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Comprehensive study of secondary metabolite profile and pharmacological effects of medicinal plant *Toddalia asiatica*

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ABSTRACT

Toddalia asiatica (L) Lam is a liana commonly known as an orange climber and is a monotypic genus belonging to the family "Rutaceae." It is one of the widely distributed medicinal plants in the countries, i.e., South Africa, north tropical regions of Africa, Asia, and also in Madagascar. Compounds that exhibit various pharmacological effects, isolated from the various parts of the plant *Toddalia asiatica*, such as root, root bark, stem, stem bark, flowers, fruits, and leaves have been of prime importance. Traditional medicinal practitioners of the Asian continent have been using this plant since ancient times to treat ailments such as pulmonary diseases and inflammation of joints known as rheumatism. The root and the root bark of the plant are said to be more potent and are used as a remedy for the conditions such as fever, malaria, cholera, diarrhea, neuralgia, sprains, and epilepsy. Fruits of the plant are used as a medication in the conditions, i.e., cough, digestive abnormalities, and viral influenza infection. The vital oil obtained from the root bark of the plant *T. asiatica* is known to produce strong larvicidal activity against the mosquito species *Aedes*. The present review emphasizes a variety of pharmacologically active secondary metabolites extracted from the medicinal plant *T. asiatica* such as coumarins, toddaculin, toddalactone, and their pharmacological effects such as in antiinflammatory, bactericidal, fungicidal, antimalarial, antidiabetic, antiviral, and antitumor activity.

INTRODUCTION

Plants are not only considered a food source but also supply an effective bioactive compound such as phytochemicals, which can be used as a drug to combat many disorders of mankind (Upendra and Khandelwal 2012). Bioactive compounds, known as phytoconstituents, are produced as secondary metabolites in plants that have beneficial effects on health when they are consumed as nutrients (Khandelwal *et al*., 2012). Phytochemicals play an important role in the development of the color, odor, and taste of the plants (Khandelwal *et al*., 2013). Traditionally used herbal (or) medicinal plants synthesize a range of phyto compounds of known therapeutic values. Presently significant members of researchers worldwide (Prithviraj *et al*., 2021; Upendra and Ahmed 2021) report on the pharmacological, healthcare, and antimicrobial activities of herbal plants. The bioactive phytocompounds originated from plant sources, i.e., alkaloids, flavonoids, phenolic compounds, and tannins have been used to treat various ailments caused by microorganisms (Upendra *et al*., 2011).

Toddalia asiatica L, widely known as the wild orange climber or orange climber, is a Rutaceae family evergreen woody liana. This plant is endemic to tropical Asia, from India to Sri Lanka to Malaysia; also, it has subsequently spread worldwide (Rajkumar *et al*., 2008). The plant is currently found in Africa's tropical and sub-tropical regions, such as South Africa, East Africa, Mauritius, and Madagascar, where it thrives in forested riverine habitats (Nabwami *et al*., 2007). *Toddalia asiatica* can reach a height of 15 m when supported by other trees, and there is abundance of hooked thorns located inside its branches (Varsha *et al*., 2013). It produces little 5–7 mm citrus-like fruits that start green but turn orange as they develop. When crushed, both the fruits and the leaves emit a lemony odor, with the fruits having a texture

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and flavor similar to that of an orange rind (Balasubramaniam *et al*., 2012). *Toddalia asiatica* is a plant with a renowned history of medical applications and used as a medicinal herb across various regions of the globe. The plant and its derivatives, for example, are employed in the creation of folkloric medicines for a variety of maladies in East Africa, including pain and inflammation (Kariuki *et al*., 2013), malaria, stomach ache, sore throat (Amuka *et al*., 2014), and skin, respiratory, and urinary tract infections (Orwa *et al*., 2015).

Toddalia asiatica is a tracheophytic plant, belongs to Angiospermae and the class Magnoliopsida under sub class Rosidae, order Sapindales and a member of Rutaceae family (Chen *et al*., 2021). *Toddalia asiatica* has long been used in India for the ailments such as cough, fever, epilepsy, and dyspepsia and as an analgesic, expectorant, diaphoretic, and antiinflammatory drug. Furthermore, pharmacological studies have demonstrated interesting biological properties of the plant, including antimalarial, anticancer, antiviral, antifungal, and antibacterial behaviors. *Toddalia asiatica* is widely used in clinical therapy of traumatic injury, tumor, rheumatic discomfort, and knife wound hemorrhage among the minority Miao (Zeng *et al*., 2021). It exhibits hemostasis, anti-tumor, anti-inflammatory, and analgesic pharmacological properties. For hundreds of years, traditional Chinese medicine (TCM) theory has been employed therapeutically in the country of China. However, because of the complex chemical contents and unexplained pharmacological mechanisms of TCM, the theory has continuously been interrogated by scholars across the globe (Zhang *et al*., 2018). Scientifically elucidating the beneficial molecules and the formulations of TCM has become an imperative challenge that must be translated as modern medicine advances.

Animal model experiments conducted in proving the hemostatic action of compounds isolated from the root bark of the plant *T. asiatica* was available in the literature, the considerable number of natural compounds such as furocoumarins isolated from *T. asiatica* plant root bark had been studied successfully by the considerable number of researchers (Luo *et al*., 2021; Ma *et al*., 2021). However, there is no scientific document available on comparative studies on pharmacologically active molecules that were isolated from the different active parts of the plant *T. asiatica*. The present review discussed the medicinal application of different compounds that were isolated from all the possible active parts of the plant *T. asiatica.*

SECONDARY METABOLITES PROFILE OF *TODDALIA ASIATICA*

Benzophenanthridine alkaloids, protoberberine alkaloids, quinoline alkaloids, benzopyrans, terpenoids, cyclohexylamides, coumarins, furanocoumarins, biscoumarins, and other miscellaneous chemicals have all been identified from the active part extracts of the plant *T. asiatica* (Wang *et al*., 2009). Nitidine, chelerythrine, dihydronitidine, and dihydrochelerythrine are among the pharmacologically important benzophenanthridine alkaloids isolated from the plant *T. asiatica* were researched for various applications (Fig. 1).

