ARTABOTRYS HEXAPETALUS (L. F.) BHANDARI: A PLANT WITH ENORMOUS BIOMEDICAL POTENTIAL

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Received: 06 Apr 2020, Revised and Accepted: 04 May 2020

ABSTRACT

This review is intended to investigate the published report regarding phytochemical, ethnomedicinal, and pharmacological activities and put forth the therapeutic potential of Artabotrys hexapetalus (L. f.) Bhandari. [A. hexapetalus]. It belongs to the family Annonaceae, one of the therapeutically important plants, broadly distributed throughout the world. An extensive review of the literature available in various recognized databases including logical writing and scientific literature, search engines such as SpringerLink, ScienceDirect, SciFinder, PubMed, Scopus, Google Scholar, and BioMed Central as well as relevant books, websites, scientific publications, and dissertations were utilized as a source of information that provided an up-to-date review. Phytochemical profiling of these species revealed the presence of some imperative phytochemicals alkaloids, terpenoids, flavonoids, butyro lactones, flavonoids, neolignans, phenolic compounds, and leucoanthocyanins as the basis of its valuable therapeutic properties. The other imperative phytoconstituents which contribute to the therapeutic properties are isoamericanin A, isoamericanol, americanin, artabotrine, and artabotrical. The pharmacological activities exhibited by Artabotrys hexapetalus as antimicrobial, antileishmanial, antioxidant, antifungal, antiinflammatory, and antihelmintic properties are attributed to the presence of valuable bioactive phytoconstituents. Considering these facts an effort was made to present a comprehensive review enlightening the taxonomical, phytochemical, and pharmacological activities of plant Artabotrys hexapetalus. Future research can be directed to an extensive investigation about phytochemistry, clinical trials, pharmacokinetics, and safety data to add new dimensions to the therapeutic utilization of Artabotrys hexapetalus and other Artabotrys species.

Keywords: Artabotrys hexapetalus, Annonaceae, Pharmacological, Phytochemicals

INTRODUCTION

Artabotrys is a genus of woody trees, shrubs, and vines comprising about 130 genera and 2,300 species, which is distributed mainly in tropical and subtropical regions of the world, especially tropical Africa and Eastern Asia and the Indomalayan region [1, 2]. Plants of Artabotrys genus are climbing herbs bearing recurved hooks borne on lateral branches and scandent shrubs are one of the largest genera of the custard-apple family [3]. Artabotrys hexapetalus (L. f.) [A. hexapetalus] Bhandari generally described as a folk drug that has a wide range of medicinal uses belonging to family Annonaceae. The family includes trees, shrubs, and lianas, found in almost all vegetation types. It is generally considered to be a natural family and one of the six members of Magnoliales [4]. It is an ornamental, medium-sized woody climber that produces aromatic flowers with fragrance. A. hexapetalus is native to India and widely distributed in the southern part of China, and is used in traditional Chinese medicine for the treatment of malaria [5]. It is a medium-sized climbing shrub, largely cultivated in India. Leaves are oblong, lanceolate, and glabrous. Flowers solitary or paired, often fragrant, usually on woody, hooked recurved branches (Peduncles) [6]. It is widely distributed throughout the southern part of China and also in the southern part of Asia. As a Chinese traditional folk medicine, its roots and fruits are used for treating malaria and scrofula, respectively [7]. The flower is acrid, bitter; useful in vomiting, diseases of the blood and the heart, leucoderma, headache. A decoction of leaves is given for cholera. Phytochemically it contains alkaloids, anthraquinones, butyro lactones, flavonoids, neolignans, phenolic compounds, leucoanthocyanins, terpenoids, and volatile oils [8-10]. Many phytochemicals in the form of flavonoids of A. hexapetalus possibly be modified or used as “lead” for developing more effective drug molecules. Hence, extensive pharmacological and phytochemical screening, together with the pharmacokinetic and toxicological assay can be aimed at future investigations. Hence an attempt is made to highlight selected phytochemical and biomedical potentials of A. hexapetalus species in this review.
Synonym: *Hornschuchiaeaceae*

**Etymology**

*A. hexapetalus* Indochina: Day cong chua.

