



Review

A comprehensive review on the watermelon phytochemical profile and their bioactive and therapeutic effects

Muhammad Nadeem¹, Maham Navida¹, Kashif Ameer^{1*}, Aqsa Iqbal¹, Faiqa Malik¹,
Muhammad Ather Nadeem², Hira Fatima³, Aftab Ahmed⁴, Ahmad Din⁵

¹Institute of Food Science and Nutrition, University of Sargodha, Sargodha 40100, Pakistan

²Department of Agronomy, College of Agriculture, University of Sargodha, Sargodha 40100, Pakistan

³Department of Botany, The University of Lahore, Sargodha Campus, Sargodha 40100, Pakistan

⁴Department of Food Science, Government College University Faisalabad, Faisalabad 38000, Pakistan

⁵National Institute of Food Science and Technology, University of Agriculture, Faisalabad 38000, Pakistan

Abstract Watermelon (*Citrullus lanatus*) is commonly consumed by humans and widely available around the world. It has impressive nutritional properties, a rich phytochemical profile, and various claimed medicinal and health benefits. The major carotenoids in watermelon include lycopene, β -carotene, phytofluene, phytoene, lutein, and neurosporene. Lycopene (approximately 6,888 $\mu\text{g}/152\text{ g}$) is the major bioactive component in the fruit and it reportedly promotes several therapeutic effects, such as anti-cancer and anti-inflammatory activities etc. in humans and animals. Watermelon is also a good source of the amino acid citrulline, which is involved in production of arginine. Pre- and postharvest factors, including fruit sampling area, application of fertilizer, climatic factors, and genetic variability, are known to affect its bioactive compounds and nutrient concentrations. This review summarizes our current understanding of the watermelon phytochemical profile and the factors affecting its bioactivities and therapeutic effects.

Keywords watermelon, phytochemical profile, bioavailability, therapeutic effects, postharvest factors



OPEN ACCESS

Citation: Nadeem M, Navida M, Ameer K, Iqbal A, Malik F, Nadeem MA, Fatima H, Ahmed A, Din A. A comprehensive review on the watermelon phytochemical profile and their bioactive and therapeutic effects. Korean J Food Preserv, 29(4), 546-576 (2022)

Received: April 21, 2022

Revised: July 13, 2022

Accepted: July 13, 2022

***Corresponding author**

Kashif Ameer

Tel: +92-48111867111

E-mail: kashifameer89@gmail.com

Copyright © 2022 The Korean Society of Food Preservation. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

1. Introduction

Watermelon (*Citrullus lanatus*) is a vine-like plant that belongs to the Cucurbitaceae family or gourd family, and it produces a succulent fruit which is widely cultivated for human consumption. It is an annual plant with well-defined growing patterns which are suitable to hot climates. The fruits usually vary in weight from 1-2 kg but can reach 20 kg in terms of succulent plant weight. In desert regions, watermelon is treasured as an alternative source of water (Perkins-Veazie et al., 2001). China is currently the top producer for watermelon globally, followed by Turkey, India, Iran, Algeria, Brazil, United States, Korea (Lin et al., 2014; Naz et al., 2013). The scientific name for watermelon, *Citrullus lanatus*, is

a combination the Greek *Citrullus* which is derived from the word for citrus and refers to the fruit, and the Latin word *Lanatus* which means fuzzy or wooly and refers to the microscopic hairs on the leaves and stems. Watermelon contains roughly 68% meat or pulp, 30% rind, and 2% seeds (Pons, 2003). Watermelon fruits have perpendicular grey or light green stripes over a deep green smooth thick outer peel. The fruit is red on the inside with dark brown or black elliptical seeds ensconced in the middle third of the flesh (Wehner et al., 2001). Seedless varieties have also been developed which have no seeds or only a few small, shrill, jelly-like white seeds (Nunes, 2008). The fruit is extremely nutritious as shown by the nutritional profile in Table 1, thirst-quenching, and known to be truncated in calories (Okonmah et al., 2011). While it is currently cultivated around the globe, the first harvest was reported in Egypt over a 5,000 years ago.

The consumption of vegetables and fruits may help to prevent lifestyle disorders, such as coronary heart disease (CHD), cataract, stroke, and cancer (Ameer et al., 2017a; Ameer et al., 2017b). This is because fruits and vegetables contain vital nutrients, including vitamins, minerals, proteins, fiber, antioxidants, and phytochemicals (Liu, 2004; Raza et al., 2019). The regular intake of 5-10 servings of various fruits and vegetables is thus widely recommended to reduce chronic disease risk and fulfill our nutritional requirements for optimal health. The pomace (rind), peel, and skin are the main parts of the watermelon fruit. Although the skin is considered a by-product of watermelon and a variety of products can now be produced from the rind including candies, desserts, ice cream, and jellies through value addition (Iqbal, 2017; Madhuri and Devi, 2003; Mohamad et al., 2012; Muhammad et al., 2015; Peter-Ikechukwu et al., 2018; Sindhuja

Table 1. Nutritional composition of watermelon

	Watermelon	Watermelon seed	Watermelon rind	Watermelon rind flour	Unshelled seed flour	Watermelon seed flour	Watermelon juice
	Quantity (Per 152 g)	Quantity (Per 100 g)	Quantity	Quantity	Quantity	Quantity	Quantity (Per 100 g)
Calories	45.60 kcal	557 kcal	NR	NR	NR	NR	30 kcal
Energy	NR	2,330 kJ	NR	NR	NR	NR	127 kJ
Moisture	NR	5.05 g	10.61%	5.12%	9.59%	9.77%	90.1–92.42 g
Lipids	0.23 g	47.37 g	2.44%	1.05%	45.66%	0.64%	0.05–0.27 g
Protein	0.93 g	28.33 g	11.17%	7.04%	25.33%	2.23%	0.4–0.84 g
Ash	0.38 g	3.94 g	13.09%	3.07%	3.36%	2.150%	0.1–0.37 g
Dietary fiber	0.61 g	NR	17.28%	2.98%	4.20%	0.65%	0.4–0.7 g
Carbohydrates	11.48 g	15.31 g	56.02%	80.75%	11.86%	84.57%	7.55 g
Total sugars	9.42 g	NR	NR	NR	NR	NR	5.74–6.59 g
Lycopene	6,888.64 μ g	NR	NR	NR	NR	NR	3,040–5,590 μ g
β -Carotene	NR	NR	96.44%	NR	NR	NR	NR
References	(Mateljan, 2020)	(USDA, 2020)	(Al-Sayed and Ahmed, 2011)	(Egbuonu, 2015)	(Akusu and Kiin-Kabari, 2015)	(Ubbor, 2009)	(USDA, 2020)

NR, not reported.

et al., 2005).

The unique composition of watermelon, including its minerals, vitamins, and phytochemicals, reportedly has specific therapeutic and pharmacological significance (Banurek and Mahendran, 2011; Jiang et al., 2020; Nkoana et al., 2021; Ubbor and Akobundo, 2009; Zhao et al., 2021). Watermelon seeds are rich in proteins, oil, and unsaturated fatty acids, such as stearic, palmitic, linoleic, and oleic acids. It is also a rich reservoir of natural organic sugars including glucose, sucrose, and fructose and it contains carotenoids such as β -carotene (Khan et al., 2020). Watermelon fruits are comprised of phytochemical compounds, such as cucurbitacins and their glycoside derivatives which exhibit a peculiar medicinal significance in terms of potent biological activities, such as hepatoprotective, anti-inflammatory, anti-tumor, antimicrobial and anthelmintic effects (Biswas et al., 2017; Nkoana et al., 2021). In Sudan, watermelon is used for the treatment of various ailments including gastrointestinal disorders, rheumatism, inflammation, and gout. In South Africa, the leaves and fruits of the watermelon plant are employed in conventional healing and alternative medicinal therapies to treat hypertension (Aderiye et al., 2020; Nkoana et al., 2021; Rashid et al., 2020). Furthermore, the roasted seeds of watermelon are utilized by consumers as an appetite stimulant and to alleviate constipation (Biswas et al., 2017). In recent years, the interest of consumers in natural plant-derived food products as alternatives to pharmacological drugs for the treatment of human diseases and ailments has increased (Ahmad et al., 2020; Biswas et al., 2017; Nkoana et al., 2021). This review summarizes our current knowledge of the phytochemical profile and therapeutic effects of watermelon, including the limited information available regarding the

ethno-medicinal benefits. This review indicates that watermelon has a superb nutritional profile, contains numerous phytochemicals, and exhibits beneficial therapeutic effects.

2. Phytochemical profile of watermelon

In desert regions watermelon can be considered a substitute for water. It contains essential minerals (Table 2) and vitamins (Table 3) and is a suitable source of lycopene and citrulline (Table 1) (Perkins-Veazie et al., 2001). Watermelon seeds are high in protein, minerals (such as magnesium, potassium, iron, zinc, sodium, phosphorus, copper, and manganese), B vitamins, and fat, among other nutrients including phytochemicals (Braide et al., 2012). Watermelon seeds are known to provide economic benefits, especially in areas where farming is becoming more intensive. Watermelon seed oil is also used cosmetically (Jensen et al., 2011) due to its moisturizing, therapeutic, and anti-oxidant properties. Watermelon comprises of vitamin C (8.1 mg/100 g) in its nutritional composition. Vitamin C is a powerful antioxidant with radical-scavenging properties that is useful in the treatment of photo-aging (Chiu and Kimball, 2003).

Watermelon is an incredibly nutrient-dense, thirst-quenching, and low calorie fruit (Okonmah et al., 2011). The water content of a watermelon is approximately 92% (Anon, 2008). Watermelon is also cholesterol-free and high in vitamins, especially B₁, B₆, C, and A (Table 3) as well as lycopene, which is a carotenoid (Table 1) and minerals (Table 2) such as magnesium and potassium (Leskovar et al., 2004). Free radicals support conditions such as atherosclerosis, arthritis, asthma, atherosclerosis, diabetes, and colon cancer by assisting in their quenching (Oyeleke et al., 2012). Watermelon is

Table 2. Mineral composition of watermelon

Minerals	Watermelon	Watermelon juice	Watermelon rind	Watermelon pulp	Watermelon rind flour	Watermelon seed flour	Watermelon seed
	Quantity (Per 152 g)	Quantity (Per 152 g)	Quantity (Per 100 g)	Quantity ppm	Quantity (Per 100 g)	Quantity (Per 100g)	Quantity (Per 100 g)
Calcium	10.64 mg	4–14 mg	29.15 mg	0.136 ppm	28.00 mg	150 mg	54 mg
Iron	0.36 mg	0.08–0.55 mg	1.29 mg	0.242 ppm	4.63 mg	12.1 mg	7.28 mg
Fluoride	NR	1–2.1 μ g	NR	NR	NR	NR	NR
Magnesium	15.20 mg	5–12 mg	1.48 mg	0.167 ppm	30.40 mg	542 mg	515 mg
Phosphorous	16.72 mg	5–19 mg	135.24 mg	NR	129.70 mg	1,279 mg	755 mg
Potassium	170.24 mg	58–191 mg	1.37 mg	0.158 ppm	21.70 mg	1,179 mg	648 mg
Sodium	1.52 mg	0–5 mg	12.65 mg	0.140 ppm	11.40 mg	33 mg	99 mg
Zinc	0.15 mg	0.04–0.63 mg	1.29 mg	0.086 ppm	1.25 mg	10.6 mg	10.24 mg
Copper	0.06 mg	0.006–0.166 mg	0.45 mg	NR	0.40 mg	2.1 mg	0.686 mg
Manganese	0.06 mg	0–0.08 mg	1.42 mg	NR	1.30 mg	9.9 mg	1.614 mg
Boron	142.50 μ g	NR	NR	NR	NR	NR	NR
Selenium	0.61 μ g	0–0.7 μ g	NR	NR	NR	NR	NR
References	(Mateljan, 2020)	(USDA, 2020)	(Gladvin et al., 2017)	(Etejere and Olayinka, 2018)	(Anthony and Egbuonu, 2015)	(El-Adawy and Taha, 2001)	(USDA, 2020)

NR, not reported.

Table 3. Vitamin composition of watermelon

Vitamins	Watermelon	Watermelon rind	Watermelon rind flour	Watermelon juice
	Quantity (Per 152 g)	Quantity (Per 100 g)	Quantity (Per 100 g)	Quantity (Per 152 g)
Vitamin-A	864.88 IU	52.13 mg	50.15 mg	28 μ g
Vitamin-C	12.31 mg	8.46 mg	7.23 mg	5.3–14.7 mg
Vitamin-B ₁	0.05 mg	1.23 mg	0.03 mg	0.023–0.046 mg
Vitamin B ₂	0.03 mg	2.71 mg	0.02 mg	0.01–0.036 mg
Vitamin B ₃	0.27 mg	4.25 mg	0.04 mg	0.11–0.21 mg
Vitamin B ₅	0.34 mg	NR	–	0.154–0.328 mg
Vitamin B ₆	0.07 mg	5.34 mg	0.04 mg	0.033–0.065 mg
Vitamin B ₉	4.56 μ g	NR	NR	2–3 μ g
Vitamin-E	0.08 mg	NR	NR	0.02–0.07 mg
Vitamin-K	0.15 μ g	NR	NR	0–0.3 μ g
References	(Mateljan, 2020)	(Gladvin et al., 2017)	(Anthony and Egbuonu, 2015)	(USDA, 2020)

NR, not reported.

also comprised of phenolic components (Jaskani et al., 2005; Kaur and Kapoor, 2001), and its seeds

contain glycosides, alkaloids, saponins, tripterpenoid, phytates, and tannins, but it does not contain

oxalate or flavonoids (Johnson et al., 2012).

