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Review Article

Green Synthesis of Chromene Derivatives with Anti-Microbial Activity: A Review

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ABSTRACT

Around the world, antimicrobial resistance (AMR) is posing a significant threat to numerous lives. It is therefore essential to develop effective techniques to counteract the ill effects of AMR. These challenges are being met with efforts from drug discovery teams by synthesizing novel antimicrobials with improved activity against the resistant microorganisms. However, of late, there has been a great emphasis on the synthesis of pharmaceuticals by environment friendly and green approaches. Chromene is a privileged structure exhibiting varied biological activities including antimicrobial activity. This article reviews various green syntheses methods for the preparation of chromene derivatives as potential antimicrobial agents. These syntheses include processes including various catalysts such as ionic liquids, nanoparticles, biocatalysts and other catalysts derived from agriculture, animal husbandry, horticulture and poultry. The development of green syntheses methods for a privilege structure like chromenes offers a much-needed boost in the fight against AMR by providing chemical leads without impacting the environment.

INTRODUCTION

The development and rapid surge of antimicrobial resistance (AMR) is a major challenge to public health today. Drugs that were once successful in eliminating microbes such as viruses, fungi, and bacteria become ineffective in eliminating these pathogens, this phenomenon is called as antimicrobial resistance (AMR). Annually AMR has been responsible for millions of fatalities worldwide.[1] These events have compelled the healthcare authorities to initiate required actions to address these challenges and recommend suitable diagnostic methods.[2–5] These measures will ensure the right activities in terms of prevention and treatment to reduce the danger of AMR. Infections that were once easily curable, such as pneumonia, tuberculosis, and urinary tract infections, have become more difficult to treat due to resistant strains, resulting in prolonged illnesses and higher death rates.[5] Additionally, resistant infections require stronger and more expensive antibiotics, leading to longer hospital stays and increased

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financial burdens on both healthcare systems and patients. The spread of resistant microbes, commonly referred to as "superbugs," further complicates the issue, as these pathogens can quickly transmit within hospitals and communities. For example, *Methicillin-resistant Staphylococcus aureus* (MRSA) spreads rapidly, making outbreaks challenging to control.[6] AMR also endangers the success of critical medical operations that depend on good antibiotics to avoid infections include organ transplants, operations and cancer therapies. As resistance continues to rise, treatment options become increasingly limited, forcing physicians to resort to older, more toxic antibiotics with severe side effects, further complicating patient care.[7,8]

Mechanisms of development of antimicrobial resistance

Microorganisms acquire resistance by multiple mechanisms, including:

1. Enzymatic Drug Inactivation: Certain bacteria make enzymes that break down or alter antimicrobial drugs so they are ineffective. For instance, beta-lactamases degrade beta-lactam antibiotics such as penicillin and cephalosporins. [9]
2. Alteration of Drug Targets: Bacteria mutate or alter target sites, so antibiotics cannot bind effectively. Mutations in *Streptococcus pneumoniae* change penicillin-binding proteins, decreasing drug effectiveness. [10]
3. Efflux Pumps: Certain bacteria create efflux pumps that actively remove antibiotics from the cell before they are able to engage their target. This system is prevalent in *Pseudomonas aeruginosa* and *Escherichia coli*. [11]
4. Reduced Permeability: Sometimes bacteria modify their outer membrane or cell membranes to prevent entry of antimicrobial agents, and this usually occurs with Gram-negative bacteria such as *Klebsiella pneumoniae*.
5. Bypassing Metabolic Pathways: Some bacteria develop alternative metabolic pathways to bypass the inhibited step. Example: Sulfonamide-resistant bacteria acquire genes that allow folic acid synthesis despite sulfonamide inhibition.[12]

6. Genetic Mechanisms of Resistance:

a) Mutation: Spontaneous mutations in chromosomal genes can lead to opposition. For instance, bacterial mutations in the rpoB protein provide resistance to rifampin.[13]
b) Bacteria can obtain resistance genes from other bacteria through a process known as horizontal gene transfer, or HGT. Conjugation is the process by which plasmids—small, circular DNA molecules—carrying resistance genes are transferred from one cell to another.[14]
c) Transformation: Free DNA fragments from the surroundings are taken up and integrated into the DNA of bacteria.[15]
d) Transduction: the transfer of resistance genes by bacteriophages, which are bacterial infection viruses.

