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Review

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Anticarcinogenic, Cardioprotective, and Other Health Benefits of Tomato Compounds Lycopene, α-Tomatine, and Tomatidine in Pure Form and in Fresh and Processed Tomatoes

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ABSTRACT: Tomatoes produce the bioactive compounds lycopene and α-tomatine that are reported to have potential health-promoting effects in animals and humans, but our understanding of the roles of these compounds in the diet is incomplete. Our current knowledge gained from the chemistry and analysis of these compounds in fresh and processed tomatoes and from studies on their bioavailability, bioactivity, and mechanisms of action against cancer cells and other beneficial bioactivities including antibiotic, anti-inflammatory, antioxidative, cardiovascular, and immunostimulating effects in cells, animals, and humans is discussed and interpreted here. Areas for future research are also suggested. The collated information and suggested research might contribute to a better understanding of the agronomical, biochemical, chemical, physiological, molecular, and cellular bases of the health-promoting effects and facilitate and guide further studies needed to optimize the use of lycopene and α-tomatine in pure form and in fresh tomatoes and processed tomato products to help prevent or treat human disease.

KEYWORDS: *anticarcinogenic effects, cardiovascular effects, lycopene, α-tomatine, tomatidine, fresh and processed tomatoes, chemistry, analysis, biosynthesis, bioactivity, bioavailability, mechanisms, human health, research needs*

INTRODUCTION

Tomatoes are a major source of nourishment for the world's population. World production of tomatoes is estimated at around 159 million tons with about 13 million tons grown in the United States.[1] Tomato plants (*Lycopersicon esculentum*) synthesize the bioactive carotenoid pigments lycopene and β-carotene and the glycoalkaloids dehydrotomatine, α-tomatine, and esculeoside A, possibly as a defense against bacteria, fungi, viruses, and insects. About 20 years ago, we initiated studies designed to increase our knowledge of the analysis, composition, and bioactivities of tomato compounds, cited here in chronological order.[2−14]

As discussed in one of our studies,[15] nature seems to have decreed that the concentration of the red lycopene pigment should increase as the tomato fruit ripens and changes color on the vine. This increase is accompanied by a concurrent decrease in the concentration of tomatine. Green tomatoes therefore have a high content of tomatine, as high as 500 mg/kg fresh wt,[8] whereas the highest content in red tomatoes is only about 5 mg/kg. Tomatoes at intermediate stages of maturity contain less lycopene and more tomatine than do mature tomatoes. For example, the reported lycopene content (in mg %) of large green tomatoes increases from 8 to 124 (breaker), to 230 (pink), then to 374 (red), and finally to 412 (red-ripe) in the stages of fruit ripening.[16] In addition, environmental factors, agricultural practice, size, and color of different tomato varieties and conditions used to process tomatoes into juices, ketchup, pastes, purees, sauces, soups, and dry tomatoes all are reported to influence the content of bioactive compounds. For example, the tomatine content of the same variety of tomatoes harvested from plants grown under "organic" soil and environmental conditions is about twice that of fruit from plants grown under conventional conditions.[17]

In addition to investigations of the beneficial properties of the tomato products described above, the use of tomato-based edible antimicrobial films has been studied as a means of preventing the adverse effects of contaminated food and promoting human health associated with the consumption of tomatoes.[18,19]

Because both lycopene and α-tomatine have been reported to elicit anticarcinogenic and other beneficial effects in vitro and in vivo, the main objective of this overview is to integrate the widely scattered information on the anticarcinogenic potential of these two bioactive tomato compounds in particular, both in pure form and in widely consumed fresh and processed tomatoes. Brief summaries of their cardiovascular and other beneficial effects are also included. The aim here is also to suggest further research approaches in these areas to potentially enhance the health-promoting effects of these natural compounds, individually and in combination with other bioactive food ingredients. The overlapping cellular and molecular mechanistic aspects of the research are described for a better understanding of the health-promoting potential of the tomato compounds. Such an understanding can lead to the development of improved tomatoes and tomato-based foods designed to enhance nutrition and health. The first part of this review covers lycopene and the second part covers the tomato glycoalkaloid α-tomatine and the aglycone tomatidine.

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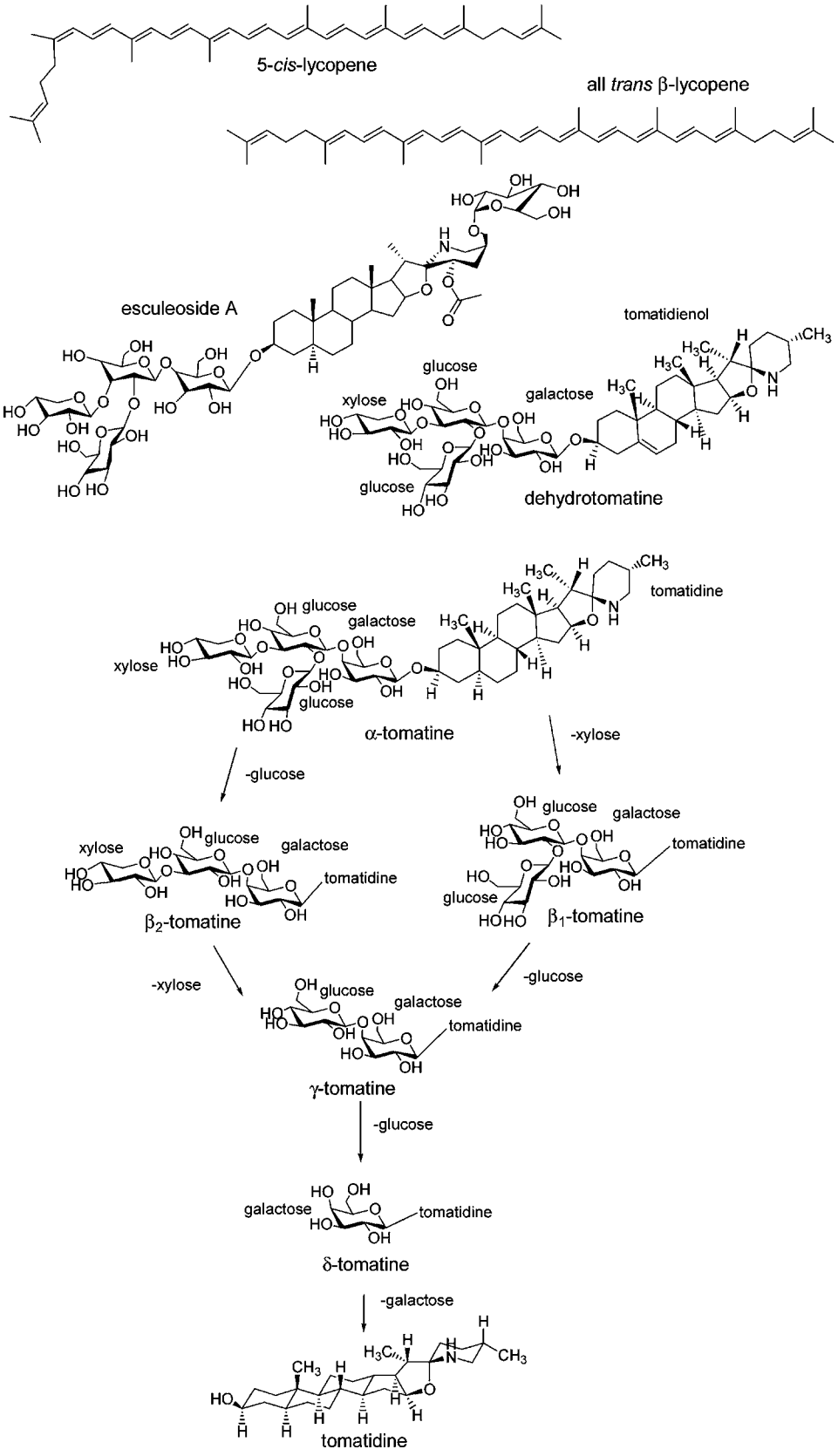

Figure 1. Structures of bioactive tomato compounds. The structure of esculeoside A was adapted from Nohara et al.,[177] and the structures of the two lycopene isomers were adapted from Hernandez-Marin et al.[27]

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LYCOPENE

Chemistry. Tomatoes seem to contain about 80% of dietary lycopene, with apricots, pink grapefruits, pink guavas, papayas, red carrots, watermelons, and algae contributing the other 20%.[20−26] The red pigment lycopene is a polyunsaturated (polyene) straight-chain molecule containing 13 double bonds with a molecular weight of 536.9 and an absorption maximum of 470 nm (Figure 1). The double bonds can exist in *trans* and *cis* configurations.[27] Although the *all-trans* form seems to be the natural form of lycopene synthesized by the tomato plant, the molecule is susceptible to isomerization under the influence of conditions used to process food, including heat, light, acids, and oxygen. The *trans* form is also partly transformed in vivo to the more bioactive *cis* form.

