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Review Article

Diversity of chemical compounds and pharmacological properties of *Cymbopogon citratus* (DC) Stapf: Richness and variation of flavonoids with a wide range of biological effects

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ABSTRACT

Cymbopogon citratus (DC) Stapf (lemongrass) is widely used in both traditional and modern medicine for the management of various ailments, owing to its chemical composition, particularly its flavonoid content. This review examines the diversity, variation, and extraction methods of these bioactive compounds, which vary depending on the plant parts used, extraction techniques, and environmental conditions. Key flavonoids identified, such as kaempferol, rutin, and quercetin, demonstrate significant pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and cardioprotective effects. They are effective against harmful pathogens, including bacteria (*e.g.*, *Vibrio*, *Salmonella*, *Staphylococcus*) and fungi (*e.g.*, *Candida*, *Fusarium*). These findings support the application of *Cymbopogon citratus* in both traditional and modern medicinal practices. However, further research is necessary to investigate the molecular mechanisms underlying the therapeutic effects of its flavonoids.

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1. Introduction

Medicinal and herbal plants are rich in a diverse array of flavonoids—such as quercetin, kaempferol, and apigenin—that demonstrate potent antioxidant, anti-inflammatory, and anticancer properties. These bioactive compounds possess significant therapeutic potential, aiding in the prevention and treatment of chronic diseases, including cardiovascular disorders, diabetes, and neurodegenerative conditions (Akinwunmi, 2020; Bailly, 2021; Thagriki, 2022). Therefore, it is logical to suggest that further research into their mechanisms of action could unveil new opportunities for natural, plant-based medicine.

Lemongrass, scientifically known as *Cymbopogon citratus* (DC) Stapf, is commonly referred to as citronella. It belongs to the Gramineae family, and its name derives from the Greek words 'kyme' meaning wave and 'pogon' meaning beard (Magotra et al., 2021a). Various populations widely utilize lemongrass as a natural remedy for debilitating conditions, including hypertension, inflammation, and diabetes (Carbajal et al., 1989; Salaria et al., 2021). Citronella has garnered significant interest due to its diverse pharmacological effects. Increasing scientific evidence underscores the importance of this plant in the food, nutraceutical, and cosmetic industries as a rich source of bioactive compounds (Martins et al., 2021). Additionally, lemongrass plays a vital economic role by supporting rural cooperatives in cultivating the plant, thereby creating employment opportunities for rural communities in Morocco.

Many cultures have relied on medicinal plants as the foundation of traditional medicine, and these plants represent a promising source of active compounds for new drug discovery with fewer adverse effects (Miri et al., 2022; Saini et al., 2022). Flavonoids are among the most intriguing groups of bioactive components found

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in medicinal herbs, offering a diverse array of benefits for human health, including antiproliferative, antioxidant, antimicrobial, and antimetabolic disorder properties (Mohammadhosseini et al., 2019; Mechchate et al., 2021; Mohammadhosseini et al., 2021; Hirazawa et al., 2022; Messaoudi et al., 2022; Kianasab et al., 2024). In this context, a new formulation for diabetes treatment was evaluated as a multi-target antidiabetic drug using a combination of plant flavonoids, including epicatechin, rutin, and catechin. This formulation demonstrated significant antihyperglycemic potential, validating its use as an alternative to conventional medications (Mechchate et al., 2021). Flavonoid drug discovery is a vibrant research field targeting multiple bodily functions. As an excellent approach, synergistic combinations of flavonoids proved their ability to eradicate fungi or stop the recurrence of fungal diseases (Al Aboody and Mickymaray, 2020), new anticancer drugs (Chahar et al., 2011), antiangiogenic combination (Touil et al., 2011; Zhou et al., 2021), inhibitors of cytomegalovirus (Cotin et al., 2012) and antiglioblastoma drugs (Zhai et al., 2021). The combination of three flavonoids (isoorientin, swertiajaponin, and isoorientin 2″-orhamnoside) isolated from *C. citractus* exhibited a remarkable inhibitory effect on malondialdehyde-thiobarbituric acid and attenuates LDL oxidation (Orrego et al., 2009). Furthermore, traditional ayurvedic medicine based on polyherbal mixtures such as *Raktavardhak kadha* provides an important antianemic potential attenuating deleterious damages induced in organs interestingly bone marrow thanks to its flavonoids content (Sheth et al., 2021).

Within this context, the present review aims to catalog the flavonoid compounds found in lemongrass and their scientifically evaluated pharmacological properties. First, we assessed the chemical composition, focusing on the concentration of flavonoids and their qualitative and quantitative variations. Second, we examined the pharmacological properties, including antioxidant, antimicrobial, antidiabetic, anti-inflammatory, and cardioprotective effects of these flavonoids. In this paper, we correlate the variation of flavonoids with extraction methods, plant material, and climatic conditions. Furthermore, we relate the pharmacological properties to the diversity and variation of flavonoids. This information is invaluable for future research and the traditional management of various diseases.

2. Methodology

Different search engines were utilized to gather data for the current review, including Scopus, Google Scholar, PubMed, and ScienceDirect. The search was conducted using the following keywords: *Cymbopogon citratus* (DC) Stapf (Fig. 1), beneficial properties of lemongrass, flavonoids, pharmacological effects, and phytochemical compounds associated with *C. citratus*. A total of 195 downloaded articles were assessed for their relevance and novelty, resulting in the selection of 127 articles that were used to structure the present manuscript.

3. Variation of chemical composition and quantity of flavonoids

C. citratus, commonly known as lemongrass, is widely recognized as one of the most sought-after plant species globally due to its extensive distribution and diverse range of applications. Various extracts of *C. citratus* have demonstrated a variety of pharmacological effects, which are generally attributed to the plant's chemical composition. In recent decades, numerous studies have investigated the chemical constituents of *C. citratus*. The results indicate that the chemical composition of the extracts and essential oils of *C. citratus* varies significantly due to several factors, including geographical origin, variety, age, the parts of the plant used, extraction techniques, and inherent plant characteristics. Among the various chemical classes identified in the isolated components of *C. citratus*, sterols, tannins, terpenoids, flavonoids, sugars, ketones, and phenols can be inferred. Soliman et al. (2017) investigated the chemical composition of essential oil from Egyptian lemongrass (*C. citratus*) in North Africa using gas chromatography (GC) analysis. The results revealed 22 chemical compounds, accounting for 97.83% of the essential oil composition, which included monoterpenes (96.37%) and trace amounts of diterpenes and sesquiterpenes. Citral was the predominant constituent, comprising 79.69% of the essential oil, and was further divided into two primary compounds: 42.86% citral A (geranial) and 39.83% citral B (neral). Additionally, the total phenolic content was measured at 7.55 ± 0.49 mg GAE/g, compared to a total flavonoid content of 1.96 ± 0.56 (mg CE/g). Recently, Zaman et al. (2022) evaluated the chemical composition of the essential oil of leaves from *C. citratus* (Asia, Malaysia) using gas chromatography-flame ionization detector (GC-FID) and gas chromatography-mass spectrometry. The authors also investigated the effect of the post-harvest drying period on the yield and chemicals. In the results, twenty-one components were identified, representing 97.53% of the total oil components. For both fresh and dried samples, α- and β-citral were the main constituents, followed by myrcene. The primary ingredients of the *C. citratus* essential oil were not significantly affected by drying times. However, the amounts of monoterpenes were significantly impacted by the post-harvest drying times. The chemical composition and quantity of flavonoids in samples of *C. citratus* vary significantly based on the plant parts used, climatic conditions, geographical location, and extraction methods (Table 1). Mirzaei et al. (2020) investigated the variation of flavonoids in Iranian samples of *C. citratus* subjected to water stress at four levels: 100% field capacity, 75%, 50%, and 25%, along with inoculation by plant growth-promoting rhizobacteria (PGPR) at three levels: uninoculated, inoculated with *Pseudomonas* sp. and inoculated with *Azotobacter* sp. The results indicated that total flavonoid content (TFC) ranged from 6.55 to 11.15 mg GA/g dry weight (DW). Compared to uninoculated plants, *Pseudomonas* and *Azotobacter* increased the maximum TFC by 6% and