Chromenes

Chromenes are heterocycles with fused rings of pyran and benzene and may also be considered as derivatives of naturally occurring coumarins. Natural and synthetic molecules possessing chromene nucleus exhibit varied bioactivity.[16] Chromene derivatives has a wide variety of biological actions, which makes them excellent options for developing new drugs. They have demonstrated significant anticancer activity by inhibiting cancer cell proliferation, inducing apoptosis and targeting specific cancer pathways. For example, 2-Amino-4*H*-chromene derivatives have exhibited cytotoxic effects against various cancer cell lines.[17] Additionally, chromenes possess antimicrobial activity, acting as potential agents against bacterial and fungal infections. Studies have highlighted the efficacy of 4*H*-chromene derivatives against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*. The anti-inflammatory characteristics develop from the ability to reduce pro-inflammatory enzymes like cyclooxygenase (COX) and

lipoxygenase, with flavonoids—naturally occurring chromenes—being particularly potent in reducing inflammation.[18] Chromenes also exhibit ability to scavenge free radicals thereby mitigating oxidative stress, linked to aging and chronic diseases. For instance, 2*H*-chromene derivatives effectively neutralize reactive oxygen species.[19] Furthermore, some chromene derivatives have demonstrated antiviral activity, showing promise against viruses such as HIV, hepatitis, and influenza by inhibiting viral replication. Flavonoid-derived chromenes, for example, possess anti-HIV properties by targeting viral enzymes. In the field of neurodegenerative diseases, chromene derivatives have shown neuroprotective activity, offering potential treatments for conditions like Parkinson's and Alzheimer's disorders via regulating neurotransmitter levels and preventing neuronal damage.[20] Lastly, chromenes have also been recognized for their antidiabetic activity, functioning as α-glucosidase inhibitors or enhancing insulin secretion to regulate blood glucose levels. Natural flavonoid chromenes, in particular, have demonstrated hypoglycemic effects in diabetic models. Given their broad-spectrum biological activities, chromene derivatives continue to attract attention as promising therapeutic agents.[21]

Antimicrobial Activity of Chromene Derivatives

Chromene derivatives exhibit superior broad-spectrum antimicrobial activity, against both Gram-positive and -negative bacteria, fungi, and few viruses. They exert their action via varied mechanisms such as the inhibition of essential bacterial enzymes such as DNA gyrase and topoisomerases, hampering DNA replication and cell division. Additionally, they can break bacterial membranes, causing cell lysis and death. These diverse mechanisms contribute to their strong antimicrobial potential, making them promising candidates for drug development.[22] Chromene derivatives exhibit antimicrobial activity by a number of methods, such as the inhibition of the production of proteins and nucleic acids. They have shown effectiveness against Methicillin-resistant *Staphylococcus aureus* (MRSA) and other drug-resistant strains of *Escherichia coli*, and *Pseudomonas aeruginosa*, making them valuable in the fight against resistant infections. These compounds are found in both natural sources, such as flavonoids and coumarins, as well as synthetic 2*H*-chromene derivatives. Additionally, they demonstrate synergistic effects when combined with existing antibiotics, enhancing their therapeutic efficacy. Given their potent antimicrobial properties and selectivity, chromene derivatives hold significant promise for drug development, offering potential leads for new, more effective antimicrobial agents.[23]

Green Synthesis

The demand for environmentally sustainable practices has resulted in the development of green synthesis, which aligns with the green chemistry concepts.[24] These principles advocate the use of natural energy sources and the decrease in formation of polluting substances and the enhancement of reaction efficiency. Traditional synthetic methods often involve toxic reagents, excessive solvent usage, and significant waste generation, making them less favorable in today's environmentally conscious world.[25]

The following are the salient features of green syntheses:

i) Prevention of Waste: Avoiding waste generation is more efficient than treating waste after production.[26]

ii) Atom Economy: Maximizing the incorporation of starting materials into the final product minimizes waste.[27]

iii) Use of Renewable Feedstock**s**: Biomass, plant extracts, and agricultural waste serve as eco-friendly raw materials.[28]

iv) Biocatalysis: Biocatalysts and reusable catalysts enhance reaction efficiency and selectivity.[29]

v) Energy Efficiency: Solvent-free reactions by dry milling, microwave or ultrasonication may reduce energy consumption compared to traditional prolonged heating methods.[30]

