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Improving the nutraceutical content of tomato (*Lycopersicon esculentum*) by advanced environmental conditions and

agricultural practices

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Abstract

The consumption of tomatoes has been associated with diminishing the risk of several lethal diseases, e.g., heart attack and cancer. This is because tomato contains high antioxidants that have been shown to protect against oxidative damage in numerous empirical and epidemiological studies. Considering the health benefits, more emphasis should be given to produce organic tomatoes. Tomatoes have been ranked as the most important fruit and vegetable in Western diets as essential source of antioxidants such as lycopene, β -carotene, phenols, vitamin E, and vitamin C. Environmental conditions and agricultural practices are key factors that affect the quantities of these compounds available in tomato. Therefore, controlling the environmental conditions, such as water availability, temperature, light, saline soil, and agricultural practices (fertilization practices, harvesting, and food storage) are valuable tools to enhance the nutritional value of tomato fruits organically. Although, the quantitative and qualitative contents of health-promoting compounds in vegetables and fruits depend on their genetic predispositions. Agricultural practices and different environmental condition have broad effects on the nutraceutical compounds. Thus, this present study emphasizes on enhancing tomato nutrition through improved agricultural practices and optimized farming, especially in saline and water-deficit conditions. This organic-oriented strategy may counteract the scepticism caused by genetically modified tomatoes (GMOs) and will prompt further exploration in future studies.

Introduction

Tomato (Lycopersicon esculentum) is an economically important crop consumed in both forms, fresh as in salad or processed food such as tomato paste and ketchup. It ranked first among vegetables in terms of cultivated area grown on 4.85 million hectares worldwide annually (FAOSTAT, 2019). The tomato gained in importance worldwide due to its nutraceutical value originating from the high content of carotenoids, such as β -carotene (provitamin), other vitamins such as vitamin C and E, tocopherols, phenolic compounds such as flavonoids and derivatives of hydroxycinnamic acid [1-4]. More importantly, tomato is a rich source of antioxidant that can further categorized into lipophilic (carotenoids and vitamin E) and hydrophilic (vitamin C and phenolic compounds) fractions [5]. Essential nutritional compounds that were identified in tomato puree are listed in (Fig.1, Table 1). The human blood contains an average of 40 different carotenoids with 9-20 of them derived from processed and fresh tomato as the main source of [6]. The major carotenoids are lycopene, α - and β carotene, β -cryptoxanthin, zeaxanthin and lutein.



Parameter	Value	
Energy (KJ)	215.0	
Protein (g)	2.3	
Fat (g)	0.5	
Carbohydrates (g)	9.5	
Vitamin C (mg)	31.2 ± 3.9	
Vitamin E (mg)	1.2 ± 0.1	
Lycopene (mg)	14.2 ± 8.1	
β -carotene (mg)	2.3 ± 4.7	
Lutein (mg)	0.4 ± 0.1	
Chlorogenic acid (mg)	8.9 ± 0.8	
Rutin (mg)	6.0 ± 1.7	
Naringenin (mg)	5.5 ± 0.3	
Zinc (µg)	569.8 ± 75.9	
Copper (µg)	459.6 ± 36.7	
Selenium (µg)	1.3 ± 0.2	

Figure 1: Nutritional profile of tomato fruits (per100 g fresh matter).

Table 1: Composition of tomato puree (per 100 g fresh matter).

Bioactive compounds of tomato have numerous health benefits since they work anti-inflammatory,

antimicrobial, vasodilation, antiallergenic, antithrombotic, and they have protective functions against cardiovascular diseases and antioxidant effects [8,9]. Currently, there is a growing demand to increase the health promoting compounds in tomato fruits in order to improve its nutraceutical content [10]. Many health professionals recommend to increase the amount of dietary antioxidants via the consumption of fresh tomatoes and tomato products [11]. Recent advancements have focused on enhancing these beneficial compounds in tomatoes through metabolic and genetic engineering or breeding approaches [12,13]. Despite these efforts, breeding remains challenging due to the intricate nature of gene interactions requiring quantitative genetic approaches to identify relevant genes and quantitative trait loci (QTLs) [14]. Besides breeding efforts, the nutritional value of tomato can be improved by optimal environmental growth condition with integrated management of new agricultural practices as synthesis of nutraceutical components is regulated by many physiological and environmental signals. Therefore, this study focuses on the factors effecting the bioactive and health promoting compounds and how their quantity can be increased by integrated management and agricultural practice.