Vitamin B is utilized by the human body to help replenish its energy and can be considered a substitute to supplements or energy drinks (Anon, 2008). Vitamin A is an influential natural antioxidant which helps to keep the hair and skin smooth and helps to maintain the healthy growth of elastin cells and new collagen (Table 3). The consumption of vitamin A is also a widely accepted strategy by which to defend against oral cavities and lung cancers (Edwards et al., 2003). Vitamin C is associated with damaging the free radicals of oxygen-scavenging and immune-boosting effects in the human body. Healthy collagen growth is also encouraged by vitamin C (Jian et al., 2005).

An imperative constituent of body fluids and the cells that assist in blood pressure and heart rate monitoring is potassium. Potassium prevents against coronary heart diseases and strokes (Jian et al., 2005). The indispensable role of osmotic progression in the body by maintaining the electrolytic balance and the extent of body fluid to make the body pH more alkaline is due to both calcium and potassium (Lee et al., 2018; MacWilliam, 2005).

Citrulline is a physiologically potent amino acid that is involved in mammalian digestion. Over the last 40 years it has been identified as a transitional metabolite and it has garnered the attention of researchers due to its involvement in human health. Watermelons have thus been identified as a natural source of citrulline for the health conscious and their demand as a functional food has increased (Perkins-Veazie et al., 2012). Citrulline with 80% of the ingested aggregate is absorbed quickly into the blood, which increases the bioavailability of arginine (Mandel et al., 2005). Citrulline has vasodilatation and antioxidant roles and in humans it is utilized in nitric oxide regulation

(Rimando and Perkins-Veazie, 2005). Skeletal and muscle strength, diabetes, immunology and neurology, and numerous other areas of human health are substantially affected by citrulline (Pérez-Guisado and Jakeman, 2010; Sase et al., 2013; Sureda et al., 2010; Wu et al., 2007). The carotenoid responsible for the red color of tomatoes and watermelons is lycopene. Lycopene and vitamin C are well known anti-oxidants which provide several health benefits to humans. Lycopene provides the potential to inhibit numerous chronic ailments like oncogenesis and diabetes. The singlet oxygen scavenging ability is central to the protective antioxidant mechanism. The oxidization of proteins, lipids, and DNA is the cause of numerous disorders of the metabolic system owing to the production of free radicals and their interactions with macromolecules. Lycopene has an important defensive role against pathogenic infections (Ilic and Misso, 2012; Sesso et al., 2004). One of the antioxidant roles of lycopene is the protection of the DNA in white blood cells (Edwards et al., 2003). In addition, approximately eight ounces of watermelon juice includes numerous vitamins and nutrients, such as vitamin C, vitamin A, potassium, β -carotene, and lycopene. Watermelon fruit extracts have moderate phenolic compound concentrations and are employed to treat constipation and stomachache and traditionally include anthraquinones.

Watermelon seeds also have therapeutic benefits, such as anti-diarrheal activity which is possibly because of their glycosides which are potent phytochemicals (Tiwari et al., 2009). Saponins have been patented pharmaceutically for the treatment of numerous disorders including cardiovascular, hypertension, pre- and postmenopausal, and inflammation symptoms (Bombardelli and Gabetta, 2001). Alkaloids were identified as significant

therapeutically imperative plant secondary metabolites and they were reported to exhibit the highest concentration in watermelon seeds used extensively worldwide as an elementary agent for antiparasitic, analgesic and antibacterial effects. Tannins also have significant effects against diabetes, tumors, proliferation, mycotic infections, and mutagenesis (Arapitsas, 2012). Phytates exhibited anti-cancer and antioxidant properties. A unique anti-inflammatory phytonutrient agent is cucurbitacin E, but triterpenoid is another name for this phytonutrient (Abdelwahab et al., 2011).

2.1. Watermelon flesh

2.1.1. Carotenoids

Watermelon is the world's third most popular fruit consumed during hot weather. The color of the watermelon's flesh is an essential characteristic. White, salmon yellow, orange, crimson red, scarlet red, pale yellow, canary yellow, and green are the eight defined flesh colors for watermelon. Except for the green flesh color, watermelon contains a variety of carotenoids that are responsible for the various flesh hues. Carotenoids are important functional components and micronutrients in watermelon. The carotenoid composition and concentration have both become a major focus during watermelon quality assessments (Zhao et al., 2013). The majority of β -carotene and lycopene were found in red-fleshed watermelons. Lycopene accounted for most of the total carotenoids (84%-97%). Carotenoid composition and content in watermelons of varying flesh colors are linked to cultivars and growing conditions (Tadmor et al., 2005).

Lycopene, β -carotene, phytofluene, phytoene, lutein, and neurosporene are some of the carotenoids that have been identified in watermelon. Lycopene

is comprised of 13 double bonds two of which are non-conjugated and 11 which are, and it is characterized by an acyclic open-chain structure. The antioxidant property of lycopene and its bright red color are attributed to its unique conjugated polyene structure (Holzapfel et al., 2013; Shi and Maguer, 2000; Stahl and Sies, 1996). In foods, the most widespread and natural lycopene configuration is the all E-isomer. During the oxidation and thermal processing, the lycopene Z and E isomerizations may exist in foodstuffs. The potent antioxidant is composed of only E-isomers, while the 5Z- lycopene is reportedly the most biologically active form. Lycopene is a suitable target for electrophilic reagents, presuming that there is an electron-rich organization due to its polyene structure. In the case of free radicals for oxygen scavenging, it has extreme reactivity (Holzapfel et al., 2013). As a free radical scavenger, the carotenoid's lycopene is reported to be the most effective and potent antioxidant and singlet oxygen quencher, and the risk of cancers and cardiovascular diseases are subsequently reduced (Holzapfel et al., 2013; Perkins-Veazie et al., 2001; Shi and Maguer, 2000; Stahl and Sies, 1996). The most important function of carotenoids is to neutralize compounds produced throughout photosynthesis (Table 4, 5). The structure of lycopene is shown in Fig. 1.

2.1.2. Amino acids

The organic constituents comprised of both amino and acid groups are designated as amino acids (AA). All AAs have optical activity and an asymmetric carbon excluding glycine. The arrangement with reference to the glyceraldehydes of AA isomers is nominated as an absolute configuration. All protein AAs allied to the α -carbon atom (hence α -AA) have a carboxyl group

Table 4. Variation in the nutritional composition of watermelon at different maturity stages

Nutrients	Maturity stages		
	Unripe	Ripe	Overripe
	Quantity	Quantity	Quantity
Moisture	94.8%	91.5%	90%
Carbohydrates	6.5%	3.5%	NR
Protein	NR	NR	1.74 g
Dietary fiber	NR	NR	1.14 g
Potassium	0.81%	0.89%	320 mg
Calcium	0.31%	0.29%	NR
Iron	0.004%	0.005%	NR
Total mineral content	1.8%	2.2%	320 mg
Vitamin A	NR	NR	1,630 IU
Vitamin C	NR	NR	23.2 mg
Lycopene	37.1 mg/kg	40.4 mg/kg	42.0 mg/kg
Citrulline	1.0 mg/g	1.1 mg/g	1.1 mg/g
References	(Abdullahi Sa'id, 2014; Rimando and Perkins-Veazie, 2005)	(Abdullahi Sa'id, 2014; Rimando and Perkins-Veazie, 2005)	(Anonymus 2022; Perkins-Veazie et al., 2001)

NR, not reported.

and a primary amino group excluding proline (Galli, 2012). AAs have an extraordinarily diverse range of biochemical properties and functions due to the differences in their side chains (Brosnan, 2009; Wu et al., 2007; Yamane et al., 2009). At biological pH, except for (1) cysteine which suffers from rapid oxidation to cysteine and (2) other is progressively to pyroglutamate cyclized at 1%/day at 1 mM is glutamine (25°C). All AAs are normally constant in aqueous solution.

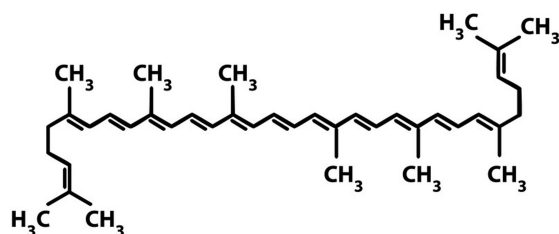
The isoforms can substitute entire AAs, except for glycine. Furthermore, except for D-lysine, D-histidine, D-threonine, D-arginine, and D-cystine in animals, the maximum D-AA via extensive transaminases and oxidases can be converted into AA (Baker and Cameron, 1999; Fang et al., 2009). Dependent on substrates and species, the effectiveness of AA consumption may be 20%-

100%, based on isomer (Baker and Cameron, 1999).

In nature, there are more than 300 AAs. However, only 20 of these function as the building blocks of protein. Significant roles in cell metabolism are performed by non-AA (such as β -alanine and taurine) and non-protein AA such as (ascitrulline, homocysteine, and ornithine) (Huh et al., 2014; Manna et al., 2009; Perła-Kaján et al., 2007). In the body for both free AAs and those that are peptide-bound, the chief reservoir is the skeletal muscle since it consists of 40%-45% of an individual's body weight (Davis and Fiorotto, 2009). Watermelon is an admirable source of citrulline (an amino acid), which is utilized to help produce another amino acid called arginine. The effectiveness of citrulline and arginine in cardiovascular health, immune function, wound soothing, and sickle cell anemia has been emphasized in previous studies

Table 5. Therapeutic studies of bioactive compounds of watermelon on human's wellness reported by different researchers

Nutraceutical compound	Subject	Duration	Condition	Dose	Treatment effect	Reference
Lycopene	Adults	19 weeks	Prevent the defects in plasma	20.1 mg/day	The enhancement in total plasma lycopene with tomato treatments or watermelon is ascribed to increase both cis and trans lycopene isomers, that maximize the plasma concentration in human body.	(Edwards et al., 2003)
Citrulline	Humans	3 days	Enhancement in the markers' concentration indicative of NO synthesis	500 mg/kg/day	Treatment of nitrite in cells with citrulline is significantly greater during <i>in vivo</i> and <i>in vitro</i> conditions.	(McKinley-Barnard et al., 2015)
β -Carotene	Females	90 days	Improve facial wrinkles and elasticity	30 and 90 mg/day	Supplementation of β -carotene is established to repair and prevent photoaging.	(Cho et al., 2010)
Phytofluene, phytoene	Rats	Two weeks	Cause improvement in tissues and plasma	1 g/kg	Trans phytoene accumulation over 9-cis phytoene in the kidney, spleen, and liver is regarded as stronger antioxidative effect.	(Werman et al., 2002)
Lutein	Rats	6 weeks	Prevent the formation of colonic aberrant crypt foci	0.01 mg/g tissue	Lutein in less doses may potentially avoid colon carcinogenesis.	(Narisawa et al., 1996)
Tripterpenoid	Mice	-	Suppression of metastasis	2.5 mL/kg/day	Active supplements for increasing the 5-fluorouracil chemotherapeutic effect on the esophageal cancer.	(Yamai et al., 2009)
Luteolin	Mice	-	Lung fibrosis therapy	10 mg/kg	Luteolin has strong antifibrotic action, by reserving lung inflammation and suppressing myofibroblast and epithelial-to-mesenchymal transition as well.	(Chen et al., 2010)
Watermelon seed extract (<i>Citrullus vulgaris</i>)	Rats	4 weeks	Examine the effect of herb on spermatogenesis	55 mg/kg/day	Enhances the population of sperm, viability and motility, preferably utilized by infertile patients.	(Khaki et al., 2013)
Watermelon juice	Rats	15 days	Reduce oxidative stress	4 mL/kg	Watermelon juice establishes anti-oxidative effects developed by ethanol-induced oxidation in the brain and liver of rats.	(Oyenihi et al., 2017)

**Fig. 1.** Structure of lycopene.

(Tong and Barbul, 2012). For citrulline, 80% of the ingested aggregate was found to be absorbed quickly

into the blood, and it has better bioavailability when compared with arginine (Mandel et al., 2005). The structures of citrulline and arginine are shown in Fig. 2 (Collins et al., 2007; Rimando and Perkins-Weazie, 2005).

2.1.3. Phenolic compounds

In *C. lanatus*, phenolic compounds, such as anthraquinones exist in moderate concentrations and are effective at relieving both stomachaches

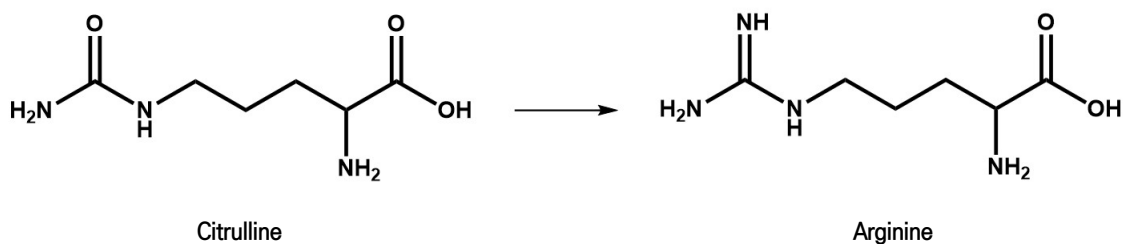


Fig. 2. Structure of amino acids.

and constipation. Anthracene produces very specific compounds known as anthranols and anthrone derivatives. At the C-8 and C-1 positions, other moieties, such as chrysophanol, luteolin, emodin, and rhein derivatives have a mutual double hydroxylation. In the plant sample, a violet color or pink identifies the anthraquinone coexistence in the base stratum (Sarker and Nahar, 2013). The structures of some phenolic compounds in watermelon are shown in Fig. 3 (Sarker and Nahar, 2013).

