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Research Article

Regular Intake of Tomato Juice by Egyptian Male Preadolescents was Associated with Significant Increase in the Plasma Lycopene Concentration and Modest Changes in the Blood Glutathione and Plasma Immunoglobulin E Levels

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Abstract

The objective of the present study is to test the impact of nutritional intervention with natural tomato juice on health among preadolescent to adolescent males. The study was coupled with quantitative measurements of selected biomarkers to validate the observed links between the regular consumption of tomato juice and impact on selected biomarkers of health status. Design of the dietary intervention trial The study consisted of 25 boys (10.5 years old), who received tomato juice for a duration of 18 days with mean daily intake of 240 g tomato juice containing 2% corn oil, which supplied 22.3 mg trans lycopene and 1.32 mg β-carotene. Blood samples were collected from the anticubital vein at 7 different time intervals according to a predetermined schedule for the analysis. Carotenoid pigments, immunoglulin E and C- reactive protein were analyzed in the plasma amples, while glutathione (GSH) was determined in the whole blood. The results showed that the plasma lycopene increased gradually with a peak at day 8, which was 2.55 fold in excess of the prefeeding period (day zero). The increases in the plasma concentrations of α and β -carotene reached a peak, which was 1.43 fold. The plasma immunoglobuline E (Ig E) a biomarker of allergy or the effect of infection on the immune system decreased but the level didn't reach significant level (P>0.05). The plasma C-reactive protein levels in all children except one child were below the detection limit (< 6 mg/L), Therefore, the analysis was not repeated after the tomato feeding. With respect to blood GSH, the increases in its concentration peaked on day 14, but the increase was not significant (P>0.05). Thus, tomato juice could be considered as a potential functional product with a high antioxidant and anti-inflammatory properties but additional studies for longer period of times are warranted.

Keywords: Male Adolescents; Infection with Intestinal Parasites; Tomato Juice; Tomato Lycopene; Plasma Lycopene; Blood Glutathione; Plasma Immunoglobulin E; C –Reactive Proteins

Introduction

Tomato (Solanum lycopersicum) is the major horticultural crop grown in the Mediterranean country Egypt. It is an important source of the carotenoid pigment lycopene. other phenolic compounds and other bioactive ingredients and its beneficial effects had been reviewed recently [1]. Also, phenolic compounds and carotenoids are the main biologically active compounds present in ripened tomatoes. In fact, the red color of tomato is because of a significant amount of lycopene, which mainly has isoprenoid structure, a very representative group includes also caroteneβ, ɤ, and z-carotene [2,3]. Estimated daily intake of tomato averaged 7.34 in Sweden up to 54.07 g in vegetarian UK citizens [4] Lycopene was reported to affect adipose tissue proinflammatory cytokine and chemokine production, thus limiting the prevalence of obesity-associated pathologies, such as insulin resistance that have been probed against various life sight related disorders owing to array of phytochemicals. Carotenoids in tomato have a very interesting nutritional value in addition to prominent antioxidant, anti-inflammatory, and anticancer activities [5]. In which, they are playing an important roles as biologically active compounds. Consumption has been associated with decreasing of chronic degenerative diseases risk. Epidemiological findings confirm the observed health effects are due to the presence of different antioxidant molecules such as carotenoids, vitamins.

Consumption of tomato and tomato-based products contribute to the absorption of carotenoids and lycopenes in human serum. Tomato lycopene ($C_{40}H_{56}$ = 536) is a bright red acyclic carotenoid hydrocarbon with 11 conjugated double bonds, in all-trans configuration (Figure 1).

Figure 2, illustrates the pathway of ingested lycopene in the human body, LYC is taken up by the mucosa of the small intestine, packaged into triacylglycerol-rich chylomicrons, and secreted into the lymph for delivering to the bloodstream where they are rapidly degraded by lipoprotein lipase. The resulting chylomicron remnants are rapidly taken up by the liver, which secretes lycopene associated with hepatic VLDL, and in the fasting state most plasma ly-

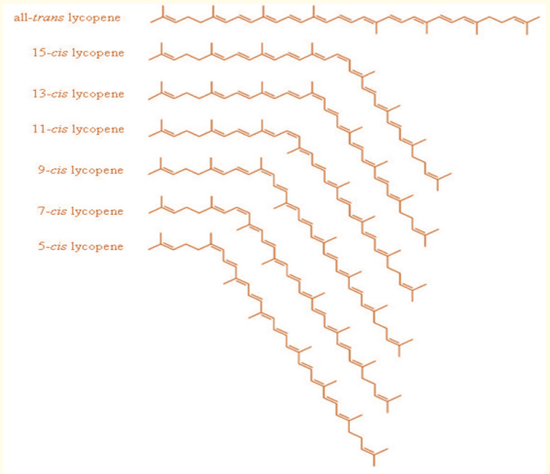

Figure 1: Chemical structure of lycopene and its isomers.

