Solanum lycopersicum and *Daucus carota*: effective anticancer agents (a mini review)

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Abstract. The high cost, scarce availability, and some extraneous side effects of some pharmaceuticals have diverted the majority's mindset towards the use of nutraceuticals as both prophylactic and therapeutic alternatives. The cancer incidence in the low and middle-income countries has risen due to several factors, but notably, it has been due to poverty and the non-availability of screening centers. The non-toxic nature, high availability, and low cost of food-based nutraceuticals have been a significant advantage to its users. Solanum lycopersicum is well-known to possess excellent antioxidant, anti-inflammatory, and anticancer potential, and this has been attributed to its potent bioactive compound, lycopene. The presence of β-carotene in Daucus Carota has also contributed immensely to its antioxidant and anticancer properties. Nutraceuticals are considered suitable for anticancer drug development due to their pleiotropic actions on target sites with multiple effects. This short review has explored the dietary characteristics, bioactive components and mild anticancer effects of tomatoes and carrots.

1. Tomatoes (Solanum lycopersicum)

Tomatoes (*Solanum lycopersicum*) has sailed high to become one of the world's most recognized vegetables. It has long been in global recognition as one of the most essential vegetable with high antioxidant activity. This juicy vegetable originated from the western South America, with a wide range of different diversities of wild tomatoes recorded in Peru [1]. Tomatoes were placed in the genus Solanum as Solanum lycopersicum by Carolus Linnaeus in 1753. Two years later, but this was modified by another researcher Philip Miller (1754), who felt the need to integrate the other species of tomatoes in the genus hence he came up with a new genus, Lycopersicon [2]. Lycopersicon esculentum Mill was coined to accommodate tomatoes and its several species. The different species of Solanum are found to be present on all temperate and several tropical continents, which is attributed to their morphological and ecological diversity. Tomato is known to be the third most vital and highly nutritious vegetable cultivated in the world, and also, it battles with banana for the most consumed fruit in the world [3]. It is an edible red fruit berry with a well-seeded ovary. The fruit colour varies from green to yellow, which further projects into yellow to orange then to red based on the maturity stage. In most cases, the quality of carotenoids embedded in the fruit determines the colour of tomatoes. Carotenoids such as lycopene, chlorophylls, and β-carotene are liable for the colour of the fruit [4]. The red and orange colours of tomatoes are attributed to the quantity of the lycopene and β-carotene, respectively. The fruit's green

coloration is attributed to the amount of chlorophyll that have a short life span because it degrades upon fruit ripening.

Water is known to be the major constituent of water, which constitute about 93-95% of the whole fruit while the remaining 5-7% consists of dry matter such as carbohydrates, proteins, vitamins, fiber which are mostly insoluble such as hemicellulose, cellulose, and lignin, minerals, [5]. According to [6], tomatoes are rich in vitamin C, Vitamin K, carotenoids, antioxidants, folate, and are free from cholesterol, which makes it soar as an excellent dietary product. Some of the major bioactive components found in tomatoes are lycopene [5], β-carotene, Naringenin [7] chlorogenic Acid [8]. Lycopene is the main antioxidant in tomatoes and it is solely accountable for the red colour in tomatoes [5]. B-carotene is a pro-vitamin A antioxidant. Naringenin, a prominent flavonoid is found in the skin of tomatoes [7]. The major polyphenol found in tomatoes is chlorogenic acid, an ester of caffeic acid and (−)-quinic acid. It is a powerful antioxidant that also helps in lowering blood pressure [8]. The consumption tomatoes and its base products has been linked to mitigating diseases such as cardiovascular diseases and cancers such as prostate, breast, and lung cancers [9,10]. This is mainly due to its antioxidant content, which differs in chemical nature, herewith providing a wide variety of dietary lipophilic and hydrophilic antioxidants such as lycopene and beta- carotene, tocopherol, ascorbic acid, and phenols [11,12].

