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Review Article

Watermelon Allsweet: A Promising Natural Source of Bioactive Products

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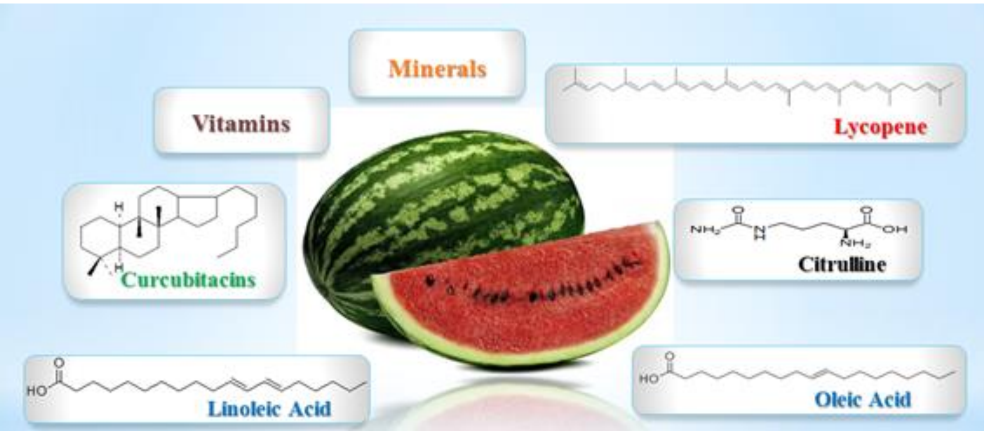
ABSTRACT

Watermelon is a nutrient-dense fruit, contrary to the popular assumption that it is primarily composed of water and sugar. Watermelon, the whole fruit, is distinguished by a variety of bioactive molecules with diverse chemical backbones, including phenolics, carotenoids, unsaturated fatty acids, citrulline, as well as numerous vitamins and minerals. Many researchers have considered watermelon as a natural source of biologically active chemicals in previous decades, primarily when evaluating some biomedical features such as antimicrobial, anti-inflammatory, and antioxidant capabilities. This study focuses on the most beneficial bioactive ingredients found in the watermelon and the possibility of utilizing these ingredients to treat a variety of ailments. The results showed that watermelon extracts are considered a valuable source of many beneficial components that can be used for medicinal purposes.

GRAPHICAL ABSTRACT



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Introduction

Nature has always been and continues to be a source of inspiration for many investigators and scientists since it is a rich source of bioactive compounds. One of the best sources of these compounds is fruits and vegetables [1–5]. Fruit intake has expanded around the world due to the tasty flavor, protection from ailments, and various benefits to health provided by nutrients like fiber, minerals, vitamins, and other biologically active substances that the human body requires to stay healthy [6–8]. One of these beneficial fruits is watermelon, scientifically known as *Citrullus lanatus* [9].

The fruit crop *Citrullus lanatus* is such a herbaceous creeping flowering plant of the family *Cucurbitaceae*, also known as cucurbits [10]. It is a tropical plant that grows best in warm climates and is primarily grown through seeds. This delightful fruit is proven to be thirst-quenching, abundant in nutrients, and low in calories [10]. A combination of fructose, sucrose, and glucose accounts for the sweetness of the watermelon. In a ripened watermelon, glucose and sucrose make up 20-40% of the total sugars, whereas fructose makes up 30-50% [11]. The nutritional value is available in each part of the fruit even rind and seed [12]. In folk medicine for some nations, watermelon is utilized as a diuretic, demulcent, tonic, as well as emetic and purgative when consumed at massive levels [13]. This fruit is also abundant in flavonoids, glycosides, tannins, phenols, and saponins [14]. That is what has sparked the researchers' interest to study the plant extensively for its medical properties, such as antioxidant, antibacterial, antifungal, anti-inflammatory, and so many more [14].

Regarding the origin of the name, the term "water" refers to the high quantity of water present in the fruit that is around ninety-two percent of its weight, while the term "melon" refers to a big, spherical-shaped fruit with a delicious, pulpy interior. The watermelon's scientific name is drawn from Greek as well as Latin roots. *Citrullus* is derived from the Greek word "citrus" which refers to the fruit. The Latin word *lanatus* means "woolly" and refers to the plant's tiny hairs on the stems and leaves [13].

Watermelon-Active Constituents Profile

The entire watermelon fruit (rind, pulp, and seed), as illustrated in Figure 1, is indeed a fantastic fountain of phytochemicals, macronutrients, and micronutrients [15]. This manuscript outlines the different bioactive chemicals found in watermelon that have been linked to health benefits, as well as their major locations in the plant.