copene are associated with LDL and HDL. It may also be possible to use whole plasma to study absorption of lycopene and carotenoids for which baseline plasma concentrations are very low. Moreover, many studies have found a direct relationship between blood lycopene levels and tomato consumption. In which, it has been found that lycopene levels in blood is preventing the body from developing of several cancers, osteoporosis, and cardiovascular diseases [3-11].

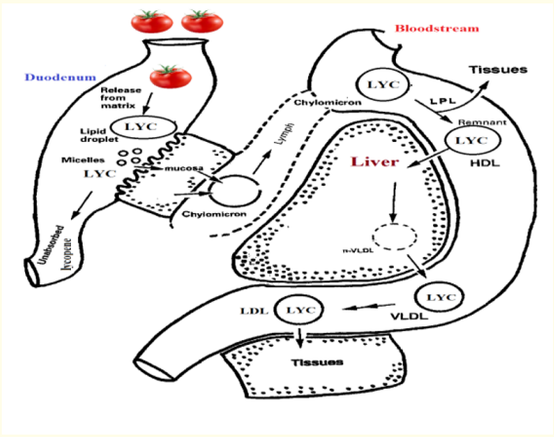

Figure 2: Schematically overview on pathway of lycopene within the human body: LYC, Lycopene; LDL, Low density lipoprotein; VLDL, Very low density lipoprotein; HDL, High density lipoprotein, LPL, Lipoprotein lipase.

On the other hand, tomato and its derivatives have also found to be beneficial in reducing inflammation and thrombosis incidence. Researches on tomato consumption revealed the positive impact of daily tomato intake on the oxidation of blood lipids [12,13].

The average polyphenolic compounds content in tomato grown in the warm sunny climate of Egypt average 25.6±1.27 mg [14], which ranks within the upper level reported. Naringenin chalcone (trans-2′4′6′4-tetrahydroxychalcone) is a flavonoid compound isolated from tomato skin with active anti-allergic properties and released histamine efficiently with an IC_{50} value of 68 µg/ml [15]. The consumption of tomato juice was reported to decrease the inflammatory marker C-reactive protein [16].

Tomato juice showed a positive effect on human immune system. A study found a significant decrease in serum levels of interleukin-8 and tumor necrosis factor-alpha in the tomato group compared with control [17]. Another study showed that tomato suppressed plasma interleukin- 6 and vascular cell adhesion molecule-1 (VCAM-1), lymphocyte function-associated antigen-1 (LFA-1) [18].

In order to get a clear understanding of the contributions of specific tomato ingredients to health promotion in diet. Moreover, some the urgent need for elaborating a national strategy based on sound scientific knowledge to assess the status and estimate the incidences of abnormalities. Priorities should be given to preadolescents and adolescents during the phase of peak growth.

In this work, three components (lycopene, α-carotene, β-carotene) contributing to the healthy quality of tomato were studied for their importance role in promoting health through dietary intervention trail. Therefore, the aim of this study was to test the impact of nutritional intervention with natural tomato juice on selected potential health biomarkers among preadolescent to adolescent males. Blood samples were collected from the antecubital vein to determine the concentration of glutathione (GSH) and hemoglobin in whole blood. Also, plasma was separated for subsequent analysis of the carotenoid pigments and C-Reactive Protein, biomarkers of cardiovascular risk.

Materials and Methods

Subjects

Total number of subjects were 49 healthy Male adolescents (mean age = 10.7 ± 0.35 y; mean BMI= 17.8 kg/m^2). Exclusion criteria: regular intake of medicine, smoking, intake of dietary supplementation < 14 d before study start, > 10 h/wk of physical activity, or dislike of tomato juice.

Tomato juice

Fresh tomatoes fruits (200 kg) were washed with water, blended by heavy duty blender (Braun MX2050, Germany). Then, stored frozen at -20o in 240 ml aliquots in airtight plastic containers. Tomato juice (240 grams) was served in bottles with blue caps, to which 4-5 g of maize oil was added with a dropper. The bottles

were turned upside down in the carton box to allow the homogenous distribution of the oil. The juice was served daily ice-cool for three weeks.

