Clinical Phytoscience

REVIEW Open Access

Active status on phytochemistry and pharmacology of *Pergularia daemia* Forsk. (Trellis-vine): a review

Devanesan Arul Ananth[1*], Garlapati Deviram[2*], Vijayaraghavan Mahalakshmi[3] and V. Ratna Bharathi[4]

Abstract

Background: Medicinal plants play a significant role in the progress of persuasive therapeutic agents. Earlier to the innovation of synthetic drugs, human beings completely relied on the plants for the treatment of various ailments. Natural product extracts, particularly those derived from different plant species, provided the main source of Siddha, Ayurveda and Folk medicines. *P. daemia* is a perennial climber, traditionally reported for the treatment in a variety of diseases. In present review, we focused on the present status of phytochemical and pharmacological activities *P. daemia*.

Methodology: With the support of electronic databases such as Science Direct, Google Scholar, Mendeley, Scirus and PubMed central. Traditional knowledge information collected by Indian taxonomical books, survey from local rural and tribal peoples. Pharmacological data's obtained from scientific journals published from 2000 to 2020.

Results: *P. daemia* extract, contains several phytochemicals, especially rich in flavonoids. These secondary metabolites synthesized from *P. daemia* have been reported for the treatment of various chronic diseases. In recent years, *P. daemia* phytoconstituents set as a key role in natural drug development as it harbours many in vitro and in vivo pharmacological activities such as anti-inflammatory, anti-cancer, anti-fertility, anti-arthritic and antimicrobial etc.,

Conclusion: *P. daemia* was the less studied plant compared to other medicinal plants. In this context more emphasis has to be laid on studies that discuss on the secondary metabolite activities and molecular mechanisms that work against various chronic diseases.

Keywords: Medicinal plants, Antioxidant activity, Phytochemicals, Flavonoids, Pharmacology

Introduction

India is one of the world's leading producers of medicinal and aromatic plant materials. Around 20,000 medicinal plants have been recorded to be procured from 15 agro-climatic zones in India so far. However, only 7000–7500 plant varieties among them are in commercial use. Unani and Ayurveda are the indigenous medicines of herbal origin in use since ancient times. The proportion of plant usage in the different Indian systems of medicine is Ayurveda (2000), Siddha (1300), Unani (1000), Homeopathy (800), Modern (200) and Folk (4500) [1]. Almost 25,000 herbal based drug formulations are used in India particularly in traditional and folk medicine system [2]. These drug formulations are either directly derived from aerial part of the plant or derived from other specific parts like leaf, root, stem, bark, flower and seed. Some of the herbal drugs are derived from plant excretory products such as latex, resins and gum [3]. In general, plants secondary metabolites that are naturally synthesized from primary metabolites comprise an extensive range of bioactive constituents. Medicinal and aromatic plants are rich in bioactive secondary metabolites like phenolic acids, flavonoids,

* Correspondence: d.arulananth@gmail.com; deviramgarlapati@gmail.com; deviram@nccr.gov.in
[1]Department of Biotechnology, Karpagam Academy of Higher Education, Coimbatore, Tamil Nadu 641021, India
[2]National Centre for Coastal Research, Ministry of Earth Sciences, Govt. of India, Chennai, Tamil Nadu 600100, India
Full list of author information is available at the end of the article

alkaloids, glycosides, phytosterols, terpenoids, tannins. These secondary metabolites are known for their pharmacological properties [4, 5]. Bioactive phytocompounds are very limited source as these are not feasible to obtain from all plant types. Medicinal plants, used in traditional medicine (Siddha and Ayurveda) have less toxicity and withhold biologically active structure that supports in the development of alternative medicines [6]. Herbal extracts and medicinal plants demands are progressively increasing in European and other developed countries. India is the one of the leading exporters of herbs and value added extracts of medicinal herbs (Export of Herbs and Herbal Products, 2019). Herbal medicine is a part of alternative treatment method and it includes the use of different medicinal plants and their extracts. This type of treatment is the most effective and safe mode for treating the patients (Source: Herbal medicine University of Maryland Medical Center). Herbal medicines are directly synthesized from various parts of plants such as leaf, stembark, roots, barks, flowers, seeds, etc. In Ayurvedic system, herbal compositions were mostly prepared through polyherbal formulations. Also, they proved a significant effect against various chronic ailments. The herbal preparations are named as powers (Churna), decoction (Kwatha), resins (Guggul), oil (Taila) and infusion (Phanta) etc., [7]. In recent decades, the development of scientific research in pharmacology and phytochemistry of medicinal plants lead to the next level of herbal medicines. Medicinal plants have the ability to produce a wide range of phytochemical compounds that are used to execute important biological functions in humans and animals. Phytochemical constituents such as polyphenolic compounds, tannins, terpenoids are reported to be effective against various disorders [8]. Many of these phytochemicals have beneficial effects on long term when consumed by humans and can be used effectively to treat various chronic diseases. A single medicinal herb contains one or more phytochemical components that are synergistically active as a pharmacological agent. Therefore, plants are recognised as major resource for phytocompounds with profound biological activities [9].

Pergularia daemia Forsk belongs to the Asclepiadaceae family. It is a perennial twining herb, which grows wild along the road sides of India. The aerial parts of *P. daemia* are used as an anti-helminthic, antiseptic and anti-venom agent. It is also used in treating gastric ulcers, uterine and menstrual complaints. On the other hand, the leaves of this plant are also used as an effective medicine for anemia, leprosy, arthritis, hemorrhoids, amenorrhea, dysmenorrheal, infantile diarrhea, body pain, asthma, bronchitis and whooping cough [10]. Latex of this plant is used to treat boils and sores. While, the stem is used to treat cold, malarial fever and pyretic [11]. Similarly, root extract is used as an abortifacient, emetic and also used to treat against asthma, constipation and gonorrhoea. Fresh leaf extract when mixed with lime or ginger exhibited strong activity against rheumatic swelling [12]. The pharmacological action of aerial parts of *P. daemia* has been reported to prevent various ailments in recent reports. Based on this background study of *P. daemia*, we confer the existing status of phytochemistry and pharmacological activities of *P. daemia* in the present review.

Methodology

Scientific information and resources related to *P. daemia* was obtained from scientific databases such as Science Direct, Google Scholar, Mendeley, Science Open, Springer Link, African Journals Online, Wikipedia, Scirus and PubMed central. Other information's obtained from local Indian taxonomical books, Ph.D. thesis and local survey.

Scientific classification

Kingdom	Plantae – Plants
Subkingdom	Tracheobionta – Vascular plants
Superdivision	Spermatophyta – Seed plants
Division	Magnoliophyta – Flowering plants
Class	Magnoliopsida – Dicotyledons
Subclass	Asteridae
Order	Gentianales
Family	Asclepiadaceae – Milkweed family
Genus	*Pergularia*
Species	*daemia* (Forsk.) Chiov.

Common and local names

Tamil	Uttamani, Seendhalkodi and Veliparuthi
English	Trellis-vine, Hariknot plant and Pergularia
Kannada	Juttuve and Talavaranaballi
Hindi	Utaran and Akasan
Malayalam	Veliparatti
Sanskrit	Kurutakah and Visanika
Telugu	Jittupaku and Dustapuchettu

Botanical description

P. daemia is widely distributed in the tropical and subtropical regions particularly India, Africa, Arabia, Malaya, Pakistan, Afghanistan and some parts of south east Asia (Fig. 1). In India, it is commonly found in hedges through cut most of cenfry to an altitude about 1000 m in Himalaya and 900 m in Southern India. *P.*

