Metabolomics: A Potential Tool for Breeding Nutraceutical Vegetables

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Abstract

Plant breeding has been quite successful to keep up with the food requirement of every growing world’s population. The new challenge for plant breeders is to incorporate human health benefits in plant based foods, also called as nutraceuticals. With the recent technological advancements in biological sciences and instrumentation, nutraceutical breeding is becoming easier. Metabolomics is a key technology available to plant breeders that can combine with existing technologies to breed healthier plant food. Onions is a widely-grown crop that has tremendous health benefits. The health benefits of onions are due to secondary metabolites. In nature, plants produce secondary metabolites in low quantities. The use of metabolomics to determine production mechanisms of secondary metabolites would help develop onion cultivars that contain high levels of secondary metabolites.

Keywords: Allium cepa; Metabolomics; Nutraceuticals; Breeding tools; Secondary metabolites

Emerging science of Metabolomics

A metabolome is the entire set of metabolites produced by any organism in its life. The study of the metabolome, known as ‘Metabolomics’, describes biochemical processes and underlying biological roles of metabolites in an organism [1,2]. Unlike genes and proteins, we cannot read metabolites in a linear form with computers. The structure of metabolites is complicated due to the order and stereo-chemical orientations of atoms [1]. Levels of plant metabolites change due to genotypic and environmental interactions. Although, genes contain information for metabolite synthesis; production of metabolites can be triggered by growth stages and environmental factors, such as, light, temperature, humidity, soil type, fertilizers, pests, and pesticides, etc. [3]. It is not possible to collect and analyze the metabolome of any plant; however, ‘metabolic profiling’ can analyze a subset of metabolites at any given time or stage of plant growth [4-5]. Our current knowledge about end products of genes, their interactions, and regulation is limited, but increasing rapidly [6,7]. Transcriptomics, proteomics, next generation sequencing, and bioinformatics are revolutionizing our understanding of genes and their functions. Putative functions for several new sequences of nucleotides and amino acids were assigned based on homology [1]. Metabolomics identifies the functions of putative genes and their associated proteins that are involved in metabolism [8]. Plants produce thousands of metabolites at any given time that cannot be distinguished into a phenotype. Unbiased differentiation of genotypes based upon their metabolic profile is possible with the help of metabolomics [9]. In certain cases, where measurable phenotypic changes are observed among genotypes, the study of biochemical causes and the consequences of metabolic pathways in different phenotypes are possible through metabolomics [9]. In agriculture, metabolomics could be used to increase specific metabolic fluxes for increasing nutritive and pharmaceutical value in plant based food, and decreasing pesticide sprays on crops [1]. The ultimate goal of metabolomics is to understand and predict the functions of metabolism along with its cellular networks. Metabolomics offers immense potential for understanding and solving complex biological systems [2]. Although, some techniques of metabolomics were discovered four decades ago, its’ importance was understood only in the last decade of the post-genomic era. Genomics, proteomics and metabolomics provide new tools to the plant breeder for breeding nutraceutical crops. This review will provide some insight on metabolomics, problems of human nutrition, nutraceuticals, secondary metabolites of onions, and the latest tools for plant breeders regarding nutraceutical breeding that utilizes a system biology approach.

Natural Remedy for Human Health: Nutraceuticals

The world is facing a dichotomous problem of food malnutrition i.e., over- and under-14 nutrition of human beings in developed and developing nations, respectively [10]. The majority of people in developed nations are suffering from obesity, diabetes, and coronary heart diseases due to the excessive intake of calories [11]. Deficiency of vitamins, minerals, and sometimes absence of food is the primary concern in developing nations [11]. A close inspection reveals that both of these circumstances are related to an imperfect diet. ‘Functional foods,’‘nutraceuticals’, or ‘bio-protective foods’ are bioactive, natural compounds beyond the traditional nutrients for health enhancement or disease prevention in humans [10,12,13]. Nutritional genomics uses high throughput genomic technologies for nutritional research and development of nutraceuticals, with a better understanding of the complexities between the human genome and diet [10,12,14]. Understanding interactions between human genes and diet will pave the way for future development of personal nutrition [14]. Several nutraceutical foods with increased amounts of vitamins (A, B, C, E), bioflavonoids, isolavones, antioxidants, lycopene, folic acid, pigments, healthy plant oils, decreased toxins, and edible vaccines are either available for the market, or will be available soon [15-17]. The current science does not provide definitive answers on the impact of secondary metabolites on human health, but new emerging techniques such as single cell metabolomics [18] motivates the scientific community for gaining deeper understanding.