Strong antioxidative and other in vitro and in vivo beneficial effects of lycopenes are associated with their ability to act as free radical scavengers.[28] Lycopene is a highly efficient singlet oxygen quencher, both in vitro and in plasma, suggesting that its antioxidant effects might involve scavenging free electrons from reactive oxygen species (ROS).[29] Free radicals are highly reactive, short-lived molecules that can react with and damage essential structural proteins, enzymes, and DNA. Such damage has the potential to cause cancer, atherosclerosis, cardiovascular, and other diseases. Lycopene has the potential to reduce such undesirable molecular events because the high-energy, highly reactive free electron on DNA is transformed to a much less reactive more stable (with a lower ground-state energy) free electron (radical) after it is dissipated (delocalized) along the conjugated 13 double bonds of the lycopene molecule. An analogous mechanism governs antioxidative effects of plant phenolic compounds such as chlorogenic acid.[30]

These observations can explain the extraordinary multidisciplinary interest in lycopene, as evidenced by the fact that the Scopus database lists more than 6400 citations under "lycopene". Here, we will discuss some of the relevant multidisciplinary studies that enhance our understanding of the role of tomato-derived lycopene in the plant and in the diet.

Analysis. The mostly *trans*-lycopene isomer in fresh tomatoes is converted both in vitro under the influence of heat and enzymatically in vivo to less stable but more bioavailable 9-, 13-, and 15-*cis*-lycopenes.[31] The following capsule summaries provide an introduction into the extensive literature on the analysis of lycopene isomers.

Because geometrical isomers of carotenoids differ in their stability to oxidants and bioavailability, with the *cis*-isomer of lycopene being more bioavailable than the *trans*-form,[32] it is important to know the content of *cis*/*trans* (*Z*/*E*) isomers for nutritional and other studies. To meet this need, Melendez-Martinez et al.[33] used an HPLC method to analyze up to 48 carotenoid (*α*-carotene, *β*-carotene, *β*-cryptoxanthin, lutein, lycopene, phytoene, phytofluene, and zeaxanthin) isomers in 62 min and to detect 26 isomers in biological samples. Ishida et al.[34−36] used an HPLC method to follow the partial transformation of *all-tetra-cis*-lycopene during heating and juicing of tangerine tomatoes to *trans*- and other *cis*-forms. In another study, Hernandez-Marin et al.[27] calculated antioxidant properties of lycopene isomers and their relative abilities to transfer one electron to the hydroxyl radical. The calculations predict that neutral *cis*- and *trans*-isomers maintain the same color, whereas the color of ionic species shifts to a longer wavelength (>700 nm).

Interestingly, refluxing a tomato resin in ethyl acetate for 1 week results in transformation of the lycopene *E*-isomer to the more stable and more bioavailable 13*Z*-, 9*Z*-, and 5*Z*-lycopene isomers.[37] Plasma levels of lycopene isomers are related to the levels present in food.[38] Consumption patterns of carotenoid isomers can be used to improve disease prevention.[39] Honest et al.[31] reviewed the literature on the relationship between lycopene isomerization and bioavailability and bioactivity properties. Additional studies designed to optimize the analysis of lycopene and its isomers in different milieus are described by Panthee et al.[13] and Luterotti et al.[40] The availability of C-13 labeled lycopene is expected to facilitate human bioavailability, metabolism, and pharmacokinetic studies.[41,42]

Content in Fresh Tomatoes. Several factors can affect the lycopene (Figure 2) content of fresh tomatoes, as highlighted in the following selected studies.

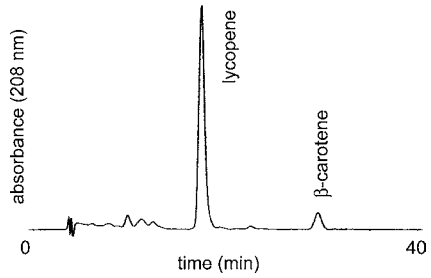

Figure 2. HPLC chromatogram showing separation of lycopene and *β*-carotene in a red tomato extract.[137]

Cherry tomatoes grown under the influence of moderate salt stress contained higher amounts carotenoids and exhibited increased lipophilic antioxidative capacity compared with tomatoes grown in the absence of stress.[43] The carotenoid content of different tomato varieties (cherry, plum, round, and others) grown in Ireland differed significantly from those grown in Spain, suggesting that geographical location has a greater effect on carotenoid content and bioaccessability, which is defined as the amount of ingested carotenoids available for absorption by the intestinal cells after digestion.[44] Tomatoes grown under "organic" conditions contained greater amounts of total phenolics (chlorogenic acid, kaempferol, myricetin, and quercetin-3-*O*-glucoside) as well as *α*-tomatine than tomatoes grown under conventional conditions.[17,45,46] Evidently, because of the absence of synthetic pesticides, tomato plants grown under organic conditions synthesize more secondary metabolites for protection against phytopathogens than do tomato plants grown under conventional conditions.

Sun et al.[47] describe genes that control lycopene content of growing tomatoes. Amplification of these genes using molecular biology techniques might make it possible to create high-lycopene tomatoes. It is also relevant to note that the carbon to nitrogen (C:N) ratio of the tomato plant seems to be a good indicator of the concentrations of phenolic compounds and tomatine that are involved in defense against phytopathogens.[48] We recently found that the lycopene and *β*-carotene contents as well as the contents of 11 phenolic compounds of 12 different varieties of greenhouse-grown commercial cherry tomatoes varied widely, suggesting that genetic factors seem to govern the biosynthesis of bioactive compounds in cherry tomatoes.[12]

Content in Processed Tomatoes. Exposure of tomatoes to processing conditions used by food processors, restaurants,

and in the home designed to prepare a wide range of edible tomato products can, in principle, adversely or beneficially affect the lycopene content of the final products, as illustrated by the following selected observations.

An early review on the influence of food processing[49] on lycopene states that (a) thermal processing (bleaching, retorting, freezing) causes some loss in tomato-based foods; (b) heat induces isomerization of the *all-trans-* to the *cis*-form; (c) dehydrated and powdered tomatoes have poor lycopene stability; (d) frozen and heat-sterilized foods exhibit excellent stability; (e) the bioavailability of the *cis*-isomers in foods is higher than that of *all -trans* -isomers; and (f) lycopene bioavailability in processed products is higher than in fresh tomatoes.

