

Bioactives Profile of Purple and Black Tomato: Potential Applications in the Pharmaceutical Field Purple and Black Tomato

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Perna *et al.*: Bioactives Profile of Purple and Black Tomato

The purple and black tomato are sources of different antioxidants such as carotenoids and flavonoids that seem to have dose-dependent antioxidant, anti-inflammatory, anti-proliferative and hypnotic effects. The aim of this review is to discuss their advantageous role in health promotion and prophylaxis against chronic conditions induced by inflammation and oxidative stress. Data research was conducted on five major databases using specific keywords to extract relevant articles. The anti-proliferative effect was seen in a deep purple tomato in two human cancer cell lines: human colorectal adenocarcinoma cell line and HeLa cell line. Potential anticancer properties were attributed to radical scavenging activity, enzyme detoxification, reduced cell proliferation, angiogenesis and invasiveness. Ingestion of purple and black tomato seeds was proven to increase circulating melatonin levels and improve hypnosis. Purple and black tomato anthocyanin treatment was also significantly associated with increased sperm motility and spermatogenic cell density. The high content of bioactives in purple and black tomato may find application in prevention of cancer and cardiovascular diseases as well as management of sleep and fertility disorders.

Key words: Black tomato, purple tomato, anthocyanin, antioxidant, cancer, fertility

Domesticated tomato (*Solanum lycopersicum* L.) is one of the most valuable fruits in human nutrition, ranking seventh in worldwide production, with a global consumption estimated at 33.20 million metric tons^[1,2]. Unlike other plant-derived products, tomatoes are harmless and appetizing for human consumption in their fresh ripe forms or when minimally treated^[3]. Thus, the tomato fruit has evolved to be both flavorful and nutritious to frugivores^[4]. Due to its remarkable nutritive value, it is recognized as a protective food that provides health-promoting antioxidants such as lycopene, β -carotene, vitamin C, hydroxycinnamic acid derivatives and flavonoids, particularly flavonols and flavones, which are known to combat inflammation and cancer^[1,5]. A variety of tomatoes exist in a range of colors, including red, orange, yellow, green, pink, white, brown, black and

purple; color being an important characteristic in attracting consumers^[5].

Accumulation of anthocyanins in some wild tomato species gives rise to black and purple tomatoes, namely; *Solanum chilense*, *S. hirsutum*, *S. cheesmanii*, and *S. lycopersicoides*^[5]. This feature has been carried into the domesticated tomato through interspecific crosses^[6]. Domesticated tomatoes produce anthocyanin in vegetative tissues but not in the peels or pulp of the fruit^[5]. Purple tomatoes contain higher levels of anthocyanin than red tomatoes,

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as well as other healthy phytochemicals, which might contribute to higher health-promoting and prophylactic activities in conditions such as diabetes, chronic degenerative diseases, cardiovascular diseases and certain types of cancers^[6]. A genetically modified (GM) purple tomato was found to have a positive impact by prolonging the life of cancer-susceptible mice. Moreover, non-GM purple tomato (breeding line V118) had stronger antioxidant activities than some commercial red tomatoes^[7].

The aim of this review is to discuss the recent studies on the nutrient content of purple tomatoes and consequently their advantageous role in health promotion and prevention of chronic diseases.

BIOACTIVE COMPOUNDS AND HUMAN HEALTH: ANTHOCYANINS AND CAROTENOIDS

A polyphenol-rich diet may ameliorate undesirable clinical outcomes, by exerting pleiotropic effect on cardiometabolic risk factors by virtue of the specific action of different polyphenol subclasses: phenolic acids, anthocyanidins, flavones, flavan-3-ols, flavonols and flavanones^[8]. Among these, anthocyanins (water-soluble plant pigments responsible for red, purple and blue coloration of many fruits, flowers, and leaves) have garnered recent interest from researchers because of their potential preventative and/or therapeutic effects on human health^[9]. There are 702 different anthocyanins and 27 anthocyanidins (the sugar-free, aglycone forms of anthocyanins) identified in nature. However, only six anthocyanidins, namely, cyanidin, delphinidin, pelargonidin, peonidin, malvidin, and petunidin are widely distributed in the human diet, accounting for more than 90 % of all known anthocyanins^[10]. Chronic consumption of anthocyanins and/or anthocyanin-rich foods has been postulated to exert an array of health benefits, including but not limited to cardiovascular protection, neuroprotection, vision improvement, antidiabetic and anti-obesity properties, anti-inflammatory effects, chemoprevention and cancer protection^[11]. Anthocyanin supplementation exerts beneficial metabolic effects in subjects with type 2 diabetes by improving dyslipidemia, enhancing antioxidant capacity, and preventing insulin resistance. These results were drawn from a 24 w randomized, controlled trial on 58 diabetic patients who received 160 mg of anthocyanins twice daily^[12]. The triglyceride (TG) lowering effect observed in anthocyanin-treated subjects resulted primarily from

