REVIEW ARTICLE

Potential medicinal benefits of *Cosmos caudatus* (Ulam Raja): A scoping review

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Cosmos caudatus is widely used as a traditional medicine in Southeast Asia. *C. caudatus* has been reported as a rich source of bioactive compounds such as ascorbic acid, quercetin, and chlorogenic acid. Studies have shown that *C. caudatus* exhibits high anti-oxidant capacity and various medicinal properties, including anti-diabetic activity, anti-hypertensive properties, anti-inflammatory responses, bone-protective effect, and anti-microbial activity. This review aims to present the potential medicinal benefits of *C. caudatus* from the available scientific literature. We searched PubMed and ScienceDirect database for articles published from 1995 to January 2015. Overall, 15 articles related to *C. caudatus* and its medicinal benefits are reviewed. All these studies demonstrated that *C. caudatus* is effective, having demonstrated its anti-diabetic, anti-hypertensive, anti-inflammatory, bone-protective, anti-microbial, and anti-fungal activity in both *in vitro* and animal studies. None of the studies showed any negative effect of *C. caudatus* related to medicinal use. Currently available evidence suggests that *C. caudatus* has beneficial effects such as reducing blood glucose, reducing blood pressure, promoting healthy bone formation, and demonstrating anti-inflammatory and anti-microbial properties. However, human clinical trial is warranted.

Key words: Anti-diabetic, anti-hypertensive, anti-inflammatory, anti-microbial, anti-oxidant, bone-protective, *Cosmos caudatus*, medicinal effect

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INTRODUCTION

Ulam refers to a group of traditional Malay vegetables, usually consumed raw. In Malaysia, the Ministry of Health has been promoting the consumption of *ulam* under the Malaysian Dietary Guidelines (2010).[1] The results from the third National Health and Nutrition Examination Survey revealed that salad and raw vegetable consumers tend to have increased serum level of vitamins, including vitamin C, vitamin E, folic acid, β-carotene, and lycopene.[2]

Cosmos caudatus, known locally as Ulam Raja or "King's Salad," belongs to the family Asteraceae. *C. caudatus* is a medicinal plant originating from Latin America and later grown in Southeast Asia.[3] It grows up to 3 m in height and bears pink or purple flowers. The leaves and shoots of *C. caudatus* can be consumed raw. The unique taste makes it a flavorful, favored side dish. It is usually eaten by dipping in shrimp and chili paste to enhance the flavors.[4] As a local delicacy, *C. caudatus* leaf can be seen served in hotels and restaurants across Malaysia.

Traditionally, *C. caudatus* has been used to boost blood circulation, to strengthen the bones, to reduce body heat, as an anti-aging agent, and to treat infectious disease.[3,5] In addition, various studies have revealed that *C. caudatus* has potential medicinal properties.[6-10] With the increasing interest in the traditional medicinal plants and herbs, there is a need to review the traditional claims about *C. caudatus* with regard to its medicinal uses before it can be used for further nutraceutical application. Therefore,

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this review aims to contribute to the substanti-al body of knowledge about the potential medicinal benefits of *C. caudatus*. Owing to the pivotal role of anti-oxidants against the development of chronic disease, we also report the bioactive compounds and the anti-oxidant potential of *C. caudatus* in this review.

METHODS

We searched Pubmed and ScienceDirect databases for articles published from 1995 to January 2015 using the key words "*Cosmos caudatus* and blood glucose," "*Cosmos caudatus* and blood pressure," "*Cosmos caudatus* and bone," "*Cosmos caudatus* and inflammation," "*Cosmos caudatus* and anti-microbial," "*Cosmos caudatus* and anti-oxidant," and "*Cosmos caudatus* and toxicity." Overall, 5 articles were retrieved on the anti-oxidant potential of *C. caudatus* and 10 articles were retrieved on the medicinal effects of *C. caudatus*. All published studies related to *C. caudatus* and its medicinal benefits are included in this review.

