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Nutritional composition and bioactive potential of watermelon seeds: a pathway to sustainable food and health innovation

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Watermelon (*Citrullus lanatus*), belonging to the Cucurbitaceae family, is a globally cultivated fruit with significant commercial value. While the fleshy part is eaten for its taste and nutritional benefits, the seeds are generally thrown away as waste, although they harbour high nutritional and bioactive contents. Watermelon seeds are rich in proteins, fats, vitamins, and minerals, and they also contain bioactive compounds such as phenolic acids, flavonoids, and carotenoids. This review seeks to investigate the proximate composition of watermelon seeds, novel techniques employed in the extraction of bioactive compounds and the various facets of therapeutic applications of these seed bioactivities, such as antioxidant, antimicrobial, antimutagenic, hypoglycaemic and anti-inflammatory properties. The effects of these seeds are assessed based on the pharmacological mechanisms underlying their therapeutic actions. Also, this review discusses the potential of using watermelon seeds and their components in the food industry as valuable functional foods and in the cosmeceuticals and nutraceuticals industries. These include health-enhancing food supplements, cosmetics, and newly developed edible products for human consumption. However, there are some issues related to its composition, yield, and safety profile that impede its optimum use. In particular, this paper highlights the sustainability problems, suggesting that converting agricultural waste into such by-products could lead to a circular economy and improve human welfare.

Sustainability spotlight

The study of watermelon seeds unveils their potential as a valuable sustainable resource that contributes to world food security as well as health improvement. With drastic growing concerns related to food waste and the increasing demand for alternate nutrient-dense food products, watermelon seeds offer an invaluable substitution. The seeds are protein-rich, loaded with healthy fats, vitamins and various bioactive compounds. Thus, in addition to being a sustainable nutritional source, they also contribute to the circular economy by agricultural waste reduction. Furthermore, their bioactive potential includes antioxidant, antimicrobial and anti-inflammatory properties, positioning watermelon seeds as an effective ingredient in natural and functional food products. By promoting and highlighting the potential of watermelon seeds, this paper provides an effective pathway aligned with the principles of sustainability in food technology. This can be further elaborated by mentioning the role of watermelon seed utilization in food waste reduction, enhancing resource efficiency as well as supporting the innovative creation and health-promoting solutions. Therefore, watermelon seeds present both environmental as well as effective health benefits, serving as an effective and key constituent in advancing sustainable food systems and fostering human nutrition globally.

1. Introduction

Watermelon, scientifically named *Citrullus lanatus* (CL), is a fruit with potential nutritional and pharmacological value. Watermelon belongs to the Cucurbitaceae family and the *Citrullus* genus.[1] This fruit is among the most extensively grown fruits in the world and holds significant commercial value. With reference to the area, watermelons are commonly cultivated in Asia (accounting for 79.5%), Africa (7.5%), and America (6.9%), with approximately 3.1 million hectares dedicated to its cultivation and a production capacity of about 104 million tons every year. China is the major producer of the crop, comprising 67% of the global production.[2,3] According to the FAO, the duration that it takes for a watermelon to attain ripeness differs with climate, typically taking between 80 and 110 days.

Consumption of watermelons (Fig. 1) has been increasing because of their taste, nutritional value, and attractive color, which ranges from red and yellow to pink. The flesh color of watermelon depends predominately on carotenoids and the degree of their deposition in chromoplasts during the ripening stage.[4] For example, red-fleshed watermelons contain lycopene and β-carotene; yellow-fleshed watermelons have neoxanthin, violaxanthin, and luteoxanthin; and orange-fleshed

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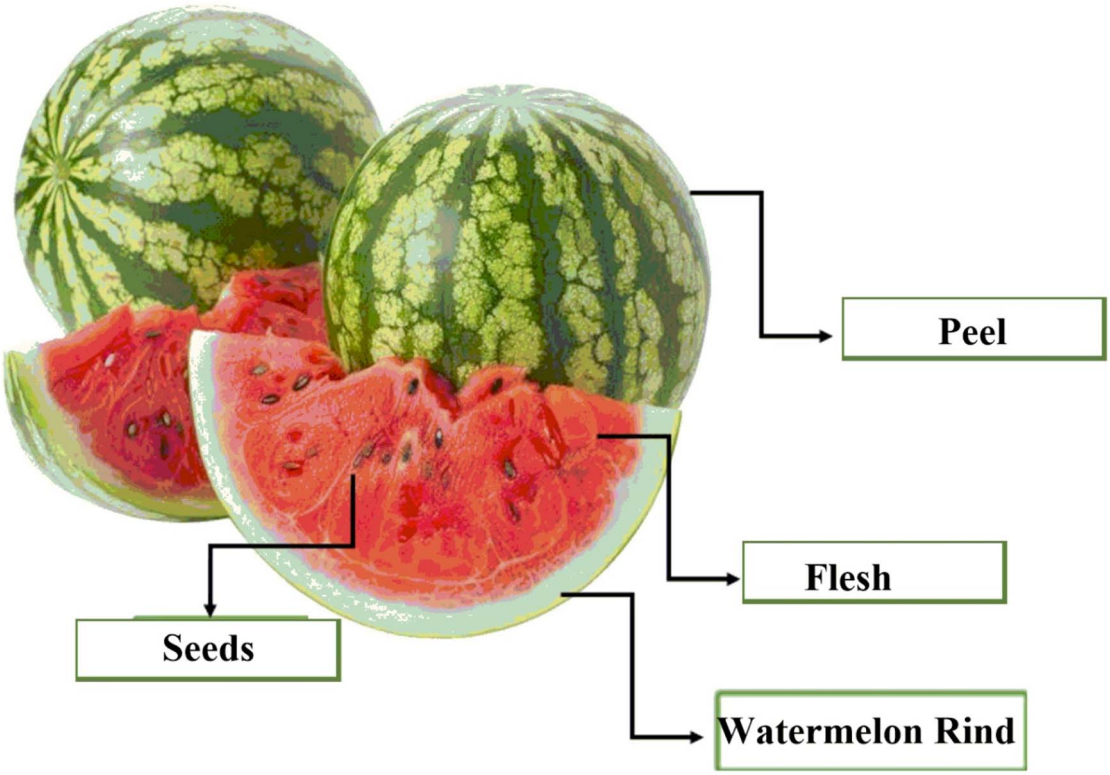

Fig. 1 Parts of the watermelon fruit.

watermelons contain β-carotene, prolycopene, phytoene and ζ-carotene. On the other hand, white-fleshed watermelons contain low levels of carotenoids, as previously shown.[5]

Watermelon is widely consumed by a large population worldwide owing to its incredibly nutrient-dense, low-calorie, and thirst-quenching properties.[6,7] The water content of watermelon is approximately 92%. Watermelon is also cholesterol-free and high in vitamins, especially B_1, B_6, and C, as well as lycopene, a carotenoid, and minerals such as magnesium and potassium. These components have positive health effects, such as better cardiovascular health, management of hypertension in hypertensive patients, lower LDL oxidation, and prevention of age-related diseases and some forms of cancer.[8–10]

However, the rising consumption of watermelon has led to the massive production of by-products, most of which are generated majorly by food processing industries, including huge amounts of peels and seeds.[11–13] The accumulation of these agri-food by-products presents economical and environmental challenges, conditions that are counterproductive to food security.[14] Organically, watermelon processing involves stripping the edible portion that makes up approximately 57–68% of the fruit, the rind forms between 30–41% of the whole fruit and the seeds form 2% of the entire fruit. Out of all by-products, watermelon rinds contribute the largest portion of waste but can be reused in jam manufacturing.[11] By-products, mostly watermelon seeds, have high concentrations of bioactive compounds, which offer prevention against various human ailments. The watermelon seeds have been proven to exhibit antimutagenic,[15] antioxidant,[16,17] antimicrobial,[18] hypoglycaemic[4] and anti-inflammatory activities.[19] In addition, the watermelon pulp contains numerous vitamins, antioxidants, minerals, and bioactive compounds that are beneficial to human health.[20]

This article comprehensively reviews the nutritional composition, bioactive compound extraction, bioactive potential, mechanisms of action, and therapeutic properties of watermelon seeds. It also explores the potential applications in food processing and discusses the challenges and future perspectives in utilizing watermelon byproducts for novel functional ingredients.

Nonetheless, seeds and peels of watermelon are usually thrown away, although they are sources of nutrients. These by-products have bioactive prospects, which make them an affordable and untapped resource in the food and drug sectors.[21] The consumption of watermelon by-products provides health benefits to the human body.[22]

This is where extensive prospects for revalorization can be viewed as highly possible for turning watermelon seed by-products into higher value, functional food ingredients, nutraceuticals, supplements, drugs or cosmetics.

