A Comprehensive Review on *Cosmos caudatus* (Ulam Raja): Pharmacology, Ethnopharmacology, and Phytochemistry

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***Abstract* — *Cosmos caudatus* or Ulam Raja in Malay originated from Latin America and transferred to Europe, Africa, and tropical Asia. It has been known for many traditional practices worldwide such as to rigidify bones and tone up blood circulation. The aim of this review is to summarize and discuss the association between phytochemical and pharmacological reports of *C. caudatus* and their traditional uses via ethnopharmacological approaches. *Cosmos caudatus* is a traditional medicinal plant used widely for culinary and therapeutic purposes. Phytochemical studies indicated the presence of Phenolic acids, flavonoids, tannins, sesquiterpene lactones, carbohydrates, minerals and vitamins in leaves while phenylpropanoids were in roots. Pharmacological data have been compiled for diverse activities for fresh leaves and extracts such as antihypertensive, antihyperlipidemic, antidiabetic, antimicrobial, antioxidant and antiosteoporotic. These activities experimented by *in vitro* and *in vivo* studies. Multiple *C. caudatus* constituents propose many potential actions in different fields such as neuroprotection, antidepression, and gastroprotection.**

***Abbreviations* - ˙OH**: hydroxyl radical, **$^1O_2$**: singlet oxygen, **AAE**: Ascorbic acid equivalent, **ACE**: angiotensin-converting enzyme, **AI**: atherogenic index, **ALP**: alkaline phosphatase, **ALT**: alaninetransaminase, **AST**: aspartate aminotransferase, **BHA**: butylated hydroxyanisole, **BHT**: butylated hydroxytoluene, **B.S.**: bacillus subtilis, **C.A.**: Candida Albicans, **E.C.**: Escherichia coli, **E.O.**: essential oil, **FTC**: Ferric thiocyanate, **GAE**: Gallic acid equivalent, **GLUT2**: Glucose transporter-2, **H_2O_2**: hydrogen peroxide, **HDL**: high-density lipoprotein, **HPLC-DAD**: high performance liquid chromatography coupled with diodearray detection, **HPLC-ESI-MS**: high performance liquid chromatography coupled with electrospray ionization mass spectroscopy, **IIUM**: International Islamic University Malaysia, **IV**: Iodine value test, **JNK-1**: c-Jun N-terminal kinases, **LDL**: low density lipoprotein, **MDA**: Malondialdehyde, **MMP-2**: matrix metalloproteinase-2, **MMU**: Multimedia University, **NMR**: nuclear magnetic resonance spectroscopy, **$O_2^{\cdot -}$**: superoxide anion radical, **P.A.**: pseudomonas aeruginosa, **PON-1**: paraoxonase-1, **PV**: peroxyl value test, **S.A.**: staphylococcus aureus, **S.C.**: saccharomyces cereviseae, **SOD**: Superoxide dismutase, **SVCT1**: sodium–dependent vitamin C transporter-1, **TBA**: Thiobarbituric acid, **TC**: total cholesterol, **TG**: triglycerides, **TLC**: thin layer chromatography, **UiTM**: Universiti Technologi Mara, **UKM**: Universiti Kebangsaan Malaysia, **UM**: Universiti Malaya, **UMP**: Universiti Malaysia Pahang, **UMS**: Universiti Malaysia Sabah, **UPM**: Universiti Putra Malaysia, **USM**: Universiti Sains Malaysia.

***Keywords* — *Cosmos caudatus*, Ulam Raja, Constituent, phytochemistry, Traditional medicine Asia**

I. Introduction

World Health Organization estimated that 80% of the world population in developing countries depends on herbal medicines for treating diseases while 56% of rural areas population still depends on traditional medicine as a primary source for curing essential health problems (Planta, Gundersen, & Petitt, 2000). In Europe and US herbal drugs sales were tripled and doubled, respectively, between the 1990s and 2000s (Kamboj, 2000). Southeast Asia has the second highest percentage in country-endemic vascular plant biodiversity (25%) after South America, and more than Meso-American and sub-Saharan African tropical regions (Sodhi et al., 2010). This shows the necessity to exploit the huge number of species to discover naturally occurring therapies through purification and fractionation. Compounds isolated from natural sources have great importance in revealing novel medicines by using the same phytochemicals or synthetically modifying its structure to overcome low affinity, selectivity, efficacy or stability problems.

The genus *Cosmos* comprises 26 to 42 species[1], this name came from Greek *Kosmos*, which means adorn, ornament and beautiful. *Cosmos* has many species that have spread throughout Europe, Asia and Africa, but all originated from Latin America and have diverse traditional

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[1] Cosmos has 26 species according to "Plants and their names A concise dictionary" R. Hyam. Whereas Thomas Melchet, 1968 nominated 36 species. On the other hand, www.Theplantlist.org has listed 42 accepted species.

uses (Quattrocchi, 1999). Table I shows a comparison between some *Cosmos* species.

Diverse bioactive ingredients are well-established in *C. caudatus*, and this was always connected with antioxidant and free radical scavenging activities (Mustafa, 2010). High contents of phytochemicals, antioxidants, proteins, amino acids, vitamins, and minerals are associated with degenerative diseases risk reduction, such as cancer, diabetes, hypertension, cardiovascular diseases and osteoporosis, as it is thought that these diseases are connected with high free radical levels (Goldberg, 2012). *Cosmos caudatus* extract has shown beneficial activities in reducing number of parameters such as peroxyl value and microbial growth when added to quail meatball as an antioxidant. These activities were comparable with butylated hydroxyanisole (BHA) as an artificial antioxidant usually used with food products (Ikhlas, Huda, & Ismail, 2012). Artificial antioxidants unfolded in detrimental effects in humans, serious hemorrhage in the peritoneal and pleural cavities was noticed after the administration of butylated hydroxytoluene (BHT) with food in rats. It has also caused bleeding in other organs such as epididymis, testes, and pancreas. BHA produced toxicity and cancers to living organisms (Farag, 1989). This is one of the important reasons for introducing natural antioxidants, such as the extracts obtained from *C. caudatus*, which can decrease the possibility of toxicity and side effects when used in food industry.

Many bioactive constituents were isolated from *C. caudatus* leaves and roots, those are mainly flavonoids, phenolic acids, vitamins, minerals and phenylpropanoids are responsible for many pharmacological activities attributed to fresh *C. caudatus* leaves or extracts. Anti-diabetic, antihypertensive, antimicrobial, anti-osteoporotic and anti-inflammatory activities were proved in clinical, *in vitro* and *in vivo* studies (Cheng, et al., 2015; Javadi, et al., 2014; Mohamed, et al., 2013; Ajaykumar, 2012; Loh & Hadira, 2011; Rasdi, et al., 2010). Additionally, bioactive compounds isolated in many phytochemical studies were connected with such pharmacological activities (Mustafa, et al., 2010; Abas, 2005; Shui, Leong, & Wong, 2005). This review comprehensively summarizes phytochemical constituents, the ethnopharmacological and pharmacological activities for *C. caudatus*.

TABLE I: COMPARISON BETWEEN SOME COMMON COSMOS SPECIES, THEIR DISTRIBUTION, USES AND LOCAL NAMES

Species	Original inhabitant	Cultivated in	Traditional uses	Local name	Reference
C. caudatus Kunth	West Indies, Central America, Meso-America	Southeast Asia, East Africa, Europe	Antibacterial, antifungal, antiaging, weedy, ornamental, vegetable,	Ulam raja, Spanish needle	Wiersema & Leon (2013); Burkill (1966)
C. bipinnatus (Cav.)	Southwest USA, North, and South Mexico	South Africa, China, East Asia, India, Australia, Europe	Ornamental, in folklore medicine	Garden cosmos	Wiersema & Leon (2013)
C. astrosanguineus	Mexico	Europe, North America	Ornamental	Chocolate cosmos	Marinelli (2005)
C. sulphureus Cav.	Mexico, Brazil	Europe, India, Cambodia, Java	Antibacterial, antifungal, anti-inflammatory, gastric ulcer, liver inflammation, arthritis, as a dye, ornamental	Yellow cosmos, orange cosmos, sulphur cosmos	Quattrocchi (1999); Hanelt (2001); Quattrocchi (2012)

II. Botanical Description

Cosmos caudatus Kunth is an annual to short-lived perennial aromatic herb, from the *Compositae* family. It grows between 0.5–2 m tall, leaves are scarcely hairy, bipinnatisect and slightly tripinnatisect, petiolate, around 5 to 15 cm long, lanceolate, and the apex is apiculate. Achenes color is dark brown or black, 0.75–1.5 cm long (Dassanayake & Fosberg, 1980).The subshrubs usually found as an individual or in clusters, flowers stem on along inflorescent stalk on auxiliary heads, itbears pink, red, yellow or white ray florets (Hassan & Mahmood, 2007). *Cosmos caudatus* trees do not need rich soil or fertilizers to grow, a well-drained soil, moisture, sunshine, and 50-55^{o}C are enough for normal growth, if fertilizers added, it grows bigger but with few flowers (Taylor, 1961). Picking up the young shoots in eight weeks of planting, produces more branches and makes the tree grows taller, but at the same time, it delays flowering process (Hassan & Mahmood, 2007)

III. Taxonomy and Vernacular names

The taxonomic hierarchy for the *Cosmos caudatus* Kunth is as follows according to the integrated taxonomy information system.