RESULTS

Nutritional composition and bioactive compounds

In general, 100 g of *C. caudatus* contains 2.9 g protein, 0.6 g carbohydrate, 0.4 g fat, and 93.1 g water, and provide 18 kcal of energy. Besides, *C. caudatus* is also rich in minerals and vitamins. The plant contains 64.6 mg of vitamin C, 3568 μg of β-carotene, 0.13 mg of vitamin B1, and 0.24 mg of vitamin B2 per 100 g fresh samples. In terms of mineral composition, it has 426 mg potassium, 270 mg calcium, 37 mg phosphorus, 50 mg magnesium, 4.6 mg iron, 0.9 g zinc, 4.0 mg sodium, and 0.2 g copper.[11]

C. caudatus was found to have high total phenolic content (1274 ± 98 GAE mg/100 g fresh weight) in the acetone/water system.[6] Furthermore, among the nine aqueous extracts of Malaysian plants, namely *C. caudatus*, *Curcuma domestica*, *Kaempferia galanga*, *Piper betle*, *Piper sarmentosum*, *Polygonum minus*, *Centella asiatica*, *Hydrocotyle bonariensis*, and *Barringtonia racemosa*, the aqueous extract of *C. caudatus* contained the highest phenolic content.[12] Table 1 depicts the biological active compounds of *C. caudatus*.[13]

Table 1: Biologically active compounds in *C. caudatus*

Compound	Total (mg/100 g)
Ascorbic acid	108.83±0.50
Quercetin	51.28±4.06
Kaempferol	0.90±0.05
Chlorogenic acid	4.54±0.18
Caffeic acid	3.64±0.14
Ferulic acid	3.14±0.28
Anthocyanin	0.78±0.05
β-carotene	1.35±0.03

Reference:[13]

Medicinal uses of *C. caudatus*

The significant findings on the medicinal uses of *C. caudatus* are summarized in Table 2.

Anti-oxidant potential

Reported evidence showed that *C. caudatus* exhibits high anti-oxidant activity.[6,14-17] Studies have shown that 100 g of fresh *C. caudatus* contains approximately 2500 mg ascorbic acid equivalent anti-oxidant capacity (AEAC) compared to local fruits with AEAC index of less than 300 mg.[14] A comparison of the AEAC value in selected foods is depicted in Table 3.[6,14] Among the 11 vegetables tested, ethanol extracts of *Pluchea indica* and *C. caudatus* exhibited the highest anti-oxidant activity when measured by ferric cyanide reducing power, 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical-scavenging, 2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS)-scavenging, and inhibition of linoleic acid.[13]

In another study, Wong *et al*. (2006) assessed the anti-oxidant activities of aqueous extracts of 25 tropical plants using DPPH scavenging and ferric ion reducing anti-oxidant potential (FRAP) assays.[15] Among the 25 plants, *C. caudatus* exhibited the highest DPPH free radical-scavenging activity and the highest ferric ion reducing activity. This result was in agreement with a recent study by Reihani and Azhar (2012), which evaluated the total phenolic content and anti-oxidant activity of five *Ulams* using DPPH and FRAP assays.[16] In this study, *C. caudatus* and *Oenanthe javanica* (Selom) aqueous extracts were found to have the highest DPPH and FRAP values. This finding has further indicated that *C. caudatus* is a good source of anti-oxidant.

Anti-diabetic activity

A previous study on obese, *C. caudatus* extract-treated rats showed a significant reduction in plasma blood glucose as compared to the control rats after one month of *C. caudatus* extract supplementation.[17] Acarbose, an alpha-glucosidase inhibitor, is widely used to treat type 2 diabetes.[22] However, excessive alpha-amylase inhibition may lead to abnormal bacterial fermentation of undigested carbohydrates in the intestine and result in unwanted side effects such as abdominal distension, flatulence, and diarrhea.[23] Hence, mild amylase inhibition is beneficial. A local study reported that the hexane extract of *C. caudatus* has high alpha-glucosidase inhibitory activity with low alpha-amylase inhibition.[7] Therefore, *C. caudatus* may be potentially useful in treating postprandial hyperglycemia *in vitro*.

Anti-hypertensive activity

The anti-hypertensive effects of *C. caudatus* in adrenaline-treated and sodium chloride-treated rat models have been reported.[9] In adrenaline-treated rats, both 500 mg/kg and 1000 mg/kg aqueous extracts of *C. caudatus* were shown to inhibit the increase of heartbeat frequency and stroke

