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Antibacterial Activity of the Flavonoid Hesperitin and Its Glycosyled Derivative Hesperidin: A Systematic Review

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ABSTRACT The high cost of medicine and the low financial condition of a large part of the global population turns alternative therapies and the use of plant-based products as allies more interesting in the fight against diseases growth. Among the compounds extracted from plants are flavonoids that belong to a class of phenolic compounds widely distributed in the plant kingdom and are important for plant growth and works as a defense mechanism. Flavanones represent a group of compounds derived from flavonoids, which contain several glycosides, among the three main ones there are hesperitin (Hst), and its aglycone form, hesperidin (Hsd), found in citrus fruits. Among the properties of these compounds antibacterial action can be included. Therefore, this paper aims to investigate the antibacterial effect of flavonoids Hst and Hsd to expand the therapeutic alternatives or complement the existing ones. On the online search 60 articles were identified, after eliminating duplicate studies, 52 articles remained. A total of 30 studies were excluded after reading the abstracts, resulting in 18 articles for reading completely. After reading the full texts, 09 articles were selected. It was observed that some studies have tried to understand the antibacterial potential of Hsd and Hst against multi-drug resistant pathogens and methicillin-resistant *Staphylococcus aureus*, as an antibioflime agent, natural preservative, and as a resource to enhance antibacterial activity in magnetic nanoparticles and in a new Schiff base ligand, however, the bacterial activity and its mechanisms of action, especially of Hst, are still poorly understood with the need for further studies.

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INTRODUCTION

A growing interest in alternative medicines and the use of plant-based products as crucial allies in the prevention and treatment of many diseases is being driven by the high expense of pharmaceuticals and the poor financial standing of a significant portion of the global population [1]. Flavonoids and their phytoconstituents are among the substances derived from plants.

Antimicrobial resistance places the effectiveness of infection prevention and treatment in jeopardy and represents a growing threat to global public health. Antimicrobial resistance develops throughout time, typically as a result of genetic alterations. Antimicrobial abuse and misuse, however, is hastening this development [2].

Increasing resistance against available antimicrobial agents is a major concern for healthcare professionals. To combat this resistance and other disadvantages of current antimicrobial drugs as well as to obtain more effective drugs, we need to develop antimicrobial agents with new mechanisms of action [3].

Many plants produce flavonoids as secondary metabolites. These organic compounds play an important role in protecting the plant against pathogenic microorganisms such as bacteria [4], fungi [5] and viruses [6], but also have potential properties in the human body [1].

Flavanones represent a small group of compounds derived from flavonoids, which contain several glycosides, among the three main ones, hesperitin (Hst) and its aglycone form, hesperidin (Hsd) stand out [7], representing the main active constituents found in citrus fruits and which have been demonstrating bio-pharmacological activities such as: anticancer, antioxidant, anti-inflammatory [8]; antiviral, antifungal [3], antibacterial, immunoprotective [9], cardioprotective, neuroprotective [10-11], hepatoprotective agents [12], antidepressants and anxiolytics [13-14], skin protectors [15], as well as maintaining bone health [8] and the gut microbiota [16].

However, it is noteworthy that although citrus flavonoids have demonstrated several beneficial effects, their mechanisms of action are not fully established [17-18].

These bioactive compounds have been established through research to have antibacterial properties. A number of processes, including activation of the host immune system, breakdown

of the bacterial membrane, and interference with microbial enzymes, have been hypothesized, but the exact mechanisms underlying its antibacterial characteristics are not fully understood. [7].

Regarding bioavailability, Hsd has low bioavailability compared to Hst, due to the presence of the disaccharide (rutinose) linked to the flavonoid. Thus, its absorption and metabolism comprise an active area of investigation, since its intestinal absorption and metabolism are not fully understood [19].

Thus, more research is required to look at specific aspects of how Hst and Hsd can treat human diseases. A significant weakness of the majority of earlier investigations is the lack of clinical data on the effects of these drugs, requiring more investigation. Since these chemicals may have an even broader variety of biological applications, it is crucial to do additional research into their biological properties [20].

Therefore, this study aimed to investigate the antibacterial activity of the flavonoids Hsd and its glycosylated derivative Hst through a systematic literature review.

MATERIAL AND METHODS

This systematic review was guided by the following question: Do Hsd and its glycosylated derivative Hst have antibacterial activity? To answer this question, research was carried out in the databases Portal Capes, Virtual Health Library (BVS), Scientific Electronic Library Online (Scielo), Latin American and Caribbean Literature on Health Sciences Information (LILACS) for studies published in peer-reviewed journals, which used english, portuguese and spanish languages, published in the period from 2012 to 2022, using the following keywords: flavonones, hesperitin, hesperidin, antimicrobials.

The inclusion criteria were studies related to the subject and that demonstrated results for the antibacterial activity of Hsd and/or Hsd. References whose title and abstracts were not aligned with the subject of the review or outside the time delimited above and studies of revision.

