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Review on the pharmacological properties of lemongrass (*Cymbopogon citratus*) as a promising source of bioactive compounds

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ABSTRACT

Despite the quantities and diversity of chemical compounds such as flavonoids discovered in lemongrass (*Cymbopogon citratus* DC.), available data are fragmentary. Their variation depending on the type of extract and origin of the plant and their effect on biological activities are not deeply discussed. Therefore, this paper provides a critical discussion of bioactive compounds including flavonoid content in extracts of *Cymbopogon citratus*, and their associated biological properties. Recorded data showed that recent studies have addressed the flavonoids qualitatively and quantitatively in various extracts of *C. citratus*. Existing literature clarified a significant variation of chemicals depending on the used parts of the plants. However, data on the effects of climate change and other environmental on the quantity and quality of flavonoids are not yet available. On the other hand, the recorded flavonoids were associated with a wide range of pharmacological properties including antioxidant, anti-inflammation, anti-microbial, and anti-diabetic effects, which are variable depending on the types of flavonoids. Other properties such as anticancer, analgesic, and diuretic activities are not yet investigated in the flavonoids extracted from the plant, thus more advanced studies are needed to optimize the extraction of biomolecules counting flavonoids, and then apply them to the most devastating diseases and pathogens.

1. Introduction

Healthcare of numerous civilizations is based on medicinal plants, which are used in traditional medicine. This is governed by the absence of advanced medicine and the richness of plants with bioactive molecules [1]. Further, medicinal plants constitute a promising source of active compounds for new drug discovery with fewer negative effects [2–4]. The literature mentions flavonoids as one of the most interesting groups of bioactive compounds of medicinal herbs with a broad range of human health benefits such as antioxidant, antiproliferative, antimicrobial, and antimetabolic disorder properties [3–6]. Within this frame, new formulation was evaluated as a new antidiabetic drug multitargets for diabetes treatment using plant flavonoids combination including catechin, epicatechin, and rutin, which showed high antihyperglycemic potential validating this approach as alternative of conventional drugs [7]. Flavonoids drugs discovery is a vibrant research field targeting multiple bodily functions [8]. As an excellent approach, synergistic combinations of flavonoids proved their ability to eradicate fungi or stopping recurrence of fungal diseases [9], new anticancer drugs [10,11], antiangiogenic combination [8,9], inhibitors of cytomegalovirus [12], and antiglioblastoma drugs [13]. Despite their benefic roles, many researchers mentioned a qualitative and quantitative variation of flavonoids depending on plant material [8], environmental factors [14], and extractions methods [15].

Lemongrass *Cymbopogo citratus* DC. Stapf is a plant known for its popular name citronella and its uses [16]. It is a member of Gramineae family and its name meaning is 'kyme-pogon' or boat-beard in the Greek language [17]. It is widely employed by different populations as a natural remedy for debilitating diseases including hypertension, inflammation, and diabetes [12,13]. Citronella attracts a great interest due to its diverse and many pharmacological properties [18,19]. Scientists confirms it importance in food, nutraceutical and cosmetic

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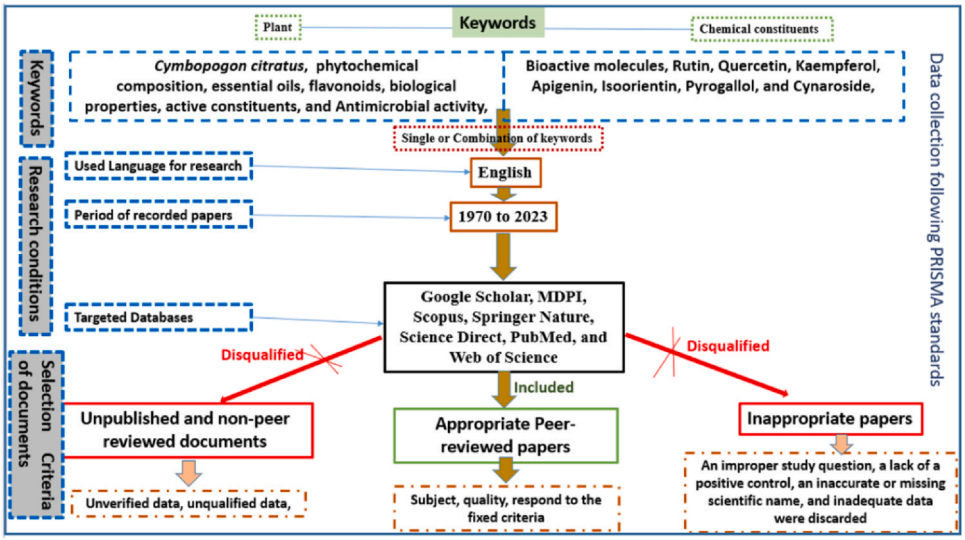

Fig. 1. Followed approach to select the papers addressing the study topics including keywords; research conditions (language and period); and selection or elimination criteria of documents.

industries as a wealthy source of bioactive compounds [20]. The importance of this plant is directly related to its chemical compounds, including polyphenols, flavonoids, terpenes, etc. [21,22]. These chemicals are widely studied mainly in the essential oils [23–25], but there no integral study that addressed qualitative and quantitative variation of bioactive compounds such as flavonoids in *Cymbopogo citratus* depending on used solvents, extractions methods, plant material, and geographical origin. Such parameters are suggested to influence the biological properties of the plant.

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 [26]. Furthermore, traditional ayurvedic medicine based on polyherbal mixture such as *Raktavardhak kadha* provides an important antianemic potential attenuating deleterious damages induced in organs interestingly bone marrow thanks to its flavonoids content [27]. However, the constituents of flavonoids extracted from *C. citractus* and their biological properties showed a significant variation and these need a deep discussion in order to clarify qualitatively and quantitatively which factors are behind these issues. These need to confront existing data from different regions to clarify the variation of diversity and amount of flavonoids in the extracts of *C. citratus*.

This study aims to review the existing literature on the chemical compounds, mainly flavonoids in the extracts of *C. citratus.* First, we discussed the main compounds discovered in the extracts of the plant, then we demonstrated the variation of flavonoids in the extracts depending on plant materials, extraction methods, geographical origin, and conditions. In the second step, we recorded the pharmacological properties of flavonoids and we discussed their variation depending on type of flavonoids. Despite the huge amount of incorporated papers in this review, we realized a critical analysis in order to reveal the aspect that need deep investigations to discover new active molecules and to test new properties for *C. citratus.*

2. Methodology

2.1. Research of papers

The methodology used in this review paper was based on a literature review of publications focusing on *C. citratus* flavonoids and bioactive compounds. In this context, different search engines and databases were checked to collect a useful information to prepare the current review such as Google Scholar, Scopus, ScienceDirect, and PubMed on the basis of the following keywords: *C. citratus*, and lemongrass beneficial properties flavonoids and pharmacological effects, phytochemical compounds. The research included papers published from 1970 to 2024, with concentration on last two decades (2000–2024). The last two decades are characterized by development of used methods and materials and huge scientific production related to our topic.

2.2. Selection criteria

During the electronic research, we downloaded papers related to the subject of our study. Then, we searched the fixed keywords in the sections of each paper including Title, Abstract, Introduction, methods, results, discussion, and conclusion. In some papers, we searched in the supplementary materials. the selection of papers includes those containing the targeted topic (based on the keywords) in the English language. Peer-reviewed papers published between 1970 and 2024 were selected, while non-peer-reviewed documents were eliminated (Fig. 1). Equally, papers with French, Arabic, and other languages were disqualified. Unverified data and papers were also disqualified. A total of 195 scientific articles were downloaded and examined for their relevance and novelty to select a final list of 122 published articles that were used to structure the present manuscript (Fig. 1).

2.3. Main compounds of C. citratus

C. citratus (**Fig.** SM1) represents one of the most sourced plants in Asia because of its distribution and application [28]. However, the plant is little known in Africa and few scientific information is still available on its bioactive compounds and its health benefits. Different extracts of *lemongrass* have shown diverse pharmacological activities that are generally attributed to it chemical composition. During the last decades many studies have addressed lemongrass chemical contents. Results reported that lemongrass essential oil and solid extracts varied according to various factors including the geographical area, age, used parts, extraction method, and genetics [29].

