

Review

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Review

A Step Forward in Enhancing the Health-Promoting Properties of Whole Tomatoes as a Global Functional Food to Lower the Impact of Non-Communicable Diseases

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Abstract: Nutritional interventions facilitating the consumption of available, affordable, and environment-compatible health-promoting functional foods (FF) are a promising strategy for controlling non-communicable diseases (NCDs) responsible for decreasing health expectancy. Given that the complex of tomato micronutrients produces healthier outcomes than lycopene, its major antioxidant component, we have devised a new controlled berry processing to improve its health-supporting properties. The newly generated whole tomato food supplement (WTFS), enriched by 2% olive wastewater polyphenols, contains a complex of healthy nutrients with converging biologic activities superior to those provided by tomato commodities. WTFS equals the antioxidant activity of N-acetyl-cysteine and interferes with multiple inflammation-eliciting and sustaining metabolic pathways. WTFS inhibits prostate experimental tumors, and improves benign prostate hypertrophy-associated symptoms. No side effects have been so far reported for dietary supplementation with WTFS compared to the culinary use of tomatoes. Although WTFS may be susceptible to further improvements and clinical scrutiny, its composition embodies the features of an advanced FF to ease adherence to dietary regimens, i.e. the Mediterranean diet, aimed at contrasting the low-grade inflammation. Ongoing investigations suggest new areas of potential translational use of WTFS, as a basis for developing more targeted FF interceptive or preventive of NCDs.

Keywords: functional food; non-communicable diseases; tomato

1. Introduction

Due to the increasing incidence of slow-progressing non-communicable diseases (NCDs), which represent the most frequent causes of long-term disability and death worldwide [1], a widening gap between life and healthy life expectancy is occurring [2]. This dichotomy is becoming a global health and economic emergency affecting associated social consequences, especially in low- and middle-income countries [3]. Paradoxically, despite being NCDs largely preventable [4], an increasing gap is occurring between what we know about their social and biological determinants and what is done for coordinated progressive corrective initiatives. Therefore, the unavoidable question of how to reduce or mitigate this alarming trend is emerging. Two main potential areas of remediation can be

envisioned, namely social and individual. As for the former, current socio-political, economic, and environmental factors are unlikely to improve rapidly. Indeed, they require a coordinated mobilization of societies, primarily in lowering disparities [5], thus buffering the impact of present conflicts and the outburst of new confrontations [6], migratory waves [7], and increasing urbanization [8]. When referring to personal choices, the well-rooted marketing policies [9], uncensored information released by social media platforms, and supporters of alternative remedies are undermining the ability to make appropriate healthy choices [10]. This lowers the efficacy of grounded health literacy alerting on the relevance of NCDs' global risk factors, i.e. physical inactivity, unhealthy diets, smoking, alcohol abuse [11], unsafe occupational conditions, changing "anthropocene" [12] and the diminishing healthcare provisions [13]. In this uncertain horizon, the compelling issue arises of what can be done to develop policies aimed at delaying the onset of NCDs and dimming their related disability in a realistic approach beneficial to the largest populations' fractions [14]. While acute inflammation can be effectively targeted pharmacologically by available drugs [15,16], not infrequently at the cost of severe side effects, low-grade chronic inflammation [17] which is a shared relevant pathological determinant in NCDs incidence and severity [18], generated by a variety of stressors, remains an unmet therapeutic target. The development of anticipatory diagnostic markers, the validation of novel (chemo)preventive approaches, and the use of new or repurposed agents, alone or in combination with registered drugs, are urgently required [19] since uncontrolled low-grade chronic inflammation may foster the development of systemic inflammation [20]. In this challenging endeavor, the lowering of excess production and increased disposal of free oxygen and nitrogen radicals, the common denominators, and culprits of the pathogenesis of various age-related diseases, remains a key objective [21].