Green synthesis refers to the development and use of chemical processes which follow to the principles of green chemistry by using renewable materials, the reduction of waste, and reduced energy consumption. To create safer and more environmentally friendly chemical products, these guidelines facilitate waste prevention, the use of non-toxic substances, and the optimization of atom economy. Green chemistry principles have revolutionized drug synthesis by minimizing toxic intermediates.[31] Ibuprofen synthesis via catalytic hydrogenation exemplifies an efficient and eco-friendly approach.[32] Green synthesis plays a crucial role in fabricating nanostructures of metal and metal oxide, which have applications in medicine, electronics, and catalysis. Biosynthesized nanoparticles exhibit excellent biocompatibility and minimal toxicity.[33] Environmentally benign pesticides and fertilizers have been developed through green synthetic methods, reducing the impact on ecosystems.[24] Biodegradable polymers, synthesized using renewable monomers, offer sustainable alternatives to petroleum-based plastics, aiding in waste reduction.[34]

Synthesis of Chromenes

Synthesis of chromene derivatives has been widely used as a model reaction for the application of green chemistry. The reason for this is that it is a relatively simple multi-component reaction between an aldehyde, an active methylene compound and a phenol. Mechanistically, the reaction is a cascade reaction composed of a Knovanagel condensation followed by a Micheal-type addition.[35–37]

Reaction:

Figure 1: General reaction scheme for synthesis of chromene derivatives

Synthesis of chromenes, a group of compounds with enormous biological activity as well as utility in materials chemistry, agrochemicals, and pharmaceuticals, has of late received enormous attention. The toxic by-products and hazardous reagents employed during conventional synthetic operations pose environmental concerns. Consequently, researchers are interested in exploring eco-friendly synthesis protocols that yield chromenes from renewable agricultural waste products as a reliable resource. The advantages of using agricultural by-products in the synthesis of chromene are emphasized in this review, which also highlights the advancements in this area. A vast and untapped resource is agricultural waste, which consists of crop, fruit, and vegetable leftovers. Utilizing these materials in chemical synthesis resolves issues of waste management and adheres to green chemistry principles. Scientists can lessen the impact that chemical processes have on the environment and their dependence on fossil fuels by employing renewable feedstocks. Agricultural residues can make processes that would otherwise require harsh conditions or toxic chemicals possible by serving

as a substrate for the production of chromenes or as a source of natural catalysts.

Reported methods for the green synthesis of Chromene Derivatives

A study by Shinde et. al. focused on Bael Fruit Extract (BFE) wherein the authors used a simple, energy efficient approach to synthesize 4*H*-benzochromenes and 4*H*-chromenes from natural sources.[38] Additionally, because of their enormous natural abundance, their production may be less costly. It is commonly acknowledged that there is an urgent need to provide sustainable and environmentally friendly methods for using natural "feedstocks" in chemical synthesis as a substitute for conventional metal-based catalysts or hazardous organic solvents. Here, the researchers highlighted BFE-catalyst as a very efficient and sustainable catalyst. A study by Kantharaju et. al.; focused on use of water extract of ash derived from waste lemon fruit shell.[39] This natural catalyst was used synthesize 2-amino-4*H* chromenes Chromene derivatives have several applications, including pigments, biological activity, biodegradable agrochemicals, and cosmetics. Various 2-amino-4*H*-benzopyrans were synthesized by a one-pot reaction of aromatic aldehyde, malononitrile, and resorcinol/naphthol using the green catalyst and water as solvent. The primary advantages of the method were green catalyst, benign solvent (water) and gentle reaction conditions. Another study by Gadhave et al.; focused on the usage of chicken egg shell waste as a catalyst for synthesis of chromene derivatives.[40] The authors used chicken eggshell waste as a catalyst for generating substituted 2-amino-4*H*-chromene compounds without the need for solvents. The positive characteristics of the present method include short reaction time, catalyst reusability, and reaction without solvent with great yields. Further, chicken eggshell waste can be utilized to produce biocellulose tissue, ultraviolet protectants, and other medical applications.[41]

