

Pharmacological Diversity of Xanthone Derivatives: A Mini Review of Their Antibacterial Properties Against Common Human Pathogenic Bacteria

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Pharmacological Diversity of Xanthone Derivatives: A Mini Review of Their Antibacterial Properties Against Common Human Pathogenic Bacteria

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Abstract: Antibiotic resistance remains one of the most serious global health issues, necessitating the discovery and development of new and novel antibacterial agents. Among the numerous natural and synthetic compounds under exploration, xanthenes have consistently emerged as promising candidates due to their broad spectrum of biological activities, most notably, their potent antimicrobial properties. Over the years, a growing body of research has highlighted the antibacterial potential of various xanthone derivatives. This review aims to provide a comprehensive overview of the antibacterial activities of xanthenes, with a particular focus on their efficacy against infectious bacterial pathogens, including *Staphylococcus*, *Salmonella*, and *Escherichia*. By organising findings based on bacterial classification, this work sheds light on structural features of xanthenes that may contribute to their antibacterial effectiveness and therapeutic relevance.

Keywords: antibacterial, bioactivity, drug discovery, pharmacological properties, xanthone derivatives.

1. INTRODUCTION

Xanthenes (**1**) (IUPAC name: 9H-Xanthen-9-one/9-Oxoxanthene/Diphenylene ketone oxide) (Fig. 1) are a class of natural products which having the molecular formula of C₁₃H₈O₂. The term "xanthone" originates from the Greek word "Xanthos", which means "yellow." Chemically, xanthenes are dibenzo- γ -pyrone framework heterocyclic chemicals which formed by the combination of two benzene rings and a pyran-4-one ring [1]. Naturally occurring xanthenes, which have approximately a thousand known members, have various classes of substituents in various positions, resulting in a wide range of pharmacological activities [2]. According to Fig. 1, a carbonyl group and an oxygen bridge connect the two aromatic rings, giving the structure the appearance of a fused ring system. Due to the withdrawing action of the electronegative oxygen atoms, both C-1 (or C-8) and C-4 (or C-5) are acidic sites in terms of molecular symmetry [3]. On the other hand, the fused ring structure restricts flexibility and enhances the rigidity of the xanthone framework.

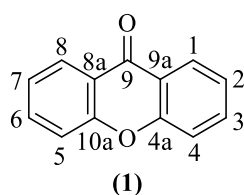


Fig. 1. The structure of the xanthone scaffold.

Bacteria are microscopic organisms in various environments, including air, soil, skin, and the gastrointestinal tract. They are classified into four main groups based on morphology, staining properties, spore production, and oxygen requirements [4]. Bacteria can be spherical, elongate, rod-shaped, or coiled. They are around one micron in size and require dyeing before being visible under a microscope [5]. The Gram stain, developed in 1884, is the most popular method. Gram-positive bacteria maintain the stain after alcohol washing, while Gram-negative bacteria do not [6]. This staining

procedure correlates with the types of disease produced and antibiotic susceptibility. Table 1 provides a summary of bacteria types and the diseases they cause.

Table 1: Different types and illnesses caused by bacterial pathogens

Bacterium	Diseases Caused	Transmission Routes
<i>Staphylococcus spp.</i> [7]	<ul style="list-style-type: none"> • Skin and soft tissue infections • Pneumonia • Bacteremia & endocarditis • Toxic shock syndrome • Food poisoning 	<ul style="list-style-type: none"> • Direct skin contact • Contaminated fomites • Ingestion of enterotoxins
<i>Salmonella spp.</i> [8]	<ul style="list-style-type: none"> • Gastroenteritis • Typhoid fever • Paratyphoid fever 	<ul style="list-style-type: none"> • Fecal-oral route • Contaminated food/water
<i>Escherichia spp.</i> [9]	<ul style="list-style-type: none"> • Diarrheagenic E. coli infections (ETEC, EHEC/STEC, EPEC) • Urinary Tract Infections • Neonatal meningitis • Sepsis 	<ul style="list-style-type: none"> • Contaminated food/water • Poor hygiene

Antimicrobial resistance (AMR) is eroding the efficacy of current antibiotics and has triggered a global public health problem [10]. In 2019, antimicrobial resistance (AMR) caused over 1.3 million deaths globally, and this number could rise to 10 million annually by 2050 if no action is taken [11]. Antimicrobial resistance has resulted in a considerable delay in the appropriate treatment course for infectious illnesses and has frequently resulted in patients receiving inadequate therapy [12]. Table 2

shows the summary of reported antimicrobial resistance against some selected bacteria.