Tomato is sold as fresh fruits and has been processed into different products like juices, paste, tomatoes soups, salsa, ketchup, and other culinary purposes due to its distinct savory flavor, and all these are to enhance its economic value. Moreover, most consumers prefer to consume the food raw, some de-skin before consumption because they are thought to be indigestible and contain low amount of nutrients while some cook tomatoes without both the skin and the seeds but in all these, the antioxidant activity of tomatoes remains undeterred [13]. Reports have reported little or no significant alteration in the antioxidant capacity of tomatoes dues to different processing methods. [14] reported the effect of three (3) processing activities (baking, boiling and frying) on the antioxidant capacity of tomatoes. A slight significant effect ($p<0.001$) on the antioxidant capacity of tomatoes was observed when it was baked and boiled while a slight decrease in antioxidant capacity ($p<0.001$) were recorded for the fried tomatoes. The activities of microorganisms, especially in the post-harvest deterioration of tomatoes, have discouraged many consumers from storing the fruit despite the juicy health benefits that can be gotten from it [15].

Figure 1. Fresh tomatoes in the harvested state (Source: Smithsonian Magazine)

Various researches have explored the anticancer activities of tomatoes. Majority of them have reported the protective effect of tomatoes consumption on cancer prevention [16]. Tomato products are known to be one of the leading functional food for the prevention and treatment of prostate cancer. An exponential increase in the apoptosis rate of prostate cancer cells and also, an improvement in prostate-specific antigen concentration were the positive highlights of the research findings [17-21]. Consumption of tomatoes has also been directly related to the reduction in cardiovascular diseases [22]

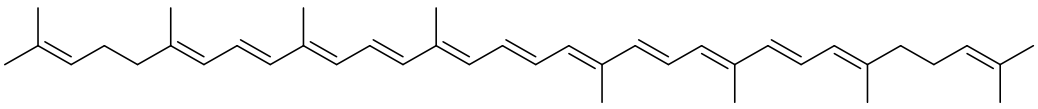
which are also precursors to the onset of different types of cancers. The results of meta- analysis on twenty-one random epidemiological studies concluded that consumption of large amount of tomatoes helps to reduce the risk of gastric cancer, a type of cancer that affects any part of the stomach [23]. The basal inhibitory and cancer preventive mechanism of tomatoes and its products could involve the radical oxygen species (ROS), intrusion with cell proliferation, prompt induction of gap-junctional communications, diverse mechanisms used in the modulation of signal transduction pathways and the effective inhibition of the cell cycle progression caused by the bioactive compounds in tomatoes [24].

Furthermore, clinical and observational studies have shown that consumption of tomatoes is associated with a reduction in the risk of human cancers at various sites in the body [25].

1.1. Lycopene

Lycopene is an important antioxidant, and also, most studied tetrapenoid in tomatoes with a molecular formula of $C_{40}H_{56}$, an open chain acyclic tetraterpene consisting of 13 double bonds (eleven (11) conjugated double bonds and two (2) unconjugated doubled bonds). The multiple conjugated bonds are responsible for the potent antioxidant activity of lycopene, which invariably makes it a potent free radical quencher. It is a highly unsaturated hydrocarbon with bright red carotenoid pigment found in tomatoes and watermelons, and it is also available in some red fruits such as berries and watermelon. It is responsible for the red colour in fruits, although some fruits are not red, yet they contain lycopene e.g. parsley and asparagus. It is hydrophobic with free solubility in ethyl acetate and n-hexane, partial solubility in ethanol and acetone [26]. Lycopene predominantly exists in its all-trans isomeric form (35-95% of the total lycopene content) in fresh tomatoes and some tomato products; however, it also consists of small amounts of cis-isomers and other related carotenoids such as β-carotene, phytofluene, phytoene, and tocopherols [27]. The red pigment in lycopene has harnessed its use as a food colourant in dairy products, cereal products, baked foods, bread, and spreads to provide colour shades from yellow to red. Lycopene has also been used as food supplements, packaged as drugs and also healthy food colourant. The quantity of lycopene used in bottle water may vary from 2 mg/L while in ready-to eat cereal, 130 mg/kg [26]. Lycopene was reported to be stable a 4°C for 37 months. At the appropriate storage condition, lycopene remained in the food matrix but dependent on the food type and processing method [26].