There are many factors that affect the nutritional value of tomatoes such as selection of the genotype, water availability, saline soil, agricultural practices, harvesting and storage of the tomato fruit.

Methods

Literature search strategy and selection criteria

This review incorporates information from highly reputable publications in SCI indexed journals, along with databases including AGRICOLA, AGRIS, SCOPUS, Web of Science, PubMed, ResearchGate, and others. The focus was on papers published in the last decade. Robust search platforms like Google Scholar, Microsoft Academics, and Worldwide Science were instrumental in sourcing suitable research material online.

Discussion

Genetics

In recent years, seed producing companies have bred new varieties of tomato with different colour and fruit sizes to meet consumer demands without paying attention to the nutritional value of the fruits. Different genotypes have different percentage of bioactive compound, especially the activity of antioxidant is highly affected by the variety. One study analysed 16 tomato varieties and found that long shaped tomatoes had significantly less antioxidant activity than round shape tomatoes [15]. Generally, smaller tomatoes tend to have higher vitamin C

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content, while cherry tomatoes, with their greater skinto-volume ratio, may have elevated flavonoid levels concentrated in the skin. Commercial processed tomato products typically exhibit higher carotenoid content such as lycopene, compared to cherry, cluster, and salad tomatoes [16-19]. Among fresh tomatoes, cherry tomato varieties contained the highest lycopene levels, followed by cluster and round tomato genotypes [20]. Considering these studies, it can be concluded that preference should be given on round shaped and small sized tomatoes as they contain more health promoting bioactive compounds. Therefore, by low consumption of tomatoes, the cherry tomatoes should be favoured since they contained more antioxidants (lycopene) and flavonoids.

The colour of tomato is also link with high carotenoids content as food ripening include the synthesis of carotenoids especially lycopene (90%) and β -carotene which ranged from 5 to 10% and also some minor carotenoids such as lutein and phytoene [3,21,22]. The orange colour of is mainly due to the high content of β -carotene [22]. Therefore, the colour of different genotypes is considered as an indirect measure of some nutritional content of tomato. Thus, red and orange tomatoes have good nutritional value and can be used for the selection of genotypes with the desired nutritional content (Fig. 2).



Figure 2: Nutraceutical contents of tomato based on the size and colour of the fruit.

Based on size and shape, the small and round size fruits are considered highly nutritious as they are rich in Vitamin C and lycopene content. Based on colour, both orange and red tomatoes are highly nutritious.

Environmental conditions

Under field conditions, crop plants encounter various environmental stresses that impact both yield and fruit quality. In general, under stress conditions, plants generate active oxygen species (AOS) such as superoxide radicals, hydroxyl radicals, hydrogen peroxide (H_2O_2), and singlet oxygen [23,24]. To cope with this stress conditions plants have developed several mechanisms to mitigate the damage caused by these AOS. These mechanism include increasing level of antioxidants such as ascorbate, α -tocopherol, carotenoids and glutathion to scavenge the AOS [25,26]. Biotic stresses such as drought, salinity, light conditions and extreme temperatures can severely modify the crops nutritional quality for human consumption. These forms of external stress are becoming steadily more important because it affects the plant mineral status which in turn effects the nutritional quality of a given crop [27] (Fig.3).



Figure 3: Effect of environmental conditions on nutraceutical contents of tomato.

It is observed that the lycopene content of tomato fruits has increased significantly under saline conditions until the threshold level (4.4 dS m-1) is reached. Controlled irrigation mimics drought-like conditions which improves the nutritional content of tomatoes. The increase in temperature to 26-30 $^{\circ}$ C increase the sweetness of tomato. High intensity and red light increase the lycopene and vitamin C content in tomatoes.

