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Review

Antifertility Potential of *Plumbago zeylanica* Linn.: A Comprehensive Review

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Abstract: *Plumbago zeylanica* Linn., which is part of the *Plumbagin*aceae family, is an important plant, for medicine. It has been used for a time to help with problems related to reproduction and metabolism. People have looked at parts of the *P. zeylanica* Linn plant, especially the roots and leaves to see what kind of effects they have on the body. They found that *P. zeylanica* Linn has benefits, including helping to fight off bad germs, reducing damage from free radicals, fighting cancer, protecting the liver, and even helping with birth control. This article looks at all the evidence that supports the idea that *P. zeylanica* Linn can help with birth control. We searched through scientific databases like Google Scholar, Scopus, and ScienceDirect to find relevant information. Out of all the articles we found, we chose 65 that were the most relevant and scientifically sound. We know that *P. zeylanica* Linn has natural chemicals that are good for us, including *plumbagin*, flavonoids, and phenolic compounds. These chemicals can affect how our bodies reproduce. Some studies have shown that extracts from *P. zeylanica* Linn. leaves can disrupt the cycle, stop ovulation, and even prevent pregnancy in animals. The chemical *plumbagin*, which is found in the roots of *P. zeylanica* Linn., is very important for its birth control effects. Since many people have reactions to man-made birth control methods, *P. zeylanica* Linn. could be a good alternative. However, we need to do research to make sure it is safe and effective for people to use as a natural birth control method. This article highlights the need for studies on *P. zeylanica* Linn to see if it can really help people with birth control.

Keywords: *P. zeylanica*; taxonomy; anti-fertility; toxicity

1. Introduction

Plants have been widely used for their therapeutic potential since ancient times and are also gradually becoming of interest to the modern scientific and medical world [1]. Most of the drugs currently being used have their origin, in one way or the other, from plants [1]. Medicinal plants have been in existence for the past thousands of years and continue to provide new drugs for various diseases. In many systems, treatment and dispensing of drugs by practitioners themselves reflect the necessity for well-documented research-based studies of these systems to support their practice with scientific evidence [2]. They offer potential advantages such as lower toxicity, greater therapeutic efficiency, and better patient acceptance [3]. Conventional treatments involving the use of medicinal plants, though many of which were not documented historically need to be documented properly so that they could be made use of rationally as well as lead to the introduction of new synthetic drugs with specified source phytochemicals or lead compounds with derivatized phytochemicals [4]. Consequently, detailed investigations of naturally occurring bioactive compounds are essential for the discovery and development of novel therapeutic agents [5].

Rapid population growth in developing countries has intensified the demand for effective and safe birth-control strategies. As a result, extensive research efforts have been directed toward fertility regulation through various approaches. Over the past six decades, the development of orally active contraceptive agents has remained a primary focus in female fertility control. In recent years, the global acceptance of herbal medicine has increased considerably. The World Health Organization (WHO) has endorsed the integration of traditional practices into maternal and child health programs, including the use of herbal contraceptives [6], and has established dedicated task forces to explore plant-based fertility-regulating agents with anti-implantation activity [7]. Early research predominantly emphasized synthetic oral contraceptives, with limited attention to plant-derived alternatives, despite the vast chemical diversity of phytoconstituents that span nearly all pharmacological classes. Currently,

approximately 25% of prescription drugs contain active ingredients of plant origin. Thus, the plant kingdom represents a valuable reservoir for the discovery of novel and effective antifertility agents. Synthetic contraceptives are often associated with adverse effects such as hormonal imbalance, hypertension, increased cancer risk, and weight gain [8], underscoring the urgent need for safer and more acceptable plant-based alternatives.