Kingdom:	Plantae
Subkingdom:	Viridiplantae
Infrakingdom:	Streptophyta
Superdivision:	Embryophyta
Division:	Tracheophyta
Subdivision:	Spermatophytina
Class:	Magnoliopsida
Superorder:	Asteranae
Order:	Asterales
Family	Asteraceae
Genus:	Cosmos Cav. – Cosmos
Species:	Cosmos Caudatus Kunth – Wild Cosmos

Cosmos caudatus Kunth has nine synonyms used in references and botanical encyclopedias; Table II summarizes it.

TABLE II: *COSMOS CAUDATUS* SYNONYMS

No.	Synonym	Reference
1	*Bidens artemisiifolia* subsp. Caudate (Kunth) Kuntze	www.theplantlist.org
2	*Bidens berteriana* Spreng.	www.theplantlist.org
3	*Bidens carnea* Heer.	www.theplantlist.org
4	*Bidens caudata* (Kunth) Sch.Bip.	www.theplantlist.org
5	*Cosmea caudata* (Kunth) Spreng.	www.theplantlist.org
6	*Cosmos caudatus* var. caudatus.	www.theplantlist.org
7	*Cosmos caudatus* var. exaristatusSherff.	www.theplantlist.org
8	*Cosmos Bipinnatus* Linn. (Not the Cav.)	Taylor (1961); Ridley (1923)
9	*Cosmos pacificus* Var. chiapensis Melchert.	Quattrocchi (2012)

The first specimen deposited for *C. caudatus* was in Cuba herbarium in March 1801 by Humboldt and Bonpland. The first publication for this species was on 26th Oct. 1818 by Humboldt, Bonpland and Kunth, and the species is sometimes named after their initials; *Cosmos caudatus* H.B.K. This publication was made in the journal “Nova Genera et species Plantarum” 4:188.1820[1818][2].

Many vernacular names in different countries are being used for *C. caudatus* Kunth, this can be considered as a sign of the widespread use of this herb and rooted conviction for its benefits. Table III summarizes local names for *C. caudatus*.

TABLE III: *COSMOS CAUDATUS* LOCAL NAMES IN DIFFERENT COUNTRIES WHERE IT IS INDIGENOUS OR EXOTIC

Country	Local name	Reference
Malaysia	Hulam Raja	Quattrocchi (2012)
	Ulan Raja	
	Ulam Rajah	Hanelt (2001)
	Pelompong	
	Ulan Rajah	Ridley (1923)
Indonesia	Kenikir*	Burkill (1966)
Costa Rica	Flor de Muerto	www.tropicos.org
El Salvador	Mozote-doradilla	www.tropicos.org
Mexico	Chactsul	www.tropicos.org
	Chacxul	www.tropicos.org
	Estrella del mar	www.tropicos.org
Philippines	Lansa-Lansa	Quattrocchi (2012)
	Onuad	
	Turai-Turai	
	Tuktukan	
Russia	Kosmos Chvostatyj	Hanelt (2001)
Germany	Cosmee	Hanelt (2001)
	Schmuckblume	
English name	Spanish needle	Quattrocchi (2012)
Porto Rico	Claveles	Cook (1903)
	Piquete	

* Kenikir in Indonesia is used for *C. caudatus* Kunth and for *Tagetuserecta* L.

IV. Origin and Geographical Distribution

The origin of *C. caudatus* is from Latin America, namely; West Indies (consists of Bahamas, Cuba, Jamaica, Haiti, The Dominican Republic, Puerto Rico, United States Virgin Islands, The Leeward Islands and Windward Islands), Central America (consists of Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama), in addition to Florida - USA[3], Mexico and Brazil. *C. caudatus* has reached Asia through the Philippines, by Spaniards in the first half of the nineteen century, when they used it as a vegetable during the long sea voyage from Europe. It is also thought that it has reached the Philippines directly from Mexico as an ornamental plant. Unlike Europeans, Malaysians and Javanese have received *C. caudatus* as a potherb, spinach and as a medicine; the leaves, stems, and flowers were cooked and used as a food seasoning. On the other hand, most Europeans planted *C. caudatus* in gardens as an ornamental plant, and they did not accept it with food due to the strong pungent flavor (Burkill, 1966; Ridley, 1923; Copeland, 1904). East African countries also have naturalized *C. caudatus* such as Madagascar, Mauritius, and Uganda from Latin America.

V. Ethnomedicinal, Traditional, and Culinary Uses

Indigenous and exotic *C. caudatus* has been used for many traditional uses. Melchert (1968) and Haneilt (2001) classified *C. caudatus* in addition to two other Cosmos species as a weedy plant in West Indies and Central America. *C. caudatus* was categorized as a garden plant and was transferred to European countries for ornamental purposes, due to the attracting floret colors (Taylor, 1961). In the agricultural aspects, *C. caudatus* was used in Southeast Asia as a cover plant to mulch gardens and as green manures, in additiontobeing anessential oil producing plant (Jansen et al., 1991). *C. caudatus* was also used traditionally for burns due to its antimicrobial properties, moreover, it was used for strains and muscular spasms (Quattrocchi, 2012). In the Philippines, local people incubate rice with *C. caudatus* leaves in order to prepare yeast (Gibbs & Agcaoili, 1912).

In Malaysia and Indonesia, *C. caudatus* has had wider traditional uses and larger space on dining tables. It is eaten cooked with rice and grilled fish, raw with salads, and dipped with anchovy sauce, shrimp paste chili sauce and with fermented shrimp sauce. They believed it has anti-aging properties; hence, indigenous people called it “awet muda” which means, “stay young”. Above all, Malays and Javanese used the leaves to tone up the blood circulation, rigidify bones, and due to the essential oils, it is used to remove bad breath. It was also planted in the gardens as an ornament and to freshen the air (Hassan & Mahmood, 2007). The local people of Malaysia and Indonesia belief that *C. caudatus* has antimicrobial characteristics, thus, they use it for human and plant bacterial and fungal diseases (Bodeker, Shekar, & Salleh, 2009). Moreover, as a crop, *C. caudatus* trees were used to arrest thatch (Burkill, 1966). Some other traditional uses have been mentioned for *C. caudatus* in pharmacological and phytochemical studies, but we could not verify it from primary sources[4].

The abovementioned traditional uses are needed to be studied systematically and documented in a scientific manner. In this review, we studied the Malaysian experience in discovering and developing new bioactive constituents

[2] www.Tropicos.org

[3] “Global Compositae checklist” lists Florida as one of *C. caudatus* originshttp://dixon.iplantcollaborative.org/compositaeweb.

[4] It has been claimed that *C. caudatus* is reducing body heat, as an insect repellent, as a carminative and used for weak stomach.

extracted from medicinal plants. Malaysia has more than 12,000 plant species, of which around 1,300 medicinal species, up to 1996 only 100 species has been studied and documented. This was achieved by ethnomedicinal research program, which was adopted by the ministry of industrial development, in co-operation with public Malaysian universities. The program employs a team of ethnobotanist and physician, they were sent to traditional healers in their original villages, to observe the plant part used, ways of treatment, and approaches applied by healers, and report the collected information to research centers that are responsible for discovering the pharmacologically active compounds and the mechanism of action (Rozhon, 1996).

We scanned public Malaysian universities namely (UKM, UM, UPM, UMP, UiTM, USM, IIUM, UMS and MMU), their libraries and repositories for undergraduate project papers, Ph.D., M.Sc. dissertations and theses and conferences related to *C. caudatus* exploitation medicinally and nutritionally, in addition to phytochemical and agricultural optimization studies. Many projects have been found for *C. caudatus*, some of them are already published in articles, and others were not. Table IV summarizes the unpublished studies for *C. caudatus*; studies in Malay language were translated into English.