2.2. Watermelon seeds

2.2.1. Triterpenoid

Cucurbitacin E is a distinctive anti-inflammatory agent that is also referred to as a triterpenoid. The neutralization of reactive nitrogen-containing molecules and the cyclo-oxygenase enzymes action blockage has been rendered by cucurbitacin E. This

agent is utilized for the neutralization of reactive nitrogen species (RNS) via an anti-inflammatory agent, but it does not neutralize the reactive oxygen species (ROS) at the cellular level (Abdelwahab et al., 2011). The structure of the triterpenoid is shown in Fig. 4 (Abdelwahab et al., 2011).

Terpenoid compounds are manufactured by terpene from chiefly isopentenyl pyrophosphate five carbon isoprene units and dimethylallyl pyrophosphate and its isomer. Terpenoids also intermingle with the furthestmost regulatory proteins and have antioxidant properties. For the mitigation of inflammatory diseases and cancer, plant extracts are traditionally used alongside traditional alternative medicines. Terpenes are used in current medicines as NF- κ B inhibitors (Prema et al., 2015). The NF- κ B system responds to disorders in the immune system as well as numerous external signals and internal

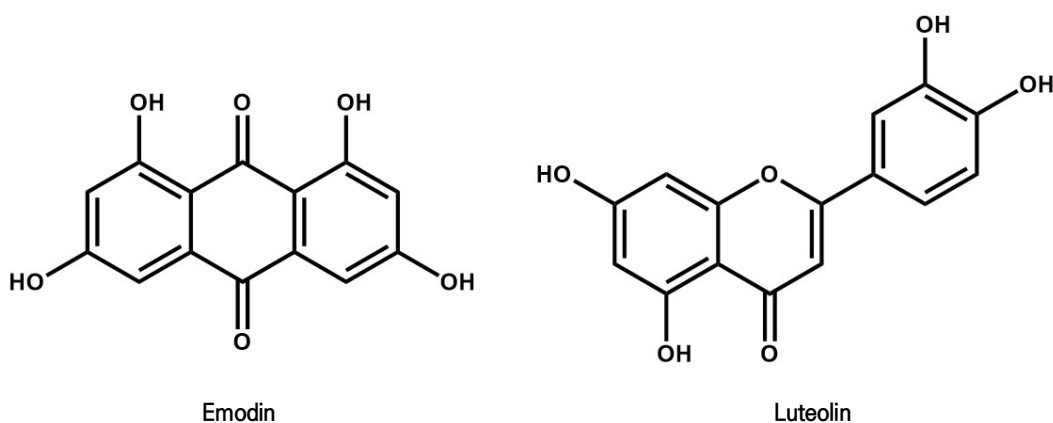


Fig. 3. Structure of phenolic compounds.

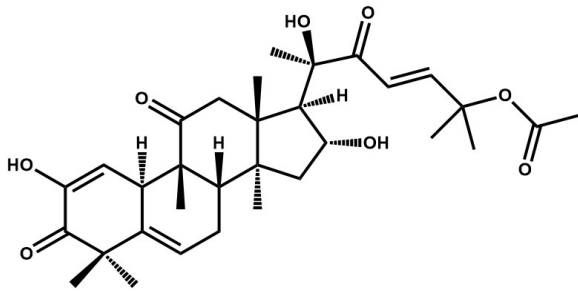


Fig. 4. Structure of triterpenoid (cucurbitacin E).

responses like genotoxic stress and hypoxia, which function as cytoplasmic sensors. Cellular resistance enlargement counters anti-apoptotic signaling and the apoptosis of NF- κ B also plays significant role. Terpenes mostly occur as the terpenoid derivatives of terpene in plants. The NF- κ B signaled inhibitory action as the foremost terpenes identified had sesquiterpenoids, while others were thought to have numerous potent inhibitors including diterpenoids and triterpenoids. In plants, a monoterpenoid that occurs as a glycoside derivative is aucubin, and it prevents the degradation of the I κ B α protein and in stimulated mast cells it inhibits the subunit P65 of the NF- κ B complex for nuclear translocation. A protective function regardless of hepatotoxicity is performed by aucubin and linalool due to their antitumor action and it has anti-inflammatory action endorsed by previous studies. The inhibitory effects on the pancreatic and mammary tumors were because of a perillyl alcohol derivative of limonene. For the inhibition of gastric cancer metastasis and proliferation, these two compounds were also identified.

2.2.2. Glycosides

The glycoside phytochemicals in watermelon seeds were identified as having anti-diarrheal benefits amongst others (Tiwari et al., 2009). Including polysaccharides, the sugar condensation products

were found to invariably be monohydrate but occasionally there were thiol compounds that host different organic hydroxyl varieties. Glycosides are present in the spare water-soluble phytoconstituents, and crystalline carbon, containing oxygen and colorless hydrogen (a few containing sulfur and nitrogen). Glycosides are comprised chemically of a non-carbohydrate part (aglycone or genin) and a carbohydrate (glucose) by alcohol, glycerol or phenolaglycones. Mineral acids and glycosides can be easily hydrolyzed into their constituents. Glycosides are categorized based on the chemical nature of the aglycone or their pharmacological actions. They are commonly found in plants from the Genitaceae family. The increased flow of saliva and gastric juices is due to a bitter action of the gustatory nerves. The bitter compounds may be the lactones diterpene (i.e., andrographolide) or triterpenoids (i.e., amarogentin) and the lactone group chemically. Due to the existence of tannic acid, to reduce thyroxine and metabolism, as antiprotozoan, several of the bitter compounds are also used as astringents. Chalcone glycosides (anti-cancer), glycosides anthracene (for skin diseases treatment and laxative), glycosides, ailanthone, gentiopicrin, polygalin, amarogentin, and rographolide are particular examples. In numerous pharmaceutical preparations, the extracts of plants are used as flavoring agents to encompass cyanogenic glycosides. For cancer treatments (malignant cells are killed in the stomach by HCN liberation), various preparations have been used as cough suppressants including amygdalin. Cyanogenic glycosides can be lethal if there is excessive consumption by the intended consumers. If not appropriately handled, particular foodstuffs may also cause poisoning (gastric damage and severe irritations) possibly due to cyanogenic glycosides (Sarker and Nahar, 2013). The cyanogenic

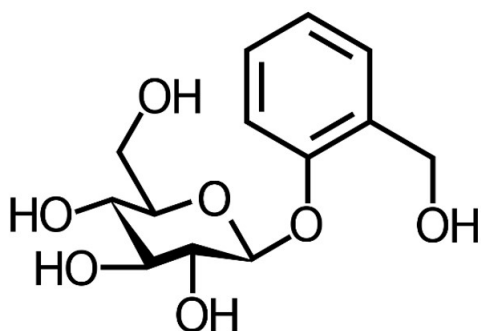


Fig. 5. Structure of glycoside (Salicin).

glycoside structure is shown in Fig. 5 (Sarker and Nahar, 2013).

2.2.3. Saponins

Saponins, which are found in watermelon seeds, are used to treat a variety of ailments, such as inflammation, pre- and postmenopausal symptoms, cardiovascular disease, and hypertension pharmaceutically (Bombardelli and Gabetta, 2001). There are two main types of saponin, steroidal and triterpenoid. In saponins, the sugar is usually attached at the C-3, which explains why there is a hydroxyl group in most saponins at this point. In saponins, the sugar is molecularly connected with a steroid aglycone or triterpene, and they are high molecular weight compounds. The saponins, triterpene, and saponins steroid are saponins belonging to the two major groups. Saponins exhibit solubility in water while these are insoluble in organic solvent, such as ether and they provide aglycones related glycosides on hydrolysis. They are identified as being the causal agents of cattle poisoning and blood hemolysis. In general, saponins are considered very poisonous. They are insoluble in non-polar organic solvents such as hexane and benzene, but are soluble in alcohol.

2.2.4. Alkaloids

In watermelon seeds, alkaloids reportedly have the highest concentration levels when compared with their other components, and they exhibit effective therapeutically important bioactivities as plant secondary metabolites and as elementary agents for antispasmodic, analgesics, and bacterial effects and are extensively used worldwide (Akshaya et al., 2018).

These are largely comprised of ammonia compounds as the principal group of secondary chemical components in the amino acid building blocks that fundamentally synthesizes nitrogen bases and encompass them in a peptide ring. These are the basic compounds that help to change red litmus paper to blue as they have basic properties. For alkaloids, the alkalinity of an alkaloid they substitute as amines 1°, 2° or 3° normally due to the presence of one or more nitrogen atoms. Due to the properties of elements, such as molecular structure, functional groups, location, and presence, the degree of basicity is known to fluctuate significantly (Sarker and Nahar, 2013). For crystalline salt formation these react with acids. Several alkaloids occur as liquids that are comprised of carbon, hydrogen, and nitrogen while, a majority are in a solid state, such as atropine. Alkaloids in water and their salts are commonly soluble, however, a majority are highly soluble in alcohol. The alkaloid solutions are extremely bitter in taste. As analgesics and CNS stimulants, alkaloids have pharmacological uses. The alkaloids with reported pharmaceutical purposes were reportedly obtained from 20% of plant species with an additional 12,000 alkaloids that have been recognized thus far. Addictive stimulants are comprised of nicotine, cocaine, caffeine, ergotamine, codeine, morphine, ephedrine,

and atropine and these have other types of plant-sourced alkaloids. The basic structures of some the pharmacologically active alkaloids are shown in Fig. 6 (Doughari, 2011).

3. Bioavailability of the bioactive compounds in watermelon

The word bioavailability refers to the systemic circulation of a composite and nutrient consumption. The term incorporates bioactivity, tissue distribution, GI assimilation, absorption, and digestion. To confirm bioavailability, it must be demonstrated that the investigated constituent is absorbed, digested and assimilated competently and that it conveys a positive outcome for human health. Measurements of bioactivity can encounter both practical and

ethical complications and thus the term “bioavailability” without considering bioactivity, is referred to as the portion or metabolite of a given compound in systemic circulation by which it is influenced (Holst and Williamson, 2008). Compound bioavailability is measured *in vivo* in animals or in humans in cases of compound underneath the curve (plasma-concentration) as the zone accomplished later of prolonged or severe dose of compound holding food or an isolated compound administration, conferring to this definition (Rein et al., 2013).

Mobility from the gastrointestinal tract to the body tissues is mediated by a chylomicron micelles mechanism, which plays a key role in assimilation. Absorption is also affected by the isomeric form of the lycopene, as when compared to the *cis*-isomeric configuration the *trans*-isomeric form is

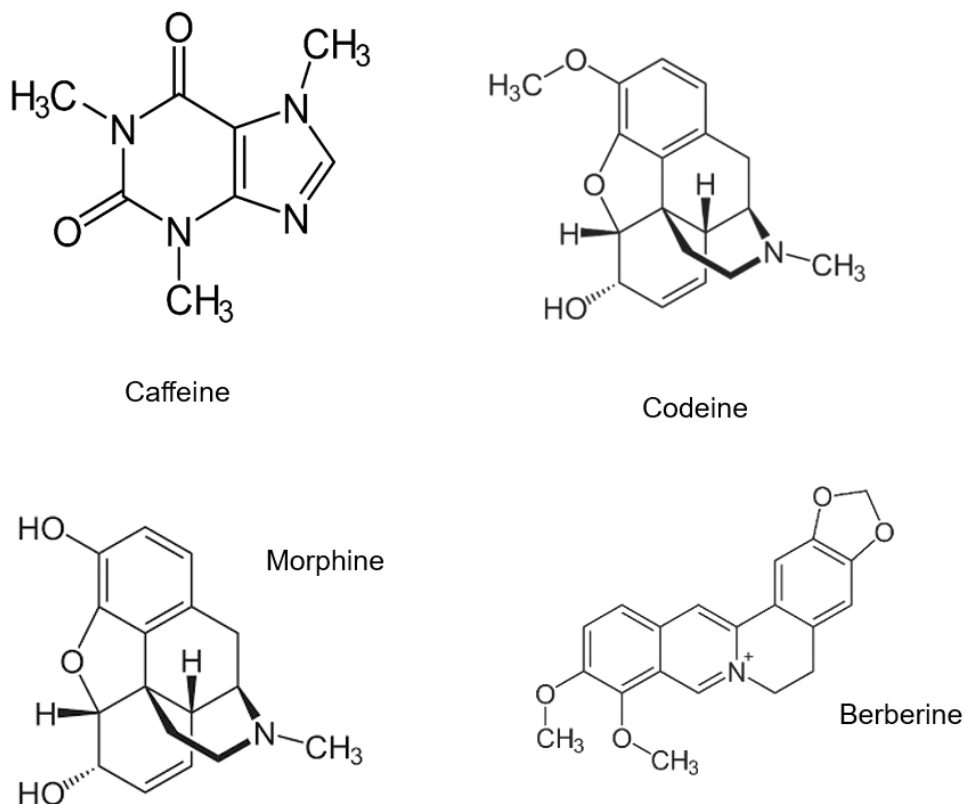


Fig. 6. Basic structures of some pharmacological alkaloids.

adsorbed less (Collins et al., 2007; Rupasinghe and Clegg, 2007). Lycopene absorption is subsequently assisted by the *cis*-isomeric arrangements and presence of fat in the prostate, adrenal glands, liver, and adipose tissues it is deposited in. The disruption of carotenoids occurs after the consumption of lycopene, as lycopene passes through the gut lumen it becomes attached to protein in the low pH of the abdominal environment. Lycopene in the blood stream is associated with the breakdown of chylomicron. Lycopene-protein complex follows hepatic pathway to reach the target tissues (Gao et al., 2008; Jian et al., 2005).

