Biological effects of naringenin and naringin: a review of bioassays

Efeitos biológicos da naringenina e naringina: uma revisão de bioensaios

Efectos biológicos de la naringenina y la naringina: una revisión de los bioensayos

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Abstract
Currently, the search for natural antimicrobial compounds has increased and, taking into account the high rate of infection by antibiotic-resistant microorganisms, the search for new compounds that have an antimicrobial effect has been stimulated. Flavonoids fit into this group because of their strong biological and medicinal properties. Biological activity such as anti-inflammatory, antioxidant, antibacterial, anti-hepatotoxic, and anti-carcinogenic are reported to occur. The objective of the current study was to collect information on the in vitro antibacterial activity of the flavonoids naringenin and naringin and to demonstrate the biological effects of these substances against bacteria. This is a integrative review of the literature on scientific articles published between 2017 and 2022 that was done using the PUMED databases. Flavonoids may be able to inhibit bacterial growth through different mechanisms, such as changing membrane and wall permeability cell, inhibition of nucleic acid synthesis and also by synergistic activity with antibiotics. The development of new antimicrobial drugs is increasingly necessary, which makes flavonoids promising candidates. Therefore, it is believed in the potential of naringenin and naringin as candidate phytoconstituents for the development and innovation of new antibiotics.
Keywords: Naringenin; Naringin; Bioassays; Antibacterial activity.

Resumo
Atualmente, a busca por compostos antimicrobianos naturais tem aumentado e, tendo em vista o alto índice de infecção por microrganismos resistentes a antibióticos, tem sido estimulada a busca por novos compostos que tenham efeito antimicrobiano. Os flavonoides se enquadram neste grupo devido às suas fortes propriedades biológicas e medicinais. Atividade biológica como anti-inflamatória, antioxidante, antibacteriana, anti-hepatotóxica e anticancerígena é relatada. O objetivo do presente estudo foi coletar informações sobre a atividade antibacteriana in vitro dos flavonoides naringenina e naringina e demonstrar os efeitos biológicos dessas substâncias contra bactérias. Esta é uma revisão integrativa da literatura sobre artigos científicos publicados entre 2017 e 2022 que foi feita usando as bases de dados PUMED. Os flavonoides podem ser capazes de inibir o crescimento bacteriano por meio de diferentes mecanismos, como alteração da permeabilidade da membrana e da parede celular, inibição da síntese de

ácidos nucléicos e também por atividade sinérgica com antibióticos. O desenvolvimento de novos fármacos antimicrobianos é cada vez mais necessário, o que torna os flavonoides candidatos promissores. Portanto, acredita-se no potencial da naringenina e naringina como fitoconstituintes candidatos ao desenvolvimento e inovação de novos antibióticos.
Palavras-chave: Naringenina; Naringina; Atividade antibacteriana.

Resumen
Actualmente, la búsqueda de compuestos antimicrobianos naturales se ha incrementado y, teniendo en cuenta la alta tasa de infección por microorganismos resistentes a los antibióticos, se ha estimulado la búsqueda de nuevos compuestos que tengan efecto antimicrobiano. Los flavonoides encajan en este grupo debido a sus fuertes propiedades biológicas y medicinales. Se informa que se produce actividad biológica como antiinflamatoria, antioxidante, antibacteriana, antihepatotóxica y anticancerígena. El objetivo del presente estudio fue recopilar información sobre la actividad antibacteriana in vitro de los flavonoides naringenina y naringina y demostrar los efectos biológicos de estas sustancias contra las bacterias. Esta es una revision integradora de la literatura sobre artículos científicos publicados entre 2017 y 2022 que se realizó utilizando las bases de datos PUMED. Los flavonoides pueden inhibir el crecimiento bacteriano a través de diferentes mecanismos, como el cambio de la permeabilidad de la membrana y la pared celular, la inhibición de la síntesis de ácidos nucleicos y también por la actividad sinérgica con los antibióticos. El desarrollo de nuevos fármacos antimicrobianos es cada vez más necesario, lo que convierte a los flavonoides en candidatos prometedores. Por lo tanto, se cree en el potencial de la naringenina y la naringina como fitoconstituyentes candidatos para el desarrollo e innovación de nuevos antibióticos.
Palabras clave: Naringenina; Naringina; Bioensayos; Actividad antibacterial.