Table 2: The summary of reported antimicrobial resistance against *Staphylococcus*, *Salmonella*, and *Escherichia* genus.

Pathogen	Commonly Resistant Antibiotics	Ref
<i>Staphylococcus</i> spp.	Amoxicillin (100%) Tetracycline (63%) Nalidixic acid (17%) Cefotaxime (13%)	[13]
<i>Salmonella</i> spp.	Amoxicillin (100%) Tetracycline (24%) Chloramphenicol (11%) Nalidixic acid (11%)	[13]
<i>Escherichia</i> spp.	Amoxicillin (100%) Tetracycline (80.95%) Erythromycin (85.71%)	[13][14]

Many advances in medicine, such as the availability of chemotherapy for cancer, organ transplantation nanotechnology treatment, are heavily reliant on good anti-infection measures [15,16]. This has both medical and economic ramifications. There are also uncountable downsides, such as persistent pain, difficulty with everyday tasks, and psychological expenses [17]. The development of new antibacterial drugs with novel structures and distinct antimicrobial actions provides a reprieve for clinical treatment of antibiotic-resistant illnesses as well as a significant tactic to combat antimicrobial resistance [18]. This review highlights various types of naturally isolated and chemically synthesised xanthone derivatives and their antimicrobial activity evaluation against Gram-positive and Gram-negative bacterial strains.

2. ANTI-BACTERIAL ACTIVITY OF XANTHONE

2.1 Genus *Staphylococcus*

Staphylococcus members are Gram-positive cocci (0.5-1.5 µm in diameter) that can be seen singly, in pairs, tetrads, short chains (three or four cells), and irregular grape-like clusters [19]. They are nonmotile, do not generate spores, and are normally unencapsulated or have just a minimal capsule development. The majority of species are facultative anaerobes that pass the catalase and benzidine tests [20].

One of the most significant bacteria that affects people and causes sickness is *Staphylococcus aureus*. It is the main factor in skin and soft tissue infections, such as cellulitis, furuncles, and abscesses (boils) [21]. *S. aureus* can cause serious infections such as bloodstream infections, pneumonia, bone, and joint infections, even though most staph infections are not dangerous [22]. The colonies of these organisms frequently have a golden or yellow colour (the Greek word aureus means golden or yellow) and may thrive in medium with up to 10% salt [23]. At temperatures ranging from 18 to 40°C, these organisms can thrive facultatively or aerobically [24]. Catalase positive (for all pathogenic *Staphylococcus* species), coagulase positive (to tell *S. aureus* from other *Staphylococcus* species), novobiocin sensitive, and mannitol fermentation positive are typical biochemical identification tests [25].

S. aureus is methicillin-resistant and is generally referred to as methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA is a major public health concern globally, generating significant morbidity and mortality [26] as well as increased health-care expenditures [27]. MRSA was responsible for more than 80,000 illnesses and 11,000 hospital deaths in 2011, according to the Centers for Disease Control and Prevention (CDC) in the United States. Furthermore, the European CDC reported that *S. aureus* is the most prevalent isolated strain from healthcare-associated illnesses. It is well known that these bacteria are extremely resistant to various medicines, including penicillin [28]. Recently, it has been reported that MRSA is the most common bacterial strain isolated from animal foods, water, and animal origins, as tabulated in Table 3 [29]. Hospital-acquired MRSA (HA-MRSA) strains are the most prevalent source of hospital-acquired infections [30]. Community-acquired MRSA (CA-MRSA) strains are also prevalent in patients who function as asymptomatic carriers [31]. The most often reported invasive MRSA-related illnesses are septic shock (56%), pneumonia (32%), endocarditis (19%), bacteremia (10%), and cellulitis (6%) (26). MRSA is an issue on a global scale and is not localised to any particular region.

Table 3: Isolated MRSA from different sources and countries.