Salinity stress

Interestingly, salinity can have positive effects on the nutritional quality of tomatoes. It's commonly acknowledged that tomato fruits grown under moderately saline conditions tend to be of superior quality. Notably, this heightened electrical conductivity (EC) environment often leads to a substantial boost in lycopene levels. Studies have found an increase in lycopene concentration in tomato fruits under saline condition (43 mg kg⁻¹ for EC 3 dS m⁻¹ to 58 mg kg⁻¹ for EC 10 dS m⁻¹) on a fresh weight basis [28]. Another study noted a pattern where lycopene content in tomato fruits (on both fresh and dry weight bases) progressively rose up to a 4.4 dS m-1 treatment and then began to decline (Table 2). This is inline withnumerous other studies, suggesting that salinity stress can enhance lycopene content in tomatoes [29]. However, it is noteworthy that the increase in total

lycopene was highly dependent on the specific cultivar, with ranges from 34 to 85% under high EC conditions [30]. Increasing the EC can be achieved through adding NaCl to a nutrient solution or by inducing water stress via restricted irrigation, which subsequently amplifies the nutrient concentration [28, 31]. However, an increased EC leads to the improvement in nutritional quality of tomato fruits as one of the studies found the positive correlation of increased EC with vitamins C content (from 97 mg kg⁻¹ to 101 mg kg⁻¹ under EC of 3 dS m⁻¹ to 10 dS m⁻¹) in tomatoes [32]. Genotypes with high nutraceutical content are of special interest for utilization of saline soil to obtain the tomatoes with increased level of health promoting compound. Additionally, these tomatos varieties will be a good source to utilize the saline soil, which cannot be utilized for other crop production [33].

EC level (dS m ⁻¹)	Lycopene	
	(mg 100 g ⁻¹ fresh weight)	(mg/fruit)
0.5	5.89	6.11
2.3	8.31	8.15
4.4	10.22	9.15
8.5	7.88	6.55
15.7	6.71	4.22

 Table 2: Impacts of Electrical Conductivity (EC) levels on the lycopene content in tomato fruits.

Although until now the exact mechanism about the enhancement of lycopene content under high EC condition has not been clearly understood, evidences suggest the basic role of ethylene synthesis that is activated under water and salt stress conditions [32]. Giuliano et al. (1993) suggested that the increased level of lycopene in tomato fruits grown under saline conditions could be due to stress- induced upregulation of the genes that are involved in the biosynthesis of lycopene [35]. However, this increase in lycopene content is up to a certain limit as the excessive salinity causes the reduction in lycopene content. This could likely be attributed to the stressinduced suppression of lycopene production, as stressful conditions lead to decreased leaf coverage, resulting in more fruits being directly exposed to sunlight in plants under salt stress [34]

Water availability

Drought is a major environmental stress that severely affects the agriculture sector [36,37]. Plants diminish drought effects by changes in the morphological, physiological and biochemical system. Tomato plants are very sensitive to drought, which is due to its limited tolerance against this stress [38]. Beside deficiency and poor quality of water affects the yield and quality of tomato crop [39]. Specifically, water deficits negatively affect dry matter content, as plants expend considerable energy on dehydration processes. Furthermore, low water availability also affects the soluble solid contents and also reduces the sugar level in the fruit. On the other hand, many other problems are associated with low availability of water such as small size fruits, lower yields, early senescence of the plants, and higher disease susceptibility [40]. In addition, high water availability for the plants has positive affect on the colour parameters of the fruit and consistency (Bostwick index) (Fig.3). While less frequent irrigations have a positive effect on the content of ascorbic acid [41]. All these studies clearly demonstrate how important an adequate amount of water is to produce the quality and quantity of tomato fruits. Interestingly, Favati et al. (2009) indicated that combining the amount of water and irrigation periods in various water regimes improved the nutraceutical content of tomato fruit, especially the antioxidant content [42]. However, there are not many studies available on the effect of irrigation practices on tomato fruit quality and such studies are required in future to mitigate the challenges of water scarcity affecting the quality of tomato fruits.

Interestingly, the low quality of irrigation water seems to have positive effects on nutritional quality of tomato fruit as in one of the studies it was observed that β -carotene content of tomato was increased as irrigation water quality is decreased [24]. This is possibly due to the decline in plant water content which in turn leads to the increased concentration of β - carotene. In another study, it was found that lycopene content and other quality parameters were increased when tomato was grown in moderately saline conditions [34] Furthermore, it was also observed that excessive water or flooding stress causes a decrease in fruit lycopene content [43]. Similarly, in red and pink cherry tomatoes, total carotene and the amount of lycopene increased in response to drought [31]. Therefore, reduction in water supply can increase the phytochemicals contents. It has also been shown that higher antioxidant was produced when plants experienced drought-like conditions imposed by deficit irrigation practices [41]. From all the studies, it can be concluded that less water or drought like conditions and low quality of water can enhance the tomato fruit quality. However, more studies are required to mitigate the challenges of water scarcity and use this less water supply condition effectively.