Lycopene has soared as an essential dietary source of antioxidants due to beneficial attributes in human health, especially in the treatment of cardiovascular disease. This has attracted some considerable interest in recent years as an essential phytochemical.



Lycopene

Study has shown the inhibition efficacy of lycopene in the synthesis of cholesterol i.e. a decrease in cholesterol, a boost in the degradation of low-density lipoprotein, and maximum prevention of a reductase enzyme (hydroxyl-methyl glutaryl-coenzyme) [28]. The singlet oxygen quenching properties of lycopene have been found to be twice as powerful as that of beta-carotene and shown to be ten times greater than that of alpha-tocopherol [29]. In relation to the above claim, [28] showed the ability of lycopene to decrease the levels of low-density lipoproteins (LDL) cholesterols in the body by subjecting six healthy male rats to a daily intake of 60 mg/day lycopene per day for three months and the result showed a significant decrease of 14% in the plasma LDL cholesterol levels and no observed reaction on the high-density lipoprotein cholesterol contents. Several works have also deduced lycopene consumption's protective roles against the menace of cardiovascular diseases, including atherosclerosis, myocardial infection, and stroke [30,31]. Furthermore, lycopene's anti-inflammatory properties have been shown in both chronic and acute models of inflammation [32].

Conventionally, lycopene has been extracted from tomatoes using organic solvent extraction techniques. Soxhlet extraction, sonication, blending and solid-liquid extractions have been used for bioactive extractions but with some disadvantages such as long extraction time, it requires a large amount of samples, sorbents, and solvents, which results in a high cost of extraction, ill-environmental impact, and adverse health issues. One major drawback of these conventional extraction methods is that the final extract will require subsequent concentration and clean-up before analysis [33,34]. These drawbacks have led to the advancement in extraction techniques; these methods can either be thermal extraction such as pressurized liquid extraction (PLE) and supercritical CO_2 extraction (SC- CO_2) or non- thermal extraction such as pulsed electric field (PEF). Thermal extractions are rapidly gaining more grounds in the extraction process because of their ability to increase target molecule specificity and the ability to cause a reduction in the waste generated in solvent production [35]. Currently, notable technologies such as micro wave assisted extraction (MAE), supercritical fluid extraction (SFE) and ultrasound-assisted extraction (UAE) have emerged with added advantages to the conventional methods of extraction, these new technologies make use of the most suitable solvent for the extraction and also reduce extraction time.

1.2. Lycopene and Cancer

Oxidative stress is a major contributor to the increased risk of cardiovascular diseases and cancer. The reactivity of lycopene in the biological system depends on their physical and molecular structure, site of action, concentration, the partial pressure of oxygen, and the ability to react with other antioxidants [36]. Lycopene's polyene structure makes it a good target for electrophilic reagents by providing an electron-rich system for the reagents, hereby performing an uttermost reactivity towards oxygen and free radicals [37]. Lycopene is also known to have the ability to disturb the reactions caused by free radicals like peroxy radicals and OH- and this makes it a viable oxygen quenching agent [38].

Singlet oxygen (O_2) oxidizes unsaturated fatty acids, amino acids, and nucleic acid which is highly detrimental to human health, lycopene which is a strong antioxidant helps in quenching the effect of the reactive oxygen species this can be explained with the equation below:

$$3O_2 + LYC \rightarrow 3O_2 + 3LYC$$
$$3LYC \rightarrow LYC + heat$$

Rotary interactions with the solvent coupled with vibrations can cause lycopene to lose the energy gained from the reaction above, thereby leading to the release of thermal energy. This can be attributed to the conjugated polyene structure of lycopene. As the molecule promptly re-establishes to its ground state, this enables another O_2 quenching to be activated immediately, thereby enabling every single carotenoid-molecule to quench about 1000 molecules of O_2 [37].