18%, respectively, while a 50% field capacity resulted in a 42% increase in TFC compared to 100% field capacity. In Ghana, Godwin et al. (2014) examined the flavonoid properties in cold and hot percolations of lemongrass. The total flavonoid concentration ranged from 6.9 to 11.3 µg/g quercetin equivalent (QE) for cold percolation and from 6.9 to 12.9 µg/g QE on a dry weight basis for hot percolation. In Nigeria, the total flavonoid content (TFC) of the edible stalks of fresh *C. citratus* ranged from 0.2 to 0.3 mg quercetin equivalent/g (Oboh et al., 2010). Boeira et al. (2018) evaluated the flavonoid content in the leaves of *C. citratus* harvested in the rural area of Santa Maria, Brazil, using conventional and ultrasound extraction methods. The study was conducted at three temperature levels: 20 °C, 40 °C, and 60 °C. The results showed that total flavonoid content was significantly higher with the conventional method compared to the ultrasound technique. In the conventional approach, TFC values were 13.99 ± 1.52, 13.53 ± 1.40, and 13.42 ± 0.27 (mgQE/g) under 20 °C, 40 °C, and 60 °C, respectively. In contrast, the ultrasound method yielded TFC values of 10.33 ± 1.16, 11.46 ± 0.64, and 12.09 ± 0.48 mg QE/g at the same temperatures. In Europe, Costa et al. (2016b) examined the influence of harvest date and material quality on the flavonoid content of *C. citratus* infusion. The results indicated that flavonoid levels significantly increased with sun exposure. Similarly, total flavonoids showed a statistically significant decline in August (4.81%) compared to June (6.63%) and September (6.62%) when harvested.

4. Citronelle flavonoids

C. citratus is a medicinal herb that contains a wide array of bioactive compounds in varying concentrations (Tavares et al., 2015; Costa et al., 2016a; Kouassi et al., 2017; Madi et al., 2020; Sousa et al., 2021). Phytochemical analysis is the initial step in establishing a clear mechanism of action that may be responsible for the diverse pharmacological properties of *C. citratus*. Recently, flavonoids have garnered significant interest due to their biological properties, and their application in drug combinations has begun (Mechchate et al., 2021). The most abundant flavonoids in *C. citratus* include luteolin and apigenin derivatives (Fig. 2), such as 6-C-hexosyl-8-C-pentosyl luteolin, 6-C-pentosyl-8-C-hexosyl apigenin, 6-C-glucosyl luteolin, 7-*O*-glucosyl luteolin, 6-C-pentosyl luteolin, and X″-*O*-rhamnosyl C-(6-deoxy-pento-hexos-ulosyl) luteolin (Figueirinha et al., 2008).

Glycosylation is a common modification of flavonoids during the biosynthesis process, which is responsible for the enhancement of natural glucoside components with significant properties (Hyung Ko et al., 2006). Flavonoids are well-known for their antioxidant potential, and previous studies have indicated that luteolin and its derivatives exhibit numerous pharmaceutical activities, including antioxidant, anti-inflammatory, antimicrobial, anti-aging, and cardioprotective effects (Manzoor et al., 2019). Conversely, some studies have reported that luteolin and its derivatives may disrupt the endocrine system and act as antagonists of progesterone (Harwood et al., 2007; Nordeen et al., 2013). The beneficial properties of various flavonoid compounds found in *C. citratus* are outlined in Table 2.

5. Pharmacological and biological properties

5.1. Antioxidant effect

Oxidative stress, characterized by the overproduction of reactive oxygen species (ROS), is considered a pathological condition. ROS play a crucial role in various physiological functions, including cellular signaling, cell differentiation, and apoptosis under normal conditions (Kaludercic et al., 2014). While ROS are essential for physiological processes, their excessive production is primarily responsible for organ damage (Tauffenberger and Magistretti, 2021). Mitigating the harmful effects of ROS is a key objective of prevention strategies that utilize natural products with high antioxidant potential (Ousaaid et al., 2022). Phytochemical exploration of *C. citratus* discovered the occurrence of a broad range of bio-compounds that have an interesting antioxidant ability viz caffeic acid, apigenin, *p*-coumaric acid, ferulic acid, luteolin, and their derivatives (Sousa et al., 2021). Studies in the laboratory have evaluated the ability of *C. citratus* to lowering and attenuate toxicities induced by cisplatin through suppression of Bid and Bcl2 gene expression (Caner et al., 2021). In an *in vitro* study conducted by Figueirinha et al. (2008), various extracts, including infusions and decoctions from the leaves of *C. citratus* were evaluated for their antiradical activity using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test. Among these, the infusion preparation exhibited the strongest activity against the free radical DPPH. The same study also confirmed the presence of different flavonoids such as flavonoid glycosides (Table 3), which may contribute to the antioxidant capacity of the extracts (Fig. 3) (Figueirinha et al., 2008). In addition, this ability was demonstrated through in vivo testing of the effects of C. citratus administration at a dosage of 60 $mgkg^{-1}$ over one week. The results indicated that *C. citratus* extract inhibits the formation of micronuclei in both polychromatic and normochromatic erythrocytes induced by nickel chloride toxicity (Rabbani et al., 2006). It has also been well-documented that the addition of lemongrass aqueous extract to VERA cell cultures for 24 and 72 h at different concentrations did not alter cell viability, cytotoxicity, or the proliferation process (Pan et al., 2021). Furthermore, the presence of *C. citratus* extract reduced the oxidative stress induced by rotenone in VERA cells through decreasing ROS levels such as nitric oxide, superoxide, and lipid peroxidation (Pan et al., 2021). A study was undertaken *in vivo* model of diabetes mellitus induced by streptozotocin showed that the administration of citral as the main bio-compounds of *C. citratus* increases the total antioxidant capacity, endothelial nitric oxide synthase (eNOS), and paraoxonase 1 (PNO1) serum levels (Khosravi Bakhtiari et al., 2021). The diversity of *C. citratus* phytocompounds could be associated with either its ability to counteract free radicals *in vitro* or *in vivo* through synergistic effects in decreasing oxidative stress.

Fig. 1. The photograph of *Cymbopogon citratus* (DC) Stapf growing wild in Morocco.

Table 1
Variation of TFC in samples of *Cymbopogon citratus* (DC) Stapf depending on geographical area, extraction methods, used part, and conditions.