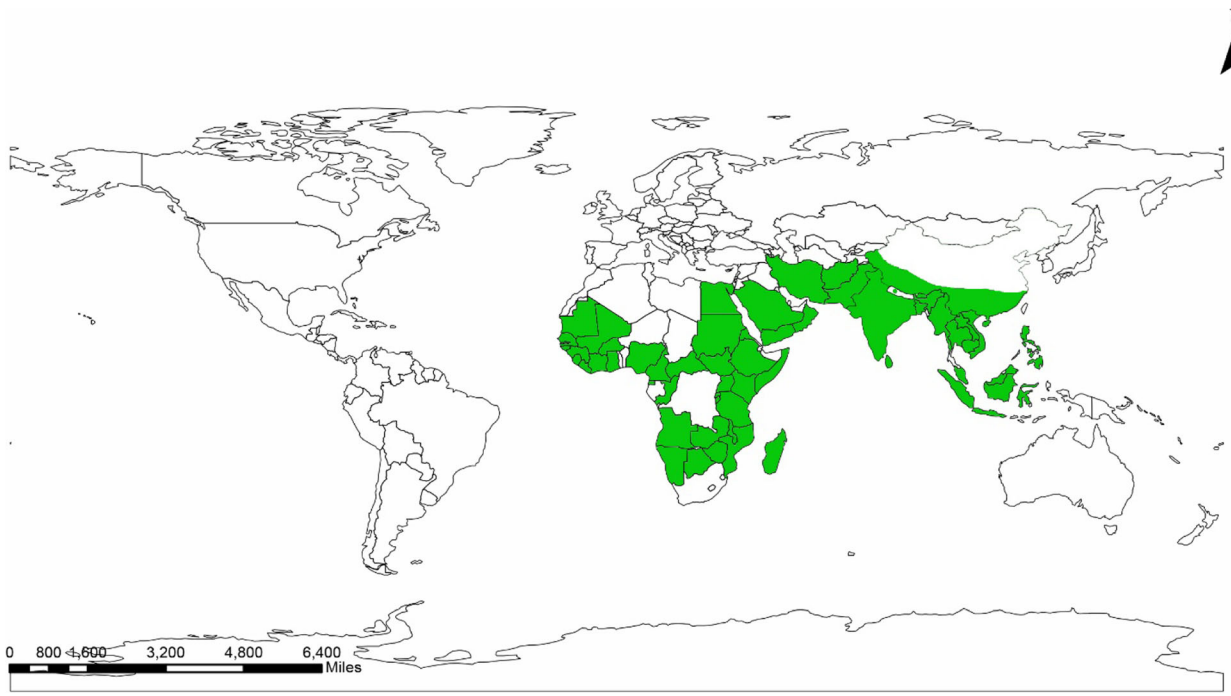

Fig. 1 Distribution of *P. daemia* in Asia and Africa

daemia is a perennial twining herb with milky sap. The stems grow upto 4 m or more, covered in soft hairs. Leaves are thin 5–10 by 3.8–9 cm in length and heart or broadly ovate or glabrous shaped and margins margin ciliate hairy and cordate at the base petioles 2–6.3 cm in length, pubescent. The flowers are in axillary pseudo umbells on long peduncles. Pendulous opens in the evening. Corella is creamy white or greenish, sometimes tinged with purple and long lobes fringed (Fig. 2).

Phytochemicals in P. daemia

Secondary metabolites extracted from the medicinal and aromatic plant extract are mostly responsible for the therapeutic and pharmacological potential of the particular plants [13]. In some cases, the crude extracts of medicinal plants are used as an agent for the treatment of various diseases. On the other hand, isolation and identification of the bioactive compounds, extraction, purification and the mechanism of action of the purified compound is very important. Hence, recently researchers are focused to validate traditionally reported medicinal property and as well as to identify bioactive compounds from medicinal plants. Both qualitative and quantitative method of analysis is very important for the validation of bioactive phytochemicals. The qualitative phytochemical analysis *P. daemia* extract are reported to exhibit various group of compounds including alkaloids, flavonoids, terpenoids, tannins, steroids, glucoside, carbohydrates, proteins, amino acids, saponins, glycosides, fixed oils, gums and mucilage (Tables 1 and 2). The extraction of bioactive compounds from plant materials is the first step in the utilization of phytochemicals in the preparation of

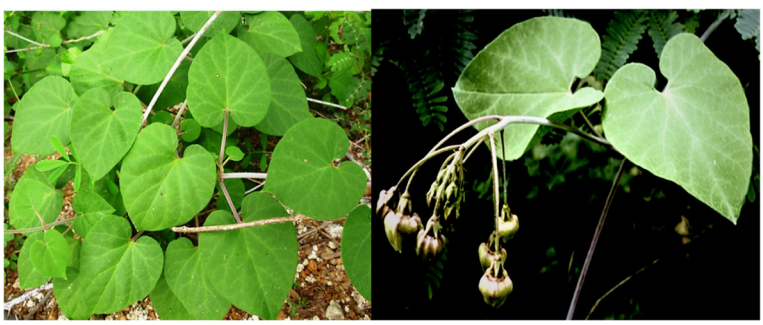

Fig. 2 *Pergularia daemia* Forsk

Table 1 Preliminary qualitative phytochemical screening of different solvent extracts on *P. daemia* leaf and root

Phytochemicals	Leaf							Root				
	AE	EE	ME	PEE	CE	ACE	EAE	AE	EE	PEE	CE	EAE
Carbohydrates	+	+	+	–	–	–	–	+	+	–	–	–
Proteins & Amino acids	–	–	–	+	–	NA	–	–	–	–	–	–
Glycosides	+	+	NA	+	+	+	–	+	+	–	–	–
Alkaloids	–	–	+	–	+	+	NA	+	–	–	+	–
Steroids	–	–	+	–	+	–	–	+	+	–	+	+
Favonoids	+	+	+	+	+	–	–	+	+	–	+	–
Saponins	+	+	NA	+	+	NA	–	+	+	–	–	–
Tannins	+	–	+	–	+	+	+	+	+	–	+	–
Fixed oils & Fats	–	+	–	+	+	NA	–	–	–	+	–	–
Gums & Mucilage's	–	–	+	–	–	NA	NA	+	+	–	–	–
Terpenoids	+	+	+	–	–	+	–	+	+	–	–	+
Coumarins	NA	+	NA	+	+	NA	–	NA	NA	NA	NA	NA
Phytosterols	NA	+	+	+	+	NA	+	NA	+	NA	NA	NA
phenols	+	+	+	–	+	NA	–	+	+	–	+	–

+ presence, – absence, *NA* not analyzed (*AE* Aqueous extract; *EE* Ethanol extract; *ME* Methanol extract; *PEE* Petroleum ether extract; *CE* Chloroform extract; *ACE* Acetone extract; *EAE* Ethyl acetate extract)

dietary supplements, pharmaceutical and products. Phytocompounds can be extracted from fresh or dried plant samples. Freeze drying extraction method, generally retains higher levels of phenolic content in plant samples when compared to dried powdered extraction [24]. Solvent extractions are the most commonly used procedure to prepare extracts from plant materials due to their ease in use, efficiency, and wide applicability. Various number of methods have been developed recently, like supercritical extraction (SCE), solid-liquid extraction (SLE), Microwave extraction (ME), Conventional Extraction (CE) and Ultrasound Extraction (USE) etc. [25]. Chromatographic techniques are widely used for identification of bioactive compounds from plant extracts. The most frequently used analytical technique for the separation of polyphenolic compounds is high performance thin layer chromatography (HPTLC), gas chromatography (GC) high performance liquid chromatography (HPLC),

Table 2 Preliminary qualitative phytochemical screening of different solvent extracts on *P. daemia* whole plant

Phytochemicals	Solvent extracts whole plant						
	AE*	EE*	PEE	CE	BE	EAE	NBE
Carbohydrates	+	+	–	+	–	+	+
Proteins & Amino acids	–	–	–	–	–	–	–
Glycosides	+	–	+	–	+	–	–
Alkaloids	+	–	–	–	–	–	–
Steroids	NA	NA	NA	NA	NA	NA	NA
Favonoids	+	+	+	–	–	–	–
Saponin	+	–	–	–	–	–	–
Tannins	+	–	–	–	–	–	–
Fixed oils & Fats	–	–	+	NA	NA	NA	NA
Gums & Mucilages	NA	NA	NA	NA	NA	NA	NA
Terpenoids	+	+	–	–	–	–	+
Coumarins	NA	NA	NA	NA	NA	NA	NA
Phytosterols	+	+	–	–	–	–	+
polyphenols	+	–	–	NA	NA	NA	NA

+ presence, – absence, *NA* not analyzed (*AE* Aqueous extract; *EE* Ethanol extract; *PEE* Petroleum ether extract; *CE* Chloroform extract; *BE* Benzene extract; *EAE* Ethyl acetate extract; *NBE* N-Butane extract)
Ref: [12–23]

with diode array detection (DAD) and mass spectrometry (MS) detection. Currently, this is one of the most widely and commonly used combination of techniques for separation, identification and quantification of polyphenolic compounds [26]. MS is a well known and successful technique for mass determination and structural elucidation of biomolecules [27]. Mass spectrometry (MS) is mainly used for both quantitative and qualitative analysis of biomolecules. This method is based on the gas phase ions that are separated to their mass-to-charge ratios (*m/z*). MS is a well known and successful technique for mass determination and structural elucidation of biomolecules. The HPLC coupled with MS is the analytical technique of choice for most tasks both in plant metabolite analysis and discovery of new drugs [28–31].