Artabotrys = arta+botrys (arta= Support, botrys=bunch of grapes)

Hexapetalus = 6 petals

A plant with 6 petalled flower and fruits resembles a bunch of grapes [13].

**Geographic distribution of A. hexapetalus**

*A. hexapetalus* probably native to South India and largely cultivated in India, Sri-Lanka, Burma, Southern China, and Taiwan. In different parts of the world, it is largely known as an ornamental plant. Within India, it is indigenous to South India and very commonly cultivated in gardens throughout the country for its fragrant flowers. Plant is propagated through stem cutting and seed. Group of fruits (usually 6) grow together at the end of the long peduncle [14].

**Characteristics of plant A. hexapetalus**

The plant is a climber with lateral branches straight, lenticellate, glabrous, dark brown when dry, young twigs sparsely pubescent shown in fig. 1.

**Leaves**

The leaves are simple, alternate, petiolated (3-8 mm), extipulate, and distichously arranged. They are thinly pubescent; oblong-lanceolate 6-10 mm long, shortly acuminate, elliptic, glabrous on both surfaces with a thinly coriaceous blade, and the base is acute cuneate. The colour of the leaves is pale green when dry. The midrib of the leaf is flat on the upper epidermis and raised at the lower epidermis with lateral anastomosing veins flat on both surfaces [15, 16].

**Inflorescence**

It has a flat peduncle, solitary or in pairs that are sparsely pubescent with two branches; 1-2 flowers; bract elliptic to oblong and bud broadly ovoid.

**Flowers**

The flowers are bisexual and actinomorphic, possessing 3 whorls of perianth with 3 segments in each whorl. Entire parts of floral are distinct, yellow, solitary or in pairs, 3.2-3.8 cm long, pedicels 15-20 mm long, sepals are 6 cm long that erect to reflexed sparsely pubescent. Flowers are thinly fleshy, ovate, with acute apex and pubescent. The petals are fleshy, connate below, tips reflexed petals are lanceolate above the saccate base, clothed with appressed silky hairs. Inner petals are narrower, flat, 20-30 x 3-6 mm; torus convex; stamen are oblong. Apical possess a cylindrical carpels prolongation flat, obovoid, glabrous with 2-3 cm in diameter. The stamens are very short and tightly packed generally fertile with central anther portion, a distal pad of fleshy connective tissue, and a short fleshy basal portion [17, 18].

**Fruit**

Appeared berries, obovoid to ellipsoid, 3.5-4 x 1.5 cm, apex mucronate; stalk 20 x 1.5 mm, sparsely pubescent. It bears berry-like fruits but sometimes forms multiple fruits like the custard apple [19].

**Seed**

Two large, ellipsoid oblong little flattened, deeply grooved on one side, more than 13 mm long. Sectioned seeds reveal channels or partitions in the ruminate endosperm [20].

**Traditional uses of A. hexapetalus**

Medicinal plants and traditional systems of medication is been continuously allied as the backbone of these systems. India has an ironic natural heritage of traditional systems of medicine. These traditional systems of medications with the perceptions of safety, efficacy, and quality will urge to protect the customary heritage [21]. The flowers of *A. hexapetalus* are tonic and stimulant. The fruits and the bark are used to treat fever, diarrhea, skin diseases, wounds, ulcers, inflammation, cough, asthma, and bronchitis. The leaves extract has antibacterial, antifertility, and antifungal activity [22]. The pulp of ripened fruits has been used traditionally in some parts of Assam for the fungal infections in the domestic animals the tribes of Malay Archipelago use a decoction of leaf for treatment of Cholera. Roots of this plant are used to treat Malaria according to Chinese traditional systems of medicine. The volatile oil from the flower in the Unani system of medicine is used in aromatherapy [23, 24]. In Ayurveda and Siddha systems of medicines flowers used as tonic...
and stimulant. Fruit and bark are used to treat fever, diarrhea, flatulence, colic, constipation, skin disorders, wound healing, cough, and bronchial asthma. The decoction of leaves used as an antimicrobial, antifertility, muscle relaxant, and cardiac stimulant [25]. Flowers used as a flavoring in tea Southern India; Sri Lanka. Used in perfumery as the source of essential oils. In Salem, Tamil Nadu, Southern India used in the preparation of stimulating tea-like beverages. In Java, Indonesia, Philippines, Southern China, India, whole plant is used as an ornamental plant and for screen planting in large gardens. In traditional Chinese systems of medicine prescribed for the treatment of malaria and scrofula [26-28].

