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REVIEW ARTICLE

Antibacterial potential of chalcones and its derivatives against *Staphylococcus aureus*

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Abstract

Chalcones are natural substances found in the metabolism of several botanical families. Their structure consists of 1,3-diphenyl-2-propen-1-one and they are characterized by having in their chains an α, β-unsaturated carbonyl system, two phenol rings and a three-carbon chain that unites them. In plants, Chalcones are mainly involved in the biosynthesis of flavonoids and isoflavonoids through the phenylalanine derivation. This group of substances has been shown to be a viable alternative for the investigation of its antibacterial potential, considering the numerous biological activities reported and the increase of the microbial resistance that concern global health agencies. *Staphylococcus aureus* is a bacterium that has stood out for its ability to adapt and develop resistance to a wide variety of drugs. This literature review aimed to highlight recent advances in the use of Chalcones and derivatives as antibacterial agents against *S. aureus*, focusing on research articles available on the Science Direct, Pub Med and Scopus data platforms in the period 2015–2021. It was constructed informative tables that provided an overview of which types of Chalcones are being studied more (Natural or Synthetic); its chemical name and main Synthesis Methodology. From the analysis of the data, it was observed that the compounds based on Chalcones have great potential in medicinal chemistry as antibacterial agents and that the molecular skeletons of these compounds as well as their derivatives can be easily obtained through substitutions in the A and B rings of Chalcones, in order to obtain the desired bioactivity. It was verified that Chalcones and derivatives are promising agents for combating the multidrug resistance of *S. aureus* to drugs.

Keywords Bioactivity · Multi-resistance · Efflux pump · Structure–activity relationship

Introduction

The emergence and availability of antibiotics have revolutionized the treatment of diseases in the 20th century, but this achievement is threatened due to the development of resistance of microorganisms, which reduces the effectiveness of several classes of antibiotics for clinical use (Dan and Dai 2019). There are several factors by which microorganisms acquire or develop resistance to a drug, the most predominant among them is through a process known as natural selection, in which the most sensitive microorganisms to the drug are eliminated and those that manage to survive the action of the antimicrobial develop resistance (Loureiro et al. 2016). Bacterial resistance has become a subject of global concern, and for this reason, more and more researchers around the world are engaged in the search for natural or synthetic products with antibacterial potential (Oliveira et al. 2020; Rezende-Junior et al. 2020).

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It is estimated that approximately 700,000 deaths are caused by infections of drug-resistant bacteria per year and this number could reach 10 million deaths per year by 2050 if urgent measures are not taken, according to the report of Neill (2016). In this perspective, the microorganism that has most concerned global health bodies is the gram-positive bacterium *Staphylococcus aureus*. This pathogenic bacterium belongs to the group of Coccus and is responsible for several diseases that affect humans. It is currently one of the pathogens of greatest clinical interest due to its high ability to colonize and acquire resistance to multiple drugs (Multiple Drug Resistance—MDR) (Grace and Fetsch 2017). Sophisticated resistance mechanisms were developed and acquired by this species after years of exposure to antibacterials (Guo et al. 2020). Enzyme synthesis; Reduction in the absorption of endogenous molecules; Molecular modification of the target; Acquisition of genetic material through mobile genetic elements, such as plasmids; and efflux pumps are examples of resistance mechanisms present in *S. aureus* (Abushaheen et al. 2020).

Natural compounds are considered a good alternative for the development of new antibiotics because they are products of natural selection, shaped by evolution to interact with cellular targets with high efficiency and selectivity, in addition to presenting important properties that allows interaction with different bacterial cellular targets, preventing cell survival after contact with the antimicrobial (Wright 2017; Rossiter et al. 2017).

Human civilization has long used natural products as the main source of products with therapeutic potential. Currently, more than half of clinical drugs come from natural products and their synthetic derivatives, according to the United States Food and Drug Administration (FDA), which analyzed in detail the introduction of new drugs in the clinic until 2014 (Dan and Dai 2019; Newman and Cragg 2016).

In this sense, Chalcones have gained prominence in medicinal chemistry due to their important pharmacological properties. Chalcones are natural substances present in the secondary metabolism of several botanical species, including the so-called medicinal plants. Medicinal plants are considered by the WHO as any plant that presents in its metabolism compounds with some therapeutic potential (Who 2021). In this sense, several botanical species that have chalcones in their composition and present therapeutic effects of clinical interest are reported in the literature (Ferreira et al. 2018). The Ficus microcarpa species presents a high content of chalcones in its roots and has already had its medicinal and antibacterial properties investigated and proven (Díaz-Tielas 2016; Kalaskar and Surana 2012). They can also be found in the leaves and fruits of species of the genus Artocarpus that is widely used for the treatment or prevention of inflammation, malaria, and vitiligo, mainly in tropical Asian regions (Pereira and Kaplan 2013).

Chemically, Chalcones are known as α, β-unsaturated ketones with a structure consisting in 1,3-diphenyl-2-propen-1-one and are the main precursors of Flavonoids and Isoflavonoids (Fig. 1) (Ferreira et al. 2018). This group of substances has drawn attention for presenting several biological activities of clinical interest, such as antitumor, anti-inflammatory, anti-oxidant and antimicrobial activities, which demonstrates the importance of these compounds (Rashid et al. 2019; Matos et al. 2015).

It is important to emphasize that Chalcones are considered important scaffolds for the synthesis of new drugs through the manipulation of their aromatic rings, which can potentiate already proven biological activities or lead to the discovery of new bioactivities, including antibacterial activity (Bitencourt et al. 2019). These compounds are currently being explored with published studies about synthesis, molecular targets and biological activities (Dan and Dai 2019). Within this context, the present review aims to highlight recent advances in the use of natural and synthetic Chalcones as well as their derivatives used as antibacterial agents against *S. aureus*, focusing on research articles published in the period of 2015–2021.

Methodology

This literature review was carried out by consulting scientific articles available in different databases. All stages of collection, screening and analysis of the articles selected for this review meet a guiding question that follows systematic methods. The research started in October 2021 and ended in January 2022. To achieve the research proposal, the following methodological procedures were applied.

Database

The data platforms used for the collection of material that led to the realization of this review were: (1) Science Direct (https://www.sciencedirect.com); (2) Pub Med (https://pubmed.ncbi.nlm.nih.gov/); (3) Scopus (https://www-periodicos-capes-gov-br.ezl.periodicos.capes.gov.br). The

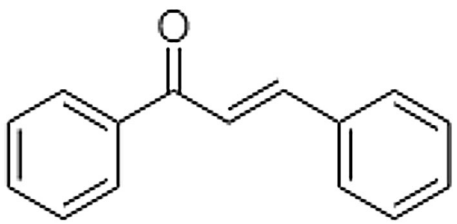

Fig. 1 Fundamental structure of chalcones. Source: Author (2022)

research was carried out with the application of specific descriptors and filters.

Descriptors and filters used

Wide-descriptors were selected in order to compile the largest number of studies and avoid missing out on relevant research to be included. Thus, the descriptors: "Chalconas AND *Staphylococcus aureus*" were inserted in a combined way in the databases cited above. To better meet the originality of studies on antibacterial activity of Chalcones on *S. aureus*, were used filters such as: Type of article, Year of publication and Language.

Eligibility criteria

In terms of data mining and the established eligibility criteria, the following inclusion criteria were defined: Original research articles focusing on the investigation of the antibacterial potential of Chalcones of natural and synthetic origin and their derivatives on *S. aureus* bacteria; in vitro studies; English, Portuguese and Spanish Language; Studies published in the period 2015–2021. The exclusion criteria were: Course Completion Works; Dissertations; Theses; Annals of events; Case reports; in silico and in vivo studies; Book; Bibliographic reviews; Duplicates; Incomplete works, with unavailable access or that do not fit the proposed theme.

Analytical approach

The articles found went through three stages of screening in order to select those that fit the proposal of this review. The first step was defined as general prospecting, where all articles found on each platform were analyzed based on the descriptors and filters used. The three screening processes were based on reading all filtered articles as well as eliminating duplicates found on the same platform and among the three databases.

After analyzing the articles, the analytical approach used consisted of producing informative tables containing the selected articles with the following information: Chemical name of the Chalcone used; Chalcone type (natural or synthetic); Synthesis method; Bacterial Strain, MIC/Inhibition Zone, Activity and Representative Reference. Tabulations were organized in Microsoft Word software. Finally, a descriptive analysis of the bibliographic sample was carried out, accompanied by a discussion on the aspects addressed by the included studies.

Results and discussion

The content of the articles researched allowed us to evaluate recent developments in scientific research involving the use of natural and synthetic Chalcones and their derivatives in the fight against infections caused by *S. aureus*. The data obtained from the three search platforms resulted in 697 articles using the descriptors and filters as a basis for the research (general prospection). With the application of pre-established eligibility criteria, this step being considered as the first screening, this number was reduced to 188 viable articles for analysis.

The second screening was carried out by reading the articles selected in the first screening and including those that met the proposal of this review, excluding duplicate articles within the same platform. The third and last step was the analysis and exclusion of duplicates between platforms. Table 1 shows in detail the number of articles obtained at each stage of collection.

The PRISMA flowchart was assembled to demonstrate the process of metabolizing the results that includes the processes of inclusion and exclusion of articles for each step of the search until reaching the final number of studies considered for this study (Fig. 2).

In Tables 2 and 3 below, containing all the articles analyzed and selected to compose the present review, it is possible to observe that 84.83% of the collected studies report the work with synthetic Chalcones to evaluate the antibacterial activity against *S. aureus* while the natural Chalcones represent 15.17% of the works. This demonstrates the interest of research in the investigation of new compounds from natural substances in order to potentiate known bioactivities or discover new activities, whether in reversing bacterial resistance or reinforcing the antibiotic effect of existing drugs.