In *P. daemia* plant extract (whole plant, leaves, stem and root) consist of different chemical compounds. *P. daemia* leaves and root extract contains β-sitosterol, lupeol, oleanolic acid, calactin, calotropin, corotoxigenin, daucosterol, sucrose, α-amyrin, β-amyrin and its acetate [12, 14, 32–35] (Fig. 3a). Also phytocompounds such as betaine, hentriacontane and pentacosanoic acid polypeptide and glucoside of *Daemia extensa* (synonymous *P. daemia*), were identified from the entire plant extract [14, 35]. *P. daemia* seed extract has phytocompounds such as calactin, calotropin, calotropigenin, corotoxigenin, dihydrocalotropigenin, protouscharin, uscharidin, uscharin [14]. Similarly, Mittal et al. [36] identified a variety of cardenolide including uscharidin and calotoxin in seed extract. In addition, they recorded other similar compounds such as coroglaucigenin, corotoxigenin, uscharidin and uzarigenin in stem extract (Fig. 3b). Flavonoids were found to be the major and important phytochemicals obtained from extract of *P. daemia* aerial part during qualitative analysis. Vegetative parts of *P. daemia* reported for hyperoside (flavonol) in the dried stem and flavonoids and saponins in fresh shoots and flowers [37, 38]. Similarly, Sinha and Dogra [37] also reported for the presence of hyperoside (flavonol) in dried stem extracts. Recently our group identified five pharmacology important flavonoids from the methanolic leaf extract of *P. daemia* [13] (Fig. 3c). Many research reports revealed the potential role of polyphenolic compounds such as flavonoids and phenolic acids for its pharmacological property. Well known examples of phytocompounds include phenols, flavonoids, phenolic glycosides, saponins and cyanogenic glycosides [39, 40]. Particularly the antioxidant activity of the plants is due to the presence of flavonoids such as flavones, isoflavones, flavonoids, anthocyanin, coumarin lignans, catechins and iso catechins [15]. Green leafy vegetables and fresh fruit juices are rich source of polyphenolic compounds like flavonoids and phenolic acids. These herbal based antioxidant compounds or drugs prevents diseases like atherosclerosis, stroke, diabetes, alzheimer's disease, cancer, and other anti-inflammatory disorders [41]. Importantly, anti-inflammatory activities of phytocompounds have been described in earlier reports and some of them are in preclinical trials at present [16]. Nowadays many people prefer these natural medicines additional for their advantage of being cost-effective and safe.

Flavonoids are the major phytocompound present in the *P. daemia* extracts and the concentration ranged from 72.549 ± 0.449 to 400.196 ± 0.339 mg/ml. On

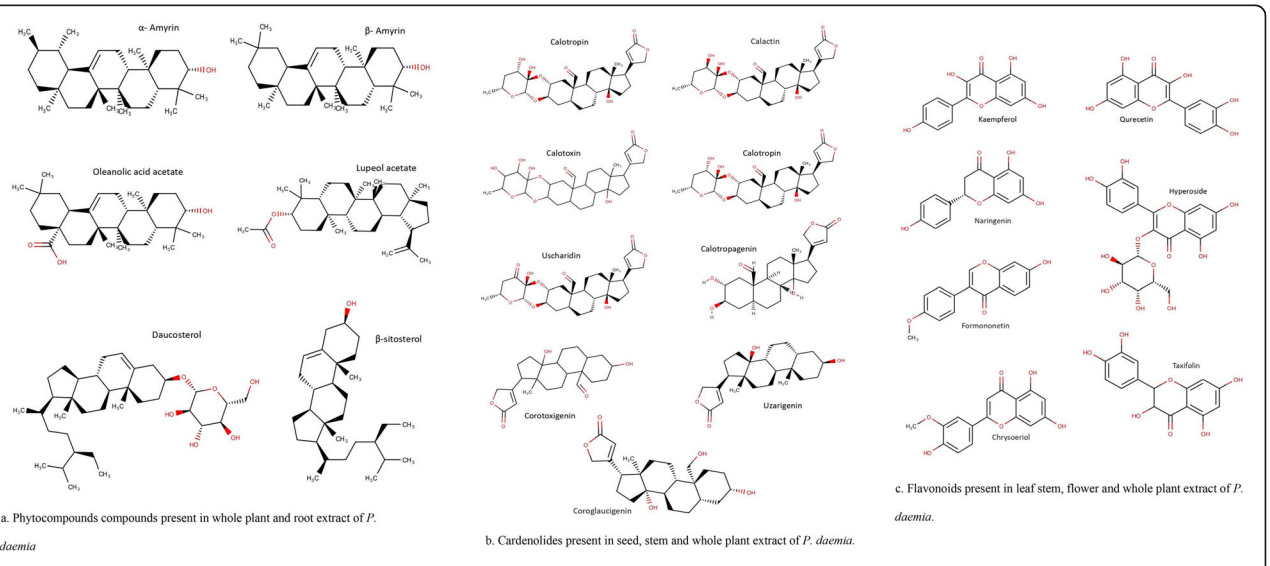

Fig. 3 Phytochemicals reported in *P. daemia*. **a** Phytocompounds compounds present in whole plant and root extract of *P. daemia*. **b** Cardenolides present in seed, stem and whole plant extract of *P. daemia*. **c** Flavonoids present in leaf stem, flower and whole plant extract of *P. daemia*

comparison with other parts in plant, leaf and stem extract exhibited the vast flavonoids content. At the concentration of 10 mg/ml n-hexane 338.725 mg/g, ethyl acetate 388.627 mg/g and 400.196 mg/g respectively with an equivalence to quercetin content [17]. Flavonoids are the most familiar and extensively distributed group of plant phenolics. It includes monomeric flavanols, flavanones, anthocyanidins, flavones and flavanols (Fig. 4). These flavonoids have the potential inhibit the pro inflammatory mediators and other inflammatory agents (Fig. 5). Ananth et al. [13] identified and reported that *P. daemia* extracts consist of five flavonoids (formononetin, qurecetin, chrysoeriol, taxifolin and naringenin) which has anti-arthritic activity against complete freund's adjuvant (CFA) induced rat model [13]. Flavonoids have wide range of heath promoting properties such as antioxidant, antimicrobial, anti-inflammatory and immunomodulatory activity. The important sub classes of flavonoids are flavanols, flavanones, isoflavones, flavones, and anthocyanidins [18, 42, 43]. On the other hand, there are plenty of medicinal plants with enormous active components which are yet to be revealed. *P. daemia* was among those and found to be a reliable source of flavonoids and other bioactive compounds. Quercetin, kaempferol, myricetin and morin are popular among the category of therapeutics due to people's reliability on emerging natural therapeutics.

Pharmacology

Antioxidant activity

Recent reports suggests that oxidative stress and its related factors cause an important problem to human