This article systematically summarises all details of the nutritional composition, bioactive compound extraction, bioactivities, modes of action, and therapeutic uses of watermelon seeds.

2. Nutritional composition of watermelon seeds

Watermelon seeds are not only edible but also highly nutritious, containing ingredients including macronutrients,

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micronutrients and phytochemical compounds. Several researchers aimed at the proximate composition of watermelon seeds, stating that they contain crude fat (48–50%), protein (18–30%), carbohydrates (10–18%), moisture (4–8%), total dietary fiber (2.5–49%) and ash content (2.3–3.8%).[23,24] The percentage yield of oil from the watermelon seeds outweighs the yields of other more conventional oil-bearing seeds such as cotton seeds, soybeans and olive seeds,[25] as shown in Table 1.

In a study assessing the fatty acid composition of fifteen cultivars of watermelon, most of the cultivars contained higher levels of unsaturated fatty acids,[38] with linoleic acid accounting for 45% to 55%, followed by oleic acid accounting for 10% to 20%, palmitic acid accounting for 10% to 15%, and the stearic acid accounts for 10.23%. Also, alpha-linolenic acid at 0.35%, palmitoleic acid at 0.29%, and myristic acid at 0.11% were detected in the seed oil.[39] In addition to fatty acids, WSO has other lipophilic compounds such as sterols, diglycerides, monoglycerides and phospholipids.[39,40] Consequently, watermelon seeds contain monounsaturated and polyunsaturated fatty acids, which help to avert heart and vascular diseases. The

Table 1 Nutritional and Bioactive Components of Watermelon Seeds

Component	Concentration/Composition	Bioactive potential	References
Protein	25.2–35.6%	Source of essential amino acids, promotes muscle growth, aids in tissue repair, and supports the immune system	25
Fats (lipids)	20.0–50.0%	High in unsaturated fatty acids, particularly omega-6 and omega-9, and beneficial for cardiovascular health	26–28
Carbohydrates	8.0–20.0%	Provides energy and dietary fiber, aiding digestion and promoting gut health	29 and 30
Minerals	Magnesium: 500–532 mg/100 g	Crucial for muscle function, nerve regulation, and bone health	30 and 31
	Iron: 7.08–7.28 mg/100 g	Vital for oxygen transport and prevention of iron deficiency anemia	32 and 33
	Zinc: 10.13–10.24 mg/100 g	Supports immune function, cell growth, and wound healing	32 and 33
	Calcium: 54 mg/100 g	Essential for maintaining bone health	29 and 30
	Phosphorus: 755 mg/100 g	Important for energy metabolism, strong bones, and cellular functions, including DNA synthesis	
Vitamins	Vitamin A (retinol, beta-carotene): 69.12 mg kg^{-1}	Essential for vision, immune function, and skin health	27, 28 and 34
	Vitamin C (ascorbic acid): 19.45 mg kg^{-1}	Antioxidant, supports skin health, and enhances immune response	
	Vitamin D (cholecalciferol): 8.76 mg kg^{-1}	Important for calcium absorption and bone health	
	Vitamin B9 (folate): 1.84 mg kg^{-1}	Crucial for DNA synthesis, cell division, and growth, especially during pregnancy	
	Vitamin E (tocopherol): 3.53 mg kg^{-1}	Antioxidant, protects cells from oxidative damage	
	Vitamin K (phylloquinone): 1.44 mg kg^{-1}	Essential for blood clotting and bone metabolism	
Amino acids	Phenylalanine: 5.15 g/100 g	Most abundant; essential for protein synthesis and neurotransmitter production	27, 28 and 35
	Arginine: 4.98 g/100 g	Vital for protein metabolism and cardiovascular health	
	Valine: 4.56 g/100 g	Essential for muscle growth, tissue repair, and energy production	
Total phenols	1494–5416 mg GAE/100 g	Antioxidant properties, may reduce inflammation, support heart health, and lower cancer risk	36
DPPH scavenging ability	56.93–94.46%	Defends against oxidative damage	37
Free radical scavenging activity	82.59–130.29 μM trolox/g	Potential to lower the risk of chronic diseases	36

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second biggest constituent found in watermelon seeds is protein. The seeds contain glutamic, aspartic, arginine and leucine amino acid distributions.[41] However, among all the phytochemical compounds, L-citrulline is specifically notable, present not only in fresh pulp but also in seeds. As a simple, non-essential amino acid, it serves as a substrate for the production of L-arginine in the urea cycle. L-Arginine, in turn, generates nitric oxide, a crucial molecule required for maintaining endothelial function and regulating vascular resistance. L-Citrulline, primarily derived from watermelon, significantly contributes to cardiovascular health by facilitating nitric oxide production, which helps regulate blood pressure and prevent conditions such as atherosclerosis and hypertension.[42] Notably, the citrulline concentration is higher in yellow and orange-fleshed watermelons compared to red-fleshed varieties.[43]

Watermelon seeds contain four major protein fractions: 46% globulin, 39% glutelin, 23% albumin and 22% prolamin. These proteins have satisfactory solubility and digestibility and show antimicrobial and antioxidant effects and have the potential to be natural food preservatives. However, due to their antioxidant activities, they can be subjected to variation depending on the pretreatment and extraction of the used methods.[44] Research has demonstrated that watermelon seed proteins exhibit antioxidant activity by upregulating the Nrf2/HO-1 pathway, an antioxidant defense system implied in combating oxidative stress.[45] These proteins generally have molecular weights between 25 kDa and 250 kDa, but with the hydrolysis process, bioactive peptides are obtained. This stability under various conditions also improves its application in food and health-related applications.[44]

It also means that watermelon seeds contain secondary metabolites that have positive effects on human health. These include alkaloids, polyphenols, phenolic acids, flavonoids, tannins, phytates and oxalates, with the alkaloids being present in the largest quantities.[46] On the other hand, saponins are found in the watermelon in every part but seeds. The seeds are especially concentrated in triterpenoids, which are known to possess antibacterial effects. Studies on the relative antioxidant and antimicrobial potential of different parts of the watermelon revealed that the peel exhibited the highest total phenol content and antioxidant potential, followed sequentially by the seed, rind, and pulp. These results confirmed the high phytochemical level and antioxidant activity of the watermelon seeds, which can act as a health-beneficial ingredient.

The watermelon seeds also contain several phenolic acids such as gallic, *p*-coumaric, caffeic, sinapic, hydroxycinnamic and cinnamic; among these, the content of sinapic is the highest.[4] Other phenolic compounds present at this concentration include naringenin-7-*O*-glycoside, apigenin, amentoflavone, rutin, quercitrin, quercetin, luteolin, and kaempferol.[39,41] Among the phenolic glycosides isolated from watermelon seeds, lanatusosides C and D have shown potential antitumor activity.[47] The watermelon seeds also contain a variety of vitamins, especially vitamin A, vitamin C, B complex, vitamin E and vitamin K. They also contain micro-elements, such as magnesium, phosphorus, iron, zinc, calcium, manganese, and copper, with potassium being the most concentrated element. Potassium is vital for maintaining electrolyte balance and supporting heart function.[4]

Watermelon seeds also contain a good proportion of carbohydrates such as glucose, sucrose, fructose and carotenoids of beta-carotene.[46] Furthermore, the arginine content of the seeds is high and has health benefits, including anti-ulcerative colitis and improved antioxidant activity.[47] Because of these nutritional components, watermelon seeds find their applications in different food products.[48] Several previous studies have quantified the phytochemicals present in watermelon seed methanol extracts, which also displayed antibacterial activities. Watermelon seeds have been reported to stimulate appetite and serve as an effective remedy for constipation.[37]

In addition to the nutritional and therapeutic effects, watermelon seeds also contain some anti-nutritional factors, including oxalates, phytates and tannins, compared to the rinds. These compounds can hinder nutrient uptake. However, these compounds can be modified by different processes like roasting, boiling and oven drying, making the antinutritional factors relatively ineffective.[49]

3. Molecular mechanisms of bioactive compounds in watermelon and its seeds: a biochemical perspective

The bioactive compounds in watermelon by-products primarily include various subclasses of cucurbitacins, glycosides, polyphenols and alkaloids, each exhibiting distinct molecular mechanisms that contribute to their health-promoting properties (Fig. 2).

3.1 Cucurbitacins

Cucurbitacins are tetracyclic triterpenoids found in several plants belonging to the Cucurbitaceae family, particularly in watermelon.[20] Terpenoid compounds are synthesized from terpene, mainly isopentenyl pyrophosphate five-carbon isoprene unit and dimethylallyl pyrophosphate and its isomer. Terpenoids also interact with the most extreme elements of regulatory proteins and exhibit antioxidant activity. For the mitigation of inflammatory diseases and cancer, plant extracts are used along with traditional and other forms of intervention medicine.[50] Present-day medicine employs terpenes as NF-κB inhibitors as described previously.[51] Under the category of cytoplasmic sensors, the NF-κB system reacts to the disturbance in the immune system and many other signals and internal signals such as genotoxic stress and hypoxia. Cellular resistance enlargement stands against anti-apoptotic signaling as well as the apoptosis of NF-κB also has a remarkable contribution.