2. Dietary Nutrients and NCDs

While innovation in drug development for NCDs is advancing at a low pace, epidemiologic and interventional studies have demonstrated that healthy dietary regimens beyond their nutritional properties may be major players in this regard [22], representing, at the present, the mainstay of both prevention and treatment of NCDs. Thus, advocating the implementation of healthier nutritional recommendations [23], supporting the resorting to widely available resources, is gaining increased attention [24]. In particular, the Mediterranean diet (MD), recommending the low consumption of oxidative stress-generating foods and high uptake of nutritional antioxidants, has received major attention [25]. MD is associated with a lower risk of chronic diseases [26], is environmentally sustainable [27], and may be potentially beneficial also to the population of non-Mediterranean countries [28]. This diet is characterized by the consumption of healthy "functional foods" (FF), which despite lacking a conclusive definition at the regulatory level [29] can be classified from the translational point of view as those "foods containing biologically active natural compounds which, in forms made highly bioavailable, produce healthy effects in addition to nutritional ones", "similar to natural food, they can also be consumed as part of a normal diet" [30,31]. Although this definition can be largely agreed upon, the following questions: which foods, in which form, how much, and when remain to be answered to optimize their consumption in the real world [32].

3. Strategies to Increase Tomato Properties as FF

The transition to more inclusive global health requires environmentally sustainable policies improving the use of accessible resources [12]; among these, tomatoes are an attractive one [33]. As a potent source of natural antioxidants, tomatoes, symbolic fruits of the MD [34], are characterized by the overall favorable economic and environmental features summarized in **Table 1**.

Table 1. Tomato economic (left) and the environmental (right) features.

				Refs.
Refs.				
Worldwide second high yield crop	[35]	High biodiversity		[42]
High consumption rate	[36]	High chemodiversity		[43]
Expected 5% increasing market in the near future	[37]	High nutrition yield		[44]
Unique culinary versatility with wide acceptance in different dietary regimens	[38]	Cultivation requires timely controlled irrigation and moderate soil tillage		[45]
High recyclability of industrial processing waste and packaging	[39]	Growth Not sensitive to increased CO2 environmental concentrations		[45]
Facilitator of circular economy	[37,40]	It is an “excluder plant” when referred to soil contaminants		[46]
It could become a scaffold for the development of a variety of dietary supplements of more targeted health claims	[41]	Organic and conventional cultivations have not no significant difference in heavy metal content		[47]
		Residues of pesticides efficiently removed by washing and cooking		[48,49]

Withstanding the above favorable features, and despite improvement of mechanical harvesting [50], tomato industry is a matter of labor exploitation [50,51]. The overall implications of tomato consumption are largely falling within frame of the newly proposed paradigm of the health role of food and nutrition [52].

Epidemiological, experimental, and clinical studies have been[37,40] primarily focused on lycopene, the red-colored, open-chain beta carotenoid lacking retinoid activity, which is present in variable concentrations in different tomato cultivars [43]. Lycopene with a daily requirement of 0,5 mg/kg [53], is generally defined as safe [54], and possesses potent free radicals scavenging properties, enhanced by its ability to induce other endogenous antioxidants, such as glutathione peroxidase, glutathione reductase, and superoxide dismutase [55]. Naturally occurring lycopene is mainly in the low bioavailable trans isomeric form [56], which follows variable extent of individual metabolic rates [56–58] and transformation into cis lycopene and other isomers [57], increased by the concomitant consumption of fats, primarily olive oil [59], acquires a broad spectrum of healthy biological properties [60] sustaining an anti-inflammatory activity [61,62]. The biologically active cis lycopene [63], formed upon heating/cooking the fruit [64], has a plasma elimination half-life of 5 days [65], and concentrates in definite anatomical sites [56] representing the preferential biological targets of the carotenoid activity [57]. Due to the limited bioavailability from dietary sources, a constant intake of lycopene-rich foods is needed to exploit its wide beneficial properties [66]. This may explain why levels of circulating lycopene do not display a relationship with low-grade inflammation (antioxidant paradox) serum markers [67].

Given the above and because of the increasing use by the health food industries [68], multidisciplinary research is ongoing to increase lycopene bioavailability through improvement of its in vivo delivery, development of new formulations [58,69], enrichment in the more bioavailable isoforms by chemical treatment [70], and devising new production methods [71].

3.1. The Strategy to Improve Tomatoes as FF Using the Whole Fruit

Comparative studies have demonstrated that the multi-target healthy properties of tomatoes derive not only from their lycopene content [72,73]. This does not come unexpectedly since several bioactive compounds endowed with a wide spectrum of biological properties are present in the fruit or are generated following cooking (Maillard's reaction) [74]. The consumption of whole fruits has been shown in fact to result in healthier effects than lycopene supplementation, as demonstrated in the laboratory [72,75] and clinical [73,76] studies. Therefore, the remarkable combination of antioxidant and anti-inflammatory nutrients with converging biological activities [77–80] supports the healthier choice of whole tomato as FF for equitable and sustainable diets [75,81].

