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Review Article

Agro-Food Waste: Harnessing the Potential Significance of Natural Biofilm Inhibitors

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ABSTRACT

A biofilm is a natural form of a surface-attached community of bacterial cells bound to each other by an extracellular matrix. The challenge of biofilm-linked infections is the noteworthy resistance of bacterial cells to both host immune responses and available antibiotics. Moreover, the misuse of antibiotics led to the emergence and widespread occurrence of antimicrobial resistance among different pathogens, consequently, increasing the chronicity of biofilm-associated infections and threatening human lives. Natural products like plant-derived antibiofilm agents could offer more therapeutic efficiency with fewer adverse effects than conventional antimicrobials. Agro-food wastes are an abundant resource of antimicrobial phytoconstituents that can modulate different biofilm formation and development mechanisms. The accumulation of food biowaste in huge amounts results in adverse economic and environmental consequences. Therefore, valorization and recycling of this bio-waste have captured the attention and sparked the research interest of scientists all over the world. The main aim of the present review is to shed light on recent studies that delve into the antibiofilm potential of agro-food by-products as a sustainable resource of innovative and promising candidates. The latest articles from various databases such as the Egyptian Knowledge Bank, Scopus, Web of Science, PubMed, Google Scholar, Elsevier databases, and Dr. Duke's Phytochemical and Ethnobotanical Databases were screened over the period from 2017 to 2023. The major keywords for searching were biofilm inhibition, agro-food waste, natural origins, environmental sustainability, quorum-sensing mechanisms, and industrial by-products. In conclusion, agro-food waste is considered a sustainable resource of several precious bioactive compounds that could offer new promising antibiofilm candidates.

Keywords**:** Antibiofilm Agents; Agro-food Waste; Quorum-sensing; Valorization; Multidrug-resistant Pathogens; Bioactive Phytochemicals.

Introduction

The importance of discovering new valuable antibacterial agents arises from the danger of antibiotic-resistant bacteria, which is considered one of the most threatening human health obstacles. Infections with antibiotic-resistant bacteria could increase the global mortality to 1×10^8 by 2050 if no actual infection-control strategies are considered.[1] Antibiotic reckless use in treating infectious diseases in humans and animals significantly contributed to the development of multidrug resistance, which might provoke diseases associated with bacterial infection.[2,3] Biofilm-forming pathogens exhibited a superior resistance pattern to antibiotics in comparison to their planktonic cells giving rise to a major challenge in their infections treatment.[3–5]
Biofilms are complex structures of highly organized microorganism aggregates followed by cell division to form small clusters and microcolonies.[6] Moreover, they enable cells to endure unfavorable growth conditions as they are embedded in a protective extracellular polymeric matrix.[7,8] Proteins, polysaccharides, lipids, and extracellular DNA are the main components of the extracellular polymeric material that is considered an underlying factor in the pathogenesis of several antibiotic-resistant bacterial infections.[6,9]

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The formation of biofilms offers many advantages to bacterial cells, such as protecting them from adverse conditions, increasing the availability of nutrients, and facilitating irreversible attachment of the bacteria to living or abiotic surfaces.[10] Quorum-sensing (QS) is a cell-to-cell signaling mechanism that plays an important role in biofilm formation and development.[4] This communication allows bacteria to respond to population mass and create cooperative actions, such as proliferation and virulence.[10]
Multidrug-resistant bacteria spread drastically decreases conventional antibiotics' effectiveness.[10] Therefore, the search for natural antimicrobials that provide novel therapeutic strategies such as adhesion and biofilm formation block and/or quorum-sensing inhibition has raised the concern of researchers all over the world. Plants represent valuable natural sources of antibiofilm agents that could be directed at bacterial growth inhibition or pathogenicity reduction through the control of different virulence factors, in addition to quorum-sensing inhibition.[11] Several natural bioactives extracted from unused parts of plants, which are considered as waste material, have been reported for their potent antibiofilm properties.[10]
Agro-industrial processing and agricultural production are the largest global food by-products and waste material generators. Food transportation, storage, processing stages, and natural deterioration are also sources of food waste.[12] It is estimated that about a quarter to one-third of the yearly worldwide food production for human consumption becomes waste, equivalent to around 1,300 million tons of food.[13] The uncontrolled disposal of waste materials, either by burning, natural decaying on the soil, or incineration has a harmful impact on the environment and could give rise to serious pollution problems and soil contamination.[12,14] The valorization and resourceful utilization of enormous amounts of agro-food waste into different value-added products offer a great opportunity to support sustainable development,

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in addition to solving the environmental issues of conventional disposal methods.[14] Such exploration holds immense importance in addressing the growing challenge of microbial resistance and the limited efficacy of the current treatments. At the same instant, agro-food wastes are rich in nutrients and bioactive compounds such as phenolic acids, anthocyanins, flavonoids, stilbenes, and lignans that are reported for their antioxidant, anti-inflammatory, antibacterial, and antibiofilm effects.[5,13,15] There are various mechanisms for the antibacterial and antibiofilm activities of plant bioactives, such as increasing the permeability of the cell membrane, inhibiting the adhesion of pathogenic bacteria to host cells, blocking the transmembrane transport of nutrients or energy substances, and inhibiting the reproduction and quorum-sensing.[1]

This review article tackles a knowledge gap by exploring the importance of directing more research efforts towards the valorization and recycling of the vast amounts of agro-food by-products generated, which could have significant anti-biofilm effects and contribute to the production of medicinal drugs from their phytocompounds. In doing so, it not only fills a critical void in literature but also implements environmental and economic challenges associated with waste accumulation. By delving into the potential of food waste valorization, the article imparts valuable insights into sustainable and cost-effective strategies for combating multidrug-resistant microbial infections.