Dietary assessment

A seven day dietary food record was completed before and during the last week of the intervention. The estimated polyphenols, lycopene and carotenoid intakes were calculated using available published data by USDA [19].

Design of the experiment

Blood samples were collected from 25 male subjects as baseline data. Then, previously prepared tomato juice was used for intervention to the study subjects for a total period of three weeks. During the intervention period, blood samples at 6 different time intervals (before consuming the tomato juice (baseline), 4th, 7th, 10th, 18th day, and washout after the termination of the intervention (one week and three weeks). The blood was processed according to standard methods for the analysis of red blood cells (GSH in whole blood, Immunoglobulin E in plasma, C-reactive proteins in plasma, and carotenoids in plasma). Each subject served as his own control.

Collection of blood samples

Five samples were collected from 20% of the subjects at 0, 4, 7, 10 and 18 days of the intervention. The fifth sample was collected at one week after the withdrawal of the juice. The plasma was collected by centrifugation and the red blood cells were washed with physiological saline solution. All samples were stored frozen at -20^{o}C.

Analytical methods

Generally, all used chemicals in the study were analytical grade.

Analysis of plasma carotenoids

Plasma carotenoids were measured according to method of Craft, Brown and Smith [20]. The two plasma samples for each subject (baseline and sample collected after 3 weeks intake of tomato juice) were analyzed on the same day. The plasma was thawed and aliquots of 460 µl were pippeted in a 2.2-ml Eppendorf centrifuge tubes. Additions of 100 µl of Apo-β-carotenal as internal standard, 460 µl absolute ethanol (containing 1 mg ascorbic acid/mL) and 900 µl of n-hexane (containing 0.1% butylated hydroxytoluene/ mL) were done in this sequence. After vigorous vortexing and centrifugation (Biofuge-Fresco, Heraues, Germany), the upper layer was aspirated, and the extraction was repeated twice. The pooled hexane supernatant was evaporated to dryness under nitrogen at 400C and the residue was resuspended in 100 µl of the mobile phase. The chromatographic system consisted of HPLC instrument equipped with pump 600 and controller 600 (Waters Associates, Milford, MA). The analytical column consisted of a 4.6x 250 mm column (GI Sciences, Japan) packed with Inertsil ODS, 5 µm and 100% isocratic mobile phase consisting of acetonitrile-dichloromethane -methanol (70:20:10 v/v) at a flow rate of 1ml/min. A Waters model multichannel photodiode detector was used to monitor absorbance at 450 nm. Calibration was performed with pure compounds of α- carotene, β- carotene, and lycopene (Sigma–Aldrich, USA). Standard β-carotene, the internal standard apo-β- carotenal (Fluka, UK) were prepared by dissolving in the recommended solvent. The concentrations of the standards were determined by visible spectrophotometry. Because the standard α-carotene was not available, this compound was quantified by using the response factor for the all-trans β- carotene isomer. Lycopene, α-Carotene, and β-Carotene peaks were appeared at 10.49, 15.7, 16.8 minutes, respectively (Table 1).

Carotenoid	Chemical structure, MW	Wavelength, nm	Molar extinction, coefficient*	Retention time, Minutes
α-Carotene	C40H56, 536	445	145256	15.7 (14.0-16.7)
β-Carotene	C40H56, 536	451	139500	16.8 (14.76-17.7)
Lycopene	C40H56, 536	470	185185	10.49 (9.3-11.0)

Table 1: Physical characteristics of the carotenoids and retention time of the carotenoid peaks.

The column was rinsed for additional 5 min with the mobile phase before the injection of the next sample; 21 min were elapsed between two consecutive injections. The carotenoid concentration was determined by the external standard curve procedure. The peak areas of the unknown samples were integrated and the results were compared with the respective peak areas of the carotenoid standard having the same retention time. These peak areas were used to create the calibration graph and to calculate the regression coefficients.

Whole blood glutathione [GSH] measurements

Reduced Glutathione (GSH) was analysed using Ellman reagent [21]. Heparinized blood aliquots (20 µl) were deproteinized by mixing vigorously with 0.18 ml distilled water plus 0.3 ml precipitating solution (Mixture of equal volumes of glacial acid acid (1.67 g) + sodium metaphosphate (5.0 g) + 0.2 g disodium EDTA + 30 g sodium chloride per deciliter distilled water). Following centrifugation, 0.4 ml aliquots of the clear supernatant were aspirated and mixed with 0.2 ml of the DTNB reagent (40 mg/deciliter). The optical density of the yellow color was read against blank soplution at 412 nm. The GSH concentration was calculated using the molar extinction coefficient of 14,150 M−1 cm−1 and the results were expressed per g hemoglobin. Hemoglobin was determined by mixing blood aliquots ((20 µl) with 5.0 ml Drabkin's Solution and the developed pink cyanmethemoglobin color was read at 540 nm.