The complete details about the active parts, their metabolites and their medicinal and pharmacological applications were presented in Table 1. The production of secondary metabolites from plant micropropagation is an intriguing method that has been proved to be effective in producing a wide range of simple and complex chemical compounds with potent pharmacological effects. When these secondary metabolites are present in trace amounts or underground parts of the plant, it is most advantageous to eliminate brutal plant exploitation. *Toddalia asiatica* callus cultures produced more Nitidine than a whole plant (Rajkumar *et al*., 2010).

MEDICINAL APPLICATIONS OF THE PLANT *TODDALIA ASIATICA*

Anti-inflammatory activity

The experimental rat models showing condition such as arthritis induced with wind-chill, and dampness were evaluated against the isolated compounds of the plant *T. asiatica* for the anti-inflammatory activity screening. Screened compounds of plant *T. asiatica* evidenced with the balanced inflammatory activity of Th17 and Treg response in arthritis-induced rat models (Liu *et al*., 2018). Feeding of arthritis-induced mice model along with collagen-infused *T. asiatica* plant extracts such as ethanol and ethyl acetate solvents containing active compounds, has shown remarkable progress in releasing the paw and other joints pain, inflammation, and edema (Yang *et al*., 2013). The histopathological examination of rat fed with the isolated compounds of the plant *T. asiatica* in comparison with control groups showed increased protection for the condition such as knee joint pains, reduced erosion of bone and cartilage, and also the deformation in the tested animal model (Tian *et al*., 2018), examined animal models also exhibited much decreased levels of tumor necrosis factor-α (TNF-α), the lesser concentration of interleukin-1β (IL-1β), and interleukin-6 (IL-6) cytokines and also shown a significant increase in the concentration of cytokine interleukin-10 (IL-10). Aqueous and mild organic solvents such as alcohol and n-butanol extracts of *T. asiatica* plant roots had shown analgesic effects (Zeng *et al*., 2021). Mechanism of action of these molecules connected with rise in the levels of serum b-endorphin (b-EP) levels by up-regulating the b-EP receptor expression and cause significant downfall in the concentration of prostaglandin E2 (PGE2), nitric oxide (NO) levels, while suppressing PGE2 receptor expression.

A research group conducted a hot plate test and explained that the rhizome extracts of the plant *T. asiatica* are evidenced to possess a strong antiinflammatory activity and analgesic property. The study also revealed that the tested extracts were efficient in reducing the writhing numbers in the glacial acetic acid-induced mice animal model. In another study, 1:1 dilution of ethanol extracts of the plant *T. asiatica* exhibited improved analgesic behavior and antiinflammatory activity in the mice model denoting the conditions of foot swelling and granuloma condition (Wang *et al*., 2007). Kariuki *et al*. (2013) examined the analgesic property and anti-inflammatory mechanism of an organic extract of the plant *T. asiatica* in the mice model developed with formalin-induced pain condition and carrageenan-induced condition of foot swelling. Results explained that the tested organic extract (methane/methanol in equal ratio) shown much improved property of analgesic activity and the mechanism of antiinflammatory.

Hu *et al*. (2000) stated that an ethanol extract from the plant *T. asiatica* in dose-dependent manner found to reduce the acetic acid-induced writhing times and agar-induced foot edema