The most isolated compounds from lemongrass are diverse chemical classes phenolic component (flavonoids, tannins), sterols, terpenoids, ketone, and sugars. Soliman et al., [30] investigated essential oil chemical composition from the Egyptian Lemongrass, with gas chromatography analysis. Results showed that 22 chemicals (97.83 % of the essential oil composition) were identified, including monoterpenes (96.37 %), and small quantities of diterpenes and

Table 1
Variation of total phenolic compounds (TFC) in samples of *C. citratus* depending on geographical area, extraction methods, used part, and conditions.

Countries	Conditions	Extract	Part of the plant	Method used	TFC (mg GA/ g DW)	References
Iran	Water stress	Essential oil	Entire plant	Aluminum chloride	6.55–11.15 (mg GA/ g DW)	[32]
Nigeria	Natural conditions	Cold and hot water extract	Edible stalks	-	0.2–0.3 mg quercetin equivalent/g	[34]
Ghana	Natural conditions	Cold and hot percolations	Entire plant	Cold and hot percolations	6.9–12.9 µg/g QE	[33]
Brazil	20˚C, 40˚C, and 60˚C	Extracts	Leaves	Conventional and Ultrasound methods	10.33–13.99	[35]
Portugal	Harvest date and material quality	Infusion	Dry leaves	spectrophotometric methods	5 %-6.7 %	[36]

sesquiterpenes. The major identified compound was citral which represents 79.69 % of total essential oil composition, and was divided into two major compounds; 42.86 % citral A (geranial) and 39.83 % citral B (neral). On the other hand, total phenolic compounds contents were 7.55 ± 0.49 (mg GAE/g) compared to total flavonoid contents of 1.96 ± 0.56 (mg CE/g). Recently, Zaman et al., [31] from Malaysia evaluated lemongrass essential oil chemical composition leaves by using gas chromatography flame ionization detector and gas chromatography-mass spectrometry. The authors also investigated the effect of post-harvest drying period on the yield and chemicals composition. A total of twenty-one components were identified, representing 97.53 % of the total oil composition. The major components were α-citral and β-citral followed by myrcene for both fresh and dried samples. The authors reported also that drying periods had no significant effect on lemongrass essential oil components. Nevertheless, the post-harvest drying periods had a marked effect on the proportions of monoterpenes [31].

Like the chemical composition, the quantity of flavonoids varies widely in samples of lemongrass depending on used part, climate conditions, geographical area, and extraction methods (Table 1). Mirzaei et al., [32] investigated the variation of flavonoids in Iranian samples of *C. citratus* growing under water stress (four levels: 100 % field capacity, 75 %, 50 %, and 25 %) and inoculation by Plant Growth Promoting Rhizobacteria (PGPR) (three levels: uninoculated, inoculated with *Pseudomonas* sp., and inoculated with *Azotobacter* sp.). The authors showed that total flavonoids vary between 6.55 and 11.15 (mg GA/g DW). Further, 50 % field capacity induced the maximum total flavonoid content (TFC) by 42 % compared to 100 % FC, while *Pseudomonas* and *Azotobacter* increased the TFC by 6 % and 18 %, respectively in comparison with uninoculated plants. In Ghana, Godwin et al., [33] investigated the flavonoid properties in cold and hot percolations of Lemongrass (*C. citratus* Stapf). The authors showed total flavonoid concentration ranged from 6.9 to 11.3 µg/g DW Quercetin Equivalent (QE) and 6.9–12.9 µg/g DW QE dry weight basis for cold and hot percolations respectively.

In Nigeria, the TFC of the edible stalks in fresh Lemongrass ranged from 0.2 to 0.3 mg quercetin equivalent/g [34,35] evaluated the flavonoid contents in the lemongrass leaves harvested in rural area of Santa Maria (Brazil) using conventional and ultrasound methods. The experiment was made under three levels of temperature: 20˚C, 40˚C, and 60˚C, and total flavonoids were significantly superior in conventional method as compared to ultrasound technique. In conventional approach TFC were 13.99 ± 1.52, 13.53 ± 1.40, and 13.42 ± 0.27 (mg QE/g DW) under 20˚C, 40˚C, and 60˚C, respectively. In conventional approach, the TFC were 10.33 ± 1.16, 11.46 ± 0.64, and 12.09 ± 0.48 (mg QE/g) under 20˚C, 40˚C, and 60˚C, respectively. In Europe, Costa et al., [37] addressed the influence of harvest date and material quality on flavonoid content of *C. citratus* infusion. Results showed that flavonoids reached significant increases with sun exposure. Equally, total flavonoids have a statistically significant decrease in a given harvest date, August (4.81 %), exhibiting their maximum values in June (6.63 %) and September (6.62 %).

2.4. Flavonoids

C. citratus is a medicinal plant that contains a large list of bioactive compounds with different amounts [36,38–41]. Phytochemical determination is the first step to establish an obvious mechanism of action that could be responsible for different pharmacological properties of *C. citratus*. Recently, flavonoids gained a huge interest for their biological properties, and their uses as drugs combination are started [7]. The most flavonoids abundant in *C. citratus* were 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-pentohexos-ulosyl) luteolin [42].

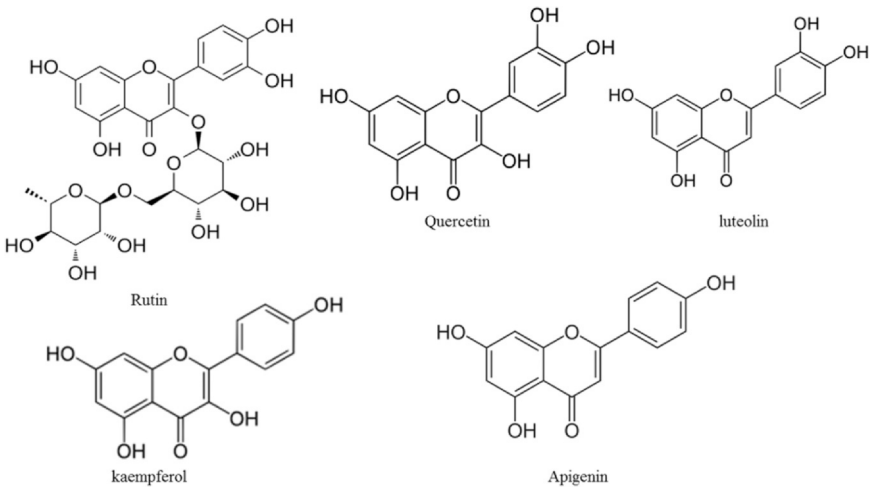

Fig. 2. Flavonoids components abundant in *C. citratus*.

Glycosylation is typical modifications of flavonoids in the biosynthesis process which is responsible for enlargement of natural glucosides components with tremendous properties [43]. Flavonoids are widely known by their antioxidant potential and earlier published reports evoked that luteolin and its derivatives provide numerous pharmaceutical activities including antioxidant, anti-inflammatory, antimicrobial, antiaging, and cardioprotective effects [44]. In contrary, some published studies reported that luteolin and its derivatives could cause endocrine system perturbations and act as an antagonist of progesterone [33,34]. The beneficial properties of different flavonoids compounds present in *C. citratus* are listed in Table 2.

2.5. Qualitative and quantitative variation of Flavonoids in the extracts

During the last decades, many investigations have addressed the chemical compounds in the extracts of various parts from *C. citratus*. Among the investigated compounds, flavonoids were the most researched in terms of diversity, quantity, and activities. The recorded results showed variability of both diversity and quantity of flavonoids depending on the used solvents, parts of the plant and growing areas.