Assay of serum IgE

The quantitative determination of immunoglobulin E (IgE) concentration in the serum was assayed by the Abbott (Abbott Laboratories, North Chicago, Ill.) IgE enzyme immune assay [IgE EIA] with

recently frozen sera according to instruction of the manufacturer. This test is a sandwich enzyme immunoassay in which the serum is incubated with polystyrene beads coated with rabbit antihuman IgE. After a 30-minute incubation, unbound material is removed by washing, and the beads are incubated for another 30 minutes with goat antihuman IgE conjugated with horseradish peroxidase. After a second wash, beads are incubated for 30 minutes with o-phenylenediamine containing hydrogen peroxide, and the reaction is stopped by the addition of 1 N H_2SO_4. IgE levels are calculated from absorbance values at a wavelength of 492 nm read by the ELISA reader.

The assay of C –reactive protein

The enhanced latex-agglutination assay was used for C- reactive protein determination (Winkdes 1987).

Stool examination for the presence of helminthes

The subjects were asked to collect a stool sample in a clean container. The detection of stool parasites was completed in a parasitological laboratory by the standard centrifugation and Kato method, followed by microscopic exe nation using bright-field microscope [Gracia *et al*.,].

Analysis of tomato juice carotenoid

The carotenoid content of the tomato juice was determined after extensive extraction of the juice with tetrahydrofuran/methanol (1:1, v/v) until the last extract was colorless (usually five times extractions). An aliquot was taken and the compound ethyl-β-apocarotenoate was added as an internal standard. HPLC separation was completed on a column packed with ET 200/4 nucleosil 100–5CN (Machery and Nagel, Duren, Germany). At a flow rate of 1.0 mL/min and column temperature of 20°C. The eluent was monitored by visible detection at 450 nm for β-carotene. In this system, α-carotene co-elutes with β –carotene, but tomato doesn't contain α –carotene [20], the HPLC response with retention time of 14–17 minutes was practically β-carotene.

Analysis of tomato lycopene

Aliquots of 10 g tomato juice was weighted and extracted with 10 mL of a mixture of ice-cold hexane-acetone- ethanol (50:25:25) (v/v/v) according to extraction method of Sadler [23]. The extract was filtered through glass wool and the residue was re-extracted with the same mixture. The pooled extract was shaken with water in a separating funnel and the distinct polar and nonpolar layers were separated. The upper hexane lycopene bearing layer was aspirated, its volume was recorded and the intensity of the color was measured by spectrophotometer at 470 nm)Shimadzu UV-160, Japan). The lycopene concentration was calculated using a molar extinction coefficient of E = 18.5 x $l0^4$ [24].

Results

The characteristics of the subjects are presented in Table 2. Age or other physical characteristics did not differ significantly between the individuals at the study baseline. At the baseline, the mean urinary [P P] excretions were 105.1 ± 13.0 mg GAE/g creatinine. Body mass index averaged 17.8 ± 0.51(17.215–27.4) kg/m^2 Hemoglobin (g/dl), 11.0 ± 0.27 (11.039 – 13.4), body weight 25.6 ± 0.53 (17.1-27.25). All subjects consumed well balance diet and.

Parameter	Unit	Mean ± S E
Age,	years	10.7 ± 0.35
Bodyweight,	kg	32.2 ± 0.65
Body mass index,	kg/m^2	17.8 ± 0.51
Blood Hemoglobin,	g/dl	11.0 ± 0.27
Urinary creatinine,	g/24 h	770.5± 87.0
Urinary creatinine,	mg/kg body weight	25.6 ± 3.27
Urinary [P P]	GAE mg/24 h	48.6± 5.5
Urinary [P P]	GAE mg/ g creatinine	89.5 ± 8.4
Infection with intestinal parasits/protozoa % of total children		
Negative	%	48
Ascaris	%	4
Entamaeba histolotica	%	40
Giarida lamblia	%	4
H nana	%	4

Table 2: Baseline characteristics of the study subjects.