TABLE IV: THE UNPUBLISHED WORK IN DIFFERENT FIELDS RELATED TO *COSMOS CAUDATUS* IN PUBLIC MALAYSIAN UNIVERSITIES AND LOCAL CONFERENCES

Study name	Conference/ Project type	Author	Year/ Venue	Results
A survey of Malayan plants for cyanogenic glycosides	Proceedings of the 3rd National Biology Symposium	Amru Nasrulhaq	1988 UKM	Sodium picrate test carried out to discover hydrocyanic acid contents in 101 species.*Cosmos caudatus* turns filter paper slightly topink-orange. This indicated the presence of small amounts of HCN.
A comparative study on two harvesting techniques in *Cosmos caudatus*	Tropical Plant Physiology Development Workshop: Constraints and Environmental Physiology	Shaharani M. L.	1991 UM	Alternate harvesting technique was significantly better for *C. caudatus* than complete technique and gave shorter plants, more leaves, and less flowering frequency.
Growth rates of various ulam species, light response and ACi curves	Tropical Plant Physiology Development Workshop: Constraints and Environmental Physiology	Norriza J.S.	1991 UM	Photosynthesis and growth rates for *C. caudatus* and other vegetative plants were not correlated with the molecular and organ levels.
Effects of ethanolic extract of Ulam raja (*Cosmos caudatus*), pegaga (*Centella Asiatica*), and selom (*Oenanthe javanica*) on the proliferation of different human cancer cell lines.	Project paper	Lailidalilati Suleiman	2001 UPM	*Cosmos caudatus* extract is cytotoxic for CACO-2 cancer cell line (IC_{50}= 91.7µg/ml) for 72 hours incubation. Whereas *C. caudatus* extract did not show inhibition of cellular proliferation for MCF-7, MDA-MB or HepG2 lines.
Antioxidant activities of some local plants and their effects on storage quality in spent hen burger with palm fat	Master of Science thesis	Nur Huda Faujan	2004 UKM	*Cosmos caudatus* ethanolic extract had the highest activity to reduce Fe^{3+}. *C. caudatus* in addition to *Polygonum hydropiper* and *Murrayakoenigii* extracts used in the study significantly slow down the sample oxidation process in TBA and FTC assays compared to control. PV on raw and cooked samples increased in two months but decreased after 3 months storage. Iodine value decreased in IV assay after 3 months storage. All treatments were decreased total plate count and yeast and mold count during frozen storage time.
Antimicrobial activity of *Cosmos caudatus* against *Staphylococcus aureus, Bacillus subtilis,* and *Candida albicans*	Project paper	Nur Hafifa Binti Johary	2006 UMS	100 mg/ml *C. caudatus* and 90 minute exposure time were effective against *Staphylococcus aureus* and *Bacillus subtilis*. While it showed slight inhibition to spore germination for *Candida albicans*
The effect of different nitrogen levels on the growth of Ulam raja (*Cosmos caudatus*) and selom (*Oenanthe javanica*)	Project paper	Noor Azwa Zulkaliph	2006 UPM	The optimum nitrogen level for commercial purposes was at a rate of 200 mg /L. This concentration increased plant biomass, chlorophyll content of leaves, leaf area, specific leaf area, ratio of root / shoot, the number of branches and the percentage content of nitrogen, phosphorus, potassium, calcium and magnesium
The effect of organic fertilizers on the growth of Ulam raja (*Cosmos caudatus*) and selom (*Oenanthe javanica*)	Project paper	Khairul Ab. Aziz	2006 UPM	The optimum concentration of organic fertilizer to obtain a higher yieldof the two crops for commercial purposes is300 kg Nitrogen ha^{-1}. Increased organic fertilizer

				application rates have increased thetotal dry weight of trees and the dry weight of shoot.
The effect of nitrogen fertilization rates on growth of Ulam raja (*Cosmos caudatus*)	Project paper	Umi Jainab Mohamad subaih	2007 UPM	The maximum yield and the best growth resulted from supplying *C. caudatus* with 90 kg Nitrogen/ha.
The effect of *Cosmos caudatus* extract in the treatment of ethanol-induced gastric lesions in rats.	Project paper	Suhili Binti Sukri	2007 UKM	Two rats groups treated with 250 and 500mg/kg *C. caudatus* extract did not show a significant reduction in ulcer index, gastric acid concentration, and plasma MDA levels, and neither increased SOD activity compared to the positive control group, which was treated with 42.8 mg/kg ranitidine.
Effect of fertilizer type on the vegetative growth for Ulam raja (*Cosmos caudatus*)	Project paper	Mohd. Firdaus Jumaat	2008 UPM	The use of compost and humic plus fertilizers showed increased leaf biomass higher than inorganic fertilizers. They increased moisture and promote media plant nutrient uptake, especially of Nitrogen. NPK fertilizer produces more root length and volume than other fertilizers.
Effects of herbal marinades on the shelf-life of chilled chicken "satay"	Project paper	Faridah Ahamad	2008 UiTM	An herbal mixture of *C. caudatus*, Murrayakoenigii and Polygonum minus, at 0.31% was better than positive control (BHA/BHT) in antioxidant activity. BHA/BHT delayed samples spoilage by mold and yeast more than the herbal mixture.
A comparison on growth performance and nutrient status of *Cosmos caudatus* fertilized with organics	National conference on Agro-environment	Siti Aisha, H	2009 Johor Bahru	The addition of organic fertilizers increased vitamin C, antioxidant activity, and nutrients and decreased nitrates.
Antioxidant effect of *Cosmos caudatus* (Ulam raja) in athletes	Project paper	See soon siang	2011 UPM	The running time, distance and total antioxidant capacity for non-athletes with *C. caudatus* group were significantly higher than non-athletes without *C. caudatus*group.
A pre-study on the potential plants to treat heavy metals in contaminated soil	Project paper	Nurul Izyatulikma, Yusoff	2012 UMP	Phytoremediation method used to extract heavy metals soil pollution. *Cosmos caudatus*accumulated mostly lead by (0.905 mg/L). Cadmium was accumulated by *Oenanthe javanica* (0.913 mg/L), chromium highly accumulated by *Centella Asiatica* (0.340 mg/L) and zinc was the highest metal accumulated by *Emilia sonchifolia* (2.460 mg/L).
Antioxidant activity of ethanolic extract of some Malaysian herbs	Project paper	AdnorAlhaimi, Adaam	2012 UMP	Vitamin C was analyzed using HPLC in three herbal extracts and found that *Cosmos caudatus* contains the highest amount followed by *Premmacordiflora* and finally*Euodia redlevi*.This amount of vitamin C was obtained by sonication for 60 minutes in 70% ethanol for *C. caudatus*. The other two species needed 90 minutes of extraction using 90% of aqueous ethanol to extract vitamin C.
Effect of different types of solvent on extraction of phenolic compounds from *Cosmos caudatus*	Project paper	Nur Ain, Sukri	2012 UMP	Soxhlet apparatus was used for extraction. 100% ethanolic extract showed total phenolic content equals to 15.61 mgGAE/g and DPPH 14.15%. 70% acetone extractobtained 7.77 mgAAE/g with DPPH activity of 84.78%
Optimization of extraction parameters of total phenolic compound from *Cosmos caudatus*	Project paper	Zulkiply Hazwani	2012 UMP	An ultrasonic method was used for extraction. Total phenolic compounds can be best extracted by employing ultrasonic frequency of 70 kHz, 2g dry sample/100mL ethanol and extraction time of 300 minutes.These parameters yielded 7.74 mg GAE/g DW
Antioxidant activity of *cosmos caudatus* extracts by using different types of extraction methods	Project paper	Nur Afeefa, Mohd Khairi	2013 UMP	Ultrasonic-assisted extraction for 1 hour was the best way to extract *C. caudatus*, followed by soxhlet for 8h and maceration extraction for 24h. The antioxidant activity was (26.59, 13.52 and 5.19 mg AAE/g) respectively.

Biosynthesis of Au, Ag and bimetallic Au-Ag nanoparticles using aqueous leaf extract of *Cosmos caudatus*	Master of Science thesis	Mohamad Rapidah	2013 UiTM	Three types of metallic nanoparticles were synthesized biologically; gold, silver and gold-silver. Particle sizes of the spheres were 22.79, 21.49 and 13.98 nm, respectively. The three types of nanoparticles were face centered cubic in structure. The nanoparticles were capped with the bioactive compounds of *Cosmos caudatus.*
The effect of drying method on the antioxidant capacity of *Cosmos Caudatus* extract	Project paper	Ibrahim Shazwani	2013 UMP	Freeze-dried sample of 70% acetone exhibits highest concentration of antioxidant (59.00 mgAAE/g) followed by spray-dried and oven-dried sample (37.00 mgAAE/g and 36.00 mgAAE/g) respectively. Antioxidant activity represented by DPPH was in the same order.
The effect of Extraction Parameters on Antioxidant Activity of *Cosmos caudatus*	Project paper	Badriah, Mohd. Nasir	2013 UMP	The total antioxidant compound was best extracted at 8 hours, using asolvent to sample ratio of 1:30 (w/v) and 66 °C of extraction temperature. The TAC obtained was 28.8 mg AAE/g which was corresponding to 10.1% of its antioxidant activity
Evaluation of antidiabetic properties of *Cosmos caudatus* Kunth leaves in obese-diabetic induced rats using metabolic approach	International health conference IIUM	Alfi Alkhatib	2014 IIUM	Glucose level for rats group treated with 300 mg/kg *C. caudatus* 80% ethanolic extract, reduced to the normal range. This result was same as the group treated with 200mg/kg metformin, except that metformin increased ethanol, alanine, and lactate serum levels.
Profiling and quantification of *Cosmos caudatus* Kunth and *Centella aciatica* Linn and *in vitro* anticancer activity of *Cosmos caudatus*	Master of Science thesis	Munira Binti Mohamad Amin Sharifuldin	2014 USM	High glucosaponins (46%) and protein (57%) contents in *C. caudatus*. Three marker compounds were identified; rutin, quercitrin, and quercetin. Extracts showed dose-dependent cytotoxicity for Hct116 cell line, and inhibition of cell migration, invasion, and clonogenicity.

