applied sciences

MDPI

Review

Recent Advances in the Antibacterial Activities of *Citrullus lanatus* (Watermelon) By-Products

Vassilis Athanasiadis, Theodoros Chatzimitakos, Dimitrios Kalompatsios, Konstantina Kotsou, Martha Mantiniotou, Eleni Bozinou and Stavros I. Lalas *

Department of Food Science & Nutrition, University of Thessaly, Terma N. Temponera Street, 43100 Karditsa, Greece; vaathanasiadis@uth.gr (V.A.); tchatzimitakos@uth.gr (T.C.); dkalompatsios@uth.gr (D.K.); kkotsou@agr.uth.gr (K.K.); mmantiniotou@uth.gr (M.M.); empozinou@uth.gr (E.B.)
* Correspondence: slalas@uth.gr; Tel.: +30-24410-64783

Abstract: Watermelon (*Citrullus lanatus*) is a popular fruit worldwide due to its refreshing taste and its high water content (92% of its weight). According to the phytochemistry of the plant, carbohydrates, saponins, glycosides, steroids, alkaloids, polyphenols, flavonoids, and tannins can be detected in watermelons. *C. lanatus* generates by-products and, as such, can be characterized by its seeds and rinds. These by-products' phytochemicals are nutritious and functional. Watermelon seeds contain many phytochemical compounds with beneficial biological activities, according to numerous scientific studies. This fact promotes watermelon seed consumption and encourages food and pharmaceutical companies to use this innovative ingredient. The watermelon rind has all the nutrients of the pulp and also more antioxidants, minerals, vitamins, and bioactive substances. Numerous studies show that watermelon peel is high in fiber and nutrients and can be used in a variety of culinary products. These residues need to be utilized for creating innovative functional food products with added value for the food chain's sustainability. More studies of watermelon by-products are required to promote functional food, nutraceutical, and pharmaceutical applications. This review aims to shed light on the underutilized portion of watermelon and its chemical properties in order to pave the way for future research.

Keywords: Cucurbitaceae; watermelon; peel; rind; seed; extract; antibacterial activity

Citation: Athanasiadis, V.; Chatzimitakos, T.; Kalompatsios, D.; Kotsou, K.; Mantiniotou, M.; Bozinou, E.; Lalas, S.I. Recent Advances in the Antibacterial Activities of *Citrullus lanatus* (Watermelon) By-Products. *Appl. Sci.* **2023**, *13*, 11063. https://doi.org/10.3390/app131911063

Academic Editor: Monica Gallo

Received: 20 September 2023
Revised: 4 October 2023
Accepted: 6 October 2023
Published: 8 October 2023

1. Introduction

The Cucurbitaceae family is considered to be the most extensive family, encompassing a total of 120 genera and an estimated 825 species [1]. These plants are mainly found in tropical areas, with limited representation in temperate regions. The vegetable crops belonging to the Cucurbitaceae family hold significant importance as horticulture crops, mostly cultivated for their succulent and delicious fruits in various warm regions across the globe [2]. *Citrullus lanatus*, commonly known as watermelon, is classified as a distinct type of berry, characterized by its spherical or oblong shape [3,4]. Its diameter typically ranges from 30 to 60 cm, while the thickness of its peel varies between 10 and 40 mm. The fruit in question exhibits a dark green hue, frequently adorned with white marbling, while its inner flesh displays a vibrant range of red and yellow tones. The presence of carotenoids, specifically β-carotene and lycopene, is responsible for the coloring of the watermelon [5]. Watermelon, commonly consumed throughout the summer, is widely valued by individuals for its sweet flavor and invigorating properties. This is due to its high water content, which is approximately 92% of its total weight [6]. The fruit is utilized in the preparation of jam and juice, and the rind is also subjected to pickling [7]. As depicted in Figure 1, the fruit consists of four basic parts. These are the skin or peel, which corresponds to the outermost layer of the fruit; the rind or exocarp, which is the green and white outer part of the fruit; the flesh, which consists of the endocarp and mesocarp and is the edible

and colored part of the fruit that contains the juice primarily; and the seeds, which are typically discarded when consuming the fruit [6].

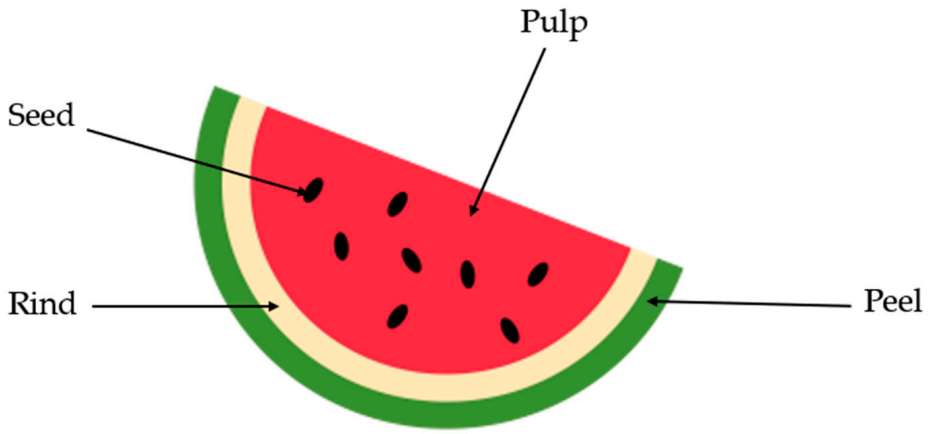

Figure 1. Watermelon anatomy.

Carbohydrates account for 7.6% of the fruit's composition. Within the carbohydrate content, sugars make up 6.2%, and dietary fiber constitutes 0.4% of it. Watermelon is devoid of lipids and cholesterol. Hence, it may be inferred that this particular fruit possesses a relatively low caloric content while exhibiting a high sugar content. Additionally, this food item serves as a valuable source of β-carotene, an antioxidant compound that acts as a precursor to vitamin A [8]. The fruit is rich in amino acids, including citrulline and arginine, which are present in high proportions. It also contains carotenoids, with the red-fleshed form having an extraordinarily high content of lycopene and the yellow-fleshed kind containing β-carotene. Additionally, watermelon contains phenolic compounds, more specifically 2.6 ± 0.3 mg gallic acid equivalents (GAE)/100 g in rind, as determined by Neglo et al. [9], and 89.5 ± 0.06 mg GAE/100 g in seed oil, as stated by Ouassor et al. [10]. Watermelon is a fruit that contains numerous minerals, such as calcium, potassium, magnesium, and iron. Furthermore, it is well acknowledged as a valuable source of vitamins A, E, C, and B complex. The by-products of the fruit also contain valuable components. Watermelon seeds include substantial quantities of proteins, lipids, carbohydrates, ash, and minerals. Hence, seeds are considered to be a valuable source of nutrition and may also possess significance in relation to their fiber, mineral, and phenolic compositions, thereby contributing to both health advantages and economic value [7,8]. The composition of watermelon rind mostly consists of celluloses, hemicelluloses, pectins, and lignins, along with entrapped sugars, lycopene, carotenoids, citrulline, and phenolics [11]. The watermelon rind extract demonstrates antioxidant and antibacterial properties because of the presence of polyphenols.

The plant itself has been utilized for ages in the traditional treatment of diverse health conditions. In particular, it holds significant medical value within the Ayurvedic and Indian traditional systems of medicine. Watermelon is a fruit that possesses nutritional properties, including minerals and bioactive compounds that have ethnomedicinal advantages for human health [12]. Among them, the antibacterial activity of watermelon has gained popularity lately [13]. Due to their high value and potential as viable additions to the human diet, watermelon by-products with substantial nutritional value have attracted significant attention. Utilizing watermelon rind and watermelon seeds as a cost-effective raw material holds promise due to their abundance and potential to contain valuable components that can be utilized in various industries [14,15]. The objective of this review is to examine the current state of research pertaining to the antibacterial properties of watermelon by-products.

2. Antibacterial Activities

Polyphenols are abundant in plant extracts and are frequently acknowledged as antioxidants, but they can also be classified as antimicrobials. These compounds demonstrate inhibitory properties against both bacteria responsible for food spoilage and pathogens that might cause food-borne illnesses [16]. In recent years, there has been a shift among the scientific community towards the utilization of this kind of antibacterial compound. The excessive use of antibiotics has led to the emergence of bacteria that are resistant to multiple drugs, necessitating the development of more potent or intricate antibiotic compositions to effectively combat them [17,18]. The notion of distinguishing between bactericidal and bacteriostatic medicines has proven to be effective in differentiating antibiotics that have the ability to kill bacteria, known as bactericidal, from antibiotics that just suppress bacterial growth, referred to as bacteriostatic. The principle that distinguishes the two types of antibiotics is that bactericidal medications possess a greater capacity for antibacterial activity, enabling them to effectively eradicate bacteria. Another way to fight bacteria is by damaging their biofilm. Biofilm is a term used to describe clusters of microbial cells that are enveloped by bacterial extracellular polymers. The process of biofilm creation encompasses three key stages: bacterial adhesion, biofilm development, and maturity. Additionally, the process of biofilm formation has the potential to enhance the resistance of bacteria against drugs and mechanical damage [19,20]. Biofilms consist of a diverse array of polymers, including alginate, exopolysaccharides, and proteins. In contrast to planktonic growth, biofilms have been found to enhance the resilience of the host immune system against antibiotics and provide a significant challenge to clinical therapy [21].

There are several antibacterial mechanisms, such as inhibition of cell proliferation, inhibition of nucleic acid synthesis, inhibition of energy metabolism, attenuation of pathogenicity, reduction in biofilm formation and cell adhesion, and damage to membranes possibly by producing hydrogen peroxide [22]. The process of suppressing cell proliferation involves the inhibition or destruction of a critical cellular organ, resulting in the suppression of cell proliferation. This inhibition can be achieved through many mechanisms. Several methods of action can be employed to achieve desired effects, including the inhibition or destruction of enzymes and proteins [23–25], tissue-specific inhibition [26], the cell autophagy signaling pathway [27], the utilization of long non-coding RNA (lncRNA) [28], as well as the application of extracts or drugs that impede certain cellular functions [29–31]. More specifically, Buranrat et al. [24] proved in their study that the *Oroxylum indicum* extracts inhibit the growth of MCF-7 cells. In another study, Mo et al. [28] discovered that the liver-specific lcRNA FAM99B was downregulated in hepatocellular carcinoma tissues relative to adjacent normal tissues. There are additional antibacterial assays that function by blocking the production of nucleic acids, specifically DNA and RNA [32–38]. Consequently, these agents disrupt regular cellular processes as well as their proliferation, ultimately resulting in cell death. Another effective way to fight bacteria is by inhibiting energy metabolism [39–46]. A Metabolic Inhibitor diminishes enzymatic activity by typically forming a relatively weak interaction with the enzyme. This pertains to competitive inhibitors. Enzymatic productivity can be diminished by impeding the entry of substrates into the active sites.

The detection of bacterial pathogens from clinical samples in clinical microbiology is predominantly dependent on culture-based methods. Historically, culture has been conducted with agar-based media of a generic nature (e.g., blood agar) that could facilitate the proliferation of a broad spectrum of pathogens. The virulence of a microorganism is determined by various factors, including the presence of specific species, strains, or genes, as well as their relative abundance. Hence, the differential proliferation of a single microorganism can lead to the transition of additional microorganisms into or out of a harmful state. This is called attenuation of pathogenicity, and it is widely utilized nowadays [47–54]. Another effective antibacterial method is the inhibition of biofilm development and cell adhesion [55–64]. The subsequent phase of biofilm formation is distinguished by the gathering of cellular aggregates on the surface [65]. The current stage is seemingly facilitated by a polysaccharide antigen that enhances intercellular adhesion.

The implementation of anti-adhesive surfaces has been shown to effectively mitigate the adhesion of bacteria to solid surfaces, thereby facilitating the elimination of germs prior to their adherence and subsequent multiplication. Finally, comes the damage to membranes by producing hydrogen peroxide [66–75]. Hydrogen peroxide (H_2O_2) is an oxidizing agent that, when present in excessive quantities, leads to cellular damage. This oxidative stress disrupts normal cell cycle progression, resulting in cell death. Emerging research suggests that hydrogen peroxide has the capacity to promote the progression of the cell cycle by oxidizing specific thiol proteins.

3. Extraction Methods

The investigation of extracting bioactive compounds from food wastes has been undertaken using a range of classical or, else, conventional techniques [76]. Among the conventional extraction techniques is Soxhlet extraction [77], which was initially established by Fraiz Ritter Von Soxhlet for the extraction of lipid and fat from food matrices [78,79]. Since then, Soxhlet extraction has been widely employed for the extraction of many compounds, and as such, Soxhlet extraction is widely recognized and commonly used as a benchmark method for evaluating alternative extraction methods [80]. The utilization of the Soxhlet extraction technique employing liquid solvents is widely regarded as a highly effective approach for the isolation and purification of bioactive chemicals derived from natural sources. This can be attributed to the use of heat during the extraction process, which enhances the solubility of compounds that are otherwise insoluble at room temperature (RT). Consequently, the extraction efficiency is significantly improved, leading to a more pronounced extraction of the desired compounds [81]. The Soxhlet extraction method has been employed for numerous decades, exhibiting a considerable time requirement and necessitating substantial volumes of solvents. The procedure also demands the utilization of specialized equipment known as a Soxhlet extractor [82]. Another often employed technique for extraction in this context is cold maceration. Maceration is also a conventional extraction technique [83,84]. Maceration is a widely used method for solid-liquid extraction in which the sample is subjected to prolonged contact with a solvent, either at ambient or elevated temperatures, with or without agitation. This process continues until all the bioactive compounds included in the sample are fully dissolved in the solvent [85]. The practice of implementing a maceration step before fermentation is commonly referred to as cold maceration or cold soak [86]. The application of elevated temperatures during thermo-maceration leads to cellular disintegration, which can have detrimental effects on sensitive compounds, including anthocyanins [87]. In contrast with Soxhlet extraction, cold maceration is a straightforward technique that does not necessitate any specialized equipment. This is achieved without compromising the integrity of the thermolabile chemicals found in the fraction, thanks to the utilization of low extraction temperatures, which is comparable to the technique of cold pressing [82]. Furthermore, extraction procedures, like magnetic stirring, are conducted within a framework of diffusion-controlled conditions. The rate-controlling step of diffusion occurs within the boundary layer between the bulk solution and extractant phase. This process can be augmented by employing effective agitation of the solution. In practical applications, the process of stirring can be executed using an external apparatus, aided by an external power supply, or by including the extraction and stirring components within a single device [88]. The compact rotating rotor possesses the ability to effectively blend fluids with varying viscosities by maintaining a consistent low rotational speed. The magnetic stirrer is employed for cell lysis due to its excellent mixing efficiency [89]. The utilization of magnetic stirring enhances the stability of the turbid condition and expedites the transfer of mass from the aqueous solution to the extraction solvent [90]. The conventional approach for dispersing soil particles involves mechanical shaking, which leads to the generation of significant mixing and turbulence at a macroscopic level. This process facilitates increased physical contact among the particles, with the extent of contact being dependent on the intensity of the mixing. Nevertheless, the utilization of mechanical shaking necessitates additional electrical energy input and

is associated with prolonged duration, potentially resulting in increased expenditure [91]. The mechanical shaking method appears to be a viable alternative to the Soxhlet method due to its simplicity, speed, cost-effectiveness, and suitability [92].