Analysis of catsup (ketchup) from 13 commercial sources showed that the content of lycopene ranged from 59.4 to 183.6 μg/g and the Trolox equivalent antioxidant capacity from 176.5 to 356.8 TEAC units.[35] The antioxidative activity of ketchup was related to its content of *trans*-lycopene.[50] Thermal processing of tomato pulp at 130 °C improved the in vitro bioaccessability of lycopene, defined as the fraction of the nutrient that is released from the food matrix.[51,52] *all-trans*-Lycopene and other carotenoids underwent isomerization during canning and storage of tomato juice.[53] Related studies showed that (a) during storage of tomato juices, lycopene degradation varied as a function of the tomato cultivar, processing method, storage temperature, and time and that the use combined pressure−heat treatments increases lycopene extractability;[54−57] and (b) exposure of tomato juice to pulsed electric fields resulted in a higher content of polyphenolic compounds (caffeic-*O*-glucoside acid, *p*-coumaric acid, chlorogenic acid, *cis*-lycopene, naringenin, and rutin)[58] and had a higher content of volatile compounds and better sensory properties than juice prepared with untreated tomatoes.[50,59] A study with tomato pasta indicates that the in vitro accessibility of lycopene seems to be influenced by the conditions applied during in vitro intestinal digestion.[60] High-pressure sterilization of a tomato puree limited lycopene isomerization compared with the equivalent thermal sterilization.[61] Aseptic thermal processing of tomato soup reduced vitamin C content but had only a minor effect on lycopene content.[52] Oven-baking of sliced tomatoes at 160 °C for 20 min resulted in significant increases in the content of lycopene, β-carotene, and α-tocopherol, isomerization of *all-E* to various *Z* isomers, and in an increased release of the carotenoids and tocopherols from the tomato matrix.[62] An investigation of industrial processing on the stability of tomato carotenoids indicates that, overall, the nutritional quality of tomato-processed products is mainly preserved during manufacture, except for vitamin C.[63]

Thermal and pressure treatment of a puree containing olive oil induced both degradation of lycopene and conversion of *trans-* to *cis*-isomers.[61] A related study found that thermal treatment of tomatoes breaks down cell walls, thus facilitating the release of carotenoids and tocopherols from the matrix, and increases isomerization of lycopene and to a lesser extent of β-carotene.[62] Postharvest treatment of vine-ripe tomatoes resulted in a 14% increase in lycopene and a decrease in β-carotene content.[64] Other tomato processing conditions that might affect the content and bioavailability of lycopene include exposure to a pulsed electric field,[65] supercritical extraction,[66] and high-pressure homogenization.[67] Real-time monitoring of lycopene content during the production of tomato juice may allow payment to tomato growers based on the lycopene content of the crops.[68]

Inhibition of Cancer. Numerous studies have been devised to attempt to determine whether the observed cancer cell-inhibiting effects of lycopene in vitro could be confirmed in vivo in animal models and in humans. Selected recent studies mentioned below show that the results do not seem to offer a definitive answer.

Because tomato and soy products have each shown anti-prostate cancer activity in laboratory studies, Zuniga et al.[69] determined the effect of dietary tomato and soy germ alone and in combination against prostate carcinogenesis in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model. The results show that the combination diet was most effective in reducing the proliferative index (PI) in the prostate epithelium of the mice. The authors suggest the need to develop tomato−soy foods with defined composition and bioactivities for clinical trials.

A structure−activity study of 11 synthetic carotenoids (apocarotinals) against breast cancer cells provides mechanistic evidence for their bioactivities in terms of activation of the electrophile/antioxidant response element (EpRE/ARE) transcription system and induced expression of phase II metabolizing enzymes.[70] Related studies suggest that some of the cellular effects of carotenoids might be mediated through their derivatives formed in vivo by chemical oxidation or enzymatic cleavage inside the cells.[71,72]

On the basis of a review of the literature, Sporn and Liby[73] concluded that although lycopene has been shown to prevent cancer in experimental animals, the compound is not potent enough to be clinically useful as a drug for prostate cancer, mainly because high concentrations above 1 μmol/L are needed to achieve meaningful biological responses in humans. Ilic et al.[74−76] came to a similar conclusion on the basis of an analysis of the literature that there is insufficient evidence to either support or refute the use of lycopene for the prevention of prostate cancer. Related studies examine differences in consumption of carotenoids by different ethnic groups[39] and the association between the prostate-specific antigen (PSA) screening test and lycopene consumption.[77]

Cellular and Molecular Mechanisms of Antineoplastic Effects. Unlike anticancer drugs, the molecular mechanisms of natural compounds involve modulation of multiple targets, including transcription factors, growth factors, tumor cell survival factors, inflammatory pathways, and invasion and angiogenesis linked to carcinogenesis.[78−84] The complex, overlapping mechanisms of lycopene action on cancer cells involving antioxidant, anti-inflammatory, immunostimulating effects, up-regulation of connexin-43, and modulation of cyclo-oxygenase pathways, growth factors, and growth factor receptors have been extensively studied.[85−90] The following brief summaries of selected biomarkers and signaling pathways offer an indication of the complexity of these mechanisms.

- Lycopene-induced apoptosis against hepatocarcinogenesis in female Balb/c mice might be due to its ability to act on apoptosis-associated genes and as a pro-oxidant.[56,91]
- Proteins in human primary prostatic epithelial cells that were most affected by lycopene were those that were involved in antioxidant responses, apoptosis, growth inhibition, androgen receptor signaling, and the Akt/mTOR signaling cascade, confirming previous studies that lycopene can prevent cancer in human prostatic epithelial cells at the stages of cancer initiation, promotion, and/or progression.[92]

• Lycopene selectively inhibited MCF-7 breast cancer cells but not MCF-10 normal mammary epithelial cells.[91] The inhibition of cell growth is associated with the modulation of cell cycle proteins such as β tubulins as well as heat shock proteins, decreasing tumors in Balb/c mice by 42%.

• Exposure of human breast (MCF-7) and endometrial (ECC-1) cancer cells to lycopene resulted in the reduction in cyclin D1, a growth factor sensor in the G1 phase of cell division, suggesting that the attenuation of cyclin D1 levels is a key mechanism for the reduction of the mitogenic action of the insulin-like growth factor (IGF-1), which plays an important role in the proliferation of normal and cancer cells.[93]

• Lycopene induces cell growth inhibition by altering the mevalonate pathway in Ras gene-activated prostatic carcinoma LBCaP cells through inactivation of Ras and reduction of intracellular total cholesterol via inhibition of the expression of the enzyme 3-hydroxy-3-methylgutaryl-coenzyme A (HMG-CoA) that catalyzes cholesterol biosynthesis.[86]

• Both lycopene and, to a greater extent, the aldehyde oxidation product formed in vivo called apo-12′-lycopenal reduce proliferation in androgen-independent DU145 prostate cancer cells and in mouse embryonic fibroblasts and rat tumors by inhibiting normal cell cycle progression without affecting the gap junction communication protein connexin 43.[72]

• A suggested mechanism underlying the antiangiogenic activity (inhibition of blood vessel formation in tumors) in mice involves inhibition of the matrix metalloproteinase-2 (MMP-2)/urokinase-type plasminogen activator (uPA) system through vascular endothelial growth factor receptor (VEGFR2)-mediated reduction in protein expression of the P13K-Akt and ERK/p38 signaling pathways.[94,95]

• Lycopene seems to act as an in vivo redox agent that protects tissues against high concentrations of ROS, thus preventing oxidative damage of cells and DNA.[96,97]

• Lycopene protected rats against induced liver tumors by altering the expression of Bax, Bcl-2, caspases, and oxidative stress biomarkers.[98]

Other Beneficial Effects. Here, we briefly mention several additional potential health-promoting effects ascribed to lycopene.