Tomato juice was served at a dose achievable with a human diet (240 mL) and was well tolerated orally by all recruited volunteers, who completed the study with no adverse effects due to the consumption of the tomato juices. In which, they received 26.2 mg/ GAE from tomato's PP (Table 3).

Parameter	Per 100 g	Per serving */ day
Lycopene	9.3 mg	22.3
β- carotene	0.55	1.32
Total [PP], mg/GAE*	10.47 ± 0.26	26.2
One serving = 240 grams; * * GAE = Gallic acid equivalent		

Table 3: Composition of tomato juice.

During the intervention with tomato juice, plasma lycopene level change % was increased significantly ($p<0.05$) at day 8 (Figure 3). In which, it became 255.15% compared to 100% in day zero. After that, it decreased again to 143.41% in day 15. On the other hand, for Plasma α-carotene level, it was increased significantly ($p<0.05$) at day 10 to 142.48% compared to control with 100. In which, its change % became 255.15% compared to 100 in day zero. After that, it decreased again to 143.41% in day 18. Also, for Plasma β-carotene level, it was increased significantly ($p<0.05$) at day 7 to 240.49%. And, it was stable until day 10 with 258.57%. After that, it decreased again to 135.61 in day 18. Also, in all studied biomarkers, the % change were back again to the baseline % after 7 days of washout process. On the other hands GSH did not changed significantly during the intervention period (Figure 4).

In the present study, the IgE was higher for respective baseline level of 450 IU Ig E/ml plasma, which was reduced down by 22% following the regular intake of tomato juice (Figure 5).

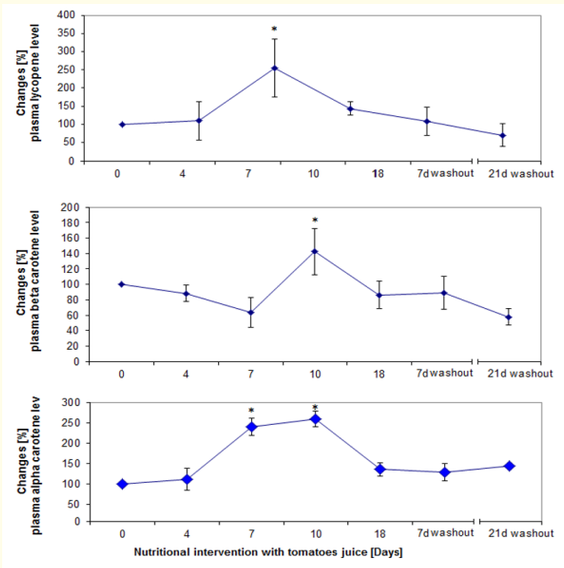

Figure 3: Changes % in plasma lycopene, α- and β- carotenes following the regular consumption of tomato juice.

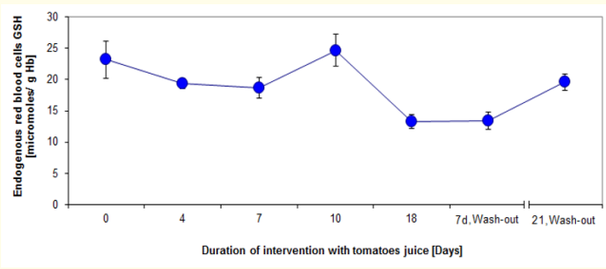

Figure 4: Changes % in plasma reduced Glutathione (GSH) following the regular consumption of tomato juice.

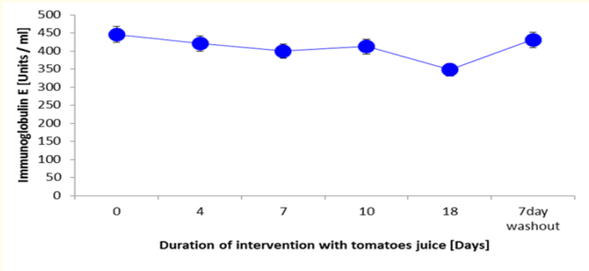

Figure 5: Changes % in plasma immunoglobulin E (IgE) following the regular consumption of tomato juice.

Discussion

Tomato lycopene is a good example of bioactive phytochemical, which play an important role. The plasma lycopene concentration increased significantly among the boys consuming the tomato juice for 2 weeks and are in good agreement with earlier findings in Italy [4]. Also, in our previous study we found that plasma concentration of lycopene increased significantly in dyslipidemic patients with type-2 diabetics following 3-week daily intake of 240 ml thermally treated tomato juice, suggesting good bioavailability of tomato lycopene [25]. It is interesting to note that about 90% of the tomato lycopene is in the linear, all-trans conformation, while in the human plasma and tissue lycopene is mainly cis-isomers [26] (Figure 1). No attempt was done in the present study to separate the isomers of tomato or plasma lycopene.