Figueirinha et al., [42] investigated and characterized the flavonoids by HPLC–PDA–ESI/MS/MS in leaves of *C. citratus*. These authors used leaves from cultivated *C. citratus* in the region of Mezio, Castro D'Aire (Portugal) which were extracted with methanol, 80 % ethanol aqueous, and water (decoction and infusion). In total, 13 flavonoid compounds were identified. Flavone glycosides (luteolin and apigenin derivatives) were found in three different fractions obtained from infusions. Méabed et al., [46] investigated the chemical compounds in the aqueous extract of commercial *C. citratus* leaves obtained from herbalists in Fayoum, Egypt. These authors investigated the diversity and quantity of flavonoids. In terms of quantity, the obtained results estimated at 23.9 ± 0.3 mg quercetin/g. in terms of richness, 10

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

Type of extraction	Technique used	Material used	Flavonoids compounds	Reference
Infusion	HPLC	Leaves	6-C-Hexosyl-8-C-pentosyl luteolin (5.08 ± 0.01 %) 6-C-Pentosyl-8-C-hexosyl apigenin (3.73 ± 0.01 %) 6-C-Glucosyl luteolin (isoorientin) (2.34 ± 0.01 %) 2"-O-Rhamnosyl isoorientin (15.1 ± 0.02 %) 6-C-Pentosyl-8-C-pentosyl luteolin (13.4 ± 0.02 %) 6-C-Pentosyl-8-C-pentosyl luteolin (6.14 ± 0.01 %) 7-O-Glucosyl luteolin (19.5 ± 0.01 %) 6-C-Pentosyl luteolin (19.3 ± 0.01 %), and X"-O-Rhamnosyl C-(6-deoxy-pento-hexos-ulosyl) luteolin (19.1 ± 0.01 %)	[42]
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)	[36]
	HPLC	Leaves	6-C-hexosyl-8-Cpentosyl luteolin, 6-C-pentosyl-8-Chexosyl apigenin, 6-C-hexosyl luteolin (isoorientin), 2"-O-rhamnosyl isoorientin, 7-O-neohesperosyl luteolin, 6-C-pentosyl-8-Cdeoxyhexosyl luteolin, 6-C-pentosyl luteolin, and X"-O-rhamnosyl C-(6-deoxy-pentohexos-ulosyl) luteolin	[40,41]
Ethanol and methanol extracts	HPLC	Leaves	Rutin, quercetin, kaempferol	[39]
Aqueous extract	HPLC	Leaves	Quercetin (3.799 %), rutin (1.843 %), pyrogallol (0.362 %), and apigenin (0.312 %)	[45]
Methanolic extract	UPLC	Leaves	Luteolin-6-C-glucosyl-8-C-arabinoside (Carlinoside), Luteolin-O-hexosyl-C-hexoside, luteolin-6-C-glucoside (Isoorientin), luteolin-2″-*O*-deoxyhexosyl-6-C-hexoside (isoorientin-2″-Orhamnoside), luteolin-6-C-pentosyl-8-C-pentoside, luteolin-C-pentosyl-O-hexoside-methyl ether, apigenin-2″-*O*-deoxyhexosyl-C-hexoside, apigenin-6-C-arabinosyl-8-C-glucoside (Isoschaftoside), luteolin-2″-*O*-deoxyhexosyl-C-hexoside-methyl ether, apigenin-*O*-hexosyl-C-deoxyhexoside, luteolin-7-*O*-glucoside (Cynaroside), luteolin-7-*O*-rhamnoglucoside (luteolin-7-*O*neohesperidoside), luteolin-2″-*O*-rhamnosyl-6-C-arabinoside (kurilensin A), luteolin-2″-*O*-rhamnosyl-6-C-(6-deoxy-ribo-hexos-3-ulosyl) (Cassiaoccidentalin B), and luteolin	[38]

Table 3
Detection, identification and quantification of flavonoids in the extracts from different parts of *C. citratus* growing in different areas.

Type of extract	Part of the plant	Origin of the plant	Sampled site	Geographical area	Flavonoids and amounts	References
Hydroalcoholic	Leaves	Cultivated	Rio Grande do Sul	Brazil (South America)	12 flavonoids	[50]
Hydroalcoholic	Leaves	Wild	Santa Maria	Brazil (South America)	13.42 ± 0.27–13.99 ± 1.52 mgQE/g	[35]
Methanolic, ethanol and aqueous	dried leaves	Cultivated		Angola (Africa)	ethanol (6.62 ± 0.65 mg CE/mL), methanol (3.47 ± 0.49 mg CE/mL), and aqueous extract (0.24 mg CE/mL)	[49]
Water, Methanol, Chloroform, and Benzene	leaves, stems, and roots	Cultivated	Chhattisgarh	India (Asia)	Low concentration in the methanol and benzene of leaves	[51]
Methanol and fractions including N-hexane, Chloroform, and Ethyl acetate	fresh leaves from	Cultivated	Benin City	Nigeria (Africa)	Ethyl acetate (192.6 mgQE/g Extract), chloroform fraction (153.0 mgQE/g Extract), crude methanol extract (143.0 mgQE/g Extract), and n-hexane fraction (80.2 mgQE/g Extract)	[48]
Methanol	Fresh leaves	Cultivated	Minia	Egypt (Africa)	193.63 ± 4.63 (µg/g)	[52]
hydroalcoholic	Fresh leaves	Wild	Paraná State	Brazil (South America)	Geraniol and Citral	[53]
					15.70 ± 1.40 mg QER g-1 extract	
Water, Methanol, Chloroform, and Benzene	leaves, stems, and roots	Cultivated	Chhattisgarh	India (Asia)	Low concentration in the Methanol and Benzene of leaves	[51]
Methanol and fractions including N-hexane, Chloroform, and Ethyl acetate	fresh leaves from	Cultivated	Benin City	Nigeria (Africa)	ethyl acetate(192.6 mgQE/g Extract), chloroform fraction (153.0 mgQE/g Extract), crude methanol extract (143.0 mgQE/g Extract), and n-hexane fraction (80.2 mgQE/g Extract)	[48]
Methanol	Fresh leaves	Cultivated	Minia	Egypt (Africa)	193.63 ± 4.63 (µg/g)	[52]
hydroalcoholic	Fresh leaves	Wild	Paraná State	Brazil (South America)	Geraniol and Citral	[53]
					15.70 ± 1.40 mg QER g-1 extract	
hydroalcoholic	Fresh leaves	Wild	Paraná State	Brazil (South America)	Geraniol and Citral	[53]
					15.70 ± 1.40 mg QER g-1 extract	

compounds were identified including Quercetin (3.799 %), Rutin (1.843 %), and Apigenin (0.312 %). Asaolu et al., [47] investigated the chemical constituents in the ethanol and aqueous extracts from powdered leaves of *C. citratus* collected in Nigeria. The concentration of flavonoids was estimated at 0.532 % in both extracts. Unuigbe et al., [48] conducted a phytochemical analysis of fresh leaves from *C. citratus*. These authors used the extract of Methanol and fractions including N-hexane, Chloroform, and Ethyl acetate. The results revealed a high content of flavonoids; the ethyl acetate fraction also had the highest flavonoid content (192.6 mg QE/g Extract), followed by the chloroform fraction (153.0 mg QE/g Extract), crude methanol extract (143.0 mg QE/g Extract) and n-hexane fraction (80.2 mg QE/g Extract). Soares et al., [49] investigated the chemical compounds including total flavonoids in dried leaves of *C. citratus* collected from Angola. In terms of detection, flavonoids were detected only in the methanolic extract compared to ethanol and aqueous. In terms of quantification, the highest value of flavonoids was recorded in ethanol (6.62 ± 0.65 mg CE/mL), followed by methanol (3.47 ± 0.49 mg CE/mL), and the aqueous extract (0.24 mg CE/mL). Boeira et al., 2020 [50] investigated and characterized the phytochemicals in the Hydroalcoholic extract of *C. citratus*. The characterization by high-resolution time-of-flight mass spectrometry recorded 22 flavonoids dominated by 8- methyl-6-prenylquercetin, 3″-O-Acetylembinin, and 8-Prenylnaringenin. In terms of extraction conditions, Boeira et al., 2018 [35] investigated the flavonoids in the Hydroalcoholic extracts under different temperatures and extraction methods. With conventional extraction methods, the value of flavonoids varied from 13.42 ± 0.27 mg QE/g at 60˚C to 13.99 ± 1.52 mg QE/g at 20˚C. with ultrasound extraction, the flavonoids varied from 10.33 ± 1.16 mg QE/g in 20˚C to 12.09 ± 0.48 mg QE/g 60˚C (Table 3).