The present review was based on studies on the bacterium *S. aureus*, justified by the importance of this microorganism as it is currently considered one of the main bacteria of clinical and epidemiological importance. This

Table 1 Number of articles prospected on each platform visited and the screening processes

Database	General prospection	First screening	Second screening	Exclusion of duplicates
Science direct	320	33	30	18 common articles among the three platforms
Pub Med	100	58	48	
Scopus	277	97	85	
Sum	697	188	163	145

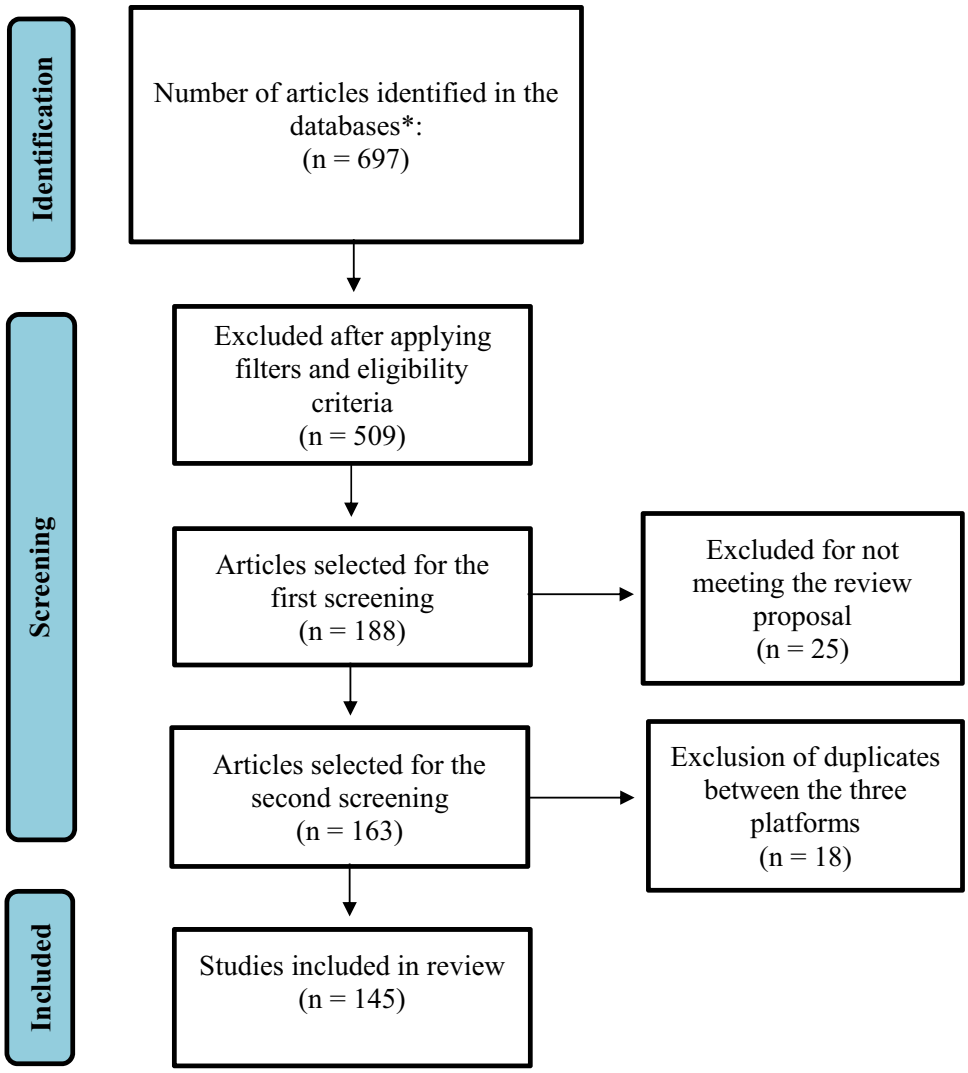

Fig. 2 - PRISMA flowchart of the analytical steps for building the review. Source: Author (2022)

importance is due to its high ability to persist as a commensal microorganism in addition to its frequent multiresistance to antimicrobials and its various virulence factors, expressing a countless variety of proteins, toxins and polysaccharides at the extracellular level (Barroso et al. 2014). It is assumed that 80% of the world population is intermittently colonized by this bacterium, acting as the main successful pathogen at hospital and community level, being mainly involved in pyogenic and toxic infections (Silva 2016).

The sequencing of genomes from different strains of *S. aureus* led to the discovery of a high number of mobile genetic elements, which explains the dissemination of increasingly resistant strains, since horizontal gene transfer is the main cause of multidrug resistance in bacteria (Assef and Neto 2020). This line of reasoning can be justified by the first case of *S. aureus* resistance to Methicillin that was identified in the United Kingdom 1 year after the introduction of this antibiotic in the clinic, resulting in one of the best known strains today, the MRSA (Methicillin-Resistant *Staphylococcus aureus*) (Kalenić 2012; Mendes 2010).

The tables also show different types of *S. aureus* strains, especially MRSA and MSSA (Methicillin-Sensitive *Staphylococcus aureus*), which are considered the second leading cause of longer hospitalizations, increasing human mortality and morbidity rates, resulting in a economic and political weight worldwide (Mendes 2010; Purrello et al. 2014).

The main methods of synthesis of Chalcones and its derivatives were also observed. Recently, derivation of products from Chalcones has been the subject of investigations due to its relatively simple structure and the variety of biological activities that they present (Ferreira et al. 2018). The set of activities expressed is in part attributed to the immense possibilities of substitutions in the aromatic rings of Chalcones, since the Claisen–Schmidt methodology, which is one of the main methodologies used for the synthesis of these compounds, promotes the obtainment of a large amount of compounds, due to the existence of numerous commercial

Table 2 Synthesis matrix of articles collected in a literature review that report the antibacterial potential of natural Chalcones against *S. aureus*

Chalcone	Type	*S. aureus* strain(s)	MIC/Inhibition Zone	Activity	Quotes
4′-Hydroxy-3–4-dimethoxy-chalcone (1); 3′-Hydroxy-3-acetate, 4-methoxy-chalcone (3); 3′,4′-dihydroxy, 3,4,4′-trimethoxy-chalcone (4); 3,4-dimethoxy-chalcone (5)	Nature Isolated from *Arrabidaea brachypoda*	ATCC 25,923; IS-58; RN-4220; SA1199-B; K2068; K4414; K4100	1024; ≥ 1024 µg/mL	Inactive for antibacterial activity	Rezende-JúNIOR et al. (2020)
3′,4′-dihydroxy, 3,4,4′-trimethoxy-chalcone (4)	Nature Isolated from *Arrabidaea brachypoda*	SA1199-B	16 µg / mL 4X	NorA efflux pump inhibitor	Rezende-JúNIOR et al. (2020)
Lophirones B, C	Nature, isolated from *Lophira alata*	ATCC 29,213	150 – 200 µg/ml	Antibacterial	Ajiboye and Haliru (2016)
4,4′,6′ trihydroxy 3 methoxy 3′ pentene chalcone	Nature, isolated from *Elatostema parasiticum*	ATCC 6538	7.8 µg/ml	Antibacterial	Mariani et al. (2016)
Grandiflorone	Nature, isolated from *Leptospermum scoparium*	-	16–32 µg/ml	Antibacterial	Killeen et al. (2016)
2′,4′-dihydroxychalcone e 2′,4′-dihydroxy-3′-methoxychalcone	Nature Isolated from *Zuccagnia punctata* Cav	ATCC 29,213, MRSA, MRSCN	250 µg/mL^{-1}	Antibacterial	Moreno et al. (2015)
Cinnamaldehydo and its Chalcones derivatives	Nature Isolated from *Cinnamomum verum*	MRSA	3.21 ± 40.0 mm	Antibacterial	Khayyat and Saddiq (2015)
2′,4′-dihydroxychalcone 7-hydroxyflavanone	Nature Isolated from *Flourensia oolepis*	ATCC 6538	31 µg/mL 62 µg/mL	Antibacterial	Joray et al. (2015)
Xanthoangelol	Nature, isolated from *Angelica keiskei*	ATCC 25,923, ATCC 700,699 (MRSA)	6,25 µM 3,12 µM	Antibacterial	Meier et al. (2019)
Isobavachalcone; corylifol B	Nature, isolated from *Psoralea corylifolia* L	MRSA OM481 OM584	8—16 µg/mL	Antibacterial	Cui et al. (2015)
20 -hydroxy-4,40,60 -trimethoxychalcone, 20 -hydroxy-4,40,60 -tetramethoxychalcone, and 3,20 -dihydroxy-4,40,60 -trimethoxychalcone	Nature, isolated from *hispidum*	ATCC 25,923	62,5 mg/mL—125 µg/ml	Antibacterial and anti-biofilm	Costa et al. (2013)
Prenylated Chalcones (xanthohumol and Desmethylxanthohumol)	Nature, isolated from *Humulus lupulus* L	8146, 8147, CIP 224, T1.1, T25.10, T25.3, T25.9, T26A4, T28.1, T36B1, T47A12, T6.7	9,8 – 19,5 µg/ml	Antibacterial, synergism with gentamicin, amoxicillin and vancomycin and anti-biofilm	Bocquet et al. (2019)
Lophirones B, C	Nature, isolated from *Bamburu village*	ATCC 29,213	Redução da MIC	Antibacterial	Ajiboye and Haliru (2016)
Calythropsin	Nature, isolated from *Calicotome villosa*	-	18 ± 1.4 mm 6 ± 0.7 mm	Antibacterial	Alhage et al. (2018)