• Physiological concentrations of lycopene attenuated the lipopolysaccharide (LPS)-mediated induction of TNF-α in RAW 264.7 macrophages at both the mRNA and protein levels, suggesting that the anti-inflammatory effect of lycopene could result in a disruption of the undesirable interactions between adipocytes and macrophages in adipose tissues in obese individuals.[99,100]

• The immune system in suckling BALV/c mice pups was not affected by lycopene-containing breast milk, and lycopene also had no effect on the colonization of the intestines, spleens, and livers by *Yersinia enterocolitica* in female neonatals and pups infected with the enteropathogen.[99]

• The cardioprotective effect of lycopene on induced oxidative stress and heart lysosomal damage in rats was accompanied by up-regulation of interleukin (IL)-12 and interferon (IFN)-γ.[101]

• Preincubation of airway cells with lycopene resulted in an 85% reduction in rhinovirus-1B replication, suggesting that the pigment might have a role in suppressing rhinovirus-induced airway inflammation.[102]

• The antineuroinflammatory effect of lycopene seems to be associated with inhibition of LPS-induced Cox-2 expression mediated by HO-1 activation through the AMPK pathway.[103]

• Lycopene reduced the DNA damage and recovered the liver and kidney tissue injuries in rats with obstructive jaundice,[104] suggesting that it might be of value in the treatment of sepsis, a virulent infection-related disease that causes 250,000 annual deaths in the United States.[105]

• Lycopene inhibited hepatic steatosis in mice fed a high-fat diet via microRNA-21-induced down-regulation of fatty acid-binding protein 7, suggesting that the compound could be used to treat nonalcoholic fatty liver disease.[106]

• Tomato juice administration partially reverted the metabolic pattern of the rat liver from a high-fat diet to a normal diet.[107]

• Lycopene, lutein, and β-carotene acted synergistically in protecting mice against peritonitis, suggesting the need for further studies on the efficacy of combinations of these phytonutrients against the production of pro-inflammatory mediators.[108]

• Lycopene and carotene protected the skin against sunburn (solar erythema) by increasing basal defense against UV light mediated damage.[109]

Bioavailability in Humans. No official recommendation exists for lycopene consumption. With this objective in mind, we will briefly mention selected studies on lycopene consumption and bioavailability in humans.

• A bioavailability study showed that plasma lycopene levels of nine healthy young adults increased during consumption of a spinach−tomato diet from 0.05 to 0.52 μM/L and that levels of the carotenoid lutein increased after spinach consumption from 0.05 to 1.59 μM/L.[110,111]

• The consumption of lunches containing 300 g of tangerine tomatoes or red tomato sauce per day by 21 healthy American adults showed that tangerine tomatoes, which contained about 3 times less of the *tetra-cis*-lycopene isomer than did tomato sauce, increased blood lycopene levels more than did the red tomato sauce, showing that the *tetra-cis*-lycopene is absorbed more efficiently than the *trans*-form from common red tomatoes and suggesting that total lycopene blood concentrations in humans can be increased by substituting *tetra-cis*-lycopene-rich tangerine tomatoes for common red tomatoes in the diet.[112]

• The average lycopene intake mostly from raw tomatoes by Canadian women (n = 101) was 6.14 ± 5.35 mg/day.[113] The mean lycopene intake by Belgian adults (n = 3083) from tomatoes (43%) and sauces (41%) was 4.1 ± 2.3 mg/day, suggesting that the intake was comparable to intakes reported in neighboring countries but was below the acceptable or desirable daily intake.[114] The mean intake of β-carotene, lycopene, and lutein by Polish adults was 6.3, 7.0, and 2.7 mg/person/day, respectively, with lycopene originating from fresh tomatoes (32%) and processed tomato products (50%).[115]

• The consumption by 26 individuals of a commercial drink sold in Italy containing a tomato extract for 26 days resulted in a significant increase in plasma and lymphocyte lycopene levels and a 42% reduction of DNA damage in lymphocytes subjected to oxidative stress, suggesting that carotenoids from tomato products can protect cells against oxidants.[116]

• The consumption of tomato and vegetable soups by 60 individuals for 15 days resulted in a significant increase in total plasma lycopene concentrations, an increase in the ratio of *cis*- to *trans*-lycopene isomers, and a significant increase in ex vivo lipoprotein lag period used as a measure of antioxidant capacity.[117]

• A cross-sectional survey of 986 Japanese individuals 70 years and older showed that a tomato-rich diet is independently related to a lower prevalence of symptoms of depression and that the intake of other vegetables had no effect.[118]

• Serum concentrations of the cytokines IL-6 and TNF-α decreased significantly in overweight female students (n = 56) but not in control females consuming 330 mL/day tomato juice, suggesting that increasing tomato intake may help reduce inflammatory diseases associated with the two cytokines.[119]

• The daily consumption of tomato products (tomato juice, ketchup, soup, and paste) containing 30 mg of lycopene by 17 individuals for 4 weeks resulted in an increase of the average serum lycopene level from 182 to 685 nmol/L and a significant reduction in lipid and protein oxidation, suggesting that a tomato-rich diet containing different sources of lycopene can increase serum lycopene levels and reduce oxidative stress.[120]

• A soy-fortified tomato juice containing a total of 14.13 μmol/100 mL lycopene + β-carotene significantly improved blood lipid and antioxidant status during an 8 week trial in healthy men and women, suggesting that this functional food can be used to deliver defined amounts of bioactive compounds in long-term clinical trials.[121]

• Human bioavailability of lycopene from "red" carrots (44%) was similar to that from tomato paste,[21] whereas it was 2.6 times more bioavailable from papayas than from tomatoes.[22]

Health-Promoting Effects in Humans. Here, we will briefly mention selected beneficial effects of lycopene-containing food in humans.

• An epidemiological study in China with 130 prostate cancer patients and 274 hospital controls showed that prostate cancer risk was reduced with increased intake of green tea and lycopene-containing fruits and vegetables and that the combination has a stronger effect than either dietary component consumed separately.[122]

• A whole food intervention study with cancer-free African-American men (n = 36) at a higher prostate cancer risk resulted in 53 and 40% increases in plasma lycopene concentrations in months 1 and 3, respectively, with no change in the control group.[123]

• An analysis of prospective cohort studies on the relationship between carotenoids and breast cancer (3055 case subjects and 3956 matched controls) suggests that women with higher circulating levels of carotenoids (α-carotene, ß-carotene, lutein + zeaxanthin, lycopene, and total carotenoids) may experience reduced risk of breast cancer.[124] A meta analysis (n = 1958) showed that a high intake of lycopene and other carotenoids is associated with a lower risk of esophageal cancer.[125]

• An inverse association seems to exist between the consumption of tomato products among middle-aged and older women (n = 39876) and cardiovascular disease (CVD).[126] Women consuming >10 servings/week of tomato-based food products (tomatoes, tomato juice, tomato sauce, pizza) compared to <1.5 servings/week had a clinically modest but significant improvement in several coronary biomarkers (total cholesterol, total cholesterol/high-density lipoprotein (HDL) cholesterol ratio, and hemoglobin A1c).[127]

• The consumption of tomato products rich in lycopene by 25 men and women on a high-fat diet attenuated induced oxidative stress and associated inflammatory response, suggesting a potentially protective role of tomato consumption in reducing CVD.[128] Overall, a greater amelioration of CVD risk factors (lipid profiles, homocysteine, intercellular adhesion molecule 1 or ICAM-1) was observed in 18 healthy women consuming tomato juice supplemented with n-3-polyunsaturated fatty acids versus plain tomato juice.[129] A study designed to determine lycopene's ability to modulate systemic and high-density lipoprotein (HDL)-associated inflammation in moderately overweight middle-aged individuals showed that the tomato compound significantly increased HDL functionality, revealing the heart-protective properties of increased lycopene intake.[130] A 2 week intervention study with Mexican individuals (n = 50) showed that consumption of two raw tomatoes per day for 2 weeks resulted in a significant increase in HDL (good) plasma cholesterol from 36.5 to 41.6 mg/DL.[131]

• An intervention trial with healthy middle-aged volunteers showed that a high daily consumption of tomato-based products (32−50 mg lycopene/day) or lycopene supplements (10 mg/day) was ineffective in reducing CVD inflammatory and insulin resistance markers.[132] Low plasma concentrations of antioxidative lutein and zeaxanthin, but not lycopene, β-cryptoxanthin, or α-carotene, were associated with increased risk of atrial fibrillation in elderly individuals.[133,134]

• The administration of tomato-based food for special medical purposes (FSMP) to 8 healthy volunteers and 39 patients with chronic hepatitis C virus (HCV) prevented carotenoid serum depletion, did not affect the therapeutic response, but was effective in improving the oxidative stress during viral therapy.[135]

• A prospective study of 1031 Finnish men aged 46−65 years showed that men with the highest quartile of serum lycopene had 59 and 55% lower risks of ischemic stroke and any stroke, respectively, compared with men in the lowest quartile.