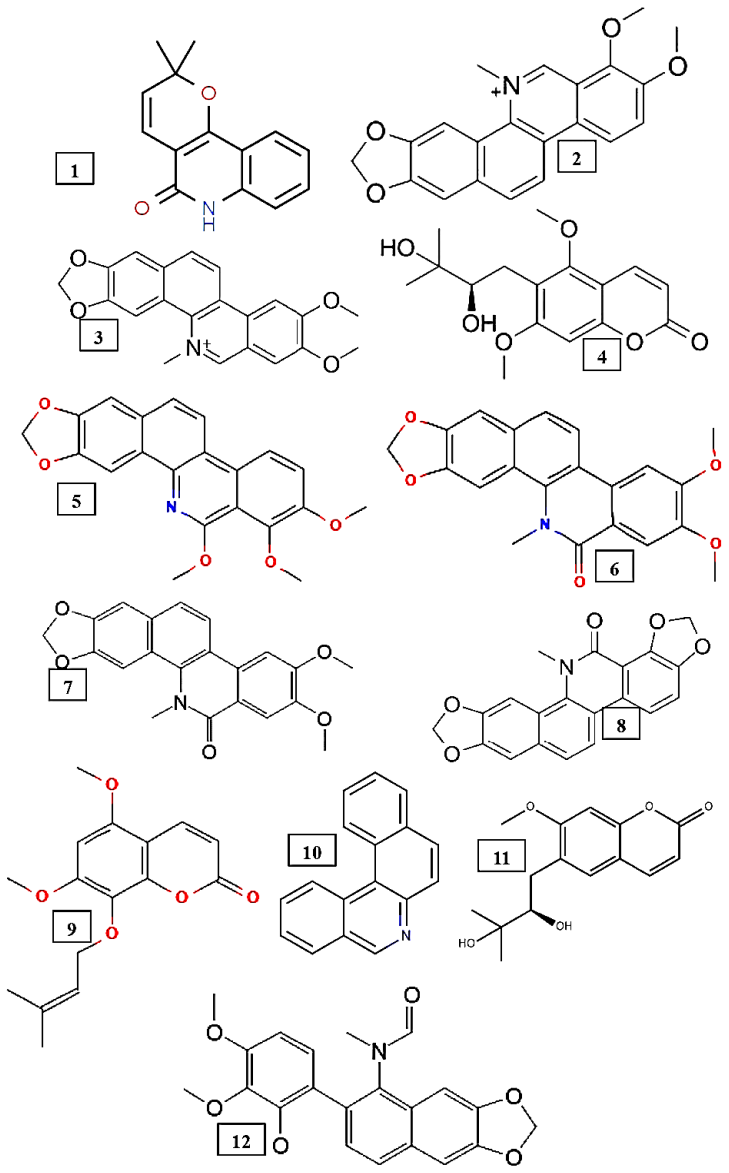

Figure 1. Structures representing medicinally significant phytocompounds of the plant *Toddalia asiatica.* 1. Flindersine, 2. Chelerythrine, 3. Nitidine, 4. Toddalolactone, 5. 8-methoxynorchelerythrine, 6. Isointegriamide, 7. Oxynitidine, 8. Oxysanguinarine, 9. Artanin, 10. Benzophenanthridine alkaloids, 11. Ulopterol, 12. Arnottianamide.

in the animal model (mice) evaluated. It is evidenced from the study that the bioactive molecules isolated from the root bark of the plant *T. asiatica* reduce the condition of ear swelling and foot swelling by inhibiting the action of xylene. The mice models assessed with the alkaloids isolated from the plant *T. asiatica* also found to inhibit migration of hemameba in the abdominal cavity primarily due to sodium carboxymethyl cellulose and writhing effects exhibited due to the exposure of acetic acid in the mice model screened. The tested mice model has shown no liver damage, which certainly indicate the non-toxic effects of the screened biomolecules of plant *T. asiatica* (Hu *et al*., 2000).

Bioactive compounds of the plant *T. asiatica* named coumarin and omphalocarpin were assessed for their anti-inflammatory behaviors in the *in vitro* cell culture of RAW264.7 cell lines. Results explained that screened biomolecules were reported to suppress the synthesis and adverse activity of iNOS and COX-2 due to the release of "TNF-α" and "IL-6" cytokines and also found to facilitate the transfer of NF-KB molecules into the cell nucleus by reducing the NO gas release (Tong *et al*., 2014). Another study revealed that an ethanol extracts from the plant *T. asiatica* reported to inhibit the migration of macrophages in the tested mice animal model (Qin *et al*., 2020). These findings

Table 1. Secondary metabolites profile of the plant *T. asiatica.*

Sl. No	Part of the plant	Type of secondary metabolite	Name of the compound	Applications	References
1	Leaf Callus	Benzophenanthridine Alkaloids	Nitidine, Chelerythrine	Anti-microbial Activity	(Praveena *et al*., 2015)
2	Roots	Coumarin	5,7-dimethoxy-8-(3'-hydroxy-3'methyl-1'-butene)-coumarin	Antiplasmodial activity	(Irudayaraj *et al*., 2022)
3	Leaves	Essential oil	Momoterpenes and Sesquiterpenes	Potential natural fumigant Food and Drug Preparation	(Nattudurai *et al*., 2014) (Thirugnanasampandan *et al*., 2012)
4	Leaves	Quinoline	Flindersine	Anti-bacterial, Anti-fungal	(Duraipandiyan *et al*., 2009)
5	Root	Coumarins	Toddolactone	Anti-inflammatory and immunosuppressive drug in the treatment of sepsis and septic shock	(Ni *et al*., 2020)
6	Roots	Coumarins, Terpenealkaloid	Toddayanin	Antimalarial Activity	(Hirunwong *et al*., 2016)
7	Root	Alkaloids	8-methoxynorchelerythrine, 11-demethylrhoifoline B, 8-methoxynitidine, 8-acetylnorchelerythrine, 8,9,10,12 Tetramethoxynorchelerythrine, Disintegrative, 1-demethyl dicentrinone, 11-hydroxy-10-methoxy-(2,3) methylenedioxytetrahydroprotoberberine etc.	Anti-proliferative and cytotoxic effects	(Hu *et al*., 2014)
8	Leaves	Alkaloids	3-(2,3-dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1H-quinolin-2-one, N-methyl-4-hydroxy-7-methoxy-3-(2,3-epoxy-3-methylbutyl)-1H-quinolin-2-one	Treatment of lung diseases, Curing pains in bowels	(Jain *et al*., 2006)
9	Fruits and leaves	Coumarin	Ulopterol	In the treatment of malaria and cough	(Raj *et al*., 2012)
10	Stem and bark	Coumarin	Toddaculin Toddanol	Anti-proliferative and cytotoxic effects	(Vázquez *et al*., 2012)
11	Twigs	Coumarins	7-geranyloxy-5-methoxycoumarin, 8-geranyloxy-5,7-dimethoxycoumarin, artanin, norbraylin, 5,7,8-trimethoxycoumarin and toddalosin	Anti-microbial activity	(Wang *et al*., 2009)

evidenced antiinflammatory effects of bioactive compounds of *T. asiatica* medicinal plant.