Table 2 (continued)

Chalcone	Type	*S. aureus* strain(s)	MIC/Inhibition Zone	Activity	Quotes
Diuvaretin, Uvaretin and Iso-Uvaretin	Nature, isolated from *Uvaria chamae*	ATCC 25,923,	0,0046 mg/mL	Antibacterial	Koudokpon et al. (2018)
Basalcone J	Nature, isolated from *Populus Balsamifera*	ATCC 25,923	0.61 µM 6 µM	Antibacterial	Simard et al. (2015)
20 -hydroxy-4,40 -dimethoxy-chalcone and isoliquiritigenin	Nature, isolated from *Coreopsis tinctoria* Nutt	-	Redução de MIC	Antibacterial	Begmatov et al. (2020)
5′-O-Methyl-3-hydroxyflemingin A and 5′-O-Methylflemingin C	Nature, isolated from *Desmodium congestum*	ATCC 43,300, NRSA-NRS 17, NRSA-NRS 1	32 µg/mL	Antibacterial	Rees et al. (2015)
Isosalipurposide	Nature, isolated from *Corylopsis coreana*	693E, MRSA 693E	1.23 ± 0.06 cm	Antibacterial	Seo et al. (2016)
Homoembelin	Nature	ATCC 1026, SA3, SA4, SA11, SA12, MRSA 3, MRSA 4, MRSA 6, MRSA 8	≥ 256 µg/mL	Inactive for antibacterial activity	Omosa et al. (2016)
Xanthoangelol	Nature Derived from *Amorpha fructicosa*	ATCC 700,699 (MRSA)	3.125 µM 12,5 µM	Antibacterial Bactericidal	Meier et al. (2019)
2', 4'-dihydroxychalcone (DHC)	Nature Isolated from *Zuccagnia punctata* Cav	(F2, F5, F7, F8, F22, F23) and F31	(25 µg/mL) *100 µg/mL	Antibacterial	Nuño et al. (2018)
2', 4'-dihydroxy-3'-methoxy-calcone (DMHC)	Nature Isolated from *Zuccagnia punctata* Cav	(F2, F5, F7, F8, F22, F23) and F31	(25 µg/mL) *100 µg/mL	Antibacterial	Nuño et al. (2018)
2', 4'-dihydroxychalcone (DHC)	Nature Isolated from *Zuccagnia punctata* Cav	F7 ATCC 25,923	12,5 µg/mL	Anti-biofilm	Nuño et al. (2018))
Isoliquiritigenin	Nature Isolated from *Platymiscium gracile* Benth	ATCC 29,223	62,5 µg/mL	Low antibacterial activity	Cuellar et al. (2020)

a) The spaces filled with (-) mean that the information was absent from the article or was not clear

Table 3 Synthesis matrix of articles collected in a literature review that report the antibacterial potential of synthetic Chalcones and derivatives against *S. aureus*