Cucurbitacin E is distinguished by the fact that it is an anti-inflammatory agent that is also cataloged as acting as a triterpenoid. The reactive nitrogen-containing molecules have been neutralized and the cyclo-oxygenase enzymes have been inhibited by cucurbitacin E. This agent is used for the reduction of RNS through an anti-inflammatory agent but fails to eliminate at a cellular level ROS.[52] For example, when cucurbitacin E was used in combination with doxorubicin, an increased

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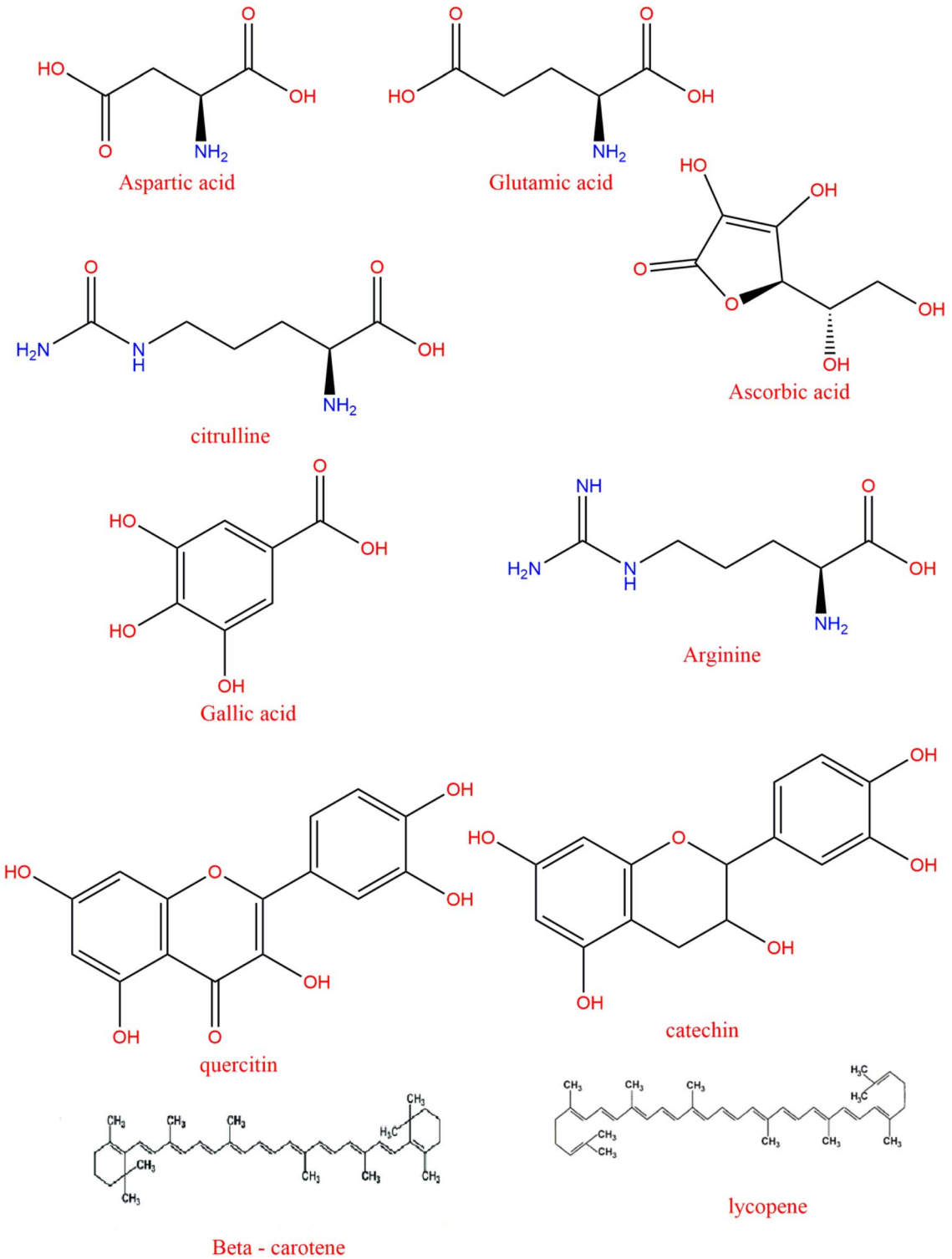

Fig. 2 Chemical structures of watermelon seed bioactive compounds.

cytotoxicity effect towards tumor cells both in the culture and experimental animals and a decrease of tumor size and mass were observed.[53,54] Likewise, when cucurbitacin B was mixed with docetaxel, there was an improvement in the anticancer effect on human laryngeal cancer Hep-2 cells.[55,56]

3.2 Glycosides

The glycoside phytochemicals in watermelon seeds were identified as having anti-diarrheal benefits, amongst others.[57] These compounds can normally exist concurrently with other bioactive agents, such as polysaccharides and thiol derivatives.

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Glycosides are chemical compounds that involve a carbohydrate pair with another non-carbohydrate component known as the aglycone or genin linked to the carbohydrate through alcohol, glycerol, or phenolic bond. The soluble material of the watermelon seed glycosides has various structures, such as a crystalline carbon–oxygen–hydrogen structure, a few carbon–oxygen–hydrogen–sulfur structure, or a carbon–oxygen–hydrogen–nitrogen structure.

Glycosides are readily susceptible to hydrolysis by acids, which makes such molecules extremely reactive in many physiological activities. These compounds are grouped according to the chemical nature of their aglycone or their pharmacological activity. For example, bitter principles like glycosides andrographolide, a diterpene lactone and amarogentin, and a triterpenoid lactone acting on gustatory nerves activate saliva as well as gastric juice release. Others, which include anthracene glycosides, are used in the treatment of the skin and to control bowel movement. Cyanogenic glycosides, in contrast, decompose to liberate hydrogen cyanide (HCN) through enzymatic splitting and although useful in controlled quantity for use such as in cough rectification (for instance, amygdalin), they are lethal and cause major gastrointestinal discomfort if ingested in large volumes.[58]

Therefore, proper processing and regulation are crucial to reduce the toxicity of cyanogenic glycosides in consumer food products, thus ensuring the health of the consumer as well as making the best use of the potential therapeutic benefits of the products that contain the glycosides.

3.3 Polyphenols

Water soluble, non-volatile organic compounds known as polyphenols are also bioactive substances present in watermelon and they are secondary metabolites of plants (Fig. 3). Its main distribution is in mesophyll cells, nucleus and areas

