH), cytosolic GAPDH, chloroplast chaperonin, cyclophilins, protein 78, COR6.6 and several RNA binding proteins. Heavy metals are potential threat to crop productivity, accumulation of these elements causes developmental and physiological changes. For example, cadmium (Cd) accumulation retards plant growth and causes chlorosis (Prasad, 1995; Moulis, 2010). Such investigation has involved several plant species such as Arabidopsis, mustard, soybean, flax, Medicago, rice, pea, tomato, and spinach to understand the cellular responses to Cd stress (Villiers et al., 2011). Cadmium induced toxicity in rice drastically affects the expression of RuBisCO, Calvin's cycle and kreb's cycle enzymes, which leads to attenuation of carbohydrate and amino acid metabolism. Further, the use of these platforms has been extended to understand biotic stress (Salekdeh and Komatsu, 2007; Lodha et al., 2013). Study of chickpea roots infected by *Fusarium oxysporum* suggested efficient and increased carbon and nitrogen metabolism, accumulation of phytoalexins, and lignification coupled with enhanced accumulation of proteins related to pathogenesis (Kumar et al., 2016). Similarly, a system biology approach to understand the response of microbial symbioses on the pea plant metabolism under *Didymella pinodes* infection reports systemic resistance via adjustment of proteome and metabolome (Desalegn et al., 2016). The rhizobia associated resistant plants showed induction of amino acid, TCA, and secondary metabolism, including the pisatin, and proteins associated with pisatin biosynthesis. Coupling metabolomics with other omics tool has enabled researchers to acquire deeper knowledge of molecular events involved in important biological process required for plant sustainability (**Figure 2**). As a result, metabolomics has been exploited in several plant species to better understand the biological phenomena including plant development and stress response (**Table 1**).

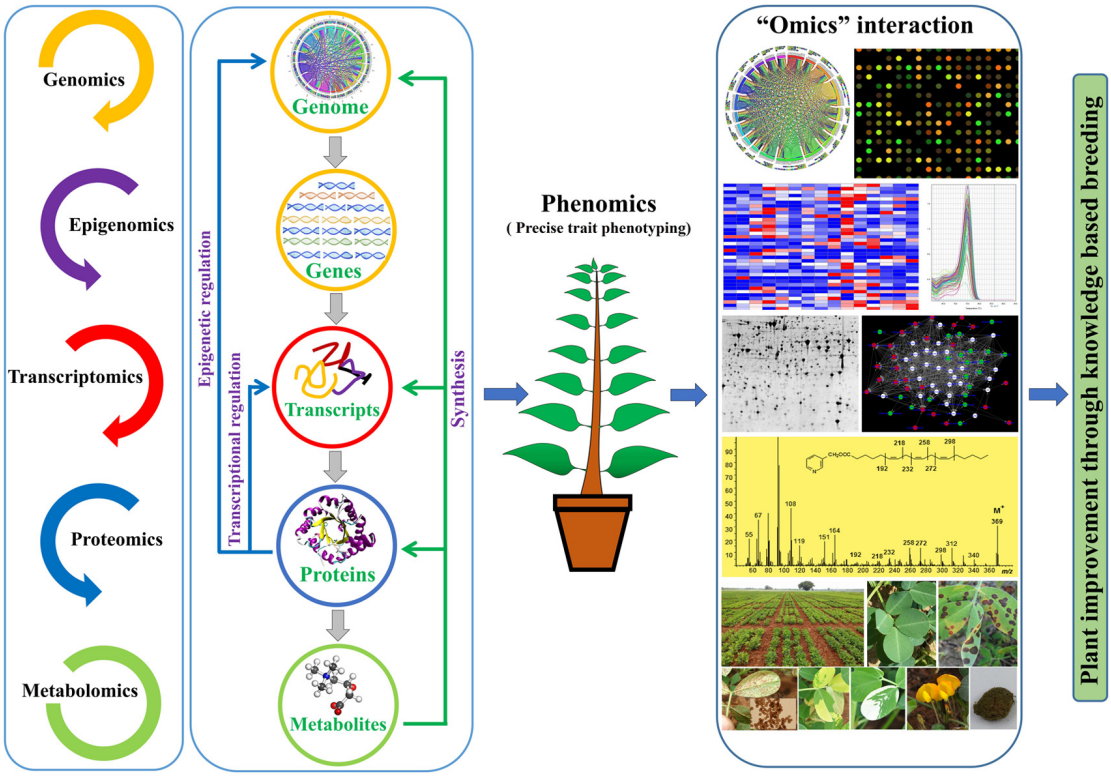

FIGURE 2 | An overview for the use of 'omics' approaches for crop improvement.

EXAMPLES OF PLANT IMPROVEMENT THROUGH METABOLIC ENGINEERING

Metabolites are the ultimate downstream factors that regulate and decide the cell fate; hence the content of metabolite directly affects organ physiology and often signifies the quality of fruits. The improvement of gene annotation is important to validate the gene function. In fact, it facilitates the use of these genes in the field of crop sciences to improve the quality and yield. This section describes significant leads achieved in the field of crop species through metabolic engineering.