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
(E)-1-(2-hydroxyphenyl)-3-(2,4-dimethoxy-3-methylphenyl)prop-2-en-1-one	Synthetic	–	1199B	↓ 50% of the MIC of the antibiotic (128 µg/mL to 64 µg/mL);	Antibacterial; Synergism with the antibiotic Norfloxacin Inactive as a NorA inhibitor	Rocha et al. (2021)
(E)-1-(2-hydroxyphenyl)-3-(2,4-dimethoxy-3-methylphenyl)prop-2-en-1-one	Synthetic	–	K2068	↓ 60.3% of the MIC of BrEt (32 µg/mL to 12.6992 µg/mL)	Inactive for direct antibacterial activity. Synergism with BrEt and potential MepA efflux pump inhibitor	Rocha et al. (2021)
(Z)-4-((bis(2-hydroxyethyl) amino)methyl)-7-((1-(4-methoxyphenyl)-3-oxo-3-(thiazol-2-yl) prop-1-en-2-yl) oxy)-2H-chromen-2-one (5i)	Synthetic	–	MRSA	0.004 mM	Antibacterial 6X better than the reference antibiotic Norfloxacin	Hu et al. (2021)
4-bromo-3'-aminochalcone (5f)	Synthetic	Claisen–Schmidt	MSSA MRSA	1.9 µg mL; 7.8 µg mL	Concentration-dependent antibacterial and antibiofilm	Garcia et al. (2021)
Chalcones derived from 2-hydroxyacetophenone (A1-A6)	Synthetic	Claisen–Schmidt	RN4220; K4414; 1199B; K2068	1024 µg/mL	Clinically irrelevant antibacterial activity; Potential IBEs	Xavier et al. (2021)
Chalcone derivative DBDCPP-3	Synthetic	Claisen–Schmidt	–	Over than 15 mm	Bactericide	Shinde et al. (2021)
(E)-3-(furan-2-yl)-1-(2-hydroxy-3,4,6-trimethoxyphenyl)prop 2-en-1-one (Hitfurfural); (E)-1-(2-hydroxy-3,4-dimethoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one (Hithiophene)	Synthetic	Claisen–Schmidt	1199B K2068	1024 µg/mL	Clinically irrelevant antibacterial activity; Potential NorA and MepA IBEs	da Silva et al. (2021)
(2E)-3-(4-Methoxyphenyl)-1-{4-[(3-phenyl-1,2,4-oxadiazol-5- yl)methoxy] phenyl}prop-2-en-1-one (6a)	Synthetic	–	–	3.12 µM 2×more efficient than the standard drug Ciprofloxacin	Antibacterial	Ibrahim et al. (2021)
(E)-3-(3-bromo-4-methoxyphenyl)-1-(thiazol-2-yl)prop-2-en-1-one (Zn 4 complex)	Synthetic	Claisen–Schmidt	MTCC 916	18 mm	Antibacterial	Johnson and Yardily (2021)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
(E)-3-(4-(dimethylamino) phenyl)-1-(2-hydroxyphenyl)prop-2-en1-one (3)	Synthetic	Claisen–Schmidt	1199B	1000 µg/mL	Clinically irrelevant antibacterial activity; NorA inhibitory potential	Leal et al. (2021)
Polymer chalcone (P3)	Synthetic	Claisen–Schmidt	–	20 mm	Antibacterial	Solmaz et al. (2021)
Hybrid Chalcona (1)	Synthetic	Claisen–Schmidt	NCIM 2122	10.05 µM	Low antibacterial activity compared to standard drug Ciprofloxacin	Konidala et al. (2021)
Chalcone with imide-Zo portion [1,2-a]pyridine (3b, 3d, 3g, 3l and 3m)	Synthetic	Claisen–Schmidt	–	32 µg/mL and 64 µg/mL	Antibacterial	Soltani et al. (2021)
E4,4'-Bromo-4-methylchalcone	Synthetic	Claisen–Schmidt	MRSA	16 µg/mL	Antibacterial	Aksöz et al. (2021)
Quinoline chalcone: 1-(4-(benzyl sulfonyl) phenyl)- 2,3dibromo-3-(chloroquinoline-3-yl) propane-1- one (7)	Synthetic	Claisen–Schmidt	–	At a concentration of 10 mg/disk: 15 mm	Low antibacterial activity compared to standard drug	Saleh et al. (2020)
Fluorinated chalcone: (E)-3-(1″H-indol-3″-yl)-1-[40 -(trifluoromethyl)phenyl]prop-2-en-1-one	Synthetic	Claisen–Schmidt	NCIM-2079	51 µM	Low antibacterial activity compared to standard drug	Lagu et al. (2020)
(E)-1-(4-aminophenyl)-3-(furan-2-yl)-prop-2-en-1-one (AFPO)	Synthetic	Claisen–Schmidt	10	≥ 1024 µg/mL	Irrelevant	Ferraz et al. (2020)
(E)-1-(4-aminophenyl)-3-(furan-2-yl)-prop-2-en-1-one (AFPO)	Synthetic	Claisen–Schmidt	10	AFPO + Gentamicin: ↓ 3X AFPO + Penicillin = ↓ 3X	Synergism (potentiation of antibiotic activity)	Ferraz et al. (2020)
Naphthyl Chalcones (3a -3p)	Synthetic	–	MTCC 96	24–162 µg/mL	Low antibacterial activity compared to standard drug	Pola et al. (2020)
Heteroaromatic Chalcones Derivatives (1a-and 3a-c)	Synthetic	Claisen–Schmidt	N5923	13 and 19 mm	Antibacterial	Farooq and Ngaini (2020)
Chalcone derivative (1d)	Synthetic	Claisen–Schmidt	–	11 mm	Antibacterial	Farooq and Ngaini (2020)
Chalcones source of the natural product 2-hydroxy-3,4,6-trimethoxy-acetophenone (1–4)	Synthetic	Claisen–Schmidt	10 (Multi-resistant); ATCC 25923;	≥ 1024 µg/mL; 645 µg/mL	Irrelevant; Low antibacterial activity and synergism with Ciprofloxacin and Gentamicin	Freitas et al. (2020)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
4'-piperazinyl Chalcone—pleuromutilin (14i; 14k)	Synthetic	Alcoholic condensation	MRSA (ATCC 33591); MRSA (ATCC 43300); ATCC 25923	0.5–1 µg/mL	Antibacterial	Xie et al. (2020)
Sulfonamides Chalcones and derivatives: (IV—XXXII)	Synthetic	–	ATCC 25923	(> 22)—10 (0.156) mm	Inactive for antibacterial activity	Bonakdar et al. (2020)
Ferrocenyl Chalcones (Decyl)	Synthetic	Acquired	NCIMB 8244 MRSA (RCH)	0.031 mg mL 0.063 mg mL	Antibacterial	Henry et al. (2020)
Bichalcones and Bispirazoline derivatives (2ª–2d) (3b–3d)	Synthetic	Acquired	–	16–32 µg/mL 8 – 32 µg/mL	Inactive for antibacterial activity	Nisa and Yusuf (2020)
Pyrimidine derived from Chalcone: 9-(Benzo[d][1,3]dioxol-5-yl)- 7-(thiophen-2-yl) pyrido[30,20:4,5] thieno[3,2-d]pyrimidin-4(3H)-one (24a)	Synthetic	Acquired	ATCC 6538	7.81 µg/mL	Antibacterial	Sanad et al. (2020)
Triazine Chalcone: 3k	Synthetic	Claisen–Schmidt	NCIM 2178	85 mm	Antibacterial	Shinde et al. (2019)
Aminochalcone derivatives: 1–3; 7–8; 11–13; 16	Synthetic	Claisen–Schmidt	DSM799	0.25 [mg/mL]; 0.125 [mg/mL]; 0.25 [mg/mL]; 0.5 [mg/mL]	Antibacterial	Kozłowska et al. (2019)
Chalcones and derivatives (6r, 12a); [6s; 12c] 7j–7m	Synthetic	Claisen–Schmidt	MSSA (ATCC 29213); MRSA (USA 300)	(1.56 – 6.25 µg/mL); [3.125 – 6.25 µg/mL]; 1.56 -12.5 µg/mL	Antibacterial	Zhang et al. (2018b)
Chalcones bonded to Biscoumarine copolyester 4a; 4b; 4c	Synthetic	Polycondensation	–	312.5 µg/mL; 625 µg/mL; 156.2 µg/mL	Antibacterial	Kandaswamy (2019)
1-(2-bromophenyl) ethanone derivatives I1-I5	Synthetic	–	NCIM 2079	They ranged from 31.25 to 500 µg/mL	Significant Antibacterial	Prasad et al. (2018)
Chalcones derivatives 11; 18	Synthetic	Claisen–Schmidt	NTCC8325-4 MRSA 97-7	50 and 70 µg/mL; 50 and 90 µg/mL	Low antibacterial activity	Vásquez-Martínez et al. (2019)
Chalcones derivatives 18; 11	Synthetic	Claisen–Schmidt	MRSA 97-7	20 µg/mL; 50 µg/mL	Synergism with the antibiotic methicillin	Vásquez-Martínez et al. (2019)
Chalcone-pyridine hybrids 5j; 5i; 5b; 5f	Synthetic	–	MTCC 121	3.12 µg/mL; 6.25 µg/mL	Antibacterial	Gondru et al. (2018)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
Pyrimidine-2(1H)-ol/-thiol derivatives derived from Chalcones 20–24; 35–39	Synthetic	–	ATCC 25923	2.1–138.8 µg/mL	Antibacterial	Fandakli et al. (2018)
Chalcones converted to pyrazoles 4h, 4j, 4l, 4m e 4n	Synthetic	Claisen–Schmidt	–	They ranged from 3.75 to 1.25 µg/mL	Antibacterial	Chowdary et al. (2019)
Benzoxazepines derived from pyrazol-Chalcones 3c; 3h, 5c, 5g; 5b; 5h	Synthetic	–	–	30 mm; 28 mm; 27 mm; 32 mm	Antibacterial	Ashok et al. (2018)
Indolyl Chalcone Derivatives 4b; 5b; 6b, 7; 11	Synthetic	–	–	27 mm; 22 mm; 24 mm, 28 mm	Antibacterial	Sayed et al. (2018)
Heterocyclic Chalcones 4b* 4c, 4g, 4k	Synthetic	Claisen–Schmidt	MTCC 096	12.5 µg/mL* 6.25 µg/mL	Antibacterial	Kaushik et al. (2018)
Pyrazole Chalcones 6b; 6c; 7b e 8b	Synthetic	Claisen–Schmidt	MTCC9886	13 ± 0.44 mm; 17 ± 1.10 mm; 15 ± 0.53 mm; 11 ± 2.01 mm	Moderate antibacterial	Kumari et al. (2018)
Triazole-based Chalcones and its derivatives 3f, 5a, 6a, 7b e 8a	Synthetic	–	–	44.59 mM; 50.15 mM; 66.61 mM; 76.63 mM; 53.86 mM	Antibacterial	Santosh et al. (2018)
Anthracene-based Chalcone derivatives ANNP, ANFL; ANID and ANPT	Synthetic	Claisen–Schmidt	–	6.25 µg mL; 3.12 µg mL	Moderate antibacterial	Prakash et al. (2018)
Chalcones derived from acetylpyridines 4; 5; 11; 12	Synthetic	–	–	–	Antibacterial	Santra et al. (2018)
β-Carboline Chalcones and their bromide salts 12b, 12c, 12e, 12f, 12g; 13a; 13h	Synthetic	–	MTCC 96	Ranged from 440 to > 900 µM	Inactive for antibacterial activity	Reddy et al. (2018)