In the online search, 60 articles were identified, after the elimination of duplicate studies, 52 articles resulted. The selection of articles for this review was carried out in two phases: reading the abstracts and reading the full articles. In the filtering phase, articles in which the titles did not

fit the subject were removed and at the end of reading the abstracts, 18 articles were selected for analysis of suitability. After reading the articles in full, 09 articles were excluded for not meeting the eligibility criteria. At the end of the selection, 09 articles were included in this systematic review. These results followed the procedure described in Figure 1.

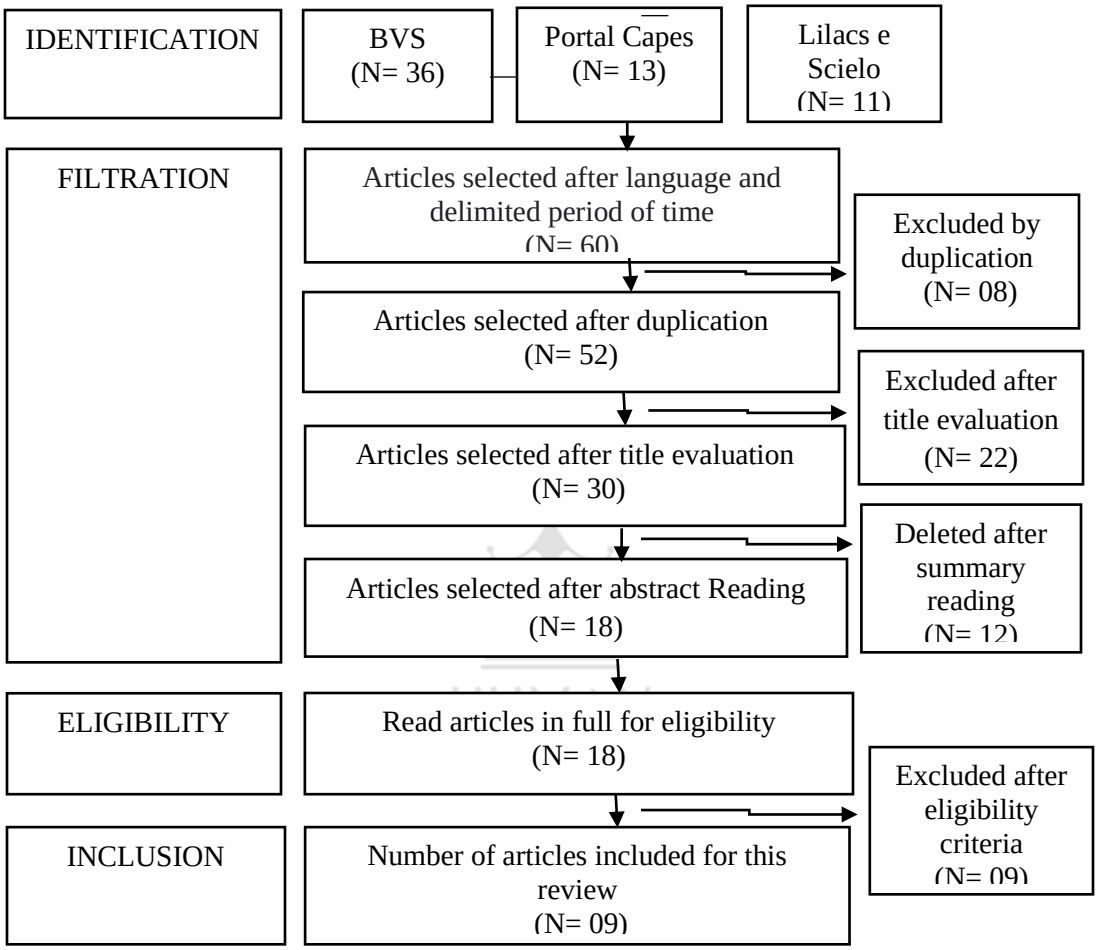

Figure No. 1: Systematic review process. Source: Author

RESULTS AND DISCUSSION

Of the nine studies included in this systematic review: seven evaluated the effects of Hsd on the *in vitro* minimal inhibitory (MIC) and minimal bactericidal (MBC) concentration, its antibacterial potential from plant extract (*Mentha pulegium L.*) and tangerine. Its synergistic and additive effects as a chemical preservative in food, in the treatment with silver nanoparticles against *Escherichia coli K1*, its antibacterial activity against multidrug resistant (MDR)

pathogens and methicillin resistant *Staphylococcus aureus* (MRSA) and as a property enhancing antibacterial agent in the synthesis of silver nanoparticles (HP-AgNPs) and two evaluated effects of Hst on clinical reference strains of *H. pylori* and as an antibacterial agent on glass surfaces.