**Phytochemical composition of *A. hexapetalus***

The literature proposes that *A. hexapetalus* possess important bioactive compounds, as shown in fig. 2. 

![Phytoconstituents of *A. hexapetalus*](image)

Interestingly almost all parts of the *A. hexapetalus* species have been explored for phytochemical analysis and various phytoconstituents are isolated to date. Various important phytoconstituents have been reported are 4-neolignan, namely isoamericanin A, isoamericanol A, americanin B and artabotricinol a semi terpenoid; (R) artabotriol. It contains β-unsaturated-β-butyrolactones. Flavonol glycosides namely arapetaloside A and B are reported. Flavonoids: taxifolin, apigenin-7-O-apiosylglucoside, and glucoluteolin. Alkaloid: artabotrine [29] table 1.
Yu J. et al. 2002 have isolated four neo-lignans–isosamburanin A, isosammaronicin A, Americanin B, and Artabotrycin A and a hemiterpenoid: (R)-artabotriol and other compounds from the seeds of A. hexapetalus and reported the presence palmitic acid, β-sitosterol, and daucosterol [30]. Wong H. et al. 2002 have reported that the dichloromethane extract of the aerial parts of A. hexapetalus contains β-methoxy-γ-methylene-δ, β-unaturated-γ-butyrolactones which are anticipated to be derived from a C-18 unsaturated fatty acid [31]. Yu J. et al. 2001 have studied the chemical constituents of the seeds of A. hexapetalus. Eight compounds were isolated and identified as four Neolignans–isosammaronin A, isosammaronicin A, Americanin B, and Artabotrycin A, a semiterpenoid: (R)-artabotriol and others [32]. Li T. et al. 1997 reported the isolation of various constituents from A. hexapetalus leaves. They isolated two new flavonol glycosides derivatives of artabotryside B and three known flavonoids: taxifolin, 7-O-gluculetolin, apigenin glycoside, and two organic acids as succinic and fumaric acid. Based on spectral analysis structures elucidated were quercetin and kaempferol [33]. Tong-Mei Li et al. 1997 reported the isolation of the flavonol glycosides–quercetin, quercetin 3-O-glucoside, 3-O-arabinoside, and 3-O-galactoside along with kaempferol, myricetin, and gallic acid from the leaves of A. hexapetalus [39]. Phan, G. et al. 2007 reported extraction, identification, and analysis of essential oil from the flower of A. hexapetalus. Compounds were analyzed by using GC and GC/MS spectroscopic techniques. Twenty-six components of the oil that were identified as sesquiterpene hydrocarbons and oxygenated sesquiterpenoids, β-caryophyllene, and caryophyllene oxide [40]. Mahidol C et al. 2005. Investigated compositions of the essential oils from flowers of A. hexapetalus the flowers were subjected to hydrodistillation, solvent extraction, solid-phase microextraction, and simple headspace solvent-trapping technique. By hydrodistillation, thirty-one components and five unidentified ones were identified together as β-caryophyllene, β-gurjunene, and globulol. Employing solvent extraction method thirty-one components were identified as 3-methyl butanol, 2-methylbutanol, ethyl butanoate, isopentyl acetate, 2-methyl butyl acetate, limonene, linalool, and two unidentified components. The other two unconventional extraction methods were employed as simple headspace solvent-trapping techniques. Using this method, seventeen components were identified as ethyl acetate, ethyl isobutanoate, isobutyl acetate, ethyl 2-methyl butanoate, ethyl isovalerate, ethyl 3-methyl-2-butoxoyl, isobutyl isovalerate, and β-caryophyllene [41].