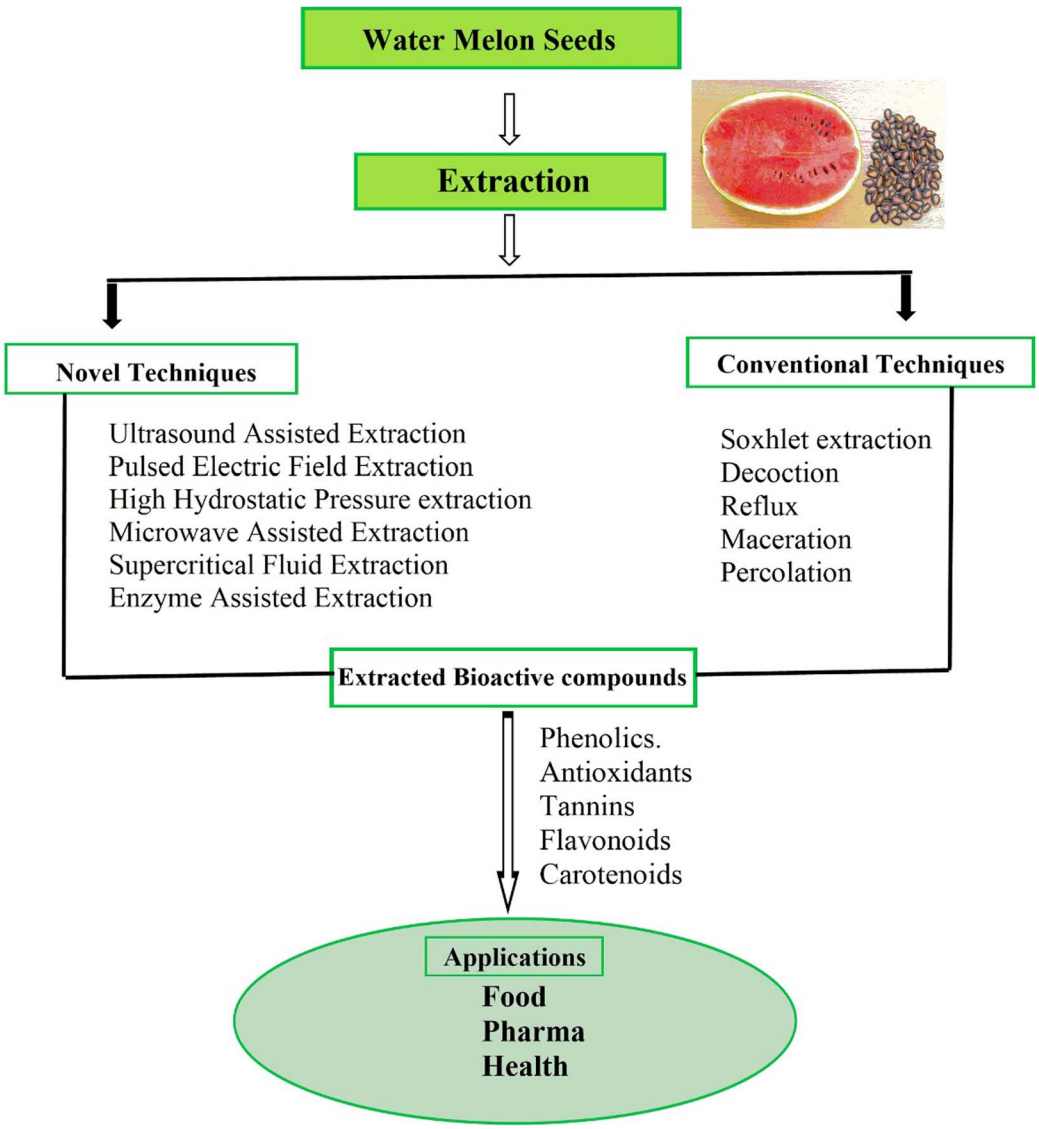

Fig. 3 Extraction techniques for watermelon seed bioactive compounds.

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where reactive oxygen species (ROS) are produced.[59,60] These compounds, produced by the phenylpropanoid pathway, conduct numerous health-promoting actions.[61,62]

Polyphenols, especially polar phenolic compounds with functional hydroxyl groups, remove free radicals, chelate metal ions, and trigger protective enzyme pathways; they serve as anticancer agents, antioxidants, and inhibitors of cardiovascular diseases and bacterial and viral infections.[63] Their antioxidant action causes a decrease in ROS formation, inhibition of enzymes contributing to free radical formation, and reactive nitrogen species (RNS) elimination.[64] Phenolic compounds such as anthraquinones are present in moderate concentrations and are known for their effectiveness in alleviating stomach aches and constipation. Anthraquinones, derived from anthracene, produce specific compounds like anthranols and anthrone derivatives. These compounds often exhibit unique structural features, such as double hydroxylation at the C-8 and C-1 positions, resulting in derivatives like chrysophanol, luteolin, emodin, and rhein. The presence of anthraquinones in plant samples can be visually identified by a violet or pink coloration in the base layer during analysis.[58]

The structure of flavonoids impacts their antioxidant capacity, with aglycones exhibiting higher degrees of activity in comparison to their glycosides.[52] Polyphenols can suppress the activities of enzymes that produce ROS and potentiate the oxidation of lipids and other compounds through glutathione and monooxygenase inhibitors and other pathways.[64,65] For instance, epicatechin and rutin reduce lipid peroxidation *in vitro* successfully.[66] Furthermore, quercetin also has a chelating and stabilizing effect on iron, through which ethanol extracts containing epicatechin and quercetin originating from winery byproducts show a potent antiplatelet activity.[67]

Such molecular interactions highlight the great prospect of cucurbitacins and polyphenols from watermelon and byproducts in the enhancement of functional food, nutraceuticals, and therapeutic agents for overall human health.

3.4 Alkaloids

Alkaloids, found in high concentrations in watermelon seeds compared to other components, are important plant secondary metabolites with significant therapeutic bioactivities. They are responsible for antispasmodic, analgesic and antibacterial actions and hence they are popular worldwide.[68] Chemically, alkaloids are composed of ammonia derivatives that form the principal group of secondary chemical compounds synthesized from amino acid building blocks. These nitrogenous bases become incorporated in peptide rings. Alkaloids can be classified as primary, secondary or tertiary, depending on the level of basicity present in the compounds, their molecular structure, their functional groups, and the position of the nitrogen atom.[58]

Alkaloids combine with acids to render crystalline salts, and they are in different physical conditions. Some, such as atropine, are solids, while others are liquids formed from carbon, hydrogen and nitrogen. These are soluble in water and most of the salts, although exhibit higher solubility in alcohol. The solutions containing alkaloids are particularly bitter and this aspect forms the part of the sensory properties. In human and medical perception, pharmacologically, alkaloids are employed as painkillers and for stimulating the central nervous system. Around one-fifth of plant species synthesise pharmaceutical alkaloids and over twelve thousand different alkaloids are known. Some of the commonly known alkaloids are nicotine, cocaine, caffeine, ergotamine, codeine morphine, ephedrine, and atropine, of which many are known stimulants or therapeutic agents.

4. Extraction methods for watermelon seeds: focus on bioactive compounds

The process of obtaining bioactive compounds from plant matrices is a key process in making optimal use of the existing data about their availability and potential usage in different fields: food industry, pharmacy and production of chemical products. Phenolics, flavonoids, terpenoids, and alkaloids act as potential bioactive compounds that deliver enormous health benefits to human beings. However, the effectiveness and quality of the extracted compounds largely depend on the extraction methodology employed. Thus, improving standardized and effective extraction techniques is crucial when capturing the maximum volume of these compounds and their bioavailability. The selection of extraction techniques plays a significant role in determining the cost, time, recovery and purity of the bioactive compounds; therefore, the assessment of the conventional and innovative extraction techniques in terms of strength and weakness is crucial. Various pre-extraction unit operations are required to increase the extraction rate. Some of them are washing, cutting, size reduction and drying as post-harvest handling activities.[69]

4.1 Conventional extraction methods for bioactive compounds

Most solvent-based extraction techniques are considered traditional because they employ factors such as polarity, ionic strength, heat, and mechanical force to extract bioactive compounds from plant samples. Among these methods are maceration, percolation, decoction, reflux extraction, and Soxhlet extraction; these methods have been used for many years in the food and pharmaceutical industry due to their simplicity and efficiency in different fields (Fig. 3).

4.1.1 Cold-pressing. Cold pressing is a method for extracting oil from watermelon seeds by applying pressure to ground seeds to release the oil. This is followed by centrifugation to separate the oil from the remaining plant material, and the process concludes with filtration to obtain purified oil.[70]

4.1.2 Maceration. Maceration is among the simplest and earliest extraction methodologies used for obtaining bioactive compounds and is also a very common method in phytochemical research. It involves reducing the size of the plant material in order to create a large surface area of the material, enhancing its ability to mix and interact with the solvent, either water or organic solvents. The mixture is then stirred for several

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hours and the liquid is filtered to eliminate unwanted material. Although maceration is a simple and inexpensive process, it still has some drawbacks, such as long extraction time and low extraction rate. It is most suitable when extracting thermolabile compounds, which tend to decompose during higher-temperature extraction conditions.[47] The efficiency of extraction is generally based on factors like the solvent type, extraction period, sample particle size, extraction temperature, and the amount of solid matter and solution.[71] Samples with small particles are easier for permeation by the solvent, and higher temperatures always favor the extraction process. However, excessive temperatures can cause the loss of the volatile oil constituents in question. If extraction time is increased, little difference to the extraction yield is observed since the concentration process starts reaching what can be considered equilibrium. However, the solid/solvent ratio should also be kept constant because, with a higher ratio of the solid phase, extraction time increases.[72] The use of maceration at room temperature offered an option to extract phenolic compounds from an oil mixture pH and solvent extractant levels of watermelon seed extracts through Soxhlet extraction and maceration with methanol inhibited DPPH radicals, as established previously.[73,74] The IC50 belonged between 1.41 and 2.60 mg mL^{-1}, possessing considerable antioxidant properties.

4.1.3 Percolation. Percolation is a more efficient procedure than maceration and includes concurrent filtration of the solvent through plant matter within a percolator. A powdered plant sample is normally steeped in boiling water and allowed to macerate for a few hours before the solvent is continuously replaced with fresh solvent. This approach enables better extraction outcomes and shortens the required period for processing thickened sludge. Following extraction, evaporation is employed to reduce the volume of extracted products proportionally. While percolation has benefits, the technique needs a special apparatus called a percolator and may not be suitable for some kinds of bioactive compounds.[75]

4.1.4 Decoction. Another extraction method is decoction and is normally used for heat-stable products mainly due to its applicability. It involves treating the plant material with water or aqueous solution at a particular temperature and duration, after which the liquid is cooled, filtered and strained. Decoction is particularly good for extracting compounds soluble in water but is unsuitable when extracting thermolabile and volatile substances, which tend to be destroyed by heat. Moreover, it may be less productive due to kinetic and mass transfer limitations, which can influence the yield and quality of the extracted compounds.