4. Antibacterial Activities of *Citrullus lanatus* By-Products

4.1. Rind and Peel

The first survey of the current topic was carried out by Othman et al. [93]. The aim of the study was to investigate the applicability of using local watermelon rind modified with clove as an adsorbent for microorganisms and toxic heavy metals in wastewater. Watermelons purchased from a local fruit market were washed with tap water, and the rind was removed and left to dry in the sun. In the rind studied, metals were removed (by injection with 5% HNO_3), and pH 6.5–7.5 was ensured by washing with water at 60 °C. The sample was composed of dried rind, which was boiled with the clove extract. For antibacterial evaluation (population of total coliform and *Escherichia coli*), a batch method of varying the mass of modified watermelon rind in three different masses of 3, 5, and 7 g of the sample was used. Specifically, 100 mL of wastewater was mixed with a modified biosorbent, and the mixture was shaken for 24 h in aerobic conditions at 125 rpm at RT. Observing the results, the total coliform (TC) and *E. coli* populations were found to be 89×10^6 for the former and 68×10^6 for the latter. By using 5 g of clove and 3 g of rind for the preparation of extracts, the population decreased to 1000 for TC and 200 for *E. coli*. Keeping the mass of clove constant, when 5 g of rind was used, the population decreased even more, to 200 for TC and 40 for *E. coli*, while at the same time, when the amount of watermelon rind was 7 g, the microbial population was detected only for TC, while the action of *E. coli* was completely inhibited. In conclusion, when clove was increased to 7 and 8 g in the extracts, the population of TC and *E. coli* was intercepted entirely, indicating that adding herbs was of great significance because it significantly increased the antibacterial activity of the rind extract. Furthermore, in this research, it was shown that the rind of watermelon itself has antibacterial properties since increasing its amount enhanced the control of bacterial activity.

In addition, *C. lanatus* peel is often reported to possess a wide range of antibacterial properties since it contains terpenoid, alkaloid, flavonoid, saponin, tannin, terpenoid, and phenolic compounds, whose main role is to protect and defend plants against bacteria [94]. However, the initial study to quantify the antibacterial activity of the peel was carried out by Harith et al. [94], investigating the activity of the peel on a Gram-positive bacterium, *Staphylococcus epidermidis*, using the disc diffusion method. Two solvents, methanol and hexane, were used to prepare the extracts through maceration in order to find the most suitable one. Regarding methanol, the antibacterial discs were injected with five different extract concentrations of 20, 40, 60, 80, and 100 mg/mL, while regarding hexane, the first four concentrations were tested. The assessment of antibacterial activity was based on zones of inhibition (in mm). Commercial ampicillin was used as a positive control for bacteria. In methanolic extracts, the inhibition zones for *S. epidermidis* were $\geq$10 mm, 5–9 mm, 5–9 mm, 5–9 mm, and 0 mm for the concentrations 20, 40, 60, 80, and 100 mg/mL, respectively, while the ampicillin showed a $\geq$10 mm inhibition zone. Furthermore, in hexanoic extracts, the inhibition zones were $\leq$4 mm, $\leq$4 mm, 5–9 mm, and 0 mm for the concentrations 20, 40, 60, and 80 mg/mL, respectively. Last but not least, ampicillin showed a zone of inhibition in the range of 5–9 mm, i.e., a moderate inhibition zone. It should be noted that the authors describe $\leq$4 mm as a weak inhibition zone, 5–9 mm as a moderate inhibition zone, and $\geq$10 mm as a strong inhibition zone. Considering the results, methanol appears to be a better solvent than hexane. However, the lower the concentration of the extract, the stronger the antibacterial activity, with an ideal concentration of 20 mg/L. In fact, at this concentration, the watermelon peel extract presents the same antibacterial activity as the positive control against *S. epidermidis*.

Almost a year later, Rai et al. [95] came up with a different study on the antibacterial activity of watermelon peel, where the peel itself rather than the peel extract was studied. In

order to examine the antibacterial activity, the conventional disc diffusion test was followed, using cultures of two Gram-positive bacteria, *Lactobacillus* spp. and *Staphylococcus aureus*, and two Gram-negative bacteria, *E. coli* and *Proteus vulgaris*. The determination of activity was performed by measuring the inhibition zone. The results showed that both *Lactobacillus* spp. and *S. aureus* had a zone of inhibition at 10 mm, whereas *E. coli* had an inhibition zone of 11 mm and *P. vulgaris* had an inhibition zone of 26 mm. In the results, it is indicated that watermelon peel can show strong antibacterial activity without being extracted. However, going deeper into the above-mentioned study, the formation of the inhibition zone for *S. aureus* was 12, 15, and 20 mm, showing a significant difference. The same conclusions were drawn for the activity against *E. coli*, where (as in the previous research) the zone of inhibition was up to 20 mm. However, the activity against *P. vulgaris* is noteworthy because, besides being detected as very effective, it also shows strong differences with previous research where the extract did not show any inhibitory effect against its growth. Therefore, it is concluded that the peel can also show bacterial resistance and can be used against some bacteria, especially *P. vulgaris*.

In the study of Osinubi et al. [96], the effect of drying methods on the antibacterial properties of both the seeds and rind of watermelon was examined. Samples were dried using three similar drying methods: air, oven, and sun. Air drying at RT was carried out in a well-ventilated room for a period of four weeks; oven drying was carried out in a hot air oven at 50 °C for 120 h; and sun drying was carried out by exposure to sunlight for three weeks. Following drying, all samples were powdered and soaked in methanol in a solid-to-liquid ratio of 1:10 for 48 h at RT. The active culture for the experiment was prepared by transferring a loop of cells from the stock cultures into a Mueller–Hinton broth test tube and incubated without agitation at 25 °C for 24 h. The well was filled with 0.2 mL of the test sample at different concentrations (5, 10, 15, 20, and 25 mg/mL) and allowed to diffuse at RT for 30 min. Gentamicin at a concentration of 10 mg/mL was used as a positive control. The antibacterial activity of the samples was tested against six bacteria: two Gram-positive, *S. aureus*, *Bacillus cereus*, and four Gram-negative, *Pseudomonas aeruginosa*, *Pseudomonas florescens*, *E. coli*, and *Salmonella typhimurium*. As far as the results are concerned, the extracts from the oven-dried sample showed better activity compared with those dried in a well-ventilated room or under the sun. At the optimum concentration (25 mg/mL), it showed an inhibition zone of 5.81 mm against *S. aureus*, 4.81 mm against *B. cereus*, 4.90 mm against *P. aeruginosa*, 6.40 mm against *P. florescens*, 6.81 mm against *E. coli,* and 6.41 mm against *S. typhimurium*. Concerning gentamycin and the concentration examined (10 mg/mL), it exhibited a minimal degree of inhibition for all bacteria. Moreover, it showed not over a 3 mm zone of inhibition on any bacteria, and when compared with the extracts, it presented less resistance even when the lower extract concentration of 5 mg/mL was tested.

The aim of further research by Patil and Jain [97] was to test two different extraction methods (Soxhlet extraction and cold filtration method) using ethanol as a solvent with regard to the antibacterial activity of watermelon peel. The samples were washed three times with tap water and three more times with distilled water, allowed to dry under the absence of light for six days, and then ground to powder. Regarding the cold percolation method, the dried sample was immersed in 95% ethanol in a 1:5 solid-to-liquid ratio. The powder was extracted using a Soxhlet apparatus for 15 h at 65 °C using the same solvent. Antibacterial activity was studied through resistance to three Gram-positive bacteria, *Bacillus* spp., *S. aureus* (ATCC 6538), *Corynebacterium diphtheriae* (ATCC 13812), and three Gram-negative bacteria, *E. coli* (ATCC 25922), *Proteus* spp., and *P. aeruginosa* (ATCC 27853). From each extract, 50 µL were used, and antibacterial activity was determined using the inhibition zones (mm). In terms of Gram-positive bacteria *Bacillus* spp., *S. aureus*, and *C. diphtheriae* using the Soxhlet method, the inhibition zones recorded were 13, 12, and 13 mm, respectively, while in terms of Gram-negative bacteria, the results were 14 mm in *E. coli,* while lack of inhibition was recorded against *Proteus* spp. and *P. aeruginosa*. Regarding the cold percolation method, a growth resistance (development zone) appeared only in

Bacillus spp. and *E. coli* bacteria and was 14 and 12 mm, while the rest of the bacteria showed complete resistance to the action of the extracts. Comparing the two methods, it is noticeable that the Soxhlet method is preferable compared with the cold filtration method. However, the interception is stronger in Gram-positive bacteria, and there is even a strong resistance to bacterial growth. Moreover, comparing this study's results with the ones of the study where the Soxhlet method but hexane as solvent were used, it can be observed that ethanol is a stronger solvent. So far, ethanol can be considered an ideal solvent.

Regarding the study conducted by Neglo et al. [9], the antibacterial activity of both the peel and rind of *C. lanatus* was evaluated. For the preparation of the extracts, a precise quantity of each sample was weighed and immersed in methanol. A hot air-dry furnace at 45 °C was used to concentrate the filtrates. The Minimum Inhibition Concentration (MIC) of the extracts against bacteria was carried out by the microdilution method. The bacteria were grown at 37 °C in Muller–Hinton broth, and the optical density was adjusted to 10^6 CFU/mL. Ten test tubes containing 200 µL of a specific bacterial suspension and 200 µL of different concentrations of peel and rind extracts (0–256.0 mg/mL) were prepared and incubated at 37 °C for 24 h. The bacteria tested were the Gram-positive bacteria *Staphylococcus albus*, *S. aureus*, *Enterococcus faecalis*, *Bacillus subtilis*, *Micrococcus luteus*, *Listeria innocua,* and *Streptococcus thermophilus*, while the Gram-negative bacteria tested were *Pseudomonas fluorescens*, *E. coli*, *Klebsiella oxytoca*, *Salmonella enterica*, *Shigella sonnei,* and *S. typhimurium*. Regarding the watermelon peel at the concentration of 500 mg/mL, the inhibition zones (in mm) detected for the Gram-positive bacteria *S. albus*, *S. aureus*, *E. faecalis*, *B. subtilis*, *M. luteus*, *L. innocua*, and *S. thermophilus* were 10, 20, 16, 16, 11, 9, and 13 mm, respectively. Meanwhile, the results for the Gram-negative bacteria *P. fluorescens*, *E. coli*, *K. oxytoca*, *S. enterica*, *S. sonnei*, and *S. typhimurium* were 8, 12, 13, 11, 16, and 9, respectively. Moreover, for the same concentration in watermelon rind, the inhibition zones (in mm) for the Gram-positive bacteria *S. albus*, *S. aureus*, *B. subtilis*, *M. luteus*, *L. innocua*, and *S. thermophilus* were 7, 13, 13, 15, 6, and 10, while no resistance capacity was developed for *E. faecalis*. For the same sample, the results for the Gram-negative bacteria *P. fluorescens*, *K. oxytoca*, *S. enterica*, and *S. sonnei* were 7, 10, 11, and 12 mm, respectively, proving that the extract of watermelon peel is a more effective antibacterial agent than the corresponding extract of watermelon rind. In conclusion, the MIC of methanol extracts (mg/mL) against the tested bacteria was also recorded and proved that for bacteria such as *L. innocua* (Gram-positive) and *S. enterica* (Gram-negative), the MIC of methanol extracts was equal (8 mg/mL) between the two extracts. However, bacteria such as *M. luteus* (Gram-positive) and *P. fluorescens* (Gram-negative) required twice the amount of watermelon rind extract compared with peel. Furthermore, there were recorded results where the minimum inhibitory methanol extract concentration for watermelon rind was fourfold, eightfold, and so on. Results that are in full agreement with previous data from the same study. The only case where rind extract was required in a smaller amount than the peel extract was against *S. aureus*, where 8 mg/mL of peel extract and only 4 mg/mL of rind extract were required to show the formation of an inhibition zone.

