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Antioxidant and anti-inflammatory activities of bioactive compounds from *Crescentia cujete* L. leaves and fruit–A review

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ABSTRACT

Crescentia cujete is one of the plants considered to have medicinal properties and is commonly used for ethnomedical purposes for its antioxidant and anti-inflammatory properties. Despite the plant's common indigenous uses, a couple of isolation and characterization studies were done and published in the past listing both identified and unidentified compounds found from the plant. However, the number of studies focusing on its pharmacological activities, specifically the antioxidant and anti-inflammatory activities of the bioactive compounds present in the plant along with their mechanism of action is underwhelming and the plant is far from being fully optimized for drug development and pharmacological advancement. Data and information collated for this review were gathered from publications, books, and articles from trusted scientific journals. In this review, available studies focusing on the antioxidant and anti-inflammatory activities of various extracts from *C. cujete* were collated and established. The most commonly studied part of the plant as well as the grey areas realized from this review regarding the antioxidant and anti-inflammatory activities of the plant consequently suggests the incorporation of *in silico* studies to help future researchers understand the mechanism of action of the plant's bioactive compounds that have antioxidant and anti-inflammatory activities which will ensure the continuous and fast-moving advances in the drug-development and pharmacological advancement of *C. cujete* extracts.

1. Introduction

Chronic diseases such as diabetes and cardiovascular diseases are proven to be one of the global health problems dealt with ever since the beginning of time. These chronic diseases caused and are continually causing deaths and disability to millions of people worldwide. One of the precursors of these chronic diseases is the overproduction of oxidants or reactive oxygen and nitrogen species in the body (Zhang et al., 2015) while one of the first biological responses the body produces in the occurrence of such diseases is inflammation (Wang et al., 2013). Overproduction of oxidants and chronic inflammation have been observed side by side for decades worth of medical studies due to their association with specific diseases such as cancer, allergies, arthritis, and cardiovascular diseases (Devi et al., 2015). Overproduction of oxidants can be mediated through the intake of antioxidants which mediates the overproduction through various mechanisms such as oxidative marker (ROS) and ROS-producing enzymes inhibition (Zhang et al., 2015; Merhan, 2017; Bernatova and Liskova, 2021). On the other hand, chronic inflammation can be mediated through the intake of anti-inflammatory drugs which also works through various mechanisms such as inflammatory markers (iNOS, NO, and COX-2) inhibition (Zhu et al., 2018; Nunes et al., 2020). Medicinal plants are widely known for their abundance of phytochemicals and bioactive compounds that are deemed essential for the treatment of various diseases, making them valuable research and source material for the advancement of pharmacological applications and drug development. *Crescentia cujete*, also known as the "miracle fruit" in the Philippines, is one of these medicinal plants that

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is widely known, especially in tropical countries, where it is highly cultivated for its numerous medicinal properties. It has a green, globular fruit with a smooth, but hard and woody exterior (Rellin et al., 2018). Traditionally, the preparation of medicinal concoctions from this plant is often made and applied directly to the target area or ingested to treat diseases and ailments such as colds, asthma, and snake bites (Morton, 1968). The flesh is also highly regarded in some countries as an effective cleansing and healing agent for cuts and other wounds (Hartati et al., 2018). Filipino locals claim to have observed some significant health effects of the intake of extracts from the plant's fruit and leave specifically: Antibacterial, anticholesterol, anti-diabetic, antioxidant, and anti-inflammatory (Billacura and Laciapag, 2017; Samaniego et al., 2018; Magno et al., 2022). Due to the medicinal claims regarding this plant throughout the world, several studies focused on specific phytochemical properties (antioxidant and anti-inflammatory), chemical constituents, and determination of the mineral composition of *Crescentia cujete* were conducted in the past (Ejelonu et al., 2011; Rellin et al., 2018; Jose et al., 2020), demonstrating the abundance of bioactive compounds known to have pharmacological properties in various parts of the plant. Although several studies have been conducted to explore its antioxidant and anti-inflammatory properties and chemical constituents, information on the secondary metabolites found in the Philippine *Crescentia cujete* (Rellin et al., 2018), and complementary in vitro, in vivo, and in silico tests is quite scarce and is still unabundant to further support ethnomedicinal claims about it. This paper highlights the antioxidant and anti-inflammatory properties of *Crescentia cujete* L. along with the phytochemicals that exhibit these properties. Confirming the presence and bioactivity of these phytochemicals on the *C. cujete* plant from recent antioxidant and anti-inflammatory studies of *C. cujete* extracts provides potential future research ideas for pharmacological applications and drug-development advancements.