4.1.5 Reflux extraction. Reflux extraction, also known as solid–liquid extraction, is said to be more effective than percolation and maceration since it uses lower solvent volume and less time to extract. In this technique, the plant material is blended in a heated and stirred container with a solvent to recover the oil. The vapors formed are cooled and are permitted to drop back into the flask, thus increasing the overall mass transfer and contact between the solvent and the plant matrix. However, this method is quite good for the extraction of heat-stable compounds but not ideal for thermolabile compounds that tend to be degraded during extraction.[47]

4.1.6 Soxhlet extraction. Soxhlet extraction is one of the oldest and most popular traditional methods for extracting bioactive compounds from plant materials. This method actually borrows features from the reflux and the percolation technique because it constantly pumps solvent through the sample, and as such, fresh solvent is constantly in contact with the sample. This results in high extraction capabilities, lesser solvent utilization and a relatively shorter time compared to conventional procedures such as maceration or percolation. However, Soxhlet extraction involves lengthy heating, which may lead to the thermal decomposition of some of the bioactive compounds and thus restricts its application to heat-stable compounds.[76]

Traditional extraction techniques like maceration, percolation, decoction, reflux extraction, and Soxhlet extraction are still considered important for the extraction of bioactive compounds due to their simplicity and wide applicability. Among the conventional methods of extraction, maceration and Soxhlet extraction are particularly significant. Conventional and non-conventional methods have been used for the extraction of different phenolic compounds from grape skin.[77] *Vernonia cinerea* leaf and feijoa peel extraction gave a total phenolic content of 48.6 to 71 mg GAE/g.[78] However, considering factors such as the choice of solvent, temperature, or extraction time provided the basis for the yield and quality of extracted bioactive compounds. Selecting the appropriate method depends on the specific properties of the compounds being extracted and the desired end-use of the extracts.

4.2 Novel extraction methods for bioactive compounds

Conventional extraction methods like Soxhlet and maceration are commonly used but may present drawbacks such as long extraction times, high solvent consumption, and potential degradation of sensitive compounds. To overcome these challenges, novel extraction methods have emerged, offering enhanced efficiency, lower solvent use, and better preservation of bioactive compounds. Below is a detailed review of these innovative techniques in the context of watermelon seeds (Fig. 3).

4.2.1 Supercritical fluid extraction (SFE) for watermelon seed lipids. Supercritical fluid extraction (SFE) uses CO_2 as the extraction solvent, making it effective for extracting nonpolar and moderately polar compounds.[79] CO_2 is non-toxic and nonpolar, has a high solute capacity and is suitable for extracting thermosensitive compounds. Watermelon seeds have very high amounts of unsaturated fats, and these fats respond poorly to high temperatures of conventional extraction techniques. SFE makes it possible to extract oil from nuts at relatively low temperatures and thus prevents the alteration of the nutritional properties of lipids. Furthermore, the method provides a high yield of bioactive lipids per unit of raw material with minimal solvent left behind, which makes it appropriate for commercial food-grade oil extraction from watermelon seeds.[80] This method has been widely used in many types of seeds, including coca,

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linseeds and sesame seeds.[81] A study found that high-density gases or supercritical fluids enhanced the pressing process since the required mechanical pressure was about 10 MPa, while the yield increased in the range of 10–20%.[82] The current filtration technologies, in combination with the SC-CO_2, have thus been tested for the purification of compounds of relatively low molecular weights of about 1500 g mol^{-1}. This method has been successfully applied in the purification of beta-carotene extracted from carrot oil and triglyceride fraction from fish oil.

4.2.2 Microwave-assisted extraction (MAE) on antioxidants. The MAE method can be applied to extract antioxidants from watermelon seeds. The seed matrix also consists of phenolic compounds, flavonoids, and tocopherol, and all of them have antioxidant values. MAE enhances the extraction process *via* the use of microwave radiation that heats both the solvent and seed matrix simultaneously. This leads to a faster extraction rate of these bioactive compounds with a small amount of solvent required. It has also been established that the method is most useful in the recovery of phenolic compounds with a high antioxidant potential. Microwave-assisted extraction (MAE) is widely used as a more efficient method for the extraction of bioactive compounds from plant and animal origins. Many benefits can be achieved with the help of this method, including increased extraction rate as well as a many-fold decrease in time for further processing. The technique increases the efficiency of cell disruption, thereby improving solvent penetration due to the effects of microwave energy and facilitating the extraction of target compounds in a shorter time than conventional methods.[83] Moreover, in contrast to most organic solvents, MAE tends to use water or other Earth-friendly solvents, so it can be considered more environmentally friendly. Due to these benefits, MAE is used in this work and generally in the separation of various biologically active substances from natural matrices.[84]

4.2.3 Instant controlled pressure drop (DIC) technology. DIC is a hydro-thermo-mechanical process that applies auto-vaporization and pressure variation to improve the qualities of organic products, including food products, cosmetics, and pharmaceutical biopolymers. The DIC system consists of four main components of the mill: (a) a pressure drop valve that provides fast and regulated release of steam pressure; (b) a vacuum chamber, fifty percent larger than the extraction vessel; (c) an extraction vessel fitted with a heating jacket autoclave where the sample is treated; (d) an extract collection chamber used for condensate collection with the tank pressure kept at roughly 5 kPa by a water ring pump. DIC is a potential substitute for handling temperature-sensitive food powders such as apples and onions.[85] Instant controlled pressure drop (DIC) pretreatment has been recognized as a superior alternative to traditional drying methods, particularly for the extraction and texturization of vegetable materials. This technique involves a rapid transition from high pressure to vacuum, causing structural modifications in the plant matrix that enhance the release of target compounds. DIC pretreatment is especially effective for delicate fruits like strawberries, preserving their quality while improving extraction efficiency. Its ability to combine gentle processing with enhanced functionality makes DIC a valuable tool in the food and nutraceutical industries.[85] They also concluded that the strawberries dried using DIC contained higher phenolic compounds, total anthocyanins, and flavonoids than other treatments.

4.2.4 Enzyme-assisted extraction for the recovery of proteins and polyphenols. Proteins are present in watermelon seeds, and the extraction of these proteins can be improved by enzyme-assisted extraction (EAE). Cellulases and pectinase can be used to disrupt the seed cell walls so that bound proteins and polyphenols become accessible for extraction. EAE also improves the yield of these compounds by lowering the surface barrier to allow easier extraction of the compounds by the solvent. Each of the factors, such as the particle size and the enzyme-to-sample ratio, determines the polyphenol yield in enzymatic hydrolysis extraction. In this method, the sample is made up of enzymes, and the solvent is maintained at a low temperature in the range of 35–50 °C and the pH of the particular enzyme is controlled. Further, the hydrolysis process is stopped by inactivating the enzymes at 80–90 °C, which does not consume high energy as seen in the high-temperature extraction, which creates degradation. Knowledge-based process of extraction using enzymes is highly appreciated for its eco-friendliness since the enzyme works under controlled pH conditions and uses water instead of hazardous chemical solvents. However, the primary downside of EAE is the prolonged extraction time, which ranges from 3–48 hours.[85] This method is especially helpful for isolating bioactive peptides and polyphenols that have operational uses in nutraceuticals.[86]

4.2.5 Pulsed electric field extraction (PEFE) for polyphenols and proteins. Pulsed Electric Field Extraction (PEFE) is another emerging technique suitable for extracting proteins and polyphenols from watermelon seeds. PEFE weakens the cell membranes, facilitating the diffusion of the matrix and an enhanced solvent entry. This technique also reduces extraction time significantly and increases the amount of biologically active compounds like polyphenols, which are responsible for the antioxidant properties of the seed. PEFE is also cost-effective and has the advantage of energy efficiency; it is suitable for the extraction of sensitive compounds such as fatty acid profiles from watermelon seeds. Niu *et al.* (2021) revealed that the pulsed electric field (PEF) technology has proven to be a valuable tool in agro-industries, enhancing the selectivity and energy efficiency of extraction processes.[87] By applying short bursts of high voltage to plant materials, PEF disrupts cell membranes, facilitating the release of intracellular components. This method has shown promise as a complement or alternative to conventional thermal treatments, particularly in sugar extraction from sugar beets. Its ability to maintain product quality while reducing energy consumption positions PEF as a sustainable and innovative solution for modern extraction technologies. The yields of compounds from plant cells as colourants (carotenoids and chlorophyll), carbohydrates such as sucrose and polyphenols, and other secondary metabolites can be enhanced when plant cells undergo PEF treatment in combination with other methods.