3. Traditional uses of *C. citratus*

Many people use plant-based medications today as a component of traditional medicine to treat a wide range of illnesses [44,54,55]. It was reported that traditional medicine use improves the socioeconomic standing and general health of agricultural populations in developing nations [56,57]. *C. citratus* is one of the most used medicinal plants by various populations from ancient times [17,45,46]. The medicinal uses of this plant are very diverse depending on variable factors including the treated illness, the used parts of the plant, and the geographical areas of the population. All the traditional uses of the plant are based on the richness of the *C. citratus* with a wide range of bioactive compounds with potential health beneficial effects [47,58].

In Africa, due to poverty, populations rely on folk medicine [48–50]. *C. citratus* and its derivatives are used differently to manage various diseases in the north, west, south, and west of Africa [51–53]. In Western Africa, the plant and its parts are used by Ethiopian populations to manage stomach-ache disorders [59]. They administrate ground parts, particularly roots orally to patients with digestive problems. In Northern Africa, the plant is widely used by the Moroccan, Algerian, and Tunisian populations in folk medicine [57,60–62]. Indeed, Moroccan populations reported the use of *C. citratus* to treat bacterial diseases [63]. In Tunisia, local population use the infusion and extract of *C. citratus* to manage diuretic and intestinal troubles [64–66]. In Egypt, Madi et al., [67] reported the use of the essential oils from the *C. citratus* as an anticholinesterase agent. In the South African continent, *C. citratus* is widely used by local people for treating stomach, gut problems, high fever, and headache [49]. In Western Africa, *C. citratus* collected from Nigeria was used as an antispasmodic agent [16], while Akono Ntonga et al., [68] reported the use of extracts, essential oils, and infusions of *C. citratus* against malaria and other fevers in Cameroon.

Many investigations from Asia reported the use of *C. citratus* by local populations to treat various illnesses [69,70]. For example, the Chinese population uses *C. citratus* as an anxiolytic agent from the ancient times

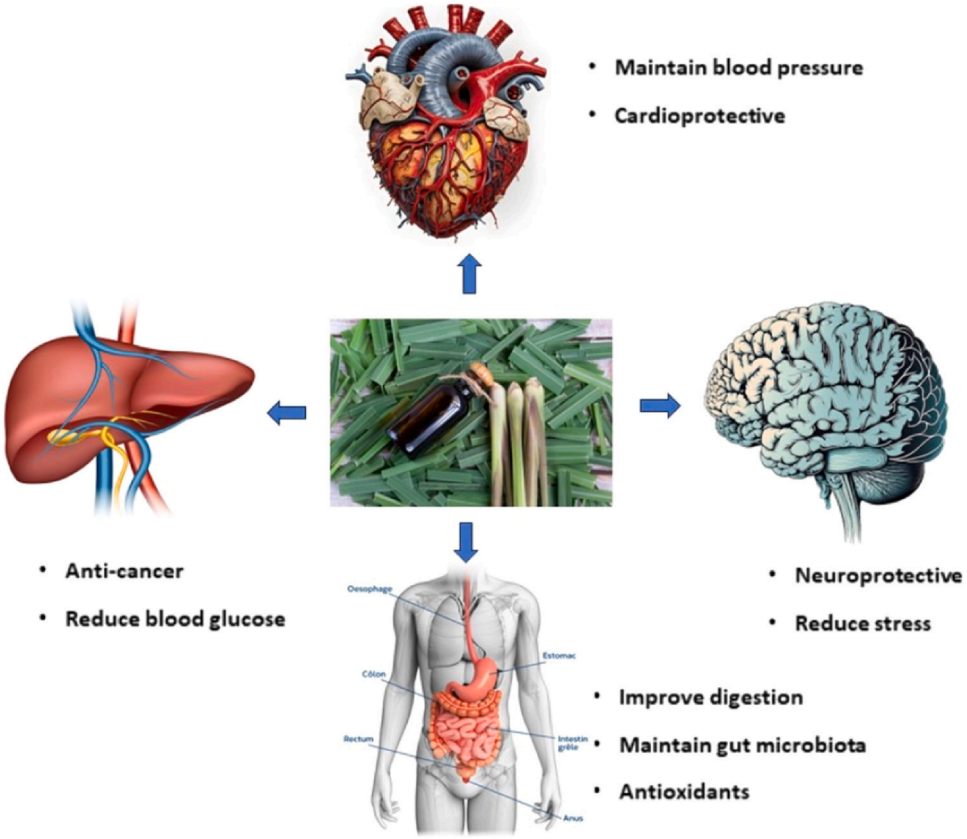

Fig. 3. Pharmacological properties of flavonoids.

[71–73]. Dry leaf infusion was the most orally used by the Chinese population [61]. Furthermore, hot water extract from the entire plant was mentioned by Indonesian population to manage the emmenagogue via oral administration [70,74,75]. In another study, Avoseh et al., [76] reported the use of aerial parts from *C. citratus* in Pakistan to manage antiseptic and stomachic, diuretic, rheumatism, and malaria.

In the American continent, *C. citratus* is used to treat various diseases including digestive, cardiac, pathogen, and bacterial diseases [45,77–79]. However, traditional uses of this plant differ depending on sampled areas. In Brazil and Argentina, leaf decoction of *C. citratus* is widely used by local populations to manage analgesic, inflammation, pyretic, spasmodic, diuretic, sedative, anxiety, and epilepsy [63,80]. In the same area, Colombian population use the grounded parts of *C. citratus* including rhizome and roots for toothbrushes [67,79]. In the Caribian zone, many populations included parts of *C. citratus* in their folk medicine. For example, leaves and hot water extract from dried leaves are administrated orally in Guatemala, Costa Rica, and Cuba to manage carminative, cough, expectorant, depurative, rheumatism, and hypotensive diseases [68,77,81]. In North America, the use of hot water extract from dried leaves of *C. citratus* to manage wound healing and bone fractures was mentioned in the USA; the Americans use *C. citratus* extracts via topical administration to patients [82].

4. Biological activities

4.1. Antioxidant effect

Oxidative stress is considered as a pathological state characterized by the overproduction of reactive oxygen species (ROS). In normal state, ROSs control different physiological functions including cellular signaling, cells differentiation, and apoptosis [83–88]. ROSs are known to fulfill a crucial role in physiological functions, however, the disadvantage of their overproduction is considered to be the main responsible for organ damages [89]. The attenuation of deleterious effects of ROS constitutes a pivotal objective of prevention strategies using natural products with high antioxidant potential [90]. Lemongrass phytochemical analysis revealed the presence of broad range of biological compounds that have an interesting antioxidant ability viz caffeic acid, ferulic acid, *p*-coumaric acid, luteolin, apigenin and their derivatives [41]. Studies have evaluated lemongrass ability on lowering and attenuating toxicities induced by cisplatin through suppression of Bid and Bcl2 gene expression [91]. *In vitro* studies, different extracts including infusion and decoction are shown in a study by Figueirinha et al., [42] to elicit the antiradical activity using DPPH test revealed that the infusion preparation was the strongest extract against free radical DPPH. The same study showed the presence of different flavonoids such as flavonoids glycosides which can contribute to its antioxidant capacity [42]. In addition the *in vivo* study, testing the effect of administration of *C. citratus* at a dose of 60 mg/kg during one week on nickel chloride-induced toxicity, revealed that lemongrass extract inhibits the micronuclei formation in polychromatic and normochromatic erythrocytes [92]. Indeed, on the other hands, Lemongrass aqueous extract added to VERA cells culture for 24 and 72 h at different concentrations had no alteration in viability cells, cytotoxicity, and proliferation process [93]. Furthermore, the presence of lemongrass extract reduced the oxidative stress induced by rotenone in VERA cells through decreasing ROS levels such as nitric oxide, superoxide, and lipid peroxidation [93]. Furthermore, an *in vivo* study of streptozotocin induced diabetes mellitus showed that the administration of citral as the main compounds of *C. citratus* increases the total antioxidant capacity, paraoxonase 1 PNO1, and endothelial nitric oxide synthase (eNOS) serum levels [94]. 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. 3).