Altering Photosynthate Levels to Change Fruit Dimensions

Fruit development and weight are significantly correlated with the metabolic composition of fruit (Osorio et al., 2014). The development of fruit represents substantial change of organic acid (predominantly citrate and malate) and sugars that determines the final quality of the ripe fruits (Azzi et al., 2015). Unlike leaves, fruits act as a sink and its development depends on the translocation of photo-assimilates of leaves than that of own photosynthesis products (Bénard et al., 2015). The impact of phloem translocate on fruit development and size was evident by concomitant increased growth for both flower and fruits with increased levels of photo-assimilate by reducing the number of flowers or fruits per truss (Baldet et al., 2006). For example, the incubation of tomato plant in the dark significantly reduces fruit size and shape due to repression of cell cycle genes of fruit which severely affects the cell number and cell size (Bohner and Ban, 1988; Bertin et al., 2002; Baldet et al., 2006).

In order to investigate the correlation between sugar content and fruit size, the *hexokinase 1* (*AtHXK1*) of Arabidopsis was over expressed in tomato plant (Menu et al., 2004). The overexpression line showed reduced fruit size due to reduction of cell expansion concomitant with reduced photosynthate. Additionally, transgenic fruits exhibited reduced respiratory rates accompanied by reducing ATP levels. The load of sucrose known to involve in the early stage of fruit development, import of sucrose in fruits is much needed in young fruits that influence fruit set and development (D'Aoust et al., 1999). The establishment of relations between glycolysis, sucrose metabolism and organic acid biosynthesis was profound from the transgenic plants expressing malate dehydrogenase (*mMDH*) in tomato (Nunes-Nesi et al., 2005). The enhanced fruit dry mass of RNAi-*mMDH* plants was concomitant with enhanced photosynthetic ability, which improved carbon assimilation. The silencing of *mMDH* promoted the accumulation of redox stabilizing compounds such as l-galactono-1,4-lactone precursor of ascorbic acid. The silencing of l-galactono-1,4-lactone dehydrogenase (*Gal-LDH*) substantially affecting cell size that resulted in smaller fruits (Alhagdow et al., 2007). Additionally, silencing of the key enzyme of ascorbate biosynthesis GDP-D-mannose 3,5-epimerase (GME) results defect in cell expansion and

TABLE 1 | List of plant species selected for metabolomics study.

Type of work	Plant name		Type of work	**Citation**
Fruit metabolome	*Solanum lycopersicum*		Carotenoid study	Long et al., 2006
			Primary metabolite analysis	Moco et al., 2008
			Metabolite QTL mapping	Perez-Fons et al., 2014
	Malus spp.		Cultivars differentation	Cuthbertson et al., 2012
			Post-harvest associated metabolic changes	Hatoum et al., 2014
			Metabolic distribution inside the fruit	Cebulj et al., 2017
	Actinidia Lindl. spp.		Fruit ripening and development	Nardozza et al., 2013
			Effect of cytokinin on fruit	Ainalidou et al., 2015
	Citrus		Mutant study	Pan et al., 2014
			Effect of GABA on fruit ripening	Sheng et al., 2017
	Vitis spp.		Effect of abiotic factor on grape quality	Son et al., 2009
			Identification of stilbenes	Flamini et al., 2015
	Pyrus communis		Fruit developmentt and ripening	Oikawa et al., 2015
	Fragaria spp.		Domestication and fruit quality	Aharoni et al., 2004
			Fruit development and ripening	Zhang et al., 2011
	Melon		Effect of environmental factor on melon quality	Bernillon et al., 2013
	Capsicum annuum		Fruit development and ripening	Jang et al., 2015
Stress Management	Biotic stress	*Fragaria spp.*	Effect of Colletotrichum nymphaeae infection	Mikulic-Petkovsek et al., 2013
			Effect of *Botrytis cinerea* and *Colletotrichum acutatum*	Nagpala et al., 2016
		Citrus	Post-harvest infection management	Yun et al., 2013
	Abiotic stress	*Lotus* spp.	Salt tolerance	Sanchez et al., 2011
		Soybean	Flooding stress	Komatsu et al., 2011
			Drought stress	Silvente et al., 2012; Tripathi et al., 2016
		Lentil	Drought and salinity	Muscolo et al., 2015
		Lupinus albus	Drought stress	Pinheiro et al., 2004
		Maize	Drought stress	Obata et al., 2015
		Rice	Drought stress	Degenkolbe et al., 2013
			Chilling stress	Zhang et al., 2016
			Herbivores stress	
		Sorghum	Drought stress	Ogbaga et al., 2016
		Barley	Salt tolerance	Shelden et al., 2016
			Chilling stress	Mazzucotelli et al., 2006
		Maize	Herbivores	Marti et al., 2013
		Rice	Herbivores	Adjei-Afriyie et al., 2000
		Rice	Effect of elevated CO_2 on yield	Cai et al., 2016

(Continued)