Generally, carotenoids are well-known for their antioxidant actions towards inhibiting free radical reactions. During lipid oxidation, there is a buildup of peroxyl radicals in the organism, and this can eventually lead to the annihilation of the lipophilic sections. Inactivation of these reactive species results in the growth of radical adducts that put up a resonance-stabilized carbon-centered radical. The carotenoid oxidation products include the creation of epoxides located at the β-ionone ring and located at the central double bond of the conjugated polyene chain. More products of this reaction are the formation of ketones and aldehydes at the β-ionone ring. Inhibition of these radical reactions by lycopene may shelter membranes from lipid peroxidation [37].

[39] evaluated the antioxidant and anti-inflammatory activities of lycopene in mice lungs exposed to cigarette smoke. Some studies have shown that patients who are exposed to cigarette smoke suffer from prolonged airway inflammation, which is associated with cell infiltration of the macrophages and neutrophils [40]. Cell viability and intracellular reactive oxygen species (ROS) were measured via the in-vitro analysis where lycopene at different concentrations (0.5, 1.0, 2.0, 4.0, 8.0, 10.0 and 25 μM) were used to incubate cigarette smoke extract with varied concentrations of 0.1%, 0.25%, 0.5%, 0.625%, 1.25%, 2.25%, 5% and 10% (J774A.1 macrophages) for 3, 6 and 24hrs. Forty mice were divided into five groups for the in vivo analysis which are: (1) a control exposed to ambient air (CG), (2) a vehicle-control group that received 200 μl of sunflower oil by orogastric gavage, (3) a group exposed to CS and

(4 & 5) two groups administered lycopene (diluted in sunflower oil) at doses of either 25 or 50 mg/kg/day before exposure to CS, the total treatment lasted for five (5) days. The result showed that there was an increase in ROS production in 24hrs in cigarette smoke compared with the control exposed to ambient air but 1 μM and 2 μM concentrations of lycopene were able to reduce the production of ROS in 24 hrs compared with the cigarette smoke. Furthermore, there was a decrease in cell viability at 10 μM and 25 μM concentrations of lycopene. This research corresponds to the findings of other researchers who reported that lycopene possesses redox properties in both in-vitro and in-vivo in a lot of biological systems [41].

[42] reported the inhibitive potential of lycopene on colorectal tumors using mouse xenograft model. Mouse fed with lycopene was found to suppress COX-2, PGE2 and phosphylated ERK1/2 proteins, potent inflammatory mediators. Lycopene was also found to augment E-Cadherin adherent molecule and the nuclear levels of cell cycle inhibitor P21CIP1/WAF1 protein. Result showed the chemo preventive ability of lycopene against the growth and progression of colorectal cancer using animal model.

[43] evaluated lycopene concentrate on the proliferation and modulation of human breast cancer cell lines MCF-7. At increasing concentrations, the cancer lines were treated with different lycopene concentrations for 24, 28 and 72h. cell morphology was observed using a light field microscopy. Cell proliferation was determined via MTT assay while cell apoptosis was measured using flow cytometry. Shrinkage in the human breast cancer cells were observed with increasing levels of lycopene which was also time dependent. MTT assay and flow cytometry showed a reduction in cell proliferation and an increase in the rate of cell apoptosis respectively. The authors concluded that lycopene inhibits proliferation and facilitates apoptosis of MCF-7 cells in vitro, possibly by regulating the expression of p53 and Bax which is an excellent pointer to the potential use of lycopene in the treatment of breast cancer.

2. Carrots (Daucus carota)

Carrot is a member of the Umbelliferae family and specifically belongs to the genus Daucus and specie Carota. It is one of the most essential vegetables root crops due to the bioactive compounds embedded in it. It is cultivated throughout the world mainly for its fleshy edible roots and numerous health benefits. It is used for human consumption as well as in feeding animals. It is highly nutritious, tasty, and crunchy. It is a good source of beta carotene, fiber, vitamins, antioxidants, and potassium [44]. Carrots are a rich source of beta-carotene with appreciable amounts of thiamine and riboflavin [45]. The consumption of carrots has been linked to a lot of health benefits such as aid weight loss, lowering of cholesterol levels, and improvement in eye health [46]. It exists in different colours such as white, yellow, orange, red, and purple. The bright colours in carrots can be attributed to the beta carotene, which the body converts into vitamin A during metabolism.