Zahid et al. [98] carried out the first study on the antibacterial activity of watermelon rind. The survey is focused on the rind of three types of watermelon. Specifically, the rinds of Charleston Grey watermelon (a characteristic light skin color), Summer Flavour 840 watermelon (elongated with dark green stripes), and Crimson Sweet watermelon (round with dark green stripes) were analyzed. The samples were dried and converted into fine powder in order to be extracted using the Soxhlet method. For this purpose, 30 g of each rind sample was extracted with *n*-hexane for 6 h. The extracts were then tested for their antibacterial activity against a Gram-positive bacterium, *S. aureus*, and a Gram-negative, *E. coli*. A modified Kirby–Bauer disk diffusion method was used to test the antibacterial activity using 100 µL of each rind extract. Both a negative (NaCl) and a positive (Ciprofloxacin) control were used. Regarding *S. aureus*, the inhibition zones were 5 mm for the Crimson Sweet rind and 10 mm for the Summer Flavor 840 rind. Charleston gray rind showed no activity against this Gram-positive bacterium. For *E. coli*, the Crimson

Sweet rind appeared to have no resistance, while both the rind of Charleston Gray and Summer Flavor 840 had the same zone of inhibition of 5 mm. It is therefore obvious that the rind from Summer Flavor 840 had the highest antibacterial capacity on both bacteria compared with the other two categories. However, the Soxhlet method with hexane as a solvent may not be the most suitable method for developing antibacterial-rich extracts. Regarding the controls tested, Ciprofloxacin (the positive control) had a 20 mm zone of inhibition against *S. aureus* and a 25 mm zone of inhibition against *E. coli*. However, the negative control did not form an inhibition zone.

A subsequent survey was conducted by Govindaraj et al. [99], where various in vitro extracts of *C. lanatus* rind against the Gram-positive bacterium *Streptococcus mutans* were studied. In order to prepare the extracts, the rind was removed from the flesh of the watermelon, crushed, and mixed with 100 mL of distilled water. The mixture was then heated until boiling in a heating mantle until 25 mL of rind extract finally remained. To test the antibacterial activity, four different quantities of the extract were prepared, namely 25, 50, 100, and 150 μL, and after that, four Muller Hinton Agar (MHA) plates coated with *S. mutans* were loaded with the different quantities of extracts, each. Finally, they were incubated for 24 h at 37 °C. For each quantity of 25, 50, 100, and 150 μL, the zone of inhibition exhibited by each sample was 26, 28, 31, and 35 mm, respectively. According to these results, it is evident that as the quantity of *C. lanatus* rind extract increases, the resistance ability of the specific bacterium also increases. In addition, the rind shows high resistance to the bacterium *S. mutans*. In fact, it shows a higher antibacterial capacity compared with other species of the genus Streptococcus, making water and boiling suitable extraction methods to combat the activity of *S. mutans*.

An approach that could be considered quite useful is the study of Toupal et al. [100], who studied the action of the most well-known and commonly used solvents, acetone, methanol, ethanol, and water, which also show a range of polarity on the antibacterial capacity of watermelon peel. For the production of extracts, the peel was removed from the rest of the fruit and cleaned with tap water, while it was sterilized with a 70% ethanol solution and rinsed with sterile distilled water. The peels were then cut to approximately 1 × 1 cm and dried in a vacuum dryer at 50 °C and 0.0045 mbar pressure for 48 h. Thereafter, *C. lanatus* peels were pulverized and weighed, and four extracts were prepared with four different solvents. For the first one, 100 mL of methanol (80%) was used; for the second, 100 mL of acetone (80%); for the third, 100 mL of ethanol (80%); and for the fourth, 100 mL of distilled water. Extraction was carried out by stirring at 22 °C at 130 rpm for 24 h. Each extract was filtered and concentrated using a rotary evaporator, except for the water extract, which was concentrated in a water bath at 90 °C for 30 min. The antibacterial activities of the extracts were tested against two Gram-positive bacteria, namely *B. cereus* and *Listeria monocytogenes*, and six Gram-negative bacteria, namely *S. aureus*, *E. coli* O157:H7, *E. coli*, *P. aeruginosa*, *Salmonella enteritidis*, and *S. typhimurium*. Penicillin G was also utilized as a positive control to ensure the validity of the results. As for the results, interesting findings were observed. In particular, the most remarkable finding was that for the Gram-negative Salmonella bacteria. Only the positive control showed inhibition activity (>15 mm). Regarding the other bacteria, in *B. cereus* the ideal solvent for generating extracts with antibacterial capabilities was found to be methanol (~20 mm), while for *E. coli* O157:H7 and *E. coli*, methanol was found to be the most suitable solvent with inhibition zones of ~20 and ~30 mm. Regarding the other Gram-positive bacteria *L. monocytogenes*, ethanolic peel extract was found to be the ideal one with an inhibition zone of ~20 mm; similar results were obtained for *S. aureus*. The only extract that showed antibacterial activity was the one prepared with ethanol solvent at an inhibition zone of 15 mm. At this point, it is worth mentioning that ethanol as a solvent also had essential results on *E. coli* O157:H7, with an interception zone identical to that of the methanol extract. Finally, the ethanol extract was also found to have greater activity against the bacterium *P. aeruginosa*, with an inhibition zone of more than 15 mm. In conclusion, it is worth emphasizing that both water and acetone are not suitable for the preparation of extracts with strong antibacterial

activity, as against most bacteria (*S. aureus*, *E. coli* O157:H7, *P. aeruginosa*, *S. enteritidis*, and *S. typhimurium*), no inhibitory activity was observed. Finally, in both *E. coli* O157:H7 and *E. coli*, the positive control showed a lower zone of inhibition than the methanolic extracts of watermelon peel.

The most recent research was carried out by Rezagholizade-Shirvan et al. [101], which presented, apart from remarkable results, a new, interesting, and nutritious product. In particular, a candy was prepared from rind extract. The preparation of the extract required drying by osmotic dehydration, cutting into small pieces, and leaving them to dry in front of an oven operated at 60 °C for 24 h. The dried rind was turned into a fine powder and sieved. Extraction took place at RT for 24 h using an orbital stirrer, where watermelon rind powder was added to a flask containing 80% aqueous ethanol in a solid-to-liquid ratio of 1:10. The antibacterial activity of the extract was evaluated through resistance to two Gram-positive bacteria, *S. aureus* and *B. cereus*, and one Gram-negative bacterium, *E. coli*. For the evaluation, 150 µL of extract solution was used on every bacterium. The antibacterial activity was quantified through inhibition zones, which were found to be 10.84 mm for *S. aureus*, 11.38 mm for *B. cereus*, and 13.64 mm for *E. coli*. These results show that an otherwise healthy snack can acquire significant properties through proper preparation. The key finding, however, was that the use of a green solvent, ethanol, was found to be the most promising for producing watermelon rind extract with strong antibacterial activity. Finally, it was proven that no high temperature was required, thus creating a relatively easy and economical method for preparing an extract with beneficial properties that can be added to further food products. The results of these studies are demonstrated in Table 1.

Table 1. Antibacterial activity of different watermelon peel/rind extracts.

Gram	Strain of Bacteria	By-Product	Solvent	Extraction Conditions	MIC Value (mg/mL)	Zone of Inhibition (mm)	Ref.
+	*Bacillus cereus*	Peel	80% Methanol	Stirring for 24 h at 22 °C	n.a.	18	[100]
		Peel	80% Acetone	Stirring for 24 h at 22 °C	n.a.	13	[100]
		Peel	80% Ethanol	Stirring for 24 h at 22 °C	n.a.	14	[100]
		Peel	Water	Stirring for 24 h at 22 °C	n.a.	10	[100]
		Rind	Methanol	Maceration for 48 h at RT	25	4.81	[96]
		Rind	80% Ethanol	Stirring for 24 h at 60 °C	n.a.	11.38	[101]
+	*Bacillus* spp.	Peel	Ethanol	Soxhlet extraction for 15 h at 65 °C	n.a.	13	[97]
		Peel	Ethanol	Cold percolation overnight at RT	n.a.	11	[97]
+	*B. subtilis*	Peel	Methanol	Mechanical shaking for 24 h at RT	2	16	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	8	13.5	[9]
+	*Corynebacterium diphtheriae*	Peel	Ethanol	Soxhlet extraction for 15 h at 65 °C	n.a.	13	[97]
		Peel	Ethanol	Cold percolation overnight at RT	n.a.	0	[97]
+	*Enterococcus faecalis*	Peel	Methanol	Mechanical shaking for 24 h at RT	8	16	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	64	0	[9]
−	*Escherichia coli*	Peel	80% Methanol	Stirring for 24 h at 22 °C	n.a.	23	[100]
		Peel	80% Acetone	Stirring for 24 h at 22 °C	n.a.	7	[100]
		Peel	80% Ethanol	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	Water	Stirring for 24 h at 22 °C	n.a.	10	[100]
		Peel	Methanol	Mechanical shaking for 24 h at RT	2	12	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	128	0	[9]
		Rind	Methanol	Maceration for 48 h at RT	25	6.81	[96]
		Rind	Hexane	Soxhlet extraction for 6 h	n.a.	5	[98]
		Rind	80% Ethanol	Stirring for 24 h at 60 °C	n.a.	13.64	[101]
		Rind	Wastewater	Mechanical shaking for 24 h at RT	n.a.	n.a.	[93]
		Peel	Ethanol	Soxhlet extraction for 15 h at 65 °C	n.a.	14	[97]
		Peel	Ethanol	Cold percolation overnight at RT	n.a.	12	[97]
		Peel	–	–	n.a.	11	[95]
−	*E. coli* O157:H7	Peel	80% Methanol	Stirring for 24 h at 22 °C	n.a.	19	[100]
		Peel	80% Acetone	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	80% Ethanol	Stirring for 24 h at 22 °C	n.a.	19	[100]
		Peel	Water	Stirring for 24 h at 22 °C	n.a.	0	[100]

Table 1. *Cont.*

Gram	Strain of Bacteria	By-Product	Solvent	Extraction Conditions	MIC Value (mg/mL)	Zone of Inhibition (mm)	Ref.
–	*Klebsiella oxytoca*	Peel	Methanol	Mechanical shaking for 24 h at RT	4	13	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	8	10.5	[9]
+	*Lactobacillus* spp.	Peel	–	–	n.a.	10	[95]
+	*L. innocua*	Peel	Methanol	Mechanical shaking for 24 h at RT	8	9.3	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	8	6.5	[9]
–	*L. monocytogenes*	Peel	80% Methanol	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	80% Acetone	Stirring for 24 h at 22 °C	n.a.	13	[100]
		Peel	80% Ethanol	Stirring for 24 h at 22 °C	n.a.	19	[100]
		Peel	Water	Stirring for 24 h at 22 °C	n.a.	0	[100]
+	*Micrococcus luteus*	Peel	Methanol	Mechanical shaking for 24 h at RT	8	11	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	16	15.5	[9]
–	*Proteus* spp.	Peel	Ethanol	Soxhlet extraction for 15 h at 65 °C	n.a.	0	[97]
		Peel	Ethanol	Cold percolation overnight at RT	n.a.	0	[97]
–	*P. vulgaris*	Peel	–	–	n.a.	26	[95]
–	*Pseudomonas aeruginosa*	Peel	80% Methanol	Stirring for 24 h at 22 °C	n.a.	15	[100]
		Peel	80% Acetone	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	80% Ethanol	Stirring for 24 h at 22 °C	n.a.	17	[100]
		Peel	Water	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Rind	Methanol	Maceration for 48 h at RT	25	4.9	[96]
		Peel	Ethanol	Soxhlet extraction for 15 h at 65 °C	n.a.	0	[97]
		Peel	Ethanol	Cold percolation overnight at RT	n.a.	0	[97]
–	*P. fluorescens*	Peel	Methanol	Mechanical shaking for 24 h at RT	16	8	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	32	7	[9]
		Rind	Methanol	Maceration for 48 h at RT	25	6.4	[96]
–	*Salmonella enterica*	Peel	Methanol	Mechanical shaking for 24 h at RT	8	11	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	8	11.5	[9]
–	*S. enteritidis*	Peel	80% Methanol	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	80% Acetone	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	80% Ethanol	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	Water	Stirring for 24 h at 22 °C	n.a.	0	[100]
–	*S. typhimurium*	Peel	Methanol	Mechanical shaking for 24 h at RT	8	9.3	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	128	0	[9]
		Rind	Methanol	Maceration for 48 h at RT	25	6.41	[96]
		Peel	80% Methanol	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	80% Acetone	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	80% Ethanol	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	Water	Stirring for 24 h at 22 °C	n.a.	0	[100]
–	*Shigella sonnei*	Peel	Methanol	Mechanical shaking for 24 h at RT	2	16	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	16	12	[9]
+	*Staphylococcus albus*	Peel	Methanol	Mechanical shaking for 24 h at RT	16	10	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	128	7.6	[9]
+	*S. aureus*	Peel	–	–	n.a.	10	[95]
		Peel	Methanol	Mechanical shaking for 24 h at RT	8	20	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	4	13	[9]
		Rind	Methanol	Maceration for 48 h at RT	25	5.81	[96]
		Rind	Hexane	Soxhlet extraction for 6 h	n.a.	10	[98]
		Peel	80% Methanol	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	80% Acetone	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	80% Ethanol	Stirring for 24 h at 22 °C	n.a.	15	[100]
		Peel	Water	Stirring for 24 h at 22 °C	n.a.	0	[100]
		Peel	Ethanol	Soxhlet extraction for 15 h at 65 °C	n.a.	12	[97]
		Peel	Ethanol	Cold percolation overnight at RT	n.a.	0	[97]
		Rind	80% Ethanol	Stirring for 24 h at 60 °C	n.a.	10.84	[101]
+	*S. epidermidis*	Peel	Methanol	Maceration	20	10	[94]
		Peel	Hexane	Maceration	60	5	[94]

Table 1. *Cont.*

Gram	Strain of Bacteria	By-Product	Solvent	Extraction Conditions	MIC Value (mg/mL)	Zone of Inhibition (mm)	Ref.
+	*Streptococcus mutans*	Rind	Water	Maceration at RT	n.a.	35	[99]
+	*S. thermophilus*	Peel	Methanol	Mechanical shaking for 24 h at RT	16	13	[9]
		Rind	Methanol	Mechanical shaking for 24 h at RT	64	10	[9]

n.a.: not applicable; RT: room temperature.