Thus, the results of this study were divided into two tables, the first one that includes studies of the effect of hesperidin as a chemical preservative in food products and can be used in the food industry, in the synthesis of nanoparticles as an enhancer of antibacterial activity and as an alternative in the treatment of some pathogens, being able to be used as an antibacterial agent against clinical reference strains and in the treatment against MDR and MRSA (Table 1) and the second table with studies that present possibilities of applications of hesperitin in the treatment of patients with *H. pylori* and as an antibacterial agent in cleaning glass surfaces (Table 2). The main information from the publications was organized and summarized in tables 1 and 2, according to the following criteria: References; Methods; Results.

Table No. 1: Characterization of studies included in the literature review in relation to the antibacterial activity of hesperidin – Source: Author.

Referências	**Métodos**	**Resultados**
[21]	Synthesis of cinnamic acid-based nanoparticles (with and without conjugated hesperidin) to assess the bactericidal efficacy of Hsd against multidrug-resistant (MDR) pathogens: Gram-positive bacteria (*Bacillus cereus, Streptococcus pyogenes*, methicillin resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae*) and Gram-negative (*Escherichia Coli K1, Pseudomonas aeruginosa, Salmonella enterica* and *Serratia marcescens*).	Antibacterial assays demonstrated that Hsd alone did not exhibit antibacterial effects, however, after conjugation with cinnamic acid-based magnetic nanoparticles, it exerted significant bactericidal activity against isolated Gram-positive and Gram-negative bacteria.
[22]	Characterization of the antibacterial	Important antimicrobial activity

	activity of phenolic compounds and flavonoids from *Mentha pulegium L.* (including hesperidin). The bacteria were isolated at the Department of Microbiology of the Pasteur Institute (Tunisia).	was observed against eight isolated human pathogenic clinical bacteria (*Klebsiella pneumoniae, Escherichia coli, Shigella boydii, Vibrio cholerae, Streptococcus aureus, Bacillus subtilis and Clostridium tetani, Enterococcus*).
[23]	Evaluation of the antibiofilm potential of hesperidin against methicillin-resistant *Staphylococcus aureus* (MRSA) *in vitro* and *in silico*.	Treatment with hesperidin showed antibiofilm activity against the staphyloxanthin synthesis of methicillin-resistant *Staphylococcus aureus* (MRSA).
[24]	Synthesis of silver nanoparticles with Hsd (HP-AgNPs) for evaluation as an antibacterial agent.	The findings suggest that HP-AgNPs have good antibacterial activity and can be developed as an effective antibacterial nanomaterial.
[25]	Spectroscopic techniques and the synergistic and additive effects of Hsd (with total tangerine extract) have been used to produce a chemical preservative in food products.	A synergistic effect of hesperidin was observed against *Bacillus cereus, Pseudomonas aeruginosa* and an additive effect against *Staphylococcus aureus* and *Escherichia Coli*. Hesperidin was able to reduce the concentration of sodium nitrite ($NaNO_2$) and replace it as a natural preservative.

[26]	*Escherichia Coli K1* (*E. Coli K1*) were treated with silver nanoparticles (with and without hesperidin conjugate) for determination of 50% MIC. Gene expression was analyzed using sequenced RNA and a set of genes involved in stress response and cellular metabolism.	The 50% MIC with the hesperidin-conjugated silver nanoparticles was achieved with 0.5 µg/ml in 1 h. Genetic analysis revealed the expression of 122 genes in *E. Coli K1* treated with hesperidin-conjugated silver nanoparticles and treated with silver alone compared to untreated *E. Coli K1*.
[27]	Evaluation of MIC and MIC *in vitro* and the effects of hesperidin and ellagic acid (EA) against bacterial colonization by a standard *Aeromonas hydrophila* strain (ATCC Cat. #7966 from Cairo University, Giza, Egypt) *in vivo*.	Both treatments (Hsd and EA) showed antimicrobial activities against *Aeromonas hydrophila* infection by significantly increasing anti-LPS IgM levels and reducing anti-LPS and anti-ECP IgA levels to their normal values compared to the infected group.

Table No. 2: Characterization of the studies included in the literature review in relation to the antibacterial activity of hesperitin. – Source: Author.

Referências	Métodos	Resultados
[28]	Synthesis of a novel hesperitin-derived Schiff base ligand (HABH (2-amino-NO-(2,3-dihydro-5,7-dihydroxychromo-4ylidene benzohydrazide) and its copper complex CuHABH [$CuLH_2(OAc)$] that have been tested for bacterial agents and antibioflime activity on glass surfaces.	The developed compounds showed antibacterial and antibiofilm activity against Gram positive and Gram-negative bacteria. The best anti-adhesive action against both bacterial strains was found for the CuHABH complex, suggesting that the molecule may play a role in exopolymer rupture and biofilm formation and can be used to prevent bacterial adhesion.
[29]	Determination of the antibacterial activity of hesperitin against clinical reference strains of *H. pylori* ATCC 49503, 43504, 51932 and ATCC 700392) and strains isolated from 46 patients with *H. pylori* infection.	Hesperitin inhibited the growth of clinical and isolated strains of *H. pylori* related to its replication, transcription and motility.

