

**Review Article*****Toddalia aculeata*: A comprehensive review of its Phytochemistry, pharmacology and its traditional use****Ravi Kant Upadhyay**

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E-mail address: [rkupadhya@yahoo.com](mailto:rkupadhya@yahoo.com)**Running Title:** Pharmaceutical potential of *Toddalia aculeata***Received: 01 September, 2016; Revised: 12 October, 2016 Accepted: 25 October, 2016**Available online at <http://www.thescientificpub.com><http://dx.doi.org/10.19046/abp.v03i05.06>**Abstract**

*Toddalia aculeata* is an important medicinal plant widely used for treatment of several diseases and disorders. Root bark of the plant is antimalarial, antiperiodic, antipyretic, tonic and carminative. Plant leaves and stem have bitter taste, minty and warming-nature and, considered antiphlogistic and analgesic in nature. Leaf essential oil is used in relieving rheumatic arthritis, sprains, contusions, intercostal neuralgia, cough, malaria, dysentery and gastralgia. The also plant shows antimicrobial, anti-plasmodial, analgesic, antihyperlipidemic, larvicidal, spasmolytic, anti-inflammatory, antidiarrhetic and dynamogenic activities and is traditionally utilized for the cure of diabetes. The plant roots contain coumarins that show antiplasmodial activity while Toddalin isolated from this plant inhibits osteoclastogenesis and enhances the osteoblastogenesis. Bio-organic components of *T. aculeata* show anti-viral, anti-tubercular and cytotoxicity against tumor cells. Present review explains therapeutic and pharmaceutical potential of *Toddalia aculeata*. Moreover, this review also summarizes the traditional uses of the plant for treatment of various ailments.

**Keywords:** *Toddalia aculeata*, ethnomedicine, coumarins, toddalin, antimicrobial.**Introduction**

*Toddalia aculeata* Pers. is a climbing shrub which grows in forests, woodlands and grasslands of Eastern and central Africa from the Sudan southwards at an altitude of 1600 meters. Plant is used medicinally in Europe under the name *Lopez Root* or *Cortex radices*. In Gabon (Africa) the macerated root bark is used as a remedy against gonorrhoea. In Philippines, its fruits are used to flavor food. All parts of the plant are claimed to have medicinal value, but the root bark is particularly believed to be more potent. Decoctions or infusions of the roots are taken orally to treat fever; rheumatism and stomach ache [1]. *Toddalia asiatica* is a commonly used medicinal plant in East Africa for the management of pain and inflammatory conditions [2]. Its leaves have been utilized traditionally for the cure of diabetes [3] by different local tribes and communities [4].

Unripe fruits and roots are rubbed with oil to prepare a stimulant liniment for treatment of rheumatism. The flower juice is applied to the stings of wasp for having immediate relief.

Plant is recognized by many local names in different languages i.e. Chikafusi (Shona), Cockspur orange or Climbing orange (English), Gato (Shona), Rukato (Shona), Kanj (Hindi) and Jangli mirch (Bengali). It is also known as Walking-stick Climber that possesses woody, corky, thorny stems that climb on trees, reaching up to 10 m in length. Plants bear shiny green lemon-scented leaves mainly ferruginous-pubescent, glabrescent with creamish white flowers. Sepals are generally 0.3-0.5 mm but varied according to species in color. Petals are ovate to elliptic of 1-3.5 mm size. Stamens in male flowers are 3-4 mm, whereas female flowers are ligulate and only 0.2-0.8 mm,

disk is 0.2-0.5 mm. Gynoecium in female flowers is ovoid to ellipsoid and 1.5-2.5 mm in size. In male flowers subcylindric androecium is found which is of 1-2 mm in size. Fruits are orange about half a cm wide that tastes like orange peel. Inflorescence is short or as long as the