Continent	Countries	Conditions	Extract	Part	Method	TFC (mg GA/g DW)	References
Asia	Iran	Water stress	Essential oil	Entire plant	Aluminum chloride	6.55-11.15 (mg GA/g DW)	Mirzaei et al., 2020
Africa	Nigeria	Natural conditions	Cold and hot water extract	Edible stalks	Aluminium trichloride	0.2-0.3 mg quercetin equivalent/g	Oboh et al., 2010
	Ghana	Natural conditions	Cold and hot percolations	Entire plant	Cold and hot percolations	6.9-12.9 µg/g QE	Godwin et al., 2014
South America	Brazil	20 °C, 40 °C, and 60 °C	Extracts	Leaves	Conventional and ultrasound methods	10.33-13.99	Boeira et al., 2018
Europe	Portugal	Harvest date and material quality	Infusion	Dry leaves	Spectrophotometric methods	5-6.7%	Costa et al., 2016b

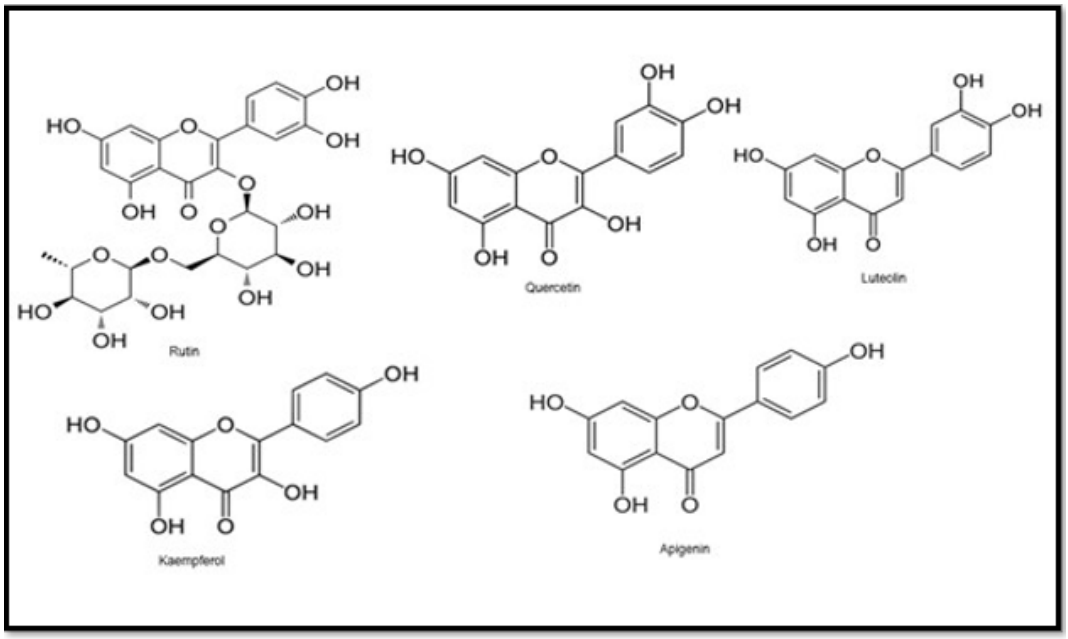

Fig. 2. Most flavonoid components recorded in *Cymbopgon citratus*.

Table 2
Flavonoid components detected in different extracts of *C. citratus*.

Extract	Technique	Material	Flavonoids compounds	Reference
Infusion	HPLC	Leaves	6-C-Pentosyl-8-C-hexosyl apigenin (mean of 3.73 ± 0.01%), 6-C-hexosyl-8-C-pentosyl luteolin (mean of 5.08 ± 0.01%), 2″-*O*-rhamnosyl isoorientin (mean of 15.1 ± 0.02%), 6-C-glucosyl luteolin (isoorientin) (2.34 ± 0.01%), X″-*O*-rhamnosyl C-(6-deoxy-pento-hexos-ulosyl) luteolin (mean of 19.1 ± 0.01%), 6-C-pentosyl-8-C-pentosyl luteolin (mean of 6.14 ± 0.01%), 7-*O*-glucosyl luteolin (19.5 ± 0.01%), 6-C-pentosyl-8-C-pentosyl luteolin (mean of 13.4 ± 0.02%) and 6-C-pentosyl luteolin (mean of19.3 ± 0.01%)	Figueirinha et al., 2008
Leaves infusion	HPLC	Leaves	Isoorientin (52.02-688.53 µg/mL), cynaroside (23.45-462.42 µg/mL), luteolin 7-oneohesperidoside (11.12-180.59 µg/mL), kurilensin A (26.48-535.69 µg/mL), and cassiaoccidentalin B (13.78-316.21 µg/mL)	Costa et al., 2016a
	HPLC	Leaves	6-C-Hexosyl-8-C-pentosyl luteolin, 6-C-pentosyl-8-Chexosyl apigenin, 6-C-hexosyl luteolin (isoorientin), 7-O-neohesperosyl luteolin, X″-*O*-rhamnosyl C-(6-deoxy-pentohexos-ulosyl) luteolin, 2″-*O*-rhamnosyl isoorientin, 6-C-pentosyl-8-C-deoxyhexosyl luteolin, and 6-C-pentosyl luteolin	Tavares et al., 2015; Sousa et al., 2021
Ethanol and methanol extracts	HPLC	Leaves	Rutin, quercetin, kaempferol	Kouassi et al., 2017
Aqueous extract	HPLC	Leaves	Quercetin (3.799%), rutin (1.843%), pyrogallol (0.362%), and apigenin (0.312%)	Méabed et al., 2018
Methanolic extract	UPLC	Leaves	Luteolin-*O*-hexosyl-C-hexoside, luteolin-6-C-glucosyl-8-C-arabinoside (carlinoside), luteolin-6-C-glucoside (isoorientin), luteolin-2″-*O*-deoxyhexosyl-6-C-hexoside (isoorientin-2″-orhamnoside), luteolin-C-pentosyl-*O*-hexoside-methyl ether, luteolin-6-C-pentosyl-8-C-pentoside, apigenin-2″-*O*-deoxyhexosyl-C-hexoside, apigenin-6-C-arabinosyl-8-C-glucoside (isoschaftoside), apigenin-*O*-hexosyl-C-deoxyhexoside, luteolin-2″-*O*-deoxyhexosyl-C-hexoside-methyl ether, luteolin-7-*O*-glucoside (cynaroside), luteolin-7-O-rhamnoglucoside (luteolin-7-oneohesperidoside), luteolin-2″-*O*-rhamnosyl-6-C-arabinoside (kurilensin A), luteolin-2″-*O*-rhamnosyl-6-C (cassiaoccidentalin B) (6-deoxy-ribo-hexos-3-ulosyl), and luteolin	Madi et al., 2020

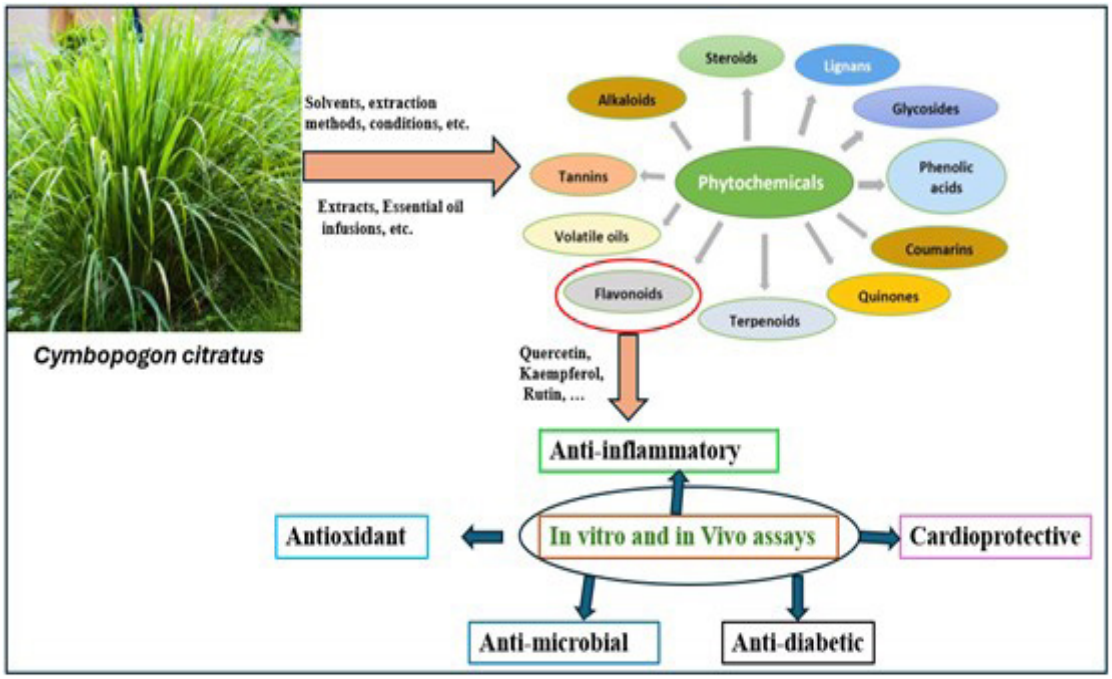

Fig. 3. Pharmacological properties of flavonoids from *C. citratus*.