It can be seen in Table 1 that hesperidin conjugated through the synthesis of magnetic nanoparticles (NPs) demonstrated bactericidal activity against multidrug-resistant (MDR) pathogens [21,24,26].

As a result, innovative formulations using NPs have been used as a strategy for therapeutic agents against infections caused by MDR pathogens and represent a significant advance and may

be a promising technique for the treatment of MDR infections [30–32]. As a consequence, it is urgently necessary to find and develop innovative antibiotics as well as new antimicrobial treatments that may complement conventional chemotherapy.

In the study by [21], Hsp alone did not exhibit antibacterial effects, however, after conjugation with cinnamic acid-based NPs, it exerted significant bactericidal activity against isolated Gram-positive and Gram-negative bacteria. Thus, secondary metabolites from natural phytochemicals, including flavonoids, are of increasing interest and these compounds loaded in NPs have shown promising results for the treatment of diseases [26].

[24,26] Synthesized silver-based nanoparticles (HP-AgNPs) loaded with Hsd and observed that HP-AgNPs also demonstrated good antibacterial activity, presenting themselves as an alternative as an effective antibacterial nanomaterial. The antibacterial mechanism of NPs suggested by [26] may be due to cell membrane disruption, oxidative stress and metabolism in *Echerichia coli K1*, however, further studies are needed in order to bring a better understanding of the genetic mechanisms underlying the treatment with nanoparticles and the identification of new candidates for antimicrobial drugs.

Conjugated Hsp in NPs have been used as antibacterial and anti-inflammatory nanomaterials in the treatment of wounds. [33] found that *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) have efficient antibacterial activities when used in animal wounds with Hsd conjugated to HP-AgNPs. In addition to significantly lowering the expression of pro-inflammatory cytokines, accelerating wound closure, encouraging collagen deposition, and promoting skin cell proliferation, HP-AgNPs also promoted the proliferation and migration of human umbilical vein endothelial cells and accelerated the healing of infected wounds, suggesting that they have significant potential for promoting the healing of infected wounds.

In table 1, it is also possible to verify the bactericidal potential of Hsd from plant extracts of *Mentha pulegium L*. against isolated human pathogenic clinical bacteria [22] and of tangerine against *B. cereus* and *P. aeruginosa*, *S. aureus* and *E. coli* suggesting its use as a natural biopreservative [25].

[22] Also identified an important antimicrobial activity against human pathogenic clinical bacteria (*Klebsiella pneumoniae*, *Escherichia coli*, *Shigella boydii*, *Vibrio cholerae*, *Streptococcus aureus*, *Bacillus subtilis*, *Clostridium tetani*, *Enterococcus*). The findings of the study suggest that the high content of total phenols in methanolic extracts present in plants may be responsible for important biological activities. In this way, medicinal plants may be promising for the development of a new generation of food supplements that can be used as an antibacterial, antitumor and antioxidant agent and to produce chemical preservatives in food products.

The results presented in Table 1 in the study by [27] suggest Hsd as a potential helper in increasing the activity of antibiotics against standard strains of *Aeromonas hydrophila*. However, further studies are needed to confirm its strong antimicrobial power against *Aeromonas* isolates and the management of microbial infections.

Antibiotic resistance, the decisive cause of high morbidity and mortality, as well as increasing treatment costs, is considered one of the main global threats to public health [34-35]. For most low- and middle-income countries, inaccessibility to antibiotics remains a major challenge [36].

[28] State that the global spread of antibiotic resistance among important human pathogens emphasizes the need to find new antibacterial drugs with a new mode of action. These new antibiofilm agents, which contain moieties like phenols, imidazole, sulfide, furanone, *etc.*, have the potential to disperse bacterial biofilms in vivo and could positively impact medicine in the future. According to [37], flavonoids have been highlighted as a group of compounds capable of inhibiting biofilm formation.

[23] When evaluating the antibiofilm and antivirulence potential of hesperidin against methicillin-resistant *Staphylococcus aureus* (MRSA) observed the inhibitory potential of the non-antibacterial biofilm of Hsd against clinical and isolated strains of *S. aureus*. Treatment with Hsd significantly prevented the production of lipase, hemolysin, autolysin, staphyloxanthine autoaggregation, decreased gene expression of the biofilm-associated gene (sarA), intracellular polysaccharide adhesion gene (icaA and icaD), autolysin (altA), protein binding to fibronectin (fnbA and fnbB) and production of staphyloxanthin (crtM). Molecular docking analysis identified the ability of Hsp to interact with SarA and CrtM proteins involved in biofilm

formation and crtM production in MRSA. Therefore, inhibition of biofilm formation is an alternative therapeutic action for the control of MRSA infections.