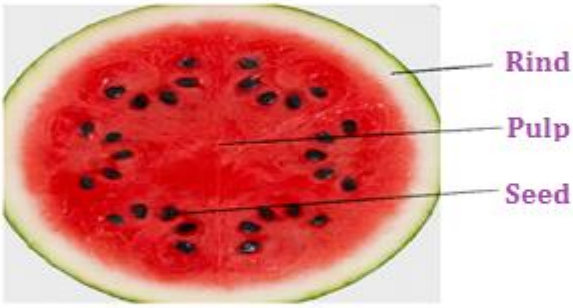


Figure 1: Cross section of watermelon that displays different aspects of the fruit

Polyphenols

Polyphenols, also known as phenolics, are water-soluble secondary metabolites derived mostly from plants. These compounds can be present in cell walls and cellular vacuoles in free or conjugated forms. Phenol is the most basic component, and thousands of the more complicated polyphenols are generated from it, each of which may be categorized into distinct groups. Flavonoids and non-flavonoids are the two primary classes [16–20]. Phenolics may be the primary polar components responsible for the antioxidant potential of watermelon, and their amounts differ in the pulp, seeds, rind, and leaves. Their abundance, however, differs among cultivars. Watermelon had previously been identified as one of the preferable dietary sources of phenolics, according to an investigation that looked at both Spanish and American diets, with seeds being the predominant source of these substances [21]. The total phenolic content of the rind is greater than that of the pulp, and its proportion is mainly dependent on the cultivars [22]. Leahy *et al*. found that total polyphenols ranged from 137-260 milligrams of gallic acid equivalent per kilogram of fresh weight [23]. The most significant polyphenols in watermelon include tannins, lignan, coumarins, iridoids, flavonoids, and phenolic acids [24,25].

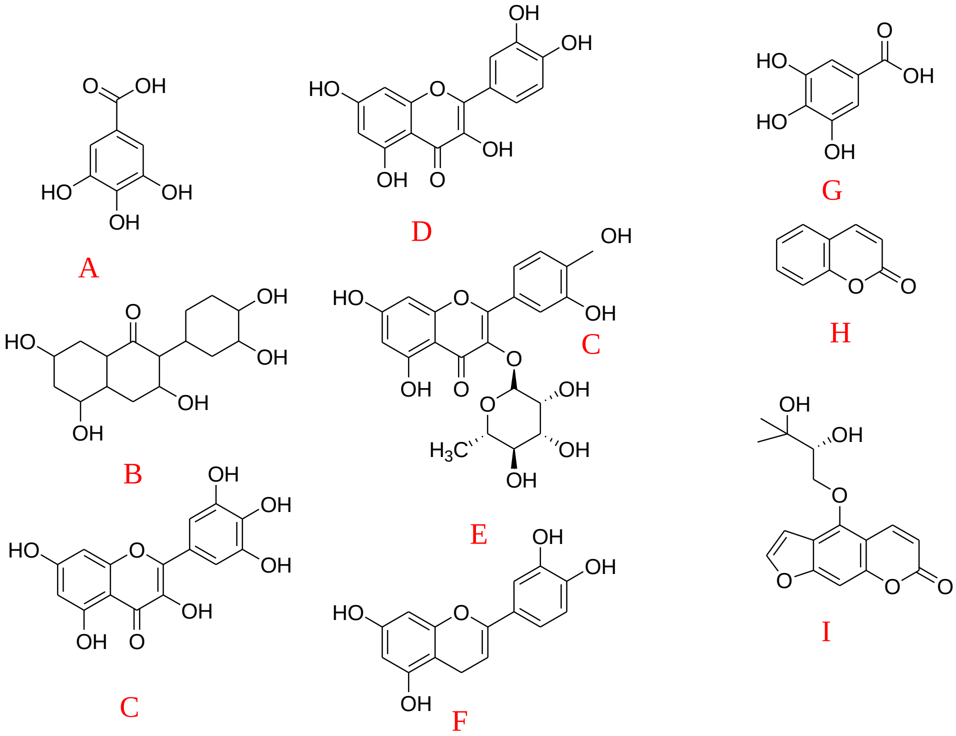
Flavonoids and Non-flavonoids

Flavonoids (C6-C3-C6) are abundant in watermelon, with a range of 111-176 milligrams of rutin equivalents per kilogram of fresh weight, albeit the total value is highly reliant on the ripening stage, environmental factors, and cultivars [26]. Twenty-three compounds of different flavonoid families have been detected in watermelon [27]. Mushtaq *et al*. identified myricetin and quercetin in the rind, whereas kaempferol, quercetin, quercitrin, rutin, luteolin, amentoflavone, naringenin-7-O-glycoside, and apigenin were found in the seeds [28,29]. Tannins are polymeric flavon-3-ol skeletons that are categorized into hydrolysable or non-hydrolysable, also called condensate. These components contain a lot of OH-groups, allowing for the attachment of additional macromolecules like proteins and polysaccharides. Tannin contents in different watermelon cultivars ranged from 5 to 6.5 grams per 100 grams of dry weight [30,31].

On the other hand, non-flavonoids are derivatives of hydroxyl-benzoic acid. These acids frequently exist through forms, in which they connect to organic acids or sugars [21]. Abu-Reidah *et al*. obtained eleven OH-benzoic acids from watermelon pulp that are derivatives of shikimic acid, salicylic acid, protocatechuic acid, vanillic acid, and phloroglucinol [27]. Jimoh *et al*. detected gallic acid in watermelon seeds, which is a valuable substance known for its role in tannin bio-synthesis, while Sultana and his colleague detected protocatechuic acid, gallic acid, 4-OH benzoic acid, vanillic acid, and chlorogenic acid [29,21]. Al-Sayed *et al*. revealed the presence of vanillin, 4-OH benzoic acid, p-anisic acid, and syringic acid in watermelon seeds [32]. And as for the hydroxy-cinnamic acids, the most prevalent ones are the derivatives of cinnamic acid, which are made up of four fundamental particles: Sinapic, ferulic, p-coumaric, and caffeic acids with acids and sugars [21]. Twenty hydroxy-cinnamic acid derivatives have been detected in watermelon pulp, the bulk of which were sugar-bound. Watermelon rind and seeds were shown to contain caffeic, sinapic, p-coumaric, cinnamic, and OH-cinnamic acids. Furthermore, coumarin derivatives have also been detected in watermelon pulp; these are obtusoside, aviprin, as well as coumarin [27,32]. Some of the most important phenolics found in watermelon are presented in Figure 1.