**Figure 1:** Floral parts of *Toddalia aculeata*; (a) leaves and flowers (b) fruits

### Medicinal uses

Recent studies have revealed that *Toddalia* is highly active against many infectious drugs resistant pathogenic organisms. *Toddalia aculeata* is widely used by many African tribes for treatment of Malaria, cough and influenza (**Figure 1**). The plant roots contain coumarins that have antiplasmodial activity. *Toddalia aculeata* is used as a pain killer [5]. Till the date several bio-chemicals have been isolated from roots, stems, leaves, flowers, fruits and seeds of this plant and its associating species (Table 1). Toddalin isolated from the *T. aculeata* inhibited osteoclastogenesis in RAW 264 cells and enhanced the osteoblastogenesis in MC3T3 –E1 cells. Plant leaves and stem is bitter-tasting, minty and of warming-nature. It activates blood; dissipates contusions and considered antiphlogistic and analgesic in nature. Volatile oil from the leaves have a pleasant odor resembling verbena of basilicum. It is used in relieving rheumatic arthritis, sprains, intercostal neuralgia, cough, malaria, dysentery and gastralgia. It is also used as an antidote against poisonous snakebites, nausea, bronchitis, wounds, contaminated ulcers, epilepsy, gonorrhoea and general debility. Root bark is considered antimalarial, antiperiodic, antipyretic, tonic and carminative. Fresh root bark is used as infusion, while fluid extract, as stimulating tonic and carminative. Pounded fresh leaves applied as poultice on furuncles mainly on over afflicted areas. The leaves of *Toddalia asiatica* are widely used in folk medicine in India to treat various ailments like cough, malaria, indigestion, influenza lung diseases and rheumatism, fever, stomach ailments, cholera and diarrhea.

subtending leaf, ferruginous-pubescent; bracteate flowers in axillary and terminal clusters or branched inflorescence, cream to pale greenish-yellow in color. Fruits are small citrus-like, orange in color when ripe (Figure 1a, 1b).

In East Africa, plant is oftenly used for the treatment of stomach problems, food poisoning, sore throat, malaria, cough, chest pains and inflammatory conditions [4]. The leaves and root of *Toddalia asiatica* (L.) are widely used in folk medicine of India for the treatment of various ailments including cough, malaria, indigestion, influenza, rheumatic fever cholera, diarrhea, and stomach ailments [6]. Plant is used in the Philippines as folkloric medicine mainly in preparation of decoction of root used as anti-diarrheic and dynamogenic during convalescence from fevers. Infusion of root bark is used as bitter stomachic, tonic and febrifuge. Floral parts exhibit antiviral activity against H1N1 influenza [7]. Toddaculin isolated from *Toddalia asiatica* (L.) has been found to inhibit the differentiation of osteoclasts via activation of the NF- $\kappa$ B, ERK 1/2, and p38 MAPK signaling pathways [8]. Additionally, Toddaculin induces differentiation and mineralization of osteoblasts by regulating differentiation factors [8]. Leaves are chewed for treatment of stomach disorders. Oil is used in making low-grade perfume. Africans use the *Toddalia* stems for walking-sticks.

### Phyto-constituents

Two alkaloids N-methyl-4-hydroxy-7-methoxy-3-(2,3-epoxy-3-methylbutyl)-1H-quinolin-2-one and 3-(2,3-dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1H-quinolin-2-one have been isolated from CH<sub>2</sub>Cl<sub>2</sub>:methanol (1:1) and methanol extracts of leaves and stems of *Toddalia aculeata* [9]. Leaf volatile oil contains 0.08% toddalolactone, citronellal and largely