Table 3
Pharmacological properties of *C. citratus*.

Antidiabetic effect				
Bioactive molecules	**Dose/Exposure route and duration of treatment**	**Models**	**Key Results/Involved Mechanisms**	**References**
Rutin	Orally for 30 days at 0, 25, and 50 mg kg^{-1} BW	Streptozotocin/Wistar rats	Prevent pancreatic β-cell destruction, ↑insulin secretion	Hasanein et al., 2020
	Take 10 milligrams kg^{-1} day orally for 28 days	Alloxan/Mice	Prevents hyperglycemia and acts synergistically with Catechin, Epicatechin	Mechchate et al., 2021
	Oral 90 mg kg^{-1} day for 10 weeks	Streptozotocin/Sprague-Dawley rats	Inhibition of polyol pathway, ↓lipid peroxidation, and ↓oxidative stress	Lu et al., 2018
Quercetin	Oral doses of 2.5, 7.5, 22.5, and 67.5 mg kg^{-1} every day for 14 days	Tamoxifen/Wistar rats	↓Blood glucose level and ↓liver, brain, intestine, and adipose butyrylcholinesterase activity	Silva et al., 2017
	lM, 10 lM, and 100 lMs during 3 or 24 h of incubation	L6 myoblasts cells	↑Glucose uptake in muscle cells by upregulating the AMPK pathway	Dhanya et al., 2014
	100 mg kg^{-1} every day for 15 days through oral	Streptozotocin/Wistar rats	Modulation of TXNIP/IRS-1/PI3K pathway, ↓hepatic TXNIP expression, ↑hepatic insulin sensitivity and ↑glucose uptake	Alkhalidy et al., 2018
Kaempferol	For 12 weeks, take 50 mg kg^{-1} day orally	Streptozotocin/Wistar rats	↑Hexokinase activity, ↓hepatic pyruvate carboxylase activity, ↓hepatic glucose production, and inhibits gluconeogenesis.	Alkhalidy et al., 2018
	Oral 200 mg kg^{-1} day for 14 days	Streptozotocin/male mice	↑ cAMP and Ca^{2+} intracellular levels and ↑GLP-1 and insulin release,	Sharma et al., 2020
	Oral of 200 mg kg^{-1}.Bwt/day, for 14 days	Streptozotocin/Wistar rats	↓abstaining glucose rates, ↑fasting insulin rates, and HOMA-β, ↓ROS, and MDA levels, stimulated GSH and SOD activities; and Upregulated the Nrf-2/HO-1 pathway	Alshehri, 2021
Apigenin	Oral 50 mg kg^{-1}.Bwt/day, for 45 day	Streptozotocin/Wistar rats	↑Insulin secretion, ↓fasting blood glucose, inhibition of advanced glycation end products (AGEs), and ↓aldose reductase (ALR) activity normalization of lipid profile parameters, prevent oxidative stress-induced hepato-nephrotoxicity.	Anandan and Urooj, 2021
	10 mg kg^{-1}.Bwt/day, by oral for 8 weeks.	High-fat diet/Mice	↓Body and epididymal fat weight, ↓fasting blood glucose, total cholesterol, and triglycerides levels. ↓Pro-inflammatory cytokines (TNF, IL-1β and IL-6	Gentile et al., 2018
	1.5 mg kg^{-1}/day, i.p for 28 days	Streptozotocin/Wistar rats	Enhances GLUT4 translocation in skeletal muscles, increases glucose uptake and down-regulates the cyclic ADP ribose hydrolase (CD38) expression	Hossain et al., 2014

Table 3
Continued

Bioactive molecules	Dose/Exposure route and duration of treatment	Models	Key Results/Involved Mechanisms	References
Isoorientin	5 weeks of 200 mg kg^{-1}.BW/day	Alloxan/Wistar rats	↓Level of blood glucose and improve markers of oxidative stress (MDA, CAT, SOD GSH, and GPx), up-regulation of NO levels.	Malik et al., 2019
	0.1, 1, 10, 50 µM isoorientin for 1 h	Tumor necrosis factor-α (TNF-α)-induced insulin resistance in murine 3T3-F442A cells	Enhances glucose uptake associated with modulation of PI3K/AKT pathway.	Poudel et al., 2015
	10, 5, 1, 0 µM, for 8 days	3T3-L1 cells	↓Lipid accumulation and insulin resistance by down-regulating the expression of adipogenesis transcriptional regulators including sterol regulatory element binding protein (SREBP)-1c, PPARγ, and CAAT/enhancer binding protein-α (C/EBPα)	
	15 mg kg^{-1} isoorientin (once a day) for 15 days	Streptozotocin /Sprague-Dawley rats	↓Fasting blood glucose concentration, ↓body weight, and depressed triglycerides (TG) and cholesterol levels	Sezik et al., 2005
Pyrogallol	2.5 mg kg^{-1}/ BW/day, (oral) for 4 weeks	High-fat diet/male mice	Improves lipid and glucose homeostasis via down-regulation of the Lox-1/PKC-α/MMP9 pathways.	Son et al., 2021
Cynaroside	50 mg kg^{-1}/ BW/day, (oral) for 15 days	Alloxan/male mice	↓Fasting blood glucose levels by modulating peroxisome proliferator-activated receptor gamma (PPAR-γ) signaling pathway	Van et al., 2022
Antioxidative effect				
Rutin	50 mg kg^{-1}/ BW, intraperitoneally 1h before reperfusion induction	ovarian ischemia-reperfusion /Wistar albino female rats	↓Blood MDA levels, ↓The interleukin 1 beta (IL-1b) expressions, cancer necrosis factor-alpha (TNF-a), and inhibits cyclooxygenase 2 (COX-2) activity; and ↑GSH activity	Nayki et al., 2018
	Oral 50 and 100 mg kg^{-1} Bw/day, for 8 days	Cisplatin/male albino Wistar rats	↓MDA, creatine kinase (CK), interleukin 1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and levels of troponin I in Blood, plasma and cardiac tissue	Topal et al., 2018
	Oral 50 mg kg-1 Bw/day, for 7 days	Lead acetate/Wistar rats	↑SOD, GPx, and CAT hepatic activities as compared to non-treated lead acetate groups	AlDrak et al., 2018
Quercetin	21 days of 50 mg kg^{-1}/day, i.p	alcohol-induced rat oxidative stress	↑GSH level, GP, GR, SOD, and CAT activity, ↓The expression of IL-1β, TNFα, and IL-6	Ince, 2020
	Oral 25 mg kg^{-1}.BW/day, for 21 days	Letrozole/male rats	Exhibits defensive effect against oxidative stress prompted by enhancing CAT, SOD, and GPX activities	Hong et al., 2018