Medicinal plants have long served as the genesis for new drug discovery [9]. Herbal medicine based on extracts from plant sources is still used by over 80% of the world's population, especially in the developing world [10]. Medicinal plants synthesize vast amounts of various types of compounds and thus have pharmacological potential for use against many diseases [11]. *P. zeylanica* Linn. [also known as Chitraka, Chitramulamu, Tellachitramulamu, Agnichela, or Agnimaala; commercially as white-flowered leadwort or Ceylon leadwort] is found in the *Plumbagin*aceae family, and it is traditionally used in Africa and Asia for medicine [12]. There are three major species of *Plumbago* and a total of 10 genera and about 280 species in the family *Plumbagin*aceae. They are *P. Indica L. (P. Rosea L.), P. Capensis L.* and *P. zeylanica* L. The herb *P. zeylanica* L. which is an erect, semi-vining perennial subshrub, is an alternative and complementary medicine used in India, Bangladesh, Sri Lanka, Australia etc. [13]. The aerial parts of the plant are used traditionally for the treatment of rheumic pain, skin disorders, scabies, wound treatment, and inflammation [14]. The root is traditionally claimed to be an abortifacient [15], antioxidant [16], CNS stimulant [17], antimicrobial [18], antimalarial [19], wound healing [20], hypolipidaemic, and antiatherosclerotic [21]. Also, this plant showed anticancer, antibacterial and antifungal [22] and antitumour [23] and anticoagulant [24] activities. The known active constituents present in *P. zeylanica* are *plumbagin*, 5-hydroxy-1,4-naphthoquinone, sitosterol glycosides, fatty alcohols, and tannins [25,26]. Studies evaluating the antifertility activity of *P. zeylanica* showed that petroleum ether, chloroform, acetone, ethanol, and aqueous leaf extracts at a dose of 200 mg/kg and 400 mg/kg body weight had significant effects on the estrous cycle of rats. The acetone and ethanol extracts had the greatest effect on disturbing the estrous cycle, with a significant increase in the duration of the diestrous phase and temporary abolition of ovulation. These anti-ovulatory activities were reversible after treatment termination, showing significant estrogenic and anti-estrogenic activity [27].

With all this in perspective, the present review is being conducted to assess and summarize the scientific evidence related to the antifertility property of *P. zeylanica* Linn. in terms of its phytochemistry, pharmacology, and therapeutical significance.

2. Botanical Description

2.1.Taxonomy

In Table 1 the taxonomical classification of *P. zeylanica* is listed [28].

Table 1. Taxonomic classification of *Plumbago zeylanica*.

Kingdom	**Plantae**
Subkingdom	Tracheobionta
Class	Magnoliopsida
Subclass	Caryophyllidae
Superdivision	Spermatophyta
Division	Magnoliophyta
Order	Caryophyllales
Family	*Plumbagin*aceae
Genus	*Plumbago*
Species	*Plumbago zeylanica*

2.2. Morphological Studies

P. zeylanica is a highly branched perennial plant; leaves are arranged alternately (Figure 1) [29]. It is a biennial plant. The height of this plant ranges from 3 to 4 feet. The leaves are succulent, sessile, oval to lanceolate elliptical. The flowers of this plant are about 10 to 25 cm and they are arranged in long terminal and axillary spikes [30].