Anti-oxidant activity

Balasubramaniam *et al*. (2012) discovered that a 50% of ethanol extract content of *T. asiatica* stem part could scavenge diphenylpicryl hydrazide radicals, hydroxyl radicals, and nitric oxide radicals *in vitro* while also chelating divalent iron ions, indicating anti-oxidant behaviors. In the tested diabetic induced rats, catalase, glutathione peroxidase, and superoxide dismutase enzyme activity were reported low. All the three enzymes evaluated were shown normal activity after the intragastric region injection of 50% ethyl acetate crude extracts of leaves of *T. asiatica,* in turn indicating stronger anti-oxidant efficacies of the plant *T. asiatica* (Balasubramaniam *et al*., 2012).

Ding *et al*. (2007) investigated the antioxidant activity of *T. asiatica* stem extract using the Fenton method, 1, 1-Diphenyl-2-picrylhydrazine (DPPH) screening method, and the Fe^{2+}- cysteine reaction method. The study reported that n-butanol based extracts exhibited noticeable hydroxyl radical scavenging property and the ethyl acetate extract possess much stronger ability to scavenge DPPH. Further study also reported the potent antioxidant activity of 70% ethanol and n-butanol extracts of *T. asiatica* (Ding *et al*., 2007). Using the Fenton and DPPH methods, Tian *et al*. (2018) revealed that polysaccharide compounds of the root part of *T. asiatica* could scavenge hydroxyl and DPPH free radicals at a concentration range of 0.2–0.4 g/l and 5 (103–101) g/l, correspondingly. The capacity to scavenge hydroxyl radicals at concentrations ranging from 0.1 to 500 mg/l was proportional to IC_{50} values shown 5.69, 2.19, and 0.745 mg/l individually. When polysaccharides were present in concentrations of up to 500 mg/l, the free radical scavenging activity rates were reached to 94% and the photostability property was superior comparison to Vitamin C and tea polyphenols (Tian *et al*., 2018).

Anti-bacterial effects

A study showed that chelerythrine has anti-bacterial properties. According to HPLC data, the highest concentration of chelerythrine was identified in the ethyl acetate fraction, while the lowest concentration was found in the petroleum ether fraction. However, the petroleum ether fraction had higher antibacterial activity than the ethyl acetate fraction, which could be due to other fraction ingredients contributing to anti-bacterial functions, and the exact causes for this need to be researched further. The content of AKP can be used to determine the integrity of the bacterial cell wall. AKP is typically found between the cell wall and the cell membrane of bacteria. When the permeability of the bacterial cell wall rises, AKP leaks into the extracellular area in an indirect way. AKP results can reflect bacterial cell wall integrity (He *et al*., 2018).

Antifungal activity

According to a detailed investigation, only the ethyl acetate extract of *T. asiatica* demonstrated potential efficacy against tested bacteria and fungus. Flindersine, an active metabolite isolated from ethyl acetate extract with antibacterial activity comparable to or greater than crude extract. *Toddalia asiatica*-derived compound demonstrated good antibacterial activity *in vitro* and could treat infectious diseases caused by dangerous germs. A related molecule, flindersine has previously been effective against fungus. Rahmani *et al*. (2004) discovered that *Glycosmis calcicola* and *Glycosmis rubestris* extracts have antifungal activity, identifying the anti-fungal molecule as Flindersine and testing it against infections. The chemical treatment suppressed *Trichophyton rubrum* 296, *Trichophyton mentagrophytes*, *T. rubrum*, *Trichophyton simii*, *Epidermophyton floccosum*, *Magnaporthe grisea*, and *Candida albicans*.

Antinociceptive activity

Toddalia asiatica extracts exhibited a significant amount of antinociceptive efficacies in all the phases of the formalin test (Fig. 2).

Dosage of screened *T. asiatica* extract equivalent to 200 mg/kg body weight exhibited enhanced antinociceptive effects in the early phase, while the dosage of extract at 100 mg/kg body weight represented high impact antinociceptive effect in late phase of the employed formalin test. The impact of the antinociceptive effect of the tested extracts was equivalent standard reference medicine range, i.e., indomethacin (50 mg/kg) and ASA (100 mg/kg). But root bark extract of the plant at a dosage of 200 mg/kg has not shown any effects at the late stage of the formalin test. With these findings, it is evident that root bark extract of the plant *T.* asiatica shown both PNS and CNS activities. At a lower dose of 100 mg/kg of body weight, antinociceptive efficacies were shown at later phase, while at a higher dosage 200 mg/kg body weight antinociceptive efficacies were represented at early phases of the formalin test (Njoroge and Bussmann, 2006).

Analgesic effects

The analgesic activity of an ethanolic solvent extract of *T. asiatica* was assessed using a test named hot plate method and positive control used was 100 mg/kg dose of acetylsalicylate. *Toddalia asiatica* crude extract has a higher analgesic activity than positive control acetylsalicylate. The effects of *T. asiatica* extract on some blood indicators revealed significant changes in cholesterol, alanine transaminase, and gamma-glutamyl transpeptidase levels after 14 days. The levels of aspartate transaminase and alkaline phosphatase (ALP) in the treated and untreated groups, however, did not change significantly. Total cholesterol (TC) and low-density lipoprotein (LDL) levels are linked to a condition of coronary heart disease (Sblendorio and Palmieri 2008). A study examines the activity of herbal extracts on blood and also on selected biochemical markers in Sri Lankan male of adult age, who has lived in Switzerland for 15 years. The patient went to the emergency room with constipation and stomach pain that he had been experiencing on and off for several weeks. Physical examination revealed a soft abdomen with no discomfort or organomegaly. Stool retention was confirmed by an abdominal X-ray, which revealed neither perforation nor intestinal obstruction. Increased alkaline phosphatase or gamma-glutamyl transferase activity in the liver shows that specific hepatobiliary damage markers may be induced directly or indirectly. This occurs in the absence of liver tissue damage and the mainly due to the activity of hepatic drug metabolizing enzyme (DME). Significant serum/plasma activity changes and other indications usually indicate hepatobiliary damage rather than DME induction.