1. Introduction

Flavonoids are phytonutrients that are frequently present in plants and vegetables and are primarily responsible for the flavor and vibrant colors. In higher plants, they function as chemical messengers, cell cycle inhibitors, and nitrogen fixers. Additionally, it is well recognized that they offer plants defense against spores and ailments. Two benzene rings (Ring A and Ring B) and a short chain of three carbon atoms, known as a closed pyran ring, are joined by fifteen carbon atoms in its chemical structure. Almost all vegetables and fruits include flavonoids, which are found in either aglycone or glycosylated form and have been modified in many ways (e.g., glycosylation, hydrogenation, hydroxylation, methylation, and sulfonation. (Tapas; et al., 2008; Alam et al., 2014; Galluzzo, 2008).

The biological activities of flavonoids and their metabolites depend on their chemical structure and their orientation in the molecule. Although they are soluble in water and are known metal chelators, the antioxidant effect of practically all classes of flavonoids is what is most documented about them. Additionally, they exhibit anti-allergic, anti-hepatotoxic, anti-carcinogenic, anti-inflammatory, and antithrombotic characteristics (Wilcox; Borradaile, 2019).

Several flavonoids, including naringenin, inhibit the action of pro-oxidant enzymes such as xanthine oxidase, nicotinamide adenine dinucleotide phosphate oxidase, lipoxygenase and cyclooxygenase, and exhibit action in metal ion chelation and free radical scavenging. In addition, naringenin increases the physiological level of several antioxidant enzymes, such as glutathione peroxidase, superoxide dismutase and catalase. It is also known to reduce the nitration and oxidation of proteins facilitated by peroxynitrite (Wang et al., 2010).

Naringenin has the skeleton structure of a flavanone with three hydroxy groups on carbons 4', 5 and 7. It can be found both in the glycol form, naringenin, and in the glycosidic form, naringin. This flavonoid is found almost exclusively in citrus fruits, mainly grapefruit and orange (Khan et al. 2014; Zeng et al. 2018). It was observed that naringenin, when compared to naringin, showed greater activity in scavenging oxidants, superoxide and hydroxyl radicals. It also showed greater ability to protect against oxidative damage caused by lipids and ion chelation (Wang et al., 2010).

It was seen in the literature that the antioxidant efficiency of naringenin, as well as other flavones, is dose-dependent (Cavia-Saiz et al., 2010). It has the ability to scavenge free radicals and can inhibit the nitrite-aided oxidation of hemoglobin to methemoglobin (Martinez et al., 2016; Sudheer et al., 2003).

Hermenean et al. (2013) showed that naringenin administered at a dose of 50 mg/kg in mice reduced CCl4-induced hepatotoxicity. Likewise, it reduced hepatocarcinogenesis, when associated with N-nitrosodiethylamine, in rats at a dose of 200 mg/kg (Arul, Subramanian, 2013). Other work has shown that naringenin (100 mg/kg) exhibits hypouricemic activity in mice and therefore may be considered therapeutically useful in the treatment of gout due to the inhibition of the oxidative enzyme, xanthine oxidase in the liver (MO et al., 2007).

A protective effect was also observed on ethanol-induced hepatotoxicity, lead-induced renal and hepatic dysfunction, and oxytetracycline-mediated liver damage, due to its potent antioxidant capacity (Spencer; Crozier, 2012; Prabu; et al., 2011).

Another well-reported property of naringenin in the literature is the anti-inflammatory effect and was attributed to the activation of the transcription factor Nrf2, which acts as an agonist of the aryl hydrocarbon receptors and further decreasing the formation of reactive oxygen species and inflammatory mediators (Pinho-Ribeiro et al., 2016).

The microbiological effect of naringenin was seen on microorganisms Staphylococcus epidermidis, Staphylococcus aureus, Bacillus subtilis, Micrococcus luteus and Escherichia coli, Lactococcus lactis, Lactobacillus acidophilus, Actinomyces naeslundii, Prevotella oralis, Prevotella melaninogencia, Porphyromonas gingivalis, Candida albicans, Candida tropicalis, and Candida krusei (Rauha et al., 2000; Mandalari et al., 2007; Koru et al., 2007; Uze et al., 2005).

In cultured hepatocytes, naringenin also shown action against the hepatitis C virus by blocking the microsomal triglyceride transfer protein, preventing cells from secreting very low-density lipoprotein. Naringenin stimulation significantly (80%) decreased HCV production in infected cells. Furthermore, it proved efficacious in primary human hepatocytes and mice at concentrations that are an order of magnitude below the lethal threshold (Nahmias et al., 2008). It has also described antiviral effects on poliovirus, HSV-1 and HSV-2 and recently, in in vitro experiments, it showed activity against SARS-CoV-2 (Mucsi; Pragai, 1985; Lyu; et al., 2005; Clementi et al. 2021).

Having listed this information regarding the bio pharmacological activities of naringenin, the objective of this article was to carry out an overview of current works and to elaborate a systematic review to verify the existence and effectiveness of the in vitro antibacterial action of naringenin and naringin.

2. Methodology

2.1 Electronic search

The study was conducted through a integrative review of scientific production on the in vitro antibacterial activity of naringenin and naringin. The integrative review of literature gathers and summarizes research results of a theme particular, which allows to substantiate the relevant scientific knowledge (Souza et al., 2017).

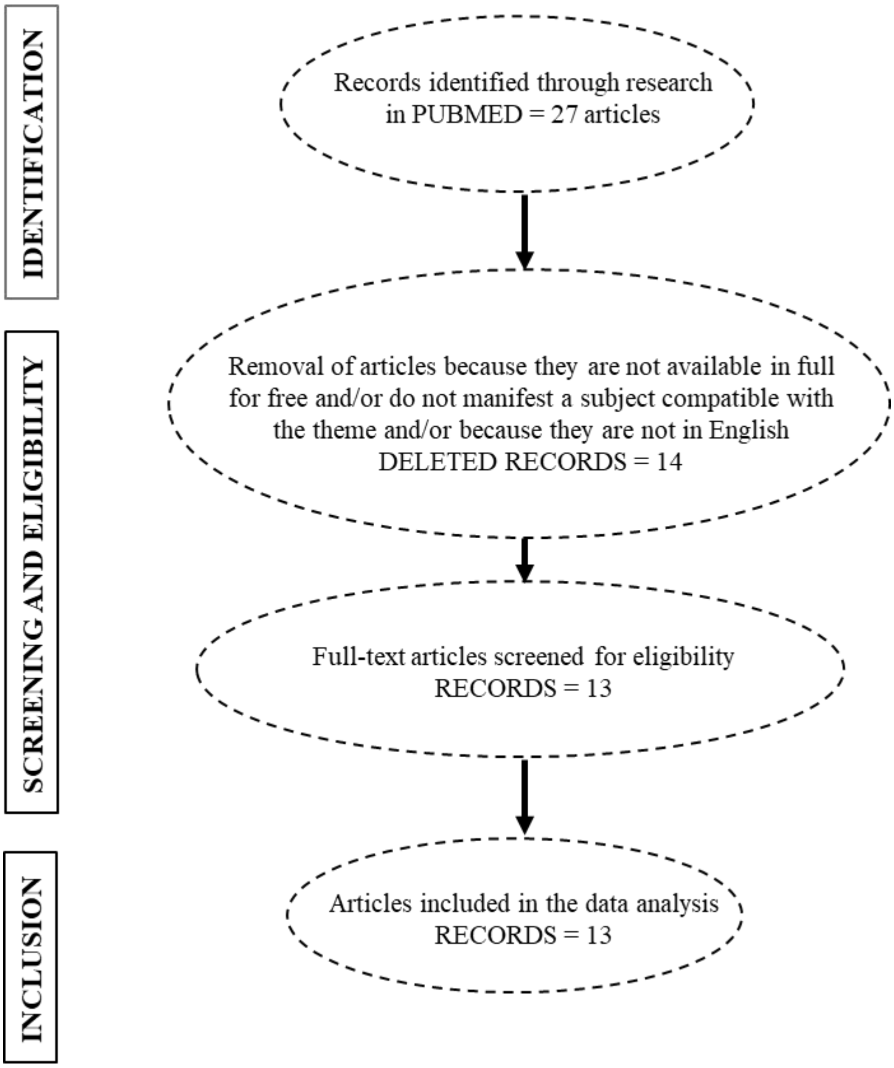
Were included original articles published in the last five years, from 2017 to 2022, in English related to the topic. Besides, were select in the PubMed database the scientific articles made available as full text and free of charge.The following exclusion criteria were used: articles that were not in full available, that had no relationship with the established theme and duplicated articles.

The descriptors used for the search strategy were: (1) naringenin; (2) antibacterial activity using among them; the Boolean operator AND. A descriptive analysis of the data was performed as shown in table containing the data: plant species, substance, microorganism, method used, results and reference.

3. Results and Discussion

Considering the articles found, the initial result of 27 scientific papers was reached. These were initially submitted to the inclusion criterion of being available online in full text with free and free access, and the link available directly in the database itself was accessed. 13 in vitro papers were selected and the titles and abstracts were read and then the 13 articles were read in full and some data extracted from each article (Figure 1).

Figure 1 - Search for data acquisition and research development.



Fontes: Dados dos Autores (2023).

With the analysis of the selected studies, it was possible to have an overview of the current research performed with naringenin to evaluate microbiological activity as shown below in Table 1.

Two papers were published in 2018, two in 2019, four in 2020, four in 2021, and one so far in 2022 out of the total number of interesting pieces. The antibacterial activity of the compound naringenin extracted from plants, such as the bark of the stem of *Uapaca heudelotti* (Achika et al., 2020), hibiscus rosa sinensis flowers (Trung et al., 2020), and the stem of *Artocarpus chama*, was described in three publications in scientific literature (Dej-Adisai et al., 2022). Studies were also found with extracts of flowers of *Acacia saligna* (Al-Huqail et al., 2019), root bark *Gnidia involucrata* (Kalbessa et al., 2019), *extract of Echinops lanceolatus miltf* (Seukep et al., 2020), extract of *Moringa oleifera* pods (Salem et al., 2021), leaves of *Cycas thouarsii* (Negm et al., 2021), flower extract of *Sambucus nigra* L. (Ferreira-Santos et al., 2021) who presented naringenin as secondary metabolite or phytoconstituent and exhibited antibacterial potential.

Table 1 – Synthesis of selected articles regarding antibacterial activity of naringenin in studies between 2017 and 2022.

PLANT SPECIES	SUBSTANCE	MICROORGANISM	METHOD USED	RESULTS	REFERENCE
NA	Naringenin 7-sulfato de naringenin	*Salmonella enterica* ATCC 14028 *Staphylococcus aureus* CCARM 0205 *Staphylococcus aureus* CCARM 0204 *Staphylococcus aureus* CCARM 3634 *Proteus hauseri* NBRC 3851, *Micrococcus luteus* KACC 13377, *Pseudomonas aeruginosa* KACC 10232, *Enterobacter cloacae dissolve* KACC 13002	Disc diffusion	Naringenin showed antibacterial activity against *S. enterica* while 7-naringene sulfate exhibited activity against Gram-positive and Gram-negative bacteria and presented a considerable inhibition zone against the other bacteria in the study. This work aimed to improve the production of sulfated flavonoids in *E. coli* manipulated. This compound also showed anticancer activity against a 375SM melanoma cancer cell line, breast MCF-7 and gastric cancer AGS.	Chu et al., 2018
Cannabis sativa L.,	Naringenin e-derivado glicosilado naringin	*Staphylococcus aureus* ATCC 29213 and three strains of clinical origin *Helicobacter* pylori (fourteen clinical strains isolated from patients with duodenal ulcer or gastritis) *Candida*, *Malassezia* spp.	MIC, MBC, Biofilm inhibition assay	The antimicrobial, bactericidal and antibiofilm activities of the organic extract of the aerial parts of *C. sativa* L. suggested that secondary metabolites could be candidates for the treatment of *S. aureus* and *H. pylori* related infections. Among the secondary metabolites found the two most important metabolites were naringenin and its glycosylated derivative, naringin. These presented properties similar to drugs already validated; however, an assessment of your safety should be made.	Zengin et al., 2018
Acacia saligna (Labil.) HL Wendl	Naringenin	*Fusarium culmorum* MH352452 *Rhizoctonia solani* MH352450 *Penicillium chrysogenum* MH352451 *Agrobacterium tumefacien* *Enterobacter cloacae* *Erwinia amylovora* *Pectobacterium carotovorum carotovorum*	MIC	It was found, in greater concentration, in the aqueous extract of flowers of *A. saligna* *nayngonine*. This extract showed moderate antifungal properties against three fungal species: *F. culmorum, R. solani and P. chrysogenum* while it presented antibacterial and antioxidant activity lower than the standards used, tobramycin and butylated hydroxytoluene (BHT). It is possible to state that there are some potential applications of this extract for wood protection.	Al-Huqail et al., 2019
Gnidia involucrata	Naringenin	*Escherichia coli* ATCC 25922 *Proteus mirabilis* ATCC 35659 *Klebsiella pneumonia* ATCC 700603 *Staphylococcus aureus* ATCC 25923	Disc diffusion assay	Naringenin was extracted from the EtOAc extract of the root bark of *G. involucrata* and showed strong antibacterial activity compared to ciprofloxacin used as positive control. The antioxidant activities exhibited by EtOAc extract were significant compared to those presented by ascorbic acid, indicating the potential of root barks of this species as natural antioxidants. Therefore, the biological activities presented by EtOAc extract and isolated compounds corroborate the traditional use of this plant against various diseases caused by bacteria.	Kalbessa et al., 2019
Uapaca heudelotti	naringenin-7-O-glycoside	*Clinical isolates of Escherichia coli, Bacillus subtilis, Salmonella typhi, Streptococcus pyogenes, Klebsiella pneumoniae, Staphylococcus aureus e Proteus mirabilis*	MIC, MBC	Naringenin-7-O-glycoside isolated from the bark of the stem of *U. heudelotti* proved to be a good antioxidant because it eliminated 80% of free radicals in the study; in addition, it showed good antimicrobial activity especially against *S. typhi* and *B. subtilis*.	Achika et al., 2020
NA	Naringenin	*Mycobacterium tuberculosis*	IC_{50}	It was validated by a computational approach and in vitro experiments that naringenin and quercetin showed good binding affinity with MTB-MurI (an enzyme involved in peptidoglycan biosynthesis) and inhibited racemization activity with structural disturbance induced in tuberculosis mycobacteria causing damage to the cell wall and death of the bacterium.	Pawar et al., 2020
Echinops lanceolatus Mattf.	Naringenin-7-O-glycoside, naringin	*Enterococcus faecalis* ATCC 29212 *Staphylococcus aureus* CCTCC AB91093 *Acinetobacter baumannii* ATCC19606 *Enterobacter cloacae* ATCC700323	MIC, MBC	Antibacterial potential and antiproliferative activities of the crude methanol extract *of E. lanceolatus* and fractions (n-hexane, dichloromethane, ethyl acetate and n - butanol) were observed. The ethyl acetate fraction was considered the most effective, in which 32 phytochemicals were identified among them: naringenin-7-O-glycoside, apigenin-7-O - glycoside, naringin, apigenin,	Seukep et al., 2020