4.2. Seeds

Sekar et al. [102] investigated and compared the active compounds present in two different watermelon varieties. The comparison was conducted through a qualitative phytochemical analysis of methanolic seed extracts. Fine seed powder was extracted through maceration in methanol for seven days at RT. Both extracts underwent a thorough antibacterial investigation and were subsequently compared. The inhibitory effects of the methanolic extract derived from red watermelon seeds were evaluated against Gram-positive bacteria like *Streptococcus pyogenes* and *S. aureus*. The results demonstrated inhibition zones of the above bacteria ranging from 7–20 mm and 7–10 mm, respectively, at concentrations ranging from 250–1000 µg/mL. On the other hand, the methanolic extract of red watermelon seeds did not exhibit any zone of inhibition against the Gram-negative bacteria *E. coli* or *P. aeruginosa*. No zones of inhibition were observed for any of the tested organisms when utilizing a methanolic extract derived from yellow watermelon seeds. The data in this study provided evidence for additional research on the potential antibacterial properties of a methanolic extract derived from red watermelon seeds, specifically in relation to its impact on Gram-positive bacteria.

In addition, the objective of the study conducted by Adunola et al. [103] was to identify the extraction technique that resulted in the greatest concentration of antibacterial compounds from the seeds of *C. lanatus*. The solvents employed in this study were chloroform, methanol, and distilled water. Two different extraction methods were utilized: cold extraction and Soxhlet extraction, which was referred to as hot extraction in this particular investigation. Cold extraction required 72 h of orbital shaking, whereas Soxhlet extraction required 6 h of extraction, with both extracts being evaporated to dryness. The antibacterial properties of the seed extracts were assessed through the utilization of the agar well diffusion method using clinical isolates of Gram-positive *Staphylococcus* spp. and Gram-negative *E. coli*, *Proteus* spp., *Klebsiella* spp., and *P. aeruginosa*. The results of the study demonstrated that the zones of inhibition ranged from 0–9 mm, 0.5–7 mm, 0–2 mm, 0–2.5 mm, and 0–8.5 mm for the above bacteria, respectively. *Staphylococcus* spp. exhibited the highest level of inhibition when exposed to cold methanol extracts, followed by hot methanol extracts, and lastly, cold chloroform extracts. Significant antibacterial potentials ($p < 0.05$) were observed only in the hot methanol and chloroform extracts when tested in the presence of *P. aeruginosa*. Saponins, which have been associated with antibacterial properties, were also identified in the hot methanol extracts at moderate concentrations and in the cold methanol extracts at high concentrations. The present study determined that the effectiveness of the extract against specific test organisms was influenced by both the solvent employed and the extraction conditions, namely cold maceration and Soxhlet extraction. Furthermore, it is possible that the observed significant zone of inhibition exhibited by the cold and hot methanol extracts against certain test organisms could be attributed to the presence of saponins.

Bello et al. [104] investigated the phytochemical composition and antibacterial efficacy of *C. lanatus* seeds against various bacterial strains. A cold maceration method took place for the extraction of watermelon seeds, with fine seed powder mixed with water or ethanol in a liquid-to-solid ratio of 8:1 for 24 h at RT, with the filtrate finally dried in an oven. The extracts contained alkaloids, flavonoids, glycosides, tannins, and saponins. Interestingly,

the screening process did not yield any saponins in either the water-based or alcohol-based extracts. The strains of Gram-positive *S. aureus* and Gram-negative *E. coli*, *P. aeruginosa*, and *Klebsiella pneumoniae* underwent antibiotic susceptibility testing. The efficacy of the extracts against *S. aureus*, *E. coli*, and *P. aeruginosa* was observed within the concentration range of 6.25 mg/mL to 50 mg/mL. The study revealed that *K. pneumoniae* exhibited a significant level of resistance, specifically against the ethanolic extract, compared with other bacterial strains, requiring concentrations greater than 50 mg/mL of extract. Most bacteria required 6.25 mg/mL of extract, regardless of the extraction solvent. Only *E. coli* required 12.5 mg/mL of either water or ethanolic extract. The concentration of the aqueous extract that exhibited the highest efficacy against *P. aeruginosa* was determined to be 50 mg/mL. Specifically, this concentration led to the formation of a zone of inhibition with a diameter of 8 mm. In most cases, a higher concentration exhibited superior efficacy compared with a lower concentration, whereas the control substance ciprofloxacin demonstrated greater activity than either of the extracts. The results obtained from the determination of MIC and MBC suggest that the components present in the extract may possess bactericidal properties, possibly attributed to their proximity. The findings also suggest that the seeds of *C. lanatus* possess bioactive compounds that have potential antibacterial properties, consistent with the rest of the plant. Consequently, these seeds hold potential for utilization in herbal formulations.

Similarly, Babaiwa et al. [105] aimed to assess the antibacterial properties and chemical composition of the ethyl acetate extract derived from the seeds of *C. lanatus* through the application of standard microbiological techniques. The seeds were macerated in ethyl acetate for 72 h and the extract was concentrated. The microorganisms targeted for evaluation included Gram-positive *S. aureus*, *B. subtilis*, and Gram-negative *E. coli*, *P. aeruginosa*. Analysis of the extract using GC-MS revealed that it contained oleic acid (31.22%), saturated fatty acids (23.85%), γ-tocopherol (8.79%), and other compounds with antibacterial activity, such as acridine and methyl phthalate. The extract, which had a yield of 18.7%, had a MIC range of 0.313–2.5 mg/mL and a Maximum Bactericidal Concentration (MBC) range of 0.313–5 mg/mL, meaning that it was effective against all tested microorganisms. The inhibition zone diameters ranged from 24 to 26 mm. *P. aeruginosa* and *S. aureus* showed the greatest resistance, whereas *E. coli* showed the lowest. This study revealed that pathogens typically associated with respiratory, gastrointestinal, and urinary tract infections could be inhibited using *C. lanatus* seed extract.

Marchwińska et al. [106] investigated the efficacy of 18 different cold-pressed cosmetic oils in terms of their ability to impede the proliferation of human pathogens. The antibacterial activity of cosmetic oils was assessed using the disc diffusion method. Bacteria such as Gram-positive *S. epidermidis* and *S. aureus* and Gram-negative bacteria such as *P. aeruginosa* and *E. coli* were the indicator microorganisms. The results showed that the efficacy of certain cosmetic oils in inhibiting indicator microorganisms exhibits variability in terms of their antagonistic effects. Among the various substances tested, it was found that tamanu seed oil had the highest efficacy in inhibiting bacterial growth; the oil showed a significant inhibitory effect on the growth of Gram-positive *S. aureus*, *S. epidermidis* and Gram-negative *P. aeruginosa*. The growth of both *S. epidermidis* and *P. aeruginosa* was inhibited by the presence of wheat germ oil. The efficacy of black cumin seed oil against *S. aureus* has been demonstrated. The remaining cosmetic oils that were tested exhibited negligible antibacterial activity against the selected microorganisms under investigation. Furthermore, their efficacy in inhibiting the proliferation of bacteria and yeast was significantly inferior to that of tea tree oil. The antibacterial properties of the oils under investigation exhibited variability, which was contingent upon both the specific oil type and the microorganism employed in the experimental analysis. However, it should be noted that no antibacterial properties were found for cold-pressed watermelon seed oil, so further investigation should be done on this cold-pressed oil.

The nutritional value and therapeutic potential of watermelon seeds have been acknowledged; however, to date, no studies have been conducted to isolate and quantify

melanin content. To that end, Łopusiewicz et al. [107] assessed the antioxidant and antibacterial properties of raw and purified (defatted) melanins extracted from watermelon seeds. Melanin was precipitated after treatment with sodium hydroxide (NaOH) and hydrochloric acid (HCl). L-DOPA melanin was used as a positive control. The microorganisms under investigation included Gram-positive bacteria *B. cereus*, *E. faecalis*, and *S. aureus,* along with Gram-negative bacteria *E. coli* and *P. aeruginosa*. The results showed that the purification of melanin increased the antioxidant activity of the extracts. For instance, 1 mg/mL of purified melanin had 92.48% antioxidant activity, while raw melanin had 79.18%. The positive control had 97.16% antioxidant activity. The antibacterial activity was assessed through zones of growth inhibition, in which it was revealed that only *E. faecalis* and *P. aeruginosa* recorded ~11 mm and ~13 mm, respectively, regardless of the extract used. Consequently, the observed antibacterial properties of extracted melanin from *C. lanatus* seeds indicate its potential therapeutic efficacy in the traditional medicinal use of this plant in treating bacterial ailments such as diarrhea, gastrointestinal infections, respiratory disorders, and dermatological conditions.

Sola et al. [108] examined the chemical composition, nutritional assessment, and antibacterial properties of *C. lanatus* seeds. Watermelon seed powder was subjected to maceration with methanol at a 4:1 liquid-to-solid ratio for 24 h at RT. The methanolic watermelon seed extract was subjected to quantitative analysis, revealing the presence of alkaloids at a concentration of 3.08 mg/g, polyphenols at 0.30 mg/g, tannins at 0.12 mg/g, saponins at 0.20 mg/g, and flavonoids at 2.67 mg/g. The vitamin B complex content of watermelon seeds was found to be 0.03 mg/100 g for vitamin B_1, 0.01 mg/100 g for vitamin B_2, 0.64 mg/100 g for vitamin B_3, 0.24 mg/100 g for vitamin B_6, and 0.01 mg/100 g for vitamin B_{12}. The bioactivities of the extract were assessed against a range of bacterial strains, including Gram-positive bacteria such as *B. cereus*, *S. aureus*, *Tsukamurella hongkongensis*, *Lactobacillus* spp., *Staphylococcus petrasii*, and *Dietzi amaris*, along with Gram-negative bacteria such as *Proteus mirabilis*, *E. coli*, *Necropsobacter rosorum*, *Neisseria sicca*, *Pseudomonas oryzyhabitans*, *Klebsiella pneumoniae*, *Advenella incenata*, *Neiserria subflava*, and *Serriatia marcescens*. The antibacterial activity of the extract revealed that not all of the tested organisms showed susceptibility. *Lactobacillus* spp. and *P. oryzyhabitans* had 12 and 16 mm of inhibition growth zones at 300 mg/mL of the extract. Regarding three gram-negative bacteria, *N. sicca*, *N. rosorum*, and *N. sicca* had inhibition growth zones of 18, 13, and 17, respectively, at 200 mg/mL. An interesting finding was that all three of them did not show any inhibition growth zone at 300 mg/mL. In addition, all other bacteria did not show any inhibition zone at any concentration of the extract. This study holds significant promise in the quest for novel biologically active compounds that show efficacy against multi-drug-resistant strains and diminish the side effects associated with antibiotics.

Another interesting study was conducted by Babaiwa et al. [109], who evaluated the antibacterial efficacy of the aqueous extract derived from *C. lanatus* seeds and investigated the concentration-effect relationship through time-kill studies. The crude powdered seeds of *C. lanatus* were subjected to extraction through the process of maceration using water as the solvent. The antibacterial activity of the aqueous extracts was assessed against Gram-positive bacteria like *B. subtilis* and *S. aureus* along with Gram-negative bacteria *E. coli* and *P. aeruginosa* through the application of established microbiological techniques. The time-kill studies were conducted using a baseline of 10^6 CFU/mL for each test strain. Concentrations at the MIC, twice the MIC, and four times the MIC were employed for a duration of 24 h. The aqueous extract showed moderate antibacterial activity, as evidenced by inhibition growth zone diameters ranging from 15 to 17 mm and a MIC range of 2.5 to 20 mg/mL. The findings from time-kill studies revealed that the antibacterial activity observed was bacteriostatic and not dependent on the concentration of the antibacterial agent. Additionally, all tested strains showed a distinct pattern of regrowth. The aqueous extract of *C. lanatus* seeds had antibacterial activity against test bacterial strains, exerting a bacteriostatic effect that was not dependent on the concentration of the extract. The extract displayed enhanced bactericidal activity against Gram-positive bacteria, specifically *Staphylococcus* and *Bacillus* species, as

evidenced by a steep pharmacodynamic time-kill curve at 4 times the MIC. Conversely, a decreased inhibitory effect was observed against Gram-negative *E. coli*, with intermittent periods of bacterial regrowth observed in the presence of *P. aeruginosa*. Additional research is necessary to isolate and purify the antibacterial compounds present in the aqueous extract of *C. lanatus* seed. This investigation holds promise for the development of a novel antibiotic that could be utilized in the treatment of bacterial infections.

In a previously reported study from Osinubi et al. [96], the results indicated that the oven-dried seed contained all of the phytochemicals. The air-dried seeds did not contain cardiac glycosides or flavonoids, whereas the sun-dried seeds did not contain phenols and phytates. The results of the antibacterial screening showed that the oven-dried seeds exhibited efficacy against all tested bacteria compared with the sun-dried and air-dried samples. The seeds that underwent oven drying exhibited notable activity against Gram-positive bacteria such as *S. aureus*, with an inhibition zone measuring 4.81 mm. It also demonstrated activity comparable to the sun-dried extract against *B. cereus*, with an inhibition zone of 3.91 mm. Conversely, the sun-dried extract displayed superior activity against four other Gram-negative bacteria: *P. aeruginosa* (3.81 mm), *P. florescens* (3.71 mm), *E. coli* (5.81 mm), and *S. typhimurium* (6.53 mm). In contrast, the sun-dried samples exhibited greater antibacterial properties compared with their air-dried counterparts. The most optimal method for drying watermelon seeds in preparation for analysis was found to be through the use of an oven. The samples that underwent oven drying exhibited the highest phytochemical composition and demonstrated superior antibacterial activity. The phenomenon could be attributed to the relatively brief drying period in comparison to exposure to sunlight, during which ultraviolet radiation leads to the depletion of plant constituents. The chemical composition of a plant can be modified by extended drying periods conducted in shaded conditions at ambient room temperature, resulting in potential alterations to its organoleptic characteristics. Consequently, it is advisable to employ oven drying for the preservation of the medicinal properties of watermelon seeds.