Table 1: Chemical constituents of A. hexapetalus

| S. No. | Part of plant | Phytochemical | Plant part | Reference |
|-------|---------------|---------------|------------|-----------|
| 1.    | Leaf          | Antioxidant Activity | Seeds | Yu J et al. [30] |
| 2.    | Bark          | Antifertility Activity | Roots | G. Yu et al. [32] |
| 3.    | Bark          | Hepatoprotective activity | Roots | Tong-mei et al. [34] |
| 4.    | Bark          | Antibacterial and Antifungal activity | Fruits | Singh et al. [39] |
| 5.    | Bark          | Anthelmintic and Cytotoxic activities | Seeds | Li T [31] |
| 6.    | Bark          | Antimicrobial activity | Flavonoids | Somanavat [35] |
| 7.    | Root          | Mosquito repellent activity | Flavonoids | QiZhou et al. [31] |
| 8.    | Root          | Antimalarial | Flavonoids | Yao Xue et al. [30] |
| 9.    | Flower        | Antipyretic | Flavonoids | Phan et al. [40] |

Table 2: Biological activities of A. hexapetalus

| S. No. | Activity reported | Reference |
|-------|-------------------|-----------|
| 1.    | Antioxidant Activity | Salaya et al. [58] |
| 2.    | Antifertility Activity | Karthik et al. [62] |
| 3.    | Hepatoprotective activity | Veena et al. [63] |
| 4.    | Antibacterial and Antifungal activity | Grainge et al. [54] |
| 5.    | Anthelmintic and Cytotoxic activities | Morshed et al. [64] |
| 6.    | Antimicrobial activity | Shankar et al. [52] |
| 7.    | Antileishmanial activity | Bajju et al. [56] |
| 8.    | Mosquito repellent activity | Rajbu et al. [62] |
| 9.    | Antimalarial | Wijesekera [66] |
| 10.   | Antipyretic | Rahini et al. [65] |
Biological and pharmacological activities of A. hexapetalus

Herbal drugs have been playing a substantial role throughout the world in treating and preventing several diseases [42]. The essential oil of this plant contains excellent antihelmintic property against human tapeworms, earthworms, and roundworms [43]. Fruits of this plant are recoded as containing fixed and volatile oil, glycosides, and resins. Extracts are reported to show hypotensive and spasmogenic, as well as cardiac stimulating effects on some animals and a cardiac depressant on others [44]. Ethanolic and benzene extracts of leaves have shown irregular oestrous cycle in albino rats. Also used as a remedy to treat abdominal and kidney pains [45]. Decoction used in the treatment of cholera. It is used as a cardiotonic, cardiac stimulant, muscle relaxant, and uterine stimulant [46-51] (table 2).

Antimicrobial activity

Shankar P, et al. 2011 investigated acetone and ethanolic extracts of leaves of A. hexapetalus for antibacterial efficacy. The phytochemical analysis confirmed the presence of flavonoids, alkaloids, tannin, leaves of Xanthomonas Campestris antibacterial activity against zones of growth inhibition [53]. Grainge M, et al. 2010 reported noteworthy microbial inhibition calculated from significant antibacterial activity against gram-positive bacteria determined against gram-negative bacteria. The leaf extracts showed Acetone extract showed the maximum zone of inhibition against Staphylococcus aureus [52]. Sowjanya K, et al. 2013 reported antibacterial and antifungal activity of methanolic extracts of A. hexapetalus leaves. The method was used for screening the agar well diffusion method. Different concentration of extracts (25-100μg/ml) was tested against Salmonella typhi, Streptococcus entericus, lactobacillus casel, streptococcus mutans, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, bacillus megaterium, Entercoccus faecalis Xanthomonas campestris Candida albicans, Aspergillus niger, Rhizopus oryzae and Candida rogasu. The results proved noteworthy microbial inhibition calculated from zones of growth inhibition [53]. Grainge M, et al. 1987 in this investigation tested leaf extracts of A. hexapetalus against Xanthomonas Campestris and Drechslera oryzae (Cochliobolus miyabeanus) and 10 other bacterial strains. The leaf extracts showed inhibition in the growth of X. campestris pv and campestris [54]. Haseena S, et al. 2019 reported the green synthesis of CuO nanoparticles using A. hexapetalus extract by co-precipitation method. The antibacterial ability of CuO nanoparticles was determined against gram-negative E. coli pathogen by the agar-agar diffusion method. Results revealed that CuO nanoparticles showed significant antibacterial activity against gram-positive E. coli strain [55].