Temperature

Optimal temperature is another environmental condition that effects the development and quality of tomato fruits [44]. Conditions of temperature play a main role in the development and quality of tomato fruits effecting directly the final size and colour [16]. Temperature has been attributed as a factor influencing the distribution of photo assimilates between

vegetative parts and fruits [16]. The optimal development of a tomato requires different ranges of temperature like suitable temperature at germination stage is from 16 °C to 29°C, the growing stage is from 18°C to 28°C and at fruit set stage is from 14°C to 24°C [45]. Variations in fruit temperature during fruit ripening can impact the biosynthesis of carotene and vitamin C biosynthesis [46-49].

The lycopene seems to be high at 24°C during the day and 14 °C during the night [45]. When the temperature range is between 26° C and 30° C the sweetness of tomato is enhanced. But when temperature exceeds above 30 °C the sweetness is reduced due to high evapotranspiration rate which in turn reduces the biosynthesis of carbohydrates [50]. Moreover, with increase in temperature above 30° C inhibits the biosynthesis of lycopene which in turn cause the change in colour from yellow to orange. In another study, it was found that the total carotene content was reduced with an increase in temperature from 21 to 26°C without affecting lycopene content. While the increase of temperature from 27 to 32 °C reduced ascorbate, lycopene, and its precursor's content [51]. Another study supports this evidence that high temperature reduce the lycopene, vitamin C, and sugar content in cherry tomatoes. In short, there are different optimal needs of temperature at different growth stages but temperature above 30 °C will affect the yield as well as the nutritional quality of tomato fruit (Fig. 3).

Light Intensity

Light affects the growth of tomato plants and quality of its fruits. Light intensity positively influences lycopene content For instance, one study demonstrated that lycopene development can be enhanced at lower temperatures with increased light exposure [52]. However, when green tomatoes were exposed to 650 Wm⁻² of light for 1.5 to 4 hours, lycopene synthesis was significantly repressed, indicating that intense solar radiation can inhibit lycopene production. It was observed that radiation and intense light condition causes the injury to tomato fruit and this might be due to the general effects of overheating on plant tissues [46,53]. Light quality also affects lycopene synthesis in tomatoes. The quality and intensity of red light positively impact carotenoid synthesis in detached mature-green fruits, and this effect is independent of temperature[54]. Moreover, Alba et al. (2000) found that treating mature-green fruit with brief red light helped to accumulate the lycopene content by 2.3-fold during fruit development [55]. However, this red light induced lycopene accumulation was reversed when plant was exposed to far-red light.

In addition, light exposure is also favourable to accumulate vitamin C as in one of the studies, significant differences were found in vitamin C content in tomato fruits in response to exposure of intensity of light for several days before harvest [46,56]. Generally, the lower light intensity leads to the reduction of vitamin C in plant tissues and increase exposure to light causes increase concentration of vitamin C, particularly in leafy greens [57, 43, 58]. Thus, it can be anticipated from the above studies that shading (by leaves or any artificial covers) can decrease the vitamin C content and thus reduce the nutritional quality of tomato fruits [59,60] . So, it has been found that greenhouse-grown tomatoes have lower vitamin C levels than those grown outdoors [61]. To summarize, it can be concluded that more exposure to light with moderate intensity can enhance the nutritional quality of tomato fruits (Fig.3).

Agricultural practices

The agricultural practices include all processes such as ploughing, levelling manuring, harvesting, and storage which are applied in farm production systems to get agricultural products. The yield and nutritional quality of food are highly dependent on cultivation practices and agricultural production systems (conventional and non-conventional). One of the studies demonstrated the effects of agricultural practices (sowing, ploughing, levelling and manuring, etc.) on final quality of tomato vield. However the discussion remains open whether the organic foods have a higher healthful nutritional value when compared with traditionally produced food or not. In this regard, a study showed that the tomato yield and some quality characteristics of fruit were influenced by cultivation system and this influence varies between cultivars [38]. The effect of production system in some cultivars was very clear on fruit soluble solids, titratable acidity, pH. While no significant effect was observed on total phenolics and lycopene in all cultivars [62]. In another study, significant differences in lycopene and naringenin content have been observed in tomatoes grown organically compared to those produced through conventional methods [63]. One study examined the impact of two different production systems on the final quality of tomato fruits. It was found that the 'Burbank' variety had significantly higher total phenolic content under organic management compared to conventional practices. However, the phenolic content of the 'Ropreco' variety did not differ significantly between the two management systems [64]. These results suggest that the selection of tomato variety is crucial in determining the outcomes of comparative studies, even when the same variety is grown under different farming systems. Similarly, another study showed that there is You're reading