linalool (Figure 2). Stem bark contains aculeatin; aculeatin hydrate. Oil has an odor suggesting a mixture of camphor and lemon grass. Stem contains sugar, protein, alkaloids, flavonoids, sterols, coumarins, and glycoside. It also contains triterpene acids: 2 $\alpha$ , 3 $\alpha$ , 19 $\alpha$ -trihydroxy-11-oxo-urs-12-en-28-oic acid, 2 $\alpha$ , 3 $\alpha$ , 11 $\alpha$ , 19 $\alpha$ -tetrahydroxy-urs-12-en-28-oic acid, 2 $\alpha$ , 3 $\alpha$ -dihydroxy-19-oxo-18, 19-seco-urs-11, 13 (18)-dien-28-oic acid, and 2 $\alpha$ , 3 $\beta$ , 19 $\alpha$ -trihydroxyolean-11, 13(18)-dien-28-olic acid, along with the known compounds euscaphic acid, arjunic acid, toddaculin, toddalolactone and  $\beta$ -sitosterol. Coumarin i.e. -5,7-dimethoxy-8-(3'-hydroxy-3'methyl-1'butene)-coumarin has been isolated from *Toddalia asiatica* roots. From ethanolic extract of roots eight new alkaloids, 8-methoxynorchelerythrine, 11-demethylrhoifoline B, 8-methoxynitidine, 8-acetylnorchelerythrine, 8,9,10,12-tetramethoxynorchelerythrine, isointegriamide, 1-demethyl dicentrinone, and 11-hydroxy-10-methoxy-(2,3)-methylenedioxytetrahydroprotoberberine, together with 10 known alkaloids were isolated [10]. Flindersine, a quinolone alkaloid was a major active principle. Ulopterol, a coumarin has also been isolated and is a major active antimicrobial principle [6]. Plant also contains alkaloids, terpenoids, coumarins, flavonoids and phenolic compounds [11] (Figure 2). Essential oil obtained by hydrodistillation of *T. asiatica* roots contains of 58 components. The essential oil also contains sesquiterpenoids (35.41 %) and monoterpenoids (31.87 %). The principal compounds in *T. asiatica* essential oil include geraniol (9.84 %), D-limonene (7.52 %), isopimpinellin (6.62 %),  $\alpha$ -gurjunene (6.25 %), and 4-vinylguaiaicol (5.94 %) [12]. From twigs of *Toddalia aculeata* yielded two new geranyloxycoumarins [13] (Figure 2).

From root bark of *Toddalia asiatica* (L.) Lam. biologically active compounds coumarins i.e. toddaculin, coumurrayin, toddanone, 8-(3,3-dimethylallyl)-6,7-dimethoxycoumarin, isopimpinellin (8), 6-(3-chloro-2-hydroxy-3-methylbutyl)-5,7-dimethoxycoumarin, 6-formylmettin, 5,7,8-trimethoxycoumarin, toddasin, (+)-toddanol, 6-(2-hydroxy-3-methoxy-3-methylbutyl)-5,7-dimethoxycoumarin, toddalolactone, toddalenol, toddalosin, 5-methoxysuberenon, toddaleneone, and 8-formylmettin were isolated. Furthermore, seven known benzo[c]phenanthridine alkaloids [des-N-ethylchelerythrine, oxychelerythrine, arnottianamide, oxyvicine, avicine, chelerythrine, and chelerythrine-psi-cyanide and four known quinoline alkaloids [N-methylflindersine, 4-methoxy-1-methyl-2-quinolone, skimmianine, integriquinolone, one known triterpenoid [beta-amyirin (3)] were isolated [14]. Furanocoumarins from *Toddalia asiatica* (L.) Lam. were isolated by using microwave-assisted extraction coupled with high-speed counter-current chromatography [15] (Figure 1).