Nelson *et al*. (1995) previously reported a case of aplastic anemia linked to a 12-year-old child's herbal medicine usage. A component of herbal medication, phenylbutazone, has been linked to the development of comparable hematologic abnormalities. Anisocytosis was observed in the blood smears of Wistar rat's model fed with the crude ethanolic extracts of T. *asiatica*. Anisocytosis is a medical term that refers to the presence of red blood cells of varying sizes. This symptom is known to be caused by anemia and other blood illnesses. Anisocytosis is assessed using the red cell distribution width. Laboratory tests of blood film revealed that 9.1 g dl^{-1} hemoglobin level indicate the condition such as reticulocytes enlargement, liver enzymes, such as bilirubin and LDH levels were increased slightly. The Coombs test resulted negative, and haptoglobin levels were undetectable (Nelson *et al*., 1995).

At the Official Food Law Enforcement Authority, leftover pills were found to trace amounts of lead per pill, as well as arsenic, mercury, and chromium. Heavy metal poisoning is becoming more common due to "herbal treatments," particularly in the Asian countries. The lead level in the blood was connected to the symptoms at the time of presentation. Lead levels less than 50 g dl^{-1} might produce symptoms like asthenia, arthralgia, hypertension, headaches, and even infertility (Doumouchtsis *et al*., 2009). *Toddalia asiatica* exhibits analgesic effects that are superior to aspirin. Despite this promising finding, crude extracts harm blood and liver functioning. In order to avoid overdose, it is prudent to suggest that *T. asiatica* should be used with caution to treat pain. There are no guidelines for standardized doses in herbal therapy because the evidence is scarce on pharmacogenetics and pharmacodynamics of herbal medicines. In addition, the possible toxicity of consuming *T. asiatica* should be considered.

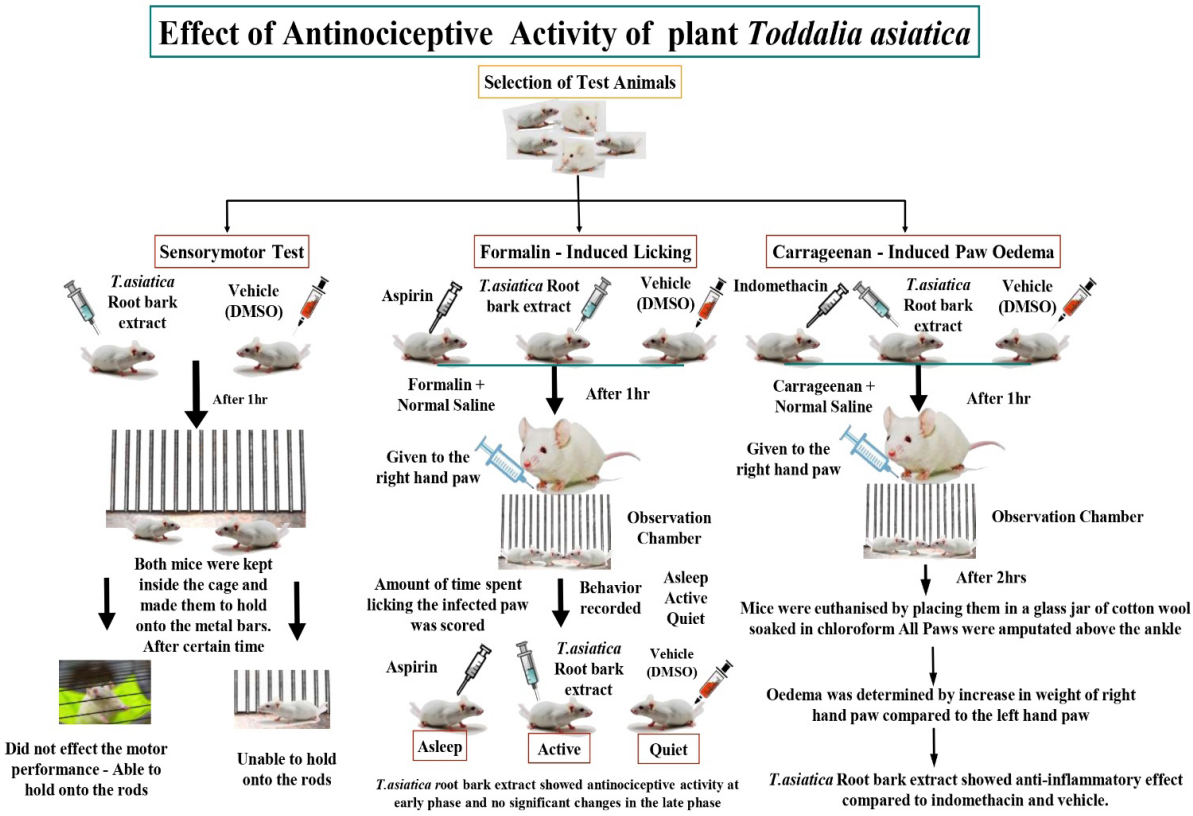

Figure 2. Mice model representing the Antinociceptive effect of extracts tested from the *T. asiatica.*