Lycopene and Other Carotenoids

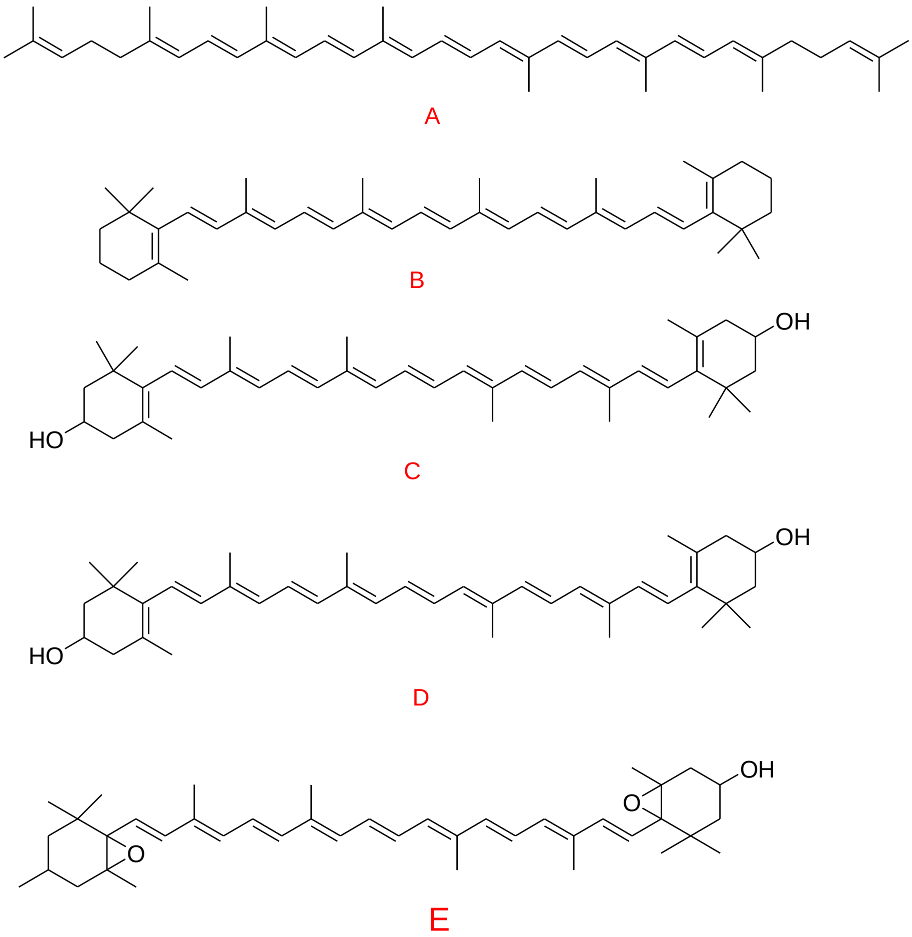
Carotenoids are a class of chemical substances with significant anti-oxidant potential including two sub-classes: Carotenes and xanthophylls. Watermelon is considered as a rich source of carotenoids. Beta carotene and its precursor lycopene are responsible for the red color in red-pulp watermelon cultivars [22]. Lycopene (Figure 2), with the molecular formula $C_{40}H_{56}$, has the highest level of unsaturation of any carotenoid [33]. It is a straight-chain hydrocarbon having thirteen double-bonds, eleven of which are conjugated [34]. Lycopene is usually found as cis-isomers in tissues and blood because cis-isomers are more bio-available than trans-isomers and are predominantly absorbed in human beings [35]. Watermelon is one of the few sources of cis-isomeric lycopene that is readily available [36]. The content of lycopene in watermelon is determined by genes and environmental influences; in fact, the proportion of this carotenoid varies greatly amongst cultivars growing in various countries throughout the world [22]. After lycopene, beta-carotene, as illustrated in Figure 3, is the second most abundant pigment in red-pulp watermelon. It is created via cyclization of the two terminal isoprene units of lycopene. Because of such a similarity and its location in the lycopene biosynthetic pathway, beta-carotene level is influenced by the same genetic and environmental factors that determine lycopene level [36]. Further, alpha-carotene-isomer has been found in red-pulp watermelon in small quantities [37]. In addition to being an antioxidant, beta-carotene serves as the most appropriate and vital precursor of the A vitamin. Xanthophylls are yellow pigments produced via the oxygenation of carotenoids. These chemicals do not just serve as natural pigments in vegetables and fruits, but they also perform a significant function in the prevention of oxidative stress-related disorders by acting as potent antioxidants [21].