Methodology

Search Strategy

The data were collected from various databases such as the Egyptian Knowledge Bank, Scopus, Web of Science, PubMed, Google Scholar, Elsevier databases, and Dr. Duke's Phytochemical and Ethnobotanical Databases, until July 2023. A comprehensive search was conducted using all possible keywords related to biofilm inhibition, agro-food waste, natural origins, environmental sustainability, quorum-sensing mechanisms, industrial by-products, and clinical studies. The time of the article published was limited to the period from 2017 to 2023. Articles were selected based on the following criteria: quality criteria during the selection of studies and scoping of research, illustrative research article, high reproducibility, inventive potential within natural products, articles in biofilm and prevalence, articles in agro-food waste and anti-biofilm topic categories, and articles with phytotherapy evidence.

Biofilm Formation and Development Stages

According to the nature of the infectious microbes, the nutritional conditions, and the local environment of infection, the biofilm's particular structure, chemistry, and physiology become different.[7] Initiation of biofilm formation is a bacterial cell response to external antimicrobial or environmental stress. Bacterial microcolonies structure can differ significantly relying on the biofilm-forming bacterial species, therefore, the extracellular matrix composition, responsible for the intra-biofilm bacterial cells connection, varies between different bacterial species.[16] Biofilm formation is a complex process involving four successive stages including the adhesion of bacteria cells to the different materials of biotic or abiotic surfaces or to each other (the starting step), cell division, microcolonies formation, development of the biofilm structure, followed by extracellular matrix generation and biofilm maturation, and at final stage bacterial dispersion from the mature biofilm to discover new niches.[4,6,16] All of these steps are coordinated by quorum-sensing (QS) chemical signaling inside the biofilm bacterial communities.[5] QS signaling is a process of facilitating cell-to-cell connection, allowing bacterial cells to identify the population density and share information about it through detecting and measuring the increase in specific signal molecules secreted by the bacterial community.[17] Additionally, QS could control many traits including the bacterial expression of genes that encode for a cluster of virulence factors, such as exoenzymes, proteases, elastases, and pyocyanin. Moreover, QS manipulates the biofilm architecture and provides an inherent shield from external factors.[18] Targeting one or more biofilm formation stages or modulating quorum-sensing could offer optimistic and effective treatment strategies for biofilm-associated infection.

Food Waste Valorization

The food industry is the greatest generator of agro-food biowaste throughout the world. Remarkably, most of this waste is generated during the transformation of raw materials into different processed products.[13] In many developing countries, especially in Egypt, the management of industrial and agricultural solid waste has received a low precedence and limited funds due to inadequate available resources.[19,20] The annual agricultural waste amount in Egypt is about 30-35 million tons, whereas industrial waste occupies about 5-6 million tons.[21] Traditional and improper handling, storage, and disposal methods of large amounts of waste could lead to several negative environmental, social, and economic impacts.[19] Therefore, it is crucial to address these issues and find solutions to reduce waste accumulation. By doing so, we can not only protect the environment but also ensure that valuable resources are not wasted unnecessarily. To tackle the waste management crisis in Egypt and all over the world, a sustainable methodology should be applied to achieve proper management of waste accumulation issues starting with reducing the generated amounts, reusing, recycling, and valorization, as well as, introducing different waste treatment strategies such as thermal and biological methods.[20] Valorizing food waste is a fundamental key for supporting the sustainable development goals of enhancing food security, environmental protection, and energy productivity.[12] Massive efforts have been made to valorize food biowaste into valuable bioresources for energy, chemicals, and other high-value products.[22]

Several studies have underlined the richness of agro-food waste material and by-products with numerous valuable phytocompounds such as hydroxycinnamic and hydroxybenzoic acids, anthocyanins, flavonoids, stilbenes, tannins, and lignans. These reports have captured the interest of many researchers worldwide who are working on agro-food wastes and by-products valorization.[13] Many recent studies have discovered valuable and promising pharmacological and therapeutic effects of the biowaste-derived natural products including antioxidant, antimicrobial, and anti-biofilm activities which could provide novel strategies for facing multidrug-resistant pathogens and treatment of biofilm-based infections.

Agro-food biowaste with biofilm inhibitory effect

Onion peel

Onion (*Allium cepa* L., Amaryllidaceae) is one of the most economically important cultivated vegetables worldwide.[23] It is reported to have several medicinal properties and has been used in herbal medicine for a long time.[24] Among its medicinal activities are the antimicrobial properties against both Gram-negative and Gram-positive bacteria and fungi. Red, yellow, and white onions are extensively reported for their content of bioactive compounds, such as organo-sulfur compounds, flavonoids, phenolic acids, and anthocyanins. The outer dry scales are richer in phytoconstituents than the edible part of the plant.[25] Ethyl acetate fraction of the outer red onion skin showed in a recent study its potent anti-quorum-sensing action that was explored via investigating its inhibitory effect on violacein pigment production in *Chromobacterium violaceum*. In addition, the extract showed a significant reduction in quorum-sensing (QS) mediated virulence factors production like elastase, the Las A protease, and pyocyanin as well QS-mediated biofilm formation, EPS production, and swarming motility with the tested pathogens of *Pseudomonas aeruginosa*, *Chromobacterium violaceum*, and *Aeromonas hydrophila*.[26] A search of the literature revealed that red onion peel ethanolic extract could inhibit biofilm formation by *Listeria monocytogenes* strains without altering bacterial growth. In addition, it decreases the cell motility which is an important contributor to *L. monocytogenes* pathogenicity. It also significantly reduced the production of violacein suggesting its quorum-sensing interfering action.[27] In another advance, it was shown that the acidified ethanolic extract of red onion scales and its anthocyanins and flavonoids-enriched fractions showed potent *in vitro* antibiofilm effects against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Acinetobacter baumannii* pathogens. Moreover, all the tested samples significantly reduced the recovered bacterial load of MRSA from the infected vaginal tissue in MRSA vaginal colonization *in vivo* model in