4. Therapeutic effects of watermelon

4.1. Oxidative stress

The primary starting point for numerous metabolic dysfunctions is the etiology of oxidative stress. Uncontrolled oxidation is known to result in extreme ROS generation (Butt et al., 2009). Diminishing the endothelium reliant vasodilatation and atherosclerosis by inactivation of nitric oxide could be a result of free radical accumulation. The ROS in customary metabolic pathways are manufactured without interruption. ROS accumulation may increase; however, because of diet, smoking, environmental variables, and exercise (Espin et al., 2007; Weisburger, 2002). In LDL oxidation, short term development and in diminishing of lymphocytes oxidative destruction, a role of lycopene specified in terms of diet-based therapy (Alshatwi et al., 2010).

ROS production upsets the oxidative balance, the oxidation of lipids, and engenders double allylic hydrogen atoms without interruption. The production of hypochlorous acid forms the basis for cellular destruction by the oxidative damage temporarily catalyzed by neutrophils. Antioxidant enzymes like

glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) are synthesized by the body in this situation. By generating singlet oxygen into hydrogen peroxide superoxide dismutase, it functions as a principal factor in the first-line of defense. Hydrogen peroxide is transformed into water though by GSH-Px and catalase enzymes. If ROS are excessively produced, disruption may take place after subsequent necrosis or apoptosis, otherwise these enzymes will normally synchronously. Dietary lycopene may function to combat disproportionate ROS production (Erdman et al., 2009).

Oxidative stress is known to be vigorous in chronic diseases. Numerous ailments, such as cancer, osteoporosis, cardiovascular complications, cataracts, and diabetes pathogenesis are usually associated with free radicals (Ratnam et al., 2006). Lycopene in hypertensive patients gradually decreased malondialdehyde (MDA) and lipid peroxide levels in a manner similar to that of the antioxidant enzymes glutathione peroxidase (GSH-Pox), superoxide dismutase (SOD), and reduced glutathione (GSH) (Bose and Agrawal, 2007). In coronary artery disease, lycopene was found to effectively increase GSH levels and decrease MDA levels (Misra et al., 2006). In men who smoke, the significance of lycopene was assessed through a double blind randomized controlled study with low fruit and vegetable consumption. It was concluded that lycopene significantly improved endothelial function and diminished oxidative stress (Table 5) (Pennathur et al., 2010). Similarly in male Wistar rats, lycopene effects on nephrotoxicity and cisplatin-induced lipid peroxidation were investigated (Dogukan et al., 2011). The rats fed lycopene showed a noteworthy reduction in renal bax protein, which is a low oxidative stress indicator. The reaction of lycopene supplementation on

oxidative stress markers was also determined. Lycopene was provided to human subjects to evaluate the effects on subsequent LDL and MDA assessments for two months. To detect any harmful consequence, lymphocytes were also investigated. For the TBARS value and LDL oxidation, a marked reduction of 21% and 17%, respectively was observed in the controlled group of subjects fed lycopene (Devaraj et al., 2008). In normal and cancer cells, the defensive DNA owing to the antioxidant properties of lycopene, has been endorsed by previous literature (Liu et al., 2005; Scolastici et al., 2008). In monkey fibroblasts, a decrease in products, such as TBARS (21%) and DNA damage markers in lipid peroxidation were similarly perceived. A shield against Fe-induced oxidative damage is due to prostate tissue and lipid peroxidation decline, as was revealed by lycopene with injections of 10 mg/day/kg for 5 days in rats (Matos et al., 2006).

4.2. Cardiovascular diseases

An inactive lifestyle is associated with cardiovascular disease (CVD). Sub-acute and long-lasting infections were found to occur due to a high cholesterol diet, which is a risk factor for cardiac disease. Factors such as LDL-cholesterol, serum amyloid A (SAA), and inter-cellular adhesion molecule (ICMA-1) may facilitate cardiovascular and atherosclerosis development (Verschuren et al., 2011). Dietary lycopene due to its extraordinary antioxidant activity has cardio-protective properties (Cauza et al., 2004).

During fasting, lycopene has been found to have therapeutic actions to protect against ischemic strokes, atherosclerosis, and heart attacks when confronted through low-density lipoprotein oxidation (Omoni and Aluko, 2005). Clotting inside blood

vessels decreased and consequently reduced the risk of myocardial infarction due to the high intake of lycopene (Zhang and Hamauzu, 2004).

Watermelon has very high levels of lycopene which means that it may help to reduce the risk of heart disease and provide effective protection from cell damage. In obese adults, the incidence of hypertension and low blood pressure can be regulated by consuming watermelon extracts. Furthermore, watermelon has also received attention as a well-known source of potassium, as it can help to control the heart rate and blood pressure (Jian et al., 2005).

For 10 weeks, 56 male albino rats were administered lycopene. The rats fed a hypercholesterolemic diet showed a noteworthy increase in squat and high-density lipoprotein, serum total lipid, and total cholesterol levels, as well as reduced echelons of malonaldehyde and glutathione. The signs and indications of hypercholesterolemia were reduced in lycopene-fed population.

4.3. Liver disease

Non-alcoholic fatty liver disease (NAFLD) can originate from unassuming steatosis and if it is not treated it may develop into smooth hepato-cellular and cirrhosis nonalcoholic steatohepatitis (NASH) (Hillenbrand et al., 2015; Younossi et al., 2016). Persistent hepatic wounds show inflammation and lobular ballooning and may ultimately lead to cirrhosis followed by nonalcoholic steatohepatitis (NASH) (Younossi et al., 2016). Cirrhosis was demonstrated to be an irreversible phase of disease whereas, NAFLD and NASH were found to be reversible (Al-Dayyat et al., 2018). Lifestyle adjustments are the only confirmed modality by which to manage NAFLD (Al-Dayyat et al., 2018; Mokhtari et al., 2017) and can include dietary

supplements (Hekmatdoost et al., 2016; Yari et al., 2016). In investigational models of NAFLD, amendments of hepatic steatosis and insulin resistance (IR), such as citrulline (Cit) specific amino acid supplementation were identified as an effective approach. It was concluded that IR, glucose tolerance, and lipid metabolism effects could be utilized to help recover from hepatic steatosis (El-Kirsh et al., 2011; Jegatheesan et al., 2016). The properties on as tumor necrosis factor α (TNF- α) and interleukin-6 (IL-6) reduction, some studies revealed the inflammatory markers possibly because of high citrulline content (Breuillard et al., 2015; Jegatheesan et al., 2016; Joffin et al., 2015) and hence, the progression of cirrhosis and NASH could thus be lowered (Saltzman et al., 2015). To inspect the effects of Cit supplementation on liver enzymes, indices of inflammation, elasticity, and echogenicity hepatic were determined in patients with NAFLD.

A placebo controlled double blind clinical trial as a prospective randomized study was designed and NAFLD patients from a private hepatology clinic were enrolled. According to the fibroscan results by a gastroenterologist, NAFLD was identified (Breuillard et al., 2015). The controlled attenuation parameter (CAP) in the fibroscan was scored as >260 in those >18 years of age and involved in inclusion criteria. Female pregnancy and lactation were rejection criteria, as was the use of hepatotoxic medications, viral hepatitis, insulin injections, and the consumption of alcohol. In the study, participating patients were randomly allocated for 12 weeks or four capsules/day to receive Cit (0.5 g) or the placebo (maltodextrin) after receiving a description of the study protocol. According to clinical guidelines and while consuming an energy-balanced diet, both groups were provided with

guidelines for the identification, evaluation, and treatment based on the North American Association of overweight and obesity and the National Institutes of Health. Subsequently the start of mediation follow-up valuations occurred every 4 weeks. In every appointment submission was assessed through capsule count. This was the first randomized study to our knowledge, in patient with NAFLD clinical test that assessed the upshot of Cit supplementation on markers of inflammation. There was significant reduction in inflammation markers after 2 g/day ingestion of the Cit.

The supplementation of Cit causes the production of TNF- α and NF- κ B activation inhibition which can diminish Toll-like receptor 4 (TLR4) gene expression (Breuillard et al., 2015; Jegatheesan et al., 2016; Joffin et al., 2015). The additional recommended mechanism involved the Cit properties for decreasing oxidative stress for its anti-inflammatory effects. The intensities of malondialdehyde (MDA) were abridged and increases in superoxide dismutase (SOD) activities resulted from the Cit supplementation (Cai et al., 2016). Signal regulated extracellular kinases1 and 2 and signaling protein activation can be reduced by SOD. TNF- α prevention of the NF- κ B is due to ERK1/2 inhibition (Perriotte-Olson et al., 2016). Furthermore, in livestock animals assessed for hepatic lipid peroxidation, Cit supplementation was found to defend against those fed a high-fructose food. The main cause of TNF- α through redox sensitive nuclear factor κ B activity is due to amplified lipid peroxidation (Locatelli et al., 2013; Sellmann et al., 2017).

4.4. Rheumatoid arthritis

Citrulline is involved in the urea cycle. Watermelon is of special interest as it contains

citrulline, while it is lacking in most other natural foods (Tarazona-Díaz et al., 2011). Citrulline content in wild watermelon is distinguished as a necessary hydroxyl radical scavenger that helps to reduce drought-mediated oxidative stress (Akashi et al., 2001). For the management of pathological conditions characterized by reduced arginine availability and oxidative stress, such as sickle cell disease, heart failure, hypertension, atherosclerosis, (Figuroa et al., 2011), erectile functions, and sexual stamina (Drewes et al., 2003) as these produce nitric oxide (NO) which has made citrulline as an outstanding candidate (Bansal et al., 2004). L-citrulline intake has other related benefits such as an antioxidant, vasodilatation roles, and due to its use in the nitric oxide system in humans following an athletic routine (Rimando and Perkins-Veazie, 2005). The ornithine and arginine levels (which are important for muscle growth) were revealed to increase with citrulline malate and this influenced growth hormone levels (Sureda et al., 2010). Lactic acid removal was also accelerated by citrulline.

The supplementation of citrulline encourages the renal reabsorption of bicarbonates, diminishes fatigue, and stimulates hepatic ureogenesis as was reported in previous studies (Jayaprakasha et al., 2011). The citrulline malate and its anti-fatigue properties limit ammonia poisoning and acidosis, and these metabolic modalities have consequences for the body's defense mechanisms (Bendahan et al., 2002). In aged rats, for example, an increase in protein and the absolute muscle rate production was induced by citrulline-supplemented food re-feeding for 1 week (at 5 g/kg/day). Smooth muscle relaxation is treated by an citrulline enriched dietary supplement (Jayaprakasha et al., 2011).

An investigation at the University of Murcia involved students from the Sport Science Department

(170.8±3.6 cm height; 68.9±3.8 kg for the body mass of 7 men; 24.0±0.6 kg m² body mass index; SD age±mean, ±22.7). The subjects participated regularly in a diverse range of sports but were not good athletes. When the placebo was administered to the muscle, soreness was considerably superior after 24 h of exercise when compared to those given the watermelon juice. However, there were no specific differences among those given enriched watermelon juice and natural watermelon juice. These results demonstrated that citrulline was adequate at 1.17 g to reduce soreness due to exercise. Even in placebo drinks, the muscle tenderness was decreased to 1 in all treatments, with no noteworthy differences observed after 48 h. A decrease in muscle tenderness 24 h and even 48 h post-exercise is associated with an 8 g citrulline malate supplement. A relief in muscle discomfort and enhancement in athletic anaerobic performance is thus associated with citrulline malate supplementation (8 g/day) (Pérez-Guisado and Jakeman, 2010).

4.5. Nephropathy

Chronic kidney malfunctions which frequently indicate kidney disease are usually termed as chronic kidney disease (CKD) or end-stage renal disease (ESRD), and these conditions are irreversible and progressive ailments. Blood pressure elevation, diabetes, interstitial nephritis, long-lasting pyelonephritis, secondary glomerulonephritis, conventional cystic diseases, and vasculitis are the main causes. An irreversible progressive fall off in kidney functionality is known as chronic renal failure (CRF), and this results in the shrinkage of the glomerular filtration rate and a gradual upsurge in plasma creatinine (Nesrallah et al., 2014). Waning functionality of the kidney, ESRD, and kidney failure are the main stages of CRF. The proportion of proteinuria,

existence of hypertension, or non-existence and underlying dysfunction are elements. Disease evolution was found to be quicker in patients who had proteinuria or hypertension (Abboud et al., 2010; Tomasello, 2008).

The consumption of lycopene according to some studies, due to its biochemical and histo-pathological factors precludes kidney damages (Amiri and Nasri, 2014; Coresh et al., 2003). In watermelon, other valuable compounds are present, including arginine and citrulline. For kidney failure patients, the addition of arginine-containing food supplements is helpful. By discontinuing biochemical procedures, non-nitric oxide (dimethyl arginine irregular activity reduced by it) formed as a result of treating of kidney disorders, and this modality may have a probable beneficial effect (Kachhawa et al., 2016; Rimando and Perkins-Veazie, 2005).