TABLE 1 | Continued

Type of work	Plant name		Type of work	**Citation**
		Wheat		Cai et al., 2016
		Barley		Schmid et al., 2016
		Soybean		Morgan et al., 2005
				Ziska and Bunce, 2007
		Potato		Miglietta et al., 1998
		Wheat	Effect of elevated CO_2 on grain quality	Bloom et al., 2014
		Soybean	Effect of elevated CO_2 on leaves metabolite	Rogers et al., 2006
		Groundnut	Effect of elevated CO_2 on seed content	Yadav et al., 2011
		Chinese cabbage	Elevated CO_2 on cabbage quality	Reich et al., 2016
		Strawberry	Elevated CO_2 on fruit quality	Sun et al., 2012b
		Mustard	Elevated CO_2 on seed oil	Chakraborty and Uprety, 2012
Study of trangenic	Oil quality	Jatropha	Lipid analysis	Qu et al., 2012
			Oil quality under drought stress	Tsuchimoto et al., 2012
		Castor	Oil quality and yield under against feeders	Malathi et al., 2006
		Sugarcane	Sugar quality	Arruda, 2012
				Hamerli and Birch, 2011
				Wu and Birch, 2007
		Barley	Sugar metabolism	Willis et al., 2016
		Potato		
		Rice		
		Sunflower		
		Tobacco		
		Arabidopsis	Altering the photosynthate load through *hexokinase1*	Menu et al., 2004
		Tomato	Alteration of sugar and organic acid levels	Nunes-Nesi et al., 2005
		Tomato	Alteration of cell wall non-cellulosic components	Gilbert et al., 2009
	Flavonoid biosynthesis	Apple	Anthocyanin content	Espley et al., 2007
		Tobacco		Takos et al., 2006
		Arabidopsis		Lin-Wang et al., 2010
		Strawberry		Lin-Wang et al., 2014
		Grapes		Walker et al., 2007
		Tomato		Butelli et al., 2008
	Altering the fruit size by targeting multiple genes	Tomato	Altering the fruit load	Baldet et al., 2006
	Fruit shelf life	Tomato	Ethylene metabolism	Picton et al., 1993
		Apple		Wang et al., 2009
	Hormone alteration	Tomato	Fruit size	De Jong et al., 2011
		Strawberry	Flavonoid content	Jia et al., 2011
		Tomato	Drought tolerance	Thompson et al., 2007

(Continued)

TABLE 1 | Continued

Type of work	Plant name		Type of work	Citation
		Rice		Xiong et al., 2001
		Canola		Wang et al., 2009
		Barley		Zalewski et al., 2010
		Maize	Flower modification	Makarevitch et al., 2012
		Rice	Senescence	Kang et al., 2009
	Vitamin enrichment	Potato	Vit-A	Diretto et al., 2010
		Rice		Paine et al., 2005
		Lettuce	Folate	Nunes et al., 2009
		Rice		Dong et al., 2014
	Aroma	Tomato	*S*-linalool accumulation	Butelli et al., 2008
		Cucumber	(E, Z)-2,6-nonadienal accumulation	Zawirska-Wojtasiak et al., 2009
		Tomato	Defense mechanism	Domínguez et al., 2010

biosynthesis of cell wall non-cellulosic components (Gilbert et al., 2009). This finding suggests the direct influence of ascorbate in the process of channeling energy during respiration and photosynthesis, and fruit metabolite levels during tomato fruit development (Azzi et al., 2015).

Exploring *MYB* Transcription Factors to Improve Fruit Quality

In eukaryotes, MYB family transcription factors represent huge family, which controls diverse function such as development, metabolism, and stress related response. Sequencing of the Arabidopsis genome leads to the discovery of the several MYB transcription factors which are mostly characterized to R2R3-MYB family (Dubos et al., 2010). In fruit anthocyanin biosynthesis regulated by R2R3-MYB transcription factor family. The red color of apple skin requires accumulation of anthocyanin, which is controlled by the expression of anthocyanin biosynthetic gene expression. MYB transcription factor *MdMYBA* and *MdMYB10* positively regulates anthocyanin content in apple fruits by binding to the promoter region of anthocyanin biosynthesis genes (Ban et al., 2007; Espley et al., 2007). Interestingly, low temperature and UV-B exposure, enhance the expression of MYB, which enhances anthocyanin accumulation (Ban et al., 2007). Expression of *MdMYBA* under 35S promoter in tobacco results remarkable increase in the anthocyanin content of flowers. MdMYB10 share homology to PAP protein and overexpression of MdMYB10 in apple up-regulate anthocyanin in the whole part of regenerated transgenic plants, including the transformed callus (Espley et al., 2007). In Arabidopsis overexpression of *MdMYB* results elevated level of anthocyanin only in seeds, but not in the leaves. Like tobacco, Arabidopsis also lacks bHLH which interact with MYB to enhance the anthocyanin accumulation (Takos et al., 2006). In addition to bHLH, MYB also interacts with WD-repeat proteins and regulates anthocyanin biosynthesis through "MBW" complex, which is formed of MYB, basic helix-loop-helix (bHLH) TFs and WD-repeat proteins (Jaakola, 2013).

In strawberry, overexpression of *FaMYB10* resulted elevated levels of anthocyanin in the leaves, flowers, fruits, and roots (Lin-Wang et al., 2010, 2014). Recent studies suggest hormonal regulation of *MYB* expression: during ripening auxin negatively, but ABA positively regulates the expression of *FaMYB10* in strawberry receptacles (Medina-Puche et al., 2014). In contrast to strawberry, overexpression of *FaMYB1* in tobacco suppressed the accumulation of anthocyanin and flavonol by repression of tobacco homolog (Aharoni et al., 2001). MYB regulates the flavonoid levels in capsicum, Chinese bayberry and grape by up-regulating flavonoid biosynthetic genes encoding chalcone synthase (CHS), chalcone isomerase, flavanone 3-hydroxylase (F3H), flavonoid 30-hydroxylase (F30H), dihydroflavonol 4-reductase (DFR), anthocyanidin synthase (ANS) and UDP glucose: flavonoid 3-*O*-glucosyltransferase (UFGT) (Walker et al., 2007; Niu et al., 2010; Li et al., 2011). In grapes, *VvMYBA1* and *VvMYBA2* regulates the anthocyanin content of berries, for instance, inactivation of *VvMYBA2* due to mutation in conserved domain results in white berries (Walker et al., 2007).