Hsd has also been studied as an antibiofilm agent by the food industry. [25] proved the synergistic action of Hsd against Bacilus cereus and additive against *Staphylococcus aureus* and *Echerichia coli* pathogenic microorganisms selected from foods. The results showed a significant decrease in the MIC values of sodium nitrite (ranging from 75% to 87.5%) depending on the strain tested.

According to [38], the knowledge of bacterial species responsible for biofilm formation in the food industry is very important due to associated health problems, since these pathogens are able to develop biofilm structures on different artificial substrates (glass, stainless steel, polyethylene, wood, polypropylene, *etc*.) and represents a special mode of growth that makes microbial cells more resistant to antimicrobial agents. Studies have analyzed the possible relationship between biofilm formation and antimicrobial resistance [39-41].

Research indicates that the glycosylated derivative of Hsd, hesperitin (Hst), also has antimicrobial activity, however, Hsd has shown greater inhibitory activity against Gram-positive bacteria than Gram-negative bacteria. It is important to highlight that the exact mechanisms behind its bacteriostatic and bactericidal properties are not fully understood, several mechanisms such as: activation of the host's immune system, bacterial membrane rupture and inhibition of metabolism energy, nucleic acid synthesis of microorganisms and interference with microbial enzymes have been proposed [7,42].

Regarding Hst, its antibacterial effect has been described against several bacteria: *Escherichia coli* (0157 H7 ATCC 51659)), *Salmonella enterica* (Typhimurium LT2), *Pseudomonas putida* (ATCC 795) and *Pseudomonas aeruginosa* (NRRLB-272), *Bacillus cereus* (EMCC 1080; KCCM 40154; KCCM 11341), *Staphylococcus aureus* (ATCC 25923; KCCM 32395; KCCM 16593) and FI10139 (food isolate) and *Listeria monocytogenes* (KCCM 15313, H7969 and H7962 serotype 4b) [33,25,7,43-44].

A study presented in table 2 by [29] showed that hesperitin was able to inhibit the growth of reference strains and clinical isolates of *H. pylori* (ATCC 49503, 43504, 51932 and ATCC

700392) and reduced the expression of genes of replication, transcription, motility and adhesion by negatively regulating major virulence factors such as cytotoxin-associated antigen A (CagA) and vacuolating cytotoxin A (VacA) decreasing the translocation of CagA and VacA proteins to gastric adenocarcinoma (AGS) cells.

In addition, metal complexes of Schiff bases, well known as active compounds for exhibiting a range of activities, including antimicrobial activity, have also been of great interest [45-46].

Studies aimed at synthesizing Schiff bases from flavanones (Hst) linked to the azomethine group associated with active fractions of benzohydrazide or thiosemicarbazide demonstrated a high potential for DNA damage and antibacterial activity [47-48].

Study carried out by [28] presented in Table 2, from a new Hst derived Schiff base ligand (HABH(2-amino-NO-(2,3-dihydro-5,7-dihydroxy-2-3-hydroxy-4methoxyphenylchromo-4 ylidene benzohydrazide) and its copper complex (CuHABH) designed to assess antibacterial activity and antibiofilm activity *in vitro* indicated a stronger interaction of CuHABH with calf thymus DNA (CT-DNA) than HABH, demonstrated antibacterial and antibiofilm activity against Gram-positive (*S. aureus*) and Gram-negative *(E. coli)* bacteria and played a crucial role in the breakdown of exopolymers (DNA/proteins) in biofilm formation, proposing its use for prevent bacterial adhesion, especially on glass equipment.

In this context, additional experimental research on these flavonoids becomes extremely relevant for a better understanding of their antimicrobial action mechanisms, as well as cultures containing flavonoids in the development of medicines, supplements and healthy foods, as well as the biotransformation of flavonoids as an alternative in the improvement of antimicrobial activities *in vitro* and *in vivo* [49].

CONCLUSION

The studies included in this review demonstrated the antibacterial potential of Hsp against pathogens MRD and MRS, and can be used as a therapeutic resource in the treatment of these pathogens, antibacterial action and ability to inhibit the formation of antibiofilm.

In this article, it was observed that some studies sought treatment with Hsd from alternative pathways, such as plant extracts, against the action of isolated human pathogenic clinical bacteria, suggesting its use as a natural biopreservative.

A limitation of this review is the greater number of studies published outside the adopted methodological time period and a smaller number of researches on the bactericidal activity of Hsd in relation to Hst, on the mechanisms of antibacterial action.

In this sense, it was possible to observe that hesperitin also has antimicrobial activity, however, it is noteworthy that Hsd has shown greater inhibitory activity against Gram-positive bacteria than Gram-negative bacteria.