VI. Phytochemistry and Structure-Activity Relationship

Studies carried out on *C. caudatus* have revealed awide range of phytochemicals. Phytochemicals in *C. caudatus* include phenolic acids, flavonoids, tannins, carotenoids, terpenes, saponins, sesquiterpene lactones, sterols and phenylpropanoids (Table VI). All of these constituents are mainly available in leavesand stems, only phenylpropanoids were extracted from roots.

A. Polyphenols

They are the most abundant antioxidants in vegetables and edible plants. More than 8000 compounds belong to polyphenols with aromatic ring(s) and one or more hydroxyl groups. Phenolics account for 4.42% of the total primary and secondary metabolites in *C. caudatus* (Sharifuldin, 2014). They play a key role in preventing oxidative stress and degenerative diseases through antioxidant activity assecondary metabolites. Polyphenols are divided into classes as follows; phenolic acids, flavonoids, tannins, stilbenes, hydroxytyrosols, diferuloylmethane and lignans and lignins (Han, Shen, & Lou, 2007).

1) Phenolic Acids

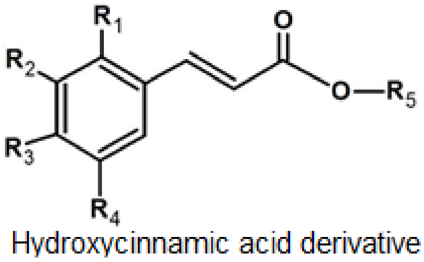
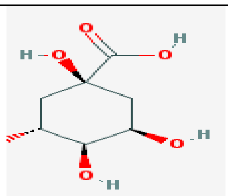
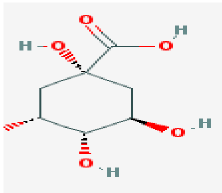
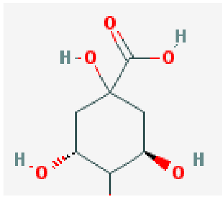
They formone-third of dietary sources of polyphenols, and are classified into two subclasses; hydroxycinnamic acids and hydroxybenzoic acid derivatives (Heleno et al., 2015). All phenolic acids screenedin *C. caudatus* up to date, are from the hydroxycinnamic acid subclass, (Table V) and (Table VI). Shui, Leong, and Wong (2005) isolated chlorogenic, neochlorogenic, cryptochlorogenic acids in *C. caudatus* aqueous acetone and aqueous ethanol fractions. The esterification of caffeic acid with quinic acid results in three isomers of caffeoylquinic acid, namely chlorogenic, neochlorogenic and cryptochlorogenic acids. In plant extracts, usually mixtures of "cis" and "trans" chlorogenic acid isomers are yielded due to auto isomerization occurs during the extraction process. Mixtures of caffeoylquinic acid derivatives isolated from some species of Compositae family such as *C. caudatus* have been known as "coffeetannins" (Morishita & Ohnishi, 2001). Coffeetannins are available in considerable amounts in 18 medicinal plants (including *C. caudatus*) of 24 tested by Andarwulan et al. (2012). Chlorogenic acid and its isomers are hydrolyzed by intestinal flora to caffeic and quinic acids; however, the three above mentioned compounds are well absorbed by human gastrointestinal tract.

2) Flavonoids

Column and liquid chromatographywere used to isolate quercetin andsixof its glycosylatedderivatives from *C. caudatus* extract (Table VI). Quercetin is a heterocyclic compound, insoluble in water, thus, it was fractionated by ethyl acetate from the methanolic extract (Abas, Lajis, & Kalsom, 2003). Unlike its glycosides, quercetinoccurs as a yellow crystalline powder, whereas the glycosides are yellow amorphous solid. The presence of dihydroxy groups on ring B increases the scavenging activity of quercetin, due to increasing electron density and stabilizing radical intermediate (Shahidi & Naczk, 2004) (Fig.1). This structural property makes quercetin effective in restoring the functionality of dysfunctional endothelial cells by scavenging superoxide that generated by NADPH oxidase hence, deactivate nitric oxide. This leads to vasodilation and consequently reduces blood pressure (Menendez et al., 2011).

Two hexamers of catechins, (+)-catechin, and quercetin deoxyl-hexose characterized in *C. caudatus* using HPLC-ESI-MS (Shui, Leong, & Wong, 2005). Catechin is a colorless solid powder, from theflavan-3-ol group of flavonoids, usually exists as anoligomer as the two hexamers found by Shui, Leong, and Wong (2005) or exists along with other flavan-3-ol compounds such as epicatechin, epigallocatechin gallate, and epicatechin gallate. It is available in nature mostly as (+)-catechin, as is the case in *C. caudatus*, but in some plants, it exists as a racemic mixture (±)-catechin.

TABLE V: PHENOLIC ACID DERIVATIVES FROM THE HYDROXYCINNAMIC ACID SUBCLASS THAT ARE EXTRACTED FROM *C. CAUDATUS* UP TO DATE

No.		Substitution	R_5= Quinic acid ester moiety*
1	Chlorogenic acid	R_1=H, R_2=OH, R_3=OH, R_4=H, R_5= $C_7H_{11}O_5$ 3-O- (Quinic acid ester)	
2	Neochlorogenic acid	R_1=H, R_2=OH, R_3=OH, R_4=H, R_5= $C_7H_{11}O_5$ 5-O-(Quinic acid ester)	
3	Cryptochlorogenic acid	R_1=H, R_2=OH, R_3=OH, R_4=H, R_5= $C_7H_{11}O_5$ 4-O- (Quinic acid ester)	
4	Caffeic acid	R_1=H, R_2=OH, R_3=OH, R_4=H, R_5=H	-
5	Ferulic acid	R_1=H, R_2=OCH_3, R_3=OH, R_4=H, R_5=H	-

*Quinic acid ester structure obtained from www.pubchem.ncbi.nlm.nih.gov.

Both enantiomers have the same antioxidant activity, NMR, HPLC retention time and R_f values (Duke et al., 2009). (+)-catechin is absorbed from gastrointestinal tract and readily converted to its metabolites by conjugation and methylation, thus, the biological effects such as the inhibition of monocyte adhesion are not due to catechin itself, but because of its metabolites (Baba et al., 2001). Even though there is asimilarity between quercetin and catechinstructures, but because that the earlier has planar structure and the latter is not, thus there are differences in the biological activities (Menendez et al., 2011).

Myricetin was found as the highest polyphenolic compound available in *C. caudatus*, followed by luteolin, quercetin, catechin and epicatechin, and the lowest percentage was found for naringenin, which all were detected by using HPLC-DAD (Mustafa et al., 2010). The relative abundance of the two flavonols, myricetin, and kaempferol in *C. caudatus* makes it eligible to be strong anticancer species. The hydroxylation on C4\` on ring B (Fig. 1) for both compounds, enables them to act as a traditional topoisomerase II poison. Further hydroxylation of myricetin on C3\` and C5\` gives redox-dependent poisonous property.

Taken together with the C4 keto group on ring C leads to anti-retrovirus activity such as HIV (Bandele, Clawson, & Osheroff, 2008). Naringeninas aglycone has stronger antioxidant activity than its glycosides (Auner, Wirth, & Valenta, 2005), given that this flavanone was extracted from *C. caudatus* as aglycone, and due to other structural features of naringenin such as the C2-C3 double bond and C4 carbonyl group, it has gastric relaxing effects (Amira, Rotondo, & Mulè, 2008).

In another study, HPLC equipped with UV-Vis detected that quercetin was the highest flavonoid found in *C. caudatus* followed by kaempferol and traces of myricetin, luteolin, and apigenin (Andarwulan et al., 2010).This variation in constituents between different studies usually happens due to different harvesting seasons and cultivars, in addition to the multiple extraction and isolation methods. It has been found that flavones; luteolin and apigenin in *C. caudatus* to be in traces. Hydroxylation on C3` or C4` (C4` in thecase of apigenin) (Fig. 1) on ring B is important for the depletion of HER2/neu protein. This protein is overexpressed in breast cancer cells, thus the activity of apigenin results in apoptosis of HER2/neu overexpressed breast cancer cells (Way, Kao, & Lin, 2005). Luteolin was extracted from *C. caudatus* as aglycone, and the aglycone form is stronger than glycosylated luteolin as a cytotoxic agent. Moreover, the dihydroxy groups on C3` and C4`on ring B and the further dihydroxylation on C5 and C7 on ring A, gives luteolin the anti-inflammatory properties (Francisco et al., 2014).