Table 2: Summary of potential medicinal benefits of *C. caudatus*

Potential medicinal benefits	Extracting solvent	Effects/properties	Author, year, references
Anti-oxidant activity	Fresh sample	*C. caudatus* contained 2500 mg AEAC per 100 g of fresh sample	Shui *et al*. 2005;[6]
	Ethanol extract	*C. caudatus* exhibited highest anti-oxidant activity when measured by FRAP, DPPH scavenging, ABTS scavenging, and linoleic acid inhibition among 11 plants	Leong *et al*. 2002[14] Andarwulan *et al*. 2010[13]
	Aqueous extract	*C. caudatus* exhibited highest DPPH scavenging and highest FRAP activity among 25 plants	Wong *et al*. 2006[15]
	Aqueous extract	*C. caudatus* exhibited the highest DPPH scavenging and FRAP activity among 5 *ulams*	Reigani and Azhar 2012[16]
Anti-diabetic activity	Ethanol extract	*C. caudatus*-treated obese rats showed significant reduction in lipid profile and plasma glucose	Perumal *et al*. 2014[17]
	Hexane extract	High alpha-glucosidase inhibitory activity with low alpha-amylase inhibition	Loh and Hadira 2011[7]
Anti-hypertensive activity	Aqueous extract	Showed similar potency to 9 mg/kg atenolol in lowering beat frequency and stroke volume amplitude induced by adrenaline	Amalia *et al*. 2012[9]
		Induced diuretic activity by increasing the pooled volume after 24 h, which is comparable to 1.8 mg/kg furosemide	Amalia *et al*. 2012[9]
	Dichloromethane extract	Moderately inhibited ACE *in vitro*	Loh and Hadira 2011[7]
Anti-inflammatory activity	Methanol extract	Showed similar potency to standard drug diclofenac sodium (10 mg/kg) in suppressing mouse paw edema induced by carrageenan	Ajaykumar *et al*. 2012[18]
Bone-protective effect	Aqueous extract	Restored bone volume, trabecular number, and trabecular separation to normal level in ovariectomized rats. *C. caudatus* extract was observed to have a better effect than calcium 1% on trabecular number and trabecular separation	Mohamed *et al*. 2012[19]
	Aqueous extract	In ovariectomized rats, *C. caudatus* extract exhibited higher double-labeled surface, increased mineral appositional rate, increased osteoid volume, and higher osteoblast surface value. Showed a better effect on osteoid volume than calcium 1%	Mohamed *et al*. 2013[20]
Anti-microbial and anti-fungal activity	n-Hexane extract; diethyl ether extract; ethanol extracts Dichoromethane extract	Significantly inhibited the growth of five microbial strains: Two Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*), two Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*), and a fungus (*Candida albicans*) Inhibited the growth of *Cladosporium cucumerinum* and *Candida albicans*	Rasdi *et al*. 2010[8] Fuzzati 1995[21]

AEAC = Ascorbic acid equivalent anti-oxidant capacity; DPPH = 1; 1-diphenyl-2-picrylhydrazyl free radical; ABTS = 2; 2′-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid); FRAP = Ferric ion reducing anti-oxidant potential

Table 3: Comparison of total antioxidant capacity (AEAC value) in selected foods

Variety	AEAC (mg/100 g)	Classification by AEAC
Ciku	3396±387.9	Extremely high
Cosmos caudatus	2511.7±285.4	Extremely high
Strawberry	472±92.9	High
Plum	312±23.2	High
Guava	270±18.8	High
Mangosteen	150±23.3	Medium
Orange	142±16.5	Medium
Mango	139±21.5	Medium
Kiwifruit	136±18.2	Medium
Apple	78.9±2.7	Medium
Tomato	38.0±1.7	Low

Reference:[6,14]

volume amplitude induced by adrenaline. This result was comparable to 9 mg/kg standard anti-hypertensive drug in lowering both parameters.[9] In sodium chloride-treated rats, treatment with 500 mg/kg and 1000 mg/kg *C. caudatus* aqueous extracts inhibited the sodium chlorid-induced increase in stroke volume amplitude. The effect was equivalent to the drug treatment of hydrochlorothiazide and captopril in lowering stroke volume. Administration of 500 mg/kg and 1000 mg/kg *C. caudatus* aqueous extracts in rats increased the pooled volume after 24 h, and this result was as good as the effect exerted by 1.8 mg/kg furosemide. This result indicates that *C. caudatus* can induce a diuretic effect, which leads to decrease in blood pressure. Loh and Hadira (2011) reported that the dichloromethane extract of *C. caudatus* can moderately inhibit angiotensin-converting enzyme (ACE) *in vitro*.[7] This shows that consumption of *C. caudatus* may mimic synthetic ACE inhibitor in reducing blood pressure. Thus, *C. caudatus* may serve as an anti-hypertensive agent.