Normally the fruits of cultivated tomatoes do not accumulate high levels of anthocyanin in the peel or flesh. However, the peel of tomatoes wild relative *S. chilense* relatively accumulate high levels of anthocyanin under control of MYB family transcription factor *anyhocynin1* (ANT1) (Mathews et al., 2003). Schreiber et al. (2012) showed overexpression of *S. chilense ANT1* and *ANT2* in tomato cultivar exceptionally increased the levels of flavonoids in the cotyledon, leaves, floral organ and fruit peel. Additionally, the accumulation of flavonoid such as naringenin chalcone in the tomato fruit peel is controlled by *SLMYB12,* downregulation of it results colourless peel phenotype in *yellow* mutant, which was rescued by overexpression of *MYB12* (Schreiber et al., 2012). In tomato, the green shoulder at the top end is very common in wild type, but this phenotype lacks in *uniform ripening* (*u*) mutant. The *U* gene encodes for protein GOLDEN2-LIKE (GLK); a transcription factor, GARP subfamily of the MYB super family. Interestingly, overexpression of either *SLGLK1* or *SLGLK2* in both *u* and U background Ailsa Craig mimicked *hp* fruit phenotype such as enhanced chloroplast and high carotenoids (Nguyen et al., 2014).

Improving Fruit Shelf Life

The initial evidence of ethylene in ripening led researchers to target genes such as *ACS* and *ACO,* which were involved in ethylene biosynthesis. The antisense *ACS* and *ACO* transgenic plants produce non-climacteric tomato fruits which ripen in presence of external ethylene (Hamilton et al., 1990; Oeller et al., 1991; Picton et al., 1993). Similar results were obtained in other agronomic crops transgenic like melon and papaya (Kumar et al., 2014). Later metabolite SAM and ACC, precursors of ethylene biosynthesis was targeted to achieve delayed ripening. SAM methyltransferases regulates the levels of SAM, which methylate homocysteine to methionine. SAM hydroxylase breaks SAM to methyl thioadenosine and homoserine instead of *S*-adenosyl-L-homocysteine thus resulting in low level of SAM. Good et al. (1994) demonstrated the expression of the SAM hydroxylase in tomatoes fruit results reduced levels of ethylene and delayed ripening. On the other hand, the expression of prokaryotic ACC deaminase in tomato plant effectively decreases the available cellular ACC, which facilitates ethylene formation. The bacterial ACC deaminase protein is able to reverse the breakdown of ACC into α-ketobutyric acid and ammonia. Transgene expression of ACC deaminase enzyme in tomato resulted reduced ethylene levels that delayed ripening and enhanced post-harvest life (Klee et al., 1991). In apple, disruption of *MdACS3* gene using a transposon-tagging technique confers prolonged shelf life of fruits (Wang et al., 2009).

Respiration has huge impact on fruit shelf life. To elucidate the role of respiration on fruit texture and post-harvest sustainability, the levels of Krebs cycle intermediates were manipulated in tomato. The recent report of Centeno et al. (2011) revealed that malate and fumarate plays significant role in the post-harvest transpirational water loss. The upregulation of both malate and fumarate in the transgenic of tomato antisense *Malate dehydrogenase* (*MDH*) resulted enhanced post-harvest shelf life due to decreased amount of post-harvest transpirational water loss (Centeno et al., 2011).

Metabolic Engineering of Phytohormones to Improve Quality and Stress Tolerance

Improving Quality

The growth and development of plant is facilitated by hormones. The function of phytohormones in the tissue and organ differentiation was evident from the hybrids in Arabidopsis (C24/Col), where increased IAA level enhanced leaf cell numbers and reduced salicylic acid (SA) level promoted size of photosynthetic cells (Groszmann et al., 2015). The overexpression of Brassica gene shoot meristemless (STM) in Arabidopsis reduced the level of abscisic acid (ABA) and cytokinins, caused an enhanced growth of SAM and the ectopic meristem, which eventually reflected as lobed leaves, and increased number of reproductive organs such as flowers and siliques (Elhiti and Stasolla, 2012).

A recent work suggests cross talk between hormones during growth and development (Kumar et al., 2014). In tomato, inhibition of *AUXIN RESPONSE FACTOR 7* (*SlARF7*) can produce seedless parthenocarpic fruits (De Jong et al., 2009; De Jong et al., 2011). Similarly, suppression of *ARF4* and *GH3* genes, combined with high ethylene production in *AP2a* suppressed transgenic lines suggest ethylene mediated response of auxin (Karlova et al., 2011). Interestingly, non-climacteric fruits, such as grape and citrus are much more dependent on the ABA (Setha, 2012).