Chalcone-thiazole hybrids (27)	Synthetic	Claisen–Schmidt	ATCC 33592—Methicillin and Gentamicin Resistant	1.4 µM	Antibacterial	Sashidhara et al. (2015)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
1,3- diphenyl-2-propen-1-ones (III-C)	Synthetic	–	JMC 2151	32 ± 1.5 mm	Antibacterial	Alam et al. (2015)
Chalcones derivatives: 3[a]–3j	Synthetic	–	ATCC 29213; (MRSA)	16–256 µg/mL 32–64 µg/mL	Low antibacterial activity	Evranos-Aksöz et al. (2015)
4.5-dihydropyrazol	Synthetic	–	ATCC 29213	10–17 mm	Antibacterial	Budak et al. (2017)
2-(4-Methyl-2-oxo-2H-chromen-7-yloxy)-N-(4-((E)-3- (3,4,5-trimethoxyphenyl)acryloyl)phenyl) acetamide	Synthetic	Claisen–Schmidt	ATTC 6538	35.8 µg/mL	Antibacterial	El-Sherief et al. (2017)
(4- (4- aryl)-1H- pyrrol-3-yl) (pyren-1-yl)meth-Anone + (3-chloro)	Synthetic	-	-	4.1 µg/mL	Antibacterial	Divakar and Shanmugam (2017)
monocarbonyl curcuminoids	Synthetic	-	ATCC 25923	250 mg/mL	Antibacterial	Ud Din et al. (2017)
2-(2-Hydroxyphenyl)-5-methyl-3-(4-(thiophen-2-yl)-6-(4- methyl-phenyl)-pyrimidin-2-yl) thiazolidin-4-one; 3-Chloro-4-(4-hydroxy-3-methoxyphenyl)-1-(4-(thiophen-2- yl)-6-(4-methyl-phenyl)-pyrimidin-2-yl)azetidin-2-one	Synthetic	Claisen–Schmidt	–	100 µg mL	Antibacterial	Patel et al. (2017)
(2E,20 E)-3,30 -(3,30 -(butane-1,4-diylbis(oxy)) bis(3,1- phenylene))bis(1-(thiophen-2-yl)prop-2-en-1-one) (2E,20 E)-3,30 -(3,30 -(pentane-1,5-diylbis(oxy)) bis(3,1- phenylene))bis(1-(thiophen-2-yl)prop-2-en-1-one)	Synthetic	Claisen–Schmidt	MTCC 96	8 µg/mL	Antibacterial	Yusuf et al. (2017)
Chalcones derived from Pyrimidines	Synthetic	–	–	9–14 mm	Antibacterial	Kumar et al. (2017b)
Phenylpropenone pyrrolyl Chalcone	Synthetic	–	–	6–11 mm	Antibacterial	Kumar et al. (2017a)
Chalcones with a triazine nucleus (P1–P3, P5, P6, S6)	Synthetic	–	MTCC 96	7–13 mm	Antibacterial	Mahmoodi et al. (2017)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
Derivatives of (3ar,4S,7R,7as)-2-(4-((E)-3-(3- aryl)acryloyl) phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole1,3(2H)-dione (7e, 7l, 7m and 7n)	Synthetic	Claisen–Schmidt	ATCC 29213	14 mm	Antibacterial	Kocyigit et al. (2017)
(2E)-3-(2,6- dichlorophenyl)-1-(4-methoxyphenyl) prop-2-en-1-one	Synthetic	–	–	50 mg/mL	Antibacterial	Sadgir et al. (2020)
Chalcones derived from Pyrazoline	Synthetic	–	–	12.5–25 µg/ml	Antibacterial	Desai and Sastry (2017)
6,6-dimethyl3-aryl-3′,4′,6,7-tetrahydro-1′H,3H-spiro[benzofuran-2,2′-naphthalene]-1′,4(5H)-dione (5a)	Synthetic	Claisen–Schmidt	ATCC 29213	16 mm	Antibacterial	Ergüntürk et al. (2017)
2-Pyrazoline (5f)	Synthetic	Claisen–Schmidt	MTCC 737	10 mg/mL	Antibacterial	Lokeshwari et al. (2017)
2-bromo-4-[3-(2-hydroxyphenyl)-4,5-dihydro-1h-pyrazol-5-yl]-6-methoxyphenol 1-[5-(3-bromo-4-hydroxy-5-methoxyphenyl)-3-(2-hydrophenyl]-4,5-dihydro-1H-pyrazol-1-yl)ethanone	Synthetic	–	FNCC 0047	7.25 mm	Antibacterial	Setyawati et al. (2017)
Cis-3-4-dihydrohamacanthin B; Bromodeoxytopsentin	Synthetic	–	RN4220; MRSA 252; ATCC 29213	12.5 µg/mL; 6.25 µg/mL	Antibacterial	Labrière et al. (2017)
(2E,2′E)-3,3′-(octane-1,8-diylbis(oxy))bis(3,1- phenylene))bis(1-phenylprop-2-ene-1-one) 1,12-bis(3-(1,3-diphenyl-4,5-dihydro-1H-pyrazol5-yl)phenoxy)dodecane	Synthetic	Claisen–Schmidt	MTCC 96	8 µg/mL	Antibacterial	Yusuf et al. (2017)
Jaceosidin; 5,7,4′-triacetoxy jaceosidin	Synthetic	–	ATCC 43,300, VRS 10, NRS 17 NRS 1	32–128 µg/mL	Antibacterial	Kumar et al. (2016)
3′-formyl-2′,4′,6′-trihydroxydihydrochalcone	Synthetic	–	ATCC 29,213 MRSA 33,591	17.4 µM 36.6 µM	Antibacterial	Zaki et al. (2016)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
Quinoline scaffold (3b, 3d, 3g, 3h–j)	Synthetic	Claisen–Schmidt	-	200 µg/mL	Antibacterial	Dave and Rahatgaonkar (2016)
Ferrocenyl chalcones with O-alkylated vanillins	Synthetic	Claisen–Schmidt	ATCC 25923	0.625–5 µg/mL	Antibacterial	Muškinja et al. (2016)
Complex Chalcones (3e, 3l)	Synthetic	–	ATCC 43300	21.8% Redução de crescimento	Antibacterial	Patil et al. (2016)
(E)-3-{5-[(2-Benzoylbenzofuran-5-yl)methyl]-2-hydroxyphenyl}-1-(3,4-dichlorophenyl) prop-2-en-1- one; {5-[3-(8-Fluoro-4-phenyl-2,3-dihydro-1H-benzo- [b][1,4]diazepin-2-yl)-4-hydroxybenzyl]benzofuran2-yl}(phenyl)methanone	Synthetic	Claisen–Schmidt	–	55 µg/mL 34 µg/mL	Antibacterial	SHankar et al. (2016)
(4-Bromo-6,7-dimethoxy-1,1-dioxido-3,4-dihydro-2H-benzo[e][1,2]thiazin-3-yl)(3-chlorophenyl) methanone (4-Bromo-6,7-dimethoxy-1,1-dioxido-3,4-dihydro-2H-benzo[e][1,2]thiazin-3-yl)(3-bromophenyl) methanone (4-Bromo-2-ethyl-6,7-dimethoxy-1,1-dioxido-3,4-dihydro-2H-benzo[e][1,2]thiazin-3-yl)(3-bromophenyl)methanone	Synthetic	–	ATCC 6538	200–400 µg/mL	No significant antibacterial activity	Patel et al. (2016)
Carbazole-based Chalcones (3a, 3h, 3i, 4a, 4h, 4i, 5a, 5h, 5i)	Synthetic	Claisen–Schmidt	ATCC 6538	20 µg/mL	Antibacterial	Ashok et al. (2016)
Glabridin-chalcone hybrid molecules (6h, 7e, 8f)	Synthetic	Claisen–Schmidt	MTCC-96 MRSA-ST 2071	12,5 µg/mL	Antibacterial	Kapkoti et al. (2016)
Chalcones derived from 1,3-diaryl pyrazole (6g, 6l and 7l)	Synthetic	–	4220	1–64 µg/mL	Antibacterial	Killeen et al. (2016)
Chalcones Derivatives (4[a], 4f)	Synthetic	Claisen–Schmidt	4220, 209 and 503	2 µg/mL	Antibacterial	Wei et al. (2016)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
1-[7-(diethylamino)-2H-chromen-2on]-3-(p-chlorophenyl)-2-propen-1-one one; 1-[7-(diethylamino)-2H-chromen-2on]-3-(p-fluorophenyl)-2-propen-1-one	Synthetic	Claisen–Schmidt	–	100 µg/mL	Antibacterial	Himangini and Pathak (2016)
4,5-Dihydro-3-(1-benzyl-1H-indol-3-yl)-5-(naphthalene-2-yl) isoxazole	Synthetic	Claisen–Schmidt	RCMB 010028	23.4 mm	Antibacterial	Abo-Salem et al. (2016)
1,3-thiazine compounds with a Schiff base portion (5a-5e)	Synthetic	Claisen–Schmidt	–	09–15 mm	Antibacterial	Babu et al. (2015)
2,8- bis(2,4-Dichlorophenyl)-4H,6H-pyrano[3,2-g] chromene-4,6-dione	Synthetic	Claisen–Schmidt	ATCC 29737	12.5 µg/mL	Antibacterial	Husain et al. (2015)
2-Chloro-N-{4-[3-(substitutedphenyl)-acryloyl]-phenyl}-acetamide	Synthetic	Claisen–Schmidt	–	9 mm	Antibacterial	Jayaramu and Maralihallia (2015)
3-(4′-*N*,*N*-dimethyl amino phenyl)-5-(2″, 2″-dimethyl, 7″-hydroxy chroman) isoxazole/3-(3′,4′-chloro-phenyl)-5-(2″, 2″-dimethyl, 7″-hydroxy chroman) isoxazole/3-(4′-methoxy-phenyl)-5-(2″, 2″-dimethyl, 7″-hydroxy chroman) isoxazole/3-(4′-cyano phenyl)-5-(2″, 2″-dimethyl, 7″-hydroxy chroman) isoxazole	Synthetic	Claisen–Schmidt	MTCC 96	5–20 µg/mL	Antibacterial	Raju et al. (2015)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
trans-3-(1H-indol-3-yl)-1-(40-benzyloxyphenyl)-2-propen-1-one (2), 1-(400-biphenyl)-3-(30 40-dihydroxyphenyl)-2-propen-1-one (11), 1-(400-hydroxy-300-methylphenyl)-3-(40 -hydroxyphenyl)-2-propen-1-one (14), 3-(40 -chlorophenyl)-1-(400-hydroxyphenyl)-2-propen-1-one (17), LTG-oxime	Synthetic	Claisen–Schmidt	ATCC 96 MRSA	12.5–50 mg mL	Antibacterial	Gaur et al. (2015)
6H-benzo[c]chromen-6-ones and Diazepines (10a,b)	Synthetic	Claisen–Schmidt	ATCC 9144	0.625 µg/mL	Antibacterial	Mazimba (2015)
Chalcone	Synthetic acquired	–	USA 300; USA 300 ΔSRTA	53.15 µM 76 µM	Antibacterial and anti-biofilm	Zhang et al. (2017)
Apchal and Achlopheny	Synthetic	Claisen–Schmidt	ATCC 25923, 10, 1199B, K2068	70% synergism of gentamicin when associated with Apchal and loss of synergism when associated with Aclo-phenyl	Antibacterial. Synergism and antagonism were observed	Siqueira et al. (2020)
Apchal and Achlophenyl	Synthetic	Claisen–Schmidt	SA-1199B; K2068	Synergism with Nor-floxacin and cipro-floxacin; synergism with ciprofloxacin and ethidium bromide	Efflux pump inhibitor	Siqueira et al. (2020)
1,3- Bis-(2-hydroxy-phenyl)-propenone, 3-(3-hydroxy-phenyl)-1-(2-hydroxy-phenyl)-propenone e 3-(4-hydroxy-phenyl)-1-(2-hydroxy-phenyl)-propenone	Synthetic	–	MRSA ATCC 43,300, MRSA CC5, CC8, CC45, CC80, CC152	37.5 ± 13.2 µg/mL; 97.5 ± 27.5 µg/mL; 110.8 ± 21.1 µg/mL	Antibacterial	Božić et al. (2015)