A=Hydrolyzable Tannins
B=Condensed Tannins
C=Myricetin
D=Quercetin
E=Quercitrin
F=Luteolin
G=Gallic acid
H=Coumarin
I=Aviprin

Figure 1: Chemical backbones of the most important phenolics in watermelon

The hydroxylation of alpha- and beta-carotene yields alpha- and beta-cryptoxanthin, respectively. Lutein is generated from alpha-cryptoxanthin, whereas beta-cryptoxanthin produces zeaxanthin. The epoxidation of zeaxanthin yields violaxanthin, which is then transformed into neoxanthin [38]. As a result, the same environmental and genetic factors, as well as different agricultural procedures that influence carotenes' biosynthesis pathway, have an impact on the quantity of xanthophylls produced [23]. Red-pulp watermelon has a low xanthophyll proportion by around 3%. Lutein, violaxanthin, and zeaxanthin, as illustrated in Figure 3, are all present in small quantities in this fruit [38].



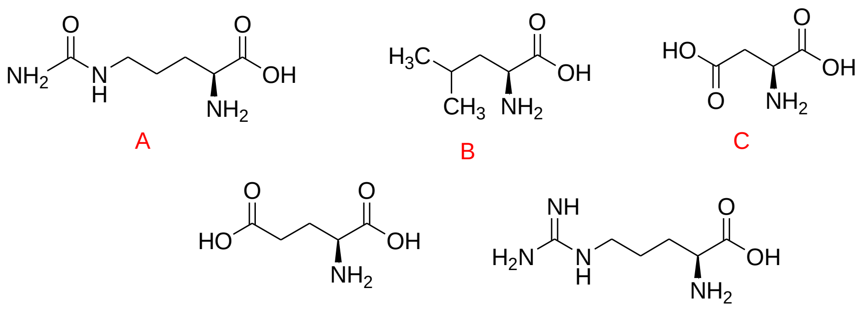
A=Lycopene
B=Beta carotene
C=Lutein
D=Zeaxanthin
E=Violaxanthin

Figure 3: Chemical backbones of the most important carotenoids in watermelon

L-citrulline and Other Amino Acids

Watermelon is a natural source of L-citrulline (Figure 4), a non-essential amino acid that is a precursor to L-arginine, whereas arginine is an essential amino acid that controls blood flow and nitric oxide levels [39]. L-citrulline is not commonly found in fruits, although watermelon is considered as one of the most abundant sources of this amino acid known to humankind, with a higher proportion in the rind than in the pulp, at around 24.7-16.7 milligrams per gram dry weight, respectively [40]. But the variation was less pronounced when measured in terms of fresh weight 1.3-1.9 milligram per gram. L-citrulline can also be observed in the leaves of watermelon [41]. In a study of samples from the United States, the researchers noted that both genetic and environmental factors might affect the L-citrulline level in watermelon pulp, the samples cultivated in Texas averaged 1.67 milligram per gram fresh weight, while those produced in Oklahoma averaged 3.1 milligrams per gram fresh weight [42].

The seeds of watermelon are abundant in protein, having proportions ranging between 25-37%, and they include a significant amount of amino acids, particularly leucine, aspartic, glutamic, and arginine (Figure 4) being the most plentiful [29]. Dash *et al.* extracted four protein fractions from the seeds: Prolamin, albumin, glutelin, and globulin, having proportions of 22, 23, 39, and 46%, respectively. They were enriched in acidic and hydrophobic amino acids and had antioxidant and antibacterial potentials [43].

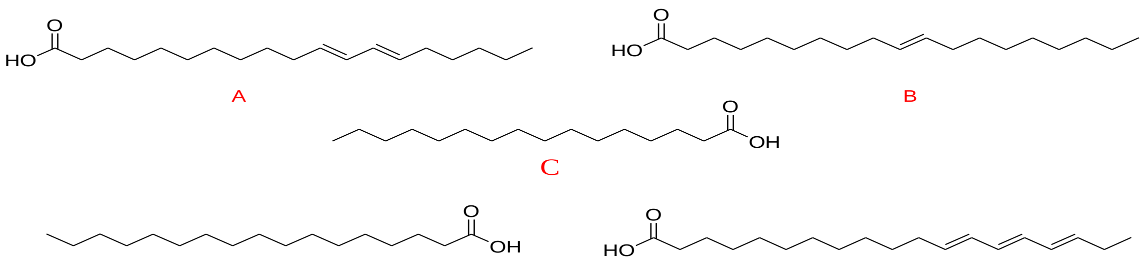


A=Citrulline
B=Leucine
C=Aspartic Acid
D=Glutamic Acid
E=Arginine

Figure 4: Chemical backbones of the most important amino-acids in watermelon

Dietary Fats

Watermelon seeds are abundant with oil, having proportions ranging between 37.8-45.4% [44]. Oko *et al*. investigated the fatty acid profile of watermelon oil and concluded that linoleic acid (61.07%) was the most predominant fatty acid, then oleic acid (13.48%), the second predominant one followed by palmitic acid 15.4%, stearic acid 8.17% as well as linolenic acid 0.52% (Figure 5) [45]. Mahla *et al*. investigated the fatty acid composition of watermelon seeds from fifteen cultivars. The monounsaturated fatty acid values range between 11.06-20.04%, while the polyunsaturated fatty acid values range between 43.95 55.29%, indicating a high amount of unsaturated fatty acids. The most prevalent monounsaturated fatty acid was oleic acid, and the prevailing polyunsaturated fatty acid was linoleic acid, which is one of the most substantial fatty acids because of its function in cardiovascular disease prevention [46].