TABLE VI: *COSMOS CAUDATUS* CONSTITUENTS CLASSIFIED ACCORDING TO PHYTOCHEMICAL, MINERAL AND VITAMIN CONTENTS

Constituent	Classification	Reference
	Flavonoids	
Quercetin	Flavonol	Abas, Lajis, & Kalsom (2003)
Quercetin 3-O-β-glycoside	Flavonol Glycoside	Duke et al. (2009)
Quercetin 3-O-α-rhamnoside	Flavonol Glycoside	Duke et al. (2009)
Quercetin 3-O-β-arabinofuranoside	Flavonol Glycoside	Duke et al. (2009)
Quercetin 3-O-galactoside	Flavonol Glycoside	Mediani et al. (2012)
Quercetin3-O-arabinoside	Flavonol Glycoside	Mediani et al. (2012)
Quercetin pentose	Flavonol Glycoside	Shui, Leong, & Wong (2005)
Proanthocyanidin	Tannins	Shui, Leong, & Wong (2005)
Catechin	Flavan-3-ol	Shui, Leong, & Wong (2005)
Rutin	Flavonol Glycoside	Mediani et al. (2012)
Myricetin	Flavonol	Mustafa et al. (2010)
Luteolin	Flavone	Cheng et al. (2015)
Epicatechin	Flavan-3-ol	Cheng et al. (2015)
Naringenin	Flavonone	Cheng et al. (2015)
Kaempferol	Flavonol	Andarwulan et al. (2010)
Apigenin	Flavone	Auner, Wirth, & Valenta (2005)
	Phenolic acids	
Chlorogenic acid	Hydroxycinnamic acid	Shui, Leong, & Wong (2005)
Neochlorogenic acid	Hydroxycinnamic acid	Shui, Leong, & Wong (2005)
Cryptochlorogenic acid	Hydroxycinnamic acid	Shui, Leong, & Wong (2005)
Caffeic acid	Hydroxycinnamic acid	Andarwulan et al. (2012)
Ferulic acid	Hydroxycinnamic acid	Andarwulan et al. (2012)
	Carbohydrates	
α and β Glucose		Perumal et al. (2014)
Sucrose		Perumal et al. (2014)
α-D-glucopyranoside		Javadi et al. (2014)
2-O-Glyceryl-α-Glucopyranoside		Javadi et al. (2014)
D-(+)-arabitol		Javadi et al. (2014)
D-fructose		Javadi et al. (2014)
	Amino Acids	
Alanine, Valine, Lysine, Tyrosine		Zanariah et al. (1986)
Histidine, Arginine, Aspartate		Zanariah et al. (1986)
Threonine, Serine, Glutamine		Zanariah et al. (1986)
Proline, Glycine, Methionine		Zanariah et al. (1986)
Leucine, Phenylalanine, Isoleucine		Zanariah et al. (1986)
	Essential Oils	
(E)-Ocimene, β-Elemene		Lee & Vairappan (2011)
2,6-Dimethyl-1,3,5,7-octatetraene		Lee & Vairappan (2011)
α-Copaene, Caryophyllene		Lee & Vairappan (2011)
α-Humulene, γ-Muurolene		Lee & Vairappan (2011)
γ-Cadinene, Bergamotene		Lee & Vairappan (2011)
β-Selinene, Bicyclogermacrene		Lee & Vairappan (2011)
α-Farnesene, δ-Cadinene		Lee & Vairappan (2011)
Butanedioic acid, (-)-Spathulenol		Lee & Vairappan (2011)
Caryophyllene oxide, α-Muurolol		Lee & Vairappan (2011)
α-Cadinol, Phytol		Lee & Vairappan (2011)

	Miscellaneous	
Formic acid	Organic acids	Mediani et al. (2012)
Malic acid, lactic acid, Succinic acid	Organic acids	Javadi et al. (2014)
Glyceric acid	Sugar acid	Javadi et al. (2014)
Choline	Quaternary Ammonium Salt	Mediani et al. (2012)
Costunolide	Sesquiterpene Lactone	Ragasa et al. (1997)
Stigmasterol	phytosterol	Andarwulan et al. (2011)
Lutein	Carotenoids	Andarwulan et al. (2011)
4,4'Bipyridine	Dipyridyls	Andarwulan et al. (2011)
Ascorbic acid	Vitamins	Andarwulan et al. (2012)
α-Tochopherol	Vitamins	Javadi et al. (2014)
β-Carotene	Vitamins	Andarwulan et al. (2012)
l',2'-Epoxy-4-O-isobutyryl-3'-O-(2-methylbutyryl)-Z-coniferyl alcohol	Phenylpropanoid	Fuzzati et al. (1995)
3'-O-Acetyl-4-O-isobutyryI-Z-coniferylalcohol	Phenylpropanoid	Fuzzati et al. (1995)
l'-Acetoxy-4-O-isobutyryleugenol	Hydroxyeugenol derivative	Fuzzati et al. (1995)
1,2'-Epoxy-3'-O-acetyl-4-O-isobutyryl-Z-coniferyl alcohol	Phenylpropanoid	Fuzzati et al. (1995)
l',2'-Epoxy-3',4-di-O-isobutyryl-Z-coniferyl alcohol	Phenylpropanoid	Fuzzati et al. (1995)
l',2'-Dihydroxy-3',4-O-isobutyrylconiferyl alcohol	Phenylpropanoid	Fuzzati et al. (1995)
Calcium	Minerals	Bodeker, Shekar, & Salleh (2009)

B. Carbohydrates and Free Fatty Acids

By employing two-dimensional-NMR to screen *C. caudatus* constituents under multiple drying methods, carbohydrates such as β and α-glucose and sucrose were detected. In addition to compounds were isolated previously, amino acids such as alanine and valine and organic acids such as formic acid have also been characterized. Fatty acids and choline with the aforementioned compounds were more yielded by freeze drying method than the oven and air drying (Medianiet al.,2012).

C. Phytosterols, Essential Oils, Vitamins, and Minerals

In a study for antimicrobial and anti-mutagenicity activities for *C. caudatus*, a number of phytochemicals have been revealed such as; stigmasterol, lutein, and 4,4'bipyridine [47]. The major essential oils (E.O.) found in *C. caudatus* were ɣ -cadinene, caryophyllene, α-farnesene and (E)-ocimene among other traces of essential oils (Lee & Vairappan, 2011) (Table VI). *Cosmos caudatus* was among the richest fresh vegetables in ascorbic acid and carotenoids contents in comparison to 24 plants were tested (Andarwulan et al., 2012). α-tochopherol (vitamin E) was revealed in the ethanolicextract by Javadi et al. (2014). In the same context, bone marrow strengthening properties has been attributed to high calcium contents in *C. caudatus* (Bodeker, Shekar, & Salleh, 2009) (Table VI).

D. Terpenes, Alkaloids, and Tannins

Alkaloids, terpenoids, and tannins are available in considerable amounts in *C. caudatus* extracts. Culvenor–Fitzgerald method was used to screen the alkaloid contents (Musa et al., 2011). While thin layer chromatography was employed to determine terpenoid and tannin contents in *C. caudatus* (Rasdi et al., 2010). Costunolide elucidated by NMR and mass spectroscopy, as the first terpene found in *C. caudatus* extracts up to date. The presence of α-methylene-ɣ-lactone in the costunolide structure isolated from the chloroform extract of *C. caudatus* indicates the antimutagenic and potential antitumoractivity (Ragasa et al., 1997). Costunolide the sesquiterpene lactone is important for plant growth. In the human biological system, α and β unsaturated carbonyls in costunolide structure react with molecules that regulate cell growth and division such as cysteine and consequently give it the antitumor activity (Fernandes et al., 2008).

Three isomers of proanthocyanidin (PA) diamers, four trimers, four tetramers and four pentamers were isolated from *C. caudatus*. Proanthocyanidins are apolymeric polyphenols belong to the condensed tannins,their building blocks in most plants including *C. caudatus*are (+/-) catechin and epicatechin (Shui, Leong, & Wong, 2005). The interflavanoid linkage determines the PA type, whether it is A or B. A-type PA are the bond type found in *C. caudatus*, which is less commonly distributed in tannin-rich vegetables compared to B-type. A-type linked PA was found to be important for bacterial anti-adhesion property (Howell et al., 2005), thus the antibacterial activity for *C. caudatus* can be attributed to this kind of PAs.

E. Saponins in C. caudatus

Saponins were detected in *C. caudatus* by a preliminary test such as the bubble testing (Musa et al., 2011). In a different assay, thin layer chromatography was employed, and saponins were isolated in all solvent systems used in *C. caudatus* extraction (Rasdi et al., 2010). Recently, Sharifuldin (2014) has found that *C. caudatus* water extract has 42.12% glycosaponins of the total primary and secondary metabolites by using high-performancethin-layer chromatography. This high percentage has not been characterized to elucidate the specific structures of saponins available in this herb up to date.