reductions in serum apo B- and apo C-III-containing TG-rich particles due to anthocyanin intervention, demonstrating reduction in potential pro-atherogenic remnant particles, a prominent component of diabetic dyslipidemia^[12].

Another randomized pilot study, on 74 subjects with non-alcoholic fatty liver disease (NAFLD), who received 320 mg/d of bilberry and blackcurrant derived anthocyanins for 12 w, suggested that purified anthocyanin supplements may have favorable effects on insulin resistance and several plasma biomarkers of liver injury in those patients. A positive correlation between changes in plasma alanine transaminase (ALT) activities and the levels of Cytokeratin-18 M30 fragment (CK-18 M30) in anthocyanin-treated patients was also observed. These results suggest that anthocyanin supplementation reduced plasma myeloperoxidase (MPO) and showed a trend toward improvement in NAFLD fibrosis score. MPO may be a factor that directly links the hepato-protective effects of anthocyanin to its well documented anti-inflammatory and antioxidant properties^[13].

A recent study showed that daily consumption of 200 ml/d of anthocyanin-rich cherry juice for 12 w improved cognitive performance (verbal fluency, short-term and long-term memory) in older adults with mild-to-moderate dementia^[14]. The study hypothesized that flavonoids may be more likely to hinder cognitive impairment through their actions on the brain's cellular and molecular architecture, rather than through halting disease progression^[14]. The bioactive components provided by cherry juice may provide benefits, such as stimulating an up-regulation of signaling cascades in areas of the brain related to memory^[15]. On the other hand, results weren't as prominent in Alzheimer's patients as the disease is associated with progressive and chronic inflammation^[16] and such pathology may mask any potential anti-inflammatory effects provided by the cherry juice.

A memory-enhancing effect was also demonstrated with daily supplementation of carotenoids; lutein, zeaxanthin, and meso-zeaxanthin in healthy subjects. Given that concentrations of these carotenoids relate positively to cognitive function, it is reasonable to hypothesize that these compounds assist in optimizing the neurocognitive environment^[17]. Lutein can facilitate the transfer of compounds from one cell to another via gap junctions. Gap junction channels contribute to sharpened neuronal activity, which

have been proposed to underlie cognitive processes such as memory, perception, and learning. Other mechanisms whereby lutein and zeaxanthin may play a neuroprotective and/or neurosupportive role have been proposed, and it has been suggested that they can enhance the structural integrity of membranes and positively impact neural efficiency^[17].

A study carried out on children demonstrated the beneficial role of mixed-carotenoid supplementation in obesity. A decrease in body mass index (BMI), z-score, waist-to-height ratio, and subcutaneous adipose tissue, was associated with the increase in the concentration of β -carotene and high-molecular-weight adiponectin by mixed-carotenoid supplementation^[18].

The health benefits of carotenoid administration on eye related-diseases, several types of cancers, cardiovascular and photosensitive disorders, have also been confirmed by recent reviews^[19,20]. Carotenoids have antioxidant and anti-inflammatory activity that may protect against cardiovascular risk factors such as markers of inflammation, hyperlipidemia, hypertension, insulin resistance, and obesity. Consequent improvements in baseline blood pressure levels, reduction of inflammation, and correction of dyslipidemias can lead to an improvement of cardiovascular health^[21].

MATERIALS AND METHODS

A data research was carried out in different databases namely: PubMed {Public Medlinerun by the National Center of Biotechnology Information (NCBI) of the National Library of Medicine of Bethesda (USA)}, Saudi Digital Library (SDL), Google scholar, Scopus, Web of Science, using the following key words: Tomato, Purple tomato, Blue tomato, Indigo rose. There were no set time limits due to the few studies conducted on this topic.