• A clinical study showed that locally delivered lycopene gel was effective in reducing gingival inflammation and injury compared to a placebo in smoking and nonsmoking subjects.[136]

The cited human consumption, bioavailability, and health-promoting studies originating from different countries clearly show that plasma lycopene levels are a function of the dietary content of fresh and processed tomatoes and that high levels are associated with lower risk of CVD and some cancers. I agree with the suggestion by a journal reviewer that because lycopenes are more bioavailable from processed than from fresh tomatoes, clinical and epidemiological studies should compare beneficial effects from both lycopene sources.

■ α-TOMATINE

Analytical and Compositional Aspects of Tomatoes. We previously reported that the tomato glycoalkaloid referred to as tomatine (mol wt 1034.18) consisted of a ~10:1 mixture of α-tomatine and dehydrotomatine (Figures 1 and 3).[5,137] The structure of dehydrotomatine is different from that of α-tomatine in that the former molecule has a double bond in the steroidal ring B of the aglycone. Note that both tomato glycoalkaloids have the same tetrasaccharide side chain, lycotetraose. α-Tomatine has lycotetraose attached to the aglycone tomatidine, whereas dehydrotomatine has lycotetraose attached to the aglycone tomatidenol.

We used two methods to identify dehydrotomatine and α-tomatine. First, retention times on HPLC peaks of pure dehydrotomatine and α-tomatine were compared to corresponding peaks from the tomato extracts. Second, samples from each peak, collected several times from the HPLC column, were then acid hydrolyzed into sugars and aglycone. The sugars were converted to trimethylsilyl ester derivatives. Individual compositions and molar ratios of sugars were determined by

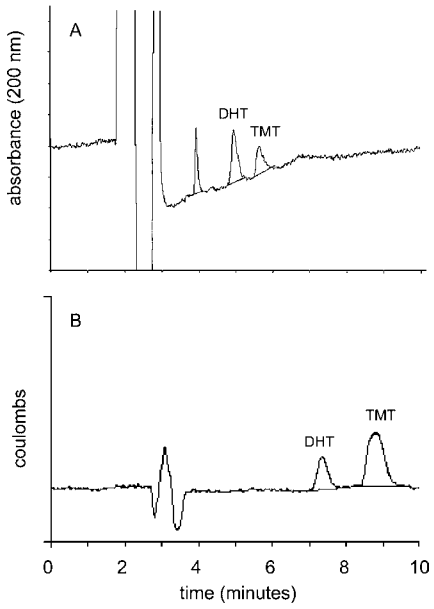

Figure 3. HPLC chromatogram showing separation of dehydrotomatine (DHT) and α-tomatine (TMT) using (A) UV detection and (B) pulsed amperometric detection. The term "tomatine" implies the presence of both glycoalkaloids. Adapted from Friedman and Levin.[5]

gas–liquid chromatography (GC). Sugars and aglycones were determined by gas chromatography–mass spectrometry (GC-MS), as described in detail in previous publications.[3,137–139] The quantification of dehydrotomatine and α-tomatine was accomplished by comparing the HPLC peak area from the sample to the peak area of known amounts of pure dehydrotomatine and α-tomatine isolated from tomato fruits.

Figure 2 shows that dehydrotomatine eluted from the HPLC column well separated from α-tomatine's elution time.[15] The detection limit was estimated at 0.39 μg for dehydrotomatine and 0.94 μg for α-tomatine. The dehydrotomatine and α-tomatine of tomatoes varied from 42 to 1498 μg/g of fresh wt and from 521 to 16285 μg/g of fresh wt, respectively. The ratio of α-tomatine to dehydrotomatine ranged from 10.9 to 12.5 in tomatoes and from 2.3 to 7.8 in other plant tissues, suggesting that the biosynthesis of the glycoalkaloids seems to be under separate genetic control in each plant part.

Another study[9] showed that (a) the dehydrotomatine content of six green tomatoes (in mg/100 g fresh wt) ranged from 0.89 to 8.05, a 9.0-fold variation from lowest to highest value; (b) the corresponding range for α-tomatine was from 5.7 to 31.40, a 5.5-fold variation; (c) the sums of the concentrations of the two glycoalkaloids ranged from 6.64 to 39.45, a 5.9-fold variation; and (d) the total glycoalkaloid content per tomato fruit (in μg) ranged from 434.0 to 1110.4, a 2.56-fold variation.

It is well-known that tomatine decreases during the ripening process.[15] The cited data show that both individual and total amounts of glycoalkaloids in green tomatoes vary widely, but less so when calculated in terms of concentration per fruit. Although the glycoalkaloid content per weight of fruit decreases as the fruit grows, the values per unit fruit remain about the same, until the fruit turns red, at which time the tomatine is nearly completely degraded. Statistical analysis showed that size, maturity, and glycoalkaloid content are well correlated. Additional studies on the analysis of tomato glycoalkaloids are described in the cited references.[8,17,48,137,140,141]

Interestingly, some wild-type potato cultivars contain high amounts of α-tomatine,[6,142] as do edible cultivars grown in the Andes mountains of Peru.[143]

Inhibition of Cancer Cells in Vitro. Inhibitory concentrations at 50% (IC_{50}) values for α-tomatine were calculated by constructing a four-parameter logistic curve using the values from percentage inhibition of normal and human cancer cells, with the aid of SigmaPlot 11 (Systat Software, Inc., San Jose, CA, USA); the IC_{50} was extrapolated from the graph at 50% cell inhibition. The IC_{50} was compared to a number of variables in the tomatoes: tomato size, ripeness, and alkaloid content.

Using a microculture tetrazolium (MTT) in vitro assay, we previously reported that tomatine is a strong inhibitor of growth for both human colon and liver cancer cell lines, as evidenced by the dose-dependent (0.1–100 μg/mL) inhibition of HT29 colon cancer cells at levels ranging from 38.0 to 81.5% and of human HepG2 cancer cells from 46.3 to 89.2%.[144] The anticarcinogenic activity against human liver cancer cells at a tomatine concentration of 1 μg/mL was greater than the corresponding activity observed with the commercial anticancer drug doxorubicin. Other beneficial effects of tomatine include lowering cholesterol and triglycerides,[145] enhancing the immune system,[146] and protecting against virulent bacteria and protozoa.[7] Tomatine is also reported to induce T-cell-mediated regression of murine lymphoid experimental tumors, EG7-Ova.[146]

To help define the possible roles of the four sugar moieties attached to α-tomatine in the inhibition of cancer cell growth, we compared the growth-inhibiting effect of α-tomatine to four hydrolysis products with three, two, one, and zero sugar side chains (Figure 1) against three cancer and two normal cell lines using the MTT cell viability and tumor necrosis factor (TNF-α) assays.[11] These compounds were prepared by partial acid hydrolysis of α-tomatine and characterized by thin layer chromatography (TLC) and mass spectrometry (LC-IT-TOF).

The results (Figure 4) show that the tetrasaccharide side chain associated with α-tomatine is a key structural feature of the molecule that influences the inhibition of both normal and

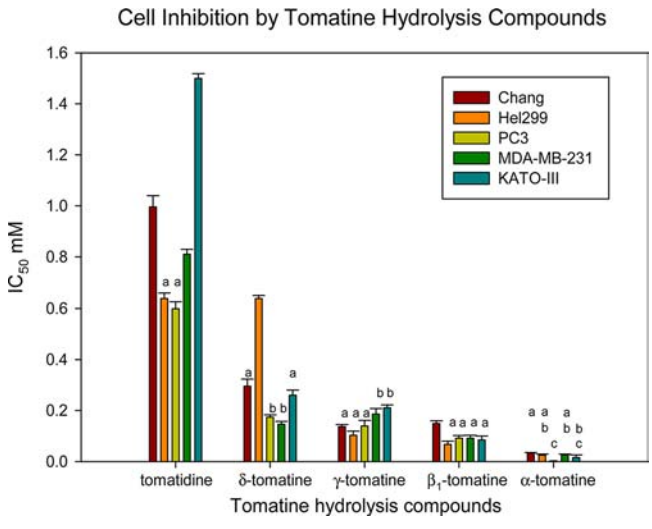

Figure 4. IC_{50} values for the inhibition of one normal and four cancer human cell lines: normal human liver (Chang) and lung (Hel299) cell lines, human prostate (PC3), breast (MDA-MB-231), and gastric adenocarcinoma (KATO-III) cell lines by α-tomatine isolated from green tomatoes and hydrolysis products. Adapted from Choi et al.[11]

cancer cells. Systematic removal of one, two, or three sugar residues from α-tomatine results in the formation of compounds with significantly reduced activity.