F. Phenylpropanoids

Phenylpropanoids were isolated for the first time from *C. caudatus* roots by HPLC-DAD and shown remarkable antifungal activity. Phenylpropanoids are listed in Table VI. The presence of five epoxy conferyl alcohol esters in addition to one hydroxyeugenolderivative in *C. caudatus*, proposes LDL protecting effects from oxidation occurs by Cu^{2+} and other enzymessincethis combination was studied by Deigner et al. (1994) indifferent species. At the same time, the epoxy moiety in the conferyl alcohol ester can be considered a crucial element for the antifungal activity of the root extracts of *C. caudatus* (Fuzzati et al., 1995).

G. Amino Acids, and Other Metabolites

Detailed *C. caudatus* amino acids have been listed in a study by Zanariah et al. (1986) using the amino acid analyzer. Lysin, histidine, arginine, aspartic acid, alanine, and valine, among other amino acids, were characterized and account for 1.4% of the total content in *C. caudatus* leaves (Table VI). Other than vitamins and phenols, two constituentswere isolated from the ethanolic extract of *C. caudatus* in a study for the α-glucosidase inhibiting activity; which are α-linolenic acid and α-D-glucopyrinoside. Thewater extract containedmore of carboxylic acids, fatty acidsand carbohydrates such as; malic acid, propane-1,2,3-tricarboxylic acid, arabitol, succinic acid, glyceric acid, octadecanoic acid, D-fructose and lactic acid in addition to other amino acids (Javadi et al., 2014).

VII. Pharmacological Activities

C. caudatus contains high amount of polyphenols as it was reported by many studies (Sukrasno et al., 2011; Yusuf et al., 2010; Shui, Leong, & Wong, 2005). Other studies compared *C. caudatus* polyphenolic contents with several tropical plants and found that it is within the richest plants in phenolics (Loh & Hadira, 2011; Lee & Vairappan, 2011; Mustafa et al., 2010; Andarwulan et al., 2010; Abas et al., 2006). This makes *C. caudatus* extracts eligible for possessing multiple pharmacological activities, which is proportionally connected to phenolic contents (Mustafa et al., 2010). The presence of other vitamins and phytochemicals increase the strength of antioxidant capabilities, as is the case with ascorbic acid (vitamin C), vitamin E, and β-carotene (vitamin Aderivative) since high contents of these vitamins were reported in *C. caudatus* (Andarwulan et al., 2012).

A. Antihypertensive Activity

Hexane and dichloromethane extract of *C. caudatus* have been tried for anti-hypertensive properties in an *in vitro* inhibitory activity against ACE, the resulting inhibitory activities were moderate (Loh & Hadira, 2011). This can be attributed to the absence of water soluble compounds like peptides, as those compounds confer the anti-hypertension activity (Lee et al., 2006). The high content of quercetin found in the extract could not be beneficial concerning reducing hypertension. By employing the aqueous extract of *C. caudatus*, better results were revealed than non-polar extracts in terms of anti-hypertension property.500 and 1000mg/kgwere comparable to 13.5mg/kg captopril, 0.45mg/kg hydrochlorothiazide and 9mg/kg atenolol. At the same time, diuretic activity of the extract was as effective as 1.8mg/kg furosemide (Amalia et al., 2012).

The suggested mechanism of action is still not conclusively proven, but the extract shows diuretic effect comparable to furosemide, and the decreased peripheral resistance through vasodilation was due to high flavonoids contents (No, 2008). Free radical scavenging and lipid peroxidation inhibition give clues about the presumed mechanism. Free radicals alter myocardial function and cause ischemia and lipid membranes peroxidation; leading to perturbation of membrane-bond enzymes and receptors (Williams, Meij, & Panagia, 1995).

B. Antidiabetic Activity

Four constituents in *C. caudatus* were α-linolenic acid, α-D-glucopyrinoside and α-tochopherol in addition to catechin found to have *in vitro* anti-diabetic property, they were screened in the ethanolic extract (Javadi et al., 2014). Another *in vitro*study includedtwo assays to examine the key enzymes affecting diabetes, α-glucosidase and α-amylase inhibition tests (Loh & Hadira, 2011). They have found that hexane extract has high α-glucosidase and low α-amylase inhibitory effects. The mild α-amylase inhibition was enough to potentiate the antidiabetic activity, due to that full inhibition of this enzymeincreases the chance for starch accumulation and the consequence of fermentation in the colon. The only clinical study wasconducted for *C. caudatus* to measure its effects on the glycemic status of type-2 diabetic patients, has concluded that short-term consumption of fresh *C. caudatus* can improve insulin sensitivity for patients (Cheng et al., 2015).

Even though quercetin was not screened by GC-MS in Javadi et al. (2014) study, and the predominant polyphenol was catechin, but it was used as a positive control due to its well-established efficacy as an antidiabetic agent. On the other side, quercetin and its glycosylated form (rutin) exist in highpercentagein the hexane fraction, which showed strong α-glucosidase inhibitory effects by Loh and Hadira (2011). Quercetin reduces blood glucose levels via inhibition of the facilitated diffusion of Glucose transporter-2 (GLUT2) and by inhibition of sodium–dependent vitamin C transporter-1 (SVCT1) (Song et al., 2002). This reduction inblood glucose levels can be interpreted by retarding the absorption of glucose through the inhibition of carbohydrate hydrolyzing enzymes such as the α-glucosidase in the digestive tract (Javadi et al., 2014), and by pancreatic α-amylase slight inhibition. The inhibition of these two enzymes participates in prolonging carbohydrate digestion time, and consequently reducing postprandial plasma glucose (Loh & Hadira, 2011).

C. Antimicrobial Activities

Costunolide was isolated from the chloroform extract of *C. caudatus* and exhibited strong inhibitory activity against *Staphylococcus aureus* (S.A.) and *Saccharomyces cereviseae* (S.C.) and partial inhibitory activity against *Bacillus subtilis* (B.S.). It has been found that it is slightly active against

Candida albicans (C.A.). In the same study, stigmasterol and 4,4'-bipyridine showedmild inhibitory activity against (C.A.) and (S.C.) (Ragasa et al., 1997). Antimicrobial effects of *C. caudatus*ethanolic extract exhibited dose-dependent relationship against (S.A.), (B.S.), *Pseudomonas aeruginosa* (P.A.), *Escherichia coli* (E.C.) and (C.A.) (Rasdi et al., 2010). Essential oils extracted from *C. caudatus* have shown moderate inhibitory activity against *Salmonella* species and *Vibrio cholerae*. Nevertheless, essential oils gave null activity against most of bacteria species treated with it (Lee & Vairappan, 2011), this was due to the absence of oxygenated E.Os. which are considered responsible for the antimicrobial activity (Lopes-Lutz et al., 2008).

Ethyl acetate extract for *C. caudatus* showed distinguished antifungal activity against black pod causing plant disease, namely; *phytophthora palmivora*, *C. gloeosporioides*, *colletotrichumgloeosporioides* and *C. truncatum*. Consequently, natural fungicide derived from *C. caudatus* can be considered as a substitute for the artificial ones (Salehan, Meon, & Ismail, 2013).

D. Antihyperlipidemic Activity

In *in vivo* study for the effects of *C. caudatus* leaves' extract on the lipid profile of hyperlipidemia–induced animal model, it showed that the extract reduced plasma triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), glucose and atherogenic index (AI), and increased high-density lipoprotein (HDL), more than atorvastatin as the positive control (Perumal et al., 2014). It is noteworthy that *C. caudatus* extract has decreased plasma glucose whereas atorvastatin has increased it by decreasing insulin sensitivity.

The presence of quercetin and catechin screened by ^{1}H-NMR in *C. caudatus*extract were suggested tohave asubstantial effect onhyperlipidemia (Perumal et al., 2014). Quercetin decreases lipid peroxidation, up-regulates serum HDL-associated paraoxonase-1 (PON-1) (Gouedard, Barouki, & Morel, 2004), and increases intracellular glutathione as an antioxidant factor (Myhrstad et al., 2002). Proanthocyanidin which was also detected in *C. caudatus* extracts (Shui, Leong, & Wong, 2005) has the potentiality to reduce cardiomyocyte apoptosis by inhibiting ischemia/reperfusion-induced activation of proapoptotic transcription factors (JNK-1) and gene (C-JUN) (Sato et al., 2001).

E. Anticancer/Antimutagenic Activity

Polyphenols, saponins, terpenes and essential oils have good reputation in treating cancer (Patel & Gogna, 2015; Yu et al., 2015; Noratto et al., 2009) and in modulating the cellular signaling cascade (Chao et al., 2010), but little have been done to discover *C. caudatus* effects as anticarcinogenic looking to its richness of bioactive ingredients. Micronucleated polychromatic erythrocytes were reduced substantially by costunolide isolated from *C. caudatus* crude extract thus it has been considered as antimutagenic agent (Ragasa et al., 1997). Separate studies were indicated an antimutagenic activity for stigmasterol and lutein Largo, Rideout, & Ragasa, 1997; Ragasa, Nacpil, & Coll.,1995), which were also isolated from *C. caudatus*. Lee and Vairappan (2011) found a weak cytotoxic activity for the ethanolic extract of *C. caudatus* against P388 murine leukemia cells while essential oils were inactive against this cell line.