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rats through strong *in vivo* antibiofilm activity.[28] Antibiofilm activity was also investigated for red onion peel methanolic extract. It displayed an effective biofilm inhibitory activity on the initial biofilm adherence and formation in addition to a little destructive effect on mature biofilm masses.[29]

Pomegranate peel

Pomegranate (*Punica granatum* L., Punicaceae) is one of the oldest cultivated fruits across the world. Its fruit juice processing industry generates a considerable quantity of waste fraction composed of the fruit residuals including the seed and the external peel.[3] Its peel (exocarp and mesocarp) constitutes about 30-50% of the total weight of the whole fresh fruit.[30] Pomegranate peel has been used globally for treating health disorders.[31] The chemical composition of the peel varies depending on the cultivar type.[32] However, it is very rich in bioactive phytoconstituents such as phenolic compounds, including hydrolyzable ellagitannins, anthocyanins, and flavonoids that have been known for their antioxidant potentials,[33] in addition to their broad spectrum of antimicrobial effects against both Gram-negative and Gram-positive bacteria, as well as fungi.[3,34] A highly potent and strong biofilm inhibitory activity of pomegranate peel aqueous extracts (Primosole variety) was recorded against *Staphylococcus aureus* and *Listeria monocytogenes* strains. *Salmonella bongori* showed the highest resistance to all tested pomegranate varieties peel extracts, and its biofilm development was not significantly reduced.[3] In another research of literature, the hydro-extract from pomegranate peels showed biofilm formation inhibition of three different *Staphylococcus aureus* strains in a dose-dependent manner.[35] Acidified extracts of pomegranate peel exhibited higher antibiofilm activities than the alcoholic ones, particularly against *Bacillus* strains and *Enterococcus faecalis* as previously reported.[30] A dose-dependent antibiofilm efficacy of pomegranate peel was also observed against six oral pathogens isolated from dental caries and supragingival plaque: (*Streptococcus mutans, Enterococcus faecalis, Gemella morbillorum, Staphylococcus epidermis, Enterococcus bugandensis,* and *Klebsiella oxytoca*). The maximum antibiofilm activity was observed with *E. faecalis* and *S. epidermis*, while the lowest was detected with *E. bugandensis*.[36]

Beet leaves

Sugar beet (*Beta vulgaris* L., Amaranthaceae) is one of the richest vegetables in sugars, flavonoids, and the red pigment betalain. It makes up 20% of global sugar production. The thickened root is the consumed part of this vegetable. The leaves are not commonly consumed and discarded as waste after their separation from the roots during food processing.[10] Few studies were found about beet leaves, as a by-product, reporting their bioactive compounds content and therapeutic applications.[37] The ethanolic extract of beet leaves was shown to have anti-quorum-sensing activity using the bio-monitor strain of *Chromobacterium violaceum* which secretes the violacein pigment. A 50% decrease in violacein production was observed without change in the cell viability confirming its ability to block the cellular interaction and signaling without inhibiting the cell growth.[10]

Citrus pomace

Citrus species (family Rutaceae) are the most important cultivated crops with high demand in comparison to other fruits. More than 143 million tons were produced worldwide in 2019.[38] *Citrus* pomace is a massive food industrial processing waste mostly composed of peels.[39] Recently several studies reported that *Citrus* species showed different therapeutic efficacies, including antimicrobial activities against pathogenic bacteria and fungi.[40] The resulting peel is reported as a rich source of antioxidant and antimicrobial compounds such as phenolic acids and flavonoids.[41] In a research study, the hot water extract of three citrus peels; citrons (*Citrus medica* [L].cv. Diamante), sweet oranges (*C. sinensis* [L.] Osbeck cv. Washington Navel), and lemons (*C. lemon* [L.] Burm cv. Sfusato di Amalfi) were evaluated for their antibiofilm activities against ten different sanitary relevant bacteria; *Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus caprae, Staphylococcus xylosus, Pseudomonas fluorescens, Pseudomonas fluorescens* ITEM 17298, *Pseudomonas fluorescens* ITEM 17299, *Pseudomonas fluorescens* ITEM 84094, *Pseudomonas putida* and *Escherichia coli* K12. The microwave-assisted extraction (MAE) method enabled the aqueous rich extracts to significantly reduce biofilm amounts than the conventional method.[39]