RESULTS AND DISCUSSION:

Pigment contents and antioxidant activities:

The antioxidant activity of purple tomato is due to its high content of anthocyanin, carotenoids, and phenolic compounds. Table 1 describes pigment contents of different colorful fruits and vegetables. It was found that the contents of anthocyanin in the whole fruit, peel, and flesh of the Del/Ros- transgenic tomato were 5.2 ± 0.5 , 5.1 ± 0.5 , and 5.8 ± 0.3 g/kg dry matter, respectively^[22]. Anthocyanin content in other

TABLE 1: ADVANTAGES OF SOLID LIPID NANOPARTICLES

Advantages of solid lipid nanoparticles

Control and/or target drug release. Improve stability of pharmaceuticals.

High and enhanced drug content (compared to other carriers). Feasibilities of carrying both lipophilic and hydrophilic drugs.

Most lipids being biodegradable, SLNs have excellent biocompatibility.

Water based technology (avoid organic solvents). Easy to scale-up and sterilize.

More affordable (less expensive than polymeric/surfactant based carriers).

Easier to validate and gain regulatory approval.

studies was around 23 mg/100 g fresh weight in Jinling Moyu purple tomato^[6], and 72.31 mg/100 g in V118 purple tomato^[23]. The purple tomato fruit peels had enhanced anthocyanin pigment accumulation, which was over 10-fold compared to any other tomato fruits evaluated in a study done by Kang *et al.*^[5]. Compared to other types of colored tomato, purple tomato was found to have the second highest amount of anthocyanin after red tomato^[24]. Comparing tomato fruits of giant purple, giant yellow, and New Zealand purple cultivators, the highest antioxidant activity and the highest anthocyanins contents were found in New Zealand purple cultivators^[25,26]. Several purple vegetables have been previously studied by Li H. *et al.*, concluding that these vegetables had high contents of anthocyanins. Although the study did not include purple tomatoes, nevertheless, the results indicated that purple vegetables generally have a high content of anthocyanins^[27].

Mladenovic *et al.* compared the phenolic compounds content in the extract of Russian Black Prince variety with that of hybrid Sidra first-generation selections. Results revealed that the total phenolic content (TPC) was higher in the former variety^[28]. Japanese blue tomato peel extract contains a large amount of anthocyanins whereas the seed and pulp extracts contain either none or a small amount of the same pigment^[29]. A recent study evaluated different pigmented rich plant materials, two fruits and two vegetables, and found that anthocyanin contents ranged from 4.9 to 38.5 mg/g dry weight (DW)^[30].

Varying amounts of carotenoids and phenolic compounds with antioxidant activity were reported on analysis of different strains of the purple tomato. The total carotenoid content of V118 was

234.78 $\mu\text{g/gDW}$, while the total phenolic content was 659.11 mg Gallic Acid Equivalent (GAE)/100 g DW^[23]. In a study that aimed to determine the levels of phenolics including flavonoids in purple tomatoes, Mladenovic *et al.*^[28] concluded that these fruits contain high amounts of bioactive compounds. The antioxidant activities of the lipophilic extract of purple tomatoes was measured by photochemiluminescence (PCL) and Oxygen Radical Absorption Capacity (ORAC-L) assays, and the results were 30.11 μmol total extract (TE)/g DW and 11.97 μmol TE/g DW respectively^[23]. Antioxidant activities of purple tomatoes are either direct or indirect effects. The direct anti-oxidant activities are denoted by decreased malondialdehyde (MDA) and nitric oxide (NO) production and the indirect activities are denoted by increased glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities in edematous tissue. This supports the conclusion that tomatoes containing anthocyanins can potentially provide better protection against oxidative stress related chronic diseases of humans^[7]. Table 2 describes the antioxidant activity of purple tomatoes and other colorful plant materials, as a result of their bioactive components, such as carotenoids or anthocyanin (Table 3).

Susceptibility to infections:

The effect of spraying the fungal pathogen, *Botrytis cinerea* spore suspension was measured in both wounded and non-wounded fruits. For non-wounded

TABLE 2: INGREDIENTS USED IN THE PREPARATION OF NANOPARTICLES

Name of the ingredients	conc	Reference
Lipid	3.33 % w/v	17
Phospholipids	0.6-1.5 %	18
Glycerol	2-4 %	--
Poloxamer 188	1.2-5 % w/w	19
Soy phosphatidyl choline	95 %	--
Compritol	10 %	--
Cetyl palmitate	10 % w/w	20
Tego care 450 (surfactant)	1.2 % w/w	--
PEG 2000	0.25 %	--
PEG 4500	0.5 %	--
Tween 85	0.5 %	21
Ethyl oleate	30 %	--
Na alginate	70 %	--
Ethanol/butanol	2 %	22
Tristearin glyceride	95 %	18
PEG 400	5 %	--
Isopropyl myristate	3.60 %	--
Pluronic F 68	40 %	--
Tween 80	50 %	21