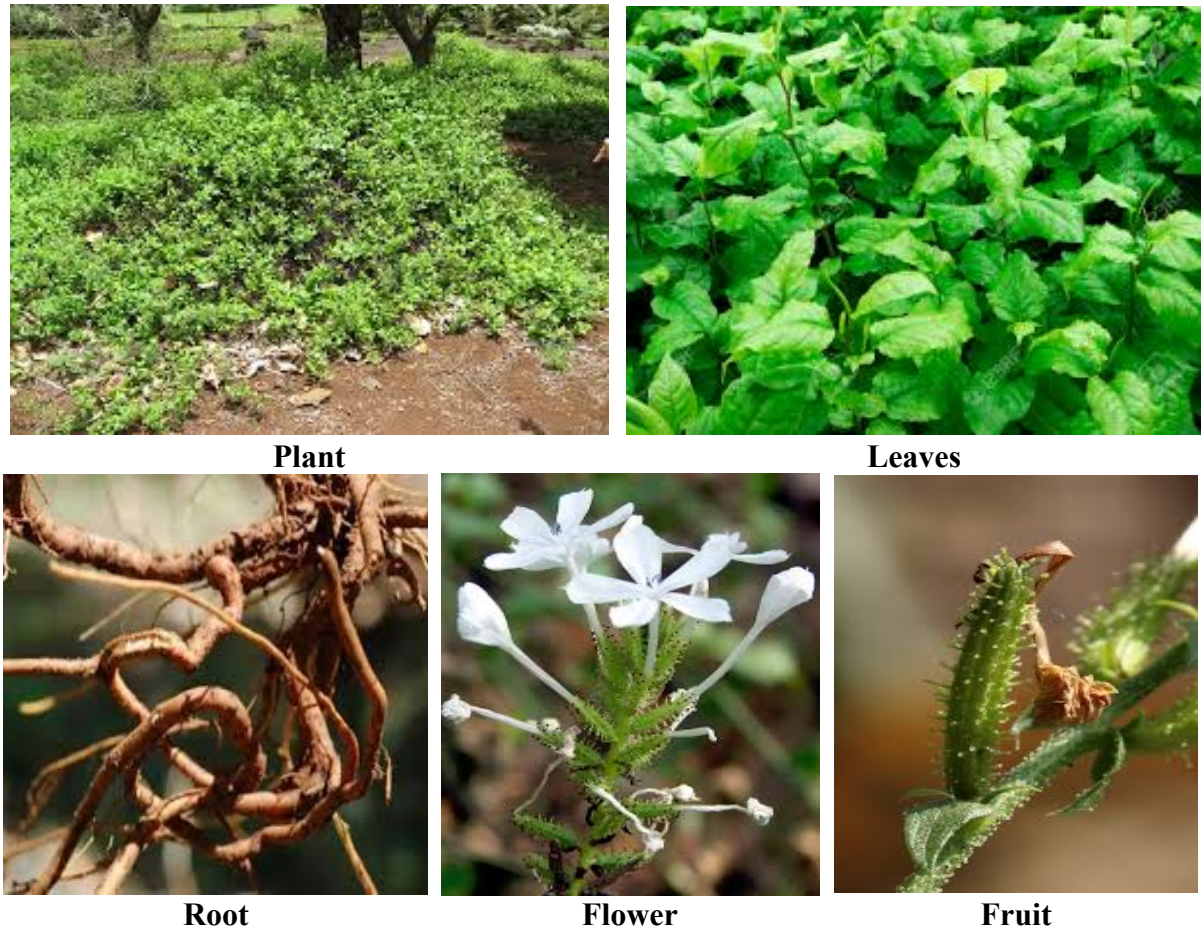


Figure 1. Morphological description of the *P. zeylanica* L.

2.3. Traditional Perspective

For centuries, various parts of *P. zeylanica* Linn. Has been utilized in the traditional medicine system due to its numerous therapeutic properties. The plant is highly regarded as a powerful medicinal herb and an 'Ayurvedic Rasayana,' i.e., restorative, which restores health, vigor, and vitality. Roots and root bark are very widely used in the preparation of several Ayurvedic medicines. It has traditionally been known to a have protective effect in case of hepatosplenomegaly and is advised as a potent stimulant and rejuvenator for conditions such as chronic cold and cough. It is used in the treatment of chronomyenorrha, viral warts, and chronic neurological disorders. An anticancer property is reported with the extract of Chitramula. Root bark is recommended for the treatment of obesity [31].

The various other uses for which it has been used traditionally are anorexia, dyspepsia, piles, worm infestation, colitis, ascites, and hepatic conditions due to its traditional use. The flowers are reported to be useful in digestion [32]. It is reported that the leaves have aphrodisiac, stimulant, and treatment of scabies, inflammatory conditions, and local pain. It has shown anti-infective and digestive effects on dysentery. Externally, the leaf paste is applied for relieving the rheumatic pain and chronic pruritic skin diseases [33]. Root has been described as laxative, expectorant, tonic, abortifacient, and appetite stimulant used in the treatment of rheumatism, laryngitis, scabies, splenics disorders, etc. Muscular pain relieved by seed decoction [34].

2.4. Medicinal Properties

According to classical Ayurvedic literature, *P. zeylanica* is effective in alleviating aggravated *Vata* and *Kapha*doshas. The plant has been traditionally used in the treatment of diarrhea, inflammation, fever, nervous paralysis, hemorrhoids, skin diseases, irritable bowel syndrome, epilepsy, amenorrhea, and anemia. The roots, in particular, are valued for their laxative, expectorant, astringent, and abortifacient properties and are prescribed for conditions such as dysentery, cirrhosis, arthritis, and other chronic disorders [35]. A summary of these medicinal applications is presented in Table 2.

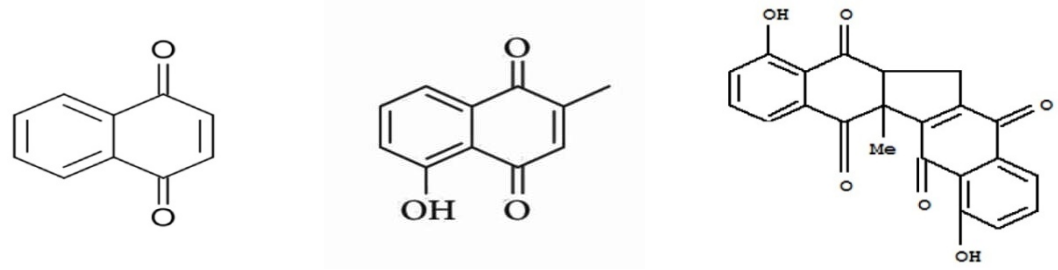
Table 2. Medicinal use of different parts of *Plumbago zeylanica.*

S.No	Disorder	Parts Used	Description
1	Diarrