Review

Cyclodextrins Inclusion Complexes Improving Antibacterial Drug Profiles: An Update Systematic Review

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Cyclodextrins Inclusion Complexes Improving Antibacterial Drug Profiles: An Update Systematic Review

Anamaria Mendonça Santos [1,†], José Adão Carvalho do Nascimento Júnior [2], Silvia Vitória Silva Cézar [3], Lucindo José Quintans Júnior [1,3], Adriano Antunes de Souza Araújo [1,2,3], Diana Marcela Aragón [4] and Mairim Russo Serafini [1,2,3]

[1] Postgraduate Program in Health Sciences, Federal University of Sergipe, Aracaju, Sergipe, Brazil
[2] Department of Pharmacy, Federal University of Sergipe, São Cristóvão, Sergipe, Brazil
[3] Postgraduate Program in Pharmaceutical Sciences, Federal University of Sergipe, São Cristóvão, Sergipe, Brazil
[4] Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, Bogotá D.C., Colombia
* Correspondence: anamariams@academico.ufs.br
† Postal address: Marechal Rondon Jardim- Rosa Elze, São Cristóvão - SE, Postal Code 49100-000.

Abstract: Antibiotics have become a widely used drug classes worldwide. Its indiscriminate use in the clinical-hospital environment ended up causing antibiotic-resistance genes. Pharmaceutical technology is an essential ally for new formulation development in the antibacterial field. Cyclodextrins (CDs) are approaches that can potentially improve the effectiveness of antibacterial drugs. Thus, this study aimed to review experimental models using CDs as inclusion complexes to improve antibacterial drugs' physicochemical characteristics and biological activities. The review was carried out using the three online journals database PubMed, Scopus, and Embase, limited to Medical Subjects Headings Index. The search protocol was registered in the Open Science Framework database. The following terms and their combinations were used: cyclodextrins and antibacterial agents in title or abstract, and a total of 1580 studies were identified in a period up to October 2022. Finally, 27 articles were selected for discussion in this review. The biological results reveal that the antibacterial effect of the compounds, complexed with CDs, was extensively improved when compared to the free drugs. CDs can improve the therapeutic effects of antibiotics, already existing on the market, natural products, and synthetic molecules. Therefore, these inclusion complexes using CDs increase the new pharmaceutical products development for clinical application.

Keywords: Antibacterial Agents; Antibiotics; Cyclodextrins; Inclusion Complex; Technology; Treatments

1. Introduction

Antibiotics have become one of the most widely used drug classes worldwide due to their power to cure diseases previously considered incurable [1]. Moreover, antibiotics have made it possible to carry out treatments and procedures that previously had low expectations of success, such as organ transplants, cancer treatment, and open-heart surgery [2]. However, its indiscriminate use in the clinical-hospital environment ended up causing microorganisms, mainly bacteria, to develop antibiotic resistance genes (ARGs). ARGs spread globally among microorganisms, thus characterizing one of the main world health problems of the 21st century [3].

In 2019, bacterial resistance to antibiotics caused around 1.27 million deaths, and projections are that 300 million deaths will occur by 2050 [3,4]. Furthermore, China, for example, is one of the main consumers of antibiotics worldwide since the percentage of prescriptions that include an antibiotic

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in China was 41%-60%, which is above the recommended threshold of 30% by the World Health Organization (WHO) [5]. For this reason, the country has suffered for some years from ARGs, mainly in relation to gram-negative bacteria resistant to carbapenem drugs [6]. Thus, in 2013, the Center for Disease Control and Prevention (CDC), in the United States of America (USA), announced that humanity lives in the post-antibiotic era, which affects the health of the entire global population, and has an impact on the economy [7]. An example of this occurs mainly in the regions of the Middle East and North Africa, including Lebanon, where in the last 40 years, a reduction in the gross domestic product has been estimated, between about US$ 2-159 billion/ year due to bacterial resistance, which could trigger global financial crises [1].

New alternatives are needed to circumvent bacterial resistance and increase the range of possibilities in clinical practice when treating bacterial infections. In this perspective, pharmaceutical technology is used as a promising ally for the development of the new formulation in the antibacterial field [8]. An example of these approaches is the supramolecular inclusion complexes using cyclodextrins (CDs). CDs are intended for the physical-chemical improvement of drugs, to contribute to better bioavailability, biodistribution, and solubilization, increasing the absorption and decreasing the efflux of drugs in the cells of microorganisms [9,10].

In the late 19th century, CDs interactions were discovered by Villiers and Schardinger, and a patent was filed on the chemistry of CDs and their complexes in 1953 [11]. Therefore, CDs are oligomers formed by the union of glucose monomers and obtained through the exposure of starch to an enzyme called cyclomaltodextrin glucanotransferase, naturally excreted by *Bacillus macerans [12]*. CDs can be found in the form of α-CD, β-CD, and γ-CD **(Figure 1)**. Furthermore, the CD molecule has hydroxyl groups at the ends, giving hydrophilicity to poorly soluble or insoluble drugs [13].

Moreover, the central molecular cavity of CDs is characterized by being lipophilic, thus having a greater affinity for hydrophobic molecules. In this way, once complexed, the drug will have its pharmacokinetics altered to improve its solubility, and consequent pharmacological efficacy due to better absorption [14–16]. CDs are a group of cyclic oligosaccharides composed of glucose molecules that can form inclusion complexes with hydrophobic drugs [10, 13]. Thus, in the case of antibacterial drugs, some of them have low solubility in water, which can limit their bioavailability and therapeutic efficacy; thus, CDs mitigate theses narrowness and potentially result in better treatment outcomes for bacterial infections and other situations that are particularly clinically difficult to manage [14,17].

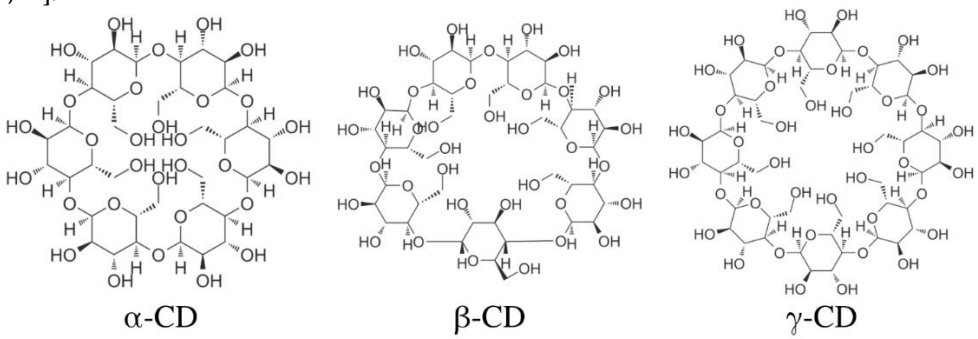

Figure 1. Structural representation of the most used cyclodextrins.

Beyond that, CDs applications also include the inhibition of drug–drug interactions, changing liquid drugs into microcrystalline powder materials, increasing the residence time of drugs in the circulation, reducing digestive and optical irritation, and masking or diminishing bitter taste and unpleasant smell [17–19]. Thus, this study aimed to review experimental models using CDs as inclusion complexes to improve antibacterial drugs' physicochemical characteristics and their biological activities.

2. Materials and Methods

Search Strategy

The present review was carried out without restriction of region and date of publication, using the three online journals database PubMed, Scopus, and Embase. The following terms and their combinations were used: cyclodextrins and antibacterial agents in title or abstract, and the total study search was conducted over a period up to October 2022. The terms used in the review were limited to Medical Subjects Headings Index (MeSH/DeCS). The search protocol was registered in the Open Science Framework (OSF) database (through the registration doi: https://doi.org/10.17605/OSF.IO/AXHUF). The organized search strategy was designed to include all published papers, which have the inclusion complexation of antibacterial agents with cyclodextrin especially, for the antibacterial activity and improvement of physicochemical characteristics studies using in vitro or in vivo model experiments. Supplementary papers were involved in our study after the analyses of all references from the selected articles.

Study Selection

The electronic databases reveal different sources of results. Meanwhile, in the search results the titles, selected abstracts, and full-text articles were independently reviewed by two reviewers (AMS and SVSC), with any disagreement being resolved by consensus or a third author (JACNJ). The final selection of the exclusion or inclusion of the articles were performed after consulting all the three coauthors. Therefore, it included research papers investigating the effect of drug molecules complexed in CDs that could significantly improve bioavailability, drugs' physicochemical properties, and increase antibacterial effect using in vivo or in vitro experimental systems. Moreover, it excluded studies using other pharmaceutical technologies, review articles, meta-analyses, book chapters, conference proceedings, editorials/letters, patents, and case reports.

Data Extraction

All the web data were extracted by one reviewer (AMS) with identical key forms and were checked for completeness and accuracy by a second reviewer (SVSC). Information about the articles was collected mainly about the type of substance, CDs (type), methods of characterization, the experimental design used, strains and animals, and results of antibacterial activity parameters.

3. Results and Discussion

3.1. Search Results

A total of 1580 citations were identified in which 642 belonged to PubMed, 540 from Scopus, and 398 from Embase. Titles replicated, review articles, conference proceeding reports, case reports of human, and initial screening process of eligible titles and abstracts were studied and then excluded from the review. Further, 27 full text articles were finalized for the inclusion criteria. The content included were the articles reported for the compounds presenting antibacterial activity with cyclodextrin inclusion complexation to improve the pharmacological effect and physicochemical characteristics. **Figure 2** illustrates the article search and screening guidelines in this review, based on the PRISMA methodology.

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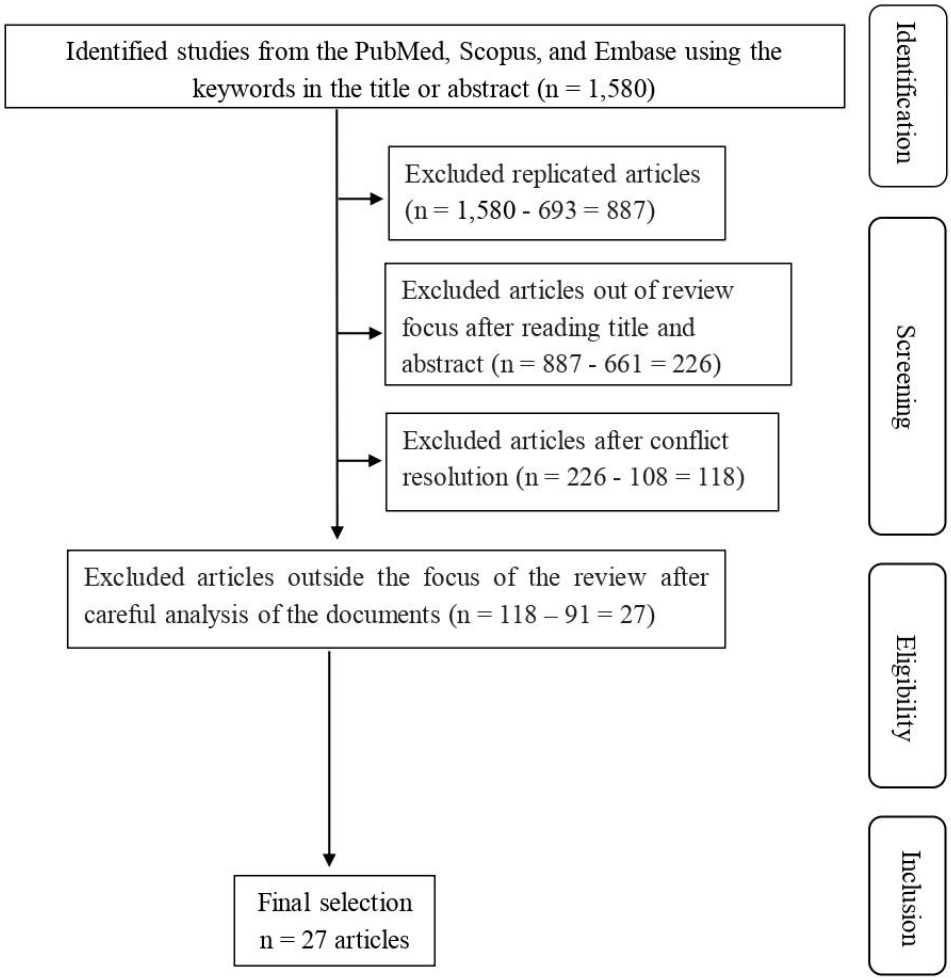

Figure 2. Flowchart of articles search and screening.

3.2. Study description

A total of 27 articles were selected for the review. The nature and content of the documents were demonstrated in **Table 1**, which represents the characteristic features including type of the active principle, cyclodextrin, method of complexation, characterization methods, and the physicochemical improvement of the inclusion complexes. Likewise, the antibacterial parameters, such as experimental design, antibacterial tests, strains used, and improvement of the biological effect presented by the complexation were discussed in **Table 2**. The CDs that appeared the most in the articles were the 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and β-cyclodextrin (β-CD). Meanwhile, there were different types of substances, in this case, antibiotics already presented in the market, natural products, and other synthetic molecules. Beyond that, various experimental designs of antibacterial effect were also discussed elaborately in which tests were used, *in vivo*, *in vitro*, or *in silico*, minimum inhibitory concentration (MIC), agar diffusion essay, antibiofilm activity, and other.

3.3. Cyclodextrins

CDs have two main types of crystalline packing, namely the cage type and the channel type, depending on the host substance and the type of CDs in question [20]. As a result of molecular complexation/packaging using CDs, a wide possibility of applicability opens. In the chemical area, for example, it is widely used to assist in the removal and detoxification of residual materials as well as in the separation of enantiomers by high-performance liquid chromatography (HPLC) [21]. In the agricultural sector, CDs manage to delay seed germination since they can inhibit some amylases and

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increase the adhesion and stickiness of some hot melts and adhesives [22]. In the pharmaceutical area, CDs stand out in the drug solubility, bioavailability, and safety [23,24].

Moreover, the type of CDs also influences these aspects due to their architecture and chemical organization. Thus, CDs chemical architecture affects the size and shape of the hydrophobic cavity, which can determine the hydrophobic molecule characteristics that can be accommodated, changing its solubility and bioavailability [25]. In the selected articles, the most presented CDs were HP-β-CD and β-CD, forming supramolecular complexes. In this context, HP-β-CD and β-CD were observed in three studies, the HP-β-CD appeared alone in nine works, and the β-CD formed inclusion complexes in 14 documents (**Figure 3a**). β-CD has been the most used pharmaceutical complexing agent since its lower cost compared to the derivatives, which tend to be more expensive, besides the improved properties [26].

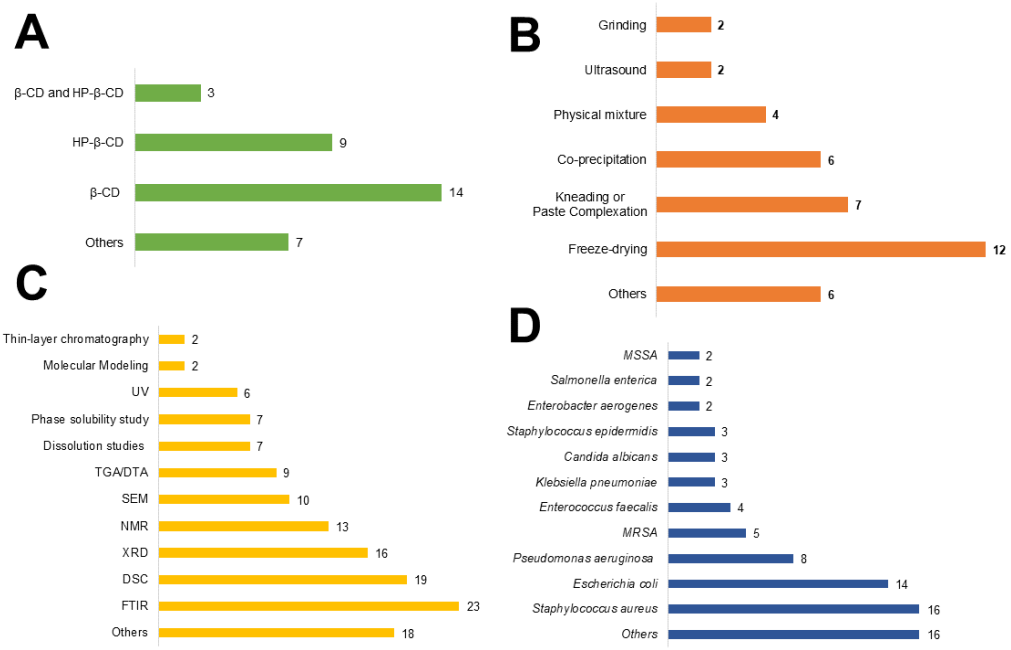

Figure 3. Distribution of articles by (**A**) Type of cyclodextrins; (**B**) Type of complexation methods; (**C**) Characterization techniques; and (**D**) Microorganisms present in the experimental tests.

Beyond that, CDs complexation requires specific molecular properties, such as the preparation method, to obtain the inclusion complexes since it can affect the performance and the product's morphometrical characteristics [27]. As seen in **Figure 3b**, the most used method was freeze-drying with 12 appearances, followed by kneading or paste complexation, and co-precipitation, seven and six complexes, respectively. Freeze-drying is known for its ability to increase the solubility of poorly water-soluble compounds as well as enhance the surface area of particles and stabilize the complexes [28]. Despite that, the kneading or paste complexation method is a moderately simple method, with high efficiency and scalability as well as the co-precipitation method, which is one of the most used due to its simplicity and efficiency [27,29].

Furthermore, the first analytical methods were developed in the 1960s and the inclusion complex formation can be properly identified through characterization techniques. These methods are commonly based on any physical or chemical property variation of the guest molecule due to the inclusion of complex formation. Fourier-transform infrared spectroscopy (FTIR) was the most used characterization method of the selected articles, appearing in 23 documents, followed by differential scanning calorimetry (DSC), X-ray diffraction (XRD), and nuclear magnetic resonance (NMR) in 19, 16, and 13 articles, respectively (**Figure 3c**). Other characterization methods, such as scanning electron microscopy (SEM) and thermogravimetry (TGA), also were used to verify the efficiency of the complexation. In many research articles, the techniques are applied together, proving their complementarity [30,31].

The ability of CDs to alter the physicochemical properties of host molecules has made them widely used to improve drug delivery to biological receptors [32]. Studies have shown that CDs cause a depletion in the cholesterol molecule, which has an essential function for the entry of the virus into the cell and is fundamental for the entry process of bacterial toxins [33]. Thus, the depletion of cholesterol from the plasma membrane reduced the internalization of some toxins, such as *Vibrio cholerae*, *Escherichia coli*, *Brucella*, and others. Therefore, explaining that CDs have an antiviral and antibacterial activity [21].

According to the **Figure 3d**, the most presented bacteria in the articles experiments was *Staphylococcus aureus* in 16 documents, followed by *E. coli* (14), *Pseudomonas aeruginosa* (8), and methicillin-resistant *Staphylococcus aureus* (MRSA) (5). *S. aureus* is one of the most infamous and widespread bacterial pathogens, causing various uncomplicated skin infections [34]. It is a leading causative agent in pneumonia and other respiratory tract infections, surgical site, prosthetic joint, and cardiovascular infections, being particularly problematic due to frequently occurring antibiotic resistance, of which MRSA is the most important clinically [34,35].

Moreover, all the cited bacteria are presented in the published list of global priority pathogens (GPP) by the World Health Organization (WHO) in 2017, which classified 12 species of bacteria in critical, high, and medium antibiotic resistance [36]. In this context, CDs encapsulate antibiotics or antimicrobial agents since bacterial virulence factors are considered valid targets for new therapies discovery [37]. Beyond that, antimicrobial activity is expressed as a function of time or concentration. Consequently, the complexation of CDs with antibiotics or antibacterial agents expects different outcomes, such as an accelerated or prolonged dissolution profile, depending on the desired properties of the selected drug and the target bacteria [38].

Therefore, the articles selected to be evaluated in full in this review are presented in **Table 1** and **Table 2**, which discloses the 27 studies, according to their physicochemical characteristics, antibacterial activity, complexation method, and characterization techniques. 14 documents are focused on the association between cyclodextrin, and antibiotics already shown on the market, 11 studies about cyclodextrin and natural products, and two documents about cyclodextrin and synthetic molecules complexes. Thus, the following section discusses the present systematic review content according to the type of molecule being complexed.

(Insert Table 1)

(Insert Table 2)

In this perspective, the analysis of the studies searched is that different types of CD chemical architecture can improve the bioavailability of water-insoluble drugs by allowing the formation of stable inclusion complexes with a wide range of hydrophobic molecules of different sizes and shapes. Therefore, antibiotics or other hydrophobic drugs can be affected by the type of CDs chosen to form the inclusion complex since improving the natural chemical properties of these drugs depends on how to accommodate them in the best CDs.

3.4. Cyclodextrins Enhance the Antibacterial Activity of Antibiotics

Antibiotics are one of the most prescribed medications worldwide, and many of these prescriptions are improper, such as in the coronavirus pandemic (COVID-19) that used broad-spectrum antibiotics to treat the SARS-Cov-2 virus empirically, increasing the chances to the bacteria strain develop antibiotic resistance [39]. Besides, the misuse of antibiotics by the population can lead to the development of resistance [40]. Antibiotics are diverse in their mechanisms of action, physicochemical properties, polarity, target point, side effects, and chemical stability, which can influence the determination of a possible inclusion complex since the CDs can inhibit the degradation of different drugs [41,42].

Meanwhile, the solubility can have a significant impact on the antibiotics volume of distribution and may influence in selecting agents, which were expected to attain adequate penetration to the site of infection [43]. For this reason, drug solubility is a factor that influences in the drug mechanism from the administration site into the bloodstream [44]. The antibiotics solubility follows the Biopharmaceutics Classification System (BCS) to classify drug substances related to their aqueous

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solubilities about the dose at three relevant pHs and intestinal permeability. The drug substances are classified in four classes. In the class I, the drug has high solubility and high permeability; in the class II, the drug presents low solubility and high permeability; in the class III, the drug has high solubility and low permeability; lastly, the class IV is classified as low solubility and low permeability [45]. Antibiotics, such as norfloxacin (NFX) and ciprofloxacin belong to the class 4 since they have low solubility and low permeability [46].

Therefore, CDs have been used to enhance the solubility and dissolution rate, improve the antibiotics' physicochemical stability in aqueous media, reduce local irritation, and mask unpleasant tastes [47]. Moreover, CDs enable the use of antibiotics in a reduced concentration, decreasing the exposure of the drug to the bacteria, which delays the onset of antibiotic resistance [48–50]. In this context, we extracted 14 articles in this review that studied the CDs combined with different classes of antibiotics **(Figure 4)**, which elaborated and explored the antibacterial activity of the compounds.

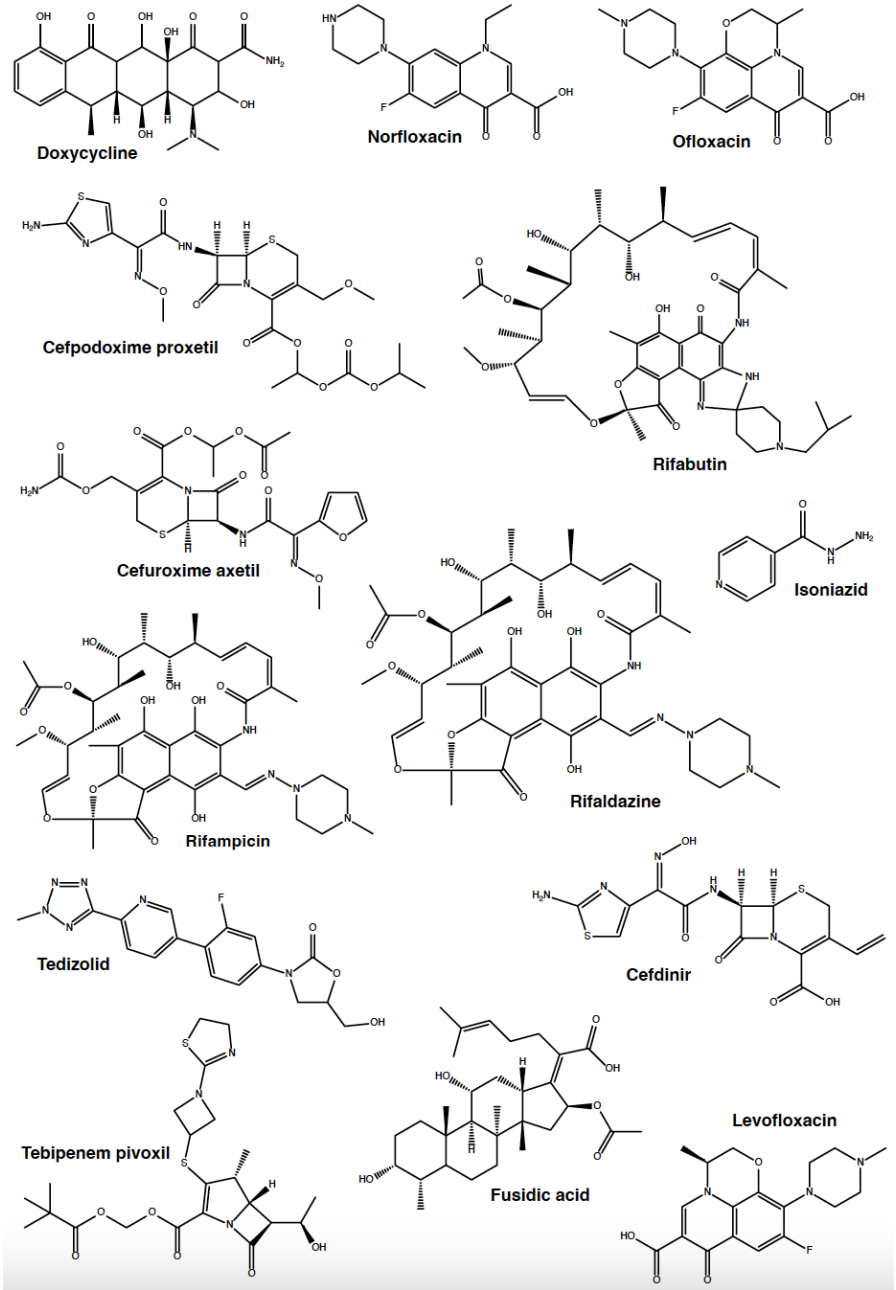

Figure 4. Chemical structures of antibiotic drugs from selected articles. Made by the author using the software *ChemDraw Professional version* 16.0.1.4.

Bhargava and Agrawal (2008) reported the complexation by solvent evaporation and freeze-drying methods of β-CD and cefpodoxime proxetil (CPDX-PR), which belongs to the class of oral cephalosporin antibiotic with poor aqueous solubility and bioavailability. According to the FTIR, DSC, PXRD, and SEM data, the inclusion complexes of CPDX-PR/β-CD showed significantly different characteristics compared to free CPDX-PR. Also, *in vitro* studies resulted in an increased solubility and dissolution rate of CPDX-PR with β-CD complexation. The antibacterial activity was measured against antibiotic-susceptible and antibiotic-resistant clinical isolates of *Neisseria gonorrhoeae strains*. CPDX-PR/β-CD inhibited all the tested strains at 0.015μg/mL concentration and chromosomally resistant strains which were not responsive to penicillin were inhibited by the complex at 0.125μg/mL concentration. Therefore, CPDX-PR/β-CD effectively enhanced the aqueous solubility and *in vitro* antibacterial activity [51].

Cephalosporins are alternative beta-lactam antibiotics highly effective and commonly used for mild to severe infectious diseases, presenting bactericidal activity to inhibit the growth by disrupting the cross-linking of the peptidoglycan chains of bacterial cell walls [52]. Consequently, Aleem et al. (2008) developed inclusion complexes comparing β-CD and HP-β-CD and using cefdinir (CEF), a semi-synthetic third-generation broad-spectrum oral cephalosporin, as an active principle. Both inclusion complexes were developed by the kneading method and characterized based on FTIR and PXRD. Moreover, the aqueous solubility of CEF was enhanced by 101% for β-CD and 23.4% for HP-β-CD, respectively. This may be due to the low value of stability constant indicating less affinity of HP-β-CD towards free CEF. Beyond that, the antimicrobial activity of CEF with β-CD and HP-β-CD against *S. aureus* and *E. coli* strains was checked through cup-plate method and compared with the free CEF. The CEF/HP-β-CD complex has shown a significant and highest zone of inhibition against both the microorganisms (11mm- *S. aureus* and 12.1mm- *E. coli)* as compared to pure CEF and the CEF/β-CD system (7mm- *S. aureus* and 8mm- *E. coli)*. Consequently, the ability of HP-β-CD to release the drug readily from the inclusion complex guarantee these results since it had a low stability constant [53].

Then, Mizera et al. (2019) also used an antibiotic of the cephalosporin class for complexation with HP-β-CD. The cefuroxime axetil (CA) exhibits a broad spectrum of activity against Gram-negative and Gram-positive bacteria. The selection of this type of CD occurred through molecular docking based on the *in silico* model, in which it was observed that HP-β-CD was the most thermodynamically favorable CD for the system. Moreover, the inclusion complex was developed through the co-precipitation model and characterized by DSC, FTIR, and PRXD methods, ensuring the effective complexation of the system. Regarding the antibacterial activity, CA/HP-β-CD was tested against 16 strains under minimum inhibitory concentration (MIC) conditions. The highest degree of change in MIC values was observed for the clinical isolate *Klebsiella pneumoniae since the MIC value was* 8 mg/L in CA-free and reduced to 2 mg/L with the CA/HP-β-CD. The same was measured with the clinical isolate *Pseudomonas aeruginosa*, which had a MIC of 32 mg/L in CA alone and decreased to 8 mg/L with the CA/HP-β-CD. This outcome suggests that the presence of HP-β-CD had a significant effect on the length of bacterial survival [54].

In this context, Paczkowska-Walendowska et al. (2020) also described an inclusion complex compounded of HP-β-CD and tedizolid, belonging to the oxazolidinones antibiotic class and presents low water solubility, which limits its use, despite the broad spectrum of activity. The complex was obtained through the kneading method and characterized by DSC, FTIR, and PRXD. Moreover, the changes in the dissolution rate of parent tedizolid, as well as tedizolid/HP-β-CD complex confirm a positive solubility effect of CD. Tedizolid/HP-β-CD dissolution speed changed from twice (at pH 4.5 and 6.8) to three times higher (pH 1.2) compared with the free tedizolid. Therefore, the different dissolution profiles show the potential of CDs as substances that significantly modify tedizolid release, especially in the gastric environment. Regarding the antibacterial activity, four bacteria species were selected for both general infections and acute bacterial skin, and skin structure infections. Tedizolid/HP-β-CD system caused an increase of activity expressed by the decrease of MIC value in the case of *Enterococcus faecium* from 0.5 to 0.25 mg/L and 1 to 0.5 mg/L in clinical isolate strains. Tedizolid/HP-β-CD inclusion complex also reduced the MIC against the *Enterococcus faecalis*,

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in which the concentration reduced from 0.5 to 0.25 mg/L and decreased from 1 to 0.25 mg/L in clinical isolate strains compared to free tedizolid. In the case of high action against *E. faecalis*, CDs blocking porin channels influence in the bacteria efflux effect [55].

Despite the higher HP-β-CD's physicochemical characteristics and its greater tendency to increase the solubility, bioavailability, and biological activity of the host molecule, in most of the studies presented in the literature the β-CD has been chosen due to its low cost and easy accessibility [56]. Therefore, Suárez et al. (2014) used the β-CD and doxycycline (DOX) to develop an inclusion complex. DOX is a semi-synthetic antibiotic used in the aerobic and anaerobic bacteria treatments. Although, the antibacterial activity of the complex was only tested against *S. aureus* strains, through MIC and minimum bactericidal concentration (MBC) methods. DOX/β-CD inclusion complex showed a decrease in MIC value compared to the DOX free, lower than 0.009 μg/L and 1.22 μg/L, respectively. Moreover, MBC also reduced the value, in this case the DOX/β-CD inclusion complex presented 78.12 μg/L and the free DOX, 625 μg/L. Thus, the interactions between DOX and β-CD were complex and were associated with greater antimicrobial activity, since the β-CD can adhere to the cell surface via hydrogen bonds, and this adhesion mediates the synergistic effect of DOX/β-CD with the ionic interactions that can form between a cationic drug and an anionic cellular surface. Moreover, in this study the inclusion complex characterization was based on FTIR, TGA, and NMR, proposing different characterization techniques compared to the other studies [57].

In the same year, Teixeira et al. (2014) also used the NMR to propose and observe the better complexation between the HP-β-CD or methyl-β-cyclodextrin (Me-β-CD) with isoniazid (INH). INH is an antibiotic successfully used in the medical clinic to treat tuberculosis since its introduction in 1952; however, there has been continual reports of drug-associated hepatotoxicity in tuberculosis patients [58]. The antibacterial activity was measured against the *Mycobacterium tuberculosis* through MIC method, which did not reduce with the complexation and the INH free drug demonstrated better results due to its mechanism of action. INH passively diffuses into *M. tuberculosis*; the prodrug is activated by a KatG catalase peroxidase to form an INH-NAD^+ adduct. This active form of INH is lethal, as it inhibits enzymes that are essential to mycolic acid synthesis and cell wall production [59]. Meanwhile, the INH/HP-β-CD complex inhibited more effectively the *M. tuberculosis* than the INH/Me-β-CD inclusion complex, showing a MIC of 1.6 μmol/L and 1.7 μmol/L, respectively [60].

Another antibiotic that has been used to treat tuberculosis and other species that belongs to the *Mycobacterium* genus is the rifabutin (RFB). According to Lee et al. (2017), RFB is a semi synthetic anasamysin and a first-line anti-tuberculosis drug for the treatment of drug-sensitive tuberculosis and is especially useful in patients who cannot tolerate rifampicin (RIF) [61]. Due to the increase of the RFB resistance and its lower solubility, Priya et al. (2013) proposed the use of this antibiotic against other bacteria attached to the inclusion complexation with β-CD. After the development of the inclusion complex through kneading and co-precipitation method, the dissolution profiles of the inclusion complexes were carried out and obvious increase in dissolution rate was observed when compared with pure RFB, which was confirmed by molecular docking [62].

In the context of the antibacterial test, the disk diffusion agar method presented better results using the co-precipitation inclusion complex, with 35mm and 40mm of zone of inhibition, against *E. coli* and *S. aureus*, respectively. Meanwhile, the kneading method presented zones of inhibition of 28 mm and 33 mm to *E. coli* and *S. aureus*, respectively. According to the *in vitro* antibiofilm studies, both the RFB free drug and RFB/β-CD inclusion complex showed inhibitory effect against *S.aureus*, *E.faecalis* and *Proteus vulgaris*, and *Pseudomonas aeruginosa*. However, in free RFB the microbial cells be likely to form large aggregates and aggregated in two different cultures easily visible in the biofilm generation. While following treatment with RFB/β-CD inclusion complex, the biofilm formation appeared to be more diffuse, and the extent of bacterial aggregation obviously reduced for all the four strains examined [62].

Rifaldazine (RAA) also belong to the list of drugs intended to treat tuberculosis cases. RAA mechanism of action occurs based on the inhibition of bacterial DNA-dependent RNA polymerase as well as the inhibition of bacterial RNA synthesis, retardation bacterial growth, and the death of bacteria. Due to this, RAA has been classified one of the most clinically effective antibiotics despite

its poor solubility and low stability [63]. To get around these limitations, Tan et al. (2013) complexed the RAA in β-CD by the solid-state grinding method and measured its antibacterial activity through the broth macrodilution method, using *S. aureus* and *E. coli* strains. As results, concentrations of RAA/β-CD and free rifaldazine were 0.125 μg/mL and 0.125 μg/mL for *S. aureus*, and 32 μg/mL and 16 μg/mL for *E. coli*, respectively. These data suggest that RAA/β-CD has good antibacterial activity against both species [64].

Following the same strategy, Córdoba et al. (2020) developed an inclusion complex composed by RIF and β-CD. RIF was first introduced into clinical use in 1968 and remains a key drug for the treatment of tuberculosis disease caused by bacilli susceptible to it [65]. The inclusion complex was acquired by freeze-drying method and characterized through FTIR, thermal analysis, PXRD, and SEM, which evidenced molecular interactions between the components, resulting in an inclusion complex with amorphous solid features. Instead of measuring the capacity of the complex to inhibit the *Mycobacterium* activity, the authors proposed new alternatives to the treatment of methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA). The MIC quantification was observed using only free RIF, which resulted in concentrations of 1.00 and 0.03 μg/mL against MRSA and MSSA, respectively. Therefore, the RIF/β-CD complex was only tested using the antibiofilm activity assay, which proved the lack of antibiofilm activity of the β-CD. Despite that, free RIF did not cause a MRSA metabolic activity reduction, while the inclusion complex produced a significant reduction in this parameter. In MSSA biofilms, the free RIF decreased the cell proliferation, and the RIF/β-CD significantly reduced it [66].

S. aureus produces a remarkable array of cell-surface and secreted virulence factors, which can facilitate infections, also developing antimicrobial resistance as fast as the development of new therapeutic agents [67]. Due to this rapid propagation of resistance, in the clinical management there has been a serious concern of staphylococcal infections and the development of MRSA and MSSA [68]. The risks of infections through these strains are shown when invasive MRSA infections are associated with an 18% mortality rate even among healthy patients [69]. For this reason, Marian et al. (2020) used strains of MRSA, MSSA, and *Staphylococcus epidermidis* to analyze the antibacterial capacity of the β-CD and fusidic acid (FA). FA belongs to fusidanes class and interferes with protein synthesis via the translocase enzyme and its introduction occurred in the early 1960s coincided with the emergence of MRSA [70,71]. Therefore, from the three synthesized inclusion complexes, kneading, co-precipitation, and freeze drying; the last one presented good antibacterial activity against MSSA, having an inhibition diameter of 28.66 mm, and relatively low antibacterial effect against MRSA, having an inhibition diameter of 26.03 mm. The freeze-drying complex also presented a diameter of 31.33 mm against *S. epidermidis* strains, which it was higher than the drug control, the cefoxitin [72].

Beyond that, Paczkowska et al. (2019) also focused their study on the development of alternatives to fight against MRSA and other strains, such as methicillin-resistant *S. epidermidis*, *E. faecalis*, *E. coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and others. In this context, the authors used the oral carbapenem analog tebipenem pivoxil (TP) and β-CD complexed by the dry mixing method. Beyond that, the MIC of TP in a free form was defined as a reference standard and the decrease in MICs needed to inhibit the growth of *S. aureus* was quadruple in the case of the TP/βCD complex (the MIC value was 15 mg/L for free TP and 4 mg/L for the TP/β-CD complex); however, it was double for *E. faecalis* (250 mg/L vs 125 mg/L), *P. aeruginosa* (250 mg/L vs 125 mg/L), and *Proteus mirabilis* (125 mg/L vs 62 mg/L –clinical isolate; 31 mg/L vs 15 mg/L – reference strain). Therefore, according to the decrease of MICs, it seems possible to suggest two mechanisms of action affecting the development of the strains in the presence of the TP/β-CD complex. Firstly, blocking porin channels contributed to the efflux effect in bacteria by CDs and interactions between β-CD and zinc atoms forming the active site in carbapenemases [73].

Then, Mendes et al. (2015) investigated the inclusion complex composed by β-CD and NFX, which belongs to the fluoroquinolone antibiotic class, mainly used in cases of urinary system and the genital tract infections [74]. The complexation was performed by different methods, such as in solution, co-evaporation, freeze-drying, and kneading followed by freeze-drying or spray-drying.

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Guest–host interactions were investigated through a complete physical–chemical characterization and the dissolution profile, in which the formation of a complex of NFX and β-CD, obtained by kneading followed by freeze drying, led to increased drug solubility and could maximize the oral drug absorption.

Regarding the antibacterial activity against the *Staphylococcus epidermidis* strains, the antimicrobial diffusion method proposed the same activity between the physical mixture and free NXF, which validated the lack of innate inhibitory activity of the β-CD. In the case of the inclusion complexes, the spray-drying sample showed slightly higher antibacterial activity and a significant increase was observed for the freeze-drying complex (23.3%). The co-evaporated complex, however, displayed poorer antibacterial potency than the free NFX (around 83.2%). The MIC study showed that the inclusion complexes had the same MIC as the free NFX (1 μg/mL), indicating that all the preparation methods maintained the drug stability. Moreover, the time-kill test showed that the bactericidal activity (≥3 $\log_{10}$ kill) was achieved at 6 to 12 hours for NFX and physical mixture; however, the inclusion complex obtained by kneading followed by freeze-drying could achieve a ≥3 $\log_{10}$ kill at 6 to 24 hours [75].

Amaro et al. (2020) also used an antibiotic of fluoroquinolone class. These antibiotics act by binding two type II bacterial topoisomerase enzymes, DNA gyrase and topoisomerase IV, thereby inhibiting DNA replication and transcription. In this context, DNA gyrase is the target for most Gram-negative bacteria, whereas topoisomerase IV is the target for many Gram-positive bacteria [76]. Therefore, in that study was used the ofloxacin (OFLOX), which is a second-generation fluoroquinolone, being classified as a multifunctional drug. OFLOX's poorly solubility influences its efficiency and requires the complexation with β-CD or HP-β-CD. Both complexes were developed by freeze-drying method and their antibacterial activity was measured against *E. coli* and *S. aureus* through MIC and time-kill curves methods. Thus, the MIC of OFLOX/HP-β-CD complex presented better results against both species, with minimal concentrations ranging from 0.03 μM to 0.14 μM to *E. coli* and a minimal concentration of 0.14 μM to *S. aureus*. In contrast to OFLOX/HP-β-CD, the OFLOX/β-CD complex presented values of the MIC between 0.04 μM to 0.16 μM and 0.16 μM to 0.33 μM, against *E. coli* and *S. aureus*, respectively. For the time-kill curves, there were no statistical differences between the kinetic profiles of OFLOX, OFLOX/β-CD and OFLOX/HP-β-CD, even with the reduction in MICs. The compounds generated a bactericidal curve against *E. coli* with a decrease of 99.9% in viable bacterial density after 24 hours. For the *S. aureus*, all compounds provided a bacteriostatic curve, since there is a slight reduction (1-2 $\log_{10}$) of the amount of CFU mL^{-1} compared to the initial inoculum [77].

Levofloxacin is also a fluoroquinolone and the levo-enantiomer of ofloxacin; it has become one of the cornerstones of antibiotic therapy of pyelonephritis since its introduction in the 1990s because of its advantages, such as exceptional pharmacokinetic and pharmacodynamic profile, broad-spectrum antibacterial action, and satisfactory tolerance. However, the emergence of widespread fluoroquinolone's resistance over the past decade has prompted to reexamine its place in some treatments [78]. Consequently, Li et al. (2022) developed an inclusion complex prepared by the freeze-drying method and characterized by DSC, PXRD, UV-Vis, and NMR confirming the successful HP-β-CD inclusion of levofloxacin. Regarding the *in vitro* antibacterial activity, the authors used four bacteria species *E. coli*, *S. aureus*, *Streptococcaceae* spp., and *Bacillus digest* spp. The HP-β-CD alone (up to 10 μg/mL corresponding to the HP-β-CD concentration in the 2 μg/mL inclusion complex) had no bacteria-killing effects in a liquid medium whereas levofloxacin alone had strong antibacterial effects against all the four bacteria with an MIC_{90} (the MIC of levofloxacin against 90% of bacteria) of 2.0 μg/mL against *B. digest* spp. and 1.0 μg/mL against the other three bacterial strains. Beyond that, the levofloxacin/HP-β-CD inclusion complex exerted a significantly higher antibacterial efficacy against all four bacterial strains, presenting the MIC_{90} of 1.0 μg/mL against *S. aureus* and *Streptococcaceae spp*. or 0.5 μg/mL against *E. coli* and *B. digest spp* [79].