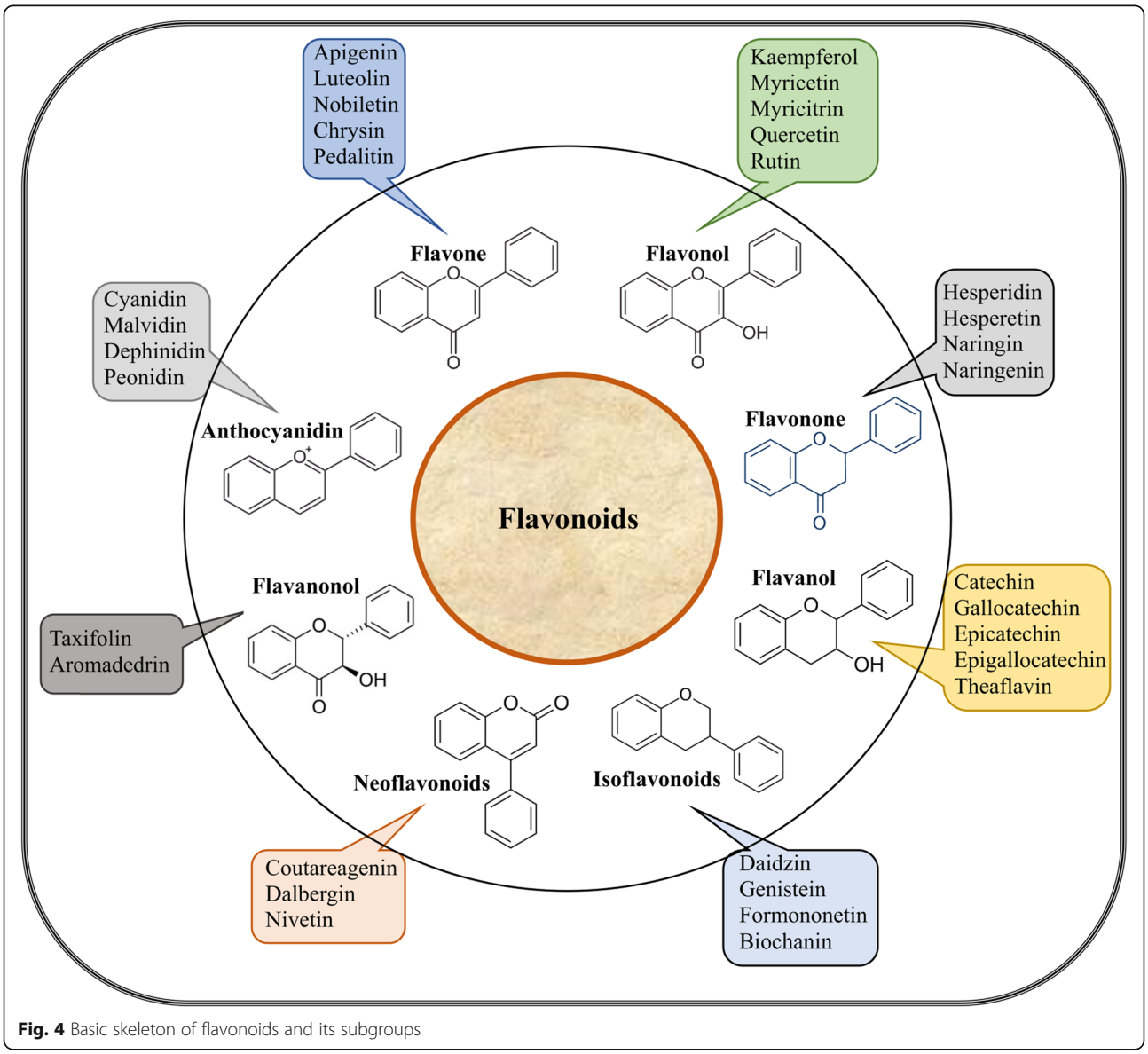

Fig. 4 Basic skeleton of flavonoids and its subgroups

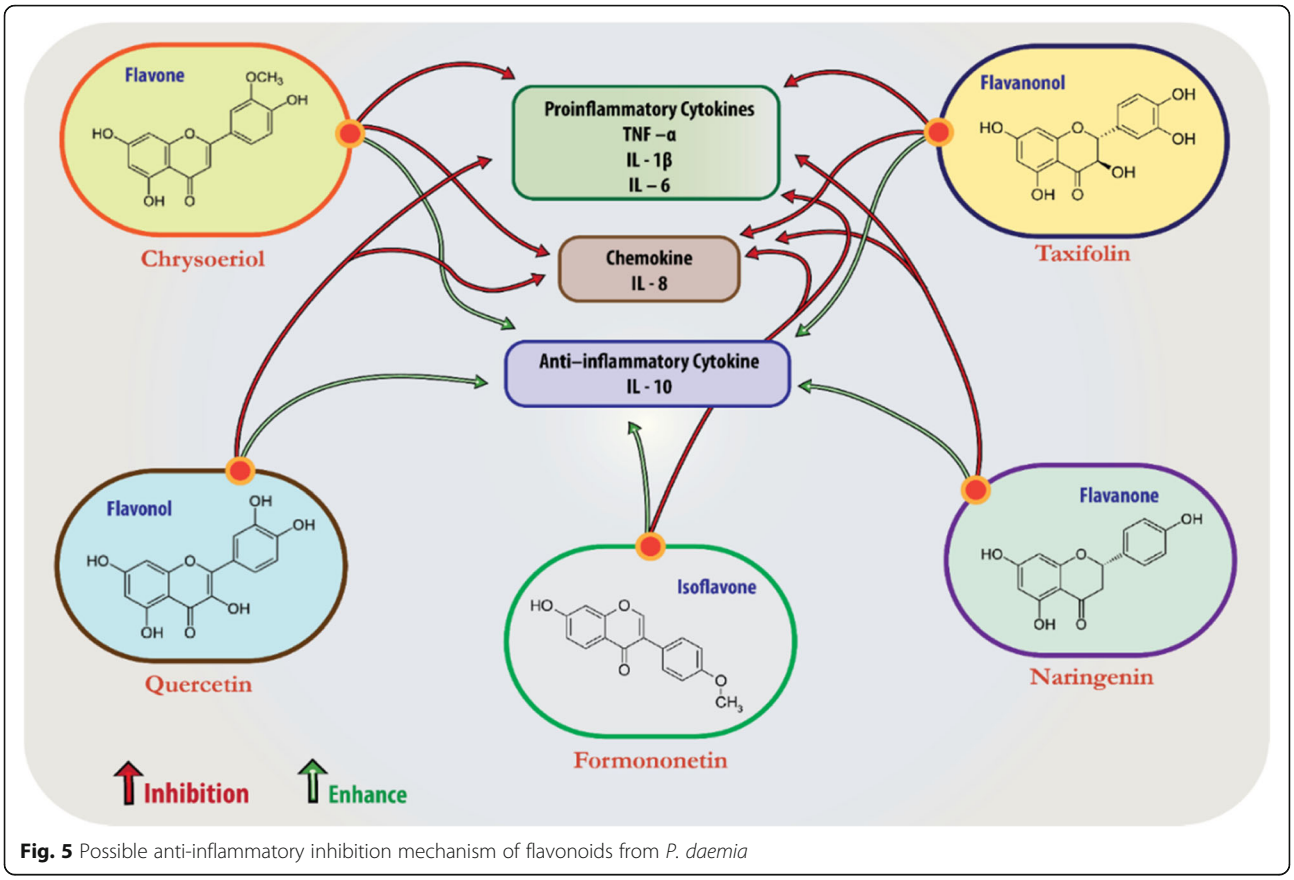

Fig. 5 Possible anti-inflammatory inhibition mechanism of flavonoids from *P. daemia*

health. Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) were over expressed during the stress condition. These reactive species promote degenerative diseases [44–46] ROS such as superoxide anion (O^-), nitric oxide (NO^-) radicals, hydrogen peroxide (H^2O^2), peroxyl radicals (ROO^-) and reactive hydroxyl radicals (OH^-) are continuously generated as a by product during electron transport system and normal cell metabolism [47]. Overproduction of ROS/RNS lead to failure in the defence mechanism by release of oxidant substances. Antioxidants are the compounds that are capable of neutralizing free radicals by interfering with oxidation process, chelating catalytic metals and acts as oxygen scavengers [48]. These compounds are reported to prevent free radical mediated oxidative damage and thereby reducing the risk of causing various degenerative diseases and disorders [44]. In nature our blood plasma consists of antioxidants like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), albumin, transferrin, ceruloplasmin, lipid and water-soluble antioxidants like tocopherol, quinines, ascorbic acid and uric acid and vitamin-E. Antioxidants act by transforming ROS/RNS to form a stable molecule and prevents damage to the biological system. Nowadays synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG) and tert-butylhydroquinone (TBHQ) are widely used in food and therapeutic industry, which cause severe toxic effects to the victims. On the other hand, number of purified compounds from medicinal plants exhibited high antioxidant activity with least or no side effects. *In vitro* antioxidant potential of *P. daemia* extracts were determined by inhibition of two different synthetic free radicals such as 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), 1,1-diphenyl-2-picrylhydrazyl (DPPH). Methanolic extract of *P. daemia* areal part was highly potent in neutralizing ABTS, DPPH and nitric oxide free radicals and was comparable with that of gallic acid. The ABTS IC_{50} concentration of *P. daemia* extract was 19.72 mg/ml and was nearly higher than of gallic acid (14.55 mg/ml). Similarly, DPPH scavenging activity IC_{50} value was at 33.36 and 34.12 mg/ml for extract and gallic acid respectively. *P. daemia* extract exhibited excellent nitric oxide scavenging activity (IC_{50}–32.37 mg/ml) compared with gallic acid standard (IC_{50-} 34.19 mg/ml) [49]. While, 70% ethanolic extract of *P. daemia* leaf revealed significant DPPH free radical scavenging activity on par with commercial standards of ascorbic acid and BHT. Leaf extract had less scavenging effect and the EC_{50} values were 0.149, 0.699 and 2.608, mg/ml respectively, and interestingly

these lower EC_{50} also showed better antioxidant activity. Also ethanolic extract effectively inhibited the formation of peroxides and hydrogen peroxides. Importantly *P. daemia* extract have the ability to reduce iron from ferric (Fe^{3+}) to ferrous (Fe^{2+}) and the EC_{50} value was recorded for extract, ascorbic acid and BHT were 17.78, 0.5239 and 0.2065 mg/ml respectively. Very recently, Dosumu et al. [17] reported inhibitory percentage from 34.65% to 84.90% in *P. daemia* leaf extract over DPPH radical scavenging activity. The IC_{50} values was found to be 6.27 μg/ml (ethanol), 17.78 μg/ml (ethyl acetate) and 22.49 μg/ml (n-hexane) and the standard ascorbic acid (5.67 μg/ml) extracts, respectively. Similarly, the IC_{50} values of *P. daemia* stem extract was 10.19 and 26.99 μg/ml for ethyl acetate stem extract, followed by 58.20 μg/ml for n-hexane extract. Phytochemicals such as phenols, alkaloids, flavonoids, phytosterols, saponins, tannins and triterpenes found in the leaf extract might be responsible for the observed antioxidant activities [17, 50, 51].