A=Linoleic Acid
B=Oleic Acid
C=Palmitic Acid
D=Stearic Acid
E=Linolenic Acid

Figure 5: Chemical backbones of the most important fatty acids in watermelon

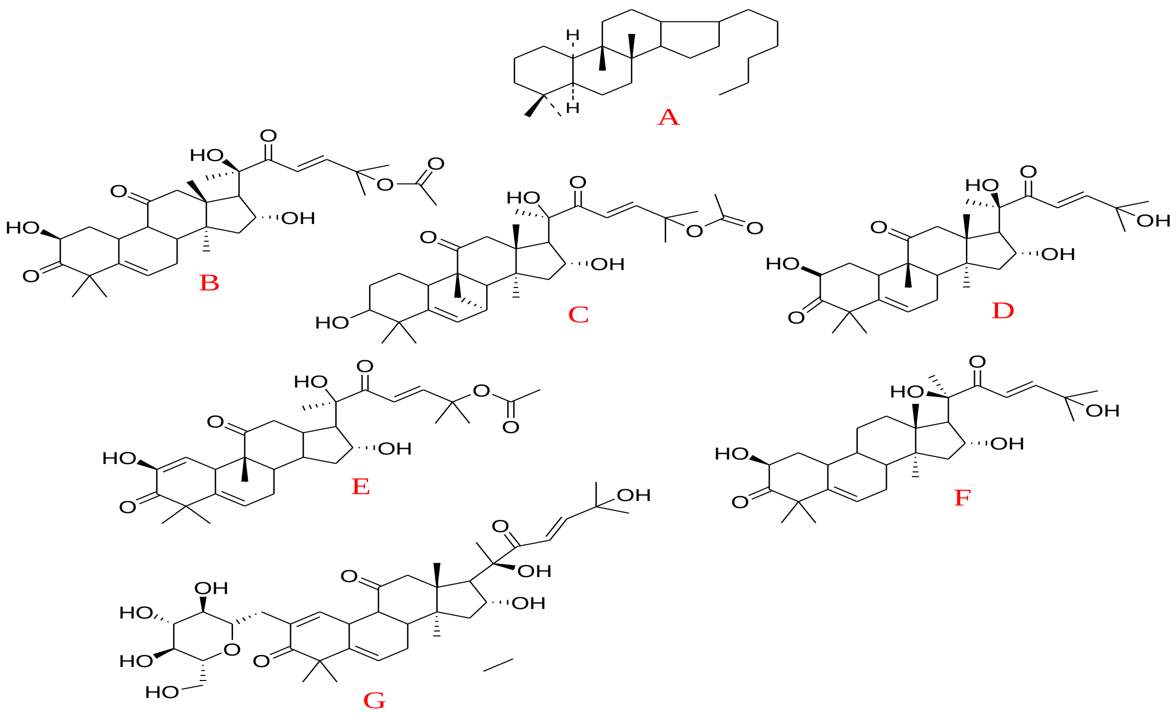
Minerals and Vitamins

Watermelon is a mineral and vitamin-dense fruit. Regarding minerals, researchers have indicated that the watermelon pulp contains five minerals. Relatively potassium is the most prominent one, at a proportion of around 112 milligrams per 100 grams, while the other four are phosphorus, magnesium, calcium, and iron. Their proportions per 100 grams of the pulp were around 11, 10, 7, and 0.24 milligrams, respectively [34]. In addition to the aforesaid minerals, rind, and seeds, also contained phosphorus, manganese, sodium, zinc, and copper [47–49].

Researchers have revealed that phosphorus is the most plentiful mineral in the rind, accounting for around 135.24 milligrams per 100 grams of rind, while copper has the lowest proportion of 0.45 milligram per 100 grams of rind [47]. Imafidon *et al*. confirmed that sodium and potassium were the two most abundant minerals in the seeds, whereas zinc was the least abundant [15]. On the other hand, Tabiri *et al*. indicated that potassium is the most prevalent mineral and sodium is the least abundant one [48]. As for vitamins, A and C vitamins are considered the most abundant two vitamins in watermelon; in addition, there are four forms of B vitamins documented in the watermelon rind, which are B-1, -3, -6, and -12, [50,47]. Besides the aforesaid vitamins, vitamin-D, -E, -K, as well as B-9, and B-2 are all available in the seeds [51].

Curcubitacins are a class of oxygenated steroidal triterpenes having a curcubitane backbone with anti-diabetic, anticancer, and anti-inflammatory potentials [52]. Curcubitacin-B, -C, -D, -E, -I, and –L 2-O- β-glucoside were extracted from watermelon pulp (cultivar citroides), as well as the leaves of watermelon (Figure 6) [53,54]. Moreover, Johnson *et al.* revealed that watermelons' rind, seeds, and pulp contain the following phytochemicals: Cardiac and cyanogenic glycosides, oxalate, alkaloids, phytates, as well as saponins [55].