According to the findings of a previous study,[88] PEF pretreatment assisted extraction has the potential to enhance

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sucrose concentration, enhance the filterability of the juice, and reduce the colloidal impurities as well as color of the produced juice. In the production of wine, PEF has been used before the maceration and fermentation step to control the polyphenol extraction and to give wines with specific organoleptic characteristics. As with prior treatment used in conventional vinification waste, the selectivity of anthocyanin extraction is extended, and colorant yields are optimized. Furthermore, mechanical expressions after moderate PEF treatments have been associated with enhanced yields in fruit juices and vegetable oils.

Experiments showed that PEF treatment does not have a detrimental effect on the taste or flavor of the extracted oil while obtaining slightly cloudy but highly aromatic apple juice with increased polyphenol concentration.

4.2.6 High-pressure extraction (HPE) for lipids and phenolic compounds. High-Pressure Extraction (HPE) is ideal for extracting lipids and phenolic compounds from watermelon seeds. By maintaining solvents in their liquid state at high pressure, HPE enhances solvent penetration into the seed matrix, improving the extraction efficiency. This method is known for reducing both solvent use and extraction time while preserving the quality of sensitive bioactive compounds. HPE has shown promise in extracting high-quality oil rich in essential fatty acids and phenolic compounds with antioxidant properties from watermelon seeds.[89]

4.2.7 Ultrasound-assisted extraction (UAE) for oils and antioxidants. Ultrasound-Assisted Extraction (UAE) is highly effective for extracting oils and antioxidants from watermelon seeds. Ultrasound waves create cavitation, which causes cell breakage, and the mass transfer increases.[90] UAE has been demonstrated as an efficient technique for extracting valuable compounds from watermelon seeds. This method significantly reduces the extraction time and the quantity of solvent required, making it a sustainable and cost-effective approach. UAE is particularly effective in recovering oils rich in unsaturated fatty acids, antioxidants, tocopherols, and phenolic compounds from watermelon seeds. This shows its potential in producing high-quality extracts for food, nutraceutical, and cosmeceutical applications. UAE is especially advantageous in recovering heat and oxidation-sensitive bioactives from foods.[91]

If done alongside other extraction approaches, ultrasound has been found to be very viable. It enhances heat and mass transfer rates, hence appropriate in extraction and complimenting other technologies.[92] A previous study showed that ultrasound with the assistance of pressurized liquid extraction (PLE) is efficient for the extraction of phenolic compounds from pomegranate peels to promote the extraction of bioactive compounds.[93] Yields increased under ultrasound treatments particularly if particle sizes were large with temperatures of 70–80 °C and ultrasound power of 480–640 W. Combined with PLE, UAE made the utilization of water as a solvent possible and shortened the extraction time. The most studied techniques included supercritical fluid extraction (SFE) and ultrasonic extraction. The influence of ultrasound on the antioxidant extraction from agave bagasse by SFE enhanced the antioxidant extraction yield when applying more than one transducer.[91] Co-acoustic extraction using ultrasound and SFE yielded 70% more antioxidant and 200% more saponin extraction than the control. They also discovered that the arrangement of the ultrasound transducers heightened the intensification effect of SFE processes in the geometry of the transducers.[91]

In the case of high-quality product processing, particularly when focusing on phenolic compounds and essential oils, it is more advantageous to use multiple extraction methods. These integrated approaches not only enhance the extraction of phenolic compounds but also offer novel alternatives for obtaining bioactive compounds from natural sources. For example, bioactive compound extraction from peppers has been reported.[94] They first used SFE to remove nonpolar fractions, followed by recovering phenolic compounds from Biquinho peppers through PLE.

5 Therapeutic potential of watermelon seed bioactive compounds

Watermelon seeds have garnered attention for their diverse bioactive potential, contributing to various health benefits (Table 2). Here is an overview of their key bioactive properties.

5.1 Antioxidant activity

Watermelon seeds have demonstrated excellent antioxidant capacity (Table 2) and are significantly capable of reducing free radicals. Various studies have reported the antioxidant effects of watermelon seeds and specific focus has been placed on different seed types, including Charleston gray, Crimson sweet, and Black diamond seeds. These varieties showed rich scavenging capability by evaluating the DPPH radical scavenger activity, which was found to be 59.88%, 94.46%, and 70.06%, respectively. A higher concentration of watermelon seeds has a linear relationship with an enhancement of the scavenging activity of up to 90% at 1000 μg mL^{-1} of concentration.[7,101] Moreover, the flour produced from watermelon seed undergoing a blending process exhibited strong antioxidant activity, adopting the ABTS and DPPH tests.[102] These *in vivo* studies have also shown that watermelon pulp and seed extracts increase the SOD and catalase, which are useful in unfolding oxidative stress.[102] In addition, studies have shown that the watermelon seed proteins release antioxidant peptides for the protection of cells subjected to oxidative stress.[103] Several research studies underscore the abundance of citrulline in watermelon flesh, which is a nonessential amino acid with antioxidant capacity and is metabolized to arginine, which is anti-inflammatory in nature.[104–106] Employing this same concept with watermelon, a source that contains high amounts of vitamin C, a hydrophilic antioxidant, hinders the oxidation of iron and clears free radicals simultaneously.[107,108] It also suggests that its antioxidant ability outperforms strawberries, tomatoes, and guava, which means the levels of protection against inflammation and cancer.[10,109] Different fractions of watermelon seeds, especially those extracted by methanol, have been proven to possess high

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Table 2 Therapeutic potential of watermelon seed bioactives

Component	Characteristics	Therapeutic applications	Mechanism of action	Reference
Triterpenoid	Cucurbitacin E, anti-inflammatory effects	Alleviates inflammation; manages conditions linked to reactive nitrogen species	Inhibits cyclooxygenase enzymes; neutralizes reactive nitrogen species (RNS)	95
Glycosides	Non-sugar (aglycone) and sugar component	Exhibits anti-diarrheal properties; used as flavoring agents	Stimulates saliva and gastric fluid secretion; astringent effects from tannins	30 and 96
Saponins	High-molecular-weight, surface-active properties	Treats inflammation, menopausal symptoms, and cardiovascular issues	Induces hemolysis; toxic in excessive doses; soluble in water	30
Alkaloids	Nitrogen-containing compounds with notable bioactivity	Antispasmodics, analgesics, and antibacterial effects	Act as stimulants for the CNS and provide analgesic properties	97
Coumarins	Exhibit anticancer properties	Effective against abnormal cell growth in cancers	Induce apoptosis and inhibit cancer cell proliferation	98
Watermelon seed extracts	Extracts from inner (KI) and outer (KD) layers	Investigated for lung and breast cancer treatment	Dose-dependent cytotoxic effects, inhibiting tumor growth	99
Amino acids	Rich in essential amino acids (*e.g.*, phenylalanine, arginine, valine)	Dietary supplements for protein synthesis and tissue repair	Contribute to protein synthesis and metabolic processes	27
Phytochemicals and cations	Bioactive compounds and essential cations	Management of hypertension and cardiovascular health	Induces vasodilation, inhibit ACE, and enhance nitric oxide synthesis	31
Proteins, lipids, and antioxidants	High in proteins, lipids, vitamins, and minerals	Anti-diabetic, cardioprotective, anti-ulcerogenic, anti-obesity	Enhance insulin sensitivity, modulates lipid profiles, reduce oxidative stress	100

antioxidant effects and can be exploited in future nutraceutical markets.[109,110]

5.2 Hypoglycemic and hypolipidemic properties

Watermelon seed extracts have been studied for their potential to manage glucose levels and lipid profiles. These extracts have been found to have the potential to suppress the alpha-amylase and alpha-glucosidase effects, which in turn help to assist insulin release from the pancreatic beta cells.[4] Studies on diabetic rats have shown an enhanced flow of serum glucose and improved lipid profiles with the addition of watermelon seed kernels, which suggests the kernels could be used as a hypoglycemic and hypolipidemic substance. Additional studies corroborate these findings, and data shows that using seed extracts positively influences plasma glucose levels in diabetic rats, thereby enhancing general lipid pmettabolism.[111]