Anti-inflammatory and analgesic activity

Inflammation is a usual biological process act against the foreign substances including microbes to protect the tissue from injury. Usually inflammation is a rapid and self limited process, but during abnormal pathological condition it generates excessive ROS/RNS leading to chronic inflammation condition. This chronic inflammation linked with serious inflammatory diseases including arthritis, cancer, neurological, metabolic and cardiovascular diseases [52, 53]. Researchers already developed steroidal and non steroidal anti-inflammatory drugs to reduce this chronic inflammatory state. These drugs effectively reduce the disease severity, but on the other hand, they also cause has many side effects. However, medicinal plants like *P. daemia* have curative effects with least side effects [13]. The ethanolic extracts of *P. daemia* has significant ($p < 0.001$) reduction in paw edema against carrageenan induced paw edema and cotton pellet granuloma methods in rats. These extracts at the concentration of 200 mg/kg showed upto 44.18% and 19.87% reduction in the granuloma formation. Other extracts such as n-butanol, benzene and chloroform showed 16.83%, 13.96% and 15.08% respectively at the same concentration [54]. Similarly Venkataraman et al. [55] investigated carrageenan induced paw edema in rats using chloroform and petroleum ether extract of whole plant. Results demonstrated that the chloroform extract treated were found to be highly significant ($p < 0.01$) improvement in comparison to the control. Very recently Hina and Rose [56] determined in vitro anti-inflammatory activity of *P. daemia* ethanolic extracts in leaf and root by human red blood cell (HRBC) membrane stabilization method. Their findings also illustrated anti-inflammatory activity by membrane stabilization method in the ethanolic leaf (54.55%) and root (45.55%) extract at a concentration of 300 μg/ml and produced most significant stabilization compared to that of standard drug diclofenac sodium (72.73%) at 100 μg/ml concentration. *P. daemia* plant extracts also showed an effective analgesic activity. Currently, these extracts are used an alternative to pain killer drugs. One of the studies conducted to evaluate the analgesic activity of *P. daemia* aqueous and alcoholic root extracts on eddy's hot plate method showed significant ($p < 0.001$) effects at the concentration of 1000 mg/kg [57]. Similar analgesic results were recorded at the concentration of 100 mg/kg ($p < 0.01$) with chloroform and petroleum extract of *P. daemia* [55]. The presence of rich flavonoids and glycosides in *P. daemia* might be a major reason for exhibiting anti-inflammatory and analgesic activity.

Anti-arthritic activity

Flavonoids are known to be effective phytocompounds in treating the anti-rheumatic condition in animal models [13]. *P. daemia* methanlolic extracts contains flavonoids such as formononetin, qurecetin, chrysoeriol, taxifolin and naringenin. Study on the methonolic extract treated rat groups effectively reduce the paw inflammation and also serum biochemical markers such as hemoglobin (11.84 ± 0.42 g/dl) and red blood cells (RBC) (8.38 ± 0.67 million/mm^3) levels were significantly increased. Whereas, other arthritis indicator biomarkers including white blood cells (WBC) count (8.91 ± 0.38 thousands/mm3), rheumatoid factor (RF) (17.94 ± 0.45 IU/ml), erythrocyte sedimentation rate (ESR) (7.91 ± 0.12 mm/h) and C-reactive protein (CRP) (22.56 ± 0.26 mg/l) levels were significantly decreased when compared arthritic induced rat group [56]. Ethanolic extract of *P. daemia* leaf and root (300 μg/ml) have the potential to have significant anti arthritic activity as per the study reports. They confirmed by membrane stabilization assay, and the highest % activity was observed in leaf (54.55%) than root (45.55%). In similar way, the root extracts of *P. daemia* showed 58.89% of inhibition than the leaf extracts which showed 53.33%. In both the cases, assays were compared with standard drug diclofenac sodium at the concentration of 100 μg/ml. Petroleum ether extract of *P. daemia* leaf at 300 mg/kg showed improvement in arthritis condition in arthritic rats by reducing the hind paw edema and inflammation [58]. It is also suggested that phytocompounds such as flavonoids and sterols might be responsible in this anti-rheumatic activity of *P. daemia* [13].

Anti-cancer activity

Worldwide cancer is the dangerous and second most important reason for mortality. Herbal based therapies by secondary metabolites from plant extracts known to

reduce the disease severity without side effects for cancer treatment. Khorombi et al. [59] reported that methanol dichloromethane (1:1 v/v) extract of the whole plant extract inhibited the growth of the cancerous cells. Alpha-amyrin is a compound responsible for the cancerous cell growth inhibition, but rate of growth inhibition was having low potency, between 15 and 50 μg/ml. Another study revealed that *P. daemia* extract has an important source to cure oral cancer disease. Particularly ethyl acetate extract (300 mg/kg b.w.) exhibited excellent in vivo antioxidant activity in comparison to the methanolic extract. The activity was compared against on 7, 12-dimethylbenz[a]anthracene (DMBA) induced hamster buccal pouch [19]. Leaf extract showed an effective cytotoxic activity against ovarian cancer cell lines (PA-1 and OAW-42) and IC_{50} value of cell lines recorded 30 and 120 mg/ml, respectively. Authors suggested that polyphenolic compounds principally triterpenoids play a vital role against growth of cancer cells. In addition, they mentioned small structural modification of triterpenoids as the ability to establish an oval drug against cancer [60].

Anti-proliferative activity

Mirunalini et al. [20] study revealed that *P. daemia* methanolic extract exhibited an anti-proliferative effect against oral keratin-forming tumor cell line HeLa (KB) cells. The activity was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (MTT). ROS generation and antioxidant status, membrane (potential) potential and cell cycle arrest were determined for the confirmation of anti-proliferative activity. At the highest concentration (160 μg/ml) of *P. daemia* methanolic extract, they confirmed maximum cytotoxic effect against oral KB cells. The IC_{50} value of methanolic extract calculated 90% on MTT assay against cancer cell lines. Pre-treated KB cells with *P. daemia* extract significantly changed the apoptotic morphology of the cells, this apoptotic morphological change occurred by the increased levels of ROS and reduction in the matrix metallopeptidases (MMPs). The death of the cancer cell initiates ROS generation and lipid peroxidation (LPO) in intra cellular region and damages DNA by initiating apoptosis in KB cell [20]. Polyphenolics (phenolic acid and flavonoids) of *P. daemia* might play a crucial role in reversing this process by promoting apoptosis and arresting proliferation in cancerous cells.

Anti- diabetic activity

Diabetes mellitus is becoming the third "killer" disease next to cancer and cardiovascular diseases in mankind. It is a long term metabolic disorder that affects our body in terms of both physical and psychological functions. The first study on *P. daemia* extract has reported the potential of anti-hyperglycaemic activity. Kumar and Ramesh [61] revealed that *P. daemia* extracts at a concentration of 300 mg/kg, decreased the blood glucose level significantly against streptozotocin (STZ) induced in diabetic rats. After 21 days of the treatment the diabetic animals with chloroform leaf extract 160.68 mg/dl, ethanol extract 132.61 ml/dl, aqueous extract 152.80 mg/dl, ethanol extract of callus showed 123.26 mg/dl and glibenclamide (600 μg /kg) 194.6 mg/dl of blood glucose. Wahi et al. [62] reported that administration of alcoholic and aqueous extracts from the whole plant of *D. extensa* produced a vital reduction and evaluated using alloxan (120 mg/kg; i.p.). Importantly, alcoholic extract twisted a significant ($P < 0.01$) decrease in blood glucose level (BGL) in a single dose after 1 h. Anti-diabetic activity was equivalent with standard drug chlopropamide. Recently, Sarkodie et al. [63] revealed that that *P. daemia* extract has anti-hyperglycaemic activity against STZ-induced rat models. The blood glucose level significantly reduced on dose dependent manner. Flavonoids and its glycosides, phytosterols, saponins, phenols, alkaloids, triterpenes, tannins and alkaloids are bioactive ingredient in hypoglycaemic activity in plants [63].