'To investigate the steady ingestion of watermelon, a case report was presented for a male patient with CKD. The patient with indications of kidney disease was a 60-year-old man, who had habitually visited his physician for five years. Following were the results of patients on the primary visit to laboratory: mm Hg blood pressure was 120/80 mm (systolic/diastolic), creatinine serum was 9.6 mg/dL, and serum blood urea nitrogen (BUN) was 75 mg/dL. The patient was diagnosed with diabetes at the age of 30 and was then given conventional treatments. The patient was subsequently treated for colonic cancer, and the level of creatinine was found to have increased to 9.6 mg/dL from 2 mg/dL at 120/80 (systolic/ diastolic) mm Hg blood pressure, and his level of BUN significantly increased from 27 mg/dL to 48 in the subsequent appointments. Without altering his drugs for diabetes, the patient consumed a significant amount of watermelon and the serum creatinine was then

found to revert to 1.7 mg/dL temporarily.

4.6. Macular disease

A steady reduction in vision results from retina macula stratum watering and is indicated by the appearance of a yellow spot. Wet and dry age-related macular degeneration (AMD) are considered to be two classifications. Hemorrhage, scars on the eye tissue and swelling are symbols indicating the expansion of such vessels. The possibility of macular and other degenerative ailments can be condensed by the consumption of carotenoids from plant sources. Subjects with low lycopene concentrations were found to be in greater danger of macular degeneration. Lycopene has also been found to be beneficial when provided alongside treatments for immune deficiency conditions such as HIV and for Austrian stroke cerebral damage microangiopathy (Kun et al., 2006).

4.7. Neurological disorders

Lycopene and its metabolites can be detected in the brain (Khachik et al., 2002). In the central nervous system, lycopene may have neuro- protective properties. In psychiatric and neurodegenerative disorders, lycopene potential has been endorsed by some studies (Yu et al., 2017; Zhang et al., 2016).

In tau transgenic mice expressing the P301 L mutation was progressed by lycopene supplementation in cultured neurons exhibiting an amyloid β ($A\beta$)-induced-cellular toxicity (Qu et al., 2011; Yu et al., 2017). An irretrievable inhibitor of succinic acid dehydrogenase that is persuaded by 3-nitropropionic acid (3-NP), in Huntington's disease (HD), lycopene was also found to prevent motor abnormality and cognitive dysfunction (Sandhir et al., 2010). To inverse mouse motor abnormality, lycopene was reported to reduce abnormality

owing to the probable effects of by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which was induced in a model of Parkinson's disease (Prema et al., 2015). In men with reperfusion/ischemia cerebral to diminish the stroke danger and to decrease neuronal apoptosis and infarct volume, the long term consumption of lycopene has been suggested (Karppi et al., 2012; Lei et al., 2016). The neuroprotective effects of lycopene in patients with CNS ailments are recognized as being mediated by the inhibition of oxidative stress and activation of microglial or the signaling of protein kinase B/activation of protein kinase and activated phosphatidylinositol-4,5-bisphosphate 3-kinase adenosine 5' monophosphate and γ -proliferator-activated receptor peroxisome (Lei et al., 2016; Lin et al., 2014 ; Yin et al., 2014; Yu et al., 2017). Throughout the world, PD is a condition that affects millions of people and is recognized as an overwhelming neurodegenerative ailment. A dopaminergic neuron degeneration that is PD, progress of motor incapacity as well as dopamine reduction in the striatum which is grounded due to featured pathological alteration in it (Cheng et al., 2017).

In mice, lycopene administration (20 mg/kg) for 7 days was found to overwhelm MPTP-induced reductions in striatal dopamine (Prema et al., 2015), which is in contradiction to PD-inducing stimuli that protect dopaminergic neurons through the supplementation of lycopene. Long PD mechanisms have been investigated and these include neuronal apoptosis and oxidative stress. For PD, neuronal apoptosis and oxidative stress inhibition are recognized as leading risk factors. Exploring new chemical modalities for PD therapy is providing new hope that could lead to the suppression of neuronal apoptosis and oxidative stress (Rios et al., 2011; Sharma et al., 2016). Lycopene is reportedly

linked to a decreasing level of oxidative stress as low levels in the striatum were found to reverse MPTP-induced dopamine when using a 20 mg/kg lycopene treatment for 7 days as it lead to an upsurge in GSH levels, which is a powerful antioxidant that reduces anti-oxidative stress and pro-oxidative stress level markers, such as reactive acid substances 2-thiobarbituric. Lycopene may thus be suggested as an alternative medicine for PD as a method by which to decrease neuronal apoptosis. In numerous mouse striatum apoptotic MPTP-induced markers, including caspase and bax, reduction was caused by treatment of lycopene at dose of 20 mg/kg for 7 days (Prema et al., 2015).

4.8. Huntington's disease

Huntington's disease is an autosomal congenital neurodegenerative disorder. Involuntary movements, seizures, cognitive decline, chorea, dystonia, emotional disturbances, and intellectual impairment are the most pronounced symptoms. Currently, there is no available treatment to minimize or treat the progress of these symptoms. The administration of 10 mg/kg lycopene for up to 15 d was found to effectively reverse oxidative stress and mitochondrial dysfunction caused by 3-nitropropionic (3-NP) acid succinic acid dehydrogenase and unalterable inhibitor: 1) inactivity of 2,4,5 mitochondrial multiplexes reduction; 2) reduced oxygen inhalation at the mitochondrial level; 3) promotion of nitric oxide/ROS levels and the peroxidation of mitochondrial lipids; and 4) disturbance of superoxide dismutase (SOD) in brain tissues and thiol content reduction as reported by Sandhir et al. (2010). Studies have shown positive effects because of 10, 5, and 2.5 mg/kg lycopene treatments for 14 days in terms of limiting lipid peroxidation mediated by 3-NP. Moreover, irregularity in catalase (CAT)

secretion was also found to lead to 3-NP and SOD reductions as well as NO formation in the cortex, striatum, and hippocampus of the rat brain (Kumar et al., 2009). The supplementation of lycopene to relieve HD symptoms may be studied in terms of lycopene effect in 3-NP-induced-HD mediated by different mechanisms (Kumar et al., 2009; Sandhir et al., 2010).

4.9. Diabetes

Several studies have shown that patients with hyperglycemia are more susceptible to diabetes-induced issues. The primary contributing factor is the increased level of oxidative stress and LDL oxidation. Glucose and its auto-oxidation progression cause cellular damage and increase the amount of free radicals successively in the human body owing to an extraordinary glycemic diet. Furthermore, phenolics which were discovered due to their hypoglycemic action include lycopene, lutein, β -carotene, and β -cryptoxanthin and they are also known for their antidiabetic activities. In hyperglycemic subjects, a positive correlation with carotenoids was revealed in research into mitigating diabetes risk factors. Lycopene considerably reduced the onset of hyperglycemia, and was demonstrated to be a fundamental deterrent against serum aminotransferases. Intracellular ROS generation and oxidative stress are amplified throughout the hyperglycemia phase. ROS harms the lipids, DNA, mitochondria, and other organelles due to this imbalance leading to apoptosis at the cellular level. Hypoglycemic effects were also demonstrated by investigators. Lipid and glycemic metabolism were found to be considerably improved by a watermelon extract that was rich in lycopene content. In most countries, obesity and diabetes are discernible as the foremost public health complications. The

number of people diagnosed with diabetes is expected to escalate from 135 to 300 million by 2025. Adipokines (cytokines and chimiokines) have a significant role in overall body physiology and they are produced during the development and progression of obesity. Type-II diabetes occurs due to enormous adipose tissue accumulation and consequent inflammation owing to extreme levels of cytokine and chimiokine production. The linked pathologies of hyperglycemic and obesity conditions are reduced by the consumption of lycopene owing to deposition of lipophilic carotenoid.

With diabetes, a decrease in the malignant transformation of oxidized cholesterol, the functional drinks have may exhibit positive impact because of rich lycopene content. Diabetes can be managed in part by treating glucose abnormalities gradually with lycopene consumption. In type-II diabetes, insulin levels are elevated and the body's glucose levels are reduced owing to antidiabetic and glucose lowering effect of lycopene.

For 28 days in rats fed on normal diet, the influence of lycopene oral supplementations were evaluated (Jian et al., 2005). The dosages used were 2000, 500, and 200 mg/kg of body weight. No abnormal or noteworthy results were found from the urinalysis, hematology, and organs weight analysis. However, with higher doses of lycopene, serum glucose levels were found to decrease accordingly. Amongst the lycopene-treated and control rats there were noteworthy differences in body glucose of 132.1 ± 35.9 mg/dL and 205.6 ± 44.3 mg/dL, respectively. For hyperglycemia, lycopene was advocated for its therapeutic potential. Learning and memory deficiencies, neurochemical, and physical abnormalities were favored when there were high intracellular glucose levels. Provisions of a lycopene-supplemented diet reduced oxidative

stress, improved cholinergic dysfunction, and cognitive deficit nitric oxide in a rat model. The supplementation of 5% lycopene at the administered dose of 4 mg/day resulted in a similar reduction in the serum glucose level. The effect of lycopene on standard Wistar rats was evaluated for 13 d, and their body glucose levels were found to be considerably reduced by a 13% lycopene interim supplementation (Mellert et al., 2002).

The nutritional profile of watermelon is crucial to its value, and within this profile, lycopene is the most predominant component. The antidiabetic potential of lycopene was assessed using a murine model. In one such study, diabetic mice were administered a 1% watermelon extract. The blood serum glucose levels decreased up to 33% while the rise in serum insulin level reached 37%. Watermelon extract was provided to the subjects as an alternative modality by which to combat hypoglycemia and hyperinsulinemic production in the blood serum. To monitor the efficacy, lycopene dietary consumption trials from 1992 to 2003 for diabetic middle-aged women in a control trial were carried out. The results of the 10 year follow-up showed a positive correlation between insulin level and that lycopene improved the insulin level in the serum by 37%-45%.

4.10. Cancer

With the growing concern about anti-cancer effects, several studies have reported on the efficacy of bioactive food components and their effects on tumor growth. The synergistic effects between the consumption of food nutrients and the regulation of gene expression is referred to as nutrigenomics. Lycopene exhibits potential antitumor effects at numerous stages of cancer development including direct effects on genes and mutation inhibition by

means of DNA mutation and tumor metastasis (Nahum et al., 2001). The impacts of lycopene and their gene interactions need to be investigated further to better understand the mechanisms involved. In carcinogen absorption in phase I and II, enzymes were found to be pivotal for lycopene synthesis. To mitigate mutagenesis, carcinogenesis, and some other forms of toxicity, transcription organization and antioxidant responses are triggered within the body (Butt et al., 2009).

Lycopene is also recognized for its anti-proliferative properties as well as being a potent antioxidant. A decrease in insulin growth factor and its functionality is likely to be correlated with a decrease in cancer incidence. Conversely, serum lycopene levels and the probability of onset for numerous cancer types is also being investigated.

The chemo-preventive effect of lycopene on pharynx, larynx, esophagus, and oral cavity cancers, or digestive tract cancers, has been investigated in numerous case studies. This led to the effect of lipid peroxidation on hamster buccal pouch carcinogenesis being assessed in a trial involving biomarkers for the chemoprevention glutathione S-transferase, 7,12-dimethylbenzanthracene, and glutathione reductase. As well as the increasing action of enzymes from the glutathione redox cycle and buccal pouch cancer biochemical measurements, the modulating effect after exposure to lycopene for 2 weeks. In the gastrointestinal tract, the carcinoma regression synergistic effects of vitamin C, phytosterols, flavonoids, and lycopene were recognized in an analogous study. The consumption of considerable quantities of lycopene by the study subjects resulted in anti-cancer effects in several cancer cell lines, particularly, prostate cancer (Prema et al., 2015). A diet high in lycopene content resulted in a 44% reduction in the threat of

other cancer in men and 25% reduction in prostate cancer. The anti-cancer mechanisms of lycopene are summarized in Fig. 7.