Because of its nutritional content, several strategies in improving tomato crop yield and quality are under exploration, i.e. selective breeding, agronomy, transgenic and gene editing techniques, meeting the scaling-up demand for tomatoes [33,37].

Stemming from the above information, we became challenged in developing a whole tomato transformation process that may efficiently use a low-cost and minimal waste-generating technology, thus representing an advancement in utilizing whole tomatoes as FF. In view that heating is the simplest and lost-cost treatment of the fruit capable of increasing its healthy properties [64,82], we focused primarily our research effort on exploring different controlled heating processing conditions. This approach originated from early studies demonstrating that a diet enriched (10%) with a whole tomato powder produced by spray drying, improved the systemic antioxidant and inflammatory status and prevented the onset of prostate cancer in the TRAMP transgenic animal model [83], more efficiently than single lycopene diet supplementation [85]. These outcomes were dose-dependent because tomato powders containing lower concentrations of lycopene were not protective [84], and were reduced by a western diet dietary regimen rich in free radicals generating food [86]. To further optimize the above-described results in terms of the content of carotenoids and flavonoids, and to favor the formation of Amadori's products [74], a new processing treatment of whole fruits was implemented, which included the production of a puree, not completely freed from seeds and peels, obtained by pre-heating at temperature between 80-90 °C, and then concentrated at low temperature (60 °C) under vacuum (300-400 mbar), which resulted in a tomato concentrate. When the refractive index of the concentrate reached 29-30 °Brix grade, the product was diluted again with hot water at a concentration of 12 °Brix, and spray dried using preferably an inlet temperature of 175-190 °C and an outlet temperature kept below 85 °C [87]. These conditions allowed an optimal recovery of carotenoids, flavonoids and, in particular, of fructosyl amino acids as a function of the selected time/temperature/pressure conditions, as reported [87].

The production yield from whole tomato to powder ranges from 8-12%, with minimal waste.

Olives are a source of chemo-preventive nutrients [88], namely hydroxy-tyrosol [89,90], which modulates relevant molecular signalings involved in inflammation (e.g. MAPK, PI3K, and NF-κB) [91,92]. Therefore, with the dual aim of protecting the tomato carotenoid content from oxidative degradation and increasing the anti-inflammatory properties of tomato components [93], 2 % of olive mill wastewater was added in the final new whole tomato formulation [87]. This wastewater was prepared from "Coratine" olive cultivar by: a) filtrating olive waste waters; (b) concentrating the retentate under reduced pressure at a temperature up to 20 °C, and to a concentration of 10-15 % w/w dry matter; (c) spray drying the concentrated product from step (b) using an inlet temperature of 150-170 °C and an outlet temperature below 80 °C.

3.2. Properties of WTFS

WTFS, which is produced by employing the "Roma" tomato cultivar [94], has the following characteristics:

- a) it has improved in nutrient composition compared to the tomato powder generated by an early exploratory protocol of heat-processing the fruit through a standard Hot Break procedure up to 40 °Brix and spray drying [87,95] (Table 2);

Table 2. Nutrient composition (100 g).

Tomato powder		WTFS		
		Tomato (98%)	Olive waste water (2%)	
Carbohydrates	66 g	63.5 g	Oleuropeinaglycon	6 g
Proteins	10.2 g	16.5 g	Ligtrosideaglycan	2 g
Lipids	1.6 g	3.4 g	Oleuropeindialdehydeaglycane	16 g
Total carotenoids	142.2 mg	500 mg		7 g
All-trans lycopene	109.2 mg	250 mg	Verbascoside	6 g
5-cis lycopene	7.4 mg	35 mg	Pinoresinol and deacetoxy-pinoresinol	5 g
Lycopene isomers	15.7 mg	190 mg	Thyrosol	3 g
β-carotene	8.7 mg	22 mg	Hydroxy-thyrosol	10 g
Lutein	1.2 mg	3 mg	Unidefined polyphenols	8 g
α-tocopherol	1.9 mg	2.3 mg	Polysaccharides	33 g
Total flavonoids	15.3 mg	200 mg	Humidity	< 4 g
Quercetin derivates	1.1 mg	140 mg		
Naringenin derivates	4.2 mg	60 mg		
Ketosamines	-	8 mg		
Fru-His	-	0.06 mg		
Fibers	ND	15.9 mg		