Source	Year	Type	Country
Blood samples at the hospital	2015	HA-MRSA CA-MRSA	Japan
Zoo animals	2016	LA-MRSA	United Kingdom
Hospital patients	2010	HA-MRSA	Brazil
Patients with skin and soft tissue infections	2009/2011	CA-MRSA	China
Hospital patients	2011/2012	CA-MRSA	Malaysia

On the other hand, methicillin-susceptible *Staphylococcus aureus* (MSSA) is another type of *S. aureus*, but usually, MSSA infections are treatable with antibiotics [32]. The differences between MSSA and MRSA in terms of pathogenicity and virulence are still not well understood. Based on Table 4, the clinical evidence demonstrated that, as compared to MSSA infections, MRSA infections result in longer hospital stays, greater fatality rates, and more expensive treatment [33].

Table 4: The comparison between MSSA and MRSA.

Parameter	MSSA	MRSA	Ref
1. Outcome of patients	n = 433	n = 382	
➤ Patients died due to infection.	22 (5.1%)	45 (11.8%)	[34]
➤ Patients with bacteremia and			

without spreading infection.			
• Total patients	406/433 (93.8%)	355/382 (92.9%)	[34]
• Death	12/206 (3.0%)	35/355 (9%)	[34]
2. Local Patients	n = 80	n = 159	
➤ abscess	23 (28.7%)	80 (50.3%)	[35]
➤ pneumonia with complications	2/13 (15.4%)	12/17 (70.6%)	[35]
3. Virulence, SCCmec subtype, and antibacterial resistance factor	n = 88	n = 104	
➤ SCCmec type III	28 (31.8%)	67 (64.4%)	[36]
➤ entE	63 (71.6%)	88 (84.6%)	[36]
➤ etb	14 (15.9%)	1 (1%)	[36]
➤ vancomycin resistance	3 (3.4%)	31 (29.8%)	[36]
➤ resistance gene distribution qacA/B	24/200 (12%)	186/297 (63%)	[37]

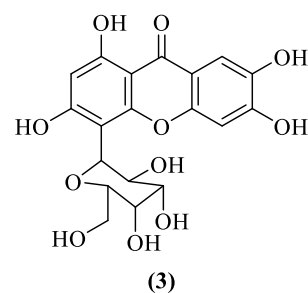


Fig. 3. The structure of Isomangiferin.

Furthermore, Resende et al. (2018) were inspired by chlorinated lichen xanthenes and their antimicrobial activities and endeavoured to synthesize new chlorinated xanthone derivatives with different substituents for their antimicrobial action against *S. aureus*. The results showed that among all the synthesized chlorinated xanthenes, only compound (4) (Fig. 4) was effective in inhibiting *S. aureus* strain with an inhibition halo of 9.5 mm. In terms of structure-activity relationship (SAR) analysis, the chlorine atom at C-3 appears to have some impact on antibacterial action, since compound (4) exhibited potential antibacterial activity against *S. aureus* [40].

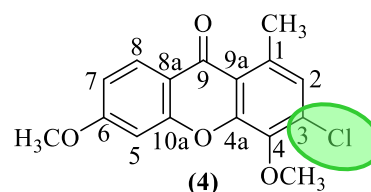


Fig. 4. The structure of chlorinated xanthenes with a chlorine atom at C-3.

Lu et al. (2023) reported a novel synthesis of α -Mangostin (α -MG) xanthone analogues and their *in vitro* antibacterial activity assessment against several *S. aureus* strains. Among all the synthesized xanthenes, α -MG (2) (Fig. 2) showed promising antibacterial activity against all tested *S. aureus* strains with the minimum inhibitory concentration (MIC) of 1-2 $\mu\text{g/mL}$ against all the tested *S. aureus* strains [38].

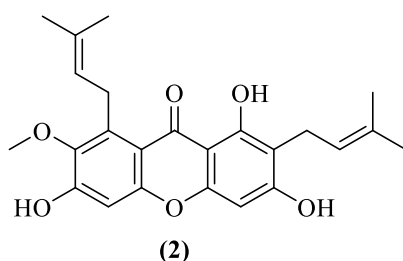


Fig. 2. The structure of α -MG.

Next, Ishaque et al. (2022) reported two isolated isomeric xanthone C-glycosides from an aqueous fraction of *Dryopteris ramose* and their antibacterial properties against several bacterial strains, including *S. aureus*. Based on the results, the MIC value of Isomangiferin (3) against *S. aureus* was 125 $\mu\text{g/mL}$, which was similar to the positive control, Cefixime [39].