In a previous study conducted by Neglo et al. [9], investigations were also made into watermelon seed extract. Seed powder was mechanically shaken with methanol as a solvent for 24 h at RT. Alkaloids, flavonoids, triterpenoids, and free-reducing sugars were found in the seed extract, while tannins, steroids, and saponins were not detected. The observed antibacterial activity in all examined extracts could potentially be attributed to the presence of alkaloids. The antioxidant activity of methanolic seed extract was measured at 4.2 mg GAE/100 g, ~61% more than the rind extract and ~107% lower than the peel extract. At a concentration of 500 mg/mL of methanolic seed extract, the mean values of inhibition zones for the previously mentioned microorganisms ranged from 9 to 18. The lowest value was observed in Gram-positive *S. albus* while the highest value was found in Gram-negative *S. sonnei*. Consequently, MIC values ranged from 2 to 32 mg/mL. Specifically, *S. sonnei* displayed the lowest MIC value, while *S. albus* exhibited the highest. The analyzed extracts showed comparable antibacterial effects against both Gram-positive and Gram-negative bacteria, indicating their potential as a valuable source of antibacterial agents. Further investigations are required to clarify the varying vulnerabilities of different organisms towards watermelon seed extracts by examining the specific compounds within each phytochemical class.

A study investigating *C. lanatus* seed extracts employing four distinct solvents, including acetone, chloroform, dichloromethane, and ether, was conducted by Jebir and Mustafa [110]. The seed powder was mixed with a solvent, dried, and then mixed with the next solvent. The process was continued up to the last solvent, while the dried extract was treated with 1 M NaOH, filtered, and finally processed with 1 M HCl. Three extraction methods were utilized, including shaking, ultrasonic bath-assisted maceration, and microwave oven-assisted maceration. Additionally, the extraction process was conducted in three different polarity modalities: non-serial, serial ascending polarity, and serial descending polarity. Out of the various approaches and modalities mentioned, they selected only one ether extract from the descending design polarity to extract five distinct

coumarins (RA1–RA5). The antibacterial efficacy of the individual chemicals was evaluated in vitro using the broth microdilution technique. The pathogen strains that were specifically targeted in this study included only Gram-negative bacteria, such as the pathogens *E. coli* (25922 ATCC), *S. typhimurium*, *Shigella dysenteriae*, *Haemophilus influenzae*, *Klebsiella pneumonia*, and *P. aeruginosa,* in addition to another *E. coli* (BAA 1427) bacteria, which is nonpathogenic, as there is a strain present that constitutes a nonpathogenic intestinal microbiota. The MBC values for every coumarin derivative in each bacterium ranged from 0.45 to 16 μg/mL. In most circumstances, the RA4 derivative has values closer to Ciprofloxacin MBC values, except for *K. pneumonia* and both *E. coli* strains, where the RA1 derivative was found to be more efficient. Some other bacteria, such as *Clostridium perfringens*, *Bacteroides fragilis*, *Prevotella melaninogenica*, and *Fusobacterium necrophorum,* were also examined. MBC values ranged from 2–16 μg/mL. In that case, RA4 was found to be the most efficient coumarin derivative of all, with its values being closest to MBC values from the antibiotic Metronidazole. In conclusion, this study has determined the potential of employing these isolated compounds as a source for developing innovative antibacterial agents.

The study by Olude et al. [111] aimed to investigate and compare the phytochemical compounds, antioxidant properties, and antibacterial activities of leaf extracts of *Bryophyllum pinnattum*, *Alchornea cordifolia,* and *Acalypha wilkesiana* and seed extracts of *C. lanatus*. The extraction took place with 70% ethanol on an orbital shaker for 24 h, with the extract finally being concentrated. The ethanolic extract was subjected to analysis in order to determine its qualitative and quantitative phytochemical profile as well as its antioxidant activity using the corresponding methods, DPPH$^{\bullet}$ radical scavenging and FRAP. The antibacterial effects of the ethanolic extracts on *Streptococcus faecalis* and *P. aeruginosa* were determined using an agar dilution assay. *C. lanatus* extracts were found to contain saponins (40.35 mg/100 g), tannins (43.91 mg/100 g), phenols (60.37 mg/100 g), flavonoids (78.36 mg/100 g), steroids (78.99 mg/100 g), cardiac glycosides (32.76 mg/100 g), and reducing sugars (43.20 mg/100 g). Notably, alkaloids were not detected in *C. lanatus* seed extract. These extracts displayed a total antioxidant capacity of ~35 mg/100 g, but remarkably, they were the only extract from the above plant extracts that did not exhibit any inhibitory effects on *S. faecalis* and *P. aeruginosa* at any concentration tested. Additionally, the organisms did not demonstrate any sensitivity to distilled water, which was utilized as the negative control. Nevertheless, conducting additional in vitro kinetic investigations and in vivo assessments of the antioxidative and antibiotic effects of *C. lanatus* seed extracts may provide insights into the absence of antibacterial properties.

The emergence of antibiotic resistance represents a significant and urgent concern within the medical community. In recent years, there has been a growing trend in the scientific community to conduct extensive examinations of plant material in order to identify and analyze pharmacologically active compounds. The objective of the study conducted by Smajovic et al. [112] was to analyze the composition of bioactive compounds, assess the antibiotic activity, determine the MIC, and evaluate the antibiofilm activity of extracts derived from the seeds of two watermelon species originating from Croatia and Greece. Fine seed powder was mixed with either methanol as a maceration agent for 24 h at RT or with ethanol in a Soxhlet apparatus for 24 h and evaporated to dryness. Gram-positive bacteria such as *B. subtilis*, *E. faecalis*, and *S. aureus* along with Gram-negative bacteria like *E. coli*, *P. aeruginosa*, and *S. enterica* were investigated. The findings suggest that flavonoids were detected in all samples and showed antibacterial effects against specific bacterial strains. Hesperidin (0.06–0.30 mg/g dry extract), genistein (0.43 mg/g dry extract), kaempferol (3.55–26.42 mg/g dry extract), isorhamnetin (0.57 mg/g dry extract), fisetin (65 mg/g dry extract), and luteolin (0.28–0.80 mg/g dry extract) were found in all four samples. In most cases, 250 μg/mL as MIC was required. The ethanolic extract of watermelon seeds from Greece had the greatest antibacterial activity against *S. enterica* subsp. *enterica* serotype Abony (NCTC 6017) (11.67 mm), with a diameter of inhibition zone measuring 11.67 mm, whereas methanolic extract from Croatian watermelon seeds showed the lowest inhibition zone against *P. aeruginosa* (ATCC 27853) (5.67 mm). The biofilm-forming capacity of

all bacteria tested was predominantly characterized as non-adherent or weakly adherent for concentrations up to 250 µg/mL. The bacterial strains exhibited varying degrees of biofilm-forming capacity when exposed to extract concentrations below 250 µg/mL. It can be assumed that a decrease in extract concentration is associated with an increase in biofilm-forming capacity. Regarding extraction solvents, although the polarity of the methanol extract would suggest that it would have a greater effect, the method with ethanol in the Soxhlet apparatus produced slightly better results. The diminished potency of the extracts on specific bacterial strains may be attributed to the limited presence of phytochemicals at a low concentration. The extracts possess inherent potential, necessitating additional research.

The production of watermelon seed protein hydrolyzed (WPSH) was conducted in a study conducted by Mighan et al. [113]. They aimed to investigate the impact of varying concentrations of WSPH (0, 1, 2, and 3%) on the overall quality of silver carp (*Hypophthalmichthys molitrix*) burgers during a period of refrigerated storage at a temperature of 4 °C. Defatted watermelon seeds were processed with 0.1 N NaOH, and the precipitated protein isolate was collected. The findings associated with the levels of total viable count (TVC) and psychrotrophic count (PTC) showed consistency and statistically significant increases ($p < 0.05$) across all treatments over the course of the 16-day storage duration. It was observed that the control group exhibited the highest level of bacteria (TVC: ~10 log CFU/g, PTC: ~9 log CFU/g) in the fish burger, while the treatment group containing 3% WSPH showed the lowest level (TVC: ~6 log CFU/g, PTC: ~6.5 log CFU/g). This significant difference suggests that the peptides possess antibacterial properties, which are of high importance. According to the International Commission on Microbiological Specifications for Foods [114], it is recommended that the permissible level of PTC and TVC not exceed 7 log CFU/g. In accordance with the results, the burgers treated with 3% WSPH showed sustainability throughout the whole storage duration. The mode of action of antibacterial peptides is predominantly attributed to the electrostatic interaction between peptides and the cell membrane of microorganisms. They have the ability to penetrate the membrane and subsequently cause its disruption. Moreover, Kumar et al. [115] asserted that the antibacterial efficacy of bioactive peptides could potentially be attributed to their ability to chelate iron. Hence, the utilization of WSPH as a natural antibacterial agent presents a viable approach to extending the longevity of fish burgers. This application enables an approximate extension of the shelf life by 8 days when stored under refrigeration conditions. The findings of the mentioned studies are summarized in Table 2.

Table 2. Antibacterial activity of different watermelon seed extracts.

Gram	Strain of Bacteria	Solvent	Extraction Conditions	MIC (mg/mL)	Zone of Inhibition (mm)	Ref.
+	*B. cereus*	1 M NaOH	Precipitation	n.a.	0	[107]
		Methanol	Maceration for 48 h at RT	25	3.91	[96]
+	*B. subtilis*	Ethyl acetate	Maceration for 72 h	2.5	26	[105]
		Methanol	Mechanical shaking for 24 h at RT	8	14.5	[9]
		Methanol	Maceration for 24 h at RT	250	0	[112]
		Water	Maceration for 48 h	25	16	[109]
–	*Bacteroides fragilis*	1 M NaOH	Precipitation	6	n.a.	[110]
+	*C. perfringens*	1 M NaOH	Precipitation	2.5	n.a.	[110]
+	*E. faecalis*	1 M NaOH	Precipitation	n.a.	11	[107]
		Methanol	Mechanical shaking for 24 h at RT	8	12	[9]
		Methanol	Maceration for 24 h at RT	250	9	[112]

Table 2. *Cont.*

Gram	Strain of Bacteria	Solvent	Extraction Conditions	MIC (mg/mL)	Zone of Inhibition (mm)	Ref.
–	*E. coli*	Chloroform	Cold extraction for 72 h	n.a.	2	[103]
		Methanol	Cold extraction for 72 h	n.a.	1	[103]
		Water	Cold extraction for 72 h	n.a.	6	[103]
		Chloroform	Soxhlet for 6 h	n.a.	0.5	[103]
		Methanol	Soxhlet for 6 h	n.a.	5	[103]
		Water	Maceration for 24 h at RT	12.5	5	[104]
		Ethanol	Maceration for 24 h at RT	12.5	7	[104]
		Ethyl acetate	Maceration for 72 h	0.31	25	[105]
		–	Cold press	n.a.	0	[106]
		Methanol	Mechanical shaking for 24 h at RT	4	11	[9]
		1 M NaOH	Precipitation	0.7	n.a.	[110]
		Methanol	Maceration for 24 h at RT	125	8.67	[112]
		Methanol	Maceration for 7 d at RT	0.25	0	[102]
		1 M NaOH	Precipitation	n.a.	0	[107]
		Water	Maceration for 48 h	25	16	[109]
		Methanol	Maceration for 48 h at RT	25	5.81	[96]
–	*E. coli(non-pathogenic)*	1 M NaOH	Precipitation	1.8	n.a.	[110]
–	*Fusobacterium necrophorum*	1 M NaOH	Precipitation	2	n.a.	[110]
–	*Haemophilus influenzae*	1 M NaOH	Precipitation	0.75	n.a.	[110]
–	*K. oxytoca*	Methanol	Mechanical shaking for 24 h at RT	16	9.3	[9]
–	*Klebsiella pneumoniae*	1 M NaOH	Precipitation	0.85	n.a.	[110]
		Water	Maceration for 24 h at RT	6.25	4	[104]
		Ethanol	Maceration for 24 h at RT	>50	0	[104]
–	*Klebsiella* spp.	Chloroform	Cold extraction for 72 h	n.a.	1	[103]
		Methanol	Cold extraction for 72 h	n.a.	0	[103]
		Water	Cold extraction for 72 h	n.a.	2.67	[103]
		Chloroform	Soxhlet for 6 h	n.a.	2.67	[103]
		Methanol	Soxhlet for 6 h	n.a.	1.5	[103]
+	*Lactobacillus* spp.	Methanol	Maceration for 24 h at RT	300	12	[108]
+	*L. innocua*	Methanol	Mechanical shaking for 24 h at RT	4	10.5	[9]
+	*M. luteus*	Methanol	Mechanical shaking	4	10	[9]
–	*Necropsobacter rosorum*	Methanol	Maceration for 24 h at RT	100	13	[108]
–	*Neisseria subflava*	Methanol	Maceration for 24 h at RT	200	18	[108]
–	*N. sicca*	Methanol	Maceration for 24 h at RT	200	17	[108]
–	*Prevotella melaninogenica*	1 M NaOH	Precipitation	3.5	n.a.	[110]
–	*Proteus* spp.	Chloroform	Cold extraction for 72 h	n.a.	0	[103]
		Methanol	Cold extraction for 72 h	n.a.	0	[103]
		Water	Cold extraction for 72 h	n.a.	2	[103]
		Chloroform	Soxhlet for 6 h	n.a.	0	[103]
		Methanol	Soxhlet for 6 h	n.a.	1.33	[103]