From the data presented, it was possible to conclude that the study presented in this review using a new Hst-derived Schiff base ligand and its copper complex demonstrated antibacterial and antibiofilm activity against Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria. (*Escherichia coli*) and played a crucial role in the breakdown of exopolymers (DNA/proteins) in biofilm formation, proposing its use to prevent bacterial adhesion, especially on glass surfaces and equipment.

REFERENCES

1. Ullah A, Munir S, Badshah SL, Khan N, Ghani L, Poulson BG, Emwas AH, Jaremko M. Important Flavonoids and Their Role as a Therapeutic Agent.**Molecules**, 2020;25(5243):2€“39.
2. Organização Mundial de Saúde. OMS. Resistencia a los antimicrobianos. 2020. 31/10/2022. Disponível em: https://www.paho.org/pt/topicos/resistencia-antimicrobiana.
3.Gowtham R, Fysal MAF, Devaraj E, Shanmugam S, Balakrishnan A. *In vitro* Antifungal Effects of Hesperetin and Silibinin. **Pharmacogn. J.,** 2018;10(4):789€“792.
4. Fathima A,RaoJR. SelectivetoxicityofCatechin anaturalflavonoidtowardsbacteria, **Appl. Microbiol. Biotechnol.,** 2016;100(14):6395€“6402.
5. LiY, Zhao J, Gao K. Activity of flavanones isolated from *Rhododendron hainanense* against plant pathogenic fungi, **Nat Prod Commun.,** 2016;11(5)611:612.
6. Lani R, Hassandarvish P, Shu MH, Phoon WH, Chu JH, Higgs S, Vanlandingham D, AbuBakar S, Zandi K. Antiviral activity of selected flavonoids against Chikungunya virus, *Antiviral* **Res.,** 2016;133:50€“61.
7. Iranshahi M, Rezaee R,Parhiz H, Roohbakhsh A, Soltani F. Protective effects of flavonoids against microbes and toxins: The cases of Hesperidinand hesperetin. **Life Sci.,** 2015;137:125€“132.
8. Ortiz AC, Fideles SOM, Reis CHB, Bellini MZ, Pereira ESBM, Pilon JPG, De Marchi MA, Detregiachi CRP, Flato UAP, Trazzi BFM, Pagani BT, Ponce JB, Gardizani TP, Veronez SF, Buchaim JDV, Buchaim, RL., Therapeutic Effects of Citrus Flavonoids Neohesperidin, Hesperidin and Its Aglycone, Hesperetin on Bone Health. **Biomolecules,** 2022;12(626):1€“20.