Moreover, Wang et al. (2017) described a novel xanthone dimer derivative, garmoxanthone (5), together with 6 known compounds and their antibacterial activity which were isolated from bark of *Garcinia mangostana*. These compounds were tested against two MRSA strains (ATCC 43300 and CGMCC 1.12409). Compounds (5) showed promising antibacterial activity against both MRSA strains, with an MIC value of 3.9 $\mu\text{g/mL}$ for both MRSA strains [41]. Thus, all the reported literature proves that the naturally isolated and synthesised xanthone compounds showed notable *in vitro* antibacterial activity against *Staphylococcus sp.*, suggesting their potential as a lead candidate for the development of anti-staphylococcal agents.

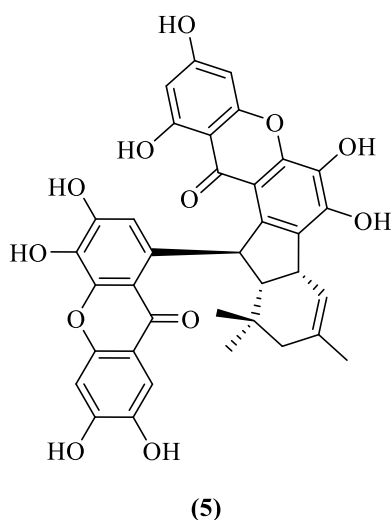


Fig. 5. The structure of garmoxanthone.

2.2 Genus *Salmonella*

For more than a century, *Salmonella* species have been known to be the culprit behind a wide range of ailments, including gastroenteritis (food poisoning), ranging from moderate to severe, typhoid (enteric fever), paratyphoid, bacteraemia, septicaemia, and a few related, long-term disorders (sequelae) [42]. The genus *Salmonella* was named in honour of American veterinary pathologist Daniel Elmer Salmon. In 1885, his research assistant, Theobald Smith, isolated a bacterium from pigs suffering from swine fever, initially termed *Bacterium suispestifer*. This organism was later renamed *Salmonella choleraesuis*, establishing the foundation for the genus *Salmonella* [43]. *Salmonella* are Gram-negative, facultatively anaerobic, rod-shaped bacteria measuring approximately 0.7–1.5 μm in width and 2.0–5.0 μm in length. They are typically motile due to peritrichous flagella, although some serovars, like *S. Gallinarum* and *S. Pullorum*, are non-motile [44]. Some of the significant biochemical traits of *Salmonella* are presented in Table 5.

Table 5: The biochemical characteristics of *Salmonella* [42].

Characteristic	Usual reaction
Catalase	+
Oxidase	-
Acid produced from lactose	-
Gas produced from glucose	+
Indole	-
Urease produced	-
Hydrogen sulphide produced from triple-sugar iron agar	+
Citrate utilised as sole carbon source	+
Methyl Red	+
Voges-Proskauer	-
Lysine decarboxylase	+
Ornithine decarboxylase	+

(+) positive reaction; (-) negative reaction

Salmonella spp. are major foodborne pathogens causing salmonellosis, which can lead to intestinal infection and, in severe cases, systemic complications [45]. High-risk groups include children, the elderly, and immunocompromised individuals. Due to its public health significance, *Salmonella* is monitored in high-risk foods like eggs, poultry, meat, seafood, and unpasteurized juices [46]. It is a key focus in food safety standards to ensure hazard control. Frequent outbreaks, especially linked to chicken and eggs in industrialized countries, highlight the need for strict monitoring and preventive actions throughout the food supply chain [47].

As reported in Ishaque et al. (2022), the antibacterial activity of two isolated xanthenes, mangiferin (MF) (6) (Fig. 6) and IsoMF (3) (Fig. 3) from *Dryopteris ramosa* against *Salmonella setubal* (ATCC 19196) was explained. The results demonstrated that (6) showed higher inhibition towards *S. setubal* (MIC = 125 $\mu\text{g}/\text{mL}$) compared to (3), with the MIC value of 250 $\mu\text{g}/\text{mL}$ [39].

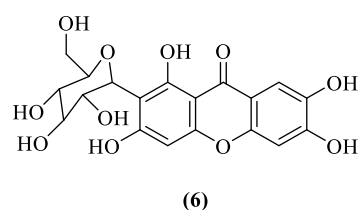


Fig. 6. The structure of mangiferin.