Pomelo (grapefruit, *Citrus maxima* (Burm.) Merr.) peel has a very high polyphenol content compared to other citrus peels. Tannins account for nearly 23% of the peel's total polyphenol content. The ethanolic extract of pomelo peel was found to have potent biofilm inhibitory and anti-quorum-sensing effects against the multidrug-resistant *Pseudomonas aeruginosa.* It inhibited the virulence factors pyocyanin and pyoverdine by downregulating the gene expression of Al-2 the quorum-sensing signal used for communication and the regulation of virulence factors.[42,43]

Citron (*Citrus medica*) is a remarkably unexploited fruit, which has been reported to have countless different metabolites such as terpenoids and phenylpropanoids.[44] The isolated phenylpropanoids and their silver nanoparticle conjugates demonstrated potent activity in inhibiting *Pseudomonas aeruginosa* biofilm formation, signifying that the phenylpropanoids valorized from the *C. medica* waste offer a therapeutic promising alternative for treating life-threatening infections associated with the multidrug-resistant pathogens.[45]

Sweet orange (*Citrus sinensis*) is the most broadly cultivated citrus species with more than 50% of the global citrus production.[38,46] Industrial processing for juice production generates a lot of solid waste amounts (mainly the peel) that constitute about 50% of the whole fresh fruit mass.[47] Sweet orange waste ethanolic extract, which is a rich source of flavonoids, displayed antibacterial activity towards the oral cariogenic pathogens *Streptococcus mutans* and *Lactobacillus casei* affecting their growth and viability. It showed a dose-dependent reduction in the viable bacteria counts in a 7-day dual-species oral biofilm model, in addition to a strong synergistic effect when combined with chlorhexidine.[46]

Grape's pomace

Grapes (*Vitis vinifera* L., Vitaceae) are grapevine species that involve an enormous variety of white and red grapes.[48] Agricultural production and the wine industry generate tons of waste material from grape pomace, which is mainly composed of skins, seeds, and stalks. The non-fermented grape pomace represents a valuable source of several value-added products obtained from waste material. Numerous bioactive phenolic compounds are detected in these by-products, including stilbenes, flavonoids, phenolic acids, catechins, proanthocyanidins, and anthocyanins.[49] These compounds are extensively reported for their antioxidant, anti-tumor, anti-inflammatory, and antifungal activities. Candidiasis is a common fungal human infection that is caused by *Candida albicans* which can adhere to host cells through forming highly resistant biofilms. To fight its biofilms, frequent high doses of conventional antifungal drugs were used, causing adverse reactions and in some cases toxicity. Grape pomace, including canes, skins, and seeds as well as some of its isolated stilbenes were reported to have strong *in vitro* and *in vivo* activities against *C. albicans* drug-resistant biofilm.[50]

The acidified ethanolic extract of grape pomace and its major pterostilbene compound showed a potent inhibitory action against *C. albicans* biofilm formation either in their free form or when loaded on (lactic-co-glycolic) acid nanoparticles (PLGA NPs).[50] Additionally, mature biofilm reduction was observed with them. Fluorescent coumarin 6-loaded PLGA NPs investigation confirmed its localization in the biofilm extracellular matrix and cells suggesting their ability to cross the cell wall and membrane.[50]

Canes of *Vitis vinifera* L. are grapevine pruning-produced waste material. Polyphenols represent most of its reported bioactive compounds, particularly stilbenes.[51] Several comprehensive applications of cane extracts have been recently described in cosmetics and skincare products. Many studies showed that cane bioactive compounds have potent antimicrobial effects.[52–54] Resveratrol is one of the detected stilbenes in cane extracts that have been used in many medicinal applications owing to its antioxidant, anticancer, and antimicrobial potentials.[55] A recent study,[56] compared the cane ethanolic extract with that of the blue grapes and pure resveratrol compound for their antifungal-biofilm activity against *C. albicans* and

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other *Candida* species. Canes extracts displayed a superior biofilm inhibitory effect against *C. albicans, C. parapsilosis,* and *C. krusei* than blue grapes and resveratrol with lower minimum biofilm inhibitory concentrations that could be attributed to its different rich polyphenols profile.

Banana bio-waste

Banana fruit is a tropical fruit belonging to the Musaceae family. The largest global banana (*Musa balbisiana* Colla) production is in India with 29.8 million metric tons of production every year.[57] Banana peel and pseudo-stem, a falsely formed stem composed of bent leaf blades and sheaths, are considered as a potential food biomass resource.[58] Peels are rich in numerous bioactive metabolites like terpenoids, flavonoids, alkaloids, and tannins which were reported to have many promising pharmacological effects such as antioxidant, anti-inflammatory, and antimicrobial activities.[59] A comparable study showed that hot water-soluble extractives of both banana **(***Musa paradisiaca***)** and watermelon **(***Citrullus lanatus***)** peels showed a great and potent antibiofilm effect against *Streptococcus Mutans* and *Escherichia coli* and this action could be attributed to their richness in saponins, tannins, and flavonoids, which extensively reported to have a damaging effect on the microbial membrane structure in addition to their ability to inhibit quorum-sensing.[60,61] Silver and gold nanocomposite were synthesized using the powdered extract of banana peels and displayed the strongest biofilm inhibitory effect in comparison with its individual AuNPs and AgNPs confirming the antibiofilm effect enhancement and synergism achieved by adding the banana peels to the gold and silver nanoparticles.[62] On the way of more exploring the antibiofilm potential of banana by-products, a study showed that the aqueous extract of banana pseudo-stem ash formulated on zinc oxide nanoparticles exhibited strong antibacterial and antibiofilm efficacies against *Pseudomonas aeruginosa* in terms of arresting its glycocalyx formation, restricting its survival besides increasing biofilm destruction.[63]