2. Phytochemicals and bioactive compounds with antioxidant and anti-inflammatory properties

Overproduction of oxidants such as reactive oxygen and nitrogen species plays important roles in the occurrence of chronic diseases such as cancer and most cardiovascular diseases. Approximately 10,000 phytochemicals were identified in various fruits, vegetables, grains, and plants but only a small percentage of these have known activities with antioxidant and anti-inflammatory as a couple of these pharmacological activities. Antioxidant compounds mediate the overproduction of reactive oxygen and nitrogen species such as superoxide and peroxide radicals through various mechanisms as shown in Table 1. One of the most common mechanisms of action is the scavenging of ROS and inhibition of ROS-producing enzymes which were done by most flavonoids (Koren et al., 2010). Another mechanism is the inhibition of both acetylcholinesterase and butyrylcholinesterase which was linked to inducing protective action on Alzheimer's disease (AD) (Cho et al., 2012).

Commonly, phytochemicals that possess strong antioxidant and free-radical scavenging properties also exhibit anti-inflammatory properties (Wu et al., 2012; Lin et al., 2021). Some of these phytochemicals are polyphenols and flavonoids. Just like the phytochemicals above, anti-inflammatory compounds mediate the overexpression or overproduction of inflammatory markers (NO, IL-1β, TNF-α, and PGE2) (Lau et al., 2007), and inflammatory marker-producing enzymes (iNOS) as their mechanisms of action (Vernaza et al., 2012). Other mechanisms of action to mediate inflammatory response are listed in Table 2. Some of these inhibitions can be observed in in vitro experimental models such as the inhibition of pro-inflammatory cytokine by naringenin in the RAW 264.7 macrophage model (Bodet et al., 2008).

3. Antioxidant and anti-inflammatory applications of *Crescentia cujete*

Crescentia cujete varieties from different parts of the world were studied for their pharmacological properties which include: Antioxidant (Parvin et al., 2015; Anwuchaepe et al., 2017; Billacura and Laciapag, 2017; Hasanah et al., 2018; Syaefudin et al., 2018; Sagrin et al., 2019; Juee and Naqishbandi, 2020), and anti-inflammatory (Autore et al., 2001; Parvin et al., 2015).

3.1. Antioxidant activity

Plants often used in phytotherapy and ethnomedicine are often found to be rich in phenolic compounds (Swallah et al., 2020), terpenoids, flavonoids, and polysaccharides, which are highly known for their many biochemical properties (Ghasemzadeh and Ghasemzadeh, 2011; Kasote et al., 2015), and due to the significant presence of these secondary metabolites, *Crescentia cujete* is expected to also harbor some if not all of the biochemical properties associated with these compounds, one of which is the antioxidant property. Therefore, there have been numerous studies regarding the antioxidant activity of different extracts from different parts of the plant.

Ethanolic extracts from leaves, bark, and fruits of *C. cujete* were found to have good antioxidant properties (Sagrin et al., 2019). Extracts of freeze-dried samples of leaves, bark, and fruit were prepared by solvent extraction with ethanol and with water. By the Folin-Ciocalteu method (total phenolic content, TPC assay), the ethanolic leaf extract revealed the highest TPC, followed by the ethanolic bark extract, and having the aqueous fruit extract with the lowest TPC. It was evident that ethanolic extracts are superior in antioxidant activity and phenolic compound extraction with the leaves and bark having the highest potential to be developed as natural antioxidants. However, it was also observed that all extracts other than the ethanolic fruit extract exceeded the potassium dichromate toxicity with the use of Meyer's toxicity index against the brine shrimp *Artemia salina*.