5.3 Anti-inflammatory properties

Watermelon seeds exhibit remarkable anti-inflammatory properties, as demonstrated in studies assessing their ability to stabilize human red blood cell membranes and prevent tissue damage. Methanolic extracts of watermelon seeds have shown a significant protection percentage of 74.8%, while aqueous extracts results are not very different from methanolic extracts, albeit to a lesser extent. Watermelon seed extracts have almost similar anti-inflammatory effects to aspirin, and extracts have a tendency to inhibit albumin denaturation. The carotenoid pigment, lycopene present in watermelon seeds and its juice, is a lipid-soluble antioxidant that can significantly decrease inflammation and cholesterol and can also protect against cancer.[30] Watermelon seed extracts, particularly those obtained using methanol as a solvent, have demonstrated significant antioxidant potential. These extracts contain bioactive compounds capable of neutralizing free radicals and preventing oxidative stress. Such properties make them promising candidates for applications in the nutraceutical industry, where they can contribute to the development of functional foods and supplements aimed at promoting health and preventing diseases linked to oxidative damage.[109] The use of watermelon rind as a source of antioxidants and anti-inflammatory has also been supported in various research studies, where rind extracts improved lipid profiles and exhibited anti-inflammatory effects in animal models.[112]

5.4 Antibacterial and antifungal activity

It is well established that watermelon seeds possess strong antimicrobial activity and can be used as replacements for normal antimicrobial substances. Consequently, the inhibition of various bacterial and fungal strains is attributed to secondary metabolisms such as flavonoids, tannins, and saponins.[88,113] It has also been observed that methanolic and aqueous extracts of watermelon seed inhibit the growth of *Staphylococcus* species; this explains the antimicrobial activity of the seeds whereby flavonoids saponin and tannin bioactive compounds have been established to inhibit bacterial as well as fungi.[114]

Also, the aqueous partition of watermelon seed showed the presence of bioactive compounds using cold and hot water, ethanol, and methanol, which exhibited antimicrobial activities

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against bacteria and fungi.[4,115] Antimicrobial activities in chloroform extracts were accelerated due to the presence of watermelon antioxidants, type of phenols, flavonoids, tannins, and saponins. It has been considered that lycopene has antioxidant activity,[4,113] but it has also been established that it has antimicrobial activity.[116,117] Ethyl acetate-treated watermelon seed extracts showed remarkable activity against *S. aureus*, *P. aeruginosa* and *Klebsiella* species.[118] It is also pointed out that melanin has antibacterial effects.[119]

5.5 Anticancer properties

Research reveals that watermelon seeds can act as anticancer agents, particularly for gastric and breast cancers. Research has further shown that watermelon seed extract possesses cytotoxic effects on gastric cancer cells with the IC50 value of 453.76 μg mL^{-1} after 24 h.[120] Studies performed on MCF-7 breast cancer cells and vaginal melanoma cancer cells also underline these findings, arguing that both watermelon pulp and seed extracts reduce cancer cell proliferation while simultaneously exhibiting high selectivity towards cancer cells.[102] One of the benefits of consuming seeds is that they contain antioxidants that can destroy cancer cells. Lycopene found in watermelon has been researched widely for its ability to slow down tumor progression and inhibit cancer in various organs.[121] This compound inhibits cancer cell growth and carcinogenic activity, and it has been found that the intake of the lycopene substance can also mitigate the negative impacts of cancer treatments like radiotherapy.[122,123] Citrullus violaceus seeds are also abundant in β-carotene and other phenolic contents that enhance this fruit's anticancer agent.[124]

5.6 Anti-ulcer properties

Watermelon seeds also exhibit anti-ulcer properties, as demonstrated in studies involving albino Wistar rats. Methanolic extracts of watermelon seeds significantly reduced ulcer indices in both pyloric ligated and water immersion stress-induced rats and were almost at par with standard drugs like ranitidine and omeprazole.[125]

5.7 Cardio-protective effects

The nutrients, phytochemicals, vitamins, minerals, and water in the watermelon enhance cardiovascular health due to the presence of lycopene, beta-carotene and unsaturated fatty acids, acting as both antioxidants and anti-inflammatory compounds. Some of these compounds aid in decreasing the chances of CVD by bringing down inflammation and stressful oxidation.[30,126] The cardio-protective effects of watermelon seeds are credited to the presence of citrulline, arginine, and lycopene in watermelon juice, which enhances vasodilator to relax and widen blood vessels, hence reducing hypertension and high blood pressure.[127] Watermelon extract helps obese adults lower their blood pressure, thus lowering the risk of hypertension. Also, potassium found in watermelon has been acknowledged to regulate heartbeat and healthy blood pressure levels due to research done previously.[128] In the same vein, the watermelon seed oil's antioxidants help prevent chronic diseases like CVDs; more *in vivo* studies show that watermelon seed extract can prevent heart diseases by lowering specific heart disease indices.[70,95]

5.8 Hepatoprotective properties

Non-alcoholic fatty liver disease (NAFLD) can originate from simple steatosis, and if left untreated, it may progress to non-alcoholic steatohepatitis (NASH). It is indicated by smooth hepatocellular damage and may result in cirrhosis.[129,130] Chronic liver injury is characterised by inflammation and lobular ballooning; it progresses to cirrhosis, the most serious and irreversible stage of the disease, whereas NAFLD and NASH are fully reversible if diagnosed early.[131] To date, only lifestyle interventions have been identified to reverse NAFLD and these include a change in diet and use of supplements.[132–134] It was observed that watermelon seed extract has the potential to prevent hepatic oxidative stress and protect the liver. Studies have shown that treatment with these extracts helps to lower the levels of such biomarkers of oxidative stress as aspartate amino-transferase (AST), alanine amino-transferase (ALT) and alkaline phosphates (ALP) in models of ethanol-induced hepatotoxicity. Further, the extracts have been shown to effectively scavenge the H_2O_2-induced oxidative injury of HepG2 cells and reduce inflammation and hepatocyte damage in acetaminophen administration models.[103] Furthermore, watermelon seed oil has the potential to prevent the liver from oxidative stress and improve hepatic enzymes in animal models.

5.9 Nephropathy

Chronic kidney malfunctions frequently indicate kidney diseases, usually termed chronic kidney disease (CKD) or end-stage renal disease (ESRD). These conditions are inexorable and cumulative and subsequently will build up gradually and persist. The main factors are hypertension, diabetes mellitus, interstitial nephritis and chronic pyelonephritis, secondary glomerulonephritis, congenital conditions including cystic diseases, and vasculitis. Chronic renal failure (CRF) is the stage of chronic kidney disease in which kidney dysfunction is irreversible and progresses to a low glomerular filtration rate accompanied by a steady increase in plasma creatinine concentration.[134]

The progression of CRF is marked by three main stages: decreasing kidney performance, ESRD and kidney failure. Some of the significant factors that dictate the progression are the degree of proteinuria, hypertension, and compromised renal function. It has been shown that patients developing proteinuria or hypertension have a shorter duration of the disease.[31] Research carried out reveals that lycopene possessing biochemical and histopathological effects prevents the occurrence of kidney disease.[27,135] However, it is also beneficial to have other compounds combined with lycopene, including arginine and citrulline, found in watermelon. Arginine-packed nutritional products are especially beneficial to patients diagnosed with kidney failure. Arginine normalizes the vasoconstrictor effect of dimethylarginine, a non-NO substrate implicated in the pathogenesis of renal diseases. The explicit

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regulation of these biochemical pathways suggests that arginine supplementation may benefit kidney-related diseases.[136,137]

Watermelon seeds have therapeutic potential against hyperuricemia, as evidenced by studies on potassium oxonate-induced hyperuricemic albino rats. It has been found that the watermelon seeds have the potential to decrease uric acid, creatinine, and urea however globulin, albumin and total level of serum proteins reduce the activity of xanthine oxidase enzyme.[138] This means that in addition to reducing kidney inflammation, the diuretic nature of watermelon seeds may prevent the formation of kidney stones as well as promote regular bowel movement, and hence the name diuretic.