The concentration of carotenoids and flavonoids was determined by high-performance liquid chromatography using C30 and C18 chromatographic columns coupled with UV-Vis detection [96]. Fru-His was determined by high resolution mass spectrometry using an ExactiveOrbitrap equipment (ThermoFisher, USA). They represent approximately 12% of the water-soluble fraction per dry weight. ND: not determined

- b) concentrations of cis lycopene and other lycopene isomers are higher than those present in tomato consumer products [97], deriving also from the presence of the berry soluble fibers [98];
- c) biological activities of different WTFS production batches have been reproducible [99], and this may contribute in reducing the individual variability in metabolizing trans to cis lycopene [57];
- d) it contains higher concentrations of flavonoids and newly formed ketosamines, carotenoids, Fru-His compounds, and β-carotene, which increases the absorption rate of lycopene [100]. The concentration of Fru-His compounds is likely to be underestimated [101];
- e) it contains olive polyphenols, endowed with converging biologic activities with lycopene in increasing apoptosis, preventing DNA damage, oxidative stress, receptors modulation, and activation of signal transducer and activator of transcription-3 (STAT-3) [99], a key modulator of the expression of a wide range of oncogenic [102] and inflammation-related genes [103], and of tumor cell energy metabolism [104] (**Figure 1**);

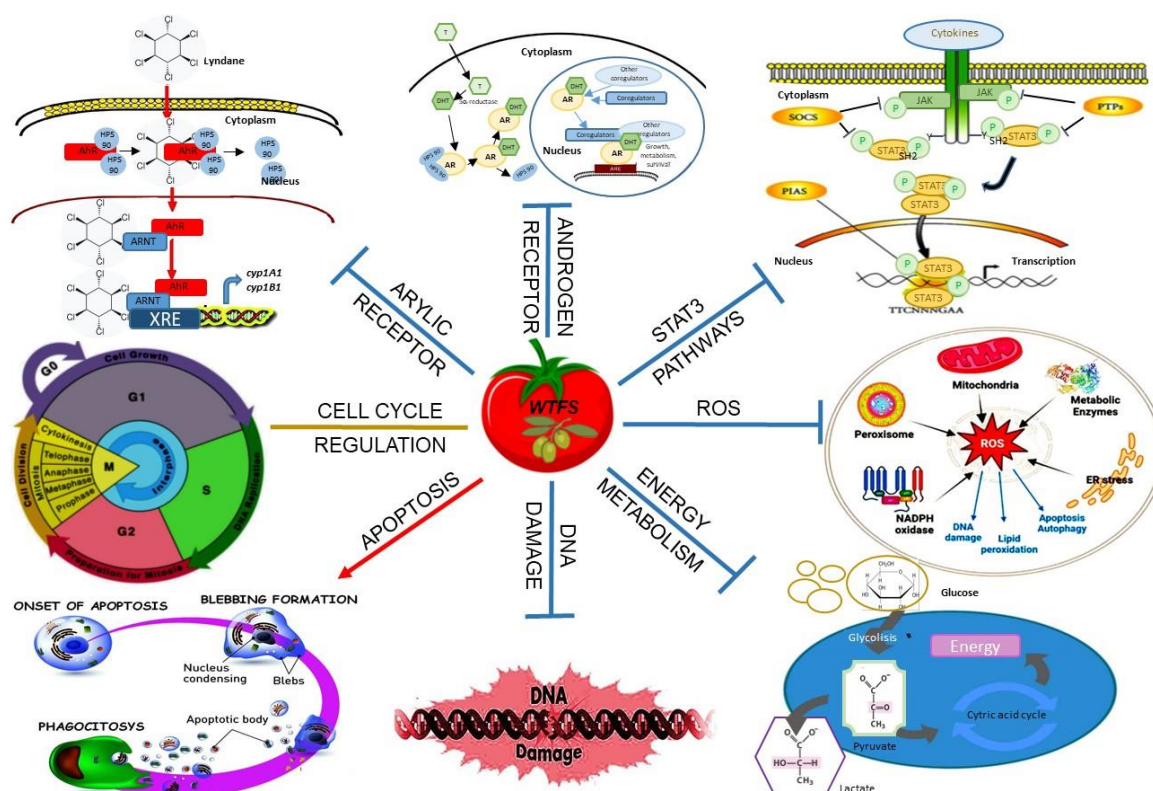


Figure 1. The complex of WTFS bioactive compounds induces activation of apoptosis, but inhibits androgen and arylc receptors receptor pathways, activation of STAT3, reactive oxygen species (ROS) production, metabolic shift towards the Warburg effect, and DNA damage. Overall, the WTFS promotes the rebalancing of the cell cycle, ensuring proper cellular homeostasis [99].

- f) its in vitro antioxidant activity is comparable to N-acetyl-cysteine [105];
- g) it has a translational potential in clinical settings. This property has been explored in human prostate benign hypertrophy (PBH), a frequent age-dependent disease sustained by chronic inflammation [106]. PBH has been proven to benefit in a dose-dependent manner from lycopene supplementation due to the property of the carotenoid [56] and its metabolite to concentrate in the gland. In the phase II prospective, randomized double-blinded, placebo-controlled study, the WTFS consumption significantly improved the patient's urinary tract symptoms and quality of life. Prostate-specific antigen (PSA) levels, when elevated prior to WTFS uptake, decreased, with unchanged free/bound fractions [108]. This improvement has been also documented in patients bearing low-grade chronic inflammation, i.e. HIV-infected individuals with PBH [109]. Differently from tomato based culinary preparations [110,111], at the max daily dosage used in clinical trials [108,109], no side effects were documented in tomato allergy-free individuals. Whether the prolonged uptake of WTFS is side-effect-free remains to be explored;