Anti-inflammatory activity

Methanol and aqueous *C. caudatus* extracts at a dose of 200 mg/kg have exhibited significant anti-inflammatory activity by suppressing mouse paw edema induced by carrageenan. The result was comparable to that of the

standard drug diclofenac sodium (10 mg/kg body weight) in inhibiting paw edema.[18] The development of inflammation induced by carrageenan occurs in two phases. The early phase, which occurs during the first 2 h of carrageenan administration, is mediated by the release of serotonin and histamine. The later phase is related to the release of leukocyte, eicosanoid, and free radical, which induces the production of prostaglandin.[24] *C. caudatus* extract suppressed paw edema during the third and fourth hours.[18]

Bone-protective effect

Ovariectomized rat is the most commonly used model for postmenopausal osteoporosis. Bone loss in the rat model resembles bone changes in postmenopausal women.[25] Ovariectomy causes loss of bone volume, decrease in trabecular number, and increase in trabecular separation in ovariectomized rats.[19] However, in both the groups of ovariectomized rats supplemented with 500 mg/kg *C. caudatus* aqueous extract and with 1% calcium for 8 weeks, an ameliorating effect was observed on bone volume, number, and separation by restoring the bone structural parameters to the normal level.[19] Surprisingly, a superior effect of *C. caudatus* on trabecular separation and trabecular number was observed as compared to calcium 1% treatment in rats.[19] This result suggests that anti-oxidant properties together with the calcium content of *C. caudatus* are beneficial to bone health.

Similarly, a study exploring the effect of *C. caudatus* on dynamic and cellular bone histomorphometry in ovariectomized rats demonstrated encouraging results. Both groups of ovariectomized rats treated with 500 mg/kg *C. caudatus* aqueous extract and with 1% calcium achieved higher double-labeled surface, increased mineral appositional rate, increased osteoid volume, and higher osteoblast surface value. A high double-labeled surface reflects a better bone mineralization process[26] and a high mineral appositional rate indicates enhanced osteoblastic activity.[27] Additionally, *C. caudatus* exhibited a result superior to calcium 1% in the osteoid volume parameter.[20] An increase in the number and activity of osteoblasts stimulates bone formation.[28] In summary, these results suggest that *C. caudatus* has the potential to promote bone formation in the animal study.

Anti-microbial and anti-fungal activities

C. caudatus was found to have anti-microbial and anti-fungal activities.[8,21] Phenylpropane derivatives isolated from a root extract of *C. caudatus* have shown anti-fungal activity against *Cladosporium cucumerinum* and *Candida albicans* using bioautographic thin-layer chromatography.[21] Rasdi *et al*. (2010) assessed the effects of different *C. caudatus* extracts against five microbial strains, that is, two Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*), two Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*), and a fungus (*Candida albicans*) by the disk diffusion method.[8] It was concluded that at minimal inhibitory concentrations (MIC) of n-Hexane (25 mg/mL), 6.25 mg/mL of diethyl ether, and 6.25 mg/mL of ethanol extracts of *C. caudatus*, all the extracts exhibited significant inhibitory activity against the growth of the five tested human pathogenic microbes.[8] These results indicate that both polar and nonpolar *C. caudatus* extracts have highly anti-microbial and anti-fungal properties.

Toxicological limits

In the cell toxicity test, ethanol extracts of *C. caudatus* exhibited low cytotoxic activity against P388 murine leukemia cells with half maximal inhibitory concentration (IC_{50}) values of 25 μg/mL.[29] The acute oral ethanol extract of *C. caudatus* was found well tolerated by rats up to 5 g/kg body weight, and they showed neither mortality nor any sign of toxicity.[30] This showed that the median lethal dose (LD_{50}) of *C. caudatus* extract was greater than 5 g/kg body weight. In addition to the acute toxic doses, subacute toxicology (28 days) was tested with repeated doses (125 mg/kg; 250 mg/kg; 500 mg/kg) and hematology, histopathology, and biochemical parameters were tested. Histopathological observations in both toxicity studies (acute and subacute) showed the normal cellular architectures of organs in the *C. caudatus*-treated rats, without any necrosis, fatty infiltration, or alteration in cell structures.[30]

DISCUSSION

Epidemiological studies have shown that an increased intake of vegetables rich in phenolic compounds is associated with a decreased risk of several chronic diseases, such as diabetes,[31] heart disease,[32] and cancer.[33] *C. caudatus* has been reported to have exceptionally high anti-oxidant capacity, mainly due to its polyphenol content.[6] Polyphenol-rich foods are potent anti-oxidants,[34] which protect cells against oxidative stress and reduce the risk of chronic disease.[35] The anti-oxidant properties of *C. caudatus* play a crucial role in promoting significant health benefits and potentially reduce the harmful effect of oxidative stress.