In tomato, suppression of ABA biosynthetic gene *9-cis-epoxycarotenoid dioxygenase1* (*NCED1*) results non-climacteric pattern of ripening due to low levels of ethylene (Sun et al., 2012a). In fact, ABA negatively regulates carotenoid levels in fruits. For example, ABA deficiency in *hp3, flc* and *sit* mutants of tomato causes over-pigmentation in fruits (Galpaz et al., 2008). Similar phenotype was evident in *SlNCED1* silenced transgenic tomato fruits, which accumulates high levels of lycopene and β-carotene (Sun et al., 2012a). In banana, ABA in coordination with ethylene promotes cell wall hydrolysis and fruit softening (Lohani et al., 2004), whereas in grapes ABA promotes fruit colouration and softening (Cantín et al., 2007). In non-climacteric fruits such as strawberry and grapes, ABA influences the flavonoid content, but in the ethylene dependent manner, because application of 1-methylcyclopropene (MCP, an ethylene inhibitor) delays anthocyanin accumulation. The role of ABA in flavonoid biosynthesis was confirmed through the rescue of colourless phenotype in *NCED* silenced strawberry fruits after exogenous ABA treatment (Jia et al., 2011). Likewise, methyl jasmonate enhances anthocyanin accumulation in the strawberry fruit peel by up-regulating phenyl-propanoid pathway related genes (*CHS, DFR, UFGT, PAL1, C4H, CHI* and *F3H*). In addition, MeJA and SA are also known to be involved in fruit softening (Srivastava and Dwivedi, 2000; Concha et al., 2013). Recent work of Liu et al. (2012) provides direct evidences for the role of jasmonate in carotenoid biosynthesis. The jasmonate deficiency in the tomato mutants *def1* (defective in the octadecanoid synthesis pathway) and *spr2* (*suppressor of pro-systemin-mediated responses2*) reduces the lycopene content due to downregulation of carotenogenesis (Liu et al., 2012).

Response to Stress

Mass spectrometry based plant metabolomics has geared up the evaluation of metabolite responses to stress (Jorge et al., 2016; Tenenboim and Brotman, 2016). For instance, ABA is recognized as the stress response hormone that signals shoot for anti-transpirant activities such as reduction of leaf size and stomatal closure during water deficit condition (Wilkinson and Davies, 2002; Davies et al., 2005) and facilitates deeper root growth by altering root architecture under scarcity of water and nitrogen deficiency (Spollen et al., 2000). ABA mediated drought tolerance in plants involves modulation of root aquaporins, and enhanced cell turgor pressure management by affecting the biosynthesis of antioxidant enzymes and soluble solutes (Chaves et al., 2003; Parent et al., 2009). The over expressing *NCED1* gene in tomato leading to stomatal closure during water deficiency confers tolerance against drought (Thompson et al., 2007). However, the increased stomatal closure in the *NCED1* over expressing transgenic line affects the overall carbon assimilation, which exerts a dramatic influence on the number of seeds. Therefore, the repercussions of the ABA-induced drought resistant in plant includes reduced crop yield, sterile pollen and seed dormancy (due to elevated levels of ABA) (Ji et al., 2011). As a remedy, use of drought inducible gene (*ABA3*/*LOS5,* in rice) and promoter (*era1*, in canola) increases the ABA level along with the crop yield.

The growth hormone cytokinin (CK), acting antagonistically to the senescence hormone ABA, and promotes proliferation and differentiation of cell or tissue, thus preventing premature senescence. Agronomic trait stay green (enhanced the photosynthetic activity) in drought tolerant genotypes allows accumulation of higher levels of CK in tissue and xylem sap. This CK accumulation promotes normal grain filling and limits premature leaf senescence (Borrell et al., 2000). Researches have used the CK biosynthetic gene *isopentenyl transferase* (*ipt*) for improving crop performance under drought stress. To date, *ipt* gene has been tested in many crop species such as rice, pea, tobacco and cassava for high yield under reduced irrigation (Qin et al., 2011). The grain productivity in barley and rice was reported to improve under limited water supply through enhancing CK content by attenuation of *cytokinin oxidase* gene (Ashikari et al., 2005; Zalewski et al., 2010).