Table 1: Major classes of some identified plant-sourced antioxidant compounds (Zhang et al., 2015; Merhan, 2017; Bernatova and Liskova, 2021)

Classification	Compound	Mechanism
Flavonols	Keampferol	Downregulation of cancer-related genes expression
	Morin	ROS-producing enzymes inhibition and ROS scavenging
	Quercetin	Chelation of divalent metal cations (Fe^{2+}, Cu^{2+}, and Zn^{2+}), ROS-producing enzymes inhibition
	Catechin	ROS-producing enzymes inhibition and ROS scavenging
	Epicatechin, epicatechin gallate and epigallocatechin gallate	Inhibition of NF-κB and NRF-2 signaling
	Taxifolin	Reduction of ROS expression and ROS scavenging
Flavanones	Eriodictyol	Acetylcholinesterase and butyrylcholinestrase inhibition
	Hesperetin	Acetylcholinesterase and butyrylcholinestrase inhibition
	Naringenin	Acetylcholinesterase and butyrylcholinestrase inhibition
Flavones	Luteolin	Activation of the mitogen-activated protein kinase signaling pathway and MAPK signaling
Isoflavonoids	Daidzein	Reduction of radicals and ROS formation by hydrogen peroxide decomposition, active singlet oxygen quenching, and radical trapping and quenching
	Genistein	Downregulation of cancer-related genes expression, demethylation and reactivation of methylation-silenced tumor suppressor gene, inhibition of DNA methyltransferase-1 expression
Organosulfur compounds	Allicin	Enhancement of nuclear factor-like 2 antioxidant signaling pathways
Phenolic acids	Caffeic acid	Adipogenesis inhibition and downregulation of gene expressions
	Chlorogenic acid	Adipogenesis inhibition and downregulation of gene expressions
	Ferulic acid	Induction of several β-cell genes and synergistic action
Polyphenols	Butein	Platelet aggregation and adhesion inhibition
	Curcumin	Prostaglandin production, nuclear factor-κB activity, enzyme production, cytokine production inhibition, modulation of hypothalamic-pituitary-adrenal axis activity, serotonergic transmission, and hippocampal neurogenesis
	Anthocyanin	Prostaglandin production, nuclear factor-κB activity, enzyme, and cytokine production inhibition
	Dehydroglyasperin C	Blood pressure reduction, inflammation decreasing action through attenuated proliferation and migration of arterial smooth muscle cells
	Phloretin	Platelet aggregation and adhesion inhibition
	Resveratrol	Prostaglandin production, nuclear factor-κB activity, enzyme production, and cytokine production inhibition, modulation of hypothalamic-pituitary-adrenal axis activity, serotonergic transmission and hippocampal neurogenesis
Stilbenes	Tetrahydroxystibene glucoside	Regulation of Klotho gene
Tannins	Ellagitannins	UV radiation-induced inflammation, oxidative stress, DNA damage and suppression of immune responses
Proanthocyanidin (Condensed tannins)	procyanidins	Platelet aggregation and adhesion inhibition, downregulation of cancer-related genes and COX-2 gene expression, modulation of hypothalamic-pituitary-adrenal axis activity, serotonergic transmission and hippocampal neurogenesis
Carotenoids	α-Carotene	Lipid-soluble Chain-breaking action, capture of oxygen radicals, inhibition of active radicals by electron transfer and superoxide inhibition
	β-Carotene	Lipid-soluble Chain-breaking action, capture of oxygen radicals, inhibition of active radicals by electron transfer and superoxide inhibition
	Lycopene	Lipid-soluble Chain-breaking action, capture of oxygen radicals, inhibition of active radicals by electron transfer and superoxide inhibition
	Crocin	Lipid-soluble Chain-breaking action, capture of oxygen radicals, inhibition of active radicals by electron transfer and superoxide inhibition
	Lutein	Lipid-soluble Chain-breaking action, capture of oxygen radicals, inhibition of active radicals by electron transfer and superoxide inhibition
	Zeaxanthin	Direct quenching of ROS
	Cryptoxanthin	Genetic regulation, oxidative and inflammatory markers inhibition

Ethanolic extracts from the leaf and bark of *C. cujete* were observed to have significant free radical scavenging activity in the DPPH assay complemented with the Ferric reducing assay and phosphomolybdate radical scavenging assay. The ethanolic leaf extract showed higher antioxidant activity (% scavenging effects=97.73%, IC_{50}=8.78 μg/mL) compared to the ethanolic bark extract (% scavenging effects=87.59%, IC_{50}=18 μg/mL) and ascorbic acid (% scavenging effects=92.12%, IC_{50}=7.68 μg/mL) (Das et al., 2014).