Chalcones and derivatives (6s e12a)	Synthetic	Claisen–Schmidt	Newman (MSSA); MN8 (MRSA); NRS70 (MRSA)	3.12 µg/mL; 6.25 µg/mL: 0.8 µg/mL	Antibacterial, anti-biofilm	Zhang et al. (2018a, b)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
(E)-N-(3-Aminopropyl)-2-(5-((3-methylbut-2-en-1-yl)oxy)-2-(3-(4-((3-methylbut-2-e n-1-yl)oxy) phenyl)acryloyl)phenoxy) acetamide	Synthetic	–	ATCC29213, MRSA N315, MRSA NCTC10442	1.56–3.13 µg/mL	Antibacterial	Lin et al. (2020)
Thiazolyl-pyrazoline derivatives (7 a)	Synthetic	Claisen–Schmidt	MSSA (ATCC 25,923), MRSA (ATCC 43,300), VISA	62.5 µg/mL; 125 µg/mL; 31.5 µg/mL;	Antibacterial	Cuartas et al. (2020)
Derivatives of benzo[4,5] isothiazolo[2,3-a]pyrazine-6,6-dioxide	Synthetic	–	ATCC 6538	> 1600 µg/mL	Inactive for antibacterial activity	Bassin et al. (2017)
Derivatives of 2′,6′-dihydroxy-4′-methoxy-3′,5′-dimethyl chalcone (10)	Synthetic	–	ATCC 43,300, Clinical isolate, VRS 10, NRS 17, NRS 1	> 128 µg/mL 64 µg/mL 32 µg/mL	Antibacterial	Kumar et al. (2016)
Derivatives of (E)-3-(4-bromophenyl)-1-(p-tolyl) prop-2-en-1-one (3a, 3e, 3j)	Synthetic	–	ATCC 29,737	25.4 mm 27.2 mm 26.4 mm	Antibacterial	Bhirud et al. (2020)
7,4′-dihydroxy-8,3′-diprenylflavone and erysubin F	Synthetic	Claisen–Schmidt	MRSA, ATCC 43,300	15.4 µM 20.5 µM	Antibacterial	Kwesiga et al. (2020)
(2Z)-3-(3-nitrophenyl)-1-{4-[(E)-(piperidin-1-yl) diazenyl]phenyl}prop-2-en-1-one	Synthetic	Claisen–Schmidt	ATCC 12,598	12.5 g/mL	Antibacterial	Sivasankerreddy et al. (2018)
Xanthohumol, naringenin, and chalconaringenin	Synthetic	–	PCM 2054	3.57 mm 3.77 mm 1.92 mm	Antibacterial	Stompor and Zarowska (2016)
2′-Hydroxychalcone; 2 0-Hydroxy-2-methoxychalcone; 2 0-Hydroxy-4-methoxychalcone; 2 0-Hydroxy-40 -methoxy-chalcone-3-yl)(3-bromophenyl)methanone	Synthetic	Claisen–Schmidt	D1	0.26 ± 0.09, 0 ± 0.03, 0.88 ± 0.10 0 ± 0.04	Antibacterial	Gładkowski et al. (2019)
4-Hydroxyphenyl 3-Hydroxyphenyl	Synthetic	Claisen–Schmidt	–	5 µg/mL 10 µg/mL	Antibacterial	Desai et al. (2017)
Aryl substituted dihydrotriazine derivatives (17h)	Synthetic	–	4220 QRSA CCARM 3505	0.5 µg/mL	Antibacterial	Zhang et al. (2018a)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
Derivatives of 1,2,3-triazoles (25)	Synthetic	Claisen–Schmidt	–	MIC decrease in 55%	Antibacterial	Syed-Aly et al. (2015)
Derivatives of (2-(Pyridinyl) methylene)-1-tetralone	Synthetic	–	MRSA	Decrease of 75%	Antibacterial	Gibson et al. (2017)
Chalcones (5h) (E)-N-(4-(3-(4-Chlorophenyl)acryloyl)phenyl)-3-(piperidin-1-yl)propanamide, (E)-N-(4-(3-(4-Methoxyphenyl)acryloyl)phenyl)-3-(piperidin-1-yl)propanamide, (E)-3-(Piperidin-1-yl)-N-(4-(3-(3,4,5-trimethoxyphenyl)acryloyl)phenyl) propanamide	Synthetic	–	IFO 3060	2.0 mg/mL 2.4–8.6 mg/mL	Antibacterial and antibiofilm	El-Messery et al. (2018)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
(2E)-3-(4-{[1-(2-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxy-phenyl)prop-2-en-1-one, (2E)-3-(4-{[1-(2,4-difluorophenyl)-1H-1,2,3-triazol-4-yl] methoxy}-3-methoxy-phenyl)-1- (2-hydroxy-4,6-dimethoxyphenyl) prop-2-en-1-one, (2E)-3-(4-{[1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl] methoxy}-3-methoxy-phenyl)-1-(2- hydroxy-4,6-dimethoxyphenyl) prop-2-en-1-one, (2E)-3-[3,4-bis({[1-(2,4-difluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}) phenyl]-1-(2- hydroxy-4,6-dimethoxyphenyl) prop-2-en-1-one, 2-[3,4-bis({[1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}) phenyl]-5,7-dimethoxy4H-chromen-4-one	Synthetic	–	ATCC 25323	6.25 µg/mL 12.5 µg/mL	Antibacterial	Kant et al. (2016)
4′-hydroxy-4-methyl chalcone	Synthetic	–	ATCC 29213	32 µg/mL	Antibacterial	Evranos-Aksöz et al. (2015)
Asymmetric heterocyclic chalcone derivatives and heterocyclic compounds (4, 6, 7, 9)	Synthetic	–	ATCC 25923	65–95% of zone of inhibition	Antibacterial	El-Hashash et al. (2015)
Derivatives of 3-hydroxy-6-(hydroxymethyl)-2-(2-phenyl-4H-chromen-4-yl)-4H-pyran-4-ones (3a, 3e, 3f e 3 l)	Synthetic	–	MLS-16 MTCC 2940	7.8–15.6 µg/mL	Antibacterial	Bingi et al. (2015)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
Chalcona derivative: (4[(1E)-3-(pentyloxy)buta-1,3-dien-1-yl]benzene-1,2-diol	Synthetic	Claisen–Schmidt	ATCC 2592 (MRSA) ATCC 33591	0.12 µM	Antibacterial and antibiofilm	Emeri et al. (2019)
N-(5a-chloro, 8a-triflouromethyl)-benzyl-N, 1a-dihydro-2H-O, N-isoliquiritigeninoxazine (IMRG4)	Synthetic Derived from the natural Chalcone Isoliquiritigenin (ISL)	–	SA-29213; SA-1199;SA-1199B*; SA-K1758; MRSA-P4423; MRSA-P4627; MRSA-P4620; MRSA-B10760; MRSA-ST315; VISA-ST207; VISA-ST1745	50 (mg/L); 25(mg/L); 50(mg/L); 25 (mg/L); 50(mg/L); 25(mg/L); 25 (mg/L); 50(mg/L); 25(mg/L); 50 (mg/L); 50(mg/L)	Antibacterial *NorA efflux pump inhibitor	Gupta et al. (2019)
(2E)-1-(3′, -methoxy-4′,-hydroxyphenyl)-3-(3-nitrophenyl) prop-2-en1-one (AVMNB)	Synthetic	Claisen–Schmidt	ATCC 25923; 10	≤ 512 mg/mL	Antibacterial	Garcia et al. (2020)
(2E)-1-(3′, -methoxy-4′,-hydroxyphenyl)-3-(3-nitrophenyl) prop-2-en1-one (AVMNB)	Synthetic	Claisen–Schmidt	ATCC 25923; 10	MIC↑	Antagonistic with Cephalexin and Gentamicin antibiotics	Garcia et al. (2020)
2E-1-(2′-hidroxi-3′,4′,6′-trimetoxifenil)-3-(fenil)-prop-2-en-1-ona (HYTPHENYL)	Synthetic Derived from the natural compound: 2-hydroxy-3,4,6-trimethoxyacetophenone	Claisen–Schmidt	358	1024 µg/L MIC↓	Inactive for antibacterial activity Antibiotic modulator: Synergism with the antibiotic Amikacin	Teixeira et al. (2019)
(E)-3-(2-methylpyrimidin-5-yl)-1-ferroceynlprop-2-en-1-one (MPFP)	Synthetic	Claisen–Schmidt	–	Concentration of 25 µg: 19 mm Concentration of 50 µg: 24 mm Concentration of 75 µg: 31 mm	Antibacterial	Twinkle et al. (2020)
Cationic derivatives of Chalcones: 5a; 5s; 5b; 5c; 5d, 5g, 5l, 5p, 5q; 5r; 5z; 5ab	Synthetic	Claisen–Schmidt	M1-M9 MRSA	Ranged from 0.25 –32 µg/mL	Antibacterial and synergism with Norfloxacin and Colistin	(CHU et al., 2018)
Cationic molecule 5g	Synthetic	Claisen–Schmidt	ATCC29213	128 µg/mL	Anti-biofilm	(CHU et al., 2018)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
Chalcones derivatives: (E)-2-(4-acetamidophenoxy)-N-(3-(3-(4-methoxyphenyl) acryloyl)phenyl)acetamide (5e); (E)-2-(4-acetamidophenoxy)-N-(3-(3-(4-chlorophenyl) acryloyl) phenyl)acetamide (5b)	Synthetic	–	–	Concentration of 100 µg/mL: 9; 10 mm Concentration of 200 µg/mL: 15 mm; 13 mm	Antibacterial	Babu and Selvaraju (2020)
Chalcones-Sulfonamides 5/6, 8a-f and 9a-f ($N = 12$ derivatives)	Synthetic	Claisen–Schmidt	Resistant clinical isolates	> 57 mcM	Inactive for antibacterial activity	Castaño et al. (2019)
Thiazole-based Chalcone (Derivative): Compound 18	Synthetic	–	IFO 3060	1 µg/mL	Antibacterial	Alrohily et al. (2019)
Ferrocenyl Chalcone Derivatives: Zn (II) (H1; H5)	Synthetic	–	ATCC 9144	1.349×10^{-8} M/mL 1.268×10^{-7} M/mL	Significant antibacterial	Liu et al. (2019)
Derivative: (E)-1-(4-brom ophenyl)-3-(4-iodophenyl) prop-2-en-1-one	Synthetic	Synthesized and characterized using XRD, FT-IR^{1} H and ^{13} C NMR	ATCC 12600	250 µg/mL	Antibacterial	Zainuri et al. (2017)
Ferrocenyl Chalcone Derivatives: 3a2,3a7 e 3b6	Synthetic	–	MRSA, ATCC 43300	Concentração de 3 g/L: 11–22 mm	Antibacterial	Liu et al. (2018)
Chalcones derivatives: 4a; 4e; 4h	Synthetic	Claisen–Schmidt	ATCC-9144	08 µg/mL 08 µg/mL 04 µg/mL	Antibacterial	Gopi et al. (2016)
(E)-1-(4-Bromophenyl)-3-(napthalen-2-yl)prop-2-en-1-one	Synthetic	Claisen–Schmidt	ATCC 12600	500 µg/mL	Antibacterial	Thanigaimani et al. (2015)
Derivatives if indolyl-4H-chromene-phenylprop-2-en-1-one (5g; 5h)	Synthetic	Claisen–Schmidt	ATCC 700699	9.3 µg/mL	Antibacterial	Subbareddy et al. (2018)
Chalcone derivative: 1-hydroxynaphth-2-yl pyrazoline (6b)	Synthetic	Claisen–Schmidt	–	3.9 µg/mL	Antibacterial	El-Desoky et al, (2018)
Chalcone derivative: Pyrazoles (5j; 5h)	Synthetic	Claisen–Schmidt	MTCC 3160	6.5 µg/mL	Antibacterial	Mishra et al. (2017)