5. Conclusions

This review has summarized and discussed the available literature on the phytochemical profile of watermelon and its bioactive and therapeutic effects. The data indicates that watermelon has a superb nutritional profile, contains numerous phytochemicals, and exhibits beneficial therapeutic effects. Specifically, the data has shown that

watermelon can be utilized as a good source of vitamin C (12.31 mg/152 g), pantothenic acid (0.34 mg/152 g), copper (0.06 mg/152 g), biotin (1.52 mcg/152 g), vitamin A (43.24 mcg RAE/152 g), vitamin B₆ (0.07 mg/152 g), and vitamin B₁ (0.05 mg/152 g). Water is the major constituent of watermelon (approximately 92%), followed by carbohydrates and protein which are more considered minor constituents (11.48 g/152 g and 0.93 g/152 g respectively), and finally the fat content, which is considered very low (0.23 g). As reported in the literature, lycopene has been identified as the major bioactive compound in watermelon

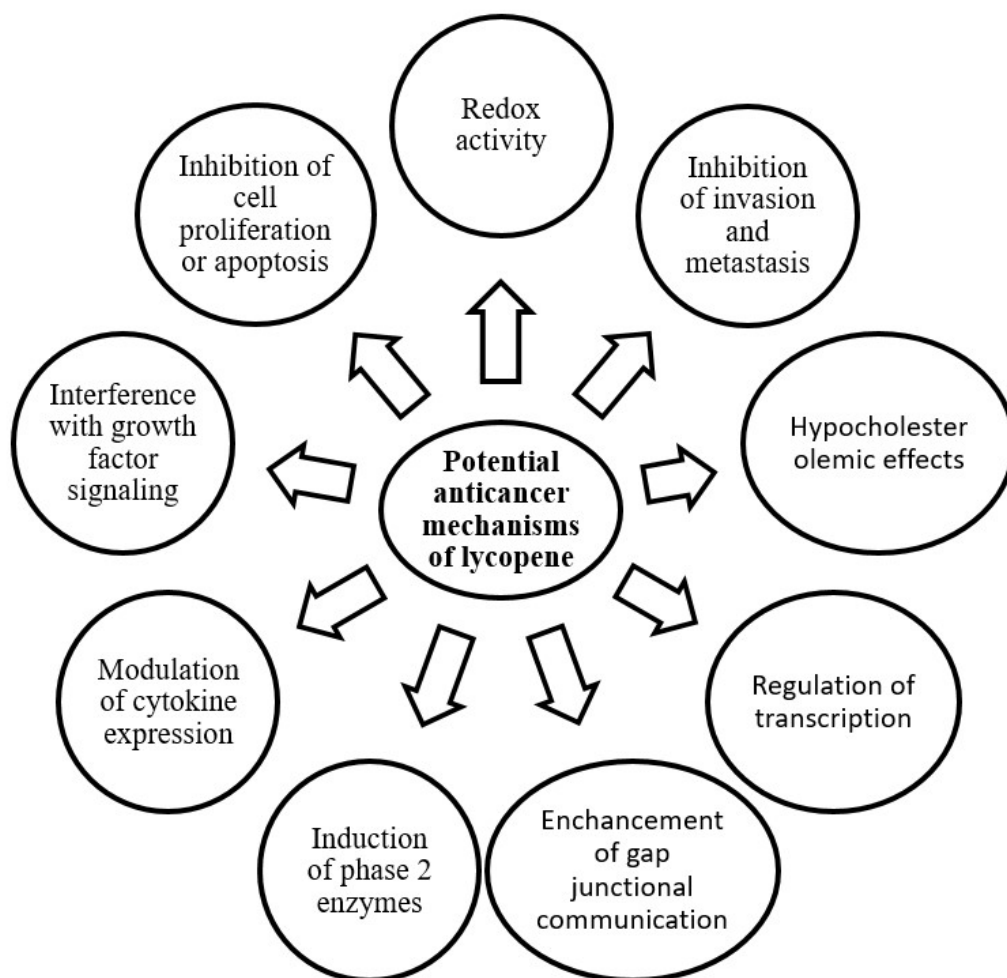


Fig. 7. Potential anti-cancer mechanism of lycopene.

(approximately 6,888 $\mu\text{g}/152\text{ g}$). Furthermore, various pre- and postharvest factors have been identified which can affect its nutritional profile. Lycopene also has potential therapeutic effects in the human body. Furthermore, major carotenoids like β -carotene, phytofluene, phytoene, lutein, and neurosporene are also reported as potentially being present in watermelon. The unique composition of watermelon means that it could be beneficial in the treatment of various diseases and disorders, such as cardiovascular diseases, liver disease, rheumatoid arthritis, nephropathy, macular disease, neurological disorders, diabetes, and various kinds of cancer. Furthermore, watermelon also possesses high levels of antioxidant activity which can help to reduce oxidative stress levels and combat lifestyle-related and metabolic disorders.

Conflict of interests

The authors declare no potential conflicts of interest.

Author contributions

Conceptualization: Nadeem M, Navida M, Ameer K. Validation: Ameer K, Iqbal A, Malik F, Nadeem MA, Fatima H, Ahmed A, Din A. Writing - original draft: Iqbal A, Malik F. Writing - review & editing: Nadeem M, Ameer K.

Ethics approval

This article does not require IRB/IACUC approval because there are no human and animal participants.

ORCID

Muhammad Nadeem (First author)

<https://orcid.org/0000-0002-7066-4334>

Kashif Ameer (Corresponding author)

<https://orcid.org/0000-0003-4019-1772>

Muhammad Ather Nadeem

<https://orcid.org/0000-0002-4246-1791>

Aftab Ahmed

<https://orcid.org/0000-0003-0912-7596>

Ahmad Din

<https://orcid.org/0000-0002-2236-3481>

References

- Abboud H, Henrich WL. Stage IV chronic kidney disease. *N Engl J Med*, 362, 56-65 (2010)
- Abdelwahab SI, Hassan LE, Sirat HM, Yagi SM, Koko WS, Mohan S, Taha MM, Ahmad S, Chuen CS, Narrima P, Rais MM, Hadi AHA. Anti-inflammatory activities of cucurbitacin E isolated from *Citrullus lanatus* var. *citroides*: Role of reactive nitrogen species and cyclooxygenase enzyme inhibition. *Fitoterapia*, 82, 1190-1197 (2011)
- Aderiye BI, David OM, Fagbohun ED, Faleye J, Olajide OM. Immunomodulatory and phytomedicinal properties of watermelon juice and pulp (*Citrullus lanatus* Linn): A review. *GSC Biol Pharm Sci*, 11, 153-165 (2020)
- Ahmad A, Amir RM, Ameer K, Ali SW, Siddique F, Hayat I, Ahmad Z, Faiz F. Ameliorative effects of fenugreek (*Trigonella foenum-graecum*) seed on type 2 diabetes. *Food Sci Technol*, 41, 349-354 (2020)
- Akashi K, Miyake C, Yokota A. Citrulline, a novel compatible solute in drought-tolerant wild watermelon leaves, is an efficient hydroxyl radical scavenger. *Febs Lett*, 508, 438-442 (2001)
- Akshaya M, Sasikala S, Nithyalakshmi V, Meenakshi N, Kiruthika DK, Pavithra MS. Effect of pre-treatments on the phytochemical composition of watermelon (*Citrullus lanatus*) rind. *Int Food Res J*, 25, 1920-1924 (2018)
- Akusu MO, Kiin-Kabari DB. Comparative studies on the physicochemical and sensory properties of watermelon (*Citrullus lanatus*) and melon (*Citrullus vulgaris*) seed flours used in "egusi"

- soup preparation. *J Food Res*, 4, 1-8 (2015)
- Al-Dayyat HM, Rayyan YM, Ttayem RF. Non-alcoholic fatty liver disease and associated dietary and lifestyle risk factors. *Diabetes Metab Syndr Clin Res Rev*, 12, 569-575 (2018)
- Alim-un-Nisa JA, Firdous S, Saeed MK, Hina S, Ejaz N. Nutritional aspects and acceptability of watermelon juice syrup. *Pak J Food Sci*, 22, 32-35 (2012)
- Al-Sayed HM, Ahmed AR. Utilization of watermelon rinds and sharlyn melon peels as a natural source of dietary fiber and antioxidants in cake. *Ann Agric Sci*, 58, 83-95 (2013)
- Alshatwi AA, Al Obaaid MA, Al Sedairy SA, Al-Assaf AH, Zhang JJ, Lei KY. Tomato powder is more protective than lycopene supplement against lipid peroxidation in rats. *Nutr Res*, 30, 66-73 (2010)
- Ameer K, Bae SW, Jo Y, Lee HG, Ameer A, Kwon JH. Optimization of microwave-assisted extraction of total extract, stevioside and rebaudioside-A from *Stevia rebaudiana* (Bertoni) leaves, using response surface methodology (RSM) and artificial neural network (ANN) modelling. *Food Chem*, 229, 198-207 (2017)
- Ameer K, Shahbaz HM, Kwon JH. Green extraction methods for polyphenols from plant matrices and their byproducts: A review. *Compr Rev Food Sci Food Saf*, 16, 295-315 (2017)
- Amiri M, Nasri H. Secondary hyperparathyroidism in chronic kidney disease patients: Current knowledge. *J Parathyroid Dis*, 2, 1-2 (2014)
- Anon M. Watermelon. Booklet of Federal Agriculture Marketing Authority (FAMA), Utusan Printcorp Sdn Bhd (2008)
- Anonymus. Live strong nutrition. Available from: <https://www.livestrong.com/article/309314-how-many-calories-does-watermelon-have/>. Accessed Jan. 21, 2022.
- Arapitsas P. Hydrolyzable tannin analysis in food. *Food Chem*, 135, 1708-1717 (2012)
- Baker RA, Cameron RG. Clouds of citrus juices and juice drinks. *Food Technol*, 53, 64-69 (1999)
- Bansal V, Rodriguez P, Wu G, Eichler DC, Zabaleta J, Taheri F, Ochoa JB. Citrulline can preserve proliferation and prevent the loss of CD3 chain under conditions of low arginine. *J Parenter Enteral Nutr*, 28, 423-430 (2004)
- Banureka VD, Mahendran T. Formulation of wheat-soybean biscuits and their quality characteristics. *Trop Agr Res Ext*, 12, 62-66 (2009)
- Bendahan D, Mattei JP, Ghattas B, Confort-Gouny S, Le Guern ME, Cozzone PJ. Citrulline/malate promotes aerobic energy production in human exercising muscle. *Br J Sports Med*, 36, 282-289 (2002)
- Biswas R, Ghosal S, Chattopadhyay A, Datta S. A comprehensive review on watermelon seed oil: An underutilized product. *IOSR J Pharm*, 7, 1-7 (2017)
- Boll MC, Alcaraz-Zubeldia M, Rios C. Medical management of Parkinson's disease: Focus on neuroprotection. *Curr Neuropharmacol*, 9, 350-359 (2011)
- Bombardelli E, Gabetta B, Indena SpA, assignee. Soya extract, process for its preparation and pharmaceutical composition. United States Patent No. 6280777, Washington, DC: U.S. Patent and Trademark Office (2001)
- Bose KSC, Agrawal BK. Effect of lycopene from tomatoes (cooked) on plasma antioxidant enzymes, lipid peroxidation rate and lipid profile in grade-I hypertension. *Ann Nutr Metab*, 51, 477-481 (2007)
- Braide W, Odiong IJ, Oranusi SU. Phytochemical and antibacterial properties of the seed of watermelon (*Citrullus lanatus*). *Int J Microbiol Res*, 2, 99-104 (2012)
- Breuillard C, Bonhomme S, Couderc R, Cynober L, De Bandt JP. *In vitro* anti-inflammatory effects of citrulline on peritoneal macrophages in Zucker diabetic fatty rats. *Br J Nutr*, 113, 120-124 (2015)
- Brosnan JT. Amino acids, then and now: A reflection

- on Sir Hans Krebs' contribution to nitrogen metabolism. *Iubmb Life*, 52, 265-270 (2001)
- Butt MS, Sultan MT, Butt MS, Iqbal J. Garlic: Nature's protection against physiological threats. *Crit Rev Food Sci Nutr*, 49, 538-551 (2009)
- Cai B, Luo YL, Wang SJ, Wei WY, Zhang XH, Huang W, Li T, Zhang M, Wu N, Roodrajeetsing G, Zhang S. Does citrulline have protective effects on liver injury in septic rats? *Bio Med Res Int*, 2016, 1-8 (2016)
- Cauza E, Jansen M, Resch U, Dunky A, Derfler K, Winklhofer-Roob BM, Kostner K. Effects of LDL-immunoapheresis on plasma concentrations of vitamin E and carotenoids in patients with familial hypercholesterolemia. *J Clin Apher*, 19, 174-179 (2004)
- Chen CY, Peng WH, Wu LC, Wu CC, Hsu SL. Luteolin ameliorates experimental lung fibrosis both *in vivo* and *in vitro*: Implications for therapy of lung fibrosis. *J Agr Food Chem*, 58, 11653-11661 (2010)
- Cheng L, Chen L, Wei X, Wang Y, Ren Z, Zeng S, Zhang X, Wen H, Gao C, Liu H. NOD2 promotes dopaminergic degeneration regulated by NADPH oxidase 2 in 6-hydroxydopamine model of Parkinson's disease. *J Neuroinflammation*, 15, 1-5 (2018)
- Chiu A, Kimball AB. Topical vitamins, minerals and botanical ingredients as modulators of environmental and chronological skin damage. *Br J Dermatol*, 149, 681-691 (2003)
- Cho S, Lee DH, Won CH, Kim SM, Lee S, Lee MJ, Chung JH. Differential effects of low-dose and high-dose beta-carotene supplementation on the signs of photoaging and type I procollagen gene expression in human skin *in vivo*. *Dermato*, 221, 160-171 (2010)
- Collins JK, Wu G, Perkins-Veazie P, Spears K, Claypool PL, Baker RA, Clevidence BA. Watermelon consumption increases plasma arginine concentrations in adults. *Nutr*, 23, 261-266 (2007)
- Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult us population: Third national health and nutrition examination survey. *Am J Kidney Dis*, 41, 1-2 (2003)
- Davis TA, Fiorotto ML. Regulation of muscle growth in neonates. *Curr Opin Clin Nutr Metab Care*, 12, 78-85 (2009)
- Dermesonlouoglou E, Giannakourou M, Taoukis P. Kinetic modelling of the quality degradation of frozen watermelon tissue: Effect of the osmotic dehydration as a pre-treatment. *Int J Food Sci*, 42, 790-798 (2007)
- Devaraj S, Mathur S, Basu A, Aung HH, Vasu VT, Meyers S, Jialal I. A dose-response study on the effects of purified lycopene supplementation on biomarkers of oxidative stress. *J Am Coll Nutr*, 27, 267-273 (2008)
- Dogukan A, Tuzcu M, Agca CA, Gencoglu H, Sahin N, Onderci M, Ozercan IH, Ilhan N, Kucuk O, Sahin K. A tomato lycopene complex protects the kidney from cisplatin-induced injury via affecting oxidative stress as well as Bax, Bcl-2, and HSPs expression. *Nutr Cancer*, 63, 427-434 (2011)
- Doughari JH. Phytochemicals: Extraction Methods, Basic Structures and Mode of Action as Potential Chemotherapeutic Agents. Intech Open Access Publisher, Rijeka, Croatia, p 1-33 (2012)
- Drewes SE, George J, Khan F. Recent findings on natural products with erectile-dysfunction activity. *Phytochem*, 62, 1019-1025 (2003)
- Edwards AJ, Vinyard BT, Wiley ER, Brown ED, Collins JK, Perkins-Veazie P, Baker RA, Clevidence BA. Consumption of watermelon juice increases plasma concentrations of lycopene and β -carotene in humans. *J Nutr*, 133, 1043-1050 (2003)
- Egbuonu AC. Comparative investigation of the proximate and functional properties of