Other Chemo-Constituents in Watermelon



A=Curcubitane Backbone
B=Curcubitacin-B
C=Curcubitacin-C
D=Curcubitacin-D
E=Curcubitacin-E
F=Curcubitacin-I
G=Curcubitacin-L 2-O-b-glucoside

Figure 6: Chemical backbones of curcubitacins in Watermelon

Biomedical Activities of Watermelon

Antimicrobial Potential of Watermelon

Watermelon extract from distinct portions of the fruit has been investigated regarding a number of pathogens and significant antimicrobial potential has been exhibited, confirming the plant's conventional use for the management of both fungal and bacterial pathologies like diarrhea, alimentary canal infection, as well as cutaneous and respiratory ailments [14]. Secondary metabolites such as flavonoids, tannins, saponins, steroids, terpenes, and alkaloids are thought to be responsible for the plant's antimicrobial properties [56,57]. Watermelon's significant antimicrobial activity towards these bacteria and fungi could serve as a model for the discovery of novel antimicrobial medicines [58].

Sathya *et al.* assessed the antimicrobial potential of the methanolic extract of watermelon seed versus ten varieties of bacteria, including *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Vibrio cholera*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Shigella dysenteriae*, *Proteus mirabilis*, and *Bacillus subtilis*, along with five varieties of fungus, including *Candida albicans*, *Penicillium notatum*, *Aspergillus niger*, *Aspergillus flavus*, and *Trichophyton mentagrophytes* [59]. Sathya *et al*., concluded that watermelon seed extract exhibited antimicrobial potential versus all of the examined varieties. As a result, such an extract can indeed be utilized to synthesize promising natural bio-active medicinal compounds, which could contribute to the creation of unprecedented antimicrobial agents [59].

Antioxidant Potential of Watermelon

Free radicals have been continually created inside living cells in response to numerous physiological as well as biochemical mechanisms. Free radicals induce oxidative injury to cellular macro-molecules due to their elevated reactivity, and when the buildup of these radicals surpasses the boundaries of what the innate cellular antioxidant functions can neutralize, a variety of degenerative outcomes can appear in cells [60–63]. As a result, reactive oxygen species, including peroxyl, superoxide, and hydroxyl radicals, as well as reactive nitrogen species like peroxynitrite and nitric oxide, can induce a variety of disorders and exacerbate the inflammatory reaction [64]. As a logical consequence, antioxidant supplements are crucial since they can minimize oxidative injury in the body tissues via scavenging free radicals [65]. The principal antioxidant components in watermelon include carotenoids, especially lycopene, unsaturated fatty acids, and phenolics [21],[66].

Asghar *et al*. proved that watermelon peel extracts possess antioxidant and radical scavengers potentials [67]. The protective potential of watermelon juice against oxidative stress induced by ethanol in rats' brains and livers was investigated by Oyenihi *et al*. In this trial, the rats were given watermelon juice (4 mL/kg) for fifteen days prior to getting ethanol [68]. The preventative impact of watermelon juice was determined using a lipid peroxidation method, depending on the reaction between malondialdehyde and 2-thiobarbituric acid, which revealed a marked decline in malondialdehyde levels in rats' brains and livers [68].

Watermelon seeds also possess an antioxidant potential, and it is reliant on the extraction solvent. Rahman *et al*. found that hexane extract had higher antioxidant potential than both ethanol and chloroform extracts [69]. In addition, Kolawole *et al*. investigated the impact of a methanolic extract of watermelon rind on erythrocytes as well as markers of lipid peroxidation and oxidative stress in rats after treatment with phenylhydrazine. Researchers have speculated that the alleviation impact is due to the combination of both the antioxidant and nutritional elements like quercetin found in watermelon rind extract on reducing nitrogen and reactive oxygen species [70].

Anti-inflammatory and Analgesic Potentials of Watermelon

Inflammation is the body's natural guard versus pathogens, toxic substances, and chemicals [71,72]. If the inflammatory process becomes chronic, it could play a vital role in the progression of a number of chronic ailments, such as neurodegenerative disorders, metabolic syndrome, coronary heart disease, as well as certain cancers [73–76].

Abdelwahab *et al*. examined the anti-inflammatory potential of cucurbitacin E isolated from watermelon pulp *in vivo* and *in vitro*, as well as the role of reactive nitrogen and oxygen species and cyclooxygenase enzymes. The anti-inflammatory potential of cucurbitacin E was thought to be due to its inhibitory activity on cyclooxygenase enzymes and reactive nitrogen species but not on reactive oxygen species [77]. Another bio-active compound contained in watermelon named lycopene has been shown to suppress a number of inflammatory responses, such as the manufacturing of pro-inflammatory signaling molecules, enzymes expression such as lipooxygenase, and cyclooxygenase, which raise the inflammatory reaction, as well as the action of molecular signaling factors [78,79].

According to an *in vitro* study conducted by Iswariya and Uma, the methanolic extract of watermelon seeds has better anti-inflammatory action than the water extract. The suppression of inflammatory reactions is accomplished by blocking the liberation of activated neutrophils, which are the primary source of the inflammation of tissues, with the possibility of tannins playing a key role in these reactions [80].

In a separate study conducted by Hong *et al*., sodium dextran sulfate was used to motivate inflammation in rats. Then, watermelon was given to these animals to see if it could affect inflammation. As a result, this study found that consuming watermelon caused inflammation to subside through the suppression of the pro-inflammatory enzyme cyclo-oxygenase-2 [81].