We also investigated six green and three red tomato extracts for their ability to induce cell death in human cancer and normal cells using an microculture MTT assay.[9] Compared to untreated controls, the high-tomatine green tomato extracts strongly inhibited the following human cancer cell lines: breast (MCF-7), colon (HT-29), gastric (AGS), and hepatoma (liver) (HepG2), as well as normal human liver cells (Chang). There was little inhibition of the cells by the three low-tomatine red tomato extracts. We also evaluated cell death induced by the pure glycoalkaloids dehydrotomatine and α-tomatine isolated from green tomatoes and characterized by HPLC, GC, and GC-MS, as well as their respective aglycones tomatidenol and tomatidine. α-Tomatine was highly effective in inhibiting all of the cell lines. Dehydrotomatine, tomatidenol, and tomatidine had little, if any, effect on cell inhibition. The results show that the susceptibility to destruction of the cells varies with the nature of the alkaloid and plant extract and the type of cancer cell.

Our discovery that α-tomatine is a potent anticarcinogen seems to have stimulated interest by other investigators in defining the detailed molecular mechanism of apoptosis. Here, we will briefly summarize published information on the inhibition of cancer by α-tomatine.

Shih et al.[147] investigated the mechanism of the antimetastatic effect of α-tomatine in human lung adenocarcinoma A549 cells. They found that the glycoalkaloid (a) inhibited cell invasion and migration and phosphorylation of Akt and extracellular signal-regulated kinase 1 and 2 (ERK1/2); (b) did not affect phosphorylation of c-Jun N-terminal kinase (JNK) and the p38 gene; (c) decreased nuclear levels of nuclear factor kappa B (NF-κB), c-Fos, and C-Jun; and (d) inhibited binding abilities of NF-κB and activator protein-1 (AP-1). These and related molecular events suggest that inhibition of metastasis occurs by reducing MMP-2, MMP-9, and u-PA activities through suppression of the phosphoinositide 3-kinase/Akt (PI3K/Akt or ERK1/2 signaling pathway and inhibition of NF-κB or AP-1 binding activities. The authors suggest that these results indicate that α-tomatine may have therapeutic value in the treatment of lung cancer.

A related study by Shieh et al.[148] confirmed that α-tomatine suppressed invasion and migration of human nonsmall lung cancer NCI-H460 cells through inactivation of the FAK/PI3K/Akt signaling pathway and lowering binding activity of NF-κB. The proposed mechanism of the antimetastatic effect occurs through inactivation of the signaling pathway and enhancement of IkBα protein expressions to reduce NF-κB DNA binding activity, resulting in down-regulation of MMP-7 expression. Additional events that contribute to inhibition of cell migration and invasion include interference with the rearrangement of the actin cytoskeleton by decreasing the expression of pFAK protein.

Lee et al.[149,150] investigated the molecular mechanism of the antiproliferative effect of α-tomatine against human prostatic adenocarcinoma PC-3 cells, which we found to be highly susceptible to α-tomatine. They found that the IC_{50} of the inhibition was 1.67 μM, with cytotoxicity against the PC-3 cells occurring after an hour of treatment. The cytotoxicity against normal liver and prostate cells was lower than against the PC-3 cells. They concluded that cytotoxicity was mainly due to induction of apoptosis, as evidenced by decreased mitochondrial membrane potential and increased nuclear condensation; polarization of F-actin potential; cell membrane permeability and cytochrome C expression; induction of activation of caspase-3, -8, and -9; inhibition of NF-κB nuclear translocation; and a decrease in NF-κB/p50 and NF-κBp65 in the nuclear fraction.

These observations imply that both intrinsic and extrinsic pro-apoptosis pathways are involved and that α-tomatine may protect against prostate cancer development and progression. The observation that TNF-α treatment enhances the motility and invasiveness of prostatic cancer cells suggests that this pro-inflammatory protein contributes to cancer metastasis[151] and that α-tomatine-induced reduction in TNF-α levels may help overcome these molecular events.

Kúdelová et al.[152] discovered that α-tomatine inhibits human leukemia MOLT-4 cells by activating cell cycle checkpoints without damaging single or double DNA strands in the cells. The induced slowing of the cell cycle seems to involve caspase-independent cell death associated with an increase in p53 and the BH3-only protein and other protein biomarkers associated in cell cycle regulation.

Anticarcinogenic Effects in Vivo. In a long-term study, we showed that feeding 2000 ppm of commercial tomatine and 224 ppm of the multiorgan carcinogen dibenzo[*a*,*l*]pyrene (DBP) to rainbow trout resulted in reduced incidences of liver and stomach tumors by 41.3 and 36.3%, respectively, as compared to the incidence of tumors observed with DBP alone (Figure 5).[153] The rainbow trout model is highly sensitive to diverse chemical carcinogens and is a statistically powerful vertebrate model used in many comparative studies of chemical carcinogenesis and its modulation by dietary inhibitors. To our knowledge, this study seems to be the first report that evaluated the anticarcinogenicity of α-tomatine in vivo. The following in vivo observations seem to confirm the health-promoting effects of α-tomatine in animal models.

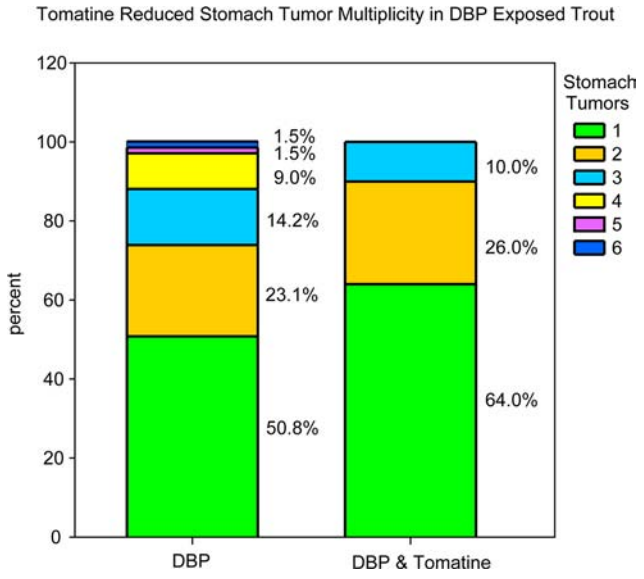

Figure 5. Reduction of multiple tumors (tumor multiplicity) by orally fed commercial tomatine in trout with dibenzo[*a*,*l*]pyrene (DBP)-induced colon cancer. Adapted from Friedman et al.[153]

Because agents that suppress NF-κB may inhibit the development of prostate cancer, Lee et al.[154] evaluated the antitumor activity of α-tomatine against androgen-independent

prostate cancer (PC-3) cell tumors grown in mice. They found that intraperitoneally (ip) administered α-tomatine (5−10 mg/kg) significantly attenuated the growth of the PC-3 cells and that the tumor suppression was associated with increased apoptosis and lower proliferation of tumor cells and by reduced nuclear translocation of the p50 and p65 gene components of the NF-κB signaling pathway. In vitro, the beneficial apoptotic effect against PC-3 cells was associated with several biomarkers of tumor inhibition. These include reduction of TNF activation and the expression of NF-κB-dependent anti-apoptotic proteins. This study seems to provide evidence that α-tomatine can inhibit the growth of prostate cancer tumors in vivo without inducing overt toxicity.