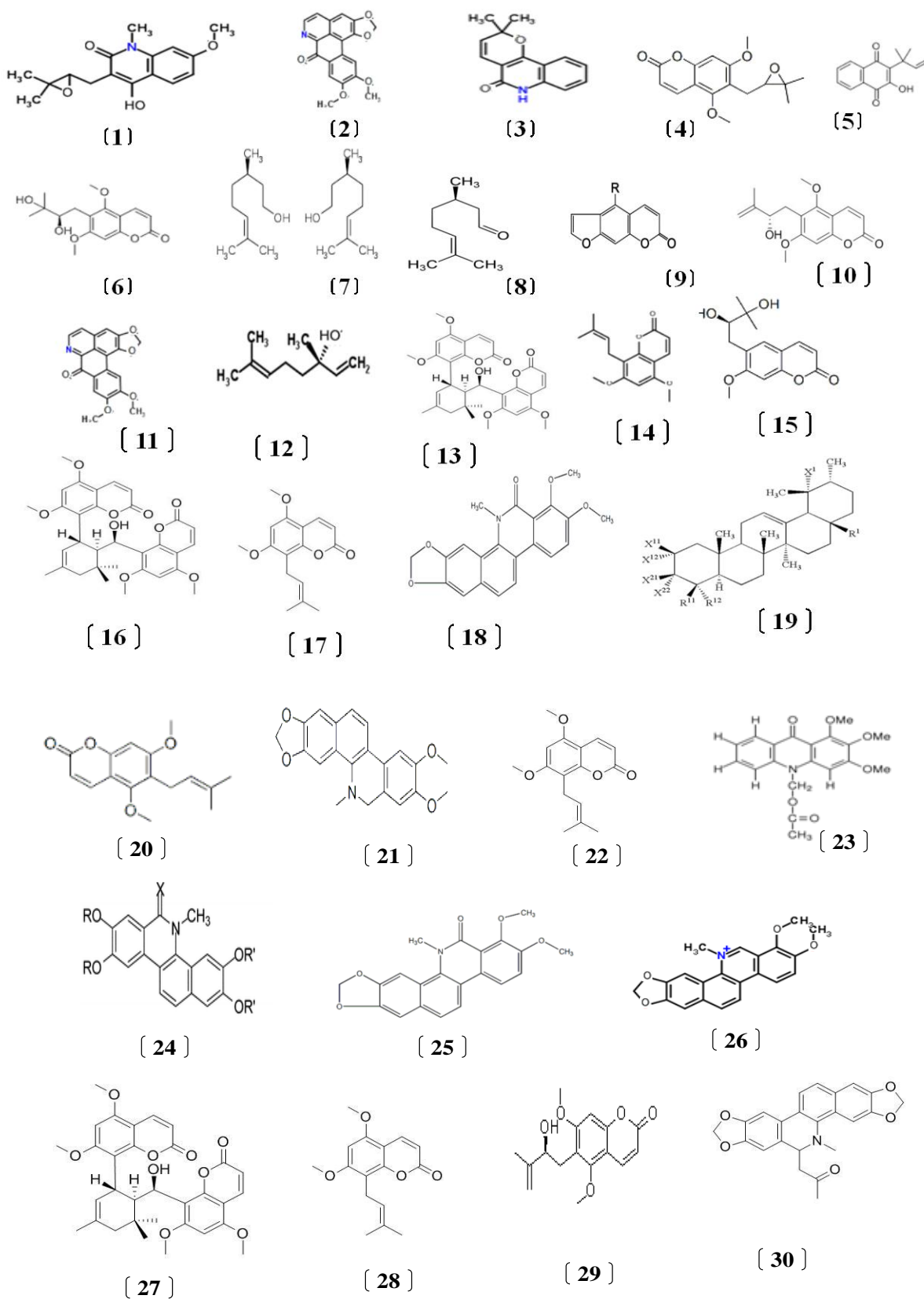
## Pharmaceutical effects

### Antimicrobial activity

*Toddalia asiatica* exhibits strong activity against *E. coli* and *P. aeruginosa*, *B. subtilis*, *S. aureus*, *S. epidermidis*, *E. faecalis*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Ervinia sp*, *P. vulgaris* [16]. Flindersine, a quinolone alkaloid as the major active principle isolated from leaves of *Toddalia asiatica* showed antibacterial and antifungal activities. Ulopterol, a coumarin isolated as another major active antimicrobial principle showed activity against the bacteria including *S. epidermidis*, *E. aerogenes*, *Shigella flexneri*, *K.pneumoniae* (ESBL-3967), *E. coli* (ESBL-3984) and fungi including *A. flavus*, *C. krusei* and *B. cinerea* [6]. Aqueous and ethanol extract of *Toddalia asiatica* were found active against *E. coli*, *K. pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Vibrio cholerae* were found to be positive for  $\beta$ -lactamase production. Ethanol extracts of *Toddalia asiatica* showed minimum inhibitory concentration values of 100-200  $\mu$ g/ml, respectively against multidrug-resistant bacteria [17]. Nanoparticles synthesized by using *T. asiatica* extract were found highly effective in inhibiting growth of *B. subtilis*, *K. pneumoniae*, and *Salmonella typhi* [18]. Coumarins and other compounds isolated from the stem bark of *Toddalia asiatica* showed cytotoxicity against the NCI-H187 cell line and MCF-7 cell line, and KB cells with IC<sub>50</sub> values ranging from 3 to 9.79  $\mu$ g/mL. Compounds 5, 9, and 16 (Table 1) exhibited anti-tuberculosis activity against *M. tuberculosis* with MIC of 50, 50, and 25  $\mu$ g/mL, respectively [19]. Alkaloids Benzo[c]phenanthridine and secobenzo [c]phenanthridine alkaloids isolated from root of *Toddalia asiatica* exhibited significant cytotoxic, antimicrobial and antifungal properties [10] (Table 1).