fruit, this exposure was associated with significantly milder symptoms for purple tomatoes as compared to red tomatoes. For wounded fruits, the inoculation of *B. cinerea* spore suspension was not associated with an increase in lesion size of either fruits on day 1 post inoculation (dpi), however, there was a greater spread of infection in red tomatoes on 2 dpi as compared to purple tomatoes. The average size of the lesions on 3 dpi was significantly smaller in purple tomatoes. This clearly indicates reduced susceptibility of purple fruits to *B. cinerea* infection^[31]. The reduced susceptibility to infection is thought to be due to the high content of anthocyanins as they alter the spread of the reactive oxygen species (ROS) burst generated as part of necrotrophic infection^[31].

Softening and Shelf life:

Purple tomatoes were compared to red tomatoes in terms of softening and shelf life. Red tomatoes softened in 21 d when stored at 18°, while the time to softening of 50 % of purple tomatoes to the same extent was 49 d. The red fruits completely collapsed after 5 w of storage, whereas the purple fruits endured up to 10 w. To measure the firmness of the fruits, a texture analyzer was used. As such, the shelf life of purple tomatoes was more than double that of red tomatoes; this is due to the expression of the transcription factors^[31]. The reduction of ROS levels may be the cause of suppression of ripening in later stages, and is caused by the hydrophilic antioxidant capacity due to the high content of anthocyanins^[31]. The prolonged shelf life is attributed to the lower susceptibility of purple tomatoes to infections as mentioned previously (fig. 1)^[31].

Anti-inflammatory and anti-proliferative effects:

Purple tomatoes antioxidant effects seem to be dose-dependent. This has been proven by a single *in vivo* study on rats. The study showed that purple tomatoes caused a significant inhibition (edematous inhibition: 7.48 % and 13.8 %) of carrageenan-induced rat paw edema^[7]. Although this was demonstrated by one study only, results were significant, which may encourage further research to explore this property. In addition, purified anthocyanin samples from four plant sources ("Sun Black" tomato, mahaleb cherry, blackcurrant and black carrot) exhibited the capability to reduce the expression of endothelial inflammatory antigens, suggesting their potential beneficial effect in cardiovascular protection. The vascular anti-inflammatory capacity of non-acylated

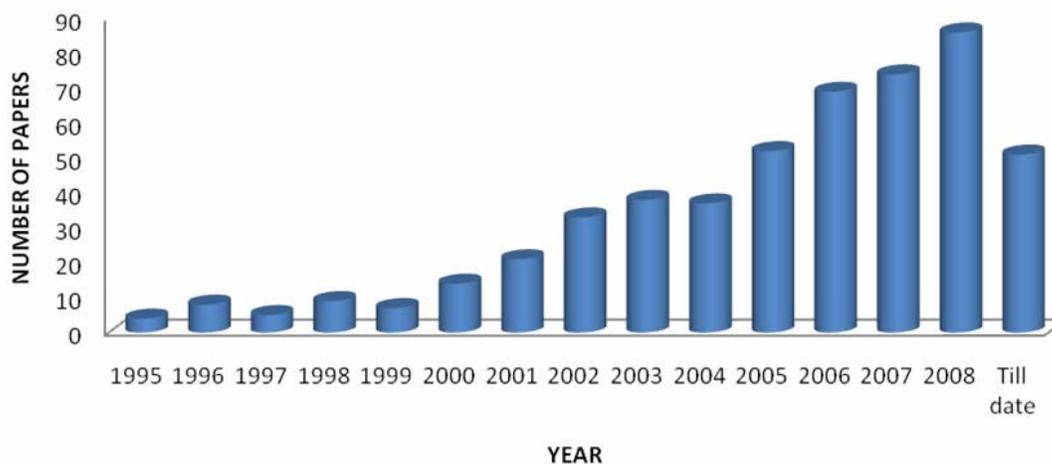


Fig. 1: Trends in Solid lipid nanoparticles research

TABLE 3: METHOD OF SLN PREPARATION

Different methods of SLNs preparation	Reference
High shear homogenization	23-25
Hot homogenization Cold homogenization	26,27
Ultrasonication/high speed homogenization	28
Probe ultrasonication Bath ultrasonication	29,30
Solvent emulsification/evaporation	31,32
Micro emulsion based SLN preparations	33-37
SLN preparation by using supercritical fluid Spray drying method	38-40
Double emulsion method	41
	42

anthocyanins was found to be higher than that of anthocyanins acylated with cinnamic acid derivatives in accordance with their corresponding antioxidant activity^[30].