Moreover, the disk diffusion test on agar plate showed the inhibition zones of levofloxacin alone and of the inclusion complex were larger than those of the two controls used, and the sizes of their inhibition zones increased with the increase of the levofloxacin concentration, which passed from 10

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μg/mL to 90 μg/mL, implying that both levofloxacin alone and the inclusion complex could exert antibacterial efficacy on agar plates. It was also observed that the inhibition zone of the inclusion complex was larger than that of levofloxacin alone further implying a higher antibacterial efficacy of the levofloxacin/HP-β-CD inclusion complex. Subsequently, it was evaluated the *in vivo* antibacterial efficacy of the inclusion complex by recruiting a scalded skin infection model in mice, using *S. aureus* and the free levofloxacin and the levofloxacin/HP-β-CD as the treatment. For this reason, the number of bacteria in burnt skin decreased significantly to a very low level ($0.443 \pm 0.115 \times 10^6$ and $0.346 \pm 0.170 \times 10^6$ CFU/100mg skin tissue, respectively) [79].

The formation of the inclusion complex with CDs also protects the drug from degradation, oxidation, and other factors that may reduce its stability and effectiveness. This can lead to higher drug concentrations in the bloodstream, which may improve the therapeutic effect of the antimicrobial [14,16,17]. CDs can improve the bioavailability of antimicrobials by increasing their solubility, stability, and protection from degradation, resulting in more effective and efficient treatments for microbial infections.

3.4. Cyclodextrins Enhance the Antibacterial Activity of Natural Products

Although plant products have several therapeutic properties, such as antibacterial, essential oils have limitations in use and activity due to their volatility, strong odor, and unstable physicochemical properties. Therefore, we extracted 11 articles in this review that studied the CDs combined with different natural products **(Figure 5)**, which elaborated and explored the antibacterial activity of the compounds.

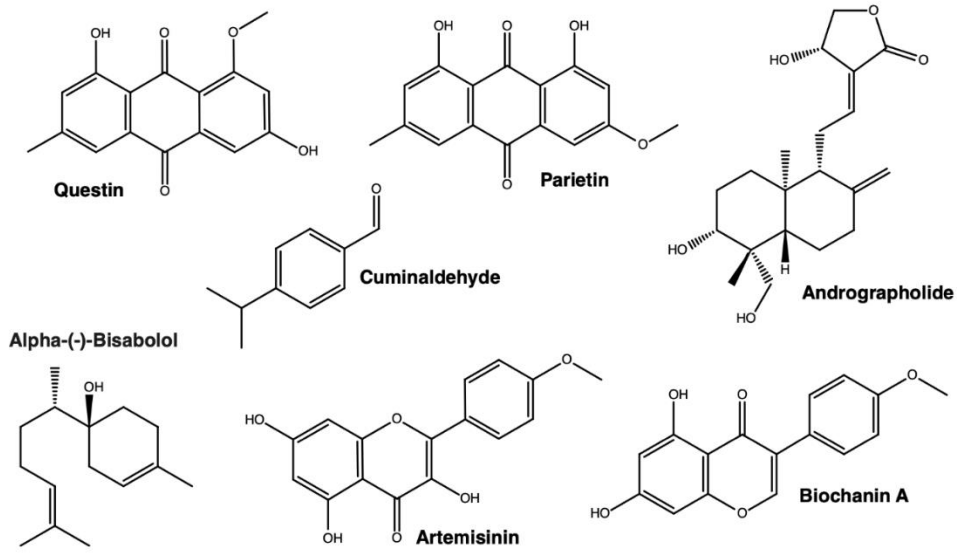

Figure 5. Chemical structures of natural products from selected articles. Made by the author using the software *ChemDraw Professional version* 16.0.1.4.

In this way, the study developed by Zhang, Yuan, and Sun (2018), sought to improve the antibacterial properties of star anise essential oil (SAEO) through encapsulation with HP-β-CD by the freeze-drying method. Based on the data obtained by FTIR and ^{1}H NMR, they observed the formation of the inclusion complex, and the Molecular Modeling made it possible to clarify that three compounds were embedded in the HP-β-CD cavity. The volatile stability test, encapsulation reduced the unpleasant odor of the SAEO, in addition to promoting a sustained release effect. The bacterial activity of free and encapsulated oil at different concentrations was evaluated against *Rhizopus stolonoifer*, *Saccharomyces cerevisiae, E. coli.* These tests also confirmed the increased antibacterial activity of the complex oil compared to the free oil due to the increased aqueous solubility. For example, the MIC of SAEO/HP β-CD showed a value of 2.5mg/mL and the SAEO free proposed a result of 20mg/mL against *Rhizopus stolonoifer* strains [80].

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Another study, also using HP-β-CD, but by methods of preparation by stirring and co-evaporation, sought to improve the aqueous solubility of questin, against *Vibrio harveyiem*. Guo et al. (2019) confirmed the HP-β-BC and questin inclusion complex formation was obtained by thin layer chromatography and ^{1}H NMR. In the solubility test, it was observed that the HP-β-BC was able to increase the water solubility of the drug more than 100 times (62.62 μg/mL) compared to free. As for the antibacterial activity, by the agar diffusion method, the inclusion complex increased the action of questin against *V. herveyiem* compared to its free form, presenting MIC values of 0.10 μM and 0.05 μM, respectively [81]. Similarly, Ayoub et al. (2020) proposed a parietin inclusion complex formation with HP-β-CD increased 28-fold aqueous solubility and photostability when compared to the free compound by the freeze-drying method. In addition, parietin complex decreased the bacterial viability of *Staphylococcus saprophyticus and E. coli* by > 4.8 log and > 1.0 log after irradiation, respectively [82].

The ultrasound technique can also be used to prepare inclusion complexes. Cui, Subramaniano, and Lin (2019) encapsulated cuminaldehyde with HP-β-CD using the ultrasound method followed by freeze drying. Molecular modeling and FTIR study confirmed the formation of the complex by insertion of the phenyl ring with the aldehyde group inserted into the HP-β-CD cavity. While the antibacterial activity confirmed the inactivation against *E. coli* and *S. aureus* by counting colonies on plates, obtaining 100% inactivation for both [83]. On the other hand, Nikolic et al. (2018) proposed by the co-evaporation method, an inclusion complex between HP-β-CD and biochanin A was obtained to increase the aqueous solubility of the compound. As expected, obtaining the complex promoted an increase in the solubility of biochanin A in 42% ethanol solution. As for its antibacterial activity, the microdilution method was applied against bacteria, yeasts, and fungi. For *E. coli and K. pneumoniae*, there was no significant difference between complexed and free compounds in terms of the reduction in the number of bacterial species. However, the complexed biochanin A showed greater activity against *Candida albicans* compared to the pure substance [84].

In addition to obtaining inclusion complexes from natural products with HP-β-CD, with the use of β-CD it can also be observed. In this first example, Oliveira et al. (2017) evaluated the antibacterial potential of α-bisabolol with β-CD was carried out. The MIC was obtained by microdilution in broth against *S. aureus, E. coli. P. aeruginosa*. Among the results found, complexed α-bisabolol showed a synergistic effect associated with norfloxacin against *S. aureus*. The synergistic effect was also observed in association with gentamicin against *E. coli* [85]. In the same context, the complexation of artemisinin with β-CD was carried out to increase the water solubility of the bioactive compound for co-precipitation method by Lin et al. (2018). This objective was observed in the solubility study, in addition to the formation of the complex promoting an increase in antibacterial activity against MRSA by 99% at a concentration of 20 mg/mL [86].