Selected fruits waste

The by-products generated during the processing of grapes, apples, and dragon fruit are promising rich sources of bioactive phenolic compounds.[64,65] Their phenolic compounds were severely reported for their antibiofilm and quorum-sensing inhibitory effects.[66] A search of the literature revealed that the enzyme-assisted extraction method was used to prepare phenolic-enriched extracts from oven-dried and lyophilized black grape (*Vitis vinifera x (Vitis labrusca x Vitis riparia*)), apple (*Malus domestica* cv. Jonagold), and yellow pitahaya (*Hylocereus megalanthus*) residues. The extracts, in addition to various individual phenolic compounds, including p-coumaric acid, gallic acid, vanillic acid, syringic acid, 4-hydroxybenzoic acid, cinnamic acid, polydatin, quercetin, (+)-catechin, (-)-epicatechin, and resveratrol, were evaluated for their quorum-sensing inhibition and antibiofilm formation activities against seven bacterial strains. All fruit residue extracts displayed different *Chromobacterium violaceum* pigment production inhibitory percentages according to the substrate and enzyme treatment, indicating their different quorum-sensing inhibitory powers. In the same context, the extracts showed the highest inhibition against biofilms of *Pseudomonas aeruginosa, Pseudomonas putida*, and *Staphylococcus aureus.* The study concluded that many phenolic compounds in fruit waste extracts have outstanding inhibitory effects against quorum-sensing and biofilm formation, making them potential sources of antibiofilm agents.[67] Finally, we provide a brief overview to correlate between the realm of plant-based ingredients, and their potential for combating biofilm-mediated infections.

Agro-food wastes and their different derived phytoconstituents used for their biofilm inhibitory effects were summarized in Table 1 and are concise in Figure (1-3).

Conclusion and Future Perspectives

The wide prevalence of multiple-drug microbial resistance and the elevated global rate of biofilm-based infections pose significant obstacles in the field of medicine and human healthcare. Clinicians and microbiologists are facing a complex challenge in the treatment of many human diseases that are linked to biofilm-associated infections. As a result, the discovery of novel natural anti-biofilm agents is urgently required to overcome the medical implications associated with the dissemination of such infectious diseases. As shown in this review, agro-food waste and by-products are considered a sustainable resource of several precious bioactive compounds that offer promising biofilm-inhibiting agents. Antibiofilm agents derived from natural origin, such as plants and their waste materials, are different in their structure and function when compared to conventional antibiotics. Up to now, numerous studies inspected food biowaste-derived natural products for their effectiveness in preventing bacterial biofilm formation and development, suggesting them as alternative antibiofilm candidates for bacterial infections. Different *in vitro* and *in vivo* models were used to explore the antibiofilm efficiency of the natural constituents that could counteract a single or more steps in biofilm formation, development, and maturation, as well as inhibit the QS network within the biofilm. As part of the perspectives and research gaps in the field, more future studies should be focused on valorizing and recycling the huge generated agro-food by-products uncovering their promising anti-biofilm effects and converting their phytocompounds into medicinal drugs. Furthermore, the promising results of current preclinical studies on natural antibiofilm agents suggest the need for further investigations, including clinical trials. These investigations should not only focus on the external use of natural products for oral biofilm-associated infections, but also evaluate their efficacy and safety for deep-located infections in visceral tissues, urinary tract infections, or other internal organs. Combination treatment of novel natural agents with traditional antibiotics needs future exploitation as it could produce potent synergistic biofilm inhibitory mechanisms that can effectively control bacterial infectious diseases throughout the world. The mechanism of action of several natural agents against biofilm is not well recognized. Further studies on their mode of action may lead to the discovery of new efficient agents and novel strategies for biofilm treatments on a broad range of pathogens. Extensive studies are necessary to evaluate the natural antibiofilm agents' safety and efficacy through quality control, pharmacokinetic, and pharmacodynamic, as well as drug interaction analyses with host metabolomics.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

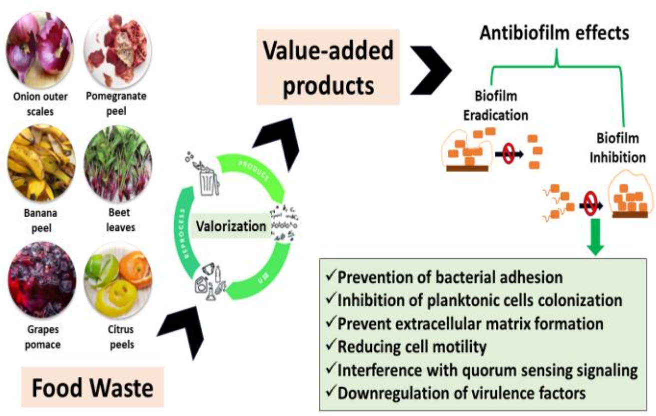

Figure 1: Possible mechanisms of antibiofilm activity of natural products from agro-food waste.