Table 2. *Cont.*

Gram	Strain of Bacteria	Solvent	Extraction Conditions	MIC (mg/mL)	Zone of Inhibition (mm)	Ref.
–	*Pseudomonas aeruginosa*	Methanol	Maceration for 7 d at RT	0.25	0	[102]
		Chloroform	Cold extraction for 72 h	n.a.	0	[103]
		Methanol	Cold extraction for 72 h	n.a.	0	[103]
		Water	Cold extraction for 72 h	n.a.	4	[103]
		Chloroform	Soxhlet for 6 h	n.a.	8	[103]
		Methanol	Soxhlet for 6 h	n.a.	8.67	[103]
		Water	Maceration for 24 h at RT	6.25	8	[104]
		Ethanol	Maceration for 24 h at RT	6.25	5	[104]
		Ethyl acetate	Maceration for 72 h	1.5	24	[105]
		–	Cold press	n.a.	0	[106]
		1 M NaOH	Precipitation	n.a.	13	[107]
		Water	Maceration for 48 h	20	17	[109]
		Methanol	Maceration for 48 h at RT	25	3.81	[96]
		1 M NaOH	Precipitation	1.05	n.a.	[110]
		70% Ethanol	Orbital shaking for 24 h	>400	0	[111]
		Methanol	Maceration for 24 h at RT	250	10	[112]
–	*P. florescens*	Methanol	Maceration for 48 h at RT	25	3.71	[96]
		Methanol	Mechanical shaking for 24 h at RT	32	12	[9]
–	*P. oryzihabitans*	Methanol	Maceration for 24 h at RT	300	16	[108]
–	*S. enterica*	Methanol	Mechanical shaking for 24 h at RT	32	9.3	[9]
		Ethanol	Soxhlet extraction for 24 h	250	11.67	[112]
–	*S. typhimurium*	Methanol	Mechanical shaking for 24 h at RT	4	10.5	[9]
		1 M NaOH	Precipitation	0.85	n.a.	[110]
		Methanol	Maceration for 48 h at RT	25	6.53	[96]
–	*S. dysenteriae*	1 M NaOH	Precipitation	0.95	n.a.	[110]
–	*S. sonnei*	Methanol	Mechanical shaking for 24 h at RT	2	18	[9]
+	*S. albus*	Methanol	Mechanical shaking for 24 h at RT	32	9	[9]
+	*S. aureus*	Methanol	Maceration	0.25	10	[102]
		Ethyl acetate	Maceration for 72 h	2.5	24	[105]
		–	Cold press	n.a.	0	[106]
		Methanol	Maceration for 48 h at RT	25	4.81	[96]
		Methanol	Mechanical shaking for 24 h at RT	16	14	[9]
		Water	Maceration for 24 h at RT	6.25	6	[104]
		Ethanol	Maceration for 24 h at RT	6.25	6	[104]
		1 M NaOH	Precipitation	n.a.	0	[107]
		Water	Maceration for 48 h	20	15	[109]
		Methanol	Maceration for 24 h at RT	125	11.33	[112]
+	*S. epidermidis*	–	Cold press	n.a.	0	[106]
+	*Staphylococcus* spp.	Chloroform	Cold extraction for 72 h	n.a.	0	[103]
		Methanol	Cold extraction for 72 h	n.a.	9.3	[103]
		Water	Cold extraction for 72 h	n.a.	0.5	[103]
		Chloroform	Soxhlet for 6 h	n.a.	5.33	[103]
		Methanol	Soxhlet for 6 h	n.a.	6	[103]
+	*Enterococcus faecalis*	70% Ethanol	Orbital shaking for 24 h	>400	0	[111]
+	*Streptococcus pyogenes*	Methanol	Maceration for 7 d at RT	0.25	20	[102]
+	*S. thermophilus*	Methanol	Mechanical shaking for 24 h at RT	4	8	[9]

n.a.: not applicable; RT: room temperature.

5. Conclusions and Future Perspectives

The findings of this study suggest that extracts obtained from the by-products of *C. lanatus* have antibacterial properties against particular strains of bacteria. The extraction methods employed, including cold maceration, Soxhlet extraction, and the use of ethyl acetate and hexane as solvents, demonstrate promising antibacterial extracts. The majority of the microorganisms that were examined exhibited susceptibility to the extracts. Consequently, the utilization of watermelon by-products as potential reservoirs of antibacterial compounds should be explored. The utilization of these by-products has the potential to enhance the sustainability of various industries, including food, pharmaceuticals, and cosmetics, as they contain valuable bioactive compounds. This approach offers a viable strategy for mitigating food waste and its associated environmental consequences. These items are expected to be beneficial, especially in underdeveloped nations where nutritional deficiencies are commonly prevalent. Furthermore, the use of waste by-products in the fields of agri-food, pharmaceutical preparation, immunonutrients, and nutraceuticals can be employed in order to prevent their disposal as landfill garbage. Additionally, the bioavailability, biological activity, and toxicological assessment of watermelon by-products should be examined in order to assess their potential interactions with other constituents of food and physiological systems, hence establishing their suitability for human ingestion. Moreover, it is recommended to conduct a compositional analysis to compare these by-products with other by-products obtained from fruit waste. The formulation and execution of strategies play a crucial role in optimizing the value of by-products derived from watermelons and efficiently harnessing them for the production of nutraceuticals and functional food products with extended shelf-life. The continuous advance of research and innovation will result in the creation of highly refined and potent preservatives that can be effectively utilized across a wide range of consumer goods. It may be possible to create new natural preservatives that have a weak antimicrobial effect over extended periods of time. This is significant both at a national and international level.

Author Contributions: Conceptualization, V.A., T.C. and S.I.L.; writing—original draft preparation, D.K., K.K., E.B. and M.M.; writing—review and editing, V.A., T.C., D.K., K.K., E.B., M.M. and S.I.L.; visualization, D.K., K.K. and M.M.; supervision, V.A., T.C. and S.I.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Deshmukh, C.D.; Jain, A.; Tambe, M.S. Phytochemical and Pharmacological Profile of *Citrullus lanatus* (THUNB). *Biolife* **2015**, *3*, 483–488. [CrossRef]
2. Zamuz, S.; Munekata, P.E.S.; Gullón, B.; Rocchetti, G.; Montesano, D.; Lorenzo, J.M. *Citrullus lanatus* as Source of Bioactive Components: An up-to-Date Review. *Trends Food Sci. Technol.* **2021**, *111*, 208–222. [CrossRef]
3. Zia, S.; Khan, M.R.; Mousavi Khaneghah, A.; Aadil, R.M. Characterization, Bioactive Compounds, and Antioxidant Profiling of Edible and Waste Parts of Different Watermelon (*Citrullus lanatus*) Cultivars. *Biomass Conv. Bioref.* **2023**, 1–13. [CrossRef]
4. Brahmi, F.; Chennit, B.; Batrouni, H.; Benallaoua, K.; Madani, K.; Boulekbache-Makhlouf, L. Valorization of Apricot, Melon, and Watermelon by-Products by Extracting Vegetable Oils from Their Seeds and Formulating Margarine. *OCL* **2023**, *30*, 11. [CrossRef]
5. Maoto, M.M.; Beswa, D.; Jideani, A.I.O. Watermelon as a Potential Fruit Snack. *Int. J. Food Prop.* **2019**, *22*, 355–370. [CrossRef]
6. Benmeziane, F.; Derradji, M. Composition, Bioactive Potential and Food Applications of Watermelon (*Citrullus lanatus*) Seeds—A Review. *J. Food Meas. Charact.* **2023**, *17*, 5045–5061. [CrossRef]
7. Jibril, M.M.; Abdul-Hamid, A.; Ghazali, H.M.; Dek, M.S.P.; Ramli, N.S.; Jaafar, A.H.; Karrupan, J.; Mohammed, A.S. Antidiabetic Antioxidant and Phytochemical Profile of Yellow-Fleshed Seeded Watermelon (*Citrullus lanatus*) Extracts. *J. Food Nutr. Res.* **2019**, *7*, 82–95. [CrossRef]

8. Elsayed, D.A.; Yousof, S.M.; Khalil, I.A.; Kolieb, E.; Zayed, M.A. Citrullus lanatus (Watermelon) Wastes: Maximizing the Benefits and Saving the Environment. In *Mediterranean Fruits Bio-wastes: Chemistry, Functionality and Technological Applications*; Ramadan, M.F., Farag, M.A., Eds.; Springer International Publishing: Cham, Switzerland, 2022; pp. 647–665, ISBN 978-3-030-84436-3.
9. Neglo, D.; Tettey, C.O.; Essuman, E.K.; Kortei, N.K.; Boakye, A.A.; Hunkpe, G.; Amarh, F.; Kwashie, P.; Devi, W.S. Comparative Antioxidant and Antimicrobial Activities of the Peels, Rind, Pulp and Seeds of Watermelon (*Citrullus lanatus*) Fruit. *Sci. Afr.* **2021**, *11*, e00582. [CrossRef]
10. Ouassor, I.; Aqil, Y.; Belmaghraoui, W.; Hajjaji, S.E. Characterization of Two Moroccan Watermelon Seeds Oil Varieties by Three Different Extraction Methods. *OCL* **2020**, *27*, 13. [CrossRef]
11. Mushtaq, M.; Sultana, B.; Bhatti, H.N.; Asghar, M. RSM Based Optimized Enzyme-Assisted Extraction of Antioxidant Phenolics from Underutilized Watermelon (*Citrullus lanatus* Thunb.) Rind. *J. Food Sci. Technol.* **2015**, *52*, 5048–5056. [CrossRef]
12. Gupta, R.; Kumar, G.; Singh, G.; Malik, J.; Siroliya, V.; Maurya, N. Ethnomedicinal Significance of *Citrullus lanatus* (Watermelon): A Pharmacological Review. *Int. J. Pharm. Clin. Res.* **2023**, *5*, 1–5. [CrossRef]
13. Sultan, R.S.; Shawkat, M.S.; Hadi, S.M. Antimicrobial, Antibiofilm and Antiplasmid Activity of Fruit Peel Extracts on Bacterial Dental Caries. *Curr. Res. Microbiol. Biotechnol.* **2017**, *5*, 1266–1272.
14. Zia, S.; Khan, M.R.; Shabbir, M.A.; Aadil, R.M. An Update on Functional, Nutraceutical and Industrial Applications of Watermelon by-Products: A Comprehensive Review. *Trends Food Sci. Technol.* **2021**, *114*, 275–291. [CrossRef]
15. Hasanin, M.S.; Hashem, A.H.; Abd El-Sayed, E.S.; El-Saied, H. Green Ecofriendly Bio-Deinking of Mixed Office Waste Paper Using Various Enzymes from *Rhizopus microsporus* AH3: Efficiency and Characteristics. *Cellulose* **2020**, *27*, 4443–4453. [CrossRef]
16. Efenberger-Szmechtyk, M.; Nowak, A.; Czyzowska, A. Plant Extracts Rich in Polyphenols: Antibacterial Agents and Natural Preservatives for Meat and Meat Products. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 149–178. [CrossRef] [PubMed]
17. Olmos, D.; González-Benito, J. Polymeric Materials with Antibacterial Activity: A Review. *Polymers* **2021**, *13*, 613. [CrossRef]
18. Yuan, G.; Guan, Y.; Yi, H.; Lai, S.; Sun, Y.; Cao, S. Antibacterial Activity and Mechanism of Plant Flavonoids to Gram-Positive Bacteria Predicted from Their Lipophilicities. *Sci. Rep.* **2021**, *11*, 10471. [CrossRef]
19. Yu, H.; Liu, Y.; Li, L.; Guo, Y.; Xie, Y.; Cheng, Y.; Yao, W. Ultrasound-Involved Emerging Strategies for Controlling Foodborne Microbial Biofilms. *Trends Food Sci. Technol.* **2020**, *96*, 91–101. [CrossRef]
20. Wang, Z.; Sun, Q.; Zhang, H.; Wang, J.; Fu, Q.; Qiao, H.; Wang, Q. Insight into Antibacterial Mechanism of Polysaccharides: A Review. *LWT* **2021**, *150*, 111929. [CrossRef]
21. Zheng, D.; Huang, C.; Huang, H.; Zhao, Y.; Khan, M.R.U.; Zhao, H.; Huang, L. Antibacterial Mechanism of Curcumin: A Review. *Chem. Biodivers.* **2020**, *17*, e2000171. [CrossRef]
22. Abou Baker, D.H. An Ethnopharmacological Review on the Therapeutical Properties of Flavonoids and Their Mechanisms of Actions: A Comprehensive Review Based on up to Date Knowledge. *Toxicol. Rep.* **2022**, *9*, 445–469. [CrossRef] [PubMed]
23. Martinez-Font, E.; Pérez-Capó, M.; Ramos, R.; Felipe, I.; Garcías, C.; Luna, P.; Terrasa, J.; Martín-Broto, J.; Vögler, O.; Alemany, R.; et al. Impact of Wnt/β-Catenin Inhibition on Cell Proliferation through CDC25A Downregulation in Soft Tissue Sarcomas. *Cancers* **2020**, *12*, 2556. [CrossRef] [PubMed]
24. Buranrat, B.; Noiwetch, S.; Suksar, T.; Ta-ut, A. Inhibition of Cell Proliferation and Migration by *Oroxylum indicum* Extracts on Breast Cancer Cells via Rac1 Modulation. *J. Pharm. Anal.* **2020**, *10*, 187–193. [CrossRef] [PubMed]
25. Li, N.; Zeng, J.; Sun, F.; Tong, X.; Meng, G.; Wu, C.; Ding, X.; Liu, L.; Han, M.; Lu, C.; et al. P27 Inhibits CDK6/CCND1 Complex Formation Resulting in Cell Cycle Arrest and Inhibition of Cell Proliferation. *Cell Cycle* **2018**, *17*, 2335–2348. [CrossRef] [PubMed]
26. Pu, W.; Han, X.; He, L.; Li, Y.; Huang, X.; Zhang, M.; Lv, Z.; Yu, W.; Wang, Q.-D.; Cai, D.; et al. A Genetic System for Tissue-Specific Inhibition of Cell Proliferation. *Development* **2020**, *147*, dev183830. [CrossRef]
27. Guo, W.; Chen, Z.; Chen, Z.; Yu, J.; Liu, H.; Li, T.; Lin, T.; Chen, H.; Zhao, M.; Li, G.; et al. Promotion of Cell Proliferation through Inhibition of Cell Autophagy Signalling Pathway by Rab3IP Is Restrained by MicroRNA-532-3p in Gastric Cancer. *J. Cancer* **2018**, *9*, 4363–4373. [CrossRef]
28. Mo, M.; Liu, S.; Ma, X.; Tan, C.; Wei, L.; Sheng, Y.; Song, Y.; Zeng, X.; Huang, D.; Qiu, X. A Liver-Specific lncRNA, FAM99B, Suppresses Hepatocellular Carcinoma Progression through Inhibition of Cell Proliferation, Migration, and Invasion. *J. Cancer Res. Clin. Oncol.* **2019**, *145*, 2027–2038. [CrossRef]
29. Bae, S.H.; Park, J.H.; Choi, H.G.; Kim, H.; Kim, S.H. Imidazole Antifungal Drugs Inhibit the Cell Proliferation and Invasion of Human Breast Cancer Cells. *Biomol. Ther.* **2018**, *26*, 494–502. [CrossRef]
30. Yoshimura, H.; Yoshida, H.; Matsuda, S.; Ryoke, T.; Ohta, K.; Ohmori, M.; Yamamoto, S.; Kiyoshima, T.; Kobayashi, M.; Sano, K. The Therapeutic Potential of Epigallocatechin-3-gallate against Human Oral Squamous Cell Carcinoma through Inhibition of Cell Proliferation and Induction of Apoptosis: In Vitro and in Vivo Murine Xenograft Study. *Mol. Med. Rep.* **2019**, *20*, 1139–1148. [CrossRef]
31. Danish, P.; Ali, Q.; Hafeez, M.M.; Malik, A. Antifungal and Antibacterial Activity of *Aloe vera* Plant Extract. *Biol. Clin. Sci. Res. J.* **2020**, *2020*, 1–8. [CrossRef]
32. Uddin, T.M.; Chakraborty, A.J.; Khusro, A.; Zidan, B.R.M.; Mitra, S.; Emran, T.B.; Dhama, K.; Ripon, M.K.H.; Gajdács, M.; Sahibzada, M.U.K.; et al. Antibiotic Resistance in Microbes: History, Mechanisms, Therapeutic Strategies and Future Prospects. *J. Infect. Public Health* **2021**, *14*, 1750–1766. [CrossRef] [PubMed]
33. Biharee, A.; Sharma, A.; Kumar, A.; Jaitak, V. Antimicrobial Flavonoids as a Potential Substitute for Overcoming Antimicrobial Resistance. *Fitoterapia* **2020**, *146*, 104720. [CrossRef] [PubMed]