- h) it retains the sensory properties, i.e. aroma, taste, and color of red tomatoes. It can easily form a "granular suspension" in any liquid;
- i) further heating for culinary use does not impair its biological activity [112];
- l) it has an average nutritional value of 3,34 Kcal/g, thus acceptable under calories restricted diets.

4. WTFS potential in Improving Healthy Dietary Regimens

The fast-evolving technologies to identify and purify foods' bioactive compounds in the recent past rekindled the hypothesis that improved nutritional health outcomes could be achieved using

single nutrient supplementation [52]. Although some selected population fractions, i.e. hypo-nutrition or underweight, frailty, and aging, may benefit from this strategy, the experience in nutritional interventions based on single nutrient supplementation to improve well-being and/or decrease disease risk has been rather disappointing in terms of unmet benefits, associated toxicities, and increased/ unjustified costs [113]. This suggests that potential areas of improvement in modulating the incidence and severity of NCDs lay ahead in an equitable development or improvement of sustainable dietary regimens [24,114], but not resorting to single nutrient supplementation [52].

Adherence to the MD recommends a high intake of antioxidants-containing food, i.e. vegetables, fruits, legumes, grains, and extra virgin olive oil [25], which has been shown to increase their healthy properties also given the cooking habits, which characterize the MD [115]. MD which improves the dietary inflammation index [116], is effective in contrasting low-grade uncontrolled sub-clinical chronic inflammation [117,118] generated by unhealthy lifestyles and dietary regimens based on the consumption of highly refined foods associated with increasing incidence of obesity and related pathologies [119]. MD dietary food [120–124] and regimen have been associated with lower overall [125] and cancer-related [79] mortality rates when complied with either as a personal choice [126] or as a result of interventional studies [127,128].

Recent reappraisals regarding MD [27], on the other hand, have also brought to the surface some intrinsic limitations from the translational point of view. Indeed, its compliance is highly influenced by sociocultural factors [129,130]. Specifically, in adulthood, the percentage of adherence to its recommendations for fruit, nuts, and fish, estimated by the PREDIME[120–124] D score, was below the dietary guidelines [131].

Since the benefit of the MD can be extended also to populations outside the Mediterranean basin [132], strategies to overcome its low adherence need to be monitored and enforced [133,134]. In this effort, the “Planeterranean” UNESCO project is advocating the use of local food which may recapitulate the healthy properties of those available in the Mediterranean basin [135].