4.2. Antimicrobial effect

Discovering new effective drugs for the treatment of human diseases with low negative impacts is nowadays among the world's research priorities Since microbial infections constitute a really threat for human health by their ability to resist to multiple antibiotics [95]. lemongrass has been shown to have promising antimicrobial ability against numerous microbial strains including *Bacillus subtilis, Staphylococcus aureus, Listeria spp., Enterococcus faecalis, Salmonella typhi, Candida tropicalis, Fusarium graminearum and Fusarium oxysporum* [95–98]. Indeed, it was reported that *C. citratus* contains numerous bioactive compounds known with their ability to eradicate different pathogenic microorganisms [99]. Among these compounds, flavonoids can exert their action on different targets including fatty acid synthase type II (FAS-II), DNA gyrase, DHFR-EGCG helicase, and virulence enzymes [88–90]. The combination of plant bioactive compounds with antibiotics can boosts antibacterial activity against multidrug-resistant microorganisms including *S. aureus, E. coli*, and *pseudomonas aeruginosa* [91–93]. Luteolin, as the most flavonoids component found in *C. citratus,* exhibited high antibacterial properties destroying the cell membrane of *S. aureus* and *L. monocytogenes* and sabotaging biofilm formation [100,101]. Moreover, luteolin derivatives were stated to be the most active components against bacterial strains such as *S. aureus, S. epidermidis, E. faecalis, Micrococcus luteus, B. subtilis, B. cereus, S. typhimurium, E. coli, Proteus mirabilis, Klebsiella pneumonia, P. aeruginosa, Helicobacter pylori,* and other pathogenic yeasts such as *Candida albicans, C. parapsilosis,* and *C. glabrata* [102].

The plant-derived flavonoids use different mechanisms than those of conventional drugs, and thus could be of importance in the enhancement of antibacterial therapy [96–98]. Numerous studies have been conducted on flavonoids, particularly catechins (recorded in lemongrass), to determine whether they have antimicrobial effects on both Gram-positive and Gram-negative bacteria [99,103]. Two processes are involved in the interactions of flavonoids with lipid bilayers [104–106]. The creation of hydrogen bonds between the polar head groups of lipids and the more hydrophilic flavonoids at the membrane interface is involved in the second process, whereas the first is related to the partitioning of the more non-polar compounds in the membrane's hydrophobic core. Additionally, non-specific interactions between flavonoids and phospholipids have the potential to alter the structure of the membrane (such as its thickness and fluctuations) [107] and subtly alter how membrane proteins are distributed and function, as well as alter the pharmacological flavonoids properties themselves [108,109]. Additionally, it has been noted that flavonols, particularly galangin, can lead to bacterial cell aggregations [102,110]. However, it should be noted that after aggregation, growth bacterial ability was reduced. It seems improbable that flavonoids promote the formation of biofilms since they presumably cause bacterial aggregation by partial lysis, which results in membrane fusion and limits active nutrient uptake through a smaller membrane surface [102,111]. Contrarily, other research groups showed that flavonoids do, in fact, prevent biofilms [112–117]. For example, Quercetin demonstrated significant effectiveness against *Vibrio parahaemolyticus* biofilm on surfaces of food and down regulates virulence genes [118–122]. The antibiofilm properties of isovitexin (apigenin-6-C-glycoside 14) and 5,7,4′-trihydroxyflavanol against *S. aureus* (ATCC 29213), for instance, were demonstrated by Awolola et al., [123]. Similarly, El-Adawi found that *S. mutans* biofilm development was reduced by 55–66 % in response to flavonoid exposure at 2–15 % [124]. In order to guard against many harmful agents and the development of biofilms, hydrophilic flavonoids can interact with the membrane surface [125]. Bacterial-type II fatty acid synthase (FAS-II) is a great target for an antibacterial drug because it differs greatly from the mammalian one (FAS-I) [126]. The following list summarizes the various inhibitors of the FAS-II components that have been reported so far.

According to Zhang et al. and Ghosh et al., 3-hydroxyacyl-ACP dehydrase from *H. pylori* is inhibited by apigenin, quercetin, and sakuranetin [89,108]. The 3-ketoacyl-ACP synthase from *E. faecalis* has been extensively studied, and 11 flavanones with various hydroxyl group configurations have been screened [127]. Further, Eriodictyol, taxifolin, and naringenin had the best results. The antibacterial activity of flavonoids depends on hydrogen bonding between their hydroxyl groups at the C-4′ and C-5′ positions of the B ring and the enzyme's amino acid residues Phe308 and Arg38. Elmasri et al. [128] observed that the flavonoids 5,6,7,4′,5′-pentahydroxyflavone and 5-hydroxy-4′,7-dimethoxyflavone reduced the activity of the MCATs, which controls bacterial FAS-II. Equally, flavonoids significantly block topoisomerases, which adds to their antibacterial effect.

For instance, DNA gyrase is only found in prokaryotes and is a crucial enzyme for DNA replication, making it a prime candidate for antibacterial medication development [129]. According to Ohemeng et al., [130], quercetin, apigenin, and 3,6,7,3′,4′-pentahydroxyflavone all inhibit DNA gyrase from *E. coli* [131]. Additionally, *in silico* analysis suggested that quercetin may target subunit B of DNA gyrase from *M. smegmatis* and *M. tuberculosis* [132]. According to several authors, treatment of *S. aureus* with flavonoids, primarily isobavachalcone and 6-prenylapigenin, led to depolarization of the bacterial membrane [108,123].

4.2.1. Inhibition of bacterial toxins

Hyaluronidases, which are produced by both Gram-positive and Gram negative bacteria, are significant virulence factors that either directly interact with host tissues or hide the bacterial surface from the host's defense mechanisms [20,124]. In the bacterial pathogenesis, hyaluronidase-mediated hyaluronan degradation raises connective tissue permeability and lowers bodily fluid viscosity [133]. Notably, hyaluronic acid lyase (Hyal B) inhibitory flavonols in *Streptococcus agalactiae* include myricetin and quercetin (found in the study plant) [134]. The amount of hydroxyl groups in the flavonoid structure correlated with an increase in the inhibitory impact of the flavonoids [135].

According to studies of [102,127], flavonoids, particularly catechins and proanthocyanidins (recorded in lemongrass), were suggested to neutralize bacterial toxic factors produced by *Vibrio cholerae, S. aureus, Vibrio vulnificus, Clostridium botulinum,* and *Bacillus anthracis* [136]. Similar to genistein, kaempferol, kaempferol-3-O-rutinoside, and quercetin glycoside suppressed the neurotoxic from *C. botulinum* [137], but *S. aureus'* exotoxin was inhibited by genistein [138]. One of *S. aureus's* most crucial virulence factors is the -hemolysin (Hla) [139], a component of the bacterial pore-forming-barrel toxins [140]. According to Soromou et al., [141], pinocembrin (flavanone) lowers the transcription level of the Hla and -haemolysin genes, which diminishes *S. aureus* -hemolysin synthesis in a concentration-dependent way Pinocembrin has also been investigated to determine how it interacts with *Neisseria gonorrhoeae* bacterial membranes [102,142,143]. Pinocembrin-induced cell lysis was detected and the action was due to induction of cellular apoptosis, ROS production and cell cycle arrest [144,145]. According to Sugita-Konishi et al., [146], gallocatechin gallate reduced the production of verotoxin from enterohemorrhagic *E. coli* cells, a and thus, catechins can be used to avoid food poisoning brought on by *E. coli*

5. Pharmacological effects

5.1. Antidiabetic effect

5.1.1. In vitro studies

Numerous *in vitro* studies have been undertaken to check the possible antidiabetic activity of many natural products. Indeed, some

carbohydrate hydrolyzing enzymes, such as alpha amylase, are implicated in the simplification of carbohydrates into sugar resulting in hyperglycemia. The control of these enzymes activity could be the effective approach to control hyperglycemia. An *in vitro* study revealed that the nanoparticles prepared using *C. citratus* exhibited similar inhibitory effect of acarbose at dose of 100 µg/mL on alpha amylase [147]. It has been reported that the flavonoid fraction is particularly strongest than the extract with an IC_{50} approx. 14.88 µg/mL on alpha glucosidase [148]. Molecular docking techniques revealed that flavonoids, such as aglycones, mono-C-glycosylflavones, *O*-glycosylflavones, and *O*,C-diglycosylflavones, established different interactions with B ring, π-π interactions, a π-cation interaction, hydrogen bonds on alpha glucosidase inhibiting its activity on carbohydrates [149]. The results obtained *in vitro* were confirmed with further studies *in vivo* as detailed below.