Antileishmanial activity

Bajaj S, et al. 2018 evaluated the in vitro antileishmanial activity of extracts of A. hexapetalus against the Leishmania donovani (L. donovani) parasites. The plant extract inhibited the growth of L. donovani in vitro after 24, 48, 72, and 96 h of incubation and had 50% inhibitory concentration (IC50). The lowermost concentration of extract showed inhibition of growth of L. donovani parasites it was measured as the maximum inhibitory concentration. This indicated after incubation at 24 and 48 h. all extracts showed antileishmanial activity in a dose-dependent mode [56].

Antioxidant activity

Manjula M, et al. 2011 reported screening of antioxidant and antimicrobial activity of A. hexapetalus flower extracts. 2,2,1-diphenyl-1-picrylhydrazyl [DPPH] and reducing power method was utilized in the screening of antioxidant activity Results indicated reducing the power of extracts increased with increase in the concentration of extracts. DPPH free radical-scavenging of chloroform, methanol, aqueous extracts, and Gallic acid as standard with half-maximal inhibitory concentration IC50 values at the concentration range of 50-250μg/ml were determined as 378.73μg/ml, 7.29μg/ml, 118.49μg/ml and 68.75μg/ml respectively [57]. Saiya K, et al. 2017 determined free radical scavenging activity of methanol extract of A. hexapetalus utilizing ascorbic acid as standard antioxidant. DPPH method was used for screening of antioxidant activity. A. hexapetalus extracts showed a 52.99% scavenging activity in the DPPH assay [58]. Rahini D, et al. 2014 carried out in vitro free radical scavenging assays of A. hexapetalus flower extract. This assay was performed by determination of total antioxidant capacity, reducing ability Nitric oxide radical, and scavenging of hydrogen peroxide. A. hexapetalus flower extract effectively scavenge free radicals at all different concentrations and showed its potent antioxidant activity [59]. Bolla pragada M, et al. 2018 determined in vitro antioxidant activity of methanolic extract of A. hexapetalus leaves. The antioxidant assay was determined using DPPH, ferric reducing antioxidant power, and total antioxidant capacity. The activity of methanolic extract at lower concentrations 10-50 μg/ml IC50 values were 33.95 μg/ml in comparison to that of standard ascorbic acid 33.2μg/ml. The results demonstrated that the extract of A. hexapetalus leaves showed a significantly higher (p<0.05) value. Hydroxyl radical scavenging activity of methanolic extract of A. hexapetalus showed 200.3±3.11 μg/ml IC50 value [60].

Mosquito repellent activity

Rajabu A, et al. 2014 investigated mosquito repellent activity of their essential oils of leaves and stem bark of A. hexapetalus. The composition of oil from the stem bark and leaves showed both β-caryophyllene oxide and 11-hexadecyn-1-ol as the main components. Essential oil from the leaves of A. hexapetalus displayed strong activity with Repellent concentrations (RC50) values 1.81×10-5 mg/cm² and 2.79×10-5 mg/cm². Against mosquitoes female Anopheles gambiae s.s. The repellency activity of essential oil in comparison to standard citronella oil used (RC50 = 4.1×10-6 mg/cm²) was found to be moderate [61].

Anti-fertility activity

Karthish Y, et al. 2012 evaluated the antifertility activity of hydroalcoholic extract of A. hexapetalus leaves in vivo on male Wistar rats and female Sprague Dawley rats and rabbits. In this study, male Wistar rats were orally fed with hydroalcoholic extract at a concentration of 200, 400, 600 mg/kg. p. o, for 45 d. This effect on the extract on reproductive organs, sperm count, serum testosterone, testicular cholesterol, and alkaline phosphates levels was noted and changes in testicular histology were compared with the control rats. Progestogenic activity assay was determined by pregnancy maintenance test in female Sprague Dawley rats. The result showed a decrease in weight of testis, seminal vesicles and sperm count, serum testosterone testicular cholesterol and alkaline phosphates level and the histological examination of testis demonstrated that decrease in the diameter of seminiferous tubule server hypercellularity of Leydig cells. The Pregnancy maintenance assay displayed non-progestogenic, pregonstatational, or anti-progestational activities [62].