C. caudatus has been shown to have hypoglycemic activity. One way to assess glycemic control is through postprandial glucose. Postprandial hyperglycemia is strongly associated with an increased risk of cardiovascular disease in type 2 diabetic patients.[36,37] Postprandial hyperglycemia can be decreased by delaying the carbohydrate absorption in the gastrointestinal tract.[38] This can be achieved by inhibiting carbohydrate-hydrolyzing enzymes, which are pancreatic alpha-amylase, and slowing glucose uptake by intestinal

alpha-glucosidase. *C. caudatus* has high alpha-glucosidase activity. Therefore, *C. caudatus* may potentially be useful for treating postprandial hyperglycemia *in vitro*.

The leaves of *C. caudatus* have been used in eastern Indonesia to lower blood pressure.[9] Lowered blood pressure is associated with a reduced risk of cardiovascular events. Blood pressure can only be reduced by decreasing the cardiac output or the total peripheral vascular resistance.[39] Stroke volume and heart rate are two integral components of cardiac output.[39] By decreasing the cardiac output, mean blood pressure is suppressed. The result suggests that *C. caudatus* has the potential for reducing the cardiac output. Besides cardiac function, *C. caudatus* also exhibited diuretic properties, which help to reduce blood pressure.[9] Diuretics work by increasing the urinary sodium excretion, reducing the plasma volume and cardiac output, and subsequently lowering the blood pressure.[40] ACE is a key enzyme in the renin-angiotensin system, which plays an integral role in regulating blood pressure and maintaining cardiovascular function.[41] ACE triggers the conversion of angiotensin I to angiotensin II, which is a vasoconstrictor, and subsequently increases the blood pressure.[42] Therefore, an inhibition of ACE is considered an effective approach to treating hypertension.[43] *C. caudatus* can moderately inhibit ACE *in vitro*.

Inflammation is one of the risk factors in developing atherosclerosis. Carrageenan-induced paw edema is a classical model to evaluate the efficacy of acute inflammation. It is widely used in the development of anti-inflammatory drugs.[44,45] The anti-inflammatory effect of *C. caudatus* was observed against a carrageenan-induced paw edema in a mouse model. It was reported that the anti-inflammatory effect of *C. caudatus* is probably due to the inhibition of prostaglandin systhesis. Therefore, *C. caudatus* may be potentially used as an alternative anti-inflammatory agent.

C. caudatus is believed to exhibit a bone-protective effect and triggers bone formation.[46] Estrogen is the primary hormone to preserve bone mass and estrogen deficiency is the main risk factor in developing osteoporosis.[47] Estrogen is a phenolic compound that has anti-oxidant properties to protect against reactive oxygen species (ROS).[48] In the postmenopausal state, estrogen deficiency lowers the anti-oxidant defense, which causes ROS to stimulate osteoclasts.[49] This scenario results in bone resorption and subsequently leads to bone loss.[50] As free radicals are involved in bone metabolism, *C. caudatus*, which exerts high anti-oxidant properties, has a positive effect on bone health.

C. caudatus was also found to have anti-microbial and anti-fungal activities.[8,21] The results indicated that both polar and nonpolar *C. caudatus* extracts possessed high anti-microbial and anti-fungal properties. Although *C. caudatus* extracts showed promising results *in vitro*, there has been no *in vivo* study to confirm anti-microbial and anti-fungal activities. Therefore, further studies, especially *in vivo* studies, should be conducted to examine the anti-microbial effectiveness of *C. caudatus*.

Considering the potential uses of *C. caudatus* as nutraceutical applications, it is important to determine whether there is any toxicological effect. *C. caudatus* was considered safe on acute oral toxicity and subacute toxicology testing. Although there is no evidence of toxicity from the acute and subacute toxicity studies, further investigation should be made to ascertain the lack of chronic toxicity and the safety of *C. caudatus* leaf intake in humans.

CONCLUSION

C. caudatus is a traditional plant and reportedly a potent anti-oxidant. Recent studies have demonstrated that *C. caudatus* and its compounds are potentially beneficial for human health, owing to their anti-diabetic, anti-hypertensive, bone-protective, and anti-microbial properties, among others. The pharmacological activities are attributed to the presence of flavonoids and polyphenolic compounds in *C. caudatus*. However, there is a limitation in this review. To the best of our knowledge, no clinical trial is available in the literature. Therefore the effects of *C. caudatus* on humans remain obscure. As firm conclusions cannot be drawn regarding the health benefits of *C. caudatus*, further research exploring the effects of *C. caudatus* on humans is required in order to assess the potential of *C. caudatus* to reduce blood glucose, reduce blood pressure, promote healthy bone formation, and demonstrate anti-inflammatory and anti-microbial properties.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

SCH contributed in the conception of the work, searched the related-references, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the

work. BNMY contributed in the conception of the work, reviewing the related-references, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AI contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. JA contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work

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