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Table 1: Summary of biofilm inhibitory effects of agro-food waste extractives

Food waste	**Chemical compounds**	**Antibiofilm activity**	**Pathogenic species**	**Experimental method**	**References**
The outer red onion skin Ethyl acetate fraction (ONE)	Quercetin-4'-*O*-D glucopyranoside	In a dose-dependent manner, ONE inhibited violacein production without altering the bacterial growth in addition to exerting a significant decrease in virulence factors levels of *P. aeruginosa*	*Chromobacterium violaceum* *Pseudomonas aeruginosa* *Aeromonas hydrophila*	Violacein Inhibition Assay Microtiter plate assay	26
Red onion outer scales Acidified ethanolic extract (RO-T) Anthocyanin-rich fraction (RO-P) Flavonoid-rich fraction (RO-S)	Flavonoids Anthocyanins	RO-S and RO-T showed the most potent *in vitro* and *in vivo* antibiofilm effects	Methicillin-resistant *Staphylococcus aureus* (MRSA) *Acinetobacter baumannii*	*In vitro* Crystal violet assay *In vivo* MRSA Vaginal Colonization Model	28
The outermost layer of the red onion peel 50% Ethanolic extract	Flavonoids Anthocyanins	ROPE reduced the biofilm formation of *L. monocytogenes* strains and the cell motility without affecting their growth	*Listeria monocytogenes* *Chromobacterium violaceum*	Microtiter plate assay with *In vitro* Crystal violet assay XTT reduction assay and Light microscopy	27
Red (RO) onion peels Methanolic extract	Quercetin derivatives Anthocyanins Phenolic acids	RO showed a promising preventive effect on biofilm attachment inhibiting its formation besides, exerting a small reduction percentage of mature biofilm masses	*Staphylococcus aureus* MRSA *Staphylococcus epidermidis* *Candida. albicans*	*In vitro* Crystal violet assay	29
The pomegranate peel hydro-extract (PPHE)	Total phenolics	PPHE achieved bacterial biofilm inhibition in a dose-dependent manner	*Staphylococcus aureus* (ATCC 29737) Milk-isolated *S. aureus* MRSA (ATCC 33591)	Microtiter plate adhesion assay with Crystal violet assay	35
Pomegranate peel Ethanolic extract	Tannins as: Peduncalagin Punicalagin Punigluconin	Inhibited the biofilm formation of all the strains in a dose-dependent manner	*Streptococcus mutans* *Gemella morbillorum* *Enterococcus faecalis* *Staphylococcus epidermis* *Klebsiella oxytoca* *Enterobacter bugandensis*	*In vitro* Crystal violet assay	36
Pomegranate peel (PPL) Ethanol, methanol, their acid combinations, and water extracts	Ellagic acid Punicalagin Organic acids	About 73–80% biofilm formation inhibition was displayed against *Bacillus* strains, while *Enterococcus faecalis* biofilms were inhibited by about 64–70%	*Bacillus cereus* *Bacillus subtilis* *Enterococcus faecalis*	*In vitro* Crystal violet assay	30
Pomegranate peel aqueous extract (PPE) 7 varieties: Wonderful (WF) Primosole (PS) Mollar de Elche (ME) Sassari 1 (SS1)	Total tannins Epicatechin Flavonoids Chlorogenic acid	PS showed the strongest antibiofilm effect against *Staphylococcus aureus* and *Listeria monocytogenes* strains. All PPES displayed no significant biofilm inhibitory effects against	*Staphylococcus aureus* *Listeria monocytogenes* *Salmonella bongori* *Escherichia coli* *Lacticaseibacillus casei*	*In vitro* Crystal violet assay	3

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Sassari 2 (SS2) Sassari 3 (SS3) Arbara Druci (AD)		*Salmonella bongori.*	*Limosilactobacillus reuteri*		
Beet leaves Ethanolic extract	Total phenolic content	Exerted no significant anti-biofilm inhibitory activity	*Escherichia coli*	Plating on agar dishes followed by crystal violet staining	10
		Anti-quorum-sensing activity was confirmed by decreasing 50% of the violacein production without affecting the viability of the cells	*Chromobacterium violaceum* wild-type strain	Violacein production quantification	
Citrus peels Microwave-assisted hot water extract MAE Citrons (*Citrus medica*) Sweet oranges (*C. sinensis* Lemons (*C. lemon*)	Phenolic content (Phenolic acids and flavonoids)	All C*itrus* peel MAE water extracts may reduce the biofilm formation of ten human skin commensal bacteria and possibly enhance the susceptibility to other disinfectants	*Staphylococcus epidermidis* *Staphylococcus saprophyticus* *Staphylococcus caprae* *Staphylococcus xylosus* *Pseudomonas fluorescens* *Pseudomonas fluorescens ITEM 17298* *Pseudomonas fluorescens ITEM 17299* *Pseudomonas fluorescens ITEM 84094* *Pseudomonas putida* *Escherichia coli K12*	Microtiter plate adhesion assay with crystal violet staining	39
Pomelo peel (*Citrus maxima*)	Tannins Flavonoids Phenol	The ethanolic extract significantly inhibited the biofilm formation of both strains	Multidrug-resistant (MDR) and *ATCC Pseudomonas aeruginosa* strains	Crystal violet assay	43
		Inhibition of the virulence factors pyocyanin and pyoverdine of MDR strain due to its anti-quorum-sensing effect		Pyocyanin and pyoverdine assay	
Citrus medica peel	Phenylpropanoids	*Citrus medica* phenylpropanoids silver nanoparticles conjugate retarded the bacterial colonization of *Pseudomonas aeruginosa* disassembling its biofilms	*Pseudomonas aeruginosa*	Platinum coating and fluorescence imaging FE-SEM	45
Sweet orange juicing waste 70% ethanolic extract (ISOWE)	Narirutin Hesperidin Quercetin Sinensetin Nobiletin	ISOWE counteracted the biofilm formation and showed synergistic effects in chlorhexidine combination	*Streptococcus mutans* *Lactobacillus casei*	The viability count and confocal images	46