F. Antiosteoporotic Activity

Due to the presence of minerals in *C. caudatus*, it has attracted the attention to study its effect on bone density. Many studies were carried out on ovariectomized rats to verify the beneficial effects of *C. caudatus* extract on bone structure. 500mg/kg *C. caudatus* aqueous extract showed better anti-osteoporotic effects than 1% calcium supplement for most of the parameters tested. Factors were examined represent structural, cellular and dynamic bone histomorphometry, which are trabecular number and separation, single and double-labeled surface, mineral appositional rate and bone formation rate (Mohamed et al., 2013; Mohamed et al., 2012). In a study for bone biomechanical parameters, *C. caudatus* ability was examined to heal bone fractures. The extract showed better effects than estrogen in strengthening and increasing the stiffness of bones, and thus repairing bone post-fracture damage in postmenopausal female animal models (Rufus, Mohamed, & Shuid, 2015).

The mechanism of action is not fully clear, but it is believed that in addition to high calcium contents in *C. caudatus*, the presence of antioxidants such as flavonoids and ascorbic acid in considerable amounts, decreases oxidative stress, which is usually accompanied by an increase in the level of malondialdehyde (Mohamed et al., 2012).

G. Miscellaneous Medicinal Uses

Cosmos caudatus aqueous extract was beneficial in releasing detoxifying enzymes in thelung, stomach, and kidneys. A dose as lowas 500 mg/kg of the extract has induced the catalase, superoxide dismutase, glutathione S-transferase and DT-diaphorase as endogenous antioxidant enzymes. At the same time, it has reduced malondialdehyde concentration as an oxidative stress biomarker in the *in vivo* study. It is assumed that *C. caudatus* has beneficial effects more than artificial preservatives and antioxidants with fewer side effects (Abdullah et al., 2015). In the study of *C. caudatus*anti-osteoporotic effects, unexpectedly, it was referred to potential weight gain prevention in animal models when supplemented with 500mg/kg aqueous extract (Mohamed et al., 2012). Furthermore, slight improvements in sperm count and viability percentage were observed when mice treated with 1000mg/kg *C. caudatus* ethanolic extract (Booh et al., 2015).

VIII. Potential Activity-Responsible Constituents and Further Therapeutic Uses for *C. caudatus* Extracts

The diversity of constituents in *C. caudatus* implies many pharmacological and therapeutic uses, thus, the availability of these compounds suggests additional uses that are not proved yet. Moreover, most of the pharmacological studies carried out for *C. caudatus* did not specify the responsible compound(s), or pointed out unspecifically to a range of constituents for the respective effect. Table 7 points outto possible compounds that can be studied in the future in *C. caudatus* extracts for a specific activity. For instance, studies were done for antiosteoporotic effects for *C. caudatus* extracts (Mohamed et al., 2013; Mohamed et al., 2012), only signifies the presence of calcium and the radical scavenging activity of polyphenols. However, Table VII shows recent studies indicate that *C. caudatus* phytochemicals have antiosteoporotic in phytochemicals such as myricetin, kaempferol, β-carotene, and costunolide. In the same context, stigmasterol has an estrogenic effect, which is an important activity in reducing postmenopausal side effects such as osteoporosis; therefore, it can be considered as one of the potential constituents that work actively as antiosteoporotic in *C. caudatus*. The extract was employed in the above-mentioned studies is the aqueous extract, and the expected phytochemicals (myricetin, kaempferol, and β-carotene) were isolated in high polarity index solvent systems, except for costunolide and stigmasterol (Table VII). Rutin as a glycoside is isolated from aqueous or polar solvents, and because it has structure similarity to 17-β-estradiol, it is considered as phytoestrogen and has estrogenic properties (Chua, 2013).

As an antihypertensive agent, Amalia et al. (2012) employed the aqueous extract of *C. caudatus* and suggested that water-soluble flavonoid glycosides were the responsible compounds for this effect *in vivo*. This effect was mediated by free radical scavenging and consequently prevents the peroxidation of membrane lipids of myocardial cells. In the same context, results yielded by Loh and Hadira (2011), showed that *in vitro* inhibition of angiotensin converting enzyme was not due to quercetin that exists in high levels in the non-polar hexane fraction. Interestingly, more than 50% inhibition of ACE was by the semi-polar dichloromethane fraction, and they suggested that the action could be due to soluble peptides. On the other side, quercetin has a well-established mechanism of action as an antihypertensive agent and was explained in details (Section 6.1.2). Additionally, quercetin glycoside (rutin), caffeic acid, and proanthocyanidin also have antihypertensive actions exerted by ACE inhibition as well as another mechanism (Table VII).

Multiple new activities can be studied for *C. caudatus* such as neuroprotection, anti-depression, anti-pruritic and memory enhancing activities, which were all proved for compounds extracted from this herb. Moreover, age-related diseases were known to be caused by oxidative stress such as cataract and Alzheimer dementia (Stohs, 1995), can be treated by highly antioxidant-enriched herbs. Saponins in *C. caudatus* have not been characterized yet; they have merely been proven that they are available in high concentrations. Antiedematous, anti-exudative, antiobesity, antipsoriatic, sedative and many other beneficial effects found for saponins in general (Güçlü-Üstündağ & Mazza, 2007), and can be tested for *C. caudatus* after thescreeningof the major saponin compounds.

TABLE VII: PHYTOCHEMICALS FROM *C. CAUDATUS* LINKED TO PHARMACOLOGICAL EFFECTS, IN ADDITION TO THE MOLECULAR FORMULA, FRACTION WHERE THE COMPOUND WAS ISOLATED AND PUBCHEM CID NUMBER

Phytochemical	Molecular formula PubChem CID	Characterized extract/fraction: Extract/Fraction	Characterized extract/fraction: Reference	Pharmacological effects	Reference*
Quercetin	$C_{15}H_{10}O_7$ 5280343	Ethyl acetate fraction isolated from methanol 50% aqueous methanol Dichloromethane Hexane 50% aqueous acetone	Abas, Lajis, & Kalsom (2013) Andarwulan et al. (2012) Loh & Hadira (2011) Shui, Leong, & Wong (2005)	Anti-inflammatory, anticancer, antihypertensive, antiatherogenic	Menendez, et al. (2011); Formica & Regelson (1995)
Quercetin 3-glucoside	$C_{21}H_{20}O_{12}$ 2280804	Ethyl acetate fraction isolated from methanol 80% aqueous ethanol 80% aqueous methanol	Abas, Lajis, & Kalsom (2013) Mediani et al. (2013) Mediani et al. (2012)	Anti-hyperlipidemic, antidiabetic, anti-influenza A and B virus	Zhang et al. (2011); Kim, Narayanan, & Chang (2010)
Quercetin 3-rhamnoside	$C_{21}H_{20}O_{11}$ 5280459	Ethyl acetate fractionisolated from methanol 80% aqueous ethanol 80% aqueous methanol	Abas, Lajis, & Kalsom (2013) Mediani et al. (2013) Mediani et al. (2012)	Anticancer, anti-influenza A virus	Shabbir et al., (2015); Choi, Song, & Kwon (2012)
Quercetin 3-arabinofuranoside	$C_{20}H_{18}O_{11}$ 10252339	Ethyl acetate fractionisolated from methanol 50% aqueous methanol	Abas, Lajis, & Kalsom (2013) Mediani et al. (2012)	Anti-bacterial	Ferrazzano et al. (2011)
Catechin	$C_{15}H_{14}O_6$ 9064	50% aqueous acetone Absolute ethanol extract	Shui, Leong, & Wong (2005) Javadi et al. (2014)	Neuroprotective, antiatherogenic, anti-viral, myocardial protective, hepatoprotective,	Suganthy & Devi (2016); Kim-Park et al. (2016); Eid et al.