HEALTHCARE BENEFITS OF *TODDALIA ASIATICA*

Antidiabetic effects

For generations, *T. asiatica* has been used to treat diabetes mellitus. A study aimed to treat the *T. streptozotocin* (STZ)-induced diabetic rats fed with leaves of plant *T. asiatica* to screen the antidiabetic and antioxidant characteristics. STZ was used routinely to induce the condition diabetes mellitus in the tested experimental rat models. When administered intraperitoneally, STZ breaks the DNA strand of insulin hormone secreting pancreatic beta-cells, resulting in the reduction in the levels of insulin secretion. In STZ-induced diabetic mice, ethyl acetate extract of leaf part of the plant *T. asiatica*, injection resulted a noteworthy reduction in blood plasma glucose quantities, while simultaneously boosting the hormone insulin levels. *Toddalia asiatica* may improve glycemic control and stimulate insulin production from a remnant or regenerated pancreatic beta-cell population in diabetic mice, according to one idea (Fig. 3) (Punitha *et al*., 2006). Different metabolic and renal problems are detected in experimental diabetes, resulting in a negative nitrogen balance, increased proteolysis, and decreased protein synthesis. *Toddalia asiatica* ethanol extract therapy raised plasma protein levels in diabetic induced rat model. Further urea and creatine levels in the tested rat model reported much higher quantities, both are critical indicators of renal function and failure.

The extract showed course of kidney impairment in diabetic induced rats, as demonstrated by a substantial reduction in blood urea concentration and serum creatinine levels in TALEe-treated diabetic rats. A considerable drop in body weight distinguishes STZ-induced diabetes. Weight loss is assumed to be caused by accelerated muscle breakdown or structural protein degradation. TALEe administration improved the body weight of diabetic induced rats in comparison with diabetic induced control rat model and standard glibenclamide-treated groups, demonstrating that it has a preventive effect against muscle wasting, i.e., gluconeogenesis reversal (Salahuddin and Jalalpure, 2010)

Furthermore, it indicates that its capacity to maintain body weight loss is attributable to lower blood sugar levels. Insulin promotes intracellular glycogen formation by increasing glycogen synthase and inhibiting glycogen phosphorylase. Glycogen is the most prevalent muscle storage form of glucose and its content in many organs reflects insulin activity directly. Diabetic mice had considerably lower hepatic glycogen stores, indicating insulin insufficiency. TALEe therapy improved liver glycogen stores to normal levels in diabetic rats by increasing the secretion of insulin. Serum glutamatic-oxaloacetic transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT), and ALP are all reliable liver function indicators. The liver of diabetic rats caused by STZ were necrotized. As a result, an increase in SGOT, SGPT, and ALP activity in plasma could be attributable to enzyme leakage from the liver's cytosol into the bloodstream, confirming STZ's hepatotoxic action. TALEe therapy suppress the activity of liver functional enzymes in blood plasma compared to the diabetes control group (Kasetti *et al*., 2010).

Antimalarial effects

Toddalia asiatica root bark extracts compounds i.e isopimpinellin, geraniol, and D-limonene were shown in Figure 4, to have anti-malarial and insecticidal properties.

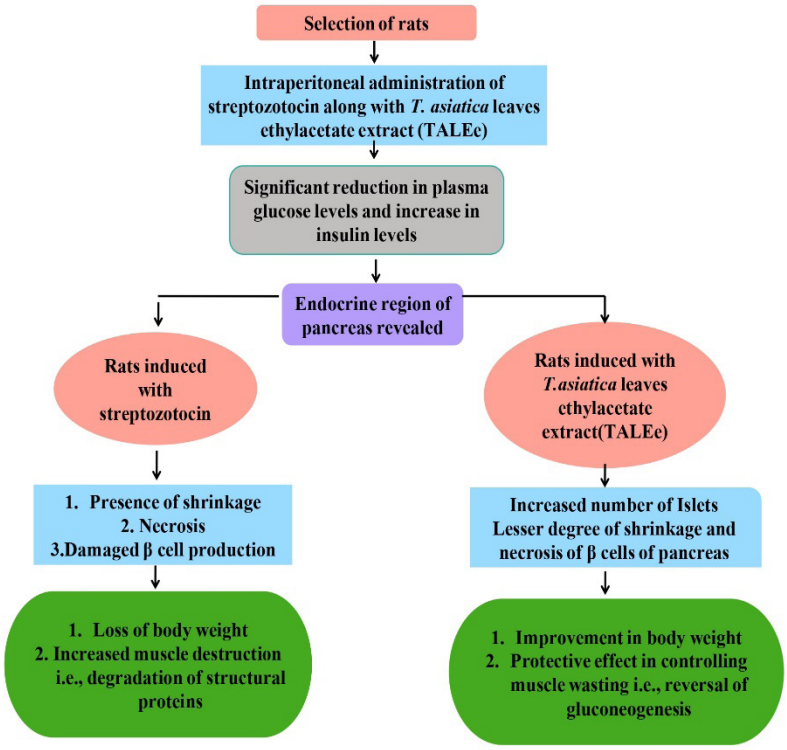

Figure 3. Flow diagram explaining the Anti-Diabetic Effects of *Toddalia asiatica.*