5.1.2. In vivo studies

Diabetes is pathologic state manifested by dysregulation of glycaemia accompanied with several long-term complications if not treated correctly. Ethnopharmacological studies evoked that the *C. citratus* is widely used as a traditional source of medication for different illnesses particularly diabetes [17,150]. *C. citratus* tea was examined in fructose-streptozotocin-induced type 2 diabetic administered at 0.25 or 0.5 % ad libitum for 4 weeks and *C. citratus* tea was found to be more effective in the lowering of both sugar and lipids blood levels, insulin level, ß-cell function, and liver glycogen [151]. Due to the larger phytochemical content, consumption of LGT decreased blood glucose by 60.3 %, showing greater effectiveness. This may once more help to support the lemongrass' strong ability to inhibit the actions of the enzymes -amylase and -glucosidase. Similar results were found for the active constituents of LGT, citral, limonene, and linalool, which showed to lessen hyperglycemia and diabetes-related problems. These phytochemicals may act individually or in concert to have antihyperglycemic effects. The comparison of antidiabetic effect of organic and non-organic cultivation of *C. citratus* concluded that the herb cultivated organically provided an important antidiabetic effect [152], and enhanced a new generation of pancreatic islets.

The ability of some plants to combat diabetes may be attributed to their inhibitory effect on gluconeogenesis, which prevents muscle atrophy, as well as to improvements in insulin production and glycemic control. In contrast, loss of first-phase insulin secretion, inability to control hepatic glucose synthesis, and muscular resistance to glucose uptake are the pathophysiology of PPG increase in type 2 diabetic circumstances. Additionally, the absence of glucagon suppression is what causes postprandial hyperglycemia, so *C. citratus* may consider acting by opposing glucagon. Recent studies initiate the analysis of *C. citratus* impact on genes implicated in diabetes particularly the protein tyrosine phosphatase-1B (PTP1B) as a potential target which modulates sugar homeostasis [139,140]. *C. citratus* contains different flavonoids compounds such as swertiajaponin that has the highest binding affinity with protein tyrosine phosphatase-1B as compared to citral, 7-epi-alpha-eudesmol, 7-epi-ent-eudesmane-5,11-diol, and e(2*E*,6*E*)-hedycaryol through hydrogen bonds interactions [153]. The control of this protein is implicated in the regulation of numerous pathways which could be explain antidiabetic effect of *C. citratus* manifested by amelioration of endocrine system [154]. Endoplasmic reticulum (ER) stress is implicated in the pathogenesis and progression of diabetes inducing pancreas destruction and insulin-resistance [155]. Within this background, *C. citratus* proved its ability to downregulate the expression of ER stress markers such as glucose regulated protein 78 (GRP78), protein kinase RNA-like ER kinase (PERK), inositol requiring enzyme 1 (IRE1), activating transcription factor 4 (ATF4), CCAAT-enhancer-binding protein-protein (CHOP), and tribbles 3 (TRB3) in pancreas of diabetic rats [156]. Bioactive ingredients of medicinal plants react synergistically controlling different pathways resulting in beneficial biological activities [153]. New combination has appeared with this regard, such as combination of three flavonoids compounds (catechin, epicatechin, and rutin) as a novel complete formulation to treat diabetes [7]. This functional combination plays a positive role preventing hyperglycemia and hypoglycemia in alloxan-induced diabetic mice [7]. Flavonoids are widely investigated for their pharmacological effects and have proved their ability to prevent and treat different polygenic ailments including diabetes. The antidiabetic, antioxidative, anti-inflammatory and cardioprotective effects of bioactive molecules extracted from *C. citratus* are summarized in Table 4.

5.2. Anti-inflammatory effect

Conventional medications to treat painful diseases such as arthritis, sciatica, cluster headaches etc., were limited due to their serious sides effects [214]. Against this evidence, scientists keep searching for new natural drugs with high efficiency and lower sides effects. *C. citratus* belongs to the long list of medicinal plants with considerable anti-inflammatory properties [12,138,150,204,215]. Thus, *C. citratus* was widely investigated *in vivo* using animal models. Costa et al. [36] examined the anti-inflammatory effect of different fractions of *C. citratus* including flavonoids fraction and tannins fraction using the carrageenan-induced rat pas edema model. Authors noticed that the combination of both fractions reduced the edema volume approx. 59 % due to their richness of bioactive compounds especially luteolin [36]. This bioactive derivative has been proven to downregulate the proinflammatory factors such as cytokines, iNOS, TNF-α, IL-ß, and IL-6 [216]. In the same context, Fransisco et al. [216] proved that the phenolic acid-rich fraction and tannin-rich fraction inhibits NF-κb activation in both human macrophages and murine macrophage pretreated with different *C. citratus* fractions. In addition, these authors evoked that fractions of *C. citratus* possessed an important decrease in the proteasome activity of murine macrophages LPS-activated and diminished significantly nitric oxide production which could explain the anti-inflammatory effect of *C. citratus* which is considered as a promising source of active and safe substances [216–221].

5.3. Cardioprotective effect

Besides the aforementioned properties, the cardioprotective effect of *C. citratus* is pointed out as an interesting beneficial property provided by the plant as reported in previous studies. Antihypertensive effect of *C. citratus* is reported in several ethnomedicinal studies [207,208], and experimental studies which confirm this beneficial properties using methanolic extract to elicit vasorelaxant properties in thoracic aorta and umbilical vein [209,210]. Regarding the impact of *C. citractus* on vascular tone using infusion and different fraction of plant suggested that the *C. citratus* contains vasoconstrictor substances [210,211]. These findings confirm that the *C. citratus* contains large group of bioactive compounds including luteolin derivatives and apigenin derivatives which boost the noradrenaline effect [222]. Previous reports linked the vasorelaxation property on the impact of bioactive ingredients of *C. citractus* on nitric oxide and calcium channels implicated in vasocontraction of arteries [209,210,212,223]. It has been shown that the prostacyclin is implicated in the vasorelaxation process and the cyclooxygenase is a complementary pathway involved in the vasorelaxation effect of *C. citratus* [210,211]. Is was noteworthy, that luteolin inhibits mitogen adenosine map kinase (MAPK) pathway, enhances the cardiomyocytes, ameliorate cardiac function, and prevents cardiac injuries [224,225] (Fig. 4).

Table 4
Antidiabetic, antioxidative, anti-inflammatory and cardioprotective effects of bioactive molecules extracted from C. citratus.