		50% aqueous methanol	Perumal et al. (2014) Mediani et al. (2012) Mustafa et al. (2010)	anti-inflammatory, antidiabetic	(2016); Liu et al. (2015); Zhang et al. (2015); Müller & Downard (2015); Mika et al. (2015)
Proanthocyanidin	$C_{31}H_{28}O_{12}$ 108065	50% aqueous acetone	Shui, Leong, & Wong (2005)	Anthelmintic, antihyperglycemic, cognitive functions promoter, anti-Alzheimer dementia, anti-inflammatory, antihypertensive	Ramsay et al. (2016); Pinent et al. (2016); Gong et al. (2016); Chu et al. (2016); Huang et al. (2015)
Rutin	$C_{27}H_{30}O_{16}$ 5280805	50% aqueous acetone	Shui, Leong, & Wong (2005)	Anti-neuroinflammatory, anti-hypercholesterolemic, antihypertensive, anti-inflammatory, antitumor,	Wu et al. (2016); Samsonowicz et al. (2015); Guardia et al. (2001)
		50% aqueous methanol	Mediani et al. (2012) Perumal et al. (2014)		
		80% aqueous methanol	Mediani et al. (2012)		
		Hexane Dichloromethane	Loh & Hadira (2011)		
Myricetin	$C_{15}H_{10}O_8$ 5281672	50% aqueous methanol	Andarwulan et al. (2010) Mustafa et al. (2010)	Anti-hyperglycemic, anti-osteoporotic, anti-inflammatory, anticancer, regulates circadian rhythm	Arumugam et al. (2016); Devi et al. (2015); Huang et al. (2014); Shin et al. (2013)
Luteolin	$C_{15}H_{10}O_6$ 5280445	50% aqueous methanol	Andarwulan et al. (2010) Mustafa et al. (2010)	Anti-inflammatory, protective against Ultraviolet A, antitumor, antibacterial	Jeong, Ha, & Park, (2016); Xu et al. (2016); Joung et al. (2016)
Naringenin	$C_{15}H_{12}O_5$ 932	50% aqueous methanol	Mustafa et al. (2010)	Antidiabetic, anti-hyperlipidemic, anticancer, colon relaxing agent	Ren et al. (2016); Bodduluru et al. (2016); Yang et al. (2014)
Apigenin	$C_{15}H_{10}O_5$ 5280443	50% aqueous methanol	Andarwulan et al. (2010)	Chemopreventive against Ultraviolet B and skin cancer, anti-depressant-like effect, anti-inflammatory, antidiabetic, antihyperlipidemic	Ren et al. (2016); Bridgeman et al. (2016); Weng et al. (2016); Zhang et al. (2015)
Kaempferol	$C_{15}H_{10}O_6$ 5280863	50% aqueous methanol	Andarwulan et al. (2012) Andarwulan et al. (2010)	Osteogenic effect, anti-inflammatory, antimicrobial, anticancer	Khedgikar et al. (2016); del Valle et al. (2016); Devi et al. (2015); Chen & Chen (2013)
Chlorogenic acid	$C_{16}H_{18}O_9$ 1794427	50% aqueous acetone	Shui, Leong, & Wong (2005)	Neuroprotective, hepatoprotective, maintains glucose homeostasis, anticancer, anti-inflammatory	Fang et al. (2016); Zhou et al. (2016); Peng et al. (2015); Chagas-Paula et al. (2011); Jin et al. (2005)
		50% aqueous methanol	Andarwulan et al. (2012) Mediani et al. (2012)		
		80% aqueous ethanol	Mediani et al. (2013) Mediani et al. (2012)		
Neochlorogenic acid	$C_{16}H_{18}O_9$ 5280633	50% aqueous acetone	Shui, Leong, & Wong (2005)	Gastroprotective, antipyretic, anti-bacterial, antiviral, anti-inflammatory, neuroprotective	Carlotto et al. (2015); Kim et al. (2015)
Cryptochlorogenic acid	$C_{16}H_{18}O_9$ 9798666	50% aqueous acetone	Shui, Leong, & Wong (2005)	Antidiabetic	Wang et al. (2014)

Caffeic acid	$C_9H_8O_4$ 689043	50% aqueous methanol	Andarwulan et al. (2012)	Hepatoprotective, prevents dementia progression, anti-pruritic, antihypertensive, antifungal, anticancer	Pang et al. (2016); Pradhananga & Shim (2015); Chang et al. (2015); Nasr Bouzaiene et al. (2015); De Vita et al. (2014); Bhullar et al. (2014)
Ferulic acid	$C_{10}H_{10}O_4$ 445858	50% aqueous methanol	Andarwulan et al. (2012)	Anti-inflammatory, anti-thrombotic, anticancer, antidiabetic	Doss et al. (2016); Hong et al. (2016); Fahrioğlu et al. (2016); Narasimhan, Chinnaiyan, & Karundevi (2015)
Costunolide	$C_{15}H_{20}O_2$ 6436243	15% ethyl acetate in petroleum ether fraction isolated from chloroform crude extract	Ragasa et al. (1997)	Antineoplastic, antiosteoporotic, normoglycemic, anti-hyperlipidemic, anti-inflammatory	Yang et al. (2011); Lee & Choi (2011); Eliza et al. (2009); Kang et al. (2004)
Stigmasterol	$C_{29}H_{48}O$ 5280794	5-20% ethyl acetate in petroleum ether fraction isolated from chloroform crude extract	Ragasa et al. (1997)	Estrogenic action, improves cognitive function, antiosteoarthritic, anti-hypercholesterolemic, anti-inflammatory, hypoglycemic	Sriraman et al. (2015); Park et al. (2012); Gabay et al. (2010); Panda et al. (2009)
Lutein	$C_{40}H_{56}O_2$ 5281243	30-40% ethyl acetate in petroleum ether fraction isolated from chloroform crude extract	Ragasa et al. (1997)	Corrects age-related macular degeneration, improves cognitive function, skin radioprotective, antitumor, antiatherosclerotic	Nwachukwu (2016); Tian et al. (2015); Juturu (2015)
β-carotene	$C_{40}H_{56}$ 5280489	50% aqueous methanol	Andarwulan et al. (2012)	Anticancer and chemosensitizer, anti-depressant, improves bone mineral density, reduces insulin resistance	Teng et al. (2016); Kim et al. (2016); Chen et al. (2015); Higuchi et al. (2015)
Ascorbic acid	$C_6H_8O_6$ 54670067	50% aqueous methanol	Andarwulan et al. (2012)	Reverses heavy metal neurotoxicity, induces insulin sensitivity, promotes wound healing, anticancer, boosts immunity	Sepehri & Ganji (2016)
α-Tochopherol	$C_{29}H_{50}O_2$ 14985	Absolute ethanol extract	Javadi et al. (2014)	Anti-inflammatory, enhances memory and learning functions, corrects many neurological diseases, alleviates nephrotoxicity, hepatoprotective, antiatherosclerotic	Shirpoor et al. (2016); Ulatowski & Manor (2015); Abdel-Hamid & Firgany (2015); Sato et al. (2015); Norouzi et al. (2015)

* References are for the pharmacological effects of the phytochemical/vitamin.

IX. Toxicity Studies

In a study of the acute toxicity of *C. caudatus* extract, it has shown that some biochemical parameters have been affected at two different doses of *C. caudatus*. Liver enzymes such as alkaline phosphatase (ALP) and alaninetransaminase (ALT) have increased after giving 500 mg/kg and 2000 mg/kg *C. caudatus* aqueous extract. Notwithstanding, kidney functions have improved, as the serum creatinine level was decreased at these two doses (Norazlina & SZ, 2013). In another study for acute and subacute toxicity of *C. caudatus* 80% ethanolic extract, 2g/kg and 5g/kg of bodyweight were found safe for acute toxicity test in rats. Hematology and histopathology parameters were parallel with the control groups in acute studies. However, a reduction in RBC, WBC, MCHC and packed cell volume has been noticed in some *C. caudatus* treated groups in repeated doses subacute test. *Cosmos caudatus* is considered in class five according to OECD guidelines, which means the lowest toxicity class (Amna et al., 2013).

X. Conclusion and Recommendations

Cosmos caudatus is originated from Latin America and cultivated in Europe, Africa and tropical and subtropical Asia, with a wide range of uses as an ornamental, food, and medicinal plant, as well as a large number of synonyms and vernacular names. In Southeast Asia, *C. caudatus* is eaten raw in salad and cooked in food, in addition to traditional uses for burns, to rigidify bones, and as antiaging. It is also used to arrest thatch and as a natural manures. We studied the Malaysian experience represented by the ethnomedicinal research program and retrieved unpublished papers, M.Sc. and Ph.D. dissertations to study the phytochemical, pharmacological and ethnopharmacological properties of *C. caudatus*. Results were beneficial to validate its uses in many fields such as in agricultural, nutritional, medicinal, and to optimize extraction techniques.

Cosmos caudatus compounds were from different chemical groups namely; polyphenols, carotenoids, terpenes, saponins, sterols, carbohydrates and essential oils. Pharmacological reports indicated that*C. Caudatus* has antihypertensive, antidiabetic, antimicrobial, antihyperlipidemic, anticancer, antioxidant and antiosteoporotic activities. Since most of these studies did not reveal the compound(s) responsible for such actions, we pointed out to a number of phytochemicals that can be extracted from the same effective extract/fraction and have the potentiality for the respective activity. Other studies are needed in different fields, which were not studied yet such as neurological, depression, allergy and immunity.

The mechanisms of action of *C. caudatus* pharmacological activities are not clarified conclusively, and the synergistic activities between constituents are important to reveal the full benefits of this medicinal herb. Saponins, terpenes, and alkaloids are organic compounds among many other constituents in *C. caudatus* and there is an urgent need to characterize and screen their structures. In order to elucidate full toxicity profile, additional studies needed to confirm safety and side effects expected from *C. caudatus* use. However, it is still a long journey for *C. caudatus* between salad dishes to reach the medicinal formulations.

Conflict of Interest

Authors have no conflict of interest to declare.

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