Importance of Secondary Metabolites

The basic needs of plant survival, growth, and development depend

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upon the synthesis of primary metabolites, such as, amino acids, organic acids, phyto-sterols, acyl-lipids, etc. However, the ecological needs of a plant depend upon the production of secondary metabolites, such as, pigments for attracting pollinators and seed dispersal agents, protection against pests, survival in specialized ecological niches, etc. [1,19,20]. Plant secondary metabolites are highly diversified and are present in more than a quarter million forms [19]. In a single plant species, a few thousand secondary metabolites could be observed easily during metabolic profiling. Four major groups of secondary metabolites are: terpenoids, alkaloids, phenylpropanoids, and sulphur containing metabolites [3,19]. Terpenoids, compounds comprised of five carbon molecules, are the most common secondary metabolites in plants. There are several types of terpenoids present in the plants, such as, monoterpenes (C10 – volatile essence and essential herbal oils), sesquerpenes (C15 – phytoalexins, antibiotics), diterpenes (C20 – phytol, giberellic acid), triterpenes (C30 – toxins, waxes, brassinosteroids), tetraterpenes (C40 – carotenoids), and polyterpenes (plastoquinone, ubiquinone, latex). Terpenoids are usually associated with specialized structures, such as, glandular trichomes, secretory cavities, petal epidermis, resin ducts, etc. Overall, terpenoids contribute to plant aroma, flavor, color and defense mechanisms against pests. Another important group of secondary metabolites is alkaloids that are nitrogen-containing, basic compounds, such as, codeine, chloroquine, and tropicamide, and are useful as purgatives, sedatives, and several other medicinal purposes. Alkaloids also build a plant’s constitutive defense mechanism against insects by synthesizing products, such as, Morphine, caffeine, nicotine, etc [19]. Phenylpropanoids are a third group of secondary metabolites in plants that use the shikimic or malonate/acetate pathway for synthesis, and are responsible for defense against pests, color, flavor, taste, wood, and bark production for durability, etc. Lignins, suberized tissues, flavanoids, furanocoumarins, stilbenes, etc. are various types of products from phenylpropanoid pathways. Lignans, lignins and suberized tissue provide woody strength to plants and help in cold acclimatization [3]. Flavonoids are present mostly in plant vacuoles and provide pigments (anthocyanins), protect from ultraviolet rays (kaempferol), act as signal molecules between different metabolic pathways, and are helpful in plant defense. Flavonols, such as, querctin, coumarins, and stilbenes are mainly associated with antimicrobial, antifeedant and nematicide properties [19]. Sulphur-containing secondary metabolites (glucosinolates) are natural insecticides because tissue disruption converts them into different forms of thiocyanates [19,21]. Our diet contains thousands of secondary metabolites depending upon the amount and variety of plant origin food. Secondary metabolites may have potential for health benefits in human beings [22], but studies designed to measure their efficacy have proven challenging and are in need of more work. Some of the potential human health benefits of secondary metabolites include modulation of the immune system, anti-inflammatory, anti- cancer, anti-viral, anti-bacterial, anti-toxic, hepatoprotective, anti-oxidant, anti-estrogenic, anti- atherosclerosis, and cholesterol reduction [3,16,19]. Fatty acids are precursors of human prostaglandins and leukotrienes that are essential components of the immune system with the help of plant sterols [3]. A wide range of plant originated vegetables and fruits are abundant sources of secondary metabolites [23-25] used tomato as a model vegetable crop to understand the nutritional value, and basic understanding of plant physiology through extensive metabolomics tools and system biology approaches. Different fruits and vegetables provide specific secondary metabolites that are unique to their family or species. The present manuscript focuses specifically on onions to illustrate the value of secondary metabolites, and use of contemporary approaches to nutraceutical breeding.

**Onions – a Great Source of Secondary Metabolites**

Onion is one of the oldest domesticated crops in the world, and is the third largest vegetable crop after tomato and cabbage in volume [26]. Onions are cultivated both in tropical and temperate regions, and its germplasm offers enormous variability in horticultural and nutritional traits. The quality of onions for nutrition depends upon the composition and functions of metabolites. Onions produce several secondary metabolites, such as, flavons (quercitin), flavnoids (kaempferol, luteolin), lignans (lariciresinol), α-tocopherol, quinon (phylloquinone, vitamin K), sterols (campesterol), saponins (tropoeides,ascalconicosides), sapogenins (gitogenin, doisgenin, β-chlorogenin, cepagenin), dialylsulphides, cysteine-sulphoxides, thio-sulphinates (zwiebelanes), vanillic acid, and cinnamic acid [3,27-30]. Diets rich in saponins and sapogenins reduce cholesterol levels, stimulate the immune system, are anti-fungal, anti-tumor and prevent cancer [3,27]. Diets rich in flavnols and flavnoids possess anti-HIV properties, lower LDL cholesterol in blood, and neutralize free radicals to reduce the risk of cancer [28,29]. Dialyl sulphides in onions may reduce LDL cholesterol, and decrease the risk of cancer and heart diseases [31,32]. Thioulate diet are anti-asthmatic and reduce platelet aggregation activity [27]. A diet rich in quinon controls blood clotting and helps the formation and repair of bones [3]. Antioxidants present in onions may protect cells by regulating DNA repair mechanism [33]. Overall, onions possess a vast array of secondary metabolites, and plant breeders could potentially develop nutraceutical onion cultivars. Traditional breeding efforts have improved the horticultural traits of onions tremendously. However, breeding for nutraceuticals needs metabolic screening and therefore, integration of metabolomics with traditional breeding is needed for releasing new cultivars with nutraceutical properties. Modified breeding programs could reveal the hidden biochemical variation for targeted crop improvement and better quality products.