In another study by Patel et.al.; solvent-free synthesis was employed as an environmentally friendly approach for the preparation of chromene derivatives, eliminating the need for harmful organic solvents.[42] This method, as demonstrated relied on thermal or microwave-assisted conditions, leading to high product yields with significantly reduced reaction times. By avoiding toxic solvents, this technique not only enhanced the sustainability of chemical processes but also minimized waste generation, making it a highly green and effective alternative for the synthesis of chromenes. As highlighted by Seth et. al.; biocatalysis and enzyme-mediated synthesis offer an efficient and sustainable method for producing chromene derivatives utilizing natural catalysts such as enzymes and microorganisms.[43] This method operated under mild reaction conditions, ensuring high enantioselectivity while significantly reducing environmental pollution. The use of biocatalysts not only enhanced reaction specificity but also eliminated the need for harsh chemicals, making it a more sustainable and environment friendly process in organic synthesis. The development of environmentally responsive and sustainable synthesis processes for chromene derivatives has been of particular interest in recent years. Green chemistry protocols seek to mitigate environmental damage through the reduction of toxic reagents, harmful solvents, and energy usage. Green methods often lead to improved atom economy, which reduces waste by incorporating more of the raw materials into the finished product and lowering production costs.[27] Various green processes developed for synthesis of chromene derivatives have been summarized in **Table1**.

Table 1: Summary of various published green processes for the synthesis of chromene derivatives.

Sr no.	Green Catalyst	Reference	Summary
1.	Solvent-Free Synthesis (SFS)	[44]	Solvent-free reactions have also proven to be a green method for chromene synthesis. Typically, thermal or microwave conditions are used to conduct these reactions with high yields and low reaction times
2.	Bael Fruit Extract (BFE)	[38]	A simple, green, and energy-efficient process for synthesizing using natural sources to produce 4*H*-benzochromenes and 4*H*-chromenes.
3.	Water extract of lemon fruit shell ash	[39]	This study used agricultural waste as a natural catalyst to synthesize 2-amino-4*H*-chromene using a green procedure.
4.	Water extract of banana peel (WEB)	[39]	WEB was used to synthesize derivatives that showed good activity against 1 gram positive and 3-gram negative pathogens.
5.	Ionic Liquid-Based Synthesis (ILS)	[45]	Ionic liquids were used as both catalysts and solvents in chromene synthesis, yielding good results with minimal waste generation
6.	Chicken Egg Shell Waste	[40,41]	The study utilized chicken eggshell waste as a catalyst in synthesizing chromene derivatives.
7.	Mechanochemical Synthesis	[46]	Mechanochemistry - allows effective chromene synthesis with little waste generation and reduced energy consumption
8.	Deep Eutectic Solvents (DES)	[47]	DES, which consist of a combination of hydrogen bond donors and acceptors, have been found to be non-toxic and biodegradable substitutes for traditional solvents. These solvents allow chromene synthesis under mild conditions with high recyclability and selectivity
9.	Biocatalysis and Enzyme-Mediated Synthesis	[48]	Biocatalysis involves the use of natural catalysts like enzymes and microorganisms as it proceeds under mild conditions, resulting in high enantioselectivity and less environmental pollution

CONCLUSION:

AMR is a significant public health issue that demands immediate action, such as prudent use of antibiotics, improved infection control, and research on new therapies. Without concerted international action, the world may be heading towards a future where infections become untreatable, and there is a public health crisis. Chromene derivatives have diverse biological activities and are of interest in drug discovery. Continued studies on their mechanisms and structure-activity relationships can result in the creation of new therapeutic agents for many diseases. Green synthesis routes for chromene derivatives provide cost-effective, environmentally friendly, and sustainable alternatives to conventional routes. In addition to improving reaction efficiency, these routes also lead to the production of greener pharmaceuticals and materials.

Green synthesis of chromenes from agricultural waste is a promising route for sustainable chemical production. Through the utilization of renewable resources, scientists can design green processes that not only lower the environmental footprint but also aid in waste valorization. As interest in sustainable chemistry grows, continued exploration of agricultural waste as a chromene synthesis feedstock will be critical in pushing the boundaries of both green chemistry and circular economy. This review attempts to provide an all-inclusive view of the recent developments in this area, discussing major methodologies, challenges, and future work areas for sustainable synthesis.

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