Regarding the analgesic potential of watermelon, the aqueous extract of watermelon peel (AEWP) was investigated by Kumari *et al*. for its analgesic impact. In a dose-dependent fashion, this extract elicited considerable analgesic potential. At dosages of 0.25, 0.5, and 1 g/kg, the AEWP demonstrated perfect analgesic impact [82]. Following ninety minutes of dosing, the response time for all these doses was around 5, 8, and 10 minutes, respectively. That was similar to diclofenac sodium at a dosage of 5mg/kg, which had a reaction time of around 12 minutes [82]. The extract's analgesic impact was comparable to that of diclofenac sodium, proposing that the extract's impact is achieved through the suppression of cyclooxygenases 1 and 2. The existence of glycosides, flavonoids, phytosterol, saponin, and tannins in this aqueous extract is thought to be responsible for its analgesic potential [82].

Gastro-protective and Anti-secretary Potentials of Watermelon

The gastro-protective impact of watermelon pulp aqueous extract was assessed in Wistar albino rats, utilizing two fashions those are indomethacin-induced ulcer and pyloric ligation [83]. In the first fashion, the administration of watermelon pulp aqueous extract orally in dosages of 0.25, 0.5, and 1 g/kg body mass, three times daily, over five days following ulcer induction resulted in a drop in the ulcer index and improvement in different biomarkers within the gastric mucosa [14]. In the second fashion, the administration of aqueous extract of watermelon pulp demonstrated a substantial elevation in pH, and enzymatic antioxidants such as catalase and superoxide dismutase. Along with a substantial reduction in acidity, gastric juice quantity, lipid peroxidase amounts, as well as carbohydrate and protein concentrations were recorded [83].

In addition, watermelon juice has been demonstrated to have anti-secretory bioactivity. In an indomethacin-induced ulcer in rats, pH, as well as gastric acid output, were investigated. The incidence of gastric injuries in these animals pre-treated with watermelon juice was drastically reduced in a dose-dependent fashion. Ulcerogenesis was also dramatically reduced in the medicated groups compared to the control groups [14],[84]. One of the factors accountable for this protective impact could be a suppression in gastric acid excretion. This suppression is speculated to be related to the great quantities of L-citrulline obtained in watermelon. L-citrulline is a nitric oxide stimulator featuring anti-secretory potential [84].

Anti-Prostatic Hyperplasia Potential of Watermelon

The potential of watermelon methanolic extract as an effective agent against murine-induced benign prostatic hypertrophy was assessed by a study conducted by Olamide *et al*. Treatment with watermelon methanolic extract over one month decreased prostatic size considerably at both elevated and low doses, but it did not recover the extreme oligospermia and original size of shrunk testicles resulting from hormones. According to the histology findings, this extract is a prospective contender in the treatment of androgen-dependent disorders such as benign prostatic hypertrophy [85].

Anti-Uterine Contractility Potential of Watermelon

In a study conducted by Munglue *et al*., the potentials of L-citrulline and watermelon extracts on rats' uterine contractility were evaluated, and it was proved that watermelon extracts of rind and pulp, as well as citrulline, substantially reduced the contractility of the uterus. In this work, L-citrulline and watermelon extracts were tested for three kinds of contractility in isolated rat wombs, including spontaneous, those induced by oxytocin administration, or by potassium chloride depolarization. In a dose-dependent fashion, the extracts of rind and pulp greatly reduced the force generated by these three mechanisms. Watermelon extracts and L-citrulline both had similar effects on the force of contraction [86].

Adding nitric oxide antagonists abolished the inhibitory activity of L-citrulline and the extracts. Pre-remediation of the myometrium with these antagonists hindered the activities of both L-citrulline and the extracts. As a result of these findings, L-citrulline and watermelon appear to have effective anti-contractile potential. The activation of the nitric oxide cyclic guanosine monophosphate relaxing pathway is thought to be their primary mechanism of action. Although more research on human-being myometrium is needed to corroborate these findings, watermelon extracts' reduction of womb motility may be a valuable source of womb relaxation in miscarriage and dysmenorrhea [86].

Purgative Potential of Watermelon

The purgative potential of watermelon was investigated in rats through research conducted by Sharma *et al*. The findings of this study revealed how an oral intake of watermelons' aqueous pulp extract enhanced rat feces production and accelerated gastrointestinal motility in a dose-dependent way [87]. These potentials seemed approximate to those of castor oil both at high and low doses, at 1 and 0.5 g/kg, respectively [87,88]. Formerly, it was established that the phytochemicals present in plants, such as flavonoids, phenols, sterols, and terpenoids, are accountable for the plants' laxative characteristics [89]. The analysis of watermelon extract identified polyphenols, glycosides, steroids, tannins, flavonoids, amino acids, carbohydrates, and proteins [90]. These components could be accountable for watermelon's purgative characteristics [87]. Furthermore, Datta and his colleagues revealed that extract of watermelon pulp, taken orally at dosages of 0.25, 0.5, and 1 g/ kg of body mass, exhibited considerable purgative efficacy and decreased loperamide-induced constipation in a dose-dependent fashion [83].