Hepatoprotective activity

Liver is an incredible organ and is fundamental chemical laboratory of our body which plays a crucial role in the metabolism and detoxification of various chemicals and toxins enter into the body. The disposition of exogenous toxins and therapeutic agents are acting as a major part in the biochemical regulation of biomolecules such as fats, carbohydrates, amino acids and protein. The ROS plays a vital role in liver damage. Liver injury or damage is a well known disease which can be caused by excessive production of ROS that lead to the hepatic cells and tissue damage. Several compounds, such as carbon tetrachloride ($CC1_4$), α-amanitin, acetaminophen, pyrrolizidine alkaloids, bromobenzene, ethanol and polycyclic aromatics and the toxin produced metabolites which cause liver injury [64]. Antioxidants play an important role to prevent the liver cells from CCl_4 induced damage because they effectively neutralize the free radicals [56]. Recent research indicated that natural antioxidants capable of preventing oxidative stress related liver problems [65–67]. Sureshkumar and Mishra [68] reported that the ethanolic and aqueous extract of *P. daemia* possesses a significant ($P < 0.05$) hepatoprotective effect against CCl_4 induced hepatic rat model. They also found that ethanolic extracts treated rats decreased the serum aspartate aminotransferase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALKP), total bilirubin (TBL) and total cholesterol (CHL) levels and increased level in total protein (TPTN) and total albumin (ALB) at dose of 200 mg/kg. Highly reactive trichloro free radical was generated by CCl_4,

which attacks polyunsaturated fatty acids. Due to the alteration in liver microsomal membrane hapatotoxicity found in experimental animals [21]. *P. daemia* roots aqueous and ethanolic extracts also have significant protective effects against paracetamol and CCl_4 induced hepatotoxicity in rats [69]. Paracetamol also caused increase of serum liver enzymes such as bilirubin and cholesterol similar like CCl_4. Both aqueous and ethanolic extracts at the dose of 100 and 200 mg/kg caused significant inhibition in the biochemical markers of SGOT and SGPT. Compared with control rats there was decrease in LPO, malonaldehyde (MDA), and increase in serum protein antioxidant enzymes glutathione (GSH) in *P. daemia* extract treatment. Hence, the presence of bioactive compounds such as flavonoids, terpenoids, glycosides and saponins in these extracts might be responsible for hepatoprotective activity. Sureshkumar and Mishra [70] suggested that *P. daemia* leaf ethanolic extract containing flavonoids and triterpenoids are the most responsible for the hepatoprotective activity. The flavonoids from ethanol extract and ethanol fraction in *P. daemia* confirmed by HPTLC using quercetin-3-glucoside as a standard. These results indicated that flavonoids are the principal bioactive compound for hepatoprotective activity [13, 71].

Diuretic activity

Bhavina et al. [72] studied the diuretic activity of the *P. daemia* extracts at a dose dependant manner by orally in rats. Lipschitzs test used for this study and furosemide used as a standard drug. Based on the results diuretic activity of *P. daemia* alcoholic extract showed a highest activity of 0.93 at 400 ml/kg concentration. Urine output of all tested extracts except the petroleum ether showed significant results ($P < 0.001$) in comparison to control. Importantly plant extracts also affect the urinary electrolyte excretion. Further alcoholic, ethyl acetate and *n*-butanol extracts increased the urinary excretion of sodium and potassium ions (Na^+ and K^+). Diuretic action of alcoholic extract was found to be 2.04 units, which was almost similar to standard furosemide (2.19 units). Extracts such as alcoholic, ethyl acetate, n-butanol and standard drug furosemide increased the urinary Na^+ and K^+ ions level and slightly acidified the urine. These findings strongly suggest that the *P. daemia* extracts act as a diuretic agent. Secondary metabolites such as alkaloids, flavonoid and steroids might be the possible candidates responsible for the diuretic activity of *P. daemia*.

Anti-tuberculosis activity

According to world health organization (WHO) report (2017), approximately 10.4 million cases of tuberculosis (TB) were reported in 2016 and one major possible cause of deaths. In Ayurvedic medicinal system, plants extract shows a potential positive effect against treating TB. Recently, Mishra et al. [73] reported that ameliorative effect of *P. daemia* hydro alcoholic leaf extracts against *anti–tuberculosis drug*s (ATDs) induced liver injury. Administration of ATDs significantly decreased the level of glucose and albumin. Besides, high levels of aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, bilirubin, triglycerides, cholesterol were also recorded. After ATDs exposure, they found reduction in glutathione, peroxidase, glutathione reductase catalase, superoxide dismutase, glutathione and glucose-6-phosphate dehydrogenase, and also increase in the level of lipid peroxidation. Hence, *P. daemia* extract significantly maintained these serum biochemical parameters and antioxidant components when compared to control [73]

Anti-fertility activity

Ethanolic extract and their steroidal fraction of *P. daemia* showed a potential anti-fertility activity. Steroidal fraction of 200 mg/kg showed significant activity against female mice at the stage of pre-implantation. Whereas, ethanolic extracts exhibited late abortifacient activity with 600 mg/kg. The extract showed 100% activity without any mortality within 48 h of drug treatment. These results reveal that *P. daemia* steroidal and ethanolic extract have potential to display anti-fertility activity on female mice [22].

Anthelmintic activity

Kumar et al. [74] reported the ethanolic extract of *P. daemia* are better than the aqueous extract in exhibiting anthelmintic potential. They evaluated the leaf extracts against round worm (*Ascarislum bricoides*), earthworm (*Eudrillus eugeniae*), and tapeworm *(Taenia solium*) taking 100 mg/ml concentration, with albendazole as a reference drug. The paralysis and time of death was recorded in ethanolic extract for round worm (20.86 ± 0.54 and 61.84 ± 0.54 min) earthworm (16.86 ± 0.74 and (27.12 ± 0.52 min) and tape warm (54.12 ± 0.49 and 110.17 ± 0.59 min) respectively. Similarly, aqueous extract showed paralysis and time of death was (32.33 ± 0.67 and 76.19 ± 0.56 min) for roundworm, (20.91 ± 0.31 and 30.89 ± 0.45 min) for earthworm and (64.44 ± 0.54 and 172.14 ± 0.81 min) for tapeworm respectively. *P. daemia* extracts induced paralysis followed by the death in the warms with a concentration of 100 mg/ml exhibiting ($P < 0.01$) anthelmintic activity compared to that of standard drug.

Anti-ulcer activity

During pathogenesis of ulcer formation dehydration, interference of mucosal cellular membranes and

cytotoxic effects was directly imposed by ethanol and finally its lead to proliferation of the inflammatory reaction [75]. In the meantime, indirectly alcohol led to destructive effects via leukocytes which generate inflammatory responses, oxidative stress and apoptosis. In this process NF-kappa B (NF-κB) plays a vital role in mediating to developing disease condition [76]. Secondary metabolites such as flavonoids, tannins and triterpenes has been extensively reported for anti-ulcerogenic activity [77]. *P. daemia* contains these phytochemicals which might be the responsible for anti-ulcer activity. *P. daemia* revealed curative effect against ethanol induced ulcer in rats. Extracts (400 mg/kg) exhibited an inhibition percentage of 63.01 and the standard drug treated group showed 78.73%. Dhananjayan et al. [23] suggested that ethanolic extracts of *P. daemia* leaf possessed excellent anti-ulcer activity in dose dependent manner.

Conclusion

P. daemia is the one of the less studied and scientifically reported medicinal plant. Based on the traditional reports and literature reviews, we propose that *P. daemia* exhibited excellent pharmacological activity. Qualitative analysis of phytochemicals including flavonoids, terpenoids, phytosterols, proteins, amino acids and saponins have been isolated and identified from different parts of *P. daemia*. Medicinal plants are known to be a natural source of phytochemicals and bioactive compounds. Natural flavonoids and cardenolides are the important bioactive compounds reported in *P. daemia* extracts. Bioactive compounds involved in pharmacological activities due to its antioxidant, anti-inflammatory and other related properties in human. Administration of solvent extracts of *P. daemia* prevents inflammation and various diseases including arthritis and cancer. Generally, it is notable that the existing phytochemistry and pharmacological status of the *P. daemia* are insufficient resources for herbal formulations. Whereas, the clinical studies and its mechanisms of action are not clear. Further studies are required to identify other bioactive compounds of *P. daemia* along with their specific mechanism in disease management. These studies will fetch in bringing the practise of *P. daemia* based herbal formulations.

Acknowledgements

D.A.A. sincerely thank DST-FIST (No: SR/FST/LS-1/2018/187) for necessary facilities.

Authors' contributions

D.A.A, G.D and V.M: Conceptualization, Methodology, Data collection, Writing- Original draft preparation. D.A.A, G.D and V.R.B: Writing- Reviewing and Editing. The author(s) read and approved the final manuscript.

Funding

No funding.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Declarations

Ethics approval

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Biotechnology, Karpagam Academy of Higher Education, Coimbatore, Tamil Nadu 641021, India. [2]National Centre for Coastal Research, Ministry of Earth Sciences, Govt. of India, Chennai, Tamil Nadu 600100, India. [3]Department of Biotechnology, Anna University, Chennai, Tamil Nadu 600025, India. [4]Department of Zoology, Dr.V.S. Krishna Government Degree College (Autonomous), Visakhapatnam 530013, India.