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	Tangeretin				
Grapes non-fermented pomace	Pterostilbene (PTB)	The crud pomace extract and PTB inhibited biofilm formation, reduced the mature one, and penetrated the biofilm matrix in its free and (lactic-co-glycolic) acid nanoparticles combined form	*Candida albicans*	XTT reduction assay and Epifluorescence microscopy analysis	50
Winter grapes canes Blue grapes	Resveratrol	Cane extract showed the most effective biofilm formation inhibition in a dose-dependent manner. The blue grape extract had an inhibitive effect with its high concentration only. Pure resveratrol was the weakest one.	*Candida albicans* *Candida parapsilosis* *Candida krusei*	Crystal violet assay, Light microscopy by Cellavista Device, and Spinning Disc Confocal Microscopy	56
Banana peel (*Musa paradisiaca*) Watermelon peel (*Citrullus lanatus*)	Phenols Alkaloids Terpenoids Tannins Saponins Glycosides Flavonoids	The hot aqueous extract showed the strongest preventive antibiofilm effect that appeared clearly through decreasing the absorption value with increasing the antibiofilm activity	*Streptococcus Mutans* *Escherichia coli*	96-microtitre well plate method with crystal violet assay	61
Banana peel (*Musa paradisiaca*)	-------	Silver and gold nanocomposite displayed the strongest biofilm inhibitory effect in comparison with its individual AuNPs and AgNPs confirming banana peel enhanced and synergistic antibiofilm effect	*Pseudomonas aeruginosa*	Crystal violet assay and 96 wells microtiter plates	62
Banana pseudo-stem (*Musa balbisiana* Colla)	-------	Banana pseudo-stem mediated ZnO NPs showed strong antibiofilm activity with significant biofilm inhibition percent	*Pseudomonas aeruginosa*	Congo red agar method 96-microtitre well plate method	63
Black grape pomace Jonagold apple residue yellow pitahaya (dragon fruit) residue	Gallic acid Vanillic acid Syringic acid P-coumaric acid 4-Hydroxybenzoic acid Cinnamic acid Epicatechins Polydatin Quercetin Resveratrol	All tested fruit extracts showed anti-quorum-sensing activity and for the tested phenolics, syringic acid, vanillic acid, (+)-catechin and resveratrol displayed high violacein production inhibition. *P. putida, P. aeruginosa,* and *S. aureus* are the most sensitive pathogens to all extracts	*Listeria monocytogenes* *Staphylococcus aureus* *MRSA* *Escherichia coli* *Salmonella enterica* *Pseudomonas putida* *Pseudomonas aeruginosa*	Violacein Inhibition Assay and Crystal violet staining method	67

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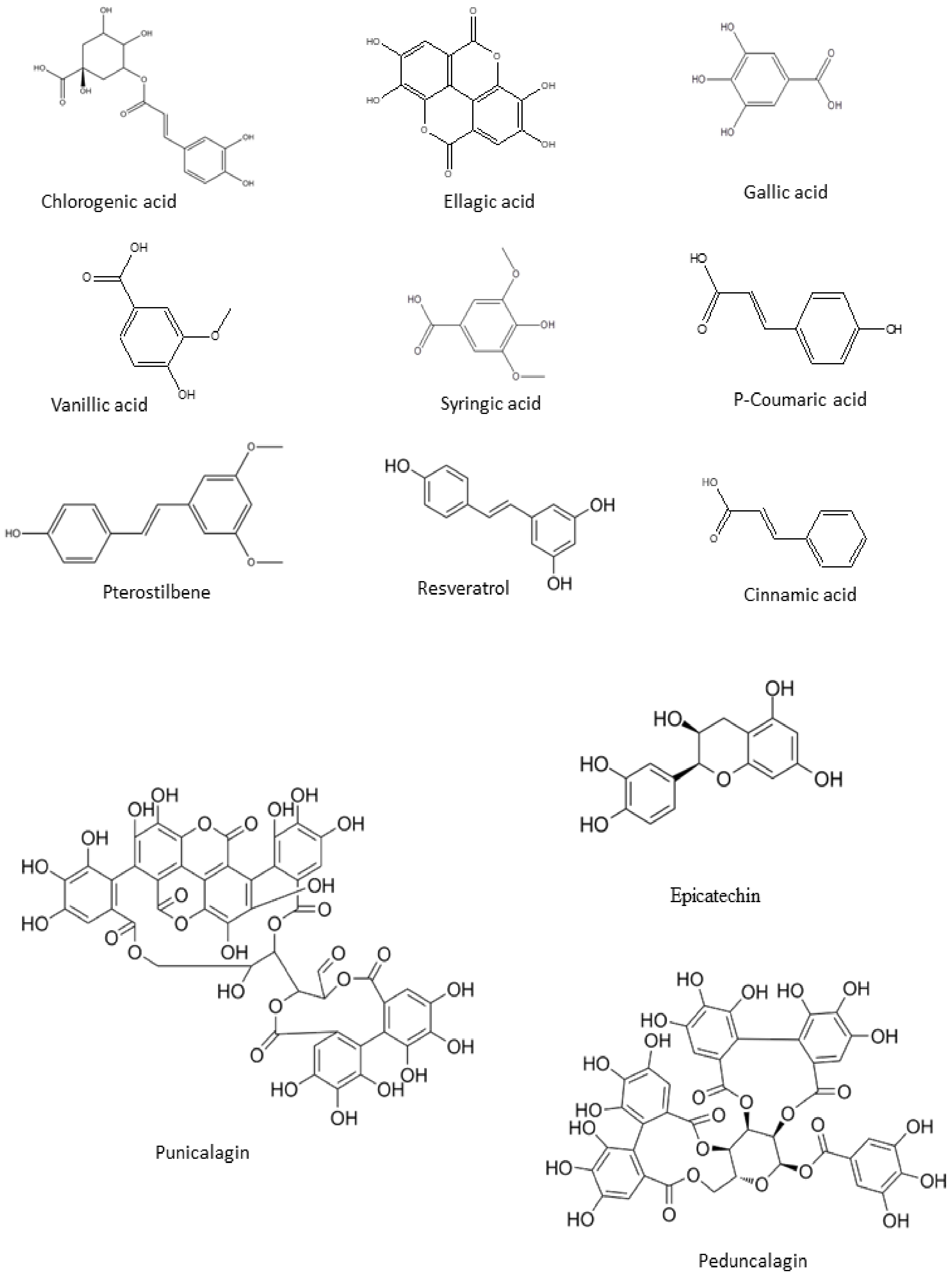