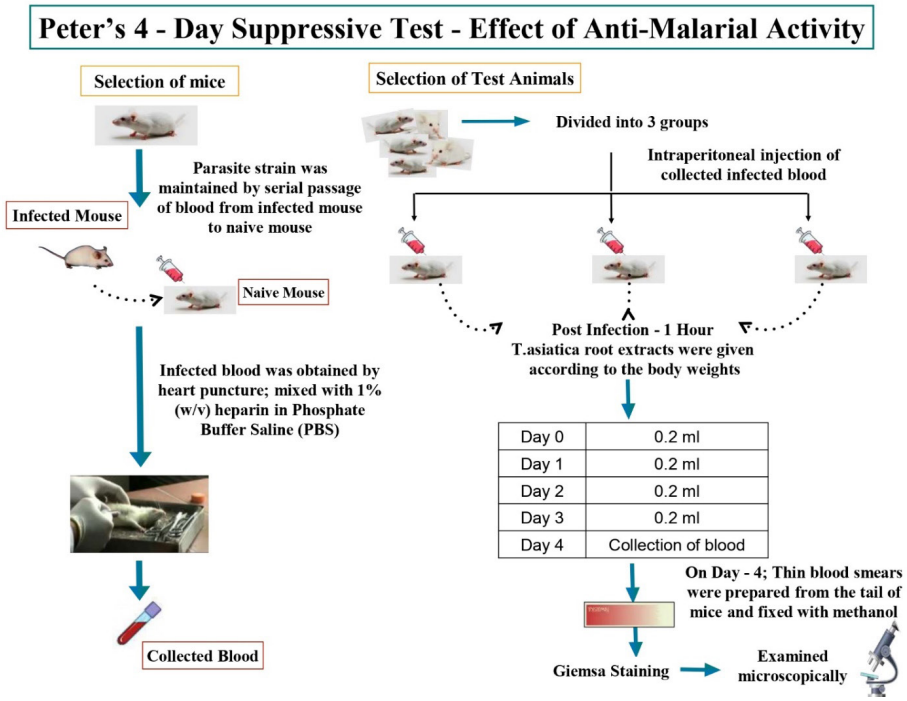

Figure 4. Flow diagram depicting the Anti-Malarial effects of *Toddalia asiatica* plant extract.

Treatment for cardiovascular diseases

Fei Long 1 (F01), an aqueous phase extract of the plant *T. asiatica*, protects against pituitrin-induced coronary artery-based contraction, isoproterenol-induced condition of myocardial muscle overexcitation and also the condition known as acute phase myocardial ischemia developed due to the obstructions of the coronary artery. F01 extract inhibits block of peripheral blood vessels connect to the heart and widens, decreases cardiac after load, myocardial exertion, and oxygen consumption rates connected to the cardiac function in the studied experimental animal domestic cats. F01 also found to reduce the oxygen consumption rates of

acutely ischemic myocardium in New Zealand rabbits without showing the ligation of pleural coronary (He *et al*., 2000).

Ren *et al*. (1993) conducted a comprehensive study on *T. asiatica* cardiovascular preventative properties. Long Jing 1 (L01, *T. asiatica* extract) reduced anaesthetized rats' blood pressure and relaxed smooth contractile muscle produced by KCl *in vitro*, with the mechanism probably connected to calcium influx inhibition. The iso-anise coumarin (Isopimpinellin) present in *T. asiatica* ethanol extract may protect the rat aortic ring against KCl-induced contraction (Guo *et al*., 2014; Ren *et al*., 1993). After the 4-week therapy, rats tested were fed a high-fat diet and given isoprenaline hydrochloride once a day for three days. According to the findings of Liu *et al*. (2018), *T. asiatica* extract may significantly alleviate Iso-induced ECG alterations in rats, reduce heart, liver and fat indices and lower TC, triglyceride, LDL.

Inhibition of Alzheimer's disease

Alzheimer's is a neurological disease that commonly leads to conditions such as dementia, chronic and progressive neurodegenerative disorders, marked significantly with symptoms such as the loss of memory, causing mental impairment, decreased learning ability, and emotional loss. Since there is no specific drug available to treat the condition, the number of AD patients increases as the world's population ages. This adds to the stress on families and medical treatment. As a result, traditional Chinese herb has grabbed the curiosity of medical experts as another promising technique that could provide a novel treatment for people living with Alzheimer's. According to Takomthong *et al*. (2020), seven of nine coumarins derived from the medicinal plant *T. asiatica* were found to be multifunctional that might prevent the pathogenesis of AD, particularly phellopterin, which demonstrated a strong protecting effect against neuronal cell damage produced by H_2O_2 and Ab1-42 toxicity.

Antitumor effects

The antitumor properties of medicinal components of plant *T. asiatica*, i.e., root bark, root core region, stem bark, stem core region, near-leaf stem part, and leaf parts were investigated applying the standard 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay method. The antitumor activity mean inhibitory rate of different medicinal components of *T. asiatica* were tested on MCF-7 cells at 100 g/ml following a pharmacodynamic action principle. From the study, it is evidenced that active parts such as root, stem bark, root & stem core, near-leaf stem, and whole leaf had shown increased inhibition rate in the tested *in vitro* cell model (MCF-7). *Toddalia asiatica* root bark active part and root core region can reduce the growth and proliferation of screened MCF-7 breast cancer cells lines in comparison with other parts of the plant evaluated. Bivariate analysis was used to establish a relationship between nineteen distinct peaks and the anti-tumor inhibition rate of different *T. asiatica* medicinal components, which was reflected in the form of peak correlation coefficients. Statistical investigations revealed that various compounds in *T. asiatica* exhibited anticancer activities, including toddalolactone, 4-methoxycinnamic acid, pimpinellin, isopimpinellin, and hesperidin appearing in that order (Luo *et al*., 2021).