Brassinosteroids (BRs) are new class of phytohormones that regulate a wide range of bio-physiological activities such as plant growth, root development, flowering and reproduction, seed germination, and biotic and abiotic responses. Arabidopsis was widely used to study the genotype to phenotype correlation in the BRs biosynthetic or signaling mutants. For example, the BRs mutants exhibit hypersensitivity to the seed germination inhibition exerted by the ABA, and the exogenous application of BRs rescues the low seed germination phenotype in gibberellin (GA) mutant (Vriet et al., 2012). Overexpression of *hydroxysteroid dehydrogenase1* (*HSD1*, encodes a putative enzyme in BRs synthesis) gene in Arabidopsis resulted reduced seed dormancy compared to wild type (Baud et al., 2009). Similarly, in Arabidopsis overexpression of *DWARF4* (*DWF4*) gene rescued the ABA seed inhibition phenotype (Divi and Krishna, 2009). Interestingly, the overexpression of *DRAWF4/CYP90B1* gene in crop plants such as rice registered a positive response with respect to agronomical traits. The overexpression *DRAWF4/CYP90B1* transgenic rice showed increased CO_2 uptake and enhanced photosynthetic efficiency, which increased the seed yield (Sakamoto and Matsuoka, 2008; Wu et al., 2008). The *CYP85A2* (encodes BRs biosynthetic enzymes) mutant confirmed the role of BRs in reproduction. The *cyp85a2* mutant exhibited phenotype similar to Arabidopsis mutant *seuss* because it lacks proper development of reproductive organs like ovule (Nole-Wilson et al., 2010). Furthermore, the downregulation of BRs in the maize *nana plant1* and *dwarf brassinosteroid-dependent1* (*brd1*) mutants result minimized male flowers (Hartwig et al., 2011; Makarevitch et al., 2012). Recently, disruption of *squalene synthase* (*SQS*) gene in rice by RNA-interference reduced the overall sterol content, including BRs, which reduced the stomatal conductance to provide drought tolerance during vegetative and reproductive stages (Manavalan et al., 2012). Apart from abiotic stress, BRs provides resistance against a broad range of diseases in potato, rape seed, rice, tomato and tobacco (Vriet et al., 2012). For example, the elevated levels of BRs in *Brassica juncea* improves the resistance against potent fungal pathogen *Botrytis cinerea* (Wang et al., 2012).

5-hydroxy tryptamine (serotonin) acts as neurotransmitter in animal system (Seo et al., 2008). Moreover, in plants, serotonin assumed as intermediate between tryptamine and IAA during auxin biosynthesis, but still more work and evidence is required to approve this hypothesis (Tivendale et al., 2010). Recently, the role of serotonin in senescence was demonstrated in rice leaf tissue (Kang et al., 2009). During senescence, leaf tissue synthesizes and accumulates high levels of serotonin to maintain cellular integrity. Additionally, inhibition of serotonin biosynthesis causes early senescence of leaf (Kang et al., 2009). Hence, serotonin could be used as a potential marker for senescence.

Biofortification Enabled Nutrient Enrichment of Crops

Enhancing the Level of Provitamin A

The deficiency of vitamin A causes night blindness, which can further result in complete blindness. Interestingly, β-carotene acts as pro-vitamin A, and it was targeted to reduce the deficiency of vitamin A. Considering rice as one of the major staple food especially in the Asian region; the supplementation of vitamin A via β-carotene was initiated by enrichment of rice endosperm to produce golden rice (Ye et al., 2000; Paine et al., 2005). This approach involved, upregulation of carotenoid biosynthetic pathways in rice endosperm, which includes transgene expression of *phytoene synthase* (*psy,* from daffodil and maize) and *phytoene desaturase* (*crt1*, from *Erwinia uridovora*) under endosperm specific Glutelin (Gt1). This resulted in an increase of up to 27 fold (37 μg/g) in the β-carotene levels in golden rice. Interestingly, transgene overexpression of three bacterial carotenoids biosynthetic genes *CrtB*, *CrtI*, and *CrtY*, encoding phytoene synthase, phytoene desaturase, and lycopene β-cyclase, respectively, resulted ∼40 fold increase of the β-carotene and

∼100–200 fold increase for total carotenoid (Diretto et al., 2010). Till date, several attempts have been made toward enrichment of β-carotene in important staple crop food species such as cassava, maize, potato and sweet potato (Martin et al., 2011; Tan and Zhao, 2017).

Enhancing the Level of Folates

Folates belongs to the class of vitamin B, act as Co-factors for C_1-metabolism (one-carbon transfer reactions) such as amino acid metabolism, nucleotide biosynthesis and the methylation cycle (Hanson and Roje, 2001). Deficiency of folate in human causes birth defect, increases cardiovascular disease and megaloblastic anemia. Plants are capable of biosynthesizing folate in mitochondria and plastids from pterins. Pterins are synthesized from guanosine-50- triphosphate (GTP) and *p*-aminobenzoate (PABA) (Hanson and Roje, 2001). The overexpression of folate biosynthetic gene *GTP-cyclohydrolase 1* (*GTPCH1*) in transgenic tomato enhanced the pterins content of ripe fruits, which resulted two-fold increase in the folate content (Díaz de la Garza et al., 2004). Recently, a transgenic lettuce expressing synthetic codon-optimized gene *GTPCH1* was generated, which had showed 2.1–8.5 fold higher levels of folate compared to non-transgenic plant (Nunes et al., 2009). However, previous attempts suggest 100 times increased folate content in the overexpression transgenic rice, which contains two transgenes from Arabidopsis, *GTPCH1* and *aminodeoxychorismate synthase* (*ADCS*) (Storozhenko et al., 2007; Dong et al., 2014). Naqvi et al. (2009) generated an elite inbred of transgenic Maize, in which, the kernel endosperm contained double amount of folate, six fold of ascorbate and 169 fold of β-carotene. Interestingly, they used four genes from different sources; *PSY1* from maize under glutenin promoter and *CRT1* from *Pantoea ananatis*, *GTPCH1* from *Escherichia coli* and *dehydroascorbate reductase* (*DHAR*) from rice under barley D-hordein promoter (Naqvi et al., 2009). Notably, the above mentioned leads are crop/genotype dependent, because transgenic lines of potato and Arabidopsis failed to accumulate higher levels of folate (Blancquaert et al., 2013). Hence, a better understanding of folate pathway is required, which could be useful and applicable to enhance the folates content in wide range of plant species.