β-carotene bleaching test was performed as a complementary antioxidant activity test for leaf extracts using the following solvents: Ethanol, methanol, hexane, chloroform, and ethyl acetate (Parente et al., 2016). In this study, the rate of β-carotene bleaching was observed to slow down due to the presence of antioxidants. The β-carotene served as the target molecule for the free radicals formed by linoleic acid oxidation that prompts the rapid degradation (bleaching) of β-carotene but is delayed by the presence of a free radical scavenger (Rodrigues et al., 2010). It was determined that the ethanolic leaf extracts exhibit antioxidant properties that are lower than the positive controls: BHA, BHT, and ascorbic acid. With a low percentage of inhibition percentage despite the abundant presence of antioxidant compounds in *C. cujete*, it was suggested that the antioxidants the plant contains are mainly hydrophilic antioxidants, which are known to be ineffective against lipophilic free radicals. This was supported by the results of the DPPH and ABTS assay, which showed the samples to have a comparable free radical scavenging activity compared to the positive controls, especially the methanolic extracts.

Observation of several fractions, *n*-hexane, dichloromethane, ethyl acetate, and water fractions, separated by liquid-liquid extraction of ethanolic stem bark extracts was focused in one study

(Syaefudin et al., 2018). Detection of antioxidants via thin layer chromatography (TLC)-autography DPPH method (Masoko and Eloff, 2007), all fractions were observed to contain adequate antioxidant compounds. Complemented with the DPPH method (Das et al., 2014), all fractions showed antioxidant activities with the dichloromethane fraction (IC_{50}=95.83±19.64 μg/mL) demonstrating the highest antioxidant activity and the ethyl acetate fraction (IC_{50}=174.56±21.93 μg/mL) demonstrating the lowest among the rest of the fractions.

Flavonoids such as quercetin, apigenin, cyanidin-3-rutoside, and ferulic acid were found to be concentrated in *C. cujete* flowers in a study of its methanolic and aqueous extracts (Cai et al., 2004). This study used an improved $ABTS^{\bullet+}$ method (Re et al., 1999) to systematically observe the total antioxidant capacity (TEAC) of the extracts. Compared to 111 more traditional Chinese medicinal plants, it is evident that the flowers of the *C. cujete* plant are also potential sources of potent natural antioxidants and beneficial chemopreventive agents.

Table 2: Major classes of some identified plant-sourced anti-inflammatory compounds (Zhu et al., 2018; Nunes et al., 2020)

Classification	Compound	Mechanism
Phenolics	Polyphenols	NO, IL-1β and TNF-α production inhibition
	Zerumbone and 3-O-methyl kaempferol	NO and PGE_2 production, iNOS expression inhibition
	Quercetin	NO and TNF-α production, iNOS expression inhibition
	Luteolin	NO and TNF-α production, iNOS expression inhibition
	Kaempferol	Decrease of iNOS, COX-2, and reactive CRP level
	Naringenin	Pro-inflammatory cytokine inhibition
	Granatin B	Inflammation stimulators inhibition
	Narirutin	NO, PGE_2, IL-1β and TNF-α release inhibition
	Flavone velutin	Excellent anti-inflammatory capacity
	Anthocyanin	Anti-inflammatory activity for penile plaque formation
	Punicalagin, punicalin, strictinin A and granatin B	NO and PGE_2 reduced production
Fatty acids	Oleic acid	ROS suppression and inhibition of inflammatory markers production
	Palmitic acid	ROS suppression and inhibition of inflammatory markers production
	Stearic acid	ROS suppression and inhibition of inflammatory markers production
	Linoleic acid	ROS suppression and inhibition of inflammatory markers production
Triterpenoids	Monomeric triterpenoids	High anti-inflammatory activity
	Pentacyclic triterpenoids	High anti-inflammatory activity
Saponins	Soyasaponins	iNOS enzyme activity suppression, down-regulation of iNOS mRNA expression, reduction of inflammatory markers, colon length, myeloperoxidase, lipid peroxide, proinflammatory cytokines and NF-κB activation in the colon
	Angularin A, angulasaponins A-C, azukisaponins III and VI	NO production inhibition
Lectins	Lectins	Inflammation reduction
	Monocot lectin	Inflammation reduction and neutrophil migration inhibition
	Soybean agglutinin	Carrageenan-induced paw oedema inhibition
Polysaccharides	Crude extract polysaccharides	Gene induction reduction of TNF-α, IFN-γ and granulocyte colony-stimulating factor
Peptides	Bioactive peptides	NO, iNOS, PGE_2, COX-2 and TNF-α inhibition
	Lunasin	Production reduction of ROS, release inhibition of pro-inflammatory cytokines (TNF-α) and IL-6
Alkaloids		
Other Compounds	Monogalactosyldiacylglycerol	High anti-inflammatory activity
	Monogalactosyldiacylglycerol	Downstream inflammatory mediators (COX-2, iNOS, NO and PGE_2)
	Phenethyl isothiocyanatae	Suppression of TRIF-dependent pathways of TLR3 and TLR4
	Indole-3-carbinol	production attenuation of pro-inflammatory mediators (NO, IL-6 and IL-1β)