		Escherichia coli CCTCC AB93154 *Klebsiella pneumoniae* CMCC(B)9027 *Pseudomonas pneumoniae* CMCC(B)46117 *Salmonella enterica* CCTCC AB94018		roifoliin, coniferyl aldehyde and secoisolarhydroresinol are well documented for their antimicrobial and antiproliferative properties. These make evidence for substance to consider *E. lanceolatus* as a plant of biological importance, a valuable source for anti-infectious and antitumor agents.	
Hibiscus rosa sinensis	Naringenin	*Helicobacter pylori* ATCC 43504 *Helicobacter pylori* ATCC 51932 *and clinical isolates OX.22, OX.63, OX.64, OX.67, OX.83*	MIC, MBC	Naringenin showed inhibitory and bactericidal activity for seven bacterial strains, including six antibiotic-resistant strains (azithromycin, erythromycin, levofloxacin, metronidazole). It also presented antibacterial antibiofilm activities.	Trung et al., 2020
Sambucus nigra L.	Naringenin	*Pseudomonas aeruginosa* PAO1 *Klebsiella oxytoca* ATCC 13182 *Klebsiella pneumoniae* ATCC 11296 *Staphylococcus aureus* ATCC 25293 *Staphylococcus epidermidis* ATCC 12228 *Candida albicans* SC 5314	MIC, MBC	The aqueous extract of S. *nigra* flowers was chemically needed and it was found that the major compound of the lipophilic fraction was naringenin. The results demonstrated the potential of S. *nigra* floral extract as promising antimicrobial against S. *aureus* and *S. epidermidis*	Ferreira-Santos et al., 2021
Cycas thouarsii R. Br	Naringenin	*Klebsiella pneumoniae*	MIC	*C. thouarsii extract* showed antibacterial activity against clinical isolates of *K. pneumoniae* and inhibited bacterial growth in 73.5% of the clinical isolates, significantly decreased the integrity of the bacterial cell membrane. The extract had a drastic effect on bacterial cell morphology confirmed by the decrease in gene expression encoding flow pumps detected in selected isolates with percentages ranging from 33.3% to 55.5%	Negm et al., 2021
Moringa oleifera	Naringenin	*Agrobacterium tumefaciens* acc# MG706145 *Erwinia amylovora* acc# LN876573 *Pectobacterium atrosepticum* acc# MG706146	Disc diffusion assay, MIC	The following phytoconstituents were identified in extract from *M. oleifera* pods: vanyl, benzoic, sysingic and ferulic acids and the flavonoid compounds myricetin, naringenine and kaempferol; in addition, moderate to significant antibacterial activity was observed against *A. tumefaciens, E. amylovora, P. atroumum.*	Salem et al., 2021
NA	Naringenin	*Staphylococcus aureus* ATCC 6538	Biofilm inhibition assay	They revealed that biofilms of *S. aureus* became thinner and separated into individual colonies when exposed to naringenin. The decrease in biofilm formation of *S. aureus* cells may be due to a decrease in the hydrophobicity of the cell surface and in the production of exopolysaccharides, which are involved in the ad take or maturation of biofilms. In addition, the transcriptional results show that there was a negative regulation in the expression of genes related to naringenin-induced biofilm. The study indicates the potential of naringenin as a natural agent to prevent the formation of *S. aureus* biofilm and possibly reduce health risks related to biofilm formation in the food industry.	Wen et al., 2021
Artocarpus chama	Naringenin	*S. epidermidis*, *S. aureus* MRSA, *C. acnes*	MIC, MBC	Three new compounds and five known compounds, including naringenin, were isolated from the stem of *A. chama*. The extract showed low antimicrobial effect.	Dej-adisai et al., 2022

SUBTITLE: MIC = Minimum Inhibitory Concentration, MBC = Minimum Bactericidal Concentration, IC50 = Average inhibition concentration. NA = not applicable. Fontes: Autoria própria.