- watermelon (*Citrullus lanatus*) rind and seed. *Res J Environ Toxicol*, 9, 160-167 (2015b)
- El-Adawy TA, Taha KM. Characteristics and composition of watermelon, pumpkin, and paprika seed oils and flours. *J Agric Food Chem*, 49, 1253-1259 (2001)
- El-Kirsh AA, Abd El-Wahab HM, Abd-Ellah Sayed HF. The effect of L-arginine or L-citrulline supplementation on biochemical parameters and the vascular aortic wall in high-fat and high-cholesterol-fed rats. *Cell Biochem Funct*, 29, 414-428 (2011)
- Erdman Jr JW, Ford NA, Lindshield BL. Are the health attributes of lycopene related to its antioxidant function? *Arch Biochem Biophys*, 483, 229-235 (2009)
- Espin JC, Garcia-Conesa MT, Tomas-Barberan FA. Nutraceuticals: Facts and fiction. *Phytochem*, 68, 2986-3008 (2007)
- Fang ZF, Luo J, Qi ZL, Huang FR, Zhao SJ, Liu MY, Jiang SW, Peng J. Effects of 2-hydroxy-4-methylthiobutyrate on portal plasma flow and net portal appearance of amino acids in piglets. *Amino Acids*, 36, 501-509 (2009)
- Figueroa A, Sanchez-Gonzalez MA, Perkins-Veazie PM, Arjmandi BH. Effects of watermelon supplementation on aortic blood pressure and wave reflection in individuals with prehypertension: A pilot study. *Am J Hypertens*, 24, 40-44 (2011)
- Galli F. Amino acid and protein modification by oxygen and nitrogen species. *Amino Acids*, 42, 1-4 (2012)
- Gao H, Zhu H, Shao Y, Chen A, Lu C, Zhu B, Luo Y. Lycopene accumulation affects the biosynthesis of some carotenoid-related volatiles independent of ethylene in tomato. *J Integr Plant Biol*, 50, 991-996 (2008)
- Gladvin G, Sudhaakr G, Swathi V, Santhisr KV. Mineral and vitamin compositions contents in watermelon peel (rind). *Int J Curr Microbiol Appl Sci*, 5, 129-133 (2017)
- Hekmatdoost A, Shamsipour A, Meibodi M, Gheibizadeh N, Eslamparast T, Poustchi H. Adherence to the dietary approaches to stop hypertension (DASH) and risk of nonalcoholic fatty liver disease. *Int J Food Sci Nutr*, 67, 1024-1029 (2016)
- Hillenbrand A, Kiebler B, Schwab C, Scheja L, Xu P, Henne-Bruns D, Wolf AM, Knippschild U. Prevalence of non-alcoholic fatty liver disease in four different weight related patient groups: Association with small bowel length and risk factors. *BMC Res Notes*, 8, 1-9 (2015)
- Holst B, Williamson G. Nutrients and phytochemicals: From bioavailability to bioefficacy beyond antioxidants. *Curr Opin Biotechnol*, 19, 73-82 (2008)
- Holzappel NP, Holzappel BM, Champ S, Feldthusen J, Clements J, Hutmacher DW. The potential role of lycopene for the prevention and therapy of prostate cancer: From molecular mechanisms to clinical evidence. *Int J Mol Sci*, 14, 14620-14626 (2013)
- Hoque MM, Iqbal A. Drying of watermelon rind and development of cakes from rind powder. *Int J Novel Res Life Sci*, 2, 14-21 (2015)
- Huh YC, Choi HS, Solmaz I, Sari N, Kim S. Morphological characterization of Korean and Turkish watermelon germplasm. *Korean J Agric Sci*, 41, 309-314 (2014)
- Ilic D, Misso M. Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: A systematic review. *Maturitas*, 72, 269-276 (2012)
- Jaskani MJ, Kwon SW, Kim DH. Comparative study on vegetative, reproductive and qualitative traits of seven diploid and tetraploid watermelon lines. *Euphytica*, 145, 259-268 (2005)
- Jayaprakasha GK, Murthy KC, Patil BS. Rapid HPLC-UV method for quantification of L-citrulline in watermelon and its potential role on smooth muscle relaxation markers. *Food Chem*, 127, 240-248 (2011)
- Jegatheesan P, Beutheu S, Freese K, Waligora-

- Dupriet AJ, Nubret E, Butel MJ, Bergheim I, De Bandt JP. Preventive effects of citrulline on Western diet-induced non-alcoholic fatty liver disease in rats. *Br J Nutr*, 116, 191-203 (2016)
- Jensen BD. African watermelons and their uses. In *Cucurbitaceae 2012. Proceedings of the Xth EUCARPIA Meeting on Genetics and Breeding of Cucurbitaceae*, Antalya, Turkey, 264-274 (2012)
- Jensen BD, Hamattal MA, Toure FA, Nantoume AD. Watermelons in the sand of Sahara: Cultivation and use of indigenous landraces in the Tombouctou region of Mali. *Ethnobot Res Appl*, 9, 151-162 (2011)
- Jian L, Du CJ, Lee AH, Binns CW. Do dietary lycopene and other carotenoids protect against prostate cancer. *Int J Cancer*, 113, 1010-1014 (2005)
- Jiang G, Wu Z, Ameer K, Li S, Ramachandraiah K. Particle size of ginseng (*Panax ginseng* Meyer) insoluble dietary fiber and its effect on physicochemical properties and antioxidant activities. *Appl Biol Chem*, 63, 1-10 (2020)
- Joffin N, Jaubert AM, Durant S, Barouki R, Forest C, Noirez P. Citrulline counteracts overweight- and aging-related effects on adiponectin and leptin gene expression in rat white adipose tissue. *Biochim*, 1, 1-5 (2015)
- Johnson JT, Iwang EU, Hemen JT, Odey MO, Efiog EE, Eteng OE. Evaluation of anti-nutrient contents of watermelon *Citrullus lanatus*. *Ann Biol Res*, 3, 5145-5150 (2012)
- Kachhawa K, Varma M, Kachhawa P, Agrawal D, Shaikh MK, Kumar S. Study of dyslipidemia and antioxidant status in chronic kidney disease patients at a hospital in South East Asia. *J Health Res Rev*, 3, 28-30 (2016)
- Karppi J, Laukkanen JA, Sivenius J, Ronkainen K, Kurl S. Serum lycopene decreases the risk of stroke in men: A population-based follow-up study. *Neurology*, 79, 1540-1547 (2012)
- Kaur C, Kapoor HC. Antioxidants in fruits and vegetables: The millennium's health. *Int J Food Sci*, 36, 703-725 (2001)
- Khachik F, Carvalho L, Bernstein PS, Muir GJ, Zhao DY, Katz NB. Chemistry, distribution, and metabolism of tomato carotenoids and their impact on human health. *Exp Biol Med*, 227, 845-851 (2002)
- Khaki A, Fathiazad F, Nouri M. Effects of watermelon seed extract (*Citrullus vulgaris*) on spermatogenesis in rat. *Int J Women's Health Reprod Sci*, 1, 99-104 (2013)
- Khan MA, Amir RM, Ameer K, Rakha A, Faiz F, Hayat I, Nadeem M, Ahmed Z, Riaz A, Ashraf I. Characterization of oat bran β -glucan with special reference to efficacy study to elucidate its health claims for diabetic patients. *Food Sci Technol*, 41, 105-112 (2020)
- Kun Y, Ssonko LU, Xiao-Lin D. Lycopene: Its properties and relationship to human health. *Food Rev Int*, 22, 309-333 (2006)
- Lee HG, Jo Y, Ameer K, Kwon JH. Optimization of green extraction methods for cinnamic acid and cinnamaldehyde from cinnamon (*Cinnamomum cassia*) by response surface methodology. *Food Sci Biotechnol*, 27, 1607-1617 (2018)
- Lei X, Lei L, Zhang Z, Cheng Y. Neuroprotective effects of lycopene pretreatment on transient global cerebral ischemia-reperfusion in rats: The role of the Nrf2/HO-1 signaling pathway. *Mol Med Rep*, 13, 412-418 (2016)
- Leskovaar DI, Bang H, Kim SL, Sun Yoo K, King SR, Crosby K. Environmental and genetic factors on carotenoids and quality in watermelon fruits. In: *International Symposium on Human Health Effects of Fruits and Vegetables*, 744, 233-242 (2005)
- Lin HY, Huang BR, Yeh WL, Lee CH, Huang SS, Lai CH, Lin H, Lu DY. Antineuroinflammatory effects of lycopene via activation of adenosine monophosphate-activated protein kinase- α 1/heme oxygenase-1 pathways. *Neurobiol Aging*, 35, 191-202 (2014)

- Liu CC, Huang CC, Lin WT, Hsieh CC, Huang SY, Lin SJ, Yang SC. Lycopene supplementation attenuated xanthine oxidase and myeloperoxidase activities in skeletal muscle tissues of rats after exhaustive exercise. *Br J Nutr*, 94, 595-601 (2005)
- Liu RH. Potential synergy of phytochemicals in cancer prevention: Mechanism of action. *The J Nutr*, 134, 3479S-3485S (2004)
- Locatelli I, Sutti S, Vacchiano M, Bozzola C, Albano E. NF- κ B1 deficiency stimulates the progression of non-alcoholic steatohepatitis (NASH) in mice by promoting NKT-cell-mediated responses. *Clinical Sci*, 124, 279-287 (2013)
- MacWilliam LD. Comparative Guide to Nutritional Supplement. Northern Dimensions Publishing (2005)
- Madhuri P, Devi K. Value addition to watermelon fruit waste. *J Food Sci Technol*, 40, 222-224 (2003)
- Mandel H, Levy N, Izkovitch S, Korman SH. Elevated plasma citrulline and arginine due to consumption of *Citrullus vulgaris* (watermelon). *J Inherit Metab Dis*, 28, 467-472 (2005)
- Manna P, Sinha M, Sil PC. Taurine plays a beneficial role against cadmium-induced oxidative renal dysfunction. *Amino Acids*, 36, 417-428 (2009)
- Mateljan G. Watermelon. Available from: <http://www.whfoods.com/genpage.php?tname=foodspice&dbid=31>. Accessed Mar. 19, 2020.
- Matos HR, Marques SA, Gomes OF, Silva AA, Heimann JC, Di Mascio P, Medeiros MH. Lycopene and β -carotene protect *in vivo* iron-induced oxidative stress damage in rat prostate. *Braz J Med Biol*, 39, 203-210 (2006)
- McKinley-Barnard S, Andre T, Morita M, Willoughby DS. Combined L-citrulline and glutathione supplementation increases the concentration of markers indicative of nitric oxide synthesis. *J Int Soc Sports Nutr*, 12, 1-8 (2015)
- Mellert W, Deckardt K, Gembardt C, Schulte S, Van Ravenzwaay B, Slesinski RS. Thirteen-week oral toxicity study of synthetic lycopene products in rats. *Food Chem Toxicol*, 40, 1581-1588 (2002)
- Misra R, Mangi S, Joshi S, Mittal S, Gupta SK, Pandey RM. Lycored as an alternative to hormone replacement therapy in lowering serum lipids and oxidative stress markers: A randomized controlled clinical trial. *J Obstet Gynaecol*, 32, 299-304 (2006)
- Mokhtari Z, Gibson DL, Hekmatdoost A. Nonalcoholic fatty liver disease, the gut microbiome, and diet. *Adv Nutr*, 8, 240-252 (2017)
- Muhammad NFH, Wan Zainon WNZ, Kormin S, Mohd Akhir N, Ali MS. Processing of watermelon rind dehydrated candy. *Int J Sci Eng*, 8, 6-9 (2015)
- Nahum A, Hirsch K, Danilenko M, Watts CK, Prall OW, Levy J, Sharoni Y. Lycopene inhibition of cell cycle progression in breast and endometrial cancer cells is associated with reduction in cyclin D levels and retention of p27 Kip1 in the cyclin E-cdk2 complexes. *Oncogene*, 20, 3428-3436 (2001)
- Narisawa T, Fukaura Y, Hasebe M, Ito M, Aizawa R, Murakoshi M, Uemura S, Khachik F, Nishino H. Inhibitory effects of natural carotenoids, α -carotene, β -carotene, lycopene and lutein, on colonic aberrant crypt foci formation in rats. *Cancer Lett*, 107, 137-142 (1996)
- Naz A, Butt MS, Pasha I, Nawaz H. Antioxidant indices of watermelon juice and lycopene extract. *Pakistan J Nutr*, 12, 255-260 (2013)
- Nesrallah GE, Mustafa RA, Clark WF, Bass A, Barnieh L, Hemmelgarn BR, Klarenbach S, Quinn RR, Hiremath S, Ravani P, Sood MM. Canadian society of nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis. *Cmaj*, 186, 112-117 (2014)
- Nkoana DK, Mashilo J, Shimelis H, Ngwepe RM. Nutritional, phytochemical compositions and natural therapeutic values of citron watermelon (*Citrullus lanatus* var. *citroides*): A review. *S Afr*