34. Mahdi, M.A.; Yousefi, S.R.; Jasim, L.S.; Salavati-Niasari, M. Green Synthesis of DyBa2Fe3O7.988/DyFeO3 Nanocomposites Using Almond Extract with Dual Eco-Friendly Applications: Photocatalytic and Antibacterial Activities. *Int. J. Hydrogen Energy* **2022**, *47*, 14319–14330. [CrossRef]
35. Farhadi, F.; Khameneh, B.; Iranshahi, M.; Iranshahy, M. Antibacterial Activity of Flavonoids and Their Structure–Activity Relationship: An Update Review. *Phytother. Res.* **2019**, *33*, 13–40. [CrossRef] [PubMed]
36. Wang, X.; Shen, Y.; Thakur, K.; Han, J.; Zhang, J.-G.; Hu, F.; Wei, Z.-J. Antibacterial Activity and Mechanism of Ginger Essential Oil against *Escherichia coli* and *Staphylococcus aureus*. *Molecules* **2020**, *25*, 3955. [CrossRef] [PubMed]
37. Bédard, F.; Hammami, R.; Zirah, S.; Rebuffat, S.; Fliss, I.; Biron, E. Synthesis, Antimicrobial Activity and Conformational Analysis of the Class IIa Bacteriocin Pediocin PA-1 and Analogs Thereof. *Sci. Rep.* **2018**, *8*, 9029. [CrossRef]
38. Simões, D.; Miguel, S.P.; Ribeiro, M.P.; Coutinho, P.; Mendonça, A.G.; Correia, I.J. Recent Advances on Antimicrobial Wound Dressing: A Review. *Eur. J. Pharm. Biopharm.* **2018**, *127*, 130–141. [CrossRef]
39. Lee, B.S.; Kalia, N.P.; Jin, X.E.F.; Hasenoehrl, E.J.; Berney, M.; Pethe, K. Inhibitors of Energy Metabolism Interfere with Antibiotic-Induced Death in Mycobacteria. *J. Biol. Chem.* **2019**, *294*, 1936–1943. [CrossRef]
40. Cui, H.; Zhang, C.; Li, C.; Lin, L. Antibacterial Mechanism of Oregano Essential Oil. *Ind. Crops Prod.* **2019**, *139*, 111498. [CrossRef]
41. Yan, Y.; Li, X.; Zhang, C.; Lv, L.; Gao, B.; Li, M. Research Progress on Antibacterial Activities and Mechanisms of Natural Alkaloids: A Review. *Antibiotics* **2021**, *10*, 318. [CrossRef]
42. Barbosa, L.N.; Alves, F.C.B.; Andrade, B.F.M.T.; Albano, M.; Rall, V.L.M.; Fernandes, A.A.H.; Buzalaf, M.A.R.; Leite, A.D.L.; De Pontes, L.G.; Dos Santos, L.D.; et al. Proteomic Analysis and Antibacterial Resistance Mechanisms of *Salmonella enteritidis* Submitted to the Inhibitory Effect of *Origanum vulgare* Essential Oil, Thymol and Carvacrol. *J. Proteom.* **2020**, *214*, 103625. [CrossRef]
43. Guo, Y.; Liu, Y.; Zhang, Z.; Chen, M.; Zhang, D.; Tian, C.; Liu, M.; Jiang, G. The Antibacterial Activity and Mechanism of Action of Luteolin Against *Trueperella pyogenes*. *Infect. Drug Resist.* **2020**, *13*, 1697–1711. [CrossRef] [PubMed]
44. Sun, X.; Zhou, T.; Wei, C.; Lan, W.; Zhao, Y.; Pan, Y.; Wu, V.C.H. Antibacterial Effect and Mechanism of Anthocyanin Rich Chinese Wild Blueberry Extract on Various Foodborne Pathogens. *Food Control* **2018**, *94*, 155–161. [CrossRef]
45. Doyle, A.A.; Stephens, J.C. A Review of Cinnamaldehyde and Its Derivatives as Antibacterial Agents. *Fitoterapia* **2019**, *139*, 104405. [CrossRef]
46. Liu, M.; Feng, M.; Yang, K.; Cao, Y.; Zhang, J.; Xu, J.; Hernández, S.H.; Wei, X.; Fan, M. Transcriptomic and Metabolomic Analyses Reveal Antibacterial Mechanism of *Astringent Persimmon* Tannin against Methicillin-Resistant *Staphylococcus aureus* Isolated from Pork. *Food Chem.* **2020**, *309*, 125692. [CrossRef]
47. Ben Lagha, A.; Andrian, E.; Grenier, D. Resveratrol Attenuates the Pathogenic and Inflammatory Properties of *Porphyromonas gingivalis*. *Mol. Oral Microbiol.* **2019**, *34*, 118–130. [CrossRef]
48. Wang, W.; Huang, X.; Yang, H.; Niu, X.; Li, D.; Yang, C.; Li, L.; Zou, L.; Qiu, Z.; Wu, S.; et al. Antibacterial Activity and Anti-Quorum Sensing Mediated Phenotype in Response to Essential Oil from *Melaleuca bracteata* Leaves. *Int. J. Mol. Sci.* **2019**, *20*, 5696. [CrossRef]
49. Jiang, L.; Yi, T.; Shen, Z.; Teng, Z.; Wang, J. Aloe-Emodin Attenuates *Staphylococcus aureus* Pathogenicity by Interfering With the Oligomerization of α-Toxin. *Front. Cell. Infect. Microbiol.* **2019**, *9*, 157. [CrossRef]
50. Liu, H.; Wang, Y.; Cao, J.; Jiang, H.; Yao, J.; Gong, G.; Chen, X.; Xu, W.; He, X. Antimicrobial Activity and Virulence Attenuation of Citral against the Fish Pathogen *Vibrio alginolyticus*. *Aquaculture* **2020**, *515*, 734578. [CrossRef]
51. Abdolhosseini, M.; Zamani, H.; Salehzadeh, A. Synergistic Antimicrobial Potential of Ciprofloxacin with Silver Nanoparticles Conjugated to Thiosemicarbazide against Ciprofloxacin Resistant *Pseudomonas aeruginosa* by Attenuation of MexA-B Efflux Pump Genes. *Biologia* **2019**, *74*, 1191–1196. [CrossRef]
52. LewisOscar, F.; Nithya, C.; Alharbi, S.A.; Alharbi, N.S.; Thajuddin, N. In Vitro and in Silico Attenuation of Quorum Sensing Mediated Pathogenicity in *Pseudomonas aeruginosa* Using *Spirulina Platensis*. *Microb. Pathog.* **2018**, *116*, 246–256. [CrossRef] [PubMed]
53. Parai, D.; Banerjee, M.; Dey, P.; Mukherjee, S.K. Reserpine Attenuates Biofilm Formation and Virulence of *Staphylococcus aureus*. *Microb. Pathog.* **2020**, *138*, 103790. [CrossRef] [PubMed]
54. Shen, Y.; Loessner, M.J. Beyond Antibacterials—Exploring Bacteriophages as Antivirulence Agents. *Curr. Opin. Biotechnol.* **2021**, *68*, 166–173. [CrossRef]
55. Barabadi, H.; Mojab, F.; Vahidi, H.; Marashi, B.; Talank, N.; Hosseini, O.; Saravanan, M. Green Synthesis, Characterization, Antibacterial and Biofilm Inhibitory Activity of Silver Nanoparticles Compared to Commercial Silver Nanoparticles. *Inorg. Chem. Commun.* **2021**, *129*, 108647. [CrossRef]
56. Mi, G.; Shi, D.; Wang, M.; Webster, T.J. Reducing Bacterial Infections and Biofilm Formation Using Nanoparticles and Nanostructured Antibacterial Surfaces. *Adv. Healthc. Mater.* **2018**, *7*, 1800103. [CrossRef]
57. Rather, M.A.; Gupta, K.; Mandal, M. Microbial Biofilm: Formation, Architecture, Antibiotic Resistance, and Control Strategies. *Braz. J. Microbiol.* **2021**, *52*, 1701–1718. [CrossRef] [PubMed]
58. Wasfi, R.; Abd El-Rahman, O.A.; Zafer, M.M.; Ashour, H.M. Probiotic *Lactobacillus Sp*. Inhibit Growth, Biofilm Formation and Gene Expression of Caries-Inducing *Streptococcus mutans*. *J. Cell. Mol. Med.* **2018**, *22*, 1972–1983. [CrossRef] [PubMed]