Table 3
Continued

Bioactive molecules	Dose/Exposure route and duration of treatment	Models	Key Results/Involved Mechanisms	References
Kaempferol	6 weeks of 100 mg kg^{-1}/day, i.p.	Aorta banding/C57BL/6 mice	Down-regulates the JNK1/2 and ASK1/MAPK and signaling pathways of p38	Feng et al., 2017
	Oral 10 mg/ BW/day, for 8 weeks.	Streptozotocin/male mice	↓Nuclear factor-κB (NF-κB) nucleus translocation, ↑nuclear factor-erythroid 2 p45-related factor-2 (Nrf-2), ↓blood sugar levels and protects the heart against fibrosis	Chen et al., 2018
	Oral 10 mg kg^{-1}. BW/day, for 4 weeks	Ang II/male C57BL/6 mice	Modulates AMPK/Nrf2 signaling pathways and NF-kB/mitogen-activated protein kinase	Du et al., 2019
Luteolin	20 mg kg^{-1}. BW/day, (oral) for15 weeks	Streptozotocin /C57BL/6 mice	Modulates the expression levels of mRNA of NAD(P)H dehydrogenase (Quinone 1) (NQO-1) and HO-1 by triggering the Nrf2 antioxidant pathway and	Li et al., 2019
	200 and 100 mg kg^{-1} .bwt/day, (oral) for 28 days.	Bisphenol A/Wistar rats	↑GSH, ↑SOD ↑GPX activities, ↓MDA level, ↑Nrf2, and ↑HO-1 Expressions.	Alekhya Sita et al., 2019
	100 and 50 mg kg^{-1} .bwt/ day, (oral) for 15 days.	Doxorubicin/Wistar rats	↓Caspases-3, ↓lipid peroxidation, and caspases-9 activities, ↓hepatic and kidney damages, ↑CAT, SOD, GST, and GPX activities as well as ↑GSH and TSH levels in kidney and hepatic tissues. ↓Reactive oxygen/nitrogen species (RONS), ↓lipid peroxidation (LPO), and ↓xanthine oxidase (XO) in renal and hepatic organs	Owumi et al., 2021
Apigenin	Oral 500, 250, and 25 mg kg^{-1}. bwt/day, for 2 weeks	Doxorubicin/Male BALB/c mic	↑Non-enzymatic and enzymatic antioxidant rates and ↓oxidative stress biomarkers	Wu et al., 2021
	Oral 25 mg kg-1 .bwt/day, for 28 days	Nickel oxide nanoparticles/ Wistar rats	↓Renal and hepatic MDA and nickel (Ni) levels, ↑GSH and SOD activities of hepatic and renal tissues	Ali et al., 2021
	Oral 0.02, 0.01, and 0.005 g kg^{-1} .bwt/day, for 28 days	ethylene glycol/Wistar rats	↑SOD, CAT, GPX activities in kidney tissue and ↓lipid peroxidation in kidney, and prevents hepatic structure disorganization	Azimi et al., 2021
Isoorientin	Oral 40, 20, and 10 mg kg^{-1} bwt/ day, for 3 days	Lipopolysaccharide/male mice	Modulates Keap1/Nrf2-HO-1, NLRP3 signaling pathways	Zhang et al., 2022
	3 days of 50 mg kg^{-1} .bwt/day, i.p, orally	Cisplatin/C57BL/6 WT mice	Enhances Nrf2 translocation and ↑the expression of HO-1 and NQO1 and ↓the manifestation level of NOX4, thus reducing oxidative stress	Fan et al., 2020
Anti-inflammatory effect				

Table 3
Continued

Bioactive molecules	Dose/Exposure route and duration of treatment	Models	Key Results/Involved Mechanisms	References
Rutin	Oral 100 mg kg^{-1}. bwt/day, for 14 days	Unilateral ureteral obstruction/Wistar rats	Signaling pathways of TGF-β1/Smad3 and ↓NF-κB activation	Wang et al., 2016
	100 and 50 mg kg^{-1}. bwt/,i.p, for 7days	Methotrexate/Wistar rats	↓Immunoregulatory cytokines (IL-10, IL-2, and IL-4)	Gautam et al., 2016
Quercetin	Oral 1 mg kg^{-1}/day, for 15 days	Sulfate sodium/male BALB/c mice	Down-regulates NF-κB signaling pathway and inhibits inducible nitric oxide synthase expression	Comalada et al., 2005
	Oral 25 mg kg^{-1}/day, for 21 days	Lipopolysaccharide/BALB/c female mice	↓Nitric oxide (NO) production, interleukin-6 (Il-6) inducible NO synthase, and ↓translocation of nuclear factor-κB (i.e., NF-κB)	Lee et al., 2018
Kaempferol	Oral 4 and 2 mg kg^{-1}/.bwt/day, for 10 days	Aged Sprague-Dawley rats	↓IL-1β, IL-18, TNF-α, and IL-6 synthesis	Park et al., 2009
	Oral of 10 and 3 mg kg^{-1} mg kg-1/day, for 22 days	Airlines sensitive inflammatory model in mice	Down-regulates the nuclear transcription NF-κB signaling pathway in the lung of mice	Rogerio et al., 2010
Luteolin	Oral 20 and 10 mg kg^{-1}/day, for 4 weeks	Streptozotocin /Wistar rats	Inhibition of RIP140/NF-κB signaling pathway.	Chen et al., 2016
	Oral 50, 10, and 10 mg kg^{-1}/day, for 3 days	Carrageenan/male mice	↓Expression of Cox-2 mRNA	Ziyan et al., 2007
Apigenin	Oral 40 and 20 mg kg^{-1}/day, for 28 days.	Ovary syndrome in rat model	↓IL-6 and TNF-α mRNA expression	Darabi et al., 2020
	10 mg kg-1.bwt/, intraperitoneally 1 h before and 3 h after lipopolysaccharide administration	Lipopolysaccharide/Wistar rats	Down-regulates NF-κB and COX-2 signaling pathway	Wang et al., 2014
Isoorientin	Oral 50 mg kg-1 and 25 mg kg-1.bwt/day, for 5 days	Lipopolysaccharide/male mice	Down-regulates the expression of COX-2, Upregulates Nrf2/HO-1 pathway inhibits the stimulation of NF-κB and ERK	Li et al., 2020
Pyrogallol	Oral 2.5 mg kg^{-1}.bwt/day, for 4 weeks	High-Fat-Diet/male C57BL/6N mice	↓The manifestation of TLR4, NF-κB in the tissue of the brain. Down-regulates SOCS3 and increases the phosphorylation of STAT3	Son et al., 2019
Cynaroside	150 μM for 4 h before exposure to H_2O_2	H_2O_2/H9c2 cardiomyoblasts	↓The overmanufacture of ROS and decrease of the NF-κB pathway	Sun et al., 2011
	2 and 20 mg kg^{-1}, 1h before carrageenan treatment	Carrageenan /male C57BL6/cmd	↓The manufacture of pro-inflammatory cytokinesL-1β, IL-4, TNF-α, and IL-6	Szekalska et al., 2020
Cardioprotective effect				