Besides, Boonnak et al. (2020) explained the antibacterial activity of the modified *tetra*-oxygenated xanthenes, which were isolated from the *Cratoxylum cochinchinense* and *G. mangostana* against *Salmonella typhi* strains. As described in the results, only (2) (Fig. 2) and (7) (Fig. 7) were promising inhibitors against the *S. typhi* strain with a MIC value of 18.75 $\mu\text{g}/\text{mL}$ [48].

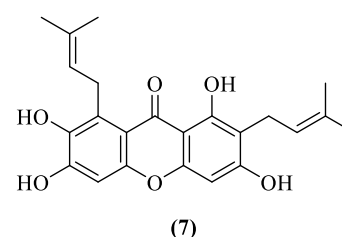


Fig. 7. The structure of modified *tetra*-oxygenated xanthenes.

Additionally, Auranwiwat et al. (2014) described the antibacterial activity of two novel *tetra*-oxygenated xanthenes, garcicowanones A (8) and B (9) (Fig. 8) against *S. typhimurium* (TISTR 292), which have been isolated from the immature fruits of *Garcinia cowa*. From the results, it was found that both the tested compounds inhibited *S. typhimurium* similarly, with the same MIC value, 64 $\mu\text{g}/\text{mL}$ [49]. Therefore, the existing literature demonstrates that both naturally derived and synthetically produced xanthone compounds exhibit significant *in vitro* antibacterial activity against *Salmonella* species, indicating their promise as lead candidates for the development of anti-salmonella agents.

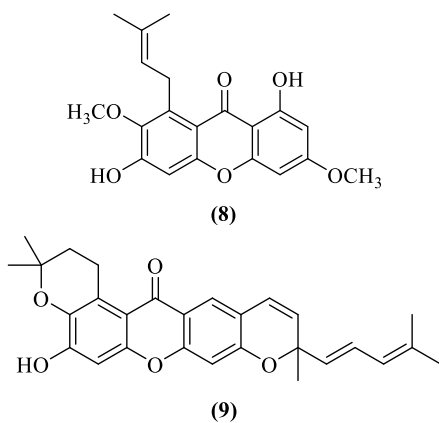


Fig. 8. The structure of garcicowanones A and B.

2.3 Genus *Escherichia*

Escherichia coli is a rod-shaped, gram-negative, non-spore-forming bacterium typically measuring 2.0–6.0 μm in length and 1.1–1.5 μm in width, though its shape can vary from cocci to elongated filaments [50]. It possesses peritrichous flagella that allow motility and is facultatively anaerobic, capable of producing acid and gas from lactose fermentation at both 37 °C and 44 °C [50,51]. Many strains are encapsulated with acidic polysaccharides and may produce extracellular slime, including colanic acid (M antigen) or K antigen variants. *E. coli* also forms hydrophobic fimbriae or pili with host-specific adhesion properties [52]. While most serogroups are harmless and part of the normal intestinal flora of warm-blooded animals, some pathogenic strains can cause severe diarrhea and, in rare cases, fatal illness [53]. Because *E. coli* is consistently found in feces, its presence in water is used as an indicator of fecal contamination, measured through the coliform index to assess water safety [54].

The majority of *E. coli* strains are capable of fermenting lactose, and when lactose is present, β -galactosidase activity causes the ortho-nitrophenyl- β -D-galactoside (ONPG) response to be positive [55]. The ability of the enzyme tryptophanase to convert the amino acid tryptophan into indole sets *E. coli* apart from other intestinal bacteria [56]. Table 6 shows the biochemical characteristics of *Escherichia*.

Table 6: The biochemical characteristics of *Escherichia* species [57].

Characteristics	Reaction
Motility	(+)
MacConkey growth	(+)
Mannitol fermentation	(+) usually gas
Lactose, 37°C	Acid (+), gas (+)
Lactose, 44°C	Acid (+), gas (+)
Adonitol	Seldom fermented
Inositol	Seldom fermented
Indole at 37°C	Usually produced
Indole at 37°C	Usually produced
Methyl red reaction	(+)
Voges-Proskauer reaction	(-)
Urea	No hydrolysis
Phenylalanine deamination	(-)
Kligler's H ₂ S (hydrogen sulphide) medium	No blackening
Møller's KCN (potassium cyanide) medium	No growth
Gluconate oxidation	(-)
Gelatin liquefaction	(-)

Glutamic acid decarboxylase	(+)
Lysine decarboxylase	(+)

Therefore, Ishaque et al. (2022) have documented the antibacterial potency of the two naturally occurring xanthenes, which were isolated from *Dryopteris ramose*, MF (6) (Fig. 6) and IsoMF (3) (Fig. 3), against *E. coli* (ATCC 25922) bacteria. The results stated that (3) inhibited the *E. coli* strains better compared to (6) since the MIC value of both was 250 and 500 $\mu\text{g/mL}$, respectively [39].