59. Wang, H.; Cai, L.; Li, Y.; Xu, X.; Zhou, G. Biofilm Formation by Meat-Borne *Pseudomonas Fluorescens* on Stainless Steel and Its Resistance to Disinfectants. *Food Control* **2018**, *91*, 397–403. [CrossRef]
60. Wasfi, R.; Hamed, S.M.; Amer, M.A.; Fahmy, L.I. Proteus Mirabilis Biofilm: Development and Therapeutic Strategies. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 414. [CrossRef]
61. Colquhoun, J.M.; Rather, P.N. Insights Into Mechanisms of Biofilm Formation in *Acinetobacter baumannii* and Implications for Uropathogenesis. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 253. [CrossRef]
62. Vazquez-Armenta, F.J.; Bernal-Mercado, A.T.; Tapia-Rodriguez, M.R.; Gonzalez-Aguilar, G.A.; Lopez-Zavala, A.A.; Martinez-Tellez, M.A.; Hernandez-Oñate, M.A.; Ayala-Zavala, J.F. Quercetin Reduces Adhesion and Inhibits Biofilm Development by *Listeria monocytogenes* by Reducing the Amount of Extracellular Proteins. *Food Control* **2018**, *90*, 266–273. [CrossRef]
63. Ong, K.S.; Mawang, C.I.; Daniel-Jambun, D.; Lim, Y.Y.; Lee, S.M. Current Anti-Biofilm Strategies and Potential of Antioxidants in Biofilm Control. *Expert Rev. Anti Infect. Ther.* **2018**, *16*, 855–864. [CrossRef] [PubMed]
64. Lee, S.W.; Phillips, K.S.; Gu, H.; Kazemzadeh-Narbat, M.; Ren, D. How Microbes Read the Map: Effects of Implant Topography on Bacterial Adhesion and Biofilm Formation. *Biomaterials* **2021**, *268*, 120595. [CrossRef]
65. Dunne, W.M. Bacterial Adhesion: Seen Any Good Biofilms Lately? *Clin. Microbiol. Rev.* **2002**, *15*, 155–166. [CrossRef]
66. Singh, A.; Dubey, A.K. Various Biomaterials and Techniques for Improving Antibacterial Response. *ACS Appl. Bio Mater.* **2018**, *1*, 3–20. [CrossRef]
67. Lim, H.-S.; Yeu, J.-E.; Hong, S.-P.; Kang, M.-S. Characterization of Antibacterial Cell-Free Supernatant from Oral Care Probiotic *Weissella cibaria*, CMU. *Molecules* **2018**, *23*, 1984. [CrossRef]
68. Jones, I.A.; Joshi, L.T. Biocide Use in the Antimicrobial Era: A Review. *Molecules* **2021**, *26*, 2276. [CrossRef]
69. Xiang, Q.; Kang, C.; Niu, L.; Zhao, D.; Li, K.; Bai, Y. Antibacterial Activity and a Membrane Damage Mechanism of Plasma-Activated Water against *Pseudomonas deceptionensis* CM2. *LWT* **2018**, *96*, 395–401. [CrossRef]
70. Ma, Y.; Xu, H.; Sun, B.; Du, S.; Cui, S.; Zhang, L.; Ding, N.; Yang, D. pH-Responsive Oxygen and Hydrogen Peroxide Self-Supplying Nanosystem for Photodynamic and Chemodynamic Therapy of Wound Infection. *ACS Appl. Mater. Interfaces* **2021**, *13*, 59720–59730. [CrossRef]
71. Elgamouz, A.; Idriss, H.; Nassab, C.; Bihi, A.; Bajou, K.; Hasan, K.; Abu Haija, M.; Patole, S.P. Green Synthesis, Characterization, Antimicrobial, Anti-Cancer, and Optimization of Colorimetric Sensing of Hydrogen Peroxide of Algae Extract Capped Silver Nanoparticles. *Nanomaterials* **2020**, *10*, 1861. [CrossRef]
72. Ijaz, M.; Zafar, M.; Islam, A.; Afsheen, S.; Iqbal, T. A Review on Antibacterial Properties of Biologically Synthesized Zinc Oxide Nanostructures. *J. Inorg. Organomet. Polym. Mater.* **2020**, *30*, 2815–2826. [CrossRef]
73. Lam, P.-L.; Wong, R.S.-M.; Lam, K.-H.; Hung, L.-K.; Wong, M.-M.; Yung, L.-H.; Ho, Y.-W.; Wong, W.-Y.; Hau, D.K.-P.; Gambari, R.; et al. The Role of Reactive Oxygen Species in the Biological Activity of Antimicrobial Agents: An Updated Mini Review. *Chem. Biol. Interact.* **2020**, *320*, 109023. [CrossRef] [PubMed]
74. Nolan, V.C.; Harrison, J.; Cox, J.A.G. Dissecting the Antimicrobial Composition of Honey. *Antibiotics* **2019**, *8*, 251. [CrossRef]
75. Masoura, M.; Passaretti, P.; Overton, T.W.; Lund, P.A.; Gkatzionis, K. Use of a Model to Understand the Synergies Underlying the Antibacterial Mechanism of H_2O_2-Producing Honeys. *Sci. Rep.* **2020**, *10*, 17692. [CrossRef]
76. Yan, L.-G.; He, L.; Xi, J. High Intensity Pulsed Electric Field as an Innovative Technique for Extraction of Bioactive Compounds—A Review. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 2877–2888. [CrossRef]
77. Lama-Muñoz, A.; Contreras, M.D.M.; Espínola, F.; Moya, M.; Romero, I.; Castro, E. Content of Phenolic Compounds and Mannitol in Olive Leaves Extracts from Six Spanish Cultivars: Extraction with the Soxhlet Method and Pressurized Liquids. *Food Chem.* **2020**, *320*, 126626. [CrossRef]
78. Rifna, E.J.; Misra, N.N.; Dwivedi, M. Recent Advances in Extraction Technologies for Recovery of Bioactive Compounds Derived from Fruit and Vegetable Waste Peels: A Review. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 719–752. [CrossRef] [PubMed]
79. Luque de Castro, M.D.; Priego-Capote, F. Soxhlet Extraction: Past and Present Panacea. *J. Chromatogr. A* **2010**, *1217*, 2383–2389. [CrossRef]
80. Nuralın, L.; Gürü, M. Berberis Vulgaris Fruit: Determination of Phenolic Compounds in Extracts Obtained by Supercritical CO_2 and Soxhlet Methods Using HPLC. *Food Anal. Methods* **2022**, *15*, 877–889. [CrossRef]
81. Kusuma, S.B.; Wulandari, S.; Nurfitriani, R.A.; Awaludin, A. The Potential Solvent for Tannin Extraction as a Feed Additive Made of Coffee Husk (*Coffea canephora*) Using Soxhlet Method. *IOP Conf. Ser. Earth Environ. Sci.* **2022**, *980*, 012024. [CrossRef]
82. Sankeshwari, R.M.; Ankola, A.V.; Bhat, K.; Hullatti, K. Soxhlet versus Cold Maceration: Which Method Gives Better Antimicrobial Activity to Licorice Extract Against: *Streptococcus Mutans*? *J. Sci. Soc.* **2018**, *45*, 67. [CrossRef]
83. Ćujić, N.; Šavikin, K.; Janković, T.; Pljevljakušić, D.; Zdunić, G.; Ibrić, S. Optimization of Polyphenols Extraction from Dried Chokeberry Using Maceration as Traditional Technique. *Food Chem.* **2016**, *194*, 135–142. [CrossRef]
84. Gori, A.; Boucherle, B.; Rey, A.; Rome, M.; Fuzzati, N.; Peuchmaur, M. Development of an Innovative Maceration Technique to Optimize Extraction and Phase Partition of Natural Products. *Fitoterapia* **2021**, *148*, 104798. [CrossRef]
85. Safdar, M.N.; Kausar, T.; Nadeem, M. Comparison of Ultrasound and Maceration Techniques for the Extraction of Polyphenols from the Mango Peel: The Potential of Ultrasound Against Maceration. *J. Food Process. Preserv.* **2017**, *41*, e13028. [CrossRef]
86. Aleixandre-Tudo, J.L.; Du Toit, W. Cold Maceration Application in Red Wine Production and Its Effects on Phenolic Compounds: A Review. *LWT* **2018**, *95*, 200–208. [CrossRef]

87. Wojdyło, A.; Samoticha, J.; Chmielewska, J. Effect of Different Pre-Treatment Maceration Techniques on the Content of Phenolic Compounds and Color of Dornfelder Wines Elaborated in Cold Climate. *Food Chem.* **2021**, *339*, 127888. [CrossRef] [PubMed]
88. Lucena, R. Extraction and Stirring Integrated Techniques: Examples and Recent Advances. *Anal. Bioanal. Chem.* **2012**, *403*, 2213–2223. [CrossRef] [PubMed]
89. Dehghan, A.; Gholizadeh, A.; Navidbakhsh, M.; Sadeghi, H.; Pishbin, E. Integrated Microfluidic System for Efficient DNA Extraction Using On-Disk Magnetic Stirrer Micromixer. *Sens. Actuators B Chem.* **2022**, *351*, 130919. [CrossRef]
90. Ranjbari, E.; Hadjmohammadi, M.R. Optimization of Magnetic Stirring Assisted Dispersive Liquid–Liquid Microextraction of Rhodamine B and Rhodamine 6G by Response Surface Methodology: Application in Water Samples, Soft Drink, and Cosmetic Products. *Talanta* **2015**, *139*, 216–225. [CrossRef]
91. Sun, T.; Beiyuan, J.; Gielen, G.; Mao, X.; Song, Z.; Xu, S.; Ok, Y.S.; Rinklebe, J.; Liu, D.; Hou, D.; et al. Optimizing Extraction Procedures for Better Removal of Potentially Toxic Elements during EDTA-Assisted Soil Washing. *J. Soils Sediments* **2020**, *20*, 3417–3426. [CrossRef]
92. Hamidi, Y.; Ataei, S.A.; Sarrafi, A. A Simple, Fast and Low-Cost Method for the Efficient Separation of Hydrocarbons from Oily Sludge. *J. Hazard. Mater.* **2021**, *413*, 125328. [CrossRef] [PubMed]
93. Othman, N.; Azhar, N.; Megat Abdul Rani, P.S.; Mohamed Zaini, H. Metal Removal and Antimicrobial Properties of Watermelon Rind Modified with Clove. *MATEC Web Conf.* **2016**, *78*, 01028. [CrossRef]
94. Harith, S.S. Studies on Phytochemical Constituents and Antimicrobial Properties of *Citrullus lanatus* Peels. *Malays. J. Anal. Sci.* **2018**, *22*, 151–156. [CrossRef]
95. Rai, P. Fruit's and Vegetable's Peels: Antimicrobial Activity. *World J. Pharm. Res.* **2019**, *8*, 1141–1153. [CrossRef]
96. Osinubi, A.D.; Banjoko, O.O.; Anselm, O.H.; Akinrinola, O.M.; Osofodunrin, A. Comparative Effects of Drying Methods on Phytochemical Contents and Anti-Microbial Activities of Watermelon (*Citrullus lanatus*) Seed and Rind. *J. Chem. Soc. Niger.* **2020**, *45*, 70–78.
97. Ashok Patil, T.; Jain, L. Natural Preservatives from Fruit Peels. *Acta Sci. Microbiol.* **2020**, *3*, 152–157. [CrossRef]
98. Zahid, A.; Mahmood, K.; Sajjad, A.; Khalid, N.; Raziq, S.A.; Zaman, S. Characterization and Antimicrobial Activity of Different Varieties of *Citrullus lanatus* Rind of Balochistan. *Eur. Acad. Res.* **2021**, *9*, 5055–5066.
99. Govindaraj, A.; Paulpandian, S.S.; Shanmugam, R. Comparative Evaluation of The Effect of Rind and Pulp Extract of *Citrullus lanatus* on *Streptococcus mutans*. *Ann. Dent. Spec.* **2022**, *10*, 34–39. [CrossRef]
100. Toupal, S.; Coşansu, S. Antioxidant and Antimicrobial Properties of Freeze-Dried Banana and Watermelon Peel Powders. *Food Humanit.* **2023**, *1*, 607–613. [CrossRef]
101. Rezagholizade-shirvan, A.; Shokri, S.; Dadpour, S.M.; Amiryousefi, M.R. Evaluation of Physicochemical, Antioxidant, Antibacterial Activity, and Sensory Properties of Watermelon Rind Candy. *Heliyon* **2023**, *9*, e17300. [CrossRef]
102. Sekar, M.; Sutharesan, N.; Mashi, D.; Hisham, M.; Shazni, M.; Meng, K.; Istiazzul, M.; Abdullah, M. Comparative Evaluation of Antimicrobial Properties of Red and Yellow Watermelon Seeds. *Int. J. Curr. Pharm. Res.* **2014**, *6*, 2014.
103. Adunola, A.T.; Chidimma, A.L.; Olatunde, D.S.; Peter, O.A. Antibacterial Activity of Watermelon (*Citrullus lanatus*) Seed against Selected Microorganisms. *Afr. J. Biotechnol.* **2015**, *14*, 1224–1229. [CrossRef]
104. Bello, H.S.; Ismail, H.Y.; Goje, M.H.; Mangga, H.K. Antimicrobial Activity of *Citrullus lanatus* (Watermelon) Seeds on Some Selected Bacteria. *J. Biotechnol. Res.* **2016**, *2*, 39–43.
105. Babaiwa, U.F.; Erharuyi, O.; Falodun, A.; Akerele, J.O. Antimicrobial Activity of Ethyl Acetate Extract of *Citrullus lanatus* Seeds. *Trop. J. Pharm. Res.* **2017**, *16*, 1631–1636. [CrossRef]
106. Marchwińska, K.; Michocka, K. The Antimicrobial Properties of Selected Oils Used as Cosmetics Compounds. *Stud. Oeconomica Posnaniensia* **2017**, *5*, 35–44. [CrossRef]
107. Łopusiewicz, Ł. Antioxidant, Antibacterial Properties and the Light Barrier Assessment of Raw and Purified Melanins Isolated from *Citrullus lanatus* (Watermelon) Seeds. *Herba Pol.* **2018**, *64*, 25–36. [CrossRef]
108. Sola, A.O.; Temitayo, O.O.; Olufunke, A.; Shittu, F. Chemical Composition, Nutritional Values and Antibacterial Activities of Watermelon Seed (*Citrullus lanatus*). *Int. J. Biochem. Res. Rev.* **2019**, *27*, 1–9. [CrossRef]
109. Babaiwa, U.F.; Eraga, S.O.; Akerele, J.O. Antimicrobial and Time-Kill Kinetics of the Aqueous Extract of *Citrullus lanatus* (Thunb.) Seeds. *Bio-Research* **2020**, *18*, 1103–1110. [CrossRef]
110. Jebir, R.; Mustafa, Y. Novel Coumarins Isolated from the Seeds of *Citrullus lanatus* as Potential Antimicrobial Agents. *Eurasian Chem. Commun.* **2022**, *4*, 692–708. [CrossRef]
111. Olude, O.; Paul, A.; Oluwatobi, A.; Patrick, I. Comparative Activities of Phytochemical, Antioxidant and Antimicrobial Properties of Leaf Extracts of *Bryophyllum pinnatum* (Lam.), Alchornea Cordifolia (Schumach. & Thonn.), Acalypha Wilkesiana (Muell. Arg) and Seed Extract of *Citrullus lanatus* (Thunb.). *Covenant J. Phys. Life Sci.* **2022**, *10*, 1–9.
112. Smajovic, A.; Deumic, S.; Crncevic, N.; Hadzic, S.; Alagic, S.; Music Elma, N.; Salihovic, M.; Pazalja, M.; Omeragic, E.; Dedic, M. Comparative Analysis of Chemical Composition and Antimicrobial Activity of Watermelon Seed Extracts (*Citrullus lanatus*). *PONTE Int. Sci. Res. J.* **2023**, *79*, 59–69. [CrossRef]
113. Mighan, N.M.; Ariaii, P.; Soltani, M.S.; Jafarian, S. Investigating the Possibility of Increasing the Microbial and Oxidative Stability of Silver Carp Burgers Using Hydrolyzed Protein of Watermelon Seeds. *Food Sci. Biotechnol.* **2023**, 1–14. [CrossRef]

114. Microbiological Specifications For, I.C.O. *Microorganisms in Foods 8: Use of Data for Assessing Process Control and Product Acceptance*; Springer: Boston, MA, USA, 2011; ISBN 978-1-4419-9373-1.
115. Kumar, P.; Kizhakkedathu, J.N.; Straus, S.K. Antimicrobial Peptides: Diversity, Mechanism of Action and Strategies to Improve the Activity and Biocompatibility In Vivo. *Biomolecules* **2018**, *8*, 4. [CrossRef] [PubMed]