Tomsik et al.[155] evaluated the effect of α-tomatine and growth and mitotic activity of solid Ehrlich tumors in mice. They found that (a) ip injected tomatine at 1 mg/kg slowed tumor growth and reduced tumor cell proliferation; (b) the combination of α-tomatine (1 mg/kg) and the cancer drug doxorubicin (2 mg/kg) acted synergistically and extended survival of the mice; and (c) ex vivo, α-tomatine inhibited intracellular DNA and protein synthesis in the tumor cells with IC_{50} values of 8.7 and 6.6 μM, respectively. The authors note that the activity against Ehrlich tumors, which are derived from adenocarcinoma of the mammary gland, seems to involve the immune system in the inhibition of tumor progression, and because the ip LD_{50} value of α-tomatine is high at 32.4 mg/kg,[152] the effectiveness of the 1 mg/kg dose seems to indicate that this is a safe dose. Because the intravenous (iv) LD_{50} dose is lower at 18 mg/kg[156] than the ip dose, the authors suggest that the ip route may be safer.

α-Tomatine improved the ability of the cancer drug paclitaxel to induce death of androgen-independent prostate cancer PC-3 cells vitro and in mice by down-regulating Akt-regulated pro-survival proteins and up-regulating Akt-regulated pro-apoptotic proteins, suggesting that the combination could be useful for the treatment of prostate cancer in humans.[150] We do not know whether oral consumption of α-tomatine, individually or in combination with lycopene or cancer drugs, would elicit similar beneficial effects in rodents and humans.

The cited studies suggest that the consumption of both high-tomatine green and red tomatoes containing tomatine and lycopene may have an additive anticarcinogenic effect compared with that of green or red tomatoes alone. Because green tomatoes turn red rapidly after harvest, to our knowledge high-tomatine green tomatoes are available commercially only as pickled green tomatoes.[157]

Other Beneficial Effects. Other beneficial effects of α-tomatine have been reported. On the basis of the following observations, Ito[158] concluded that α-tomatine induces programmed cell death by ROS in the fungal pathogen *Fusarium oxysporum*: (a) cell death occurred only under aerobic condition and was blocked by mitochondrial ATPase, caspase, and protein inhibitors; (b) fungal cells showed depolarization of the transmembrane potential of mitochondria and ROS accumulation; and (c) α-tomatine activates phosphotyrosine kinase and G-protein signaling pathways, leading to the elevation of calcium ions and a ROS burst in the cells.

α-Tomatine, the potato glycoalkaloid α-chaconine, and the eggplant glycoalkaloid α-solamargine strongly suppressed during the 4 day test the infection of mice by *Plasmodium yelli* 17XL, the cause of the serious protozoan topical disease malaria, suggesting that the tomato, potato, and eggplant glycoalkaloids have the potential to protect against malaria.[159] α-Tomatine was also shown to be effective in a rodent model as an adjuvant of protective immunity to a vaccine candidate of malaria caused by *Plasmodium berghei*.[146,160,161]

TOMATIDINE

As mentioned above, the aglycone part of α-tomatine, tomatidine, must also contribute to the overall bioactivity because authentic tomatidine also inhibited cancer cells, but at a significantly lower rate than the carbohydrate-containing glycoalkaloid. Here, we will briefly mention anticarcinogenic and other beneficial effects of tomatidine.

Our studies showed that (a) both α-tomatine and tomatidine changed the membrane potential of frog embryos and affected active transport in frog skin[162] and (b) orally consumed tomatidine did not significantly affect organ weights of mice.[163,164] Lavie et al.[165] reported that tomatidine acted as a potent and effective chemosensitizer in multidrug-resistant tumor cells, sensitizing the cells to the cytotoxic action of adriamycin and verapamil. The authors suggest that tomatidine could serve in combination chemotherapy with cytotoxic drugs for treating multidrug-resistant cancer.

Although tomatidine did not inhibit A549 human lung carcinoma cells, Yan et al.[166] discovered that nontoxic doses of the alkaloid inhibited the invasion of the A549 cells by reducing metalloproteinase expression. They found that (a) tomatidine does not effectively inhibit the viability of the A540 cells and (b) nontoxic doses of the compound suppressed cell invasion, did not affect cell migration, reduced mRNA levels of MMP-2 and MMP-9, increased the expression of tissue inhibitor metalloproteinase-1 (TIMP-1), and inhibited NF-κB activity and ERK and Akt signaling pathways. The mechanism for the suppression of cell invasion is similar to the one we observed with mushrooms.[82]

Chiu and Lin[167] investigated anti-inflammatory effects of tomatidine and solasodine (the aglycone of α-solamargine) in LPS-stimulated macrophages. Tomatidine decreased inducible nitric oxide synthase and cyclooxygenase-2 expression through suppression of I-kBα phosphorylation, NF-κB nuclear translocation, and JNK activation. The results imply that the anti-inflammatory effect seems associated with the blockage of NF-κB and JNK signaling, suggesting that the aglycone could prevent cancer and inflammatory diseases. Solasodine, the structure of which is identical to that of tomatidine except that it lacks a double bond in the 5,6-position of the B ring, was less potent.

Mitchell et al.[168] investigated the inhibition by tomatidine of *Staphylococcus aureus* small-colony variants (SCVs) in cystic fibrosis airway epithelial cells. SCVs are often associated with *S. aureus* infection encountered by cystic fibrosis patients. The authors found that tomatidine was a potent growth inhibitor of SCVs at a minimum inhibitory concentration (MIC) of 0.12 μg/mL. The authors suggest that tomatidine in combination with antibiotics could eliminate persistent forms of *S. aureus* that adversely affect the airways of cystic fibrosis patients. It would be of interest to find out whether the olive compound 4-hyroxytyrosol, which we found to inhibit *S. aureus* bacteria in vitro, would also inhibit SCVs.[169−171]

A related study by Mitchell et al.[172] found that tomatidine potentiates the effect of aminoglycoside antibiotics against multiresistant *S. aureus* pathogens by preventing expression of virulence microbial genes. Tomatidine also inhibited growth (IC_{50} = 124 nM) of *Leishmania amazonensis promastigotes* flagellated protozoan parasites that cause about 2 million new

infections annually.[172] The mechanism of inhibition seems to involve interference with the growth, ultrastructure, sterol content, and mitochondrial function of the protozoa. Because tomatoes are reported to be contaminated by *Salmonella* and other foodborne pathogens,[173,174] it would be of interest to find out whether lycopene and tomatine can inactivate the pathogens.

Fujiwara et al.[175] found that dietary tomatidine significantly ameliorated hyperlipidemia and atherosclerosis in apoE-deficient mice by inhibiting acyl-A:cholesterol acyl-transferase (ACAT) activity. Shao et al.[176] found that dietary tomato pomace, seed oil, and defatted seed also reduced cholesterol in hamsters. Orally fed esculeoside A (Figure 1), a minor glycoalkaloid isolated from ripe tomatoes, reduced serum levels of cholesterol, triglycerides, and LDL-cholesterol and ameliorated atherosclerosis in apoE-deficient mice by a mechanism similar to that mentioned for tomatidine.[177] Serum cholesterol and blood antiplatelet effects elicited by green tomatoes have been reported,[178] effects that are most likely due to the high tomatine content of green tomatoes mentioned above. It seems that both α-tomatine[145,179] and tomatidine have the potential to protect against CVD.

CHEMOPREVENTION MECHANISMS AND DIETARY ASPECTS

Mechanisms responsible for the anticarcinogenic effects of tomato glycoalkaloids differ from mechanisms proposed for lycopene present in red tomatoes. To place the above-mentioned observations on mechanistic aspects in perspective, we will summarize additional reported biological effects of α-tomatine and tomatidine.

Tomatine alone and tomatine-rich green tomato diets reduced both dietary cholesterol bioavailability and endogenous cholesterol.[145,179] Tomatine inhibited active transport by increasing the general permeability of membranes of the surface of averted rat jejunal sacs[180] and removed cholesterol from mucosal cells as well as the output of cholesterol into the lymph.[181] Unlike tomatine, tomatidine did not induce cell membrane disruptions in fungi and yeasts.[182] Tomatine and tomatidine exhibited weak inhibition of the Hedgehog (Hh) signaling pathway in the embryonic zebra fish developmental assay.[183] Such inhibition seems to be associated with developmental defects.