One potential option may rely in the improvement of the healthy properties of its single food components of wide culinary use and proven efficacy [136]. Within this conceptual frame, we focused our attention on tomatoes [137] since the dose-dependent healthy outcomes deriving from their consumption are significantly superior to those achieved by dietary supplementation with its major antioxidant/inflammatory nutrients, i.e. lycopene [78,138–140].

From the dietary point of view, WTFS may represent a step forward in:

- a) facilitating the adherence to the MD, which is of not easy compliance [141] and penalized by increasing high costs [130];
- b) contrasting aging-related carotenoid deficiency [21,142,143]. Indeed, the consumption of whole heat-processed tomatoes ameliorates the carotenoid status of healthy subjects and prevent their depletion in antiviral-treated patients, resulting in improved oxidative status [96] and associated NCDs [21];
- c) buffering the unhealthy effects of the spreading Western diet [144].

Because the culinary use of tomatoes is often associated in large population fractions with the consumption of dishes of high-calorie intake content, i.e. pasta/pizza dishes, the healthy benefit deriving from their use may be reduced in patients with glucose intolerance [145]. Since lycopene has been proven to increase insulin sensitivity through inhibition of STAT-3 [146], WTFS may increase metformin efficacy [147] and improve type II diabetes [148,149], allowing tomato nutrient consumptions with low calorie uptake.

4.1. WTFS Use According to Whole Tomato Health Claims

According to Council of Europe guidelines, tomatoes have two health claims: antioxidant and prostate health [150,151]. Therefore, the overall features of the WTFS as an antioxidant may find areas of potential exploration in the prevention or dimming the degree of inflammation, which can develop

in tissues where cis-lycopene is known to preferentially accumulate [152]. For instance, an improved FF may contribute to “internal” skin protection from UV light-induced aging and cancer pollutants [153–155].

Although encouraging, the results obtained with WTFS in the treatment of human PBH require further validation. Indeed, in view that PBH is a heterogeneous group of diseases [156] of variable clinical and pathological evolution, additional studies need to be performed addressing WTFS, dosage, scheduling, monitoring efficacy, amenability to combination therapies, and side effects upon prolonged use.

Despite lycopene and tomatoes having been extensively assayed as supplements or food as protective against prostatic cancer development and management, this relevant issue has not been fully settled. Since WTFS is a product of reproducible activity [105], validated in laboratory and animal experimental settings, is indeed a step forward in facilitating adherence to the otherwise hard-to-follow prostate dietary index [157]. This may help in readdressing areas of intervention generating human trials for prostate cancer management, i.e. in the prevention of early occurring malignancy [158], i.e. familiar form [159], in obesity [160], or in supporting current therapies of prostate cancer [161]. In addition, WTFS may represent a candidate to conclusively establish the superiority of whole tomatoes compared to lycopene alone in these patients [158].

4.2. *Exploratory/Potential Use of WTFS*

We are currently addressing the following areas of investigation.

Dietary components endowed with anti-platelet activity may offer a safe strategy to extend their possible health benefits from cardiovascular health to inflammatory and infectious conditions [162]. Indeed, tomato is a rich source of carotenoids and flavonoid compounds able to reduce platelet aggregation [163–167]; similarly, water extracts of fresh tomatoes as well as other forms of tomato extracts have been shown to decrease in vitro, ex vivo and in vivo platelet activity [162,168,169]. WTFS, being enriched with a complex of anti-platelet aggregating nutrients [170], is capable of dose-dependent inhibition of the STAT-3 transcription factor phosphorylation [99], a relevant player in platelet production [171] and activation [172], responsible for inflammation-inducible platelets hyperactivity, which is a target of JAK2/STAT-3 signaling inhibitors [173]. Therefore, because WTFS lacks the side effects of the culinary use of the fruit [111], ongoing studies are focused on defining its potential efficacy as an alternative to current aspirin in individuals with gastrointestinal intolerance. Since lycopene is an inhibitor of endothelial cell stress-induced damage [174,175], WTFS may also be explored in aging persons at higher risk of brain bleeding and in those individuals who may become more vulnerable to bleeding during and after surgery [176,177].