The application of thin-layer chromatography screening as a supporting test to observe the antioxidant activity of fresh and ethanolic extracts of *C. cujete* helped to identify which compounds are abundant and possible contributors to the observed activity (Billacura and Laciapag, 2017). The extracts, specifically the crude ethanolic extract with the highest decoction ratio exhibited an abundance of phenolic compounds. According to a study by Al-Jaber et al. (2011), derivatives of oxygen are considered the most essential free radicals in biological systems. Due to their abundant presence in phenolic compounds, these compounds possess the largest group among any other phytochemical groups to exhibit exceptional antioxidant activity. Proving the abundance of these phenolic compounds in the fruit extracts of *C. cujete* supports the claims of the plant as a promising source of natural antioxidants.

Catalase (CAT), Superoxide dismutase (SOD), and Lipid peroxidation (LPO) *in vivo* assays tested on Swiss albino mice paired with 2,2-diphenyl-1picrylhydrazil (DPPH) and ferric reducing antioxidant power (FRAP) *in vitro* assays to evaluate the antioxidant activity of the methanolic leaf extracts from *C. cujete* (Anwuchaepe et al., 2017) showed the concentration dependence of the antioxidant activities with the ethyl acetate fraction showing the highest activity. Presence of the phenolic compounds: Chlorogenic acid, protocatechuic acid, and several quercetin derivatives were also reported from the HPLC-DAD analysis of the ethyl acetate fractions and crude methanol extract. The *in vivo* assays are targeted at the liver antioxidant enzyme activity and lipid peroxidation. Catalase activity was evaluated by the enzyme's hydrogen peroxide degrading ability which was described by Sinha (1972) while the SOD activity was evaluated by the enzyme's auto-oxidation inhibition of adrenaline ability which was described by Olatosin et al. (2014). Lastly, lipid peroxidation was evaluated through malondialdehyde (MDA), an aldehyde product of lipid peroxidation with the use of the method developed by Gutteridge and Wilkins (1982).

Ultrasonic-assisted fruit liquid extracts using the following solvents: Petroleum ether, chloroform, methanol, and water were evaluated for their antioxidant activities using 2,2-diphenyl-1,1-picrilhydrazil (DPPH) (Blois, 1958), and 2,2'-azino-bis(3)-ethylbenzothiazoline-6-sulfonic acid (ABTS) (Re et al., 1999) free radicals, and 2,9-dimethyl-1,10-phenanthroline (neocuproin) with a copper chloride compound (Apak et al., 2004). These assays also demonstrated a dose-dependent effect in all sample extracts with the aqueous extract showing the highest scavenging activity of ABTS radicals. Compared to tested standards, it was evident that the extracts showed lower antioxidant activity within the experiment environment (Juee and Naqishbandi, 2020).