Table 3 (continued)

Chalcone	Type	Synthesis technique	*S. aureus* strain (s)	MIC/Inhibition Zone	Activity	Quote
Derivative of Chalcone (4-bromophenyl)-1-(4-chlorophenyl)prop-2-en-1-one (I): 4-[(E)-[[4-(4-bromophenyl)-6-(4-chlorophenyl)pyrimidin-2-yl]imino]methyl] benzene-1,3-diol (IJ)	Synthetic	Claisen–Schmidt	NCIM 2079	500 µg/mL	Antibacterial	Prasad et al. (2019)
[(Chloroquinolin-4-yl) amino]chalcones 8a–f	Synthetic	Claisen–Schmidt	ATCC 25923 (MSSA) ATCC 43300 (MRSA)	> 1000 µg/mL	Inactive for antibacterial activity	Ramírez-Prada et al. (2017)
Bichalcones 8 (a–h)	Synthetic	Claisen–Schmidt	–	16–32 µg/mL	Low antibacterial activity	Yusuf and Solanki (2017)

a) The spaces filled with (–) mean that the information was absent from the article or was not clear

benzaldehydes and acetophenones that can be combined, providing the structural variety intended (Ducki et al. 1998; Narender and Papi Reddy 2007).

Antibacterial activity of natural Chalcones

Generally, Chalcones can be categorized into single and hybrid Chalcones with the central skeleton of 1,3-diaryl-2-propen-1-one. In plants, Chalcones (*cis* and *trans*) are intermediates in the biosynthesis of flavonoids, which increased interest in this substance, and in 1910 occurred its first isolation in the laboratory (Shimokoriyama 1962; Ferreira et al. 2018). Chalcones can be found in dicotyledonous plants, some monocotyledons, pteridophytes and gymnosperms, but they are synthesized as main components in the Leguminosae, Asteracea and Moracea families, which are currently still used in folk medicine in the form of teas (Banoth and Thatikonda 2020).

The biological potential of Chalcones has been investigated since the 1940s, but it was only in the 1970s that researchers became more interested in exploring natural Chalcones when they showed anti-parasitic activities (Nowakowska 2007). With the discovery of antiparasitic activity, the search for more biological activities of Chalcones intensified, since then researchers around the world isolate and test natural Chalcones for various purposes, especially antibacterial activities, which is an emerging issue in a globalized world with so many human deaths by increasingly resistant bacteria.

In this context, Moreno et al. (2015), solated the Chalcones 2′,4′-dihydroxychalcone and 2′,4′-dihydroxy-3′-methoxychalcone from the *Zuccagnia punctata* plant against a standard strain of *S. aureus* and a Methicillin-resistant strain (MRSA), which exhibited antibacterial potential with MIC of 250 µg mL. In the following year, Costa et al. (2016), tested the antibacterial potential of the natural Chalcone 20-hydroxy-4,40,60-trimethoxychalcone isolated from the botanical species *Piper hyspidium*, which obtained an MIC of 125 µg/mL showing potential antibacterial activity. In the same way Mariani et al. (2016) tested the antibacterial potential of natural Chalcone 4,4′,6′ trihydroxy 3 methoxy 3′ pentene chalcone isolated from *Elatostema parasiticum* which exhibited an MIC of 7.8 µg/mL which was considered to be good antimicrobial activity against a *S. aureus* clinic strain.

In 2018, Chalcone 2′,4′-dihydroxychalcone was isolated from aerial parts of *Zuccagnia punctata* which showed noticeable antibacterial and anti-biofilm activity against a series of *S. aureus* strains, reaching MIC of 25 µg/mL and 12.5 µg/mL, respectively (Nuño et al. 2018). In the following year, Meier et al. (2019) isolated Chalcone Xantoangelol from the fruits of *Amorpha fruticosa* which demonstrated

a potent bactericidal effect against MRSA strain, reaching MIC of 12.5 µM.

In Table 2 below, studies in which natural Chalcones do not show clinically relevant antibacterial activity can be observed, but they were able to inhibit known resistance mechanisms, such as efflux pumps. Results like these are demonstrated in the study by Rezende-Júnior et al. (2020). In the aforementioned study, the natural Chalcone 3′,4′-dihydroxy, 3,4,4′-trimethoxy-chalcone (4) was isolated from the botanical species *Arrabidaea brachypoda* and tested its antibacterial effect against a series of clinical strains of *S. aureus*, including a strain carrying the NorA efflux pump, SA-1199B. In the direct antibacterial activity clinical trial, results were determined as clinically irrelevant with an MIC of ≥ 1024 µg/mL. However, in the Ethidium Bromide (BrEt) trial, natural Chalcone reduced the MIC to 16 µg/mL, acting as a potential efflux pump inhibitor.

Antibacterial activity of synthetic Chalcones and derivatives

Due to advances in synthetic organic chemistry, it is possible to obtain bioactive compounds with a diversity of substituents in an increasingly versatile way, such as several Chalcones that are synthesized from the manipulation of the aromatic rings of natural Chalcones (Fonseca 2012). The Claisen–Schmidt condensation methodology between aryl ketones and benzaldehyde derivatives is revealed as the most used methodological strategy for the construction of various chalconic nuclei (Winter 2016).

A series of Chalcones and derivatives were synthesized by the Claisen–Schmidt condensation in the study by Zhang et al. (2018a, b). The antibacterial evaluation revealed that an A ring substituted with R1 hydroxy groups in the 6 series of Chalcones produced active compounds with considerable antibacterial activity, such as the compound 6s ((E)-3-(4-(Diethylamino)phenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one) which exhibited an MIC of 3.12 µg/mL and 6.25 µg/mL against MSSA and MRSA strains, respectively. The α,β-unsaturated ligand between rings A and B was shown to be important for antibacterial activity.

Cuartas et al. (2020) also tested the potential of Chalcones against MSSA and MRSA strains. Chalcones derived from N-substituted pyrazolines proved to be excellent candidates for the development of new antimicrobials. The compound 5-{2-[Bis(2-chloroethyl)amino]-4-chlorothiazol-5-yl}-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (7a) exhibited a MIC of 61.25 µg/mL for MSSA and 125 µg/mL for MRSA, exhibiting a lower MIC value (31.5 µg/mL) for the VISA strain (Vancomycin—intermediate *Staphylococcus aureus*).

Zhang et al. (2017), obtained good antibacterial and anti-biofilm activity of a commercially purchased chalcone against two strains of *S. aureus* carrying an important virulence-related enzyme, Sortase A (SrtA). The use of chalcone against USA 300 and USA 300 ΔSRTA strains expressed an MIC of 53.15 µM and 76 µM, respectively, which can be considered a good anti-virulence strategy in the fight against infections by *S. aureus*.

In the frame built to show all the studies included in this review, it is possible to observe that there are also many works using hybrid Chalcones. Molecular hybridization is an efficient strategy, widely used for drug design. Hybrid molecules or compounds can provide more biological targets, which facilitates the achievement of the desired bioactivity (Dan and Dai 2019). Therefore, in the study by Kapkoti et al. (2016) ome hybrid molecules of Glabridin-chalcone (6h, 7e, 8f) were synthesized and tested their antibacterial potential against MTCC-96 and MRSA-ST 2071 strains, obtaining a MIC of 12.5 µg/mL, among all compounds tested, compound 8H exhibited marked synergism and reduction of up to 16 times in MICs with Norfloxacin (FICI range from 0.312 to 0.375).

When it comes to synergism, it was observed that several articles report antibiotic potentiation by synthetic Chalcones, such as the work carried out by Siqueira et al. (2020). The Chalcones (2E)-1-(4′-aminophenyl)-3-(phenyl)-prop-2-en-1-one (APCHAL) and (2E)-1-(4′-aminophenyl)-3-(4-Chlorophenyl)-prop-2-en-1-one (ACLO-PHENYL) were synthesized by Claisen–Schmidt condensation and tested against a number of standard and multidrug-resistant strains. It was observed that Chalcone Apchal reduced the MIC by up to 70% of the antibiotic Gentamicin (synergism) while expressing antagonism with the antibiotic Penicillin. Regarding Chalcone Aclo-phenyl, due to the addition of a chlorine group in the substance, a loss of synergism with Gentamicin was observed.

The Chalcones mentioned above were also tested as potential efflux pump inhibitors on SA-1199B strain carrying the NorA efflux pump and K-2068 strain carrying the MepA efflux pump. In the evaluation of inhibition of this resistance mechanism, both Chalcones exhibited a synergistic effect with the antibiotics Norfloxacin and Ciprofloxacin, although Aclo-phenyl is less pronounced. On the other hand, Aphcal showed synergism with both Ciprofloxacin and BrEt, showing good results with the inhibition of the MepA efflux pump. The results also demonstrate that both compounds bind approximately to the same region of the 1199B binding site and that this region overlaps with the preferred binding region of Norfloxacin. Based on these results, the authors state that Chalcone Aphcal can significantly contribute to the prophylaxis or therapy of diseases caused by multidrug-resistant *S. aureus*.

All the studies, presented and their relevance to the scientific community in terms of public health, reveal the importance of investigating natural compounds and the synthesis

of new substances to solve the problem of bacterial resistance worldwide, as well as proving that the bacterium *S. aureus* is currently one of the bacteria with the greatest investigative focus, given all the complications generated in public health and in the global economy (Table 3).