Because of its anti-oxidative, free-radical scavenging, chelating, and anti-apoptotic properties, lycopene has been demonstrated to protect from several chemical and natural toxins [49,178]. Despite the production of lindane, also known as β -hexachlorocyclohexane, a class 1 carcinogen [179] was discontinued over 30 years ago, over 7 million tons remain to be disposed worldwide [180], still representing a relevant environmental risk factor for a wide range of NCDs [181]. Due to its remarkable stability, at the present, the only remediation to this environmental pollutant, upfront of high costs, resides in concentrating contaminated soil in restricted areas to allow its natural long-lasting decay. The evidence that WTFS is capable of in vitro blocking the biological effects of lindane [99], opens the possibility of exploring a new remediation strategy relying on tomato-dietary supplementation in the form of WTFS or other comparable products [182,183].

This interventional initiative is likely to be informative in a relatively short time if focused on the young population (18-25 years old) who, because of lindane exposure, is affected by impaired spermiogenesis [184], which can be remediated by adherence to the MD [185,186].

5. Conclusions

The steady increase in NCD incidence is imposing both health and non-health-related direct and indirect costs on all economies [187]. In the absence of converging remediation policies, these costs

are foreseen to progressively exceed the capacity of the gross national products to cope with their burden [99].

While nutrient deficiency diseases can be controlled by providing single nutrients, in NCDs generated and sustained by the consumption of unhealthy foods [144], healthy diet and nutrition are recognized of primary relevance in addressing their management [188,189], since their advocacy can reach numerous aspects of society, thus bearing more cost-effective results when suitably tailored [189,190].

In this regard, the development of methods of enhancing the healthy properties of FF of broader sustainability may be the primary choice since they may integrate the dual aim of disease prevention and reduction of disease risk/severity as well across the homeostasis model [150].

We acknowledge that this review, addressing the advancements in enhancing tomato properties as FF using the whole fruit, may have some limitations, since information not funneled through a no peer-reviewing process or in languages other than English may have been missed. Furthermore, comparative analyses have been impaired by the lack of a detailed composition of the whole tomato preparations described [191]. Concentrations of lycopene in more bioavailable isoforms reported fall below those contained in WTFS [137], which is enriched also in other micronutrients of the berry.

Withstanding these limitations, we have described an advancement in devising a new friendly, no-waste-generating technology that improves tomato healthy properties. The identification of the spray dry conditions to produce the WTFS is advantageous in exploiting the significant economic and processing advantages of this processing which can be more easily replicated [192].

WTFS in the form of a powder of defined formulation compared to tomato commodities contains 2% of olive wastewater micronutrients and is endowed with the ability to interfere with metabolic pathways mediating oxidative stress and inflammation, as demonstrated by in vitro [99] and in vivo in animal [83] and human settings of known susceptibility to tomato micronutrients benefits [105].

WTFS, although representing a step ahead in exploiting tomatoes as FF, may nevertheless be considered at its inception and seminal to further improvements relying on:

- a) selection of tomato cultivars with a higher “index of antioxidant nutritional quality (IQUAN)” [43] or higher lycopene content [193];
- b) devising heating processing which increases the concentrations of Amadori’s products [101,137,194] especially of Fru-His compounds;
- c) increasing the olive mill wastewater content [195];
- d) exploring the possibility of developing more focused healthy properties by increasing the concentration of some of its components, i.e. lutein [196], or combining with other healthy micronutrients which may further improve the biological activity of those present in WTFS.

Given available results and preliminary findings, WTFS represents an advanced FF biofortifier of a variety of foodstuffs [197], especially in developing countries where supplementation of nutrients-poor diets is increasingly relying on the use of widely available phytoproducts, such as moringa oleifera [198], of high nutritional content [199] and economic value [200]. Furthermore, in consideration that WTFS retains tomato sensory properties and it may undergo further cooking, it may represent a strategy to increase the fruition of the benefits of the MD at global level by a combined consumption with legumes, tapioca, tuff, and okra which share nutritional properties with foods available in the Mediterranean area (135).

WTFS may be a candidate for exploratory in vitro and in vivo experimentations relevant to the management of disease conditions [201] fueled by low-grade inflammation and to settle still partially contentious issues regarding the benefits of lycopene versus whole tomato dietary supplementation.

Patent: Euro Patent 3 052 113 B1.

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