no significant differences in quality of fruits (colour, soluble solids, pH and acidity), bioactive and antioxidant (lycopene, β -carotene, total phenolic and ascorbic acid) compound when growing in both farming systems [65]. From these studies it can be concluded that there is no effect of agricultural practice systems (conventional vs organic) on nutritional quality of tomato fruits. Both systems are equally important for good quality of tomato fruit.

Fertilization Practices

Soil fertility and implication of fertilizer have significant influence on tomato quality. Good quantity and high quality fruits require the optimum supply of all the necessary elements needed for plant growth [34]. In recent years, diversify and enhance fertilization practices have been adopted to boost the nutritional quality of tomatoes particularly their antioxidant content. Tomatoes can grow by using organic as well as traditional fertilizers. Such comparison between conventional and organic agriculture should be of great importance because in both agricultural systems the amount of supplied nutrient are not same. Typically, traditional fertilizers provide nitrogen (N) in a form that is better available to plants better than organic fertilization. The N accessibility is likely affecting the synthesis of phenolic antioxidants and soluble solids. Interestingly, excessive availability of nutrient in soil has some negative effects on fruit quality. One of the studies showed that there is a decrease in phenolic and antioxidants content in plants when the nutrient availability is increased [66-68]. There are several overlapping hypotheses that attempt to clarify this relationship, including the growth-differentiation balance (GDB) hypothesis, carbon/nutrient balance (CNB) hypothesis and protein competition model (PCM) [45,69]. Generally, these theories propose that while high nutrient availability enhances plant growth and development, it can lead to a reduced allocation of resources for the production of secondary metabolites, including phenolic antioxidants.

Tomatoes grown with grass-clover mulch and chicken manure had ascorbic acid and total phenolic contents that were 29% and 17.6% higher, respectively, compared to those grown with mineral nutrient solutions. In contrast, tomatoes grown with high chloride levels and grass-clover mulch had 40% less lycopene content (11.5 mg/100 g dry matter) compared to other treatments (19.2 mg/100 g dry matter). Additionally, the antioxidant activity of tomatoes treated with ammonium was 14% lower than that of tomatoes treated with other nutrients. These findings underscore the crucial role that nutrient sources play in determining the antioxidant levels in tomatoes [70]. Previous studies have noted that plants cannot equally

allocate resources to both growth and defence due to competition between protein and phenolic synthesis [71]. As a result, plants grown with organic fertilizers tend to exhibit slower growth rates, likely due to the slower nutrient release from grass-clover mulch and chicken manure (see Fig. 4). Nevertheless, with adequate light for photosynthesis, excess carbon (C) can be used for the production of carbon-based secondary compounds like phenolics in plants treated with organic fertilizers [70].



Figure 4: Comparison of raditional and organic fertilizer application on the nutraceutical content a tomato fruit.

The traditional fertilizer slowly released the nutrients and causes the better utilization by plants. On the other hand organic fertilizer releases the nutrient very fast which may cause the excessive availability of nutrients which in turn harms the growth of plant.

It is common knowledge that the availability of N promotes plant growth and yield. Besides the impact of the N amount applied, the form of the N applied may have an effect on plant growth and chemical composition of plants [5, 72, 73]. N is available for plant either in organic forms or as inorganic ions (NH4⁺ or NO3-). It has been noted that fruit quality can be affected by amount of N supply. A study demonstrated that the fruit quality is improved when supplied low NO₃⁻ and high NH₄⁺ levels [74]. Nitrate (NO₃⁻⁾ is readily mobile in plants and can be stored in vacuoles, also when but if NO3⁻ is used in the biosynthesis of proteins and other organic compounds in plants, it must be reduced to ammonium [75]. Numerous field experiments conducted throughout the world has shown that N is the most important growth limiting factor. The data about the effect of N form on the composition of secondary metabolites in tomatoes is still scarce and needs further investigation [50].