Received: 7 December 2020 Accepted: 10 June 2021
Published online: 30 June 2021

References

1. Pandey M, Rastogi S, Rawat A. Indian traditional ayurvedic system of medicine and nutritional supplementation. Evid-Based Complement Altern Med. 2013;2013:376327.
2. Subhose V, Srinivas P, Narayana A. Basic principles of pharmaceutical science in Ayurvĕda. Bull Indian Inst Hist Med Hyderabad. 2005;35(2):83–92.
3. Pandey MM, Rastogi S, Rawat A. Indian herbal drug for general healthcare: an overview. J Evid Based Integr Med. 2008;6(1):1–12.
4. Santosh MK, Sharanabasappa GK, Shaila D, Seetharam YN, Sanjeevarao I. Phytochemical studies on *Bauhinia racemosa* lam., *Bauhinia purpurea* Linn. And *Hardwickia binate* Roxb. E-J Chem. 2007;4:21–31.
5. Jain C, Khatana S, Vijayvergia R. Bioactivity of secondary metabolites of various plants : a review. IJPSR. 2019;10(2):494–504.
6. Patwardhan B, Warude D, Pushpangadan P, Bhatt N. Ayurveda and traditional Chinese medicine: a comparative overview. Evid-Based Complement Altern Med. 2005;2(4):465–73. https://doi.org/10.1093/ecam/neh140.
7. Frawley D, Ranade S. Ayurveda, nature's medicine. Wisconsin: Lotus Press; 2000. p. 1–7.
8. Shad AA, Ahmad S, Ullah R, AbdEl-Salam NM, Fouad H, Ur Rehman N, et al. Phytochemical and biological activities of four wild medicinal plants. Sci World J. 2014;2014:857363.
9. Meena AK, Bansal P, Kumar S. Plants-herbal wealth as a potential source of ayurvedic drugs. Asian J Tradit Med. 2009;4:152–70.
10. Yoganarasimhan SN. Medicinal plants of India (Vol. 1). Bangalore: Interline Publishing Pvt. Ltd.; 2000.
11. Dokosi OB. Herbs of Ghana. Accra: Ghana Universities Press; 1998.
12. Karthishwaran K, Mirunalini S. Therapeutic potential of *Pergularia daemia* (Forsk.): the Ayurvedic wonder. Int J Pharmacol. 2010;6(6):836–43. https://doi.org/10.3923/ijp.2010.836.843.
13. Ananth DA, Rameshkumar A, Jeyadevi R, Aseervatham GSB, Sripriya J, Bose PC, et al. Amelioratory effect of flavonoids rich *Pergularia daemia* extract against CFA induced arthritic rats. Biomed Pharmacother. 2016;80:244–52. https://doi.org/10.1016/j.biopha.2016.03.019.
14. Bhaskar V, Balakrishnan N. Veliparuthi (*Pergularia daemia* (Forsk.) Chiov.) as a phytomedicine: a review. Int J Pharm Tech Res. 2009;1(4):1305–13.
15. Aqil F, Ahmad I, Mehmood Z. Antioxidant and free radical scavenging properties of twelve traditionally used Indian medicinal plants. Turk J Biol. 2006;30(3):177–83.
16. Subramanya S, Venkataraman B, Meeran M, Goyal S, Patil C, Ojha S. Therapeutic potential of plants and plant derived phytochemicals against acetaminophen induced liver injury. Int J Mol Sci. 2018;19(12):E3776.
17. Dosumu OO, Ajetumobi OO, Omole OA, Onocha PA. Phytochemical composition and antioxidant and antimicrobial activities of *Pergularia daemia*. J Med Plant Economic Develop. 2019;3(1):1–8.