Figure 2: Chemical structures of selected phenolic acids and tannins derived from agro-food waste with antibiofilm potential.

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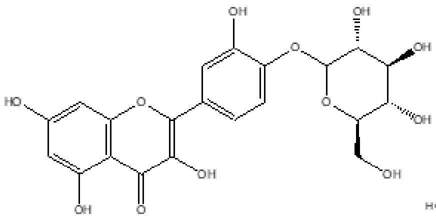
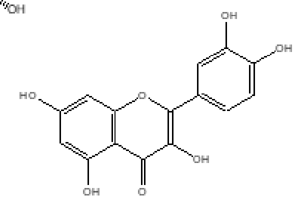


Quercetin-4'-*O*-D-glucopyranoside



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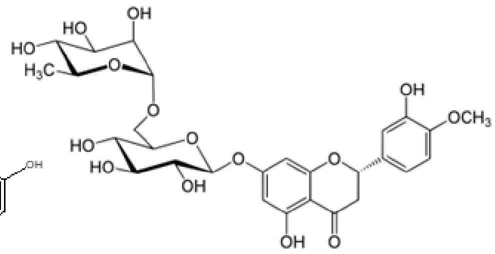
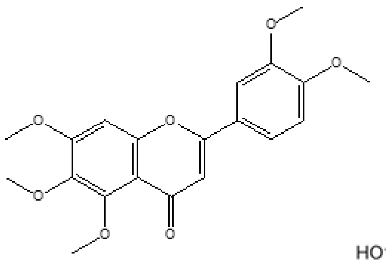


Hesperidin



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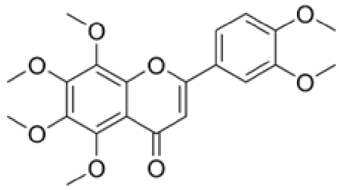

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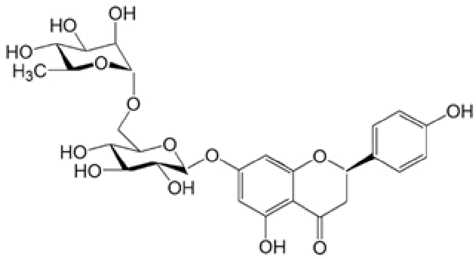
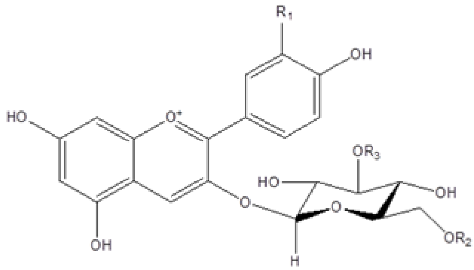
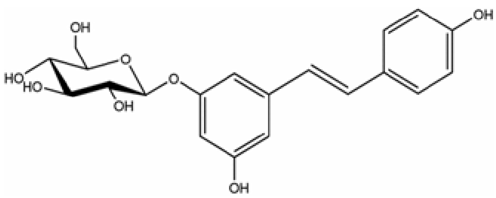


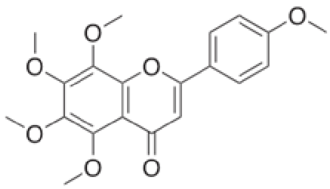
Narirutin



Compound name	R1	R2	R3
Cyanidin-3-*O*-glucoside	OH	H	H
Cyanidin-3-*O*-laminaribioside	OH	H	O-glu
Cyanidin-3-*O*-(3"-malonylglucoside)	OH	H	Malonic acid
Cyanidin-3-*O*-(6"-malonylglucoside)	OH	Malonic acid	H
Cyanidin-3-*O*-(6"-malonyl-laminaribioside)	OH	Malonic acid	O-glu
Peonidin-3-*O*-glucoside	OCH3	H	H
Peonidin-3-*O*-malonylglucoside	OCH3	Malonic acid	H



Polydatin



Tangeretin

Figure 3: Chemical structures of selected flavonoids and anthocyanins derived from agro-food waste with antibiofilm potential.

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