Bioactive molecules	Dose/Exposure route and duration treatment	Models	Key results/Involved Mechanisms	References
Antidiabetic effect				
Rutin	0, 25 and 50 mg/kg B.W., orally for 30 days	Streptozotocin/Wistar rats	Prevent pancreatic β-cell destruction, ↑insulin secretion	[157]
	10 mg/kg/day, orally for 28 days	Alloxan/Mice	Prevents hyperglycemia and acts synergistically with Catechin, Epicatechin	[7]
	90 mg/kg/day, orally for 10 weeks	Streptozotocin/ Sprague-Dawley rats	Inhibition of polyol pathway, ↓lipid peroxidation and ↓oxidative stress	[158]
Quercetin	2.5, 7.5, 22.5, and 67.5 mg/kg/day, orally for 14 days	Tamoxifen/Wistar rats	↓Blood glucose level and ↓liver, brain, intestine, and adipose butyrylcholinesterase activity	[159]
	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	[160]
	100 mg/kg/day, orally for 15 days	Streptozotocin/Wistar rats	Modulation of TXNIP/IRS-1/PI3K pathway, ↓hepatic TXNIP expression, ↑hepatic insulin sensitivity and ↑glucose uptake	[161]
Kaempferol	50 mg/kg/day, orally for 12 weeks	Streptozotocin/Wistar rats	↑Hexokinase activity, ↓hepatic glucose production, ↓hepatic pyruvate carboxylase activity and inhibits the gluconeogenesis.	[161]
	200 mg/kg/day, orally for 14 days	Streptozotocin/male mice	↑ cAMP and Ca^{2+} intracellular levels and ↑GLP-1 and insulin release,	[162]
	200 mg/kg b.w./day, orally for 14 days	Streptozotocin/Wistar rats	↓fasting glucose levels, ↑fasting insulin levels and HOMA-β, ↓ROS and MDA levels, stimulated GSH and SOD activities; and Upregulated the Nrf-2/HO-1 pathway	[163]
Apigenin	50 mg/kg b.w./day, orally for 45 day	Streptozotocin/Wistar rats	↑Insuline secretion, ↓fasting blood glucose, inhibition of Advanced glycation end products (AGEs) and ↓Aldose reductase (ALR) activity normalization of lipid profile parameters, prevents oxidative stress induced hepato-nephrotoxicity.	[164]
	10 mg/kg b.w./day, orally 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	[165]
	1.5 mg/kg/day, i.p for 28 days	Streptozotocin/Wistar rats	Enhances GLUT4 translocation in skeletal muscles, increase glucose uptake and down regulates the cyclic ADP ribose hydrolase (CD38) expression	[166]
Isoorientin	200 mg/kg b.w./day for 5 weeks	Alloxan/Wistar rats	↓Blood glucose level and improve oxidative stress markers (MDA, CAT, SOD GSH and GPx), up-regulation of NO levels.	[167]
	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.	
	0, 1, 5, or 10 μM, for 8 days	3T3-L1 cells.	↓Lipid accumulation and insulin resistance by down-regulating the expression of adipogenesis transcriptional regulators including PPARγ, CAAT/enhancer binding protein-α (C/EBPα) and sterol regulatory element binding protein (SREBP)-1c	[168]
	15 mg/kg isoorientin once a day for 15 days	Streptozotocin /Sprague-Dawley rats	↓Fasting blood glucose concentration, ↓body weigh and lowered cholesterol and triglycerides (TG) levels	[169]
Pyrogallol	2.5 mg/kg/ B.W./day, orally for 4 weeks	High-fat diet/male mice	Improve glucose and lipid homeostasis by down-regulation the Lox-1/PKC-α/MMP9 pathways.	[170]
Cynaroside	50 mg/kg/ B.W./day, orally for 15 days	Alloxan/male mice	↓Fasting blood glucose levels by modulating peroxisome proliferator-activated receptor gamma (PPAR-γ) signaling pathway	[171]
Antioxidative effect				
Rutin	50 mg/kg/ B.W., intraperitoneally 1 h before reperfusion induction	ovarian ischemia-reperfusion /Wistar albino female rats	↓Blood MDA levels, ↓The expressions of interleukin 1 beta (IL-1b), tumor necrosis factor alpha (TNF-a), and inhibits the activity of cyclooxygenase 2 (COX-2); and ↑GSH activity	[172]
	50 and 100 mg/kg b.w./day, orally for 8 days	Cisplatin/male albino Wistar rats	↓ MDA, interleukin 1 beta (IL-1β), creatine kinase (CK), tumor necrosis factor alpha (TNF-α), and troponin I levels in Blood, plasma and cardiac tissue	[173]
	50 mg/kg b.w./day, orally for 7 days	Lead acetate/Wistar rats	↑SOD, CAT, and GPx hepatic activities as compared to non-treated lead acetate groups	[174]
Quercetin	50 mg/kg/day, i.p for 21 days.	alcohol-induced rat oxidative stress	↑GSH level, SOD, GR, GP and CAT activity, and ↓the expression of TNFα, IL-1β, and IL-6	[175]
	25 mg kg b.w./day, orally for 21 days	Letrozole/male rats	Exhibits protective effect against oxidative stress induced by enhancing CAT, SOD and GPX activities	[176]
Kaempferol	100 mg/ kg/day, i.p for 6 weeks.	Aorta banding/C57BL/6 mice	Down-regulates the ASK1/MAPK and JNK1/2 and p38 signaling pathways	[177]
	10 mg/ B.W./day, orally for 8 weeks.	Streptozotocin/male mice	↓Nuclear factor-κB (NF-κB) nucleus translocation, ↑nuclear factor-erythroid 2 p45-related factor-2 (Nrf-2), ↓blood glucose levels and prevents cardiac fibrosis	[178]
	10 mg/kg b.w./day, orally for 4 weeks	Ang II/male C57BL/6 mice	Modulates NF-kB/mitogen- activated protein kinase and AMPK/Nrf2 signaling pathways.	[179]

(*continued on next page*)

Table 4 (*continued*)

Bioactive molecules	Dose/Exposure route and duration treatment	Models	Key results/Involved Mechanisms	References
Luteolin	20 mg/kg b.w./day, orally for15 weeks	Streptozotocin /C57BL/6 mice	Modulates the expression of mRNA levels of HO-1 and NAD(P)H dehydrogenase (Quinone 1) (NQO-1) by activating the Nrf2 antioxidant pathway and	[180]
	100 and 200 mg/kg b.w./day, orally for 28 days.	Bisphenol A/Wistar rats	↑GSH, ↑SOD ↑GPX activities, ↓MDA level, ↑Nrf2 and ↑HO-1 Expressions.	[181]
	50 and 100 mg/ t/ day, orally for 15 days.	Doxorubicin/Wistar rats	↓Lipid peroxidation, ↓caspases-3 and caspases-9 activities, ↓hepatic and kidney damages, ↑ SOD, CAT, GPX, and GST activities as well as ↑GSH and TSH levels in kidney and hepatic tissues. ↓Lipid peroxidation (LPO), ↓ reactive oxygen/nitrogen species (RONS) and ↓ xanthine oxidase (XO) in renal and hepatic organs	[182]
Apigenin	25, 250, and 500 mg/k.b.w./day, orally for 2weeks	Doxorubicin /Male BALB/c mic	↓Oxidative stress biomarkers and ↑enzymatic and non-enzymatic antioxidant levels	[183]
	25 mg/kg b.w./day, orally for 28 days	Nickel oxide nanoparticles/Wistar rats	↓Renal and hepatic MDA and nickel (Ni) levels, ↑GSH and SOD activities of renal and hepatic tissues	[184]
	0.005, 0.01, and 0.02 g/kg b.w./day, orally for 28days	ethylene glycol/Wistar rats	↑SOD, CAT, GPX activities in Kidney tissue and ↓lipid peroxidation in kidney, and prevents hepatic structure disorganization	[185]
Isoorientin	10, 20, 40 mg/kg b.w./day, orally for 3days	Lipopolysaccharide/male mice	Modulates Keap1/Nrf2-HO-1, NLRP3 signaling pathways	[186]
	50 mg/kg b.w./day, i.p, for 3 days	Cisplatin/C57BL/6 WT mice	Enhances Nrf2 translocation and ↑ the expression of HO-1 and NQO1, ↓the expression level of NOX4, thus decreasing oxidative stress	[187]
Anti-inflammatory effect				
Rutin	100 mg/kg b.w./day, orally for 14 days.	Unilateral ureteral obstruction/Wistar rats	↓NF-κB activation and TGF-β1/Smad3 signaling pathways	[188]
	50 and 100 mg/kg b.w./,i.p, for 7days.	Methotrexate/Wistar rats	↓ Immunoregulatory cytokines (IL-2, IL-4 and IL-10)	[189]
Quercetin	1 mg/kg/day, orally for 15 days.	Sulfate sodium/male BALB/c mice	Down-regulates NF-κB signaling pathway and inhibites inducible nitric oxide synthase expression	[190]
	25 mg/kg/day, orally 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 (NF-κB).	[191]
Kaempferol	2 and 4 mg/kg b.w./day, orally for 10 days.	Aged Sprague-Dawley rats	↓IL-1β, TNF-α, IL-18, and IL-6 synthesis	[192]
	3 and 10 mg/kg mg/kg/day, orally for 22 days	Airways allergic inflammatory model in mice	Down-regulates the nuclear transcription NF-κB signaling pathway in in the lung of mice,	[193]
Luteolin	10 and 20 mg/kg/day, orally for 4 weeks.	Streptozotocin /Wistar rats	Inhibition of RIP140/NF-κB signaling pathway.	[194]
	1, 10 and 50 mg/kg/day, orally for 3 days	Carrageenan/male mice	↓Cox-2 mRNA expression.	[195]
Apigenin	20 and 40 mg/kg/day, orally for 28 days.	Ovary syndromein rat model	↓TNF-α and IL-6 mRNA expression	[196]
	10 mg/kg b.w./, intraperitoneally 1 h before and 3 h after lipopolysaccharide administration	Lipopolysaccharide/Wistar rats	Down-regulates COX-2 and NF-κB signaling Pathway	[197]
Isoorientin	25 mg/kg and 50 mg/kg b.w./day, orally for 5 days	Lipopolysaccharide/male mice	Down-regulates the expression of COX-2, Upregulates Nrf2/HO-1 pathway, inhibits the activation of ERK and NF-κB.	[198]
Pyrogallol	2.5 mg/kg b.w./day, orally for 4 weeks	High-Fat-Diet /male C57BL/6 N mice	↓The expression of TLR4, NF-κB in the brain tissue. Down-regulates SOCS3 and increases the phosphorylation of STAT3.	[199]
Cynaroside	150 μM for 4 h before exposure to H2O2	H2O2/H9c2 cardiomyoblasts	↓The over production of ROS and Down-regulates of the NF-κB pathway	[200]
	2 and 20 mg/kg, 1 h before carrageenan treatment	Carrageenan /male C57BL6/cmd	↓ The production of pro-inflammatory cytokinesL-1β, IL-4, IL-6 and TNF-α.	[201]
Cardioprotective effect				
Rutin	20, 48 and 80 mg/kg b.w., i.p, 30 min before surgical process	Myocardial ischemia/Sprague-Dawley rats	Up-regulates mRNA antioxidant expression in heart, Upregulates SIRT1/Nrf2 signaling pathway, Prevents myocardial oxidative damages	[202]
	100 mg/kg b.w./day, orally for 8 days	Lipopolysaccharide /Male BALBE/c mice	Improves cardiac markers oxidative enzymes (↑SOD and ↑CAT activities MDA, as well as ↓MDA and↓ H2O2 levels), Improves myocardium morphological changes, Control inflammatory responses	[203]