Often, natural products of traditional Chinese medicine have been studied for their therapeutic properties. In this case, andrographolide (AG), extracted from the herb *Andrographis paniculata*, underwent complexation with β-CD to improve its solubility and bioavailability. Zhang et al. (2017) obtained the complex by the freeze-drying method to be used by inhalation against *S. aureus* pneumonia. Pulmonary administration of complexed and free AG promoted bacterial inhibition and reduction of inflammatory factors, with relief of inflammation and immune response, while penicillin only had a bactericidal effect [87].

In this context, Li et al. (2017) also evaluated the improvement of antibacterial properties against bacterial pneumonia. Tea tree oil (TTO) with β-CD were used to prepare inclusion complexes by grinding method. The test was carried out in rodent models with fungal (*C. albicans*) and bacterial (*Acinetobacter baumannii*) pneumonia with administration of free and complexed TTO via the pulmonary route. Regarding TTO/β-CD, an improvement in the pneumonic effects was observed in treated animals compared to treatment with penicillin and fluconazole. Pathological and biological findings reported blocking inflammatory cell recruitment, regulation of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), COX-2 suppression, and reduction of lung injury [88].

In addition to HP-β-CD and β-CD, other types of CDs can be used to prepare the complexes and improve the properties of the compounds incorporated into the cavity. For example, Siva et al. (2020)

encapsulate cuminaldehyde and isoeugenol in Me-β-CD using the ultrasonication method. The characterization tests confirmed an increase in the aqueous solubility and stability of the two complexed compounds. In addition to the high antibacterial activity against strains of *S.aureus* and *E. coli* [89].

Finally, Magalhães et al. (2020) evaluated the antimicrobial activity of the inclusion complex of *Euterpe oleracea* Mart oil in β-CD or HP-β-CD using the kneading or paste technique. As for the microbial properties of the oil, the activity was expressed in MIC and the modulating activity of antibiotic resistance as a subinhibitory concentration against *E. coli, Streptomyces aureus, Pseudomonas aeruginosa*, and *Enterococcus faecalis*. As for the MIC, the values conclude that the greater antibacterial activity was exerted by the β-CD or HP-β-CD complexes by the two preparation methods compared to the free oil. In the evaluation of the modulatory response, the free oil and complexes with the two types of CD, revealed a synergistic effect with ampicillin against *E. coli* [90].

3.5. Cyclodextrins Enhance the Antibacterial Activity of Synthetic Molecules

CDs supramolecular host molecules that have been often used as building blocks for drug carrier system, which have been the focus of many studies since they have advantages, such as non-toxicity, good water-solubility, facile modification, and high biological availability [91]. For this reason, new alternatives have been searched to increase the range of possibilities regarding the emergence of drugs that seek to treat bacterial infections, especially bacteria that are already resistant to antibiotics on the market [92]. Thus, we extracted two articles in this review that studied the CDs combined with different synthetic molecules, which elaborated and explored the antibacterial activity of the compounds.

In this context, Briñez-Ortega et al. (2020) described the synthesis of a new partial inclusion complex of bis(1,10-phenanthroline) silver(I) salicylate in β-CD since silver complexes containing 1,10-phenanthroline as a coordinated ligand have been of great interest due to their antibacterial. The complexation was performed by freeze-drying method and characterized through FTIR, ^{1}H, ^{13}C NMR including $^{1}H–^{1}H$ COSY, TGA/DSC, elemental analysis (CHN), and PXRD, proposing the presence of non-covalent interactions such as hydrogen bonds, van der Waals forces, and hydrophobic interactions in the formation of the partial inclusion compound between β-CD and bis(1,10-phenanthroline) silver(I) salicylate. For the antibacterial tests, it used four disks respectively moistened with each sample of aqueous solution with *S. aureus* and *P. aeruginosa*, adopting a specific agar medium for each species. The halo of inhibition presented by the inclusion complex increased compared to the free components, presenting a halo of 10±1.0 mm of *S. aureus* and 10±2.1mm of *P. aeruginosa*. This improvement probably occurred since the permeability of microorganisms caused by host guest interactions between the β-CD and the cell membrane phospholipids enhanced [93].

In the same year, Brancaccio et al. (2020) proposed to use frog-skin temporins, in this case the temporin L (TL) and different types of CDs with the purpose to develop a new alternative to fight against the antibacterial resistance. The inclusion complexes were prepared by freeze-drying method using sulfobutylated-β-CD (SB-β-CD), poly(sulfobutylated-β-CD) (pSB-β-CD), HP-β-CD, poly-β-CD (p-β-CD), carboxymethyl-β-CD sodium salt (CM-β-CD), and poly(carboxymethyl-β-CD) (pCM-β-CD). All the complexes were tested against *Bacillus globigii, P. aeruginosa*, MRSA, and *Salmonella enterica subsp. enterica serovar Typhimurium* through the MIC assay, and the *P. aeruginosa* and MRSA were used to propose the antibiofilm effect of the inclusion complexes. According to the MIC results, TL/SB-β-CD presented the best concentration against *P. aeruginosa* and MRSA strains (15.6 μM), TL/pCM-β-CD had the higher MIC against *S. enterica* (7.9 μM), in *B. globigii* strains the best MIC belonged to TL/pSB-β-CD and TL/pCM-β-CD (3.9 μM). The obtained results highlight that the complexes TL/CDs are more able to inhibit the biofilm attachment with respect to the TL alone in the case of TL/SB-β-CD, TL/HP-β-CD and TL/pβ-CD considering MRSA, and in the case of TL/HP-β-CD and TL/pβ-CD for *P. aeruginosa*. A reduction of biofilm mass was also observed when preformed biofilms were treated at the lowest concentration (0.25 μM) of TL and TL/CDs with respect to the control, for both bacterial strains [94].

4. Conclusions

The indiscriminate use of antibiotics causes an increase in bacterial strains that develop resistance to these drugs. Thus, new technologies have been developed to manage this problem. Among these alternatives are CDs, which, through the formation of inclusion complexes, can influence the physicochemical characteristics of these drugs, improving their biological activity. Furthermore, CDs are excipients already used in the market in pharmaceutical product development. Therefore, this systematic review discussed the articles that performed studies describing the antibacterial activity improvement of compounds after incorporation into CDs. All the research articles reveal the formation of inclusion complexes between CDs and antibiotics already existing on the market, natural products, or new synthetic molecules, which with the inclusion complexes formation enhance the antibacterial activity in relation to the free drugs. β-CD was the most used cyclodextrin followed by HP-β-CD due to their unique structures with a hydrophobic cavity and outer shell hydrophilic portion, which produces many applications in the delivery of a hydrophobic, unstable, volatile, and liquid form of drugs [19]. Beyond that, antibiotics were the group that most appeared to form inclusion complexes, followed by natural products. In the antibiotic group, cephalosporins were the classes that stood out the most in the use of technologies for the improvement of physicochemical characteristics of the compounds. Overall, CDs as drug delivery vehicles have been shown to improve antibiotics solubility, stability, and bioavailability, leading to enhanced antibacterial activity. However, it is essential to note that the specific effects of CDs may vary depending on the drug and the specific formulation used. Therefore, this systematic review is essential to the scientific development that will execute studies with drugs that present antibacterial effects since their encapsulation in CDs become necessary to improve the solubility and the pharmacological effects, which increase the alternatives in clinical application as new therapeutic agents' formulation. For more information seen complementary reviews performed by Karginov (2013) [37], Vandera et al. (2020) [95], Boczar and Michalska (2022) [14] and Santos et al. (2023) [96].

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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