Hexane, chloroform, ethyl acetate, methanol and water extracts of *Toddalia asiatica* leaves have shown antibacterial and antifungal [20]. Flindersine (2,6-dihydro-2,2-dimethyl-5H-pyrano [3,2-c] quinoline-5-one-9c) isolated from the ethyl acetate extract showed MIC values of against bacteria *B. subtilis* (31.25  $\mu$ g/mL), *S. aureus* (62.5  $\mu$ g/mL), *S. epidermidis* (62.5  $\mu$ g/mL), *E. faecalis* (31.25  $\mu$ g/mL), *Pseudomonas aeruginosa* (250  $\mu$ g/mL), *A. baumannii* (125  $\mu$ g/mL) and fungi *T. rubrum* 57 (62.5  $\mu$ g/mL), *T. mentagrophytes* (62.5  $\mu$ g/mL), *T. simii* (62.5  $\mu$ g/mL), *E. floccosum* (62.5  $\mu$ g/mL), *M. grisea* (250  $\mu$ g/mL) and *C.albicans* (250  $\mu$ g/mL) were determined [20] (Table 1). Hot water extracts of *Toddalia asiatica* (root bark) showed *in vivo* anti-malarial activity in mice against a chloroquine (CQ) resistant *Plasmodium berghei* NK65, either alone or in combination with CQ. Chemosuppression obtained was in the range 51%-75%. [21].

**Figure 2:** Chemical structures of phytochemicals isolated from *Toddalia aculeata* and its associated species.



**Table 1:** Compounds derived from *Toddalia aculeata* with their reported bioactivities

Plant part	Name of compound	Class of compound	Biological effectiveness
Leaves and stems	N-methyl-4-hydroxy-7-methoxy-3-(2,3-epoxy-3-methylbutyl)-1H-quinolin-2-one	Alkaloid	Antimicrobial, insecticidal
Leaves and stems	3-(2,3-dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1H-quinolin-2-one	Alkaloid	Antimicrobial, insecticidal
Leaves	Toddalolactone	delta-lactone of coumarinic acid	Antiplasmodial activity
Leaves and fruits	Citronellal, linalool	Alcohol A	Antimicrobial activity against <i>Salmonella Typhimurium</i>
Stem bark	Aculeatin, aculeatin hydrate	Alcohol A	Anticancer
Twigs	Geranyloxycoumarins	Geranyl and carbonyl group	Disrupt mitochondrial respiration
	2 $\alpha$ ,3 $\alpha$ , 11 $\alpha$ , 19 $\alpha$ -tetrahydroxy-urs12-en-28-oic acid	Triterpene acids:	Antimalarial
Root	- 5,7-dimethoxy-8-(3'-hydroxy-3'methyl-1'butene)-coumarin	Carbonyl group	Antiplasmodial
Root	8-methoxynorchelerythrine	Alkaloid	Cytotoxic, antimicrobial and antifungal
Root	Flindersine	Quinolone alkaloid	Antibacterial and antifunga
Root	Ulopterol		
Leaf essential oil	Sesquiterpenoids and monoterpenoids geraniol, D-limonene, isopimpinellin, $\alpha$ -gurjunene, and 4-vinylguaiacol	Terpenoids alcohols	Antibacterial and antifunga
Root bark	Toddanone	Alkaloid	Antimicrobial activity
Root bark	Coumurrayin	Aalkaloid	Antimicrobial activity.
Root bark	8-(3,3-dimethylallyl)-6,7-dimethoxycoumarin	Alkaloid	Antimicrobial activity.
Root bark	5,7,8-trimethoxycoumarin	Alkaloid	Antimicrobial activity.
Root bark	toddalolactone	Coumarins	Anti-hypertension, anti-inflammatory and anti-fungal activities
Root bark	Coumurrayin	Coumarins	Antimicrobial activity.
Root bark	Toddalolin	Coumarins	Anti-inflammatory, analgesic, antipyretic
Root bark	Toddalenol	Coumarins	Anti-oxidant
Root bark	Arnottianamide	Amide-alkaloids	Antibacterial
Root bark	Integriquinolone	Quinolone	Antibacterial
Root bark	Skimmianine	Quinoline	Anti-acetylcholinesterase activity
Root bark	8-formyllimettin	Coumarins	Antimalarial
Root bark	Oxyavicine	Alkaloids	Anti-tumor
Leaves	Oxychelerythrine	Alkaloids	Anti-tumor
Root bark	benzo[c]phenanthridine alkaloids [des-N-methylchelerythrine	dimeric benzophenanthridine alkaloid	Anti-tumor
Root	dihydroneitidine		Antimalarial and anti-HIV-1