Likewise, Kurniawan et al. (2025) acknowledged the xanthone-fatty acid ester and its antimicrobial properties against *E. coli* (ATCC 27922). When the *E. coli* strain was exposed to compound (10) (Fig. 9), the MIC value (25.00 $\mu\text{g/mL}$) was lower than the other tested compounds, such as xanthyl laurate, indicating the strong antimicrobial activity according to the measured zones of inhibition (18.00 mm) [58].

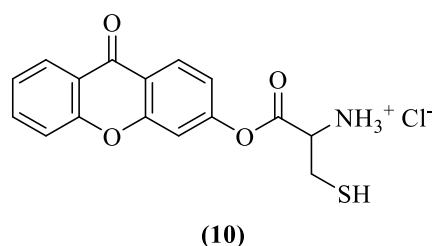


Fig. 9. The structure of xanthone-fatty acid ester

In the year of 2014, Auranwiwat et al. described the antibacterial activity against *E. coli* TISTR 780 of tetra-oxygenated xanthenes, which have been isolated from the immature fruits of *G. cowa*. Based on the result, only three compounds, (2) (Fig. 2), (11), and (12) (Fig. 10) exhibited the *E. coli* bacteria with significant activity with the MIC value of 64 $\mu\text{g/mL}$ [49].

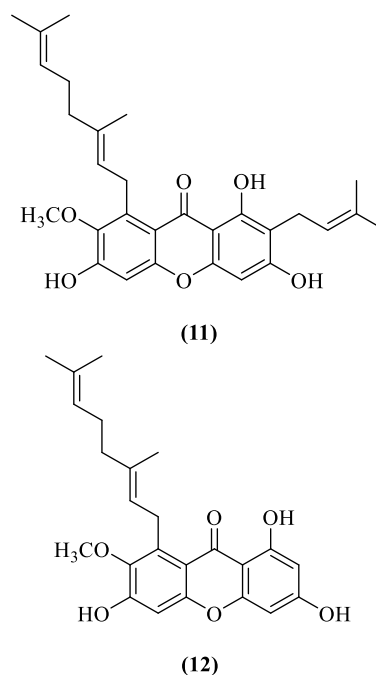


Fig. 10. The structure of tetra-oxygenated xanthenes

Additionally, Siridechakorn et al. (2012) also reported the antibacterial activity of the naturally isolated

xanthenes against *E. coli* TISTR 780, which was obtained from the stem barks of *G. cowa*. As mentioned in the results, it was found that compound (13) (Fig. 11) showed potent antibacterial activity with the MIC value of 64 µg/mL [59]. Research findings indicate that both natural and synthetic xanthone derivatives possess notable in vitro antibacterial activity against *Escherichia*, making them attractive prospects for the development of drugs for inhibiting the *Escherichia coli* bacteria.

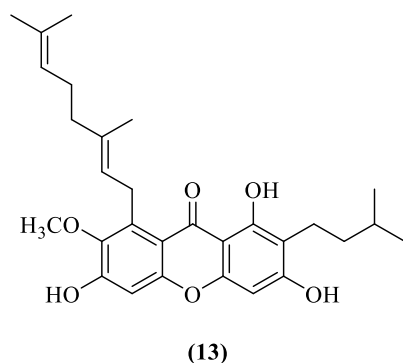


Fig. 11. The structure of isolated xanthone stem barks of *G. cowa*

3. CONCLUSION

This review highlights the antibacterial potential of a wide range of novel and known xanthone compounds, derived either from natural plant sources or through various synthetic methods. It provides an overview of significant xanthone derivatives reported over the past two decades, focusing on their antimicrobial activity against pathogenic bacterial strains, particularly those responsible for serious and contagious human infections. While the current findings are promising, they underscore the need for further in vivo studies to validate the efficacy and safety of these compounds for therapeutic use. Overall, this review aims to support the ongoing search for new antibacterial agents by offering insights into the potential of xanthenes as a foundation for drug development from both natural and synthetic origins.

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