18. Saito K, Yonekura-Sakakibara K, Nakabayashi R, Higashi Y, Yamazaki M, Tohge T, et al. The flavonoid biosynthetic pathway in Arabidopsis: structural and genetic diversity. Plant Physiol Biochem. 2013;72:21–34. https://doi.org/10.1016/j.plaphy.2013.02.001.
19. Vaithiyanathan V, Mirunalini S. Assessment of anticancer activity: A comparison of dose response effect of ethyl acetate and methanolic extracts of *Pergularia daemia* (Forsk). Oral Sci Int. 2016;13(1):24–31.
20. Mirunalini S, Karthishwaran K, Vaithiyanathan V. Antiproliferative potential of *Pergularia daemia* (Forsk.) on human oral epidermoid carcinoma (KB) cells by inducing apoptosis and modifying oxidant antioxidant status. Asian J Pharm Clin Res. 2014;7(5):89–95.
21. Shenoy KA, Somayaji S, Bairy K. Hepatoprotective effects of *Ginkgo biloba* against carbon tetrachloride induced hepatic injury in rats. Indian J Pharmacol. 2001;33(4):260–6.
22. Sadik MG, Gafur M, Bhuiyan MSA, Rahman MM, Biswas HU. Antifertility activity of the alkaloidal fraction of *Pergularia daemia*. J Med Sci. 2001;1:217–9.
23. Dhananjayan K, Venugopal V, Majumder P. Evaluation of *in-vivo* antiulcer activity of extracts from leaves of *Pergularia daemia* (Forsk.) against ethanol induced ulcer in albino rats. Ind J Res Pharma Biotech. 2014;2(3):1141.
24. Abascal K, Ganora L, Yarnell E. The effect of freeze-drying and its implications for botanical medicine: a review. Phytother Res. 2005;19(8):655–60. https://doi.org/10.1002/ptr.1651.
25. Naczk M, Shahidi F. Extraction and analysis of phenolics in food. J Chromatogr A. 2004;1054(1–2):95–111. https://doi.org/10.1016/S0021-9673(04)01409-8.
26. Downey MO, Rochfort S. Simultaneous separation by reversed-phase high-performance liquid chromatography and mass spectral identification of anthocyanins and flavonols in shiraz grape skin. J Chromatogr A. 2008;1201(1):43–7. https://doi.org/10.1016/j.chroma.2008.06.002.
27. Dai J, Mumper RJ. Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. Molecules. 2010;15(10):7313–52. https://doi.org/10.3390/molecules15107313.
28. Hamburger M, Wolfender JL, Hostettmann K. Search for chlorinated sesquiterpene lactones in the neurotoxic thistle *Centaurea solstitialis* by liquid chromatography-mass spectrometry, and model studies on their possible artifactual formation. Nat Toxins. 1993;1(6):315–27. https://doi.org/10.1002/nt.2620010602.
29. Fang N, Yu S, Prior RL. LC/MS/MS characterization of phenolic constituents in dried plums. J Agric Food Chem. 2002;50(12):3579–85. https://doi.org/10.1021/jf0201327.
30. Ye M, Yan Y, Da G. Characterization of phenolic compounds in the Chinese herbal drug Tu-Si-Zi by liquid chromatography coupled to electrospray ionization mass spectrometry. Rapid Commun Mass Spectrom. 2005;19(11):1469–84. https://doi.org/10.1002/rcm.1944.
31. Seeram NP, Lee R, Scheuller HS, Heber D. Identification of phenolic compounds in strawberries by liquid chromatography electrospray ionization mass spectroscopy. Food Chem. 2006;97(1):1–11. https://doi.org/10.1016/j.foodchem.2005.02.047.
32. Anjaneyulu A, Raju D, Rao S. Chemical examination of *Pergularia extensa*. Indian J Chem B. 1998;37:318–20.
33. Seshadri T, Vydeeswaran S. Chemical examination of *Luffa echinata*. Phytochem. 1971;10(3):667–9. https://doi.org/10.1016/S0031-9422(00)94717-4.
34. Rakhit S, Dhar MM, Anand N, Dhar ML. Chemical investigation of *Daemia extensa*. J Sci Ind Res (India). 1954;18B:422–6.
35. Raman SP, Barua A. Chemical investigation of *Daemia extensa* R. Br J Am Pharm Assoc (Scientific ed). 1958;47(8):559–60.
36. Mittal OP, Tamm C, Reichstein T. Die Glykoside von *Pergularia extensa* (JACQ.) NE Br. Glykoside und Aglykone, 227. Mitt. Hel Helv Chim Act. 1962;45(3):907–24. https://doi.org/10.1002/hlca.19620450320.
37. Sinha S, Dogra J. A survey of the plants of Bhagalpur and *Santhal pargana* for saponin, flavonoids and alkaloids. Int J Crude Drug Res. 1985;23(2):77–86. https://doi.org/10.3109/13880208509069006.
38. Subramanian SS, Nair A. Flavonoids of some asclepiadaceous plants. Phytochemistry. 1968;7(9):1703–4. https://doi.org/10.1016/S0031-9422(00)88630-6.
39. Shahidi F. Antioxidant factors in plant foods and selected oilseeds. Biofactors. 2000;13(1–4):179–85. https://doi.org/10.1002/biof.5520130129.
40. Shahidi F, McDonald J, Chandrasekara A, Zhong Y. Phytochemicals of foods, beverages and fruit vinegars: chemistry and health effects. Asia Pac J Clin Nutr. 2008;17(S1):380–2.
41. Devasagayam T, Tilak J, Boloor K, Sane KS, Ghaskadbi SS, Lele R. Free radicals and antioxidants in human health: current status and future prospects. J Assoc Physicians India. 2004;52:794–804.
42. Lin J-K, Weng M-S. Flavonoids as nutraceuticals. In: The science of flavonoids: Springer; 2006. p. 213–38.
43. López-Lázaro M. Distribution and biological activities of the flavonoid luteolin. Mini-Rev Med Chem. 2009;9(1):31–59. https://doi.org/10.2174/138955709787001712.
44. Ambriz-Pérez DL, Leyva-López N, Gutierrez-Grijalva EP, Heredia JB. Phenolic compounds: natural alternative in inflammation treatment. A review. Cogent Food Agric. 2016;2:1131412.
45. Emerit J, Edeas M, Bricaire F. Neurodegenerative diseases and oxidative stress. Biomed Pharmacother. 2004;58(1):39–46. https://doi.org/10.1016/j.biopha.2003.11.004.
46. Kumar KR, Lohmann K, Klein C. Genetics of Parkinson disease and other movement disorders. Curr Opin Neurol. 2012;25(4):466–74. https://doi.org/10.1097/WCO.0b013e3283547627.
47. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. Indian J Clin Biochem. 2015;30(1):11–26. https://doi.org/10.1007/s12291-014-0446-0.
48. Jayaprakash G, Singh R, Sakariah K. Antioxidant activity of grape seed (*Vitis vinifera*) extracts on peroxidation models *in vitro*. Food Chem. 2001;73(3):285–90. https://doi.org/10.1016/S0308-8146(00)00298-3.
49. Cook NC, Samman S. Flavonoids—chemistry, metabolism, cardioprotective effects, and dietary sources. J Nutr Biochem. 1996;7(2):66–76. https://doi.org/10.1016/0955-2863(95)00168-9.
50. Karthishwaran K, Mirunalini S. Assessment of the antioxidant potential of *Pergularia daemia* (Forsk.) extract *in vitro* and *in vivo* experiments on hamster buccal pouch carcinogenesis. Asian Pac J Trop Dis. 2012;2:S509–S16. https://doi.org/10.1016/S2222-1808(12)60212-6.
51. Sarkodie J, Squire S, Kretchy I, Domozoro C, Ahiagbe K, Twumasi M, et al. The antihyperglycemic, antioxidant and antimicrobial activities of *Ehretia cymosa*. J Pharmacogn Phytochem. 2015;4(3):105–11.
52. Calder PC, Albers R, Antoine J-M, Blum S, Bourdet-Sicard R, Ferns G, et al. Inflammatory disease processes and interactions with nutrition. Br J Nutr. 2009;101(Suppl):S1–45.
53. Libby P. Inflammatory mechanisms: The molecular basis of inflammation and disease. Nutr Rev. 2007;65(suppl-3):S140–S46.
54. Usman MRM, Salgar SD, Pati SA. Anti-inflammatory activity of whole plant of *Pergularia daemia* Linn. Int J Pharma Sci Res. 2012;3:258–67.
55. Venkataraman S, Sini B, Meera R, Devi P. Anti-inflammatory, analgesic and antipyretic activity of *Pergularia daemia* Forsk. Int J Pharm Biol Sci Arch. 2010;1(4):371–5.
56. Hina I, Rose JC. *In vitro* anti-inflammatory and anti arthritic activity of *Pergularia daemia* leaves and roots. J Int J Drug Dev Res. 2018;10:10–3.
57. Nikajoo LT. Analgesic activity of aqueous and alcohol root extracts of *Pergularia daemia* (Forsk.) Chiov. Int J Pharm Pharm Sci. 2009;1(Suppl-1):33–7.
58. Sutar NG, Pal SC. Evalution of anti arthritic activity of leaf extracts of *Pergularia daemia* [Forsk] plant in experimental animals. Int J Pharm Pharm Sci. 2014;6(10):198–200.
59. Khorombi TE. A chemical and pharmacological investigation of three south African plants. Pietermaritzburg: University of KwaZulu-Natal; 2006.
60. Martin S, Kavitha PD, Rathi MA, Kumar DG, Gopalakrishnan VK. Cytotoxic activity of *Pergularia daemia* against ovarian cancer cell lines OAW-42 and PA-1. J Nat Pharm. 2011;2(4):203–9.
61. Kumar PV, Ramesh N. Anti-hyperglycaemic activity of *Pergularia daemia* (Forssk.) Chiov. J Phytopharmacol. 2014;3(1):29–34.
62. Wahi A, Ravi J, Hemalatha S, Singh P. Anti-diabetic activity of *Daemia extensa* R. Br J Natl Remedi. 2002;2(1):80–3.
63. Sarkodie JA, Squire SA, Bekoe EO, Domozoro CYF, Kretchy IA, Ahiagbe MKJ, et al. Antioxidant and antimicrobial capacities of ethanolic extract of *Pergularia daemia* leaves: a possible substitute in diabetic management. J Comp Integr Med. 2016;13(3):239–45.
64. Adesanoye OA, Farombi EO. Hepatoprotective effects of *Vernonia amygdalina* (Astereaceae) in rats treated with carbon tetrachloride. Exp Toxicol Pathol. 2010;62(2):197–206. https://doi.org/10.1016/j.etp.2009.05.008.
65. Tan BL, Norhaizan ME, Liew WP, Sulaiman RH. Antioxidant and oxidative stress: a mutual interplay in age-related diseases. Front Pharmacol. 2018;16(9):1162.
66. Dhanasekaran D, Sivamani P, Panneerselvam A, Thajuddin A. Rajakumar, Selvamani S. biological control of tomato seedling damping off with

Streptomyces sp. Plant Pathol J. 2005;4(2):91–5. https://doi.org/10.3923/ppj.2005.91.95.
67. Wang BJ, Liu CT, Tseng CY, Wu CP, Yu ZR. Hepatoprotective and antioxidant effects of Bupleurum kaoi Liu (Chao et Chuang) extract and its fractions fractionated using supercritical CO_2 on CCl_4 induced liver damage. Food Chem Toxicol. 2004;42(4):609–17. https://doi.org/10.1016/j.fct.2003.11.011.
68. Sureshkumar S, Mishra S. Hepatoprotective effect of extracts from *Pergularia daemia* Forsk. J Ethnopharmacol. 2006;107(2):164–8. https://doi.org/10.1016/j.jep.2006.02.019.
69. Bhaskar V, Balakrishnan N. Protective effects of *Pergularia daemia* roots against paracetamol and carbon tetrachloride-induced hepatotoxicity in rats. Pharm Biol. 2010;48(11):1265–72. https://doi.org/10.3109/13880201003730667.
70. Sureshkumar S, Mishra S. Hepatoprotective activity of extracts from *Pergularia daemia* Forsk. Against carbon tetrachloride-induced toxicity in rats. Pharmacogn Mag. 2007;3(11):187–91.
71. Sureshkumar S, Mishra S. Hepatoprotective effect of *Pergularia daemia* (Forsk.) ethanol extract and its fraction. Indian J Exp Biol. 2008;46(6):447–52.
72. Bhavin V, Ruchi V. Diuretic potential of whole plant extracts of *Pergularia daemia* (Forsk.). Iran J Pharm Res. 2011;10(4):795–8.
73. Mishra G, Chandra HK, Sahu N, Nirala SK, Bhadauria M. Ameliorative effect of *Pergularia daemia* (Forssk.) Chiov. Leaves extract against anti-tuberculosis drugs induced liver injury in rats. Asian Pac J Trop Med. 2018;11(9):518–25.
74. Kumar VK, Kumar P, Venkatachalam T. Investigation of anthelmintic activity of *Pergularia daemia* leaves. Pharmacophore. 2014;5(1):44–8.
75. Park SW, Oh TY, Kim YS, Sim H, Park SJ, Jang EJ, et al. *Artemisia asiatica* extracts protect against ethanol-induced injury in gastric mucosa of rats. J Gastroenterol Hepatol. 2008;23(6):976–84. https://doi.org/10.1111/j.1440-1746.2008.05333.x.
76. Sangiovanni E, Vrhovsek U, Rossoni G, Colombo E, Brunelli C, Brembati L, et al. Ellagitannins from *Rubus berries* for the control of gastric inflammation: *In vitro* and *in vivo* studies. PLoS One. 2013;8(8):e71762. https://doi.org/10.1371/journal.pone.0071762.
77. Borrelli F, Izzo AA. The plant kingdom as a source of anti-ulcer remedies. Phytother Res. 2000;14(8):581–91. https://doi.org/10.1002/1099-1573(200012)14:8<581::AID-PTR776>3.0.CO;2-S.

Publisher's Note