Metabolic Syndrome Healing Potential of Watermelon

The term "metabolic syndrome" describes a set of clinical symptoms that include hypertension, abdominal obesity, as well as low high-density lipoprotein, high triglyceride, and high blood glucose levels [91,92]. Watermelon consumption may have a positive impact on metabolic syndrome. Through a crossover trial, Lum *et al*. investigated the effects of watermelon on thirty-three obese or overweight volunteers who received two cups of watermelon every day over four weeks. Researchers concluded that watermelon intake substantially reduces body mass index, body weight, waist-to-hip ratio, and systolic blood pressure [93]. Also, Massa *et al*. assessed the effect of watermelon extract on blood pressure. Researchers found that consuming six grams of watermelon extract every day for six weeks lowers diastolic and systolic blood pressure among pre-hypertensive and hypertensive subjects [94].

The researchers credit such hypotensive impact to the L-citrulline that exists in watermelon, which transforms into L-arginine effectively, leading to enhanced generation of the vasodilator nitric oxide by endothelial cells [94]. Also, another constituent in watermelon, lycopene, possesses anti-hypertensive features because it suppresses the angiotensin-converting enzyme as well as its antioxidant feature, which lowers oxidative stress caused by angiotensin II and indirectly boosts nitric oxide generation in the endothelium [95].

In a study, Francis and his colleagues revealed that administering an ethanolic extract of watermelon seed lowered glucose levels as well as LDL, triglyceride, and cholesterol levels related to diabetes. According to this research, L-citrulline, flavonoids, and saponins are the major constituents responsible for the hypoglycemic impact of watermelon [96]. In addition to watermelons' seeds, their rind and pulp also exhibit hypoglycemic properties and can trigger beta cell regrowth in human and animal fashion studies, comparable to oral hypoglycemic agents [97].

Other Potentials of Watermelon

Watermelon has been studied and found to have a substantial anti-hepatotoxic potential [98,99]. A study conducted on Wister rats showed that watermelon seed extract could protect their livers from oxidation caused by ethanol. The antioxidant phyto-constituents nature of watermelon seed extract, principally phenolics, and flavonoids, serves to attribute this impact [98]. Moreover, watermelon juice can protect hepatocytes from toxicity induced by carbon tetrachloride, according to Altaş *et al*. [99].

Watermelon also possesses neuroprotective potential. In a study conducted by Owoeye *et al*., the neuroprotective ability of watermelon seed extract was proved by alleviating mercury chloride toxicity in the rats' brains at a dose of 200 mg/kg body mass [100]. In another study, Finbarrs *et al*. concluded that ethanolic watermelon seed extracts boost immuno-reactivity to neurofilament protein antibodies and hence enhance rats' cognitive performance [101].

Toxic Potentials Evaluation of Watermelon

Arojojoye *et al.*, studied the watermelon impact on biomarkers of kidney and liver in rats to acquire scientific proof on its safety for human-being ingestion. Watermelon rind extracts were given orally for four weeks to rats at doses of 0.5, 1.5, and 3.5 g/kg of body mass [102]. In comparison to control, there was no substantial rise in the levels of aspartate aminotransferase and alanine aminotransferase. Also, there were no other considerable alterations in superoxide catalase and dismutase levels, no alteration in glutathione levels, and no stimulation of lipid peroxidation [102].

Also, Garuba *et al.*, studied the acute toxic effects of hydro-ethanolic extracts of watermelon seeds in rats via delivering a high single oral-dose of 5mg/kg body mass and monitoring the animals for two weeks. There were no behavioral alterations, hematological changes, evidence of intoxication, or fatalities associated with the treatment [103]. Those researchers also assessed the sub-chronic toxic effects of extracts by giving daily oral doses of 0.1, 0.5, and 1 g/kg body mass for two weeks. When compared with the control group, the extracts showed no substantial changes in hematological or clinical biochemical parameters but a substantial drop in serum aspartate aminotransferase level at 0.1 and 0.5 g/kg body mass and an increase in body mass [103].

Likewise, Belemkar *et al*. investigated recurrent and acute toxic effects of watermelon seeds' ethanolic extracts given orally at doses of 0.25, 0.5, and 1 g/kg body mass over four weeks [104]. When compared with the control group, there were no remarkable effects on water consumption, body mass, biochemical, behavioral, as well as histo-pathological, or hematological markers. They found that at a dose of 1 mg/kg body mass, watermelon seeds' extract demonstrated no observed adverse effect and is suitable to use in pharmacological research, as well as pre-clinical and clinical assessment for curative capabilities [104].

In addition, Oyenihi *et al*., evaluated the toxicological effects of watermelon seeds on rats, particularly long-term usage of watermelon seeds containing food. Rats were fed a diet comprising watermelon seeds at a rate of 2.5% or 5% for three weeks [105]. Watermelon seeds containing food resulted in a considerable drop in body mass but did not affect brain and liver weight. Furthermore, there were no substantial differences in the actions and blood levels of alkaline phosphatase, alanine aminotransferase, cholesterol, and triglycerides in all rats when compared with the control group [105].

Conclusions

As proven by the previously listed research studies, watermelon comprises a wide variety of bioactive constituents that are detected in the pulp, rind, and seeds of the fruit that have significant medical benefits. The availability of diverse sets of bioactive molecules, extending from hydrophilic ones like phenolics to intermediate hydrophilic ones like cucurbitacins to hydrophobic ones like polyunsaturated fatty acids as well as carotenoids, endows watermelon with a wide range of pharmacological and biological potentials. As a result of this substantiation, the whole watermelon fruit could be employed for a variety of purposes thanks to its nutritious worth.

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All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

Conflict of Interest
We have no conflicts of interest to disclose.

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