The consumption of 5–20 mg lycopene provided by tomato products was reported to lower down the oxidative stress expressed by 10% [27].

Glutathione (GSH) tripeptide (cysteine, glycine, and glutamic acid) is a major cellular redox regulator, which neutralizes potentially harmful reactive oxygen species produced during normal biochemical processes such as cellular respiration, or negligent diet. GSH is also an antioxidant, protecting cells from damage induced by reactive oxygen species [28] and catalytically detoxifies hydroperoxides and lipid peroxides [29]. To optimize the body's endogenous glutathione status, the single/multi-component grown foods had been recommend as relatively simple, low cost and safe approach to improve health in an individual and in a clinical setting. Tomato GSH content averages 64±10 nM/g wet weight [30] ranks high among other fruits and vegetables. The baseline GSH concentration of 25 μM/ L is much higher than the figure of 5 (Beutler et al); reported in the old literature and lower than the respective figure of 41.8 μM, suggested recently as the cut-off for normal range, to be used in clinical settings [31]. According to these authors, the use of a common methodology is needed for defining the normal range. The measurement of GSH is a challenging task because, during sample manipulation, a large percentage of the aminothiol can be artificially oxidized in consequence of the acidification step that is commonly used to remove thiol proteins that interfere with the assay [32]. The % increase in the GSH following 18 day daily intake of g tomato juice was 22% over the respective baseline level and din't attain significant level (P>0.05). Similar conclusion was also reported with Italian adults, whose blood GSH concentration didn't increase following the daily intakes of tomato juice for three weeks [16].

The plasma C –reactive protein was below the detection level in all studied subjects except one boy, therefore, we could not examine the effectiveness of drinking tomato juice on the biomarker of inflammation. While it was shown that drinking 500 ml of tomato juice by daily for 2 weeks reduced the inflammation marker of C-Reactive Protein by % [33].

Routine measurements of serum IgE levels have become part of the diagnostic assessment of the subjects with suspected allergic disease, which depend on the availability of standards of normal ranges for given populations. Information reported in the literature are based on population studies outside Egypt. The plasma immunoglobulin level of 45.4 IU/ ml was reported among healthy American children [34] and 87 IU/ml among Pakistani children [35]. In the present study, higher respective baseline level of 450 IU Ig E/ ml plasma, which was reduced down by 22% following the regular

intake of tomato juice (Figure 5). It is noteworthy, that 52% of our subjects had intestinal infection with parasites or protozoa, and according to a previous study, their stool was rich in Proteobacteria, which contains many known human gut pathogens, exposing the Egyptian children to heavy bacteriophage pressure [36]. Similar situation was found in Mexico, where half of the paediatric population is infected with at least one species of intestinal parasite [37]. The plasma Ig E concentrations of our children were quite overlapping with those in Ugandan years old infected with Schistosome andHookworm 336 IU/mL) [38]. Higher plasma Ig E levels ranging between > 88 – 3000 IU/ ml were reported among Pakistanian children with skin dermatitits [Ahmed – Neasreen,2007]. Immunoglobulin E (IgE) provides protective immunity against helminth parasites and is accepted as a "gate keeper." Immune globulin E (IgE) antibody programming to interact with specific antigens is produced by lymphoid tissue and binds to IgE receptors. The immune globulin E [Ig E] is compromised to the dietary nutrients and environmental factors leading to unhealthy gut due to infection with intestinal parasites and pathogenic bacteria.

Conclusion

Well-designed nutritional supplementation trials are needed to establish the optimal dose, duration of tomato intake and the effectiveness of different supplements as prophylactic and on correcting different metabolic disorders in hospital settings and among free-living individuals [39].

The urgent need for elaborating a national strategy based on sound scientific knowledge to assess the status and estimate the incidences of abnormalities. is an issue with far greater implications for public health affecting both medical and food policy. To release dietary guidelines appropriate for the Egyptian population. Capacity buildings particularly those of relevance to the analytical methodologies for the precise quantitation of bioactive compounds in foods and in the biological tissues Detection of stress biomarkers.

Conflict of Interest

We thank the supervisors and the participants for their collaborations in this study.

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