Altering the Levels of Flavonoids

Flavonoids play an important role in the maintenance of fruit quality. It represents a huge family of secondary metabolites that consists of more than 6000 compounds (Hichri et al., 2011). The peel of fleshy fruits like grape and strawberry accumulates flavonoids such as anthocyanin, catechin, epicatechin, quercetin, kaempferol, myricetin, and isorhamnetin. Butelli et al. (2008), ectopically expressed the *Del*/*Ros1*gene (from snapdragon plant) in tomato under fruit specific E8 promoter. As a result, the fruits of *Del*/*Ros1* tomato transgenic lines accumulated substantial amount of anthocyanin (lycopene is the major secondary metabolite in cultivated tomatoes) due to the increased expression of anthocyanin biosynthetic genes (Butelli et al., 2008). Recently, the genetically engineered purple tomato was investigated to demonstrate the impact of anthocyanin (antioxidant) on prolonging fruit shelf life and resistance against fungal infection (Zhang et al., 2013b).

Altering Flavor and Aroma

The flavor and aroma of fruit are important and it influences the customer choices. Over the past decades, most of the research on fruit and vegetable crop species was mainly focused on the yield and resistance. Genome wide association mapping and metabolite assisted quantitative trait loci analysis has helped to fish out useful genes that confers aroma of rice grain (Daygon, 2016). The recent advancement in the field of metabolomics and the available metabolic network databases has fascinated researcher to focus on flavor and aroma. Breeding has long served toward improvement of flavor; however, it was dedicated more toward a balance between sugar: organic acid ratio and the post-harvest management (Jones and Scott, 1983). Recent studies on flavor and aroma include metabolic engineered tomato. The heterologous expression of *Clarkia breweri* plant S-*linalool synthase* (*LIS*) gene in tomato resulted accumulation of *S*-linalool and 8-hydroxylinalool at the ripe stage of fruit (Lewinsohn et al., 2001). In addition to *S*-linalool, the transgenic exhibited increased levels of geranial, limonene, myrcene, and β-ocimene, and a decrease in nor-isoprenes. Similarly, the metabolic analysis of fruits from the overexpression lines of tomato *alpha-Zingiberene synthase* (*ZIS*, encodes for sesquiterpene synthase) transgenic showed higher levels of alpha-zingiberene and other sesquiterpenes, such as 7-epi-sesquithujene, alpha-bergamotene, beta-bisabolene and beta-curcumene, whereas control fruit showed absence of sesquiterpenes (Davidovich-Rikanati et al., 2008). Zawirska-Wojtasiak et al. (2009) studied the aroma in transgenic cucumber. The GC/MS based study of transgenic cucumber expressing transgene preprothaumatin II gene under 35S promoter showed enhanced production of (E, Z)-2,6-nonadienal (Zawirska-Wojtasiak et al., 2009).

Fragrance of flowers is known to play multiple roles including attraction of pollinators and the interaction between plant and their surroundings. The ornamental plants like lisianthus (*Eustoma grandiflorum*) produces beautiful flowers, but these lacks floral scent (Aranovich et al., 2007). Transformation of lisianthus with *benzyl alcohol acetyltransferase* (*BEAT;* obtained from *Clarkia breweri*) under constitutive CaMV 35S promoter generated substrate dependent transgenic which produced 5–7 times higher levels of benzyl acetate (aromatic compound) when treated with benzyl alcohol (Aranovich et al., 2007). Interestingly, the recent report displayed the role of the aroma profile in stress tolerance. For example, *omega-3 fatty acid desaturases FAD3* and *FAD7* genes (involves in the conversion of C18:2 to C18:3, a precursor for hexanals and its derivatives) were over expressed in tomato to achieve cold stress tolerance (Domínguez et al., 2010). The overexpression transgenic tomato exhibited increased levels of 18:3/18:2 and (Z)-hex-3-enal/hexanal ratio with enhanced cold stress tolerance. Similarly, ectopic expression of aroma biosynthetic transgenes, such as strawberry *linalool/nerolidol synthase* (*FaNES1*) in Arabidopsis and potato, maize *terpene synthase* (*TPS10*) gene in potato, and *patchoulol synthase* (*PTS*) coupled with FPP synthase in tobacco was used to improve

defense management from plant pest (Dudareva and Pichersky, 2008).