Daucus carota has been suggested as an alternative treatment for the treatment of leukaemia in traditional medicines, this has led to its study as a potential anticancer agent. Beneficial bioactive compounds embedded in carrot juice extract such as beta-carotene and polyacetylene were reported to accelerate the induction of apoptosis and also, inhibited progression in leukemic cell line via in-vitro analysis using flow cytometry [47]. Furthermore, a comparison between isolated fractions from carrots juice (polyacetylene and carotenoids) showed polyethylene extracts exhibited more cytotoxic effects on leukaemia cell lines when compared to the carotenoid extract, beta carotene [48]. [49] affirmed that pentane/dietyly ether (50/50 v/v) extract fraction of daucus carota exhibit potent cytotoxic ability on skin, lungs, breast and glioblastoma cancer cell lines by causing a pronounced decrease in the motility rate of the cancer cell lines and an observed increase in cell adhesion. A study on the anticancer and potential of daucus carota oil extract on MCF-7, HT-29, MDA-MB-231 and Caco-2 cell lines recorded a significant increase in the death of the four cancer cell lines and decrease in cell proliferation [50].

2.1. Beta-Carotene

β-Carotene is a known secondary metabolite with an acyclic structure, only synthesized by plants and belongs to an unoxidized compound group of carotenoids. It is a known pro-vitamin A carotenoid that enhances embryonic development, enhances overall body growth, and improves eye health. It is abundantly present in the human diet and also be found in the human blood, a bright yellow coloured carotenoid, an isomer of lycopene and commonly present in fruits such as apricots, sweet potatoes, pumpkins but highly abundant in orange carrots which is the main known source. β-carotene has the same molecular formula as lycopene, $C_{40}H_{56}$.

B-carotene is highly bioavailable in the human body system, and this encourages its wide usage in medicine; also, it is a good gene inhibitor with some recorded antioxidant and anticancer properties [51, 52, 53]. The bioavailability of this carotenoid has been attributed to its lipophilic nature which is also as a result of the structural properties of the carotenoid i.e the presence of 40 carbons with 15 conjugated double bonds and 2 β-ionone rings [54,55]. Food industries have also adapted the use of beta-carotene as an orange-red food pigment because of its physical and biological properties [55].

2.2. β-Carotene and Cancer

Aside, being an attractive food colourant, provitamin A activity and antioxidant properties are some of the carotene's added health benefits. Study has shown that β-carotene has the highest provitamin A activity among other known provitamin A, carotenoids such as α-carotenes and [56]. Its ease of efficient conversion to vitamin A has enhanced further research on the carotenoid [57]. B-carotene is a potent lipid scavenger and an active singlet oxygen quencher due to its highly conjugated double bonds and inone rings [58]. Some of the health benefits of β-carotene includes a significant decrease in viability and possible apoptosis of some cancer cell lines, treatment of cardiovascular diseases, macular degeneration, increased immune response etc which has been verified by epidemiological studies and clinical trials [58, 60]. Some of the proposed physiological parameters responsible for the health benefits include ability to quench singlet oxygen, prevention of oxidative damage, a good precursor of Vitamin A, and it also alters transcriptional activity [61,62,63].

Supplementation of antioxidants with radiation therapies for the treatment of certain types of cancers has been reported to interfere with the cancer quenching efficacies of the therapies [64-66]. A median follows up of about 10.5yrs showed no significant difference between the risk of lethal prostate cancer when beta-carotene was combined with radiation therapies for the treatment of prostate cancer [67]. Research has also shown that beta carotene is an effective cancer cells tumour suppressor. A study on the treatment of Neuroblastoma with beta carotene using a xenograft model revealed an extensive inhibition of both tumour incidence also the growth of the tumour cells [68-69].

3. Conclusion

The use of food-based nutraceuticals has proved to be a cheaper and safe method for preventing and treating certain types of cancer. The consumption of tomatoes and carrots has been attested to be a good prophylactic treatment for certain types of cancer.

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