- J Bot, 145, 65-77 (2022)
- Nunes MC. Pome and stone fruits. In: Color Atlas of Postharvest Quality of Fruits and Vegetables, Joh Wiley & Sons, New York, USA, p 123 (2008)
- Okonmah LU, Agbogidi OM, Nwagu OK. Evaluation of four varieties of watermelon (*Citrullus lanatus* Thumb) in Asaba agro-ecological environment. Int J Adv Biol Res, 1, 126-130 (2011)
- Olayinka BU, Etejere EO. Proximate and chemical compositions of watermelon [*Citrullus lanatus* (Thunb.) Matsum and Nakai cv red and cucumber (*Cucumis sativus* L. cv Pipino)]. Int Food Res J, 25, 1060-1066 (2018)
- Omoni AO, Aluko RE. The anti-carcinogenic and anti-atherogenic effects of lycopene: A review. Trends Food Sci Technol, 16, 344-350 (2005)
- Oyeleke GO, Olagunju EO, Ojo A. Functional and physicochemical properties of watermelon *Citrullus lanatus* seed and seed-oil. J Appl Chem, 2, 29-31 (2012)
- Oyenihi OR, Afolabi BA, Oyenihi AB, Ogunmokin OJ, Oguntibeju OO. Hepato-and neuro-protective effects of watermelon juice on acute ethanol-induced oxidative stress in rats. Toxicol Rep, 3, 288-294 (2016)
- Pennathur S, Maitra D, Byun J, Sliskovic I, Abdulhamid I, Saed GM, Diamond MP, Abu-Soud HM. Potent antioxidative activity of lycopene: A potential role in scavenging hypochlorous acid. Free Radic Biol Med, 49, 205-213 (2010)
- Perez-Guisado J, Jakeman PM. Citrulline malate enhances athletic anaerobic performance and relieves muscle soreness. J Strength Cond Res, 24, 1215-1222 (2010)
- Perkins-Veazie P, Collins JK, Clevidence B, Wu G. Watermelons and health. Acta Hort, 731, 121-128 (2007)
- Perkins-Veazie P, Collins JK, Davis AR, Roberts W. Carotenoid content of 50 watermelon cultivars. J Agri Food Chem, 54, 2593-2597 (2006)
- Perkins-Veazie P, Collins JK, Pair SD, Roberts W. Lycopene content differs among red-fleshed watermelon cultivars. J Sci Food Agric, 81, 983-987 (2001)
- Perkins-Veazie P, Davis A, Collins JK. Watermelon: From dessert to functional food. Isr J Plant Sci, 60, 395-402 (2012)
- Perła-Kajan J, Twardowski T, Jakubowski H. Mechanisms of homocysteine toxicity in humans. Amino Acids, 32, 561-572 (2007)
- Perriotte-Olson C, Adi N, Manickam DS, Westwood RA, Desouza CV, Natarajan G, Crook A, Kabanov AV, Saraswathi V. Nanoformulated copper/zinc superoxide dismutase reduces adipose inflammation in obesity. Obesity, 24, 148-156 (2016)
- Peter-Ikechukwu AI, Omeire GC, Kabuo NO, Eluchie CN, Amandikwa C, Odoemenam GI. Production and evaluation of biscuits made from wheat flour and toasted watermelon seed meal as fat substitute. J Food Res, 7, 112-123 (2018)
- Pons L. Exploring important medicinal uses for watermelon rinds. Available from: <http://www.ars.usda.gov/is/pr/2003/030221.htm>. Accessed Jan. 21, 2022.
- Prema A, Janakiraman U, Manivasagam T, Arokiasamy JT. Neuroprotective effect of lycopene against mptp induced experimental Parkinson's disease in mice. Neurosci Lett, 599, 12-19 (2018)
- Qu M, Li L, Chen C, Li M, Pei L, Chu F, Yang J, Yu Z, Wang D, Zhou Z. Protective effects of lycopene against amyloid β -induced neurotoxicity in cultured rat cortical neurons. Neurosci Lett, 505, 286-290 (2011)
- Rashid F, Ahmed Z, Ameer K, Amir RM, Khattak M. Optimization of polysaccharides-based nanoemulsion using response surface methodology and application to improve postharvest storage of apple (*Malus domestica*). J Food Measur Charac, 14, 2676-2688 (2020)
- Ratnam DV, Ankola DD, Bhardwaj V, Sahana DK, Kumar MR. Role of antioxidants in prophylaxis

- and therapy: A pharmaceutical perspective. *J Control Release*, 113, 189-207 (2006)
- Rayyan YM, Tayyem RF. Non-alcoholic fatty liver disease and associated dietary and lifestyle risk factors. *Diabetes Metab Syndr Clin Res Rev*, 12, 569-575 (2018)
- Raza H, Ameer K, Zaaboul F, Sharif HR, Ali B, Shoaib M, Akhtar W, Zhang L. Effects of ball-milling on physicochemical, thermal and functional properties of extruded chickpea (*Cicer arietinum* L.) powder. *CyTA-J Food*, 17, 563-573 (2019)
- Reeve E. Domestication of plants in the old world: The origin and spread of cultivated plants in West Asia, Europe, and the Nile Valley. *Genet Res*, 66, 181-183 (1995)
- Rehman MHU, Ahmad A, Amir RM, Ameer K, Ali SW, Siddique F, Hayat I, Ahmad Z, Faiz F. Ameliorative effects of fenugreek (*Trigonella foenum-graecum*) seed on type 2 diabetes. *Food Sci Technol*, 41, 349-354 (2020)
- Rein MJ, Renouf M, Cruz-Hernandez C, Actis-Goretta L, Thakkar SK, da Silva Pinto M. Bioavailability of bioactive food compounds: A challenging journey to bioefficacy. *Br J Clin Pharmacol*, 75, 588-602 (2013)
- Rimando AM, Perkins-Veazie PM. Determination of citrulline in watermelon rind. *J Chromatogr A*, 1078, 196-200 (2005)
- Rupasinghe HV, Clegg S. Total antioxidant capacity, total phenolic content, mineral elements, and histamine concentrations in wines of different fruit sources. *J Food Compos Anal*, 20, 133-137 (2007)
- Said MA. A study in the variability of some nutrient contents of watermelon (*Citrullus lanatus*) before and after ripening consumed within Kano Metropolis, Nigeria. *Int J Sci Res*, 3, 1365-1368 (2014)
- Saltzman ET, Palacios T, Thomsen M, Vitetta L. Intestinal microbiome shifts, dysbiosis, inflammation, and non-alcoholic fatty liver disease. *Front Microbiol*, 9, 1-11 (2018)
- Sandhir R, Mehrotra A, Kamboj SS. Lycopene prevents 3-nitropropionic acid-induced mitochondrial oxidative stress and dysfunctions in nervous system. *Neurochem Int*, 57, 579-587 (2010)
- Sarker SD, Nahar L. *Chemistry for Pharmacy Students: General, Organic, and Natural Product Chemistry*. John Wiley & Sons (2013)
- Sase A, Dahanayaka S, Hoger H, Wu G, Lubec G. Changes of hippocampal beta-alanine and citrulline levels are paralleling early and late phase of retrieval in the Morris Water Maze. *Behav Brain Res*, 249, 104-108 (2013)
- Scolastici C, de Lima RA, Barbisan LF, Ferreira AL, Ribeiro DA, Salvadori DM. Antigenotoxicity and antimutagenicity of lycopene in HepG2 cell line evaluated by the comet assay and micronucleus test. *Toxicol in Vitro*, 22, 510-514 (2008)
- Sellmann C, Jin CJ, Engstler AJ, De Bandt JP, Bergheim I. Oral citrulline supplementation protects female mice from the development of non-alcoholic fatty liver disease (NAFLD). *Eur J Nutr*, 56, 2519-2527 (2017)
- Sesso HD, Buring JE, Norkus EP, Gaziano JM. Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in women. *Am J Clin Nutr*, 79, 47-53 (2004)
- Shi J, Maguer ML. Lycopene in tomatoes: Chemical and physical properties affected by food processing. *Crit Rev Food Sci Nutr*, 40, 1-42 (2000)
- Sindhuja A, Sudha ML, Rahim A. Effect of incorporation of amaranth flour on the quality of cookies. *Eur Food Res Technol*, 21, 597-601 (2005)
- Souad AM, Jamal P, Olorunnisola KS. Effective jam preparations from watermelon waste. *Int Food Res J*, 19, 1545-1549 (2012)
- Stahl W, Sies H. Lycopene: A biologically important carotenoid for humans? *Arch Biochem Biophys*, 336, 1-9 (1996)

- Sureda A, Cordova A, Ferrer MD, Perez G, Tur JA, Pons A. L-citrulline-malate influence over branched chain amino acid utilization during exercise. *Eur J Appl Physiol*, 110, 341-351 (2010)
- Tadmor Y, King S, Levi A, Davis A, Meir A, Wasserman B, Hirschberg J, Lewinsohn E. Comparative fruit colouration in watermelon and tomato. *Food Res Intr*, 38, 837-841 (2005)
- Tarazona-Diaz MP, Viegas J, Moldao-Martins M, Aguayo E. Bioactive compounds from flesh and by-product of fresh-cut watermelon cultivars. *J Sci Food Agric*, 91, 805-812 (2011)
- Tiwari BK, ODonnell CP, Muthukumarappan K, Cullen PJ. Effect of sonication on orange juice quality parameters during storage. *Int J Food Sci*, 44, 586-595 (2009)
- Tomasello S. Secondary hyperparathyroidism and chronic kidney disease. *Diabetes Spectr*, 21, 19-25 (2008)
- Tong BC, Barbul A. Cellular and physiological effects of arginine. *Mini Rev Med Chem*, 4, 823-832 (2004)
- Ubbor SC, Akobundu EN. Quality characteristics of cookies from composite flours of watermelon seed, cassava and wheat. *Pak J Nutr*, 8, 1097-1102 (2009)
- USDA. Food data central. Available from: <https://fdc.nal.usda.gov/fdc-app.html#/food-details/169134/nutrients>. Accessed May. 29, 2020.
- Verschuren L, Wielinga PY, van Duyvenvoorde W, Tijani S, Toet K, van Ommen B, Kooistra T, Kleemann R. A dietary mixture containing fish oil, resveratrol, lycopene, catechins, and vitamins E and C reduces atherosclerosis in transgenic mice. *J Nutr*, 141, 863-869 (2011)
- Weisburger JH. Lycopene and tomato products in health promotion. *Exp Biol Med*, 227, 924-927 (2002)
- Werman MJ, Mokady S, Ben-Amotz A. Bioavailability of the isomer mixture of phytoene and phytofluene-rich alga *Dunaliella bardawil* in rat plasma and tissues. *J Nutr Biochem*, 13, 585-591 (2002)
- Wu G, Bazer FW, Davis TA, Jaeger LA, Johnson GA, Kim SW, Knabe DA, Meininger CJ, Spencer TE, Yin YL. Important roles for the arginine family of amino acids in swine nutrition and production. *Livest Sci*, 112, 8-22 (2007)
- Yamai H, Sawada N, Yoshida T, Seike J, Takizawa H, Kenzaki K, Miyoshi T, Kondo K, Bando Y, Ohnishi Y, Tangoku A. Triterpenes augment the inhibitory effects of anticancer drugs on growth of human esophageal carcinoma cells *in vitro* and suppress experimental metastasis *in vivo*. *Int J Cancer Res*, 125, 952-960 (2009)
- Yamane H, Asechi M, Tsuneyoshi Y, Kurauchi I, Denbow DM, Furuse M. Intracerebroventricular injection of L-aspartic acid and L-asparagine induces sedative effects under an acute stressful condition in neonatal chicks. *J Anim Sci*, 80, 286-290 (2009)
- Yari Z, Rahimlou M, Eslamparast T, Ebrahimi-Daryani N, Poustchi H, Hekmatdoost A. Flaxseed supplementation in non-alcoholic fatty liver disease: A pilot randomized, open labeled, controlled study. *Int J Food Sci Nutr*, 67, 461-469 (2016)
- Yin Q, Ma Y, Hong Y, Hou X, Chen J, Shen C, Sun M, Shang Y, Dong S, Zeng Z, Pei JJ. Lycopene attenuates insulin signaling deficits, oxidative stress, neuroinflammation, and cognitive impairment in fructose-drinking insulin resistant rats. *Neuropharmacology*, 86, 389-396 (2014)
- Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*, 64, 73-84 (2016)
- Yu L, Wang W, Pang W, Xiao Z, Jiang Y, Hong Y. Dietary lycopene supplementation improves cognitive performances in tau transgenic mice expressing P301L mutation via inhibiting oxidative stress and tau hyperphosphorylation.

- J Alzheimers Dis, 57, 475-482 (2017)
- Zhang D, Hamauzu Y. Phenolics, ascorbic acid, carotenoids and antioxidant activity of broccoli and their changes during conventional and microwave cooking. Food Chem, 88, 503-509 (2004)
- Zhao CC, Ameer K, Eun JB. Effects of various drying conditions and methods on drying kinetics and retention of bioactive compounds in sliced persimmon. LWT, 143, 111149 (2021)
- Zhao W, Lv P, Gu H. Studies on carotenoids in watermelon flesh. Agri Sci, 4, 13-20 (2013)