### Antiparasitic activity

Chelerythrine and chloroxylinone isolated from *Toddalia asiatica* were found active against parasitic ciliate *Ichthyophthirius multifiliis* that infects all species of freshwater fish and causes severe economic losses in fish breeding [22]. *In vitro* antiparasitic assays chelerythrine and chloroxylinone were found 100% effective against *I. multifiliis* at the concentration of 1.2 mg/L and 3.5 mg/L with the median effective concentration ( $EC_{50}$ ) of 0.55 mg/L and 1.90 mg/L respectively. The acute toxicity ( $LC_{50}$ ) of chelerythrine for goldfish was 3.3 mg/L [22].

### Anti-plasmodial activity

Nitidine an alkaloid isolated from *Toddalia asiatica*, is a major antimalarial component that shows *in vitro*  $IC_{50}$  against *Plasmodium falciparum* in the range of 9 to 108 ng/mL for a range of chloroquine-susceptible and -resistant strains. A lack of cross-resistance between chloroquine and nitidine was observed [23]. Coumarin -5,7-dimethoxy-8-(3'-hydroxy-3'-methyl-1'butene)-coumarin isolated from *Toddalia asiatica* roots showed anti-plasmodial activity [24]. Aqueous, ethyl acetate, hexane and methanol extracts were obtained from *Toddalia asiatica* root bark, fruits and leaves also have shown *in vitro* anti-plasmodial activity in chloroquine-sensitive (D6) and chloroquine-resistant (W2) *Plasmodium falciparum* strains. Similar activity was also obtained under *in vivo* conditions by administering mice with *P. berghei* strains for four consecutive daily doses of the extracts through oral route following. More-specifically, ethyl acetate extract of the fruits was found active against chloroquine resistant *P. falciparum* as well as against *P. berghei* [1]. Inhibitory concentrations of ethyl acetate extract of *Toddalia asiatica* fruits showed high activity against chloroquine resistant (W2) strains of *P. falciparum* ( $IC_{50}$ ; 1.87  $\mu$ g/ml), followed by root bark aqueous extract ( $IC_{50}$ ; 2.43  $\mu$ g/ml). From the n-hexane, ethyl acetate and methanol extracts of *Toddalia asiatica* have shown *in vitro* anti-plasmodial activity against D6 (chloroquine-sensitive) and W2 (chloroquine-resistant) strains of *P. falciparum* [25]. Coumarins also showed antimalarial activity against *P. falciparum* with an  $IC_{50}$  value of 3.66  $\mu$ g/mL [26] (Table 1).

### Anti-diabetic and antioxidant activities

Ethyl acetate extract of *T. asiatica* leaves showed significant antidiabetic and antioxidant effects in STZ-induced diabetic rats. Histopathology of pancreas in the treated group showed regeneration of  $\beta$ -cells [3]. Alcoholic and aqueous extracts of *Toddalia asiatica* exhibited significant *in vitro* and *in vivo* antioxidant activity [27]. In Triton WR-1339 induced hyperlipidemic rats, oral

treatment with *T. asiatica* leaves ethyl acetate extract produced a significant ( $P \leq 0.005$ ) decrease in the levels of serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), and significant increase in high-density lipoprotein cholesterol (HDL-C) in comparison with hexane and methanol extracts. In high fat diet-fed hyperlipidemic rats, the ethyl acetate extract (200 and 400 mg/kg) significantly altered the plasma and liver lipids levels to near normal [11]. Stem bark of *T. asiatica* also showed antioxidant activity [28].