Anti-proliferative effect was reported in a deep purple tomato fruit named Sun Black. Its skin extract was tested on two human cancer cell lines; HT-29 cell line, derived from human colorectal adenocarcinoma, and HeLa cell line, derived from human ovarian cancer. The extract had significantly inhibited cell proliferation in a dose-dependent manner^[32]. In a recent pilot test, cancer-susceptible Trp53^{-/-} mice, fed a diet supplemented with the high-content anthocyanin tomatoes, showed a significant extension of their life spans^[33].

The potential anticancer properties of anthocyanins, revealed from *in vitro* studies, are attributed to their radical-scavenging activity; stimulation of phase II detoxifying enzymes; reduced cell proliferation, inflammation, angiogenesis and invasiveness; and induction of apoptosis and differentiation. Anthocyanins bring about these effects through

modulating the expression and activation of multiple genes associated with these cellular functions, including genes involved in the phosphatidylinositol 3-kinase/protein kinase B PI3K/Akt, extracellular-signal-regulated kinase, c-Jun N-terminal kinase, and mitogen-activated protein kinases pathways^[34].

Hypnotic/Somnifacient effects:

Recent studies quantified melatonin concentrations in black tomato, and two commercial tomato juices as well as beefsteak tomato, which was found to contain the highest level of melatonin^[35].

The latest study on this topic demonstrated that supplying beefsteak tomatoes to obese postmenopausal women with sleep problems for 8 w raised their circulating melatonin (quantified by measuring the 6-sulphatoxymelatonin level in the morning's first-void urine), and their sleep quality was improved with extended durations of tomato consumption. Black tomato seeds prove the hypothesis that ingestion of melatonin-rich foods can increase circulating melatonin levels and improve sleep^[35].

Previous studies have reported a wide range of melatonin levels in tomatoes, ranging from 0.03 to 23.87 ng/g. This may be due to the varied growth conditions, however, further studies are necessary for addressing this issue^[36].

Effects on testosterone, sperm and prostate parameters:

It has been proposed that the lycopene found in tomatoes (*Solanum lycopersicum* L.) may be beneficial for prostate health due to its antioxidant properties. A 30 study meta-analysis by Rowles

et al. in 2018, showed an inverse association between prostate cancer risk and the consumption of tomatoes among 24 222 cases reported from 260 461 participants; when cooked or used as a sauce^[37]. Moreover, a recent finding demonstrated that anthocyanin treatment significantly increased testes weight, sperm motility and spermatogenic cell density as well as significantly decreased apoptotic body count and 8-hydroxy-2'-deoxyguanosine(8-OHdG) concentrations^[38]. The high content of anthocyanins in purple tomatoes makes it very suitable for transgenic labeling. It was used by Juarez P *et al.*, to produce neutralizing antibodies against rotavirus^[3].

Black and purple tomatoes are found to have significant antioxidant, anti-inflammatory, anti-proliferative and hypnotic effects. They also have beneficial effects on sperm count and motility. Purple tomatoes have also demonstrated slower ripening and softening than red tomatoes, as well as better resistance to infections, which contributes to their longer shelf life. These effects are generally attributed to their content of anthocyanins, carotenoids and phenolic compounds; which vary greatly between the different strains, their cultivation conditions and the parts of the fruit itself. Although the antioxidant activity has been studied sufficiently well, further research into the anti-inflammatory and anti-proliferative effects is needed. The high content of phytochemicals of these fruits contributes to their health benefits and prophylactic properties against an array of diseases caused by oxidative stress and inflammation. Previous studies by Campestrini *et al.*, 2019, suggested that a new variety of nutrient-rich purple tomato (*Solanum lycopersicum* L. cv Micro-Tom) displayed the best antioxidant activities which can be associated to its highest content of carotenoids, specially lutein and β -carotenes and the Purple peel CRF had antiproliferative activity against HepG2 line (liver hepatocellular carcinoma) at non-toxic concentrations^[39].

In addition, as suggested in 2020 by Colanero *et al.*, the genetic characterization of the Abg mutation in purple Tomato, stronger than Aft in inducing fruit pigmentation, certainly represents an interesting new step in this direction^[40].

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