Nitrogen (N) availability has exclusively positive effects on tomato fruit quality. One of study it was found that N availability increases the carotenoid biosynthesis in higher plants [76]. However, in another

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study, it was found that there is a negative relationship between N availability and lycopene content in tomato fruits [46]. Other contrasting studies also showed that when tomatoes are grown in pots and rate of N fertilizer is increased (up to 600kg N ha-1), then lycopene content in fruit also increased [77]. However, it has been observed that the quality and taste of tomato fruit improved when supplied the tomato plants by reduced N forms such as organic or ammonium. In addition, the ammonium source is equivalent to nitrate for the nutrition of tomato plants [78]. Interestingly, it has been discovered that reduced N forms such as high NH₄⁺ and low NO₃⁻ levels improved fruit quality [74]. It has been suggested in these studies that used low N plants may save energy and this may lead to an increased production of secondary metabolites that improve fruit quality and taste.

It has been observed in an organic production system of tomato that the soil contains higher ammonium and chloride compared to non-organic systems [79]. It is also noted that there is some reduction in ascorbic acid content at the high N application, apparently for secondary reasons, since N supply might improve the foliage and in consequence the shading of the fruit on plants unevenly illuminated by straight sunshine [46]. Decrease of ascorbic acid with the use of high levels of N fertilizers has been reported in other previous studies [80,81].

Camille et al. (2009) revealed that the quality of fruit can be improved by lowering the acid content (10-16%) and increasing the soluble sugar content (5-17%). The fruits with the lowest N supply have higher content of total ascorbic acid and some phenolic compounds (rutin, a caffeic acid glycoside, and a caffeic acid derivate). Similar results were obtained in another study which revealed that with increasing the N supply from 2.25 to 36 mm also increased the sugar and acid contents, thus improved the tomato quality [30] On the other hand, the β -carotene content seemed to increase with increased nitrogen supply. However, the impact of N supply on lycopene content is more controversial and need further investigations [82].

Apart from N, Phosphorus (P) also has an impact on improving the fruit quality of tomato as in some studies it has be found that soil or foliar P fertilization enhanced the lycopene content in tomato [83]. Apart from this, P can also improve nutrient and water-use efficiency, and increases the final yield of tomato fruits [84]. Furthermore, supplementary potassium (K) in either through the soil or by foliar-spray also improved lycopene content and also reduced colour disorders in ripe tomato fruit [85]. Furthermore, plants grown in nutrient solution containing high level of K followed by Magnesium (Mg) application leads to higher lycopene accumulation [86]. Thus, from the above studies, it is comprehended that the type of fertilizers has a huge impact on nutritional quality of tomato fruits.

Conclusion

Tomatoes are an economically important crop with significant nutraceutical value through the high content of carotenoids, β -carotene vitamin A, antioxidants, vitamins such as vitamin C and E, tocopherols, phenolic compounds such as flavonoids and derivatives of hydroxycinnamic acid. While genetic improvements by breeding and biofortification can increase the content of these bioactive compounds. environmental conditions and agricultural practices are equally crucial. This review highlights that optimal growing conditions and effective management practices can significantly increase the levels of bioactive compounds in tomatoes. Improving the quality by breeding programs needs long time to achieve the goal. In addition, a large part of the society does not accept genetically modified plants (GMOs). Thus, growing tomatoes on salty soil, optimal environmental conditions, the right application of fertilizers and good agricultural practices can be effective methods for improving fruit quality and increasing the phytochemical compounds. Since the critical evaluation about GMOs is increasing, the demand for organically produced crops is growing. Although molecular and conventional breeding can varieties with improved phytochemical give compounds, unsuitable environmental condition and poor agricultural practices will reduce the quality of tomato fruits. Selection of suitable genotypes growing in optimal environmental conditions, under good agricultural practices, and the application of suitable crop technology can be the key for improving the nutritional value of tomatoes. More focus should be given on such genotypes which can grow on saline soil and water deficit condition without losing the nutritional values of tomato fruits. Interestingly, these conditions improve the nutritional values of tomato fruits, which on another hand can be a good utilization of saline soil.

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Author Contributions

AA collected the literature and formally wrote the first draft of the manuscript. MSA and HSM helped by collecting the literature and write-up. MA and SH reviewed the manuscript. MAJ formulated the concept. RMX and MAJ final proofread the manuscript.

Conflict of Interest

No potential conflict of interest was reported by the authors.

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