### Radical Scavenging Activity

*T. asiatica* leaves ethyl acetate extract showed very good scavenging activity on 2, 2-diphenyl-picrylhydrazyl (DPPH) ( $IC_{50}$  605.34 $\pm$ 2.62  $\mu$ g/mL), hydroxyl ( $IC_{50}$  694.37 $\pm$ 2.12  $\mu$ g/mL) and nitric oxide ( $IC_{50}$  897.83 $\pm$ 1.48  $\mu$ g/mL) radicals, as well as high reducing power [11]. It exhibits antioxidant activity through inhibition of hydroxyl radical of *Toddalia asiatica* polysaccharides [29]. *Toddalia asiatica* essential oil also exhibits considerable DPPH free radical, hydroxyl radical scavenging, iron chelation and inhibition of lipid peroxidation activities [30]. *T. asiatica* leaves ethyl acetate extract (TALee) showed highly significant blood glucose lowering effect.

### Anti-hyperlipidemic activity

*Toddalia asiatica* (L) Lam. leaves showed *in vitro* antioxidant and anti-hyperlipidemic activity of in Triton WR-1339 and high fat diet-induced hyperlipidemic rats. *T. asiatica* leaves ethyl acetate extract produced a significant ( $P \leq 0.005$ ) decrease in the levels of serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), and significant increase in high-density lipoprotein cholesterol (HDL-C) in comparison with hexane and methanol extracts. In high fat diet-fed hyperlipidemic rats, the ethyl acetate extract (200 and 400 mg/kg) significantly altered the plasma and liver lipids levels to near normal [11]. Aculeatin isolated from *T. asiatica* extracts act on the differentiation of 3T3-L1 preadipocytes. Aculeatin enhanced the differentiation of preadipocytes into adipocytes when these cells were treated with aculeatin isolated from *T. asiatica* in the presence of insulin. Aculeatin increased the cellular triglyceride levels and glycerol-3-phosphate dehydrogenase activity [31]. The various coumarins isolated from this plant show spasmolytic activity prominent effect in cardiovascular system [32, 33] (Table 1).

### Analgesic / Anti-Inflammatory

Crude alkaloids of *T. asiatica* showed anti-inflammatory and analgesic effects [34]. Administration of ethyl alcohol

extract and ethyl acetate fraction remarkably reduce paws and joints swelling and decrease the spleen indexes. Further, histopathological examination displayed that RTA effectively protected bone and cartilage of knee joint from erosion, lesion and deformation versus those from the control group [34]. Besides, the concentration of cytokines like TNF- $\alpha$ , IL-1 $\beta$ , IL-6 were significantly lower than the ones from the control group respectively, while cytokine like IL-10 was remarkably higher compared with the control group [35]. *T. asiatica* shows antinociceptive and the anti-inflammatory effects in formalin-induced pain test and the carrageenin-induced oedema paw. Plant extract is used in the management of painful and inflammatory conditions [2]. A reduction in carrageenin induced acute inflammation paw oedema was significant ( $p < 0.01$ ) following administration of 100 mg/kg dose but not with the 200 mg/kg dose. *T. asiatica* shows significant antinociceptive and anti-inflammatory effects using the carrageenin-induced paw edema and formalin-induced pain tests, and supports the anecdotal use for painful and inflammatory conditions [2] (Table 1).

#### Anti-arthritic activity

Dry root bark of *Toddalia asiatica* (L.) Lam. has been used as a traditional ethnic Chinese medicine for alleviation of pain and inflammation in patients suffering from rheumatism [36]. Administration of ethyl alcohol extract and ethyl acetate fraction remarkably reduced paws and joints swelling and decreased the spleen indexes [36] (Table 1).

#### Anti-platelet aggregation

*Toddalia asiatica* contains coumarin, alkaloids, a benzoquinone and an amine which showed strong anti-platelet aggregation activity *in vitro* [37].