Hepatoprotective activity

Veena R, et al. 2016 screened the alcoholic extract of A. hexapetalus for in vivo hepatoprotective activity in rats, which were intoxicated by paracetamol. The hepatoprotective activity and oxidative stress of A. hexapetalus were determined using parameters like serum enzyme levels like SGOT, SGPT, ALP, ACP, Total Bilirubin, Direct Bilirubin, SOD, GSH, Vitamin C and catalase levels of the animals treated with hepato-toxic paracetamol. The alcoholic extract of A. hexapetalus overturned the hepatotoxicity that was induced by paracetamol in the rats, indicating their hepatoprotective activity. This histopathological studies revealed structural damage occurred due to paracetamol, which was further supported by the DNA fragmentation studies that showed the absence of fragmentation of DNA in alcoholic extract-treated groups, indicating the hepatoprotective activity of A. hexapetalus [63].

Anthelmintic activity

Niaz M, et al. 2012 investigated the methanolic extract of bark of A. hexapetalus for in vitro anthelmintic and cytotoxic activities. Brine shrimp lethality bioassay was used for the evaluation of the cytotoxic activity. The methanolic extract presented noteworthy cytotoxic potential (LC50 value of 7.68 μg/ml) in comparison to standard vincristine (0.839 μg/ml). To evaluate anthelmintic activity the methanolic extract of A. hexapetalus at 68.33 min and death at 84.0 min. In comparison to the standard vincristine (0.839 μg/ml). To evaluate anthelmintic activity the methanolic extract of A. hexapetalus at 68.33 min and death at 84.0 min. In comparison to the standard vincristine (0.839 μg/ml). To evaluate anthelmintic activity the methanolic extract of A. hexapetalus at 68.33 min and death at 84.0 min. In comparison to the standard vincristine (0.839 μg/ml). To evaluate anthelmintic activity the methanolic extract of A. hexapetalus at 68.33 min and death at 84.0 min. In comparison to the standard vincristine (0.839 μg/ml).
confirmed the significant anthelmintic activities of bark extract of A. hexapetalus.[64]

Antipyretic activity

Rahini D, et al. 2014 reported antipyretic activity of ethanolic extract of flowers of A. hexapetalus tested on yeast induced pyrexia in albino rats. To carry out screening of the antipyretic flower extract at oral doses of 100, 250, and 500 mg/kg was used. A significant reduction in body temperature on yeast induced pyrexia was observed at a dose of 500 mg/kg body weight when compared with standard Paracetamol drug (200 mg/ml).[65]

CONCLUSION

The present review comprises of a perspective to show current advances in the phytochemical and pharmacological activities of A. hexapetalus as a prognostic therapeutic agent. According to the literature review, it is uncovered that A. hexapetalus possesses valuable therapeutic uses as antimicrobial, antileishmanial, antioxidant, antifungal, antifertility, anthelmintic, mosquito repellent, hepatoprotective, and cytotoxic activity. It has a potent free radical scavenging property which sufficiently demonstrated in different assays. Its potential as an antioxidant and antimicrobial agent needs to be undermined in future research work. It may perhaps be advised that alkaloids, terpenoids, anthraquinones, butyrolactones, flavonoids, neolignans, phenolic compounds, and leucoanthocyanins might be valued as a principal molecule in the development of new drugs to treat various diseases. Various unique constituents in the form of flavonoids of A. hexapetalus can also be chemically modified or used as “lead” for developing more effective drug molecules. Therefore, extensive pharmacological and phytochemical screening, together with the pharmacokinetic and toxicological assay, will be a focus for forthcoming investigation. Furthermore, a well-designed study to measure its toxicity from its long-term use is another urgency. This review article emphasizes the potential of A. hexapetalus that can be employed in new therapeutic drugs and will offer the base for future research on the application of herbal medicines.

ACKNOWLEDGMENT

The authors would like to extend our gratitude to Mr. Albert W. D’Souza, Chairman Adel Education Trust and Dr. (Mrs.) Savita J. Tauro, Principal, St. John Institute of Pharmacy and Research, Palghar for the generous support, motivation, encouragement and providing necessary facilities to carry out inscription of this manuscript.

AUTHORS CONTRIBUTIONS

Abhijeet Puri: Being a single author, I carried out a compilation of literature, an inscription of a manuscript, read-through, revising, and improving the standard of the manuscript. No other co-author contributed to this work.

CONFLICTS OF INTEREST

The authors declare that he has no conflicts of interest.

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