**Emerging Technologies – Tool Kit for Plant Breeders**

The use of molecular markers in traditional plant breeding is increasing rapidly. The identification of new molecular markers for quality traits requires a thorough understanding of the biochemical basis of intricate pathways for metabolites. The integration of metabolomics with genomics will provide new molecular markers of quality traits for marker assisted selection in existing breeding programs. Conventional breeding practices face challenges to produce cultivars that possess both better quality and abundant quantity. While wild progenitors are rich in several metabolites, existing cultivars show lower quantities. The poor nutrition value of existing cultivars is a result of continuous breeding for higher yield, easier processing, and pest resistance [34]. In a typical plant biochemical pathway, a single precursor synthesizes multiple metabolites. So the presence of a precursor does not assure the synthesis of any specific metabolite [35]. Several plant biochemical pathways cross-talk for effective regulation of cellular processes in an organism. An end product of one pathway becomes the precursor or intermediate substrate for another pathway. Furthermore, a single enzyme affects several biochemical pathways. Therefore, a single point mutation could lead to significant changes in a metabolome [29]. Alteration in one pathway could potentially change the flux in non-target metabolites [15]. Quality-enhancing metabolites are often governed by quantitative trait loci, and epistatic interactions make a major contribution to these phenotypic variations [36,37]. The diversity in quality-enhancing metabolites in plants, not only comes from genes, but also from divergent, substrate-specific enzymes and sub-cellular, non-enzymatic activities [38].

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Metabolomics-assisted Breeding

A plant breeder needs new tools for enhancement of crop quality. Metabolomics-assisted breeding, in conjunction with genomics and proteomics, offer such tools for nutraceutical breeding. Techniques, such as, mass spectrometry, nuclear magnetic resonance spectroscopy, chromatography, etc., have been utilized to study the impact of time, stress, and environmental conditions and to analyze hundreds of metabolites simultaneously [35]. In a recent review, Allwood and coauthors described several mainstream and specialized techniques of metabolomics plant analyses [24]. This enormous amount of information could be utilized to bio-refine current cultivars by applying selection pressure, and to optimize nutraceutical breeding. Instead of monitoring a single putative bioactive metabolite, hundreds of biosynthetically-related metabolites and enzymes could be analyzed by metabolic profiling; which in turn could be used to develop stable genotypes for nutraceutical cultivars [35]. Transcription factors play a major role in secondary metabolite biosynthesis and offer new hope for nutraceutical breeding through their integration into marker assisted breeding [15,29]. Many people have concerns about transgenically-enhanced foods due to the potential and perceived risks of epistatic transgenes [39]. The use of intragenic and famigenic techniques, in conjunction with metabolomics, offers immense potential for nutraceutical breeding to obtain greater acceptability in the market [36]. The development of hybrid cultivars instead of open-pollinated cultivars could potentially increase certain metabolites without any yield decrease [37]. Recent estimates of metabolite heritability are 25-35%, encouraging future breeding efforts with metabolomics [37]. The presence of gene co-suppression and inherent feedback metabolic loops for maintaining homeostatic nutrient levels in plants, pose problems in increasing expression levels of anabolic biosynthetic genes [40]. New techniques for decreasing catabolic enzymes and anti-nutritional compounds are therefore required for nutraceutical breeding. RNAi techniques show potential for developing nutraceuticals by shutting down specific pathways related to the production of toxins and other undesirable substrates [29], summarized the achievement of ‘omics’ technologies on 20 most important agricultural crops, including onions. With these rapid advancements, the future of various ‘omics’ looks brighter for developing healthy food for our growing populations. Drought and salt stresses were found to be associated with increased secondary metabolites in onions, which suggest potential for developing nutraceuticals for areas with stress-affected soils [41]. Sweet onions like Vidalia®, are popular among consumers, although low in sulphur-containing secondary metabolites. Recent experiments demonstrated that a RNAi technique decreased the production of the lachrymatory factor, which eventually leads to increased amounts of zwiebelanes. Zwiebelanes belong to thiolsulphinates and possess anti-platelet aggregation, sensory, and health promoting benefits to human beings. Several precursors of the γ-glutamyl peptide pathway in onions are unstable, and degrade before converting sulphur into metabolites [42]. A range of potential sulphur-containing nutraceuticals could be developed in onions by altering the γ-glutamyl peptide pathway to make stable metabolites.

Future of Plant Breeding – a System Biology Approach

Targeted metabolic profiling could be applied to identify onion cultivars that possess desirable levels of nutraceuticals. The future of nutraceutical breeding is bright for most cultivated crops, including onions. Scientists are gradually appreciating the integrated approach of ‘system biology’, where genomics and metabolomics are coupled to study the organism at a cellular and organ levels and describe networks of biological regulation in a most inclusive way. Although basic research work on human health in relation to consumption of secondary metabolites remains unclear; many new scientific discoveries provide hope for health benefits through increased consumption of nutraceutical cultivars. Plant breeders will benefit from a system biology approach to develop nutraceutical cultivars for improvement in overall human health. The collaborations between public and private crop breeding institutions, with human health research centers would play a key role in the success of this endeavor.

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