Chalcones synthesis

Several methodologies are reported in the literature for the preparation of Chalcones, but the best known and most used is the synthesis through the Claisen–Shmidt condensation, in which the reaction of a chosen derivative of acetophenone with suitable aromatic aldehydes occurs, using ethanol or methanol as solvent and sodium hydroxide or potassium hydroxide as catalyst or different reaction conditions, such as aldol condensation in solid phase, by microwave and without the use of solvent. It is a very simple and convenient methodology although, in some cases, it results in a lower income (Mahapatra et al. 2015; Souza 2014).

The general steps for the synthesis of Chalcones using Claisen Schmdth condensation start with aldol condensation followed by basic dehydration (Lindoso and Lindoso 2009). The initial step of reaction is the deprotonation of the ketone group, where the basic catalyst removes the acid alpha hydrogen of the molecule to produce a carbanion which can be stabilized by resonance. From this, a nucleophilic attack occurs against the carbonyl carbon of the aldehyde, structuring a tetrahedral intermediate (alkoxide ion). This intermediate is protonated by a hydrogen in water generating the condensation product and regenerating the basic catalyst. The condensation product occurs by dehydration and for this to happen it is necessary to remove a hydrogen from the alpha position to result in the enolate ion, which by equilibrium eliminates the OH– group, thus forming the Chalcone (Chiaradia 2010).

Other less common methodologies in the synthesis of Chalcones are described in the literature such as Heck, Sonogashira, and SuzukiMiyaura coupling, Friedel–Crafts reaction. However, there is an advantage in using the aldol condensation methodology (Claisen–schmidt) which is its accessibility when compared to the others, as it does not require high temperatures or expensive catalysts. Different methodologies, such as coupling reactions, can become inconvenient by causing environmental impacts caused by metals that are used in the process (Mahapatra et al. 2015; Souza 2014).

Bacterial resistance and efflux pump

Resistance mechanisms and their inhibition by Chalcones is widely cited by many studies in this review. This is due to the emergence of several complex mechanisms and rapid dissemination of multidrug-resistant microorganisms that have been worrying global health agencies, as these characteristics impose a barrier to existing treatments, which many of these treatments have suffered decreases in terms of use and effectiveness (Anvisa 2018). One of the effective resistance mechanisms employed by *S. aureus* is the active pumping of antimicrobials through membrane transporters, known as efflux pumps (Jang 2016; Rao et al. 2018). Efflux pumps are proteins capable of extruding several types of chemically different substrates, mainly antibiotics (Costa et al. 2013; Hassanzadeh et al. 2020), contributing significantly to a high level of resistance.

With the knowledge about the functionality of efflux pumps and with the goal of reversing bacterial resistance through the inhibition of this mechanism, new Chalcones are being synthesized for the investigation of their inhibitory potential, which can act as efflux pump inhibitors (EPIs) (Labrière et al. 2017; Siqueira et al. 2020). The administration of antibiotics and EPIs simultaneously can reduce the amount needed of a drug to achieve the same effect (Prasch and Bucar 2015; Seukep et al. 2020). Many studies reported in the synthesis tables show the activity of synergisms or antibiotic potentiators of several Chalcones, such as the works carried out by Vásquez-Martínez et al. (2019) and Ferraz et al. (2020).

In the findings of this review, the following studies that worked with pumps were reported: (1) NorA: belonging to the largest and oldest pump family, the Major Facilitator Superfamily (MFS) and is present in the SA-199B strain.; (2) MepA: belonging to the Multidrug and Compound Extrusion Family (Multidrug and Toxic Compound Extrusion—MATE), this pump is expressed in K-2068 strains, both are reported in the works of Rezende-Júnior et al. (2020), Siqueira et al. (2020), Rocha et al. (2021), Xavier et al. (2021) and Da Silva et al. (2021); (3) MsrA: present in the RN-4220 *S. aureus* strain and belongs to the ABC protein group, this pump was used in the studies by Labrière et al. (2017), Xavier et al. (2021) and Rezende-Júnior et al. (2020); This last author also worked with the efflux pumps (4) QacA/B present in K4414 e (5) QacC overexpressed in K4100 strain, belonging to the family of transporters MFS and SMR, respectively.

The works mentioned above, for the most part, presented relevant results for the research, either by the inhibition of this mechanism by Chalcones or by the reduction of the MIC of the antibiotics used through synergisms, thus potentiating the antibiotic activity.

Structure–activity relationship

In medicinal chemistry, the term structure–activity relationship can be understood as the effect that the chemical structure of a compound has on its biological activity. The main objective of this analysis is to investigate how variation

in chemical structure can affect the biological potential of a substance or the ligand/receptor affinity (Marino 2014). According to Guido et al. (2010), the structure–activity relationships can be defined from changes in the prototype molecule and the evaluation of its subsequent biological activities.

In the study by Kozłowska et al. (2019) the effect of structure on the biological activity of synthetic Chalcones is clearly shown. The author of the work synthesized 18 aminochalcones and it was possible to observe that the presence of an amino group in the meta position with the addition of the aromatic ring in compound 14, increased the hydrophobicity of the molecule, facilitating penetration of Chalcone into the cells of microorganisms. Babu and Selavaraju (2020) demonstrated that compounds tested for antibacterial activity that contained the methoxy portion exhibited excellent activity.

In another study also reported in the tables, it demonstrates the synthesis of heterocyclic Chalcones where the reactivity of the produced Chalcones (Chalcones 3) allowed the construction of several heterocyclic systems such as pyrazoline, isoxazoline, benzoflavone and benzocoumarin (El-Desoky et al. 2018). It is possible to observe in the cited study that the modification in the structure of the derivatives of Chalcones 3b to the corresponding flavonone 9b destroyed the antibacterial activity; however, the more the modification to flavone improved in the compound 11b the more the activity was restored beyond the reference antibiotic.

A comparative study was carried out between Chalcones and pyrazole derivatives about the antibacterial activity against *S. aureus*. There was a great difference in the antibacterial potential between these two compounds due to the presence of a hydroxy group in the fourth position of the A ring. The 2-pyrazoline functions did not increase the antimicrobial activity, while the Chalcones showed better activity (Evranos-Aksöz at al. 2015a, b). In the study by Teixeira et al. (2019) the presence of the hydroxy group in the compound 2E-1-(2′-hydroxy-3′,4′,6′-trimethoxyphenyl)-3-(phenyl)-prop-2-en-1-one (HYTPHENYL) did not determine any antibacterial activity against *S. aureus*; however, a synergism was noticed when this Chalcone was associated with the antibiotic Amikacin. This change in antimicrobial activity may be related to both the position of the hydroxy group and the presence of the methoxy group in Chalcone.

The Chalcona derivative (E)-1-(4-bromophenyl)-3-(4-iodophenyl)prop-2-en-1-one reported in the work by Zainuri et al. (2017) demonstrated good antibacterial activity against a standard strain of *S. aureus* with an MIC of 250 µg/mL. However, when the Iodine group was replaced by naphthalene in the study by Thanigaimani et al. (2015), forming the compound (E)-1-(4-Bromophenyl)-3-(napthalen-2-yl) prop-2-en-1-one the antimicrobial activity decreased considerably reaching a MIC of 500 µg/mL, demonstrating the importance of the effects caused by the change in the conformation of a chemical structure or the substitution of functional groups by others.

In the study by Ramírez-Prada et al. (2017) the antibacterial potential of Chalcones and some derivatives is described. Although the Chalcone [(7-Chloroquinolin-4-yl) amino]chalcones (8a–f) described in the table did not show relevant antibacterial activity, compound 6: 3-((7-Chloroquinolin-4-yl)amino)benzaldehyde which contains the parental benzaldehyde in its structure was the most active of the compounds tested, showing inhibitory activity against *S. aureus*. The results obtained with aldehyde 6 show that the 7-chloro-4-aminoquinoline nucleus confers antibacterial activity, but this activity is abolished when the nucleus is functionalized by other chemical groups.

The structure–activity relationship was summarized based on the antibacterial activity data presented in the summary tables. It was observed during the analysis of the articles that the α, β-unsaturated ketone fraction in Chalcones is essential for the maintenance of antibacterial activity and that the change in the A and B rings can drastically change the biological activity of a compound. It has also been observed that hybrid molecules can significantly improve the desired antimicrobial activity.

Conclusion

This literature review presented the recent advances in the research of natural and synthetic Chalcones with antibacterial potential, organized through informative tables on the articles that constituted the research sample. The main methodology used for the synthesis of Chalcones was described, as well as the main resistance mechanism reported in the articles, how it contributes to the multidrug resistance of *S. aureus* and the efforts that are being made to inhibit this mechanism. Furthermore, the structure–activity relationship was briefly discussed, to which it can be evidenced that several bioactive portions can be incorporated in the A and B rings and in the α,β-unsaturated ketone fragments. It was observed that the compounds based on Chalcones showed great antibacterial potential and demonstrated the ease of obtaining different skeletons of this group through the Claisen–Schmidt condensation methodology. Future perspectives in the study of Chalcones may be based on the investigation and synthesis of new antibacterial drugs based on Chalcones or substances composed of hybrid molecules, enrich studies about resistance reversal through inhibition of the mechanism cited in the present review and investigate the toxicity of Chalcones as antibacterial agentes.

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Data availability All data will be available after a reasonable request to the corresponding author.

Declarations

Conflict of interest The authors declare that they have no known conflict of interest to disclose.

Ethical statements This article is according with to the international, national and institutional rules considering biodiversity rights.

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