SAFETY ASPECTS

Here, we will mention the available information on the safety of tomatine in animal models. The following LD_{50} values have been reported for tomatine in mice (in mg/kg body weight): ip, 25−33.5; iv, 18; oral, 500; subcutaneous, >1000.[156,184−186] Tomsik et al.[155] note that the 1 mg/kg dose of tomatine they used in their mouse study is a safe dose.

As part of the anticarcinogenic feeding study of tomatine to rainbow trout mentioned earlier, we found that the tomatine-containing diets did not induce changes in mortality, fish weights, liver weights, or tissue morphology.[153] No adverse pathological effects in the tissues of the fish on the tomatine diets were observed. The apparent lack of acute toxicity in the rainbow trout reinforces the reported low toxicity in animal models. We observed a similar lack of toxicity in hamsters orally fed α-tomatine.[8,145,179]

A key consideration for the use of pure α-tomatine and of high-α-tomatine tomatoes in cancer prevention and treatment should be the ratio of effective preventive or therapeutic to toxic dose. The apparent nontoxicity of tomatine in animal models is reinforced by the fact that Peruvians consume without deleterious effects high-tomatine red tomatoes and that in some countries high-tomatine pickled green tomatoes are part of the human diet.[143,187] The bioavailability and safety of α-tomatine and tomatidine merit further study.

SIGNIFICANCE FOR THE HUMAN DIET

The cited observations suggest that the mechanism(s) of the chemopreventive effect of tomatine may be the result of multiple molecular events including the formation of complexes with cholesterol, potentiation of the immune system, and direct destruction of cancer cells via disruption of cell membranes, reviewed previously.[7] Because tomatine induces antigen-specific cellular immunity in mice, it possesses remarkable potential as a vaccine adjuvant for infectious diseases as well as for cancer immunotherapy.[146] By stimulating the immune system, tomatine-rich green tomatoes may also protect against lethal infections by foodborne pathogens such as *Salmonella*, as has been reported for potato glycoalkaloids[188] and mushroom and herbal extracts.[189,190]

Red tomatoes contain numerous health-promoting ingredients, including antioxidative carotenoids (lycopene, β-carotene, lutein), anthocyanins, phenolic compounds (caffeic acid, chlorogenic acid), and flavonoids (kaempferol, naringenin, quercetin) as well as vitamins A, B, and C[191] and lectins.[192] Unlike green tomatoes, which contain high levels of tomatine and chlorophyll but no lycopene, red tomatoes contain high levels of lycopene and very low amounts of glycoalkaloids.[2,15,137]

The cited information on anticarcinogenic, anticholesterol, and other beneficial effects of tomatine suggests the desirability of developing new varieties of tomatine-rich red tomatoes. These tomatoes would contain two classes of anticarcinogenic compounds: (a) tomato glycoalkaloids that stimulate the immune system, form complexes with cholesterol, and disrupt cell membranes and inhibit growth and metastasis of cancer cells in vivo; and (b) antioxidative lycopene that may act by suppressing free radicals that damage DNA by mechanisms discussed elsewhere.[193] This objective could be accomplished by breeding high-tomatine tomatoes into commercial lines or by suppressing the genes that govern the formation of enzymes that degrade tomatine during postharvest ripening of green to red tomatoes. The cited studies suggest that plant breeders and plant molecular biologists should create new red tomato varieties containing high amounts of both lycopene and α-tomatine. It may also be possible to develop tomatine-containing potatoes by crossing high-tomatine-containing accessions of the wild potato *Solanum acaule* with cultivated *Solanum tuberosum* varieties.[6,142] In the meantime, consumers may benefit from eating both lycopene-rich red and tomatine-rich green tomatoes as well as processed tomato products.

OUTLOOK

According to Wattenberg,[194] a pioneer in chemoprevention, chemoprevention of cancer is a means of cancer control in which the occurrence of the disease is prevented by chemical compounds that can block and prevent carcinogens from reaching or reacting with critical tissue target sites and suppressing agents that prevent the evolution of the neoplastic process in cells that could otherwise become malignant.

Wattenberg also noted that the great chemical diversity of natural inhibitors suggests the possibility of selecting optimal and safe natural products for human studies.

These considerations stimulated worldwide interest in the development of phytomedicines against various types of cancer. The attempt of this review to integrate and interpret results from our studies and from studies by other investigators on the anticarcinogenic and other desirable activities of two bioactive tomato compounds, lycopene and α-tomatine, is, in part, designed to prove Wattenberg's prophetic predictions.

The results of the cited studies suggest that both lycopene and α-tomatine might contribute to the prevention and therapy of human cancers and possibly also cardiovascular diseases. The cited studies imply that, aside from the need to confirm in vitro results with corresponding studies in animals and humans, possible synergism of combinations of lycopene and α-tomatine, both in pure form and in red and in green tomatoes and tomato products, is expected to provide health-promoting benefits that require lower concentrations of each bioactive compound.

The combination of a tomato-based diet with other food that has been shown to exhibit anticarcinogenic effects is also a major challenge for future studies. Combining bioactive food ingredients with other foods has the potential to elicit additive or synergistic anticarcinogenic effects with lower plasma levels of lycopene and tomatine. This is a largely unexplored area. For example, it would be of interest to find out whether different combinations of red tomatoes containing high levels of lycopene and green tomatoes containing high amounts of the tomato glycoalkaloid tomatine with, for example, the citrus compounds nobiletin[195] and poncirin,[196] pomegranate compounds,[197,198] resveratrol from grapes and berries,[199] and combinations with the rice bran ingredient γ-oryzanol,[84] black rice bran,[81] wheat bran,[200] *Hericium erinaceus* mushrooms,[82] cruciferous vegetables,[201] jujube fruit,[202] curcumin-containing turmeric spices,[203,204] and green and black tea catechins and theaflavins,[205,206] all of which exhibited anticarcinogenic effects in vivo, would be effective against breast, colon, prostate, and other cancers. Because the content of bioactive compounds in teas varies widely and storage might reduce their content, in vivo studies of combinations of lycopene with teas should use high-catechin green teas and/or high-theaflavin black teas of known composition.[207−218] Such dietary combinations, in which the individual components might exert their anticarcinogenic effects by different mechanisms, might act as multifunctional foods and might make it possible to use lower amounts of lycopene and tomatine in the final formulations. Expectations are that multiple, food-based anticarcinogens that elicit cell responses by different mechanisms may provide enhanced efficacy against a variety of cancers.

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Notes

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ABBREVATIONS USED

ACAT, acyl-CoA:cholesterol acyltransferase; AKT, protein kinase B; AP-1, activator protein-1; COX, cyclooxygenase; CVD, cardiovascular disease; DBP, dibenzo[*a*,*l*]pyrene; ECM, extracellular matrix; EpRE/ARE, electrophile/antioxidant response element; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; FSM, food for special medical purpose; HDL, high-density lipoprotein; IC_{50}, concentration of test substance that inhibited 50% of the cancer cells; ICAM-1, intercellular adhesion molecule 1; ip, intraperitoneal; iv, intravenous; JNK, c-Jun N-terminal kinase; LD_{50}, concentration of test substance that killed 50% of the animals; LDL, low density lipoproteins; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MIC, minimum inhibitory concentration; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; MTT, tetrazolium dye, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NF-κB, nuclear factor kappa B; NrF2, nuclear factor 2; PI3K, phosphoinositide 3-kinase; PI3K/AKT/mTOR pathway, intracellular signaling pathway; PI, proliferative index; PSA, prostate-specific antigen; PUFAs, n-3-polyunsaurated fatty acids; ROS, reactive oxygen species; SCV, small-colony variants; TIMP, tissue inhibitor metalloproteinase; TNF-α, tumor necrosis factor-α; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TRAMP, transgenic adenocarcinoma of mouse prostate model; u-PA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor

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