Table 3
Continued

Bioactive molecules	Dose/Exposure route and duration of treatment	Models	Key Results/Involved Mechanisms	References
Rutin	80, 48, and 20 mg kg^{-1}.bwt, i.p, 30 min before surgical process	Myocardial ischemia/ Sprague-Dawley rats	Up-regulates mRNA antioxidant expression in the heart, upregulates SIRT1/ Nrf2 signaling pathway, prevents myocardial oxidative damages	Lin et al., 2018
	100mg kg^{-1} .bwt/day, oral for 8 days	Lipopolysaccharide /Male BALBE/c mice	Improves cardiac markers oxidative enzymes (↑CAT and ↑SOD activities MDA, as well as ↓MDA and↓ H2O2 levels), improves myocardium morphological changes, controls inflammatory responses	Xianchu et al., 2018
Quercetin	100 nM during 10 min, Intravenous perfusion	Myocardial ischemia/ reperfusion	Improves LVDP, ↓the release of creatine kinase (CK) into the cardiac effluent, IL-6, TNF-α, and IL-1β rates in the heart. Inhibits mitoKATP channels and NO synthesis	Liu et al., 2021
	120 and 60 mg kg^{-1} /day	Isoproterenol/Adult Sprague–Dawley rats	Inhibits Ca2+ channel, Improves heart pathologic morphology, ↑CAT, ↑SOD, ↑GSH, ↑GST, and ↑GPx activities; and relative ROS levels in the heart tissue	Liang et al., 2020
Kaempferol	Oral 10 mg kg^{-1}. bwt/day, for 2 weeks before cisplatin administration	Cisplatin/ C57BL/ 6 mice	Inhibits STING/NF-κB-mediated inflammation, inhibits the mRNA expression of caspase-3, BAK, and BAX (pro-apoptotic proteins of the BCL-2 family) in the tissues of the heart	Qi et al., 2020
	10, 3, and 1 mg kg^{-1} .bwt/day, intraperitoneally, 7 days before Isoprenaline treatment.	Isoprenaline /male Wistar rats	Prevents myocardial infarcted area and heart rate, regulates systolic and diastolic blood pressure, ↑CAT and ↑SOD and activities; and ↓MDA levels in heart tissue, ↓pro-MMP-2 manifestation, and MMP-9 rate	Vishwakarma et al., 2018
Luteolin	Oral 100 mg kg^{-1}. bwt/day, for 2 weeks	Ischemia-reperfusion/Male Sprague-Dawley diabetic rats	Ameliorated myocardial viability and cardiac function. ↑mRNA expressions of oxygenase-1 (HO-1) in heme, CAT, SOD, and GSH; and ↓MDA rates in heart, Upregulates eNOS/Nrf2 pathway and its related antioxidative signaling pathways	Xiao et al., 2019
	10 μg kg^{-1}.bwt/day, intraperitoneally for 10 days	Lipopolysaccharide/ C57BL/6 mice	Inhibits cardiac apoptosis, prevents cardiac oxidative stress, enhances autophagy activity, ↓the phosphorylation of AMP-activated protein kinase (AMPK)	Wu et al., 2020

Table 3
Continued

Bioactive molecules	Dose/Exposure route and duration of treatment	Models	Key Results/Involved Mechanisms	References
Apigenin	Oral 75 mg kg^{-1} .bwt/day, for 14 days	Isoproterenol/Diabetic rats	Prevents myocardial infarction, improves left ventricular end-diastolic pressure, attenuates edema, myonecrosis, oxidative stress, and cell death, and down-regulates PPAR-γ in the rat's myocardium	Mahajan et al., 2017
	10 µM for 2 hours before Isoproterenol hydrochloride treatment	Isoproterenol hydrochloride/ ardiomyoblast H9C2 cells	↑CAT, SOD GPx and GSH activities, ↓MDA and LHP levels in H9C2 cells. Prevents DNA damages and apoptotic cells.	Thangaiyan et al., 2018
Isoorientin	Oral 40 and 20 mg kg^{-1}. bwt/ day, for 56 days	High-fructose/Wistar rats	Prevents cardio-metabolic complications by increasing antioxidant enzyme activities CAT, SOD, and GPx) and improving lipid profile. Reduction of the manufacture of pro-inflammatory cytokines IL-6, IL-1, and TNF-α	Yuan et al., 2016
	0.1–100 µM for 4 hours	3T3-L1 adipocytes	Blocks lipid storage, increases glycerol release, upregulates the expression of AKT and AMPK pathways, ↑mitochondrial respiration, ↑ATP, and oxygen consumption.	Ziqubu et al., 2020
Cynaroside	150 µM for a period of 4 h before contact with H_2O_2	H_2O_2/H9c2 cardiomyoblasts	↓The overproduction of ROS modulates the JNK and P53 signaling pathways	Sun et al., 2011

5.2. Antimicrobial effect

Plant-derived flavonoids may play a major role in enhancing antibacterial treatments due to their distinct mechanisms of action compared to traditional drugs (Jubair et al., 2021; Huang et al., 2022; Vaou et al., 2022). Microbiological infections pose a significant risk to human health due to their resistance to multiple drugs (Ngogang et al., 2021). Therefore, it is crucial to develop novel, less hazardous treatments for human use. Research has demonstrated that *C. citratus* may possess antimicrobial properties against a variety of microbial strains, including *S. aureus*, *B. subtilis*, *Listeria* spp., *E. faecalis*, *S. mutans*, *L. rhamnosus*, *S. typhi*, *C. tropicalis*, *F. graminearum*, and *F. oxysporum* (Olukunle and Adenola, 2019; Sahal et al., 2020; Ngogang et al., 2021). *C. citratus* contains numerous bioactive composites well-known for their aptitude to remove diverse pathogenic microorganisms (Biharee et al., 2020). Several targets are affected by flavonoids, such as including gyrase, fatty acid synthase type II (FAS-II), and DHFR-EGCG helicase (Pearson et al., 2000; Zhang et al., 2008; Biharee et al., 2020). Antibiotic-paired plants are those that are combined with antibiotics to exhibit inhibition against multidrug-resistant pathogens, including *S. aureus*, *P. aeruginosa*, and *E. coli* (Fadli et al., 2016; Subramaniam et al., 2020). Luteolin, a predominant component in *C. citratus*, demonstrates strong antibacterial activity by disrupting the membranes of both *S. aureus* and *L. monocytogenes*, as well as inhibiting the growth of both strains (Qian et al., 2020). Furthermore, it was reported that substances effective against pathogenic yeasts such as *C. parapsilosis*, *C. glabrata*, and *C. albicans*, as well as certain bacterial strains including *P. mirabilis*, *K. pneumoniae*, *S. typhimurium*, *E. coli*, *H. pylori*, and *P. aeruginosa*, were identified as luteolin derivatives (Zhumakanova et al., 2021).

Several studies have investigated flavonoids, particularly catechins found in lemongrass, to determine their antimicrobial effects on both Gram (+) and Gram (-) germs of bacteria (Wrońska et al., 2022; Zhou et al., 2022). The interactions between flavonoids and bacterial lipid bilayers involve two primary mechanisms (Veiko et al., 2020; Altunayar-Unsalan et al., 2022; Strawa

et al., 2023). In the first phase, less polar substances are incorporated into the membrane's hydrophobic core. In the second phase, the polar head groups of lipids on one side interact with the more hydrophilic flavonoids on the other side, forming hydrogen bonds at the membrane interface. Furthermore, non-specific interactions between phospholipids and flavonoids can alter the membrane's structure, including its thickness and dynamics (Mandić et al., 2019), and subtly influence the distribution and function of membrane proteins, thereby affecting the pharmacological activities of the flavonoids (Arora et al., 2000). Additionally, it has been observed that flavonols, particularly galangin, can induce bacterial cell aggregation (Górniak et al., 2019; Lobiuc et al., 2023). However, it is important to note that following aggregation, the bacteria's ability to grow is diminished. It seems unlikely that flavonoids promote biofilm formation, as they likely induce partial lysis of bacteria, leading to membrane fusion and a reduced membrane surface area that limits active nutrient absorption (Górniak et al., 2019; Alías-Villegas et al., 2022). In contrast, other research groups have demonstrated that flavonoids can inhibit biofilm formation (Chen et al., 2022; Salatin et al., 2022). For instance, quercetin has shown significant effectiveness against the biofilm of *Vibrio parahaemolyticus* on food surfaces and has reduced the activity of pathogenic genes (Roy et al., 2022).