#### Anti-tumor and anti-HIV activities

DHN (dihydroneitidine) NTD (nitidine), and DMN (demethylnitidine) are benzo[c] phenanthridine derivatives, were also isolated from *Toddalia asiatica* Lam. Among which NTD and DHN selectively reduced the growth of murine and human lung adenocarcinoma *in vitro* [38]. Two alkaloids (1,3) benzodioxolo (5,6-c) phenanthridine, 12,13-dihydro-2,3-dimethoxy-12-methyl-(dihydroneitidine) were found cytotoxic to human lung adenocarcinoma (A549) cells [39]. Coumarins were isolated from the stem bark of *Toddalia asiatica* showed cytotoxicity against the NCI-H187 cell line with IC<sub>50</sub> values ranging from 6 to 9  $\mu\text{g/mL}$  [19]. Toddaculin, a natural coumarin from *Toddalia asiatica*, induces differentiation and apoptosis in U-937 leukemic cells [40]. Compounds 5, 9, and 16 exhibited anti-tuberculosis activity against

*Mycobacterium tuberculosis* with MIC values of 50, 50, and 25  $\mu\text{g/mL}$ , respectively [19] (Table 1).

*T. aculeata* plant extract also showed anti-HIV activity into fractions rich in quaternary alkaloids. In an *in vitro* XTT-based anti-HIV assay, 1-10  $\mu\text{g/mL}$  nitidine inhibited human lymphoblastoid cell killing by HIV-1 [41]. Similarly, docking studies based on free energies of binding ( $\Delta G$ ) showed that toddanol, toddanone, and toddalenone are to be potent inhibitors of HIV-1-RT. Toddanol and toddanone with more rotatable bonds were found to have a drug-likeness score of 0.23 and 0.11, respectively [42] (Table 1).

#### Cytotoxic effects

The essential oil isolated from the leaves of *Toddalia asiatica* (L.) Lam. contains  $\beta$ -phellandrene (21.35%) which shows significant cytotoxicity against H<sub>2</sub>O<sub>2</sub> induced genotoxicity in human lymphocytes [30]. Its essential oil also showed cytotoxicity against breast (MCF-7) and colorectal (HT-29) cancer cells with the IC<sub>50</sub> of (7.80 $\pm$ 0.03)  $\mu\text{g/mL}$  and (100.00  $\pm$  0.16)  $\mu\text{g/mL}$  respectively (Table 1).

#### Larvicidal activity

Hexane extract of fruits of *T. asiatica* showed highest larvicidal activity against fourth instars larvae of Dengue vector, *Aedes aegypti* and Filarial vector, *Culex quinquefasciatus* [43]. The LC<sub>50</sub> of *T. asiatica* was 47.893, 50.992, 54.461 and 61.278 on first to fourth instars. Similarly, smoked exposed gravid females hatched a lower percentage of eggs compared to unexposed females [44]. *T. asiatica* aqueous extract and green-synthesized AgN showed excellent larvicidal and pupicidal toxicity against *Culex quinquefasciatus* the filariasis vector. AgN LC<sub>50</sub> ranged from 16.48 (I instar larvae) to 31.83 ppm (pupae). Geraniol, D-limonene, and isopimpinellin exhibited strong larvicidal activity against *A. albopictus* with LC<sub>50</sub> values of 30.13, 19.84, and 32.05  $\mu\text{g/mL}$ , respectively, while the essential oil of *T. asiatica* had an LC<sub>50</sub> of 69.09  $\mu\text{g/mL}$  [12]. Extracts of *T. asiatica* have shown potential larvicidal activity against *Anopheles gambiae* [43]. Isolated compounds from *T. asiatica* showed the highest level of larvicidal activity. *Toddalia asiatica* exhibited strong larvicidal effects against *Aedes aegypti* due to presence of sibiricin and coumarins compounds [45]. Aqueous extract of *Toddalia asiatica* Lam. Shows antifeedant activity in gram pod borer, *Helicoverpa armigera* (Hbn) [46] (Table 1).

## Conclusion

*Toddalia aculeata* has been reported to exhibit biological effectiveness against various diseases and ailments. Traditionally this plant and its associating species are used as folk medicine by various tribal groups in different parts of the world. This plant synthesizes series of bio-organic compounds which show chemotypic variations, possess multiple biological activities and therapeutically highly useful. These components show lipid-lowering effects, anti-platelet, anti-plasmodial, anti-inflammatory, antidiabetic, anti-tumor, antioxidant and larvicidal activity. No doubt phytochemicals from *Toddalia aculeata* and its derived herbal products could provide optimal health and

quality of life. This plant has enough therapeutic and pharmaceutical potential and can be used as a basic resource material for production of modern pharmaceuticals which may prove handy in maintaining public health.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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