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Table 4 (*continued*)

Bioactive molecules	Dose/Exposure route and duration treatment	Models	Key results/Involved Mechanisms	References
Quercetin	100 nM during 10 min, Intravenous perfusion	Myocardial ischemia/reperfusion	Improves left ventricular developed pressure (LVDP), ↓the creatine kinase (CK) release into the coronary effluent, TNF-α, IL-6 and IL-1β levels in the heart. Inhibits mitoK_{ATP} channels and NO synthesis	[204]
	120 and 60 mg/kg/day	Isoproterenol/Adult Sprague–Dawley rats	Inhibits Ca2+ channel, Improves heart pathologic morphology, ↑SOD, ↑CAT, ↑GSH, ↑GPx, ↑GST activities; and relative ROS levels in the heart tissue.	[205]
Kaempferol	10 mg/kg b.w./day, orally for 2 weeks before cisplatin administration	Cisplatin/ C57BL/ 6 mice	Inhibits STING/NF-κB-mediated inflammation, Inhibits the mRNA expression of caspase-3, BAX and BAK (pro-apoptotic proteins of BCL-2 family) in the cardiac tissue,	[206]
	1, 3 and 10 mg/k b.w./day, intraperitoneally, 7 days before Isoprenaline treatment.	Isoprenaline /male Wistar rats	Prevents myocardial infarcted area and heart rate, regulates systolic and diastolic blood pressure, ↑SOD and ↑CAT activities; and ↓MDA levels in heart tissue, ↓pro-MMP-2 expression and MMP-9 level,	[207]
Luteolin	100 mg/kg b.w./day, oraly for 2 weeks	Ischemia-reperfusion/Male Sprague-Dawley diabetic rats	Ameliorated myocardial viability and cardiac function. ↑ mRNAexpressions of heme oxygenase-1 (HO-1), SOD, CAT, and GSH; and ↓MDA levels in heart, Upregulates eNOS/Nrf2 pathway and it related antioxidative signaling pathways	[208]
	10 μg/kg b.w./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)	[209]
Apigenin	75 mg/kg b.w./day, orally for 14 days	Isoproterenol/Diabetic rats	Prevents myocardial infarction, improves left ventricular end-diastolic pressure, attenuates edema, myonecrosis, oxidative stress, and cell death, down-regulates PPAR-γ in the rats myocardium.	[210]
	10 μM for 2 h before Isoproterenol hydrochloride treatment	Isoproterenol hydrochloride/ardiomyoblast H9C2 cells	↑SOD, CAT, GPx and GSH activities as well as ↓MDA and LHP levels inH9C2 cells. Prevents DNA dmages and apoptotic cells	[211]
Isoorientin	20 and 40 mg/kg b.w./day, orally for 56 days	High-fructose/Wistar rats	Prevents cardio-metabolic complication by increasing antioxidant enzyme activities 8 SOD, CAT and GPx) and improving lipid profile. Decreases the production of pro-inflammatory cytokines IL-1, IL-6 and TNF-α.	[212]
	0.1–100 μM for 4 h	3T3-L1 adipocytes	Blocks lipid storage, increases glycerol release, upregulates the expression of AKT and AMPK pathways, ↑mitochondrial respiration, ↑ ATP and oxygen consumption	[213]
Cynaroside	150 μM for 4 h before exposure to H2O2	H2O2/H9c2 cardiomyoblasts	↓The over production of ROS and modulates the JNK and P53 signaling pathways	[200]

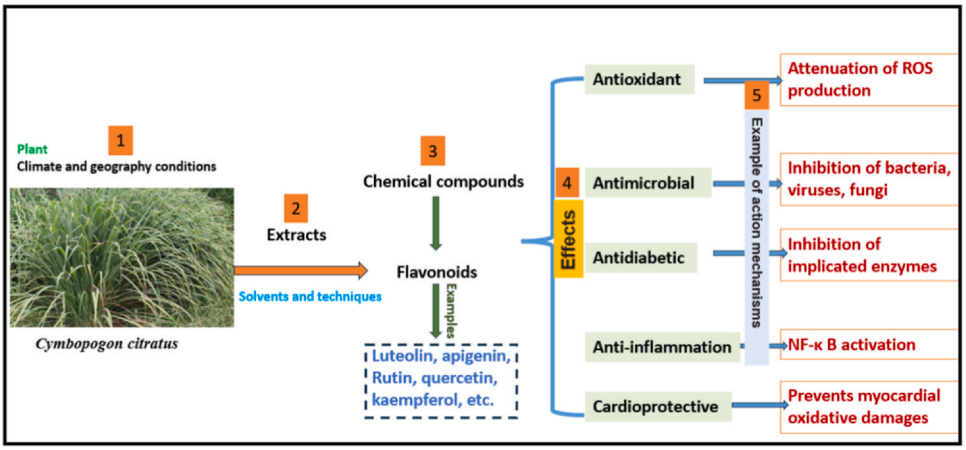

Fig. 4. Summary of the pharmacological effects of *C. citratus* extracts. **1**: plant material under different factors; **2**: extraction with different techniques and solvents; **3**: diversity of chemicals, mainly flavonoids; **4**: properties of extracts; and **5**: examples of action mechanisms of flavonoids.

6. Conclusion

Besides the pharmacological interest of *C. citratus*, its traditional use is confirmed worldwide. Thus, the plant is widely used in traditional applications, and especially known for its antimicrobial and anti-inflammatory effects. This statement makes this species attractive as a supply of pharmacoactive extracts and compounds, mainly flavonoids. Indeed, several studies have highlighted the role of these compounds which are responsible for multiple functional abilities such as antioxidant, antimicrobial, antidiabetic, anti-inflammatory, and cardioprotective properties. Moreover, most of recent investigations pointed off that flavonoids extracted from *C. citratus* are associated with numerous biological activities and act synergistically to provide several beneficial effects as aforementioned above. However, few information is available regarding other aspects including the optimization of extraction conditions to isolate flavonoids from the plant. Similarly, the investigations have not yet addressed the toxicity of chemical compounds extracted from *C. citratus*. This is suggested to guarantee the use of the plant in traditional medicine. Therefore, more advanced studies are needed to explore new usages of both plant and their chemical components including flavonoids. Future research studies should focus also on the application of green extraction methods to optimize the extraction of active biomolecules, and further treat emerging diseases (metabolic, chronic, etc.) or to counteract new infectious agents or pathogens. In this option in *silico* assays are needed to simulate the effectiveness of biomolecules in a cost-effective and save manner.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prenap.2024.100046.

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