3.2. Anti-inflammatory activity

Flavonoids such as quercetin, proteinkinase C, protein tyrosine kinases, phospholipase A_2 and phosphodiesterases, as well as tannins (Serafini et al., 2010) are known to have an effective ability to reduce acute inflammation. One study used the human red blood cell (HRBC) membrane stabilization method to evaluate the *in vitro* anti-inflammatory activity of the crude ethanol extract (CEE) and chloroform fractions (CHF) of the leaves and bark of the *C. cujete* plant (Parvin et al., 2015). A promising anti-inflammatory activity was observed for the crude leaf and bark crude ethanol extracts and chloroform fractions with the following percentage inhibition: 53.86±6.37, 61.85±5.56, 48.74±0.56, and 43.55±6.20, respectively, compared to the percentage inhibition of standard drug aspirin of 75.80±5.04. It is evident that the crude ethanol leaf and bark extracts possess a better anti-inflammatory response to the hypotonicity-induced lysis of the erythrocyte membrane. Erythrocyte membrane stabilization is a common *in vitro* assay done to assess anti-inflammatory activity as it is analogous to the lysosomal membrane. Lysosomal membrane stabilization is one of the precursors to limiting the inflammatory response by the prevention of the lysosomal constituent release of activated neutrophils which causes further tissue inflammation and damage upon extracellular release (Murugesh et al., 1981).

Observation of the NO production and iNOS expression aids in the evaluation of *C. alata* methanolic leaf extracts (Autore et al., 2001). Using carrageenin paw edema in Male Wistar rats for an *in vivo* assay while *Escherichia coli* lipopolysachaccharide-(LPS)-induced nitric oxide (NO) production and inducible nitric oxide synthase (iNOS) expression in the macrophage cell line J774.A1, the 500 mg/kg methanolic extract treated test organism showed a significant reduction in the enema, inhibiting carrageenin rat paw edema by 50±0.09% (P<0.01), 53.6±0.09% (P<0.001) and 28.3±0.04% (P<0.04) at 2, 3, and 4 hours after injection, respectively. The decrease in NO production after 24 h incubation of the J774.A1 cells with LPS $(6 \times \frac{10^3 u}{mL}; 24\ h)$ also showed the significant anti-inflammatory effect of the methanolic extracts (1-100 µg/mL) in a concentration-dependent pattern. The same pattern was also observed upon evaluating the iNOS expression of cell lysates incubated with the methanolic extract-kaempferol while the other isolates showed no significant iNOS expression inhibition by western blot analysis, complementing the results from the NO assay. These results validate the ability of *C. cujete* methanolic extracts to prevent inflammatory responses against the endotoxin-induced response in J774.A1 macrophages, directly inhibiting the L-arginine-NO pathway.

4. Conclusion

Although there have been several studies exploring the antioxidant and anti-inflammatory activities of *C. cujete*, their mechanism of action has not yet been explored. Most studies focused on observing these activities on crude alcoholic extracts from the plant with a minimal observation of specific extract fractions or isolated compounds from the plant. Therefore, the exploration of different extraction and isolation methods to obtain extract fractions or isolates with optimized antioxidant and anti-inflammatory activities will be essential to obtain the maximum potential of the plant as a natural source of antioxidant and anti-inflammatory compounds/extracts. The abundance of phytochemicals and bioactive compounds with antioxidant and anti-inflammatory activities in the plant proves the possibility of the plant as a natural and cost-effective source of these compounds for drug development and pharmacological applications. In light of this review, future researchers are encouraged to explore the least explored areas related to *C. cujete* to better understand its full potentials, such as a detailed analysis of the phytochemical analysis of the plant's seeds, bark, and flower extracts. It should be noted that the commonly used method of preparation is primarily polar solvent extraction (ethanol, methanol, and aqueous/decoction), which is the most common extraction method also used in indigenous medicine preparations. However, a deep understanding of how these extracts and bioactive compounds work inside the body of an organism is necessary. Therefore, more in-depth studies (*in silico*, *in vivo*, and *in* vitro) of purified and isolated bioactive compounds responsible for the antioxidant and anti-inflammatory activities of the plant. The involvement of '-omics' (proteomics, transcriptomics, genomics, and metabolomics studies) is also recommended as it will complement the results obtained from the studies conducted, which will lead to the understanding of the mechanism of action of the plant's bioactive compounds and will benefit the development of new pharmacological/drug designs to fully maximize the economic benefits of the plant. All things considered, the review highlighted that most studies on the antioxidant and anti-inflammatory activities of the plant are preliminary (*in vitro*) with the use of crude alcoholic and aqueous extracts, while the mechanism of action of the plant's bioactive compounds has not yet been investigated. Therefore, this review serves as a reference and inspiration for future researchers interested in the antioxidant and anti-inflammatory potentials of *C. cujete* to focus on these gray areas that are left to be explored to maximize the benefits of the plant.

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Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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