The antibiofilm properties of 5,7,4′-trihydroxyflavanol and isovitexin against *S. aureus* ATCC (29213) were demonstrated by Awolola et al. (2014). Similarly, El-Adawi and El-Deeb (2012) found that the development of biofilm from *S. mutans* was reduced by 55-66% in response to exposure to EC flavonoids at concentrations ranging from 2% to 15%. To protect against various harmful agents and the formation of biofilms, hydrophilic flavonoids can interact with membrane surfaces (Oteiza et al., 2005). Bacterial-type II fatty acid synthase (FAS-II) is an excellent target for antimicrobial drugs because it differs significantly from the mammalian counterpart, FAS-I (Bibens et al., 2023). The following list summarizes the various inhibitors of the bacterial-type II fatty acid synthase components that have been described so far. According to Ghosh et al. (2023) and Zhang et al. (2008), 3-hydroxyacyl-ACP dehydrase from *Helicobacter pylori* is inhibited by apigenin, quercetin, and sakuranetin. The 3-ketoacyl-ACP synthase from *E. faecalis* has been extensively studied, and 11 flavanones with various hydroxyl group configurations have been selected (Jeong et al., 2009). Further, eriodictyol, taxifolin, and naringenin had the best results. Hydrogen bonding between the hydroxyl groups of flavonoids at the C-5′ and C-4′ positions of the B circle and the residues of amino acids Phe308 and Arg38 of the enzyme is responsible for the antiseptic action of flavonoids. Elmasri et al. (2015) observed that the flavonoids like 5-hydroxy-4′,7-dimethoxyflavone and 5,6,7,4′,5′-pentahydroxyflavone reduced the activity of the MCATs, which regulate bacterial FAS-II. Flavonoids also significantly block topoisomerases, which enhances their antibacterial properties. For instance, DNA gyrase is exclusively found in prokaryotes and is a crucial enzyme for DNA replication, making it a prime candidate for the development of antibacterial medications (Seukep et al., 2023). According to a report by Ohemeng et al. (1993), 3,6,7,3′,4′-pentahydroxyflavone, apigenin, and quercetin all inhibit DNA gyrase from *E. coli* (Mohamed et al., 2022). Additionally, quercetin may target DNA gyrase subunit B from *Mycobacterium tuberculosis* and *M. smegmatis*, as suggested by an *in silico* study (Suriyanarayanan et al., 2013). Furthermore, Dzoyem et al. (2013) and Ghosh et al. (2023) reported that the management of *S. aureus* with two flavonoids, primarily isobavachalcone and 6-prenylapigenin, led to membrane depolarization in the treated bacteria.

5.2.1. Inhibition of bacterial toxins

Both Gram (+) and Gram (-) bacteria produce hyaluronidases, which are crucial virulence factors that either interact directly with the host's tissues or shield the bacterial surface from the host's immune defenses (Mirzaei et al., 2020; Mirzaei and Ranjbar, 2022). Hyaluronidase-mediated degradation of hyaluronan increases the permeability of connective tissue and reduces the viscosity of bodily fluids, contributing to bacterial pathogenesis (Zamboni et al., 2023). Notably, in *Streptococcus agalactiae*, the activity of hyaluronic acid lyase is inhibited by flavonols such as myricetin and quercetin, which are present in the studied plant (Pan et al., 2022). The number of hydroxyl groups in the flavonoid structure is associated with an increase in the inhibitory effects of these flavonoids (Hertel et al., 2006).

Based on the findings of Delehanty et al. (2007) and Górniak et al. (2019), flavonoids—particularly catechins and proanthocyanidins found in *C. citratus* (Aboagye et al., 2021)—have been suggested to neutralize bacterial toxins produced by *B. anthracis*, *V. vulnificus*, *C. botulinum*, *S. aureus*, and *V. cholerae* (Ghosh et al., 2023). Similar to quercetin glycoside, genistein and kaempferol-3-*O*-rutinoside have been shown to suppress neurotoxicity from *C. botulinum* (Veiko et al., 2023), while genistein specifically inhibits the exotoxin produced by *S. aureus* (Sharifi-Rad et al., 2021). One of the most critical virulence factors of *S. aureus* is Hla (α-hemolysin) (Tang et al., 2019), which is part of the barrel-forming bacterial toxins (Jahn et al., 2022). According to Soromou et al. (2013), pinocembrin, also known as flavonone, decreases the transcription rate of the α-hemolysin and Hla genes, thereby inhibiting the production of α-hemolysin by *S. aureus* in a dose-dependent manner. Pinocembrin has also been studied for its interaction with the bacterial membranes of *Neisseria gonorrhoeae* (Górniak et al., 2019; Elbatreek et al., 2023). Cell lysis induced by pinocembrin was observed, attributed to the induction of ROS production, cellular apoptosis, and cell cycle arrest (Shao et al., 2021). Additionally, food poisoning caused by *E. coli* can be mitigated through the use of catechins. Gallocatechin gallate has been demonstrated to reduce verotoxin production in enterohemorrhagic *E. coli* cells

(Sugita-Konishi et al., 1999).

5.3. Antidiabetic effect

5.3.1. *In vitro* studies

In vitro studies investigating the potential antidiabetic activity of various natural products have been extensively designed and conducted. Carbohydrate-hydrolyzing enzymes, such as alpha-amylase, play a crucial role in the breakdown of carbohydrates into sugars, which can lead to hyperglycemia. Controlling the activity of these enzymes may provide an effective strategy for managing hyperglycemia. An *in vitro* study demonstrated that nanoparticles prepared from *C. citratus* exhibited an inhibitory effect on alpha-amylase comparable to that of acarbose at a concentration of 100 µg/mL (Agarwal et al., 2021). It has been shown that the flavonoid fraction is significantly more potent than the extract, with an IC_{50} of approximately 14.88 µg/mL against alpha-glucosidase (Borges et al., 2021). Molecular docking techniques revealed that flavonoids, including aglycones, mono-C-glycosylflavones, *O*-glycosylflavones, and *O*,C-diglycosylflavones, established various interactions with the B ring, including π-π interactions, π-cation interactions, and hydrogen bonds, thereby inhibiting the activity of alpha-glucosidase on carbohydrates (Borges et al., 2021). The findings obtained *in vitro* were corroborated by subsequent *in vivo* studies, as detailed below.

5.3.2. *In vivo* studies

Diabetes is a disease characterized by dysglycemia, which, if left untreated, can lead to several long-term complications. Ethnopharmacological studies have indicated that *C. citratus* is commonly used as a traditional remedy for various ailments, particularly diabetes (Oladeji et al., 2019; Karami et al., 2021). In a study, type 2 diabetics induced by fructose and streptozotocin were given *C. citratus* tea at concentrations of 0.25% or 0.5% ad libitum for four weeks. The authors found that *C. citratus* tea was more effective in reducing blood sugar and lipid levels, insulin levels, β-cell function, and liver glycogen (Garba et al., 2020). The consumption of *C. citratus* tea resulted in a nearly 60.3% reduction in plasma glucose, demonstrating superior effectiveness, likely due to its higher concentration of phytochemicals. This further supports lemongrass's potent ability to inhibit the actions of the enzymes α-amylase and α-glucosidase. Similar findings were reported for the active constituents of *C. citratus* tea, including citral, limonene, and linalool, which were shown to alleviate hyperglycemia and diabetes-related complications. The plant contains compounds that may exert antihyperglycemic effects, either individually or in combination. A comparison of the antidiabetic effects of organically and conventionally grown *C. citratus* revealed that the organically cultivated herb enhanced the regeneration of pancreatic islets and exhibited a significant antidiabetic effect (Fig. 2) (Itankar et al., 2019).