5.10 Improvement in reproductive health

Watermelon seeds have been found to improve reproductive health, especially male fertility. The number of sperms in a sample and its motility and viability in Wistar rats increased by the administration of hydroalcoholic extracts of watermelon seeds, as revealed by Khaki and his team in their study. Also, these extracts have effectiveness against toxicity-mediated reproductive health complications, sexual viability, and benign prostatic hyperplasia, and experimental models have demonstrated shrinkage in size and weight of the prostates.[139] The seeds contain arginine and phenolic compounds, which may contribute to their potential effectiveness in addressing erectile dysfunction.[96]

5.11 Neurological disorders

Lycopene and its metabolites have been identified in the brain, where they are expected to have neuroprotective effects. Several studies have endorsed the potential of lycopene in treating psychiatric and neurodegenerative diseases.[140] Lycopene also reduced Aβ-induced cellular toxicity in cultured neurons in tau transgenic mice expressing the P301L mutation.[140] This finding is based on a study that showed lycopene possesses the potential to mitigate motor dysfunction and learning disability, which are features of HD in animal subjects caused by 3-NP, which inhibits succinic acid dehydrogenase. Similarly, a study conducted on a PD model demonstrated that lycopene has the potential to suppress motor dysfunction resulting from MPTP, a compound that produces PD-like manifestations. It was also established that lycopene has neuroprotective effects against CNS disorders by decreasing oxidative stress and bioactive molecules influencing signal transduction cascades, including activation of protein kinase B, phosphatidylinositol-4,5-bisphosphate 3-kinase, adenosine 5′ monophosphate-activated protein kinase and peroxisome proliferator-activated receptor-γ.[68]

5.11 Analgesic properties

The vibrant red color of watermelon is attributed to substantive doses of lycopene present in it, which accounts for its analgesic attributes. The antinociceptive effect of watermelon seed extracts has also been investigated through *in vivo* approaches, suggesting their potential as functional ingredients in the formulation of pain-relieving products.[30,112]

6. Applications of water melon seeds

Watermelon seeds are rich in phytochemical compounds and high unsaturated fatty acids, demonstrating significant biological activity, particularly in combating free radicals.[15] Due to these properties, watermelon seeds are considered valuable economic ingredients with potential applications across various industries, including food, cosmeceuticals, and nutraceuticals. The seeds have the highest oil content among their components, followed by protein, making them particularly useful in food products where these nutrients are desirable. In food applications, the protein and phytochemical contents are often emphasized, while the high unsaturated fatty acids and phytochemicals make them attractive for cosmeceutical uses. By harnessing these beneficial properties, watermelon seeds can be effectively utilized in commercial products, offering a range of health and nutritional benefits.

6.1 Food applications of water melon seeds

Watermelon seeds are widely used in food applications due to their rich protein (14–30%) as well as oil (40–50%) content. After the extraction of oil from watermelon seeds, the rest of the defatted watermelon seed meal, which is highly rich in proteins, can be used. In several areas of Africa, Arabia, India and Asia, salted and roasted watermelon seeds are consumed as snacks and are used in confectionery.[70] The seeds provide high-quality proteins and can be used as protein supplements in food manufacturing (Table 3). For example, watermelon seed kernel flours have been used in the production of biscuits for people with gluten intolerance as well as low-carb consumers. Not only does the addition of toasted watermelon seed flour increase the protein quantity of these biscuits, but it also gives unique flavours and structures.[148] According to a previous study,[149] there is a possibility of using WSF at 5% as a functional ingredient that can boost the nutritive value of low-carbohydrate, high-protein bread for the elderly and active people.

Apart from biscuits, watermelon seed flour has also been used in bread, fortification leading to a drastic increase in bread proteins, iron, calcium, potassium and phosphorus content without negative effect on bread sensory attributes as noted previously.[150] With some applications, the complete watermelon seed matter, including the oil fraction, is employed. Spray drying is commonly used to change watermelon seeds into a powdery form to enhance their applicability in various foods. The dehulled watermelon seed flour has also been used as a margarine substitute in the cookies, improving the functional properties such as water and oil absorption.[24]

The oil extracted from watermelon seeds contains essential and unsaturated fatty acids, such as linoleic and oleic acids, which are conspicuous and beneficial for frying and cooking processes across Africa and some parts of the Middle East due to their unique flavor.[70] The seeds are eaten in Nigeria, such as Ootanga, and the extracted oil is known as Kalahari oil.[151] Another new product is watermelon seed milk; the work indicates this product's potential to be used as a partial replacement for cow's milk in yogurt production. The biochemical

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Table 3 Application of watermelon seeds in the food industry

Food products	Processing	Results	References
Fortified bread	0, 15, and 25% watermelon seed flour in wheat flour	Nutrient content (protein, iron, calcium, potassium, phosphorus) increased significantly; sensory attributes unchanged	141
Brown rice-watermelon seeds snacks	90% brown rice flour, 10% watermelon seed powder, 120–140 °C, 300–420 rpm	Protein content increased; phenolic content enhanced; intermediate glycemic index	142
Watermelon seed extruded snacks	Rice-corn flour blend with 10%, 15%, and 20% seed flour	Maintained quality over 90 days; favourable proximate composition and sensory attributes	143
Toasted watermelon seed meal biscuits	Composite flour with toasted seed meal	Increased protein, fat, crude fiber, and ash content; desirable sensory attributes	144
Cookies with watermelon seed flour	Substituting wheat flour with seed flour at 0%, 10%, 20%, 30%, 40%	Higher protein, fat, and fiber; favourable sensory evaluations across formulations	145
Bread from wheat-watermelon seed flour	Blends of wheat and watermelon seed flour	Bulk density, water absorption, oil absorption, moisture, and protein content varied; preferred blend noted	146
Ice cream	Milk fat and solid substitution with seed flour	Increased fat, protein, total solids; best sensory quality at 10% substitution	147

compositions of yogurt made from watermelon seed milk and those of the control cow's milk yogurt show that the milk yogurt contains 2.72% more total solids, 2.25% more ash, 1.78% more fiber content and 1.5 times more bioactive compounds than control yogurt. It also possesses a high antioxidant potential and is a better option.[123]

Watermelon seeds have also been used in ice cream as fat replacers because they have a high fat content, which gives a creamy texture to the final product. Watermelon seed flour-added ice creams contain higher fat and protein compared with cow's milk ice cream but this product may experience lower viscosity since the seeds contain unsaturated fatty acids. In traditional Nigerian snack foods – "robo," watermelon seeds add up to amino acid contents, vitamin, and minerals content.[152] Also, fermented condiments with watermelon seed pulp contain higher fat and protein compared to its seed flour and improved as an additive for soup thickeners, like increasing water and oil absorption capacity as well as calcium and thiamine content as postulated.[151,153]

6.2 Nutraceutical applications of watermelon seeds

Watermelon seeds are rich in essential fatty acids, proteins, minerals, and bioactive compounds, and they are becoming a promising source for nutraceutical supplementation. Unsaturated fatty acids, especially oleic and linoleic acids, which are good for the heart, are present in large amounts in these seeds. Watermelon seeds have a high concentration of antioxidants, including flavonoids and phenolic compounds, which help prevent oxidative stress and free radical damage linked to chronic illnesses like diabetes, cancer, and cardiovascular disease. The Na/K ratio of watermelon seeds varies from 0.06 to 0.29, depending on whether the values are for the whole, peeled, or skinned seed. Because of this lower Na/K ratio, watermelon seeds may help lower blood pressure and other cardiovascular diseases such as hypertension.[154] Furthermore, a previous study [70] identified the presence of phytosterols in watermelon seed oil, including β-sitosterol, camp sterol, and stigmasterol.

Watermelon seeds have a particularly noteworthy protein content when it comes to nutraceuticals. They are an important source of protein, particularly for plant-based diets, since they offer the full spectrum of essential amino acids. The minerals magnesium, potassium, and iron, which are abundant in the seeds, support a number of body processes, including the health of the bones, muscles, and oxygen transport. Watermelon seed protein has been shown to contain antioxidant peptides with pharmaceutical properties. After the purification of five peptides, it was found that peptide RDPEER protected HepG2 cells against H_2O_2-induced oxidative damage by decreasing ROS, raising antioxidant enzyme levels, and decreasing the amount of malondialdehyde (MDA).[23,155] Watermelon seed meal was utilized to make a defatted flour and a protein isolate.[52] They concluded that watermelon seeds are a good source of protein, although they have moderate quality, with methionine and cysteine identified as the limiting amino acids. The bioactive compounds present in watermelon seeds, including cucurbitacin, have shown anti-inflammatory, antioxidant and anti-cancer properties in preliminary studies. These properties make watermelon seeds a powerful nutraceutical ingredient with the potential to support overall health and prevent various chronic conditions.[30]

7. Conclusion

Watermelon seeds, often regarded as agricultural waste, hold immense potential as a source of essential nutrients and

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bioactive compounds. The present review highlights the pharmacological prospects of watermelon seeds, such as their antioxidant, antimicrobial, antimutagenic, hypoglycemic and anti-inflammatory effects and importance to human health. This review discusses various extraction methods that have not been utilized fully in the current healthcare practices, reviews their working mechanisms, and highlights the huge research space involved in the medical research of these by-products. The proposed revalorization of watermelon seeds shows potential for generating innovation in food processing and nutraceutical and cosmeceutical sectors and can contribute towards sustainability and a circular economy. However, the limitations, including variation in the composition of seeds, technology for extraction, and safety of bioactive extracts, remain problematic in order to popularize bioactive compounds.

Further studies should also emphasise how to improve extraction methods to become consistent, confirm the safety and effectiveness of the products from watermelon seeds and search for other opportunities for their usage to come into full effect. Therefore the changing the perspectives of these by products from waste to potential resources, watermelon seeds have a great significance to positively influence human health and act as a push for paving way for sustainable food processing.

Consent form

No animal and human studies were conducted as this is a review article.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Conflicts of interest

There is no conflict of interest between the authors.

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