9. Miles EA, Calder PC. Effects of Citrus Fruit Juices and Their Bioactive Components on Inflammation and Immunity: A Narrative Review. **Front. Immunol.,** 2021;*12(712608):2*€“*18.*
10. *Evans JA, Mendonca P, Soliman KFA. Neuroprotective Effects and Therapeutic Potential of the Citrus Flavonoid Hesperetin in Neurodegenerative Diseases.* ***Nutrients,*** *2022;*14(11):2*€“*25.
11. Muhammad T, Muhammad I, Ullah R, Rehman S U, Kim M O. Hesperetin, a Citrus Flavonoid, Attenuates LPS-Induced Neuroinflammation, Apoptosis and Memory Impairments by Modulating TLR4/NF-B Signaling. **Nutrients**, 2019;11(648):1€“20.
12. Kaltalioglu K, Balabanli B, Coskun-Cevhe S. Alleviation of Cisplatin-Induced Hepatotoxic Damage: the Synergistic Effect of Morin and Hesperidin against Oxidative Stress. **Res. j. Pharmacogn.**, 2019;6(2):9**€“**18.
13. Xia Z, Zhang Y, Zhang M, Chen Y, Yao-Wu L. Hesperetin ameliorates diabetes-associated anxiety and depression-like behaviorsin rats via activating Nrf2/ARE pathway. **Metab** *Brain* **Dis.,** 2021;6(7):1969€“1983.
14. Antunes M S, Cattelan L S, Ladd FVL, Lobo AAB, Moreira A L, Bortolotto V C, Machado A S, Prigol M, Nogueira C W, Boeira S P. Hesperidin Ameliorates Anxiety-Depressive-Like Behavior in 6-OHDA Model of Parkinson's Disease by Regulating Striatal Cytokine and Neurotrophic Factors Levels and Dopaminergic Innervation Loss in the Striatum of Mice. **Mol Neurobiol.,** 2020;57(7):3027€“3041.
15. Bino A, Vicentini C B, Vertuani S, Lampronti I, Gambari R, Durini E, Manfredini S, Baldisserotto A., Novel Lipidized Derivatives of the Bioflavonoid Hesperidin: Dermatological, Cosmetic and Chemopreventive Applications. **Cosmetics**, 2018;5(72):2€“15.
16. Sost M.M, Ahles S, Verhoeven J, Verbruggen S, Stevens Y, Venema KA. Citrus Fruit Extract High in Polyphenols Beneficially Modulates the Gut Microbiota of Healthy Human Volunteers in a Validated *In Vitro* Model of the Colon. **Nutrients,** 2021;13(11)*:*2€“13.
17. Salehi B, Cruz-Martins N, Butnariu M, Sarac I, Bagiu I C, Ezzat S M, Wang J, Koay A, Sheridan H, Adetunji C O, Semwal P, Schoebitz M, Martorelli M, Sharrifi-Rad J. Hesperetin's health potential: moving from preclinical to clinical evidence and bioavailability issues, to upcoming strategies to overcome current limitations. **Crit. Rev. Food Sci. Nutr.,** 2022;62(16):4449€“4464.
18. Mahmoud A M, Bautista RJH, Sandhu M A, Hussein O E., Beneficial effects of citrus flavonoids on cardiovascular and metabolic health. **Oxid. Med. Cell. Longev.,** 2019;2019(5484138):2€“19.
19. Actis-GorettaL, Dew T P, Léveques A, Pereira-Caro G, Rein M, Tem L A, Schäfer C, Hofmann U, Schwab M, *et al.* Gastrointestinal absorption and metabolism of hesperetin-7-0-rutinoside and hesperetin-7-0-glucoside in healthy humans**. Mol Nutr Food Res.,** 2015;59(9):1651€“1662.
20. Roohbakhsh A, Parhiz H, Soltani F, Rezaee R, Iranshahi M. Neuropharmacological properties and pharmacokinetics of the citrus flavonoids hesperidin and hesperetin — A mini-review. **Life Sci.,** 2014;113(1-2):1**€“**6.
21. Akbar N, Muhammad K, Khan NA, Shah M R, Alharbi A M, Alfahemi H, Siddiqui R. Hesperidin, Curcumin and Amphotericin B- Based Nano-Formulations as Potential Antibacterials. **Antibiotics**, 2022;11(696):2€“22.
22. Jebali J.; Ghazghazi H, Aouadhi C, Elbini-Dhouib I, Salem R B, Srairi-Abid N, Marrakchi N, Rigane G. Tunisian Native *Mentha pulegium* L. Extracts: Phytochemical Composition and Biological Activities. **Molecules,** 2022;27(314): 1€“12.
23. Vijayakumar K, Muhilvannan S, Vignesh A., Hesperidin inhibits biofilm formation, virulence and staphyloxanthin synthesis in methicillin resistant *Staphylococcus aureus* by targeting Sar A and Crt M: an *in vitro* and *in silico* approach. **World J. Microbiol. Biotechnol.,** 2022;38(44):1€“20.
24. Zhao, Z, Li P, Xie R, Cao X, Su D, Shan Y. Biosynthesis of silver nanoparticle composites based on hesperidin and pectin and their synergistic antibacterial mechanism. **Int. J. Biol. Macromol.,** 2022;214: 220€“229.
25. Attia GH, Marrez D A, Mohammed M A, Albarqi HA, Ibrahim AM, Raey MAEL. Synergistic Effect of Mandarin Peels and Hesperidin with Sodium Nitrite against Some Food Pathogen Microbes. **Molecules,** 2021;26(11):2€“14.
26. Masri A, KhanN A, Zoqratt MZHMD, Ayub Q, Anwar A, Rao K, Shah M R, Siddiqui R.Transcriptome analysis of *Escherichia coli* K1 after therapy with hesperidin conjugated with silver nanoparticles. *BMC* **Microbiol.,** 2021; 21(1):51€“57..