The plant's ability to combat diabetes may be attributed to its inhibitory effect on gluconeogenesis, which helps prevent muscle atrophy, as well as to improvements in insulin production and glycemic control. On the other hand, the pathophysiology of postprandial glucose (PPG) rise in type 2 diabetes is due to the failure of the first phase of insulin secretion, inadequate regulation of glucose production in the liver, and resistance of muscle cells to glucose absorption. Additionally, the lack of glucagon suppression contributes to postprandial hyperglycemia, suggesting that *C. citratus* may act by countering glucagon. Recent studies have begun to analyze the impact of *C. citratus* on genes implicated in diabetes, particularly the protein tyrosine phosphatase-1B (PTP1B), which is a potential target for modulating glucose homeostasis (Dwivedi et al., 2021; Kaszubska et al., 2002). *C. citratus* contains various flavonoid compounds, such as swertiajaponin, which exhibit the highest binding affinity to PTP1B compared to other compounds like 7-*epi*-alpha-eudesmol, 11-diol, (2*E*,6*E*)-hedycaryol, and 7-*epi*-ent-eudesmane-5, as well as citral, through hydrogen bond interactions (Dwivedi et al., 2021). The regulation of this protein is implicated in numerous pathways, which may explain the antidiabetic effects of *C. citratus*, particularly its ability to improve the endocrine system (Dwivedi et al., 2021). The endoplasmic reticulum (ER) stress is implicated in the pathogenesis and progression of diabetes, contributing to pancreatic destruction and insulin resistance (Salvado et al., 2015). In this context, *C. citratus* demonstrated its capacity to downregulate the expression of ER stress markers, including protein kinase RNA-like ER kinase (PERK), activating transcription factor 4 (ATF4), tribbles homolog 3 (TRB3), inositol-requiring enzyme 1 (IRE1), CCAAT-enhancer-binding protein (CHOP), and glucose-regulated protein 78 (GRP78) in the pancreas of diabetic rats (Elekofehinti et al., 2020). The bioactive compounds found in medicinal plants interact synergistically to modulate various pathways, resulting in beneficial biological activities (Dwivedi et al., 2021). Recent developments include a novel formulation combining three flavonoid compounds—epicatechin, catechin, and rutin—designed to treat diabetes (Mechchate et al., 2021). This functional combination has shown a positive effect in preventing both hyperglycemia and hypoglycemia in alloxan-induced diabetic mice (Mechchate et al., 2021). Flavonoids are extensively studied for their pharmacological properties and have demonstrated efficacy in preventing and treating various polygenic disorders, including diabetes. However, further research is necessary to elucidate the molecular mechanisms underlying the antidiabetic effects of each biomolecule.

5.4. Anti-inflammatory effect

Conventional medications for treating painful conditions such as arthritis, sciatica, and cluster headaches are often limited due to their serious side effects (Barut et al., 2021). In light of this evidence,

scientists continue to search for new natural drugs that offer high efficacy with fewer side effects. *C. citratus* is among the extensive list of medicinal plants known for their significant pharmacological effects (Carbajal et al., 1989; Rabbani et al., 2006; Itankar et al., 2019; Karami et al., 2021; Magotra et al., 2021a). The effects of *C. citratus*, particularly its anti-inflammatory properties, have been extensively studied *in vivo* using animal models (Fig. 2). Costa et al. (2016a) examined the anti-inflammatory effects of various fractions of *C. citratus*, including flavonoid and tannin fractions, using a carrageenan-induced edema model in rats. The authors observed that the combination of both fractions reduced edema volume by approximately 59%, attributed to their richness in bioactive compounds, especially luteolin (Costa et al., 2016a). This bioactive compound has been shown to decrease pro-inflammatory factors, including cytokines, iNOS, TNF-α, IL-6, and IL-β (Francisco et al., 2014). In a related study, Francisco et al. (2014) demonstrated that the phenolic acid and tannin-rich fractions inhibit NF-κB activation in both human and murine macrophages pretreated with different fractions of *C. citratus*. Additionally, the authors noted that these fractions significantly reduced proteasome activity in LPS-activated murine macrophages and markedly diminished nitric oxide production, which may explain the anti-inflammatory effects of *C. citratus* (Francisco et al., 2014). Furthermore, *C. citratus* is regarded as a promising source of new and safe anti-inflammatory agents (Tavares et al., 2015).

5.5. Cardioprotective effect

Besides the aforementioned properties, the cardioprotective effect of *C. citratus* is highlighted as a significant benefit provided by the plant, as evidenced by several studies (Fig. 2). The antihypertensive effect of *C. citratus* has been reported in numerous ethnomedicinal surveys (Shah et al., 2011; Ekpenyong et al., 2015), and experimental studies confirm this beneficial property by utilizing methanolic extracts to demonstrate vasorelaxant effects in the thoracic aorta and umbilical vein (Devi et al., 2012; Campos et al., 2014). Research on the impact of *C. citratus* on vascular tone, using infusions and various plant fractions, suggests that *C. citratus* contains vasoconstrictor substances (Devi et al., 2012; Simões et al., 2020). These findings indicate that *C. citratus* is rich in bioactive compounds, including luteolin and apigenin derivatives, which enhance the effects of noradrenaline (Simões et al., 2020). Previous reports have linked the vasorelaxation properties of the bioactives from *C. citratus* to their impact on nitric oxide and calcium channels involved in arterial vasoconstriction (Devi et al., 2012; Campos et al., 2014; Olorunnisola et al., 2014). Investigations have shown that prostacyclin plays a role in the vasorelaxation process, while cyclooxygenase serves as a complementary pathway involved in the vasorelaxation effects of *C. citratus* (Devi et al., 2012; Simões et al., 2020). Notably, luteolin inhibits the mitogen-activated protein kinase (MAPK) pathway, enhances cardiomyocyte function, improves cardiac performance, and prevents cardiac injuries (Luo et al., 2017).

6. Concluding remarks

C. citratus is a valuable medicinal plant rich in bioactive compounds with various functional properties, including cardioprotective, antioxidant, antidiabetic, antimicrobial, and anti-inflammatory effects. The key molecules in *C. citratus* are flavonoids, which are associated with its biological activities and work synergistically to provide the aforementioned benefits. This paper reviews the chemical composition and pharmacological properties of *C. citratus*, with a particular focus on flavonoids. The discussed topics include diversity, qualitative and quantitative variation depending on plant materials, extraction approaches, and growing conditions. In conclusion, bioactive compounds, mainly flavonoids vary from the aerial to ground parts of the plant, depending on extraction conditions and materials, as well as growing soil and climate of vegetal materials. In terms of pharmacological properties, we discussed the antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and cardioprotective effects of different flavonoid molecules. Kaempferol, rutin, and quercetin were the most common flavonoids identified in *C. citratus* extracts and were characterized by various properties. They showed significant effects against pathogenic strains such as bacteria (*i.e., Vibrio*, *Salmonella*, and *Staphylococcus* genus), fungi (*i.e., Candida* and *Fusarium* genus), and their toxins. Therefore, different populations use the plant and its derivatives in both traditional and modern medicine due to their antimicrobial, antioxidant, and anti-inflammatory properties. However, more advanced studies are needed to explore new usages of both plants and their chemical components including flavonoids. At this point, we suggest that researchers should apply new extraction methods that can optimize the extraction of biomolecules, and then treat more pathogens, such as viruses that affect human health (*i.e.*, rebound of SARS-CoV-2) and those impaction crops (*i.e.*, potato virus Y).

Author contribution statement

Conceptualization and literature search were performed by Ahmed Tazi, Noura Jaouad and Faouzi Errachidi. The first draft of the manuscript was prepared by Ahmed Tazi and Noura Jaouad. Faouzi Errachidi critically analyzed and gave suggestions to finalize the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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