DISCUSSION

Toddalia asiatica (L.) Lam., a member of the *Toddalia* genus in the Rutaceae family, has been used as a traditional medicine in China (Zeng *et al*., 2021). The entire plant can be used as medication, particularly the roots were utilized in traditional folk medicine (Arul and Veerappa, 2019). With extensive investigation from both local and foreign experts in recent decades, it has gradually been established that the chemical components of *T. asiatica* are primarily coumarins and alkaloids (Zhu *et al*., 2019). Its pharmacological activities include antiinflammatory and analgesic properties, hemostatic coagulation, antitumor properties, therapy of cardiovascular illnesses, etc. (Alagaraj *et al*., 2020). It has numerous clinical applications and substantially impacts rheumatism, discomfort, wound bleeding, and bruising discomforts (Qiu *et al*., 2022). Recent studies highlight the importance of *T. asiatica* phytochemical research, in view, the present review discussed chemical compositions, and pharmacological effects of different extracts of the plant *T. asiatica* to give a reference for relevant research and uses of medicinal phytochemicals of the plant *T. asiatica*. Although herbs are frequently viewed as "natural" and safe, many adverse effects have been observed.

Herbal pharmaceuticals play a significant role in healthcare systems worldwide and there is a renewed interest in herbal medicines for the treatment of a variety of disorders, including hepatopathy. Furthermore, there is a lack of scientific evidence to support the safety and efficacy of most herbal products. *Toddalia asiatica* is a vital medicinal plant with a broad pharmacological spectrum. The most common ingredients the plant *T. asiatica* have been identified as benzo[c]phenanthridine, secobenzo[c] phenantridine, aporphine, berberine, and indole alkaloids (Singh *et al*., 2022). Benzo[c] phenan-thridine alkaloids show a broad spectrum of biological activity compared to other alkaloids. Many cancers cell lines, including human promyelocytic leukemia HL-60 cells, have mostly antiproliferative and cytotoxic effects (Fialova *et al*., 2017). In reaction to stress, benzo[c]phenanthridine alkaloids are generated and employed as a phytoalexin against fungal and bacterial diseases (Roshan *et al*., 2022). This plant's root bark is also used to treat diarrhoea, gonorrhoea, cough, influenza, and toothache (Hu *et al*., 2014). The fresh leaves cure respiratory disorders and intestinal problems (Hirunwong *et al*., 2016). The fruits are thought to help treat malaria and cough (Ngarivhume *et al*., 2015). Rheumatism has been treated with an ointment made from the roots and unripe fruits (Ye *et al*., 2021). There have been numerous studies conducted on this plant's chemical contents and biological activity, including prenylated and geranylated coumarins, triterpenes, phenanthridine alkaloids, and volatile oils (Saxena and Sharma, 1999). Compounds from this plant have been studied for their biological effects, including anticancer activity against the U-937 cell line (Önder, 2020), antidiabetic, antioxidant (Irudayaraj *et al*., 2022), and antibacterial activity. The analgesic potential of *T. asiatica* (L.) was astounding. However, compared to the untreated negative controls, the crude extract of *T. asiatica* (L.) triggered nephrotoxicity, liver enzyme modulation, and increased TC in the test organisms.

The ethyl acetate extracts effectively reduced plasma, and hepatic lipid levels in hyperlipidemic rats fed a high-fat diet. Oxidative stress contributes significantly to the pathophysiology

of many clinical illnesses, including cardiovascular dysfunction, atherosclerosis, inflammation, carcinogenesis, medication toxicity, reperfusion injury, and neurodegenerative disease (Liguori *et al*, 2018). Numerous studies support the use of antioxidant supplements in lowering oxidative stress and decreasing or preventing the development of disease-related consequences. Furthermore, by scavenging free radicals, antioxidants may aid in preventing diseases such as cancer, cardiovascular disease, Alzheimer's disease, and muscle degeneration (Akbari *et al*., 2022). The reducing power assay was first performed to explore the Fe^{3+} to Fe^{2+} transformation in the presence of *T. asiatica* ethyl acetate extract. The reducing power of *T. asiatica* ethyl acetate extract increased with increasing concentration (Irudayaraj *et al*., 2022).

Monoclonal medications' pharmacological mechanisms are still inaccurate, and further research is needed in the future. *Toddalia asiatica* is also plentiful. However, the medicinal component of the plant is the root and stem, which has resulted in a decline in the quantity of wild *T. asiatica*. As a result, additional magnificent work is required to close gaps in the preservation of medicinal resources.

CONCLUSION

Toddalia asiatica plant as a whole and its various extracts were widely used as a traditional medicine in the mountain regions of Wuling province of southwest China. *Toddalia asiatica* plant was reported scientifically with significant clinical application, most notably anti-inflammatory properties, and used as a medicine in the condition of analgesia, hemostasis, and the condition of coagulation disorders. Few new active natural compounds, as well as novel pharmacology formulations of the plant *T. asiatica*, is yet to be explored along with this, there is a scarcity of data on its safety which could be explored and scientifically proved to improve the possibilities of developing novel biomolecules and formulation from this unexplored medicinal plant. Present work finds its importance in studying the plant *T. asiatica* as one of the most important medicinal resources.

ABBREVIATIONS

ALP:	Alkaline phosphatise
b-EP:	Endorphin
DME:	Drug metabolizing enzymes
DPPH:	1,1-Diphenyl 1-2-Picrylhydrazine
IL:	Interleukin
LDL:	Low-density lipoprotein
NO:	Nitric oxide
PGE_2:	Prostaglandin E_2
SGOT:	Serum glutamatic-oxaloacetic transaminase
SGPT:	Serum glutamic pyruvic transaminase
STZ:	Streptozotocin
TC:	Total cholestrol
TNF-α:	Tumor necrosis factor-α

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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