Metabolomics to Cater Biofuel Demand

Burgeoning petroleum demand worldwide motivates researchers to explore renewable and alternative sources, such as biodiesel. In the current omics era, a refined understanding of biochemical pathways is being used to genetically improve biodiesel crop species, including jatropha, soybean, mustard, pongamia, algae, etc. The oil composition of the plant determines its quality. Currently, agronomical suitable jatropha (*Jatropha curcas*) is extensively grown as an alternative source of energy (Kumar et al., 2015). The oil content of jatropha seed is rich in polyunsaturated fatty acid mainly linoleic acid, which is vulnerable to oxidation and has negative impact on the quality. Silencing of *fatty acid desaturase* (*FAD2s*) in jatropha by Qu and colleagues significantly lowered the level of linoleic acid, while increasing the oleic acid content by 78%. To improve the yield and oil quality of jatropha under water deficient condition, three transgenics were raised by overexpressing genes *GSMT* and *DMT* (encodes enzyme catalyzes glycine betaine catalyses), *PPAT* (encodes an enzyme that catalyzes CoA biosynthetic pathway) and *NF-YBI* (encodes transcription factor NF-Y subunit) (Tsuchimoto et al., 2012). A range of candidate genes have been identified and characterized so far in jatropha, which are either involved in the metabolism of fatty acid or contribute to improve the seed oil content during stress. These genes include *PIP2* encoding aquaporin protein, *betaine aldehyde dehydrogenase*, *Δ6-fatty acid desaturase*, *ω6-fatty acid desaturase*, *ω3-fatty acid desaturase*, *diacylglycerol acyltransferase* and *long chain acyl coenzyme A synthetase* (Kumar et al., 2015). Similar to jatropha, castor is another excellent source of biodiesel because of its transesterified oil, which is soluble in alcohol without heating (Sujatha et al., 2008). Castor yield was improved by overexpressing the *Cry1Ab* gene, which provides resistance against feeders (Malathi et al., 2006). A non-transgenic method targeting induced local lesions in genomes (TILLING) was also used to increase the quality of caster seed oil by knocking out the gene that encodes ricin (alkaloid inhibits protein synthesis)[4]. The use of seed oil as biodiesel has been extended to many plant species such as coconut, cotton, mustard, pongamia, sunflower, etc. (Vaughn et al., 2009; Dwivedi et al., 2011; Lafont et al., 2015; Ortiz-Martínez et al., 2016; Saydut et al., 2016).

Photosynthetic water micro algae are also a rich source of oils that are mainly composed of unsaturated fatty acids. The simple cellular structure of these microorganisms, and their only dependency on CO_2, water and the sunlight for their rapid growth renders algal derived biodiesel more accessible than that obtained from higher plants. Attempts aiming at genetic manipulation of algae were undertaken to increase the oil content (Beer et al., 2009). The overexpression of *DGAT* (gene from the fatty acid biosynthetic pathway) in *Chlamydomonas reinhardtii*, however, produced unintended result, i.e., no increase for total fatty acid content (La Russa et al., 2012).

[4]www.arcadiabio.com

Biofuels are also obtained through fermentation of sugars yielding alcohol such as ethanol and butanol. In sugarcane, the load of sucrose, trehalulose and isomaltulose was obtained by overexpressing trehalulose synthase and sucrose isomerase (Wu and Birch, 2007; Hamerli and Birch, 2011; Arruda, 2012). Similarly, xylanases from bacterial and fungal source was expressed in crop plants such as barley, potato, rice, sunflower, and tobacco (Willis et al., 2016). Xylanases degrade β-1,4-xylan to pentose sugar, which can easily be fermented to alcohols. In addition, several other hydrolases (endo-Glucanases, cellobiohydrolases, β-glucosidases, glycosyl hydrolase etc.) were overexpressed to improve the biofuel availability from plants (Willis et al., 2016).

METABOLOMICS: AN INTEGRAL PART OF KNOWLEDGE-BASED PLANT BREEDING

The last decade has witnessed tremendous advancements in technologies followed by their deployment in understanding different facets of biology to understand the complex biology of desired traits. Knowledge-based plant breeding (KPB) utilizes all the meaningful information inferred from analysis of the large-scale data pertaining to genome, epigenome, transcriptome, metabolome, and proteome that collectively lead to a particular phenotype. The data generated from these 'Omics' approaches enable better understanding of the systems biology of the trait, so far mostly contributed by systems genetics and genomics, and to some extent transcriptomics. The other 'Omics' approaches, including metabolomics and proteomics have also started contributing toward generating important information, which can become an integral component of KPB, thereby strengthening the approach further for achieving higher genetic gain.

Technological advancement has contributed to improve the efficiency of plant breeding techniques via precise selection of desired plants. An easy access to the different 'Omics' platforms will cause a paradigm shift in breeding process by facilitating plant selections based on the genome-scale information generated at different levels of biological processes. The plant breeders will gradually embrace these developments, which in turn will help them to make informed decisions.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Advances in plant metabolomics in recent time has allowed the precise selection of desirable traits along with offering opportunities to undertake metabolic engineered plants. The shift of technology from single metabolite analysis to high throughput assays generating footprints of a variety of metabolites in one go has paved the way for discovery/construction of better models for metabolite networks, and the identification of robust biomarkers. In the last decade, the implementation of metabolomics in conjunction with other omics technologies

has not only uncovered a plethora of known as well as novel metabolites, but also allowed to determine their specific contribution toward improving key plant attributes such as quality, yield, shelf life, etc. To this end, high throughput genotyping/sequencing platforms based on NGS technology has been a tremendous support as a cost-effective and high-throughput means to elucidate the architecture of metabolic traits. The newly created avenues such as GWAS, GS and EWAS that allow efficient integration of metabolite profiling could provide a great impetus to metabolomics assisted breeding. We anticipate that the integration of metabolomics and the other omics tools greatly improves the ability of a plant breeder in order to design and develop agronomically superior plants, thus enabling rapid development of high-performing crop genotypes that adequately meet the challenges of 21st century agriculture.

AUTHOR CONTRIBUTIONS

RK, AB, MKP, and AK designed the article. RK and AK wrote the article. AB, AP, RK, and MKP corrected the article and finally all authors read and approved the final article.

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