27. Abuelsaad ASA, Imad MAD, Gamal A C, Al-Solumani A A., Antimicrobial and immunomodulating activities of hesperidin and ellagic acid against diarrheic Aeromonas hydrophila in a murine model. **Life Sci.,** 2013;93, 714:722.
28. Kim H W, Woo H. J, Yang J Y, Kim J, Kim S. Hesperetin Inhibits Expression of Virulence Factors and Growth of *Helicobacter pylori***. Int J Biol Macromol.,** 2021;22(10035):1€“17.
29. Sykula A, Łodyga-chruscinska E, Garribba E,, Egiel D K, Dzeikala A, Klewicka E; Piekarska-Radzik L., From the Physicochemical Characteristic of Novel Hesperetin Hydrazone to Its *in vitro* Antimicrobial Aspects. **Molecules,** 2022;27(845):2€“23.
30. Baptista P V, Mccusker M P, Carvalho A, Ferreira D A, Mohan N M, Martins M, Fernandes A R., Nano-Strategies to Fight Multidrug Resistant Bacteria—“A Battle of the Titans”. **Front Microbiol.,** 2018;9(1441)2:26.
31. Hayat S. Nanoantibiotics Future Nanotechnologies to Combat Antibiotic Resistance. **Frontiers in Bioscience**, 2018;10:352€“374.
32. Slavin Y N, Asnis J, Hafeli U O, Bach H. Metal Nanoparticles: Understanding the Mechanisms behind Antibacterial Activity. **J. Nanobiotechnology**, *2017;*15(65):2€“20.
33. Ren X, Hu Y, Chang L, Xu S, Mei X, Chen Z. Electrospinning of antibacterial and anti-inflammatory core-shell nanoparticles into nanofibers used for promoting infected wound healing. **Regenerative Biomaterials**, 2022;9:1€“11.
34. Dadgostar P., Antimicrobial resistance: Implications and costs. **Infect. Drug Resist.,** 2019;12: 3903€“3910.
35. Jasovský D, Littmann J, Zorzet A, Cars O. Antimicrobial resistance-a threat to the world's sustainable development. **Ups.** *J. Med. Sci***.,** 2016;121(3):159€“164.
36. Gandra, S, Klein E Y, Pant S, Malhotra-Kumar S, Laxminarayan R. Faropenem Consumption Is Increasing in India. **Clin Infect Dis.**, 2016;62:1050€“1052.
37. Roy R, Tiwari M, Donelli G, Tiwari V. Strategies for combating bacterialbiofilms: A focus on anti-biofilm agents and their mechanisms of action. **Virulence**, 2018;9:522€“554.
38. Galie S, Garcia-Gutiérrez C, Miguélez EM, Villar C J, Lombó F., Biofilms in the Food Industry: Health Aspects and Control Methods. **Front Microbiol.,** 2018;9(898)1:18.
39. Cepas V, López Y, Munoz E.; Rolo D, Ardanuy C.; Martí S.; Xercavins M, Horcajada J P, Bosch J, Soto S M. Relationship Between Biofilm Formation and Antimicrobial Resistance in Gram-Negative Bacteria. *Microb***. Drug Resist.,** 2019;25:72€“79.
40. Del Pozo J L. Biofilm-related disease**.** *Expert* **Rev Anti Infect Ther.**, 2017; 16, 51:65.
41. Hall C W, Mah T. F. Molecular mechanisms of biofilm-based antibiotic resistanceand tolerance in pathogenic bacteria. *FEMS Microbiol***.** *Rev***.,** 2017;41: 276€“301.
42. Ahmad A, Kaleem M, Ahmed Z, Shafiq H. Therapeutic potential of flavonoids and their mechanism of action against microbial and viral infections—A review. **Food Res Int.**, 2015;77:221€“235.
43. Min K Y, Kim H J, Lee K A, Kim K, Paik H. Antimicrobial activity of acid-hydrolyzed Citrus unshiu peel extract in milk. *J. Dairy* **Sci.,** 2014;97(4):1955€“1960.
44. Mandalari G, Bennett R N, Bisignano G, Trombetta D, Saija A, Faulds C B, Gasson M J, Narbad A. Antimicrobial activity of flavonoids extracted from bergamot (*Citrus bergamia* Risso) peel, a byproduct of the essential oil industry. **J Appl Microbiol.,** 2007;103:2056€“2064.
45. Rakesh K, Kumara H, Ullas B, Shivakumara J, Gowda D C. Amino acids conjugated quinazolinone-Schiff's bases as potential antimicrobial agents:Synthesis, SAR and molecular docking studies. **Bioorg Med Chem Lett.,** 2019;90: 093€“103.
46. Oliveira A A, De Oliveira APA, Franco L L, Ferencs M O, Ferreira J, Bachi SMPS, Speziali N L, Farias L M, Magalhães P P, Beraldo H., 5-Nitroimidazole-derived Schiff bases and their copper (II) complexes exhibit potent antimicrobial activity against pathogenic anaerobic bacteria. **BioMetals**, 2018;31:571€“584.
47. Brodowska K, Correia I, Garribba E, Marques F, Klewicka E, Lodyga-Chruscinska E, Pessoa J C, Dzeikala A, Chruscinski L. Coordination ability and biological activity of a naringenin thiosemicarbazone. **J. Inorg. Biochem.,** 2016;165:36€“48.

48. Łodyga-Chruscinska E, Symonowicz M, Sykula A, Bujacz A, Garribba E, Rowinska-Zyrek M, Oldziej S, Klewicka E,˙Janicka M, Krolewska K, Cieslak, M , Brodowska K, Chruscinski L. Chelating ability and biological activity of hesperetin Schiff base. **J. Inorg. Biochem.,** 2015;143:34€“47.
49. Yanpeng H, Wei Z, Wang Z, Li G, Yao Y, Dun B. Biotransformation of Flavonoids Improves Antimicrobial and Anti-Breast Cancer Activities *in vitro*. **Foods,** 2021;10(10):2€“16.
50. John JC. ACE inhibitors and NSAIDs. Med J Euro. 2010;777:181€“195.

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