According to Table 1, we can see that the plants mentioned were those that had studies related to antibacterial potential and presented naringenin as one of the phytoconstituents. Regarding microorganisms, the most cited bacteria were Staphylococcus aureus, Klebsiella pneumoniae and Escherichia coli; among which S. aureus presented the highest number of studies corresponding to 46% of our research. This bacterium is gram-positive coccus residing in the human microbiota, but that can cause from simple infections or even sepsis, being considered an opportunistic pathogen. S. aureus was one of the first bacteria to be controlled with the discovery of antibiotics, due to its enormous adaptability and resistance, has become one of the most important species in public health. Therefore, the search for new antibacterial agents remains high (Marmitt et al., 2015).

According to the Brazilian Society of Microbiology, about 700,000 deaths are caused by infections derived from multidrug-resistant bacteria per year and it is estimated that by 2050 there will be about 10 million deaths per year. According to the World Health Organization, bacteria such as A. baumannii, P. aeruginosa, K. pneumoniae and E. coli are classified as a critical priority of resistance, and the need for the production of new antibiotics, especially for these bacteria, is evident. Therefore, studies with new substances opens possibilities for the development of medicines (Mota et al., 2018).

According to the data collected, the studies show differences in concentrations for the effect of the substance on antimicrobial activity. This may be associated with the solvents used in obtaining and/or concentrating the extracts of the plants, in the concentration of naringenin in that extract as well as the morphological structure of the microorganisms used in the studies. This information reiterates the research by Tavares et al. (2020), which showed gram-positive bacteria requiring concentrations higher than gram-negative, in case of antimicrobial activity. However, in this review, we found antibacterial effect of naringenin in both gram-positive and gram-negative bacteria.

Studies reporting the mechanism of action of antimicrobial compounds suggest a possible association of substances in the target microorganism by the cell membrane, attacking it and releasing cellular constituents, inhibiting the action of specific enzymes. Therefore, it is believed that the antibacterial effects of a substance vary according to the strain of bacteria studied (Belém et al., 2021).

Due to the relevance of flavonoids as bioactive compounds, it is worth mentioning here for the possibility of innovation in pharmacology, as a strategy to obtain drugs with potential for control of microorganisms that cause human diseases. Naringenin is a secondary metabolite and widely distributed in plants, in addition to functioning naturally with defense in plant species, a use of the benefits of consumption of fruits and other vegetables is generally attributed to flavonoids once consumed. Both industry and researchers and consumers have shown great interest in flavonoid compounds for the potential of their role in the prevention of cancer and cardiovascular diseases due mainly to their antioxidant properties. Therefore, the potential of naringenin and naringin is believed to be promising phytoconstituents for the development and/or innovation of new antibiotics.

4. Conclusion

Bacterial infections are a global challenge for public health and can result in serious infections, complications, longer hospital admissions and higher mortality. As we report, Naryingenin and Naringina are phytochemical compounds present in various plant extracts that demonstrated antibacterial activity. From the findings of this literature survey, we suggest conducting more research, in vitro and in vivo, with these substances in isolation and in association with reference antimicrobials, in order to elucidate which ideal concentrations for pharmacological effectiveness and which mechanisms of action that are responsible for demonstrating bactericidal or bacteriostatic activity and can in the future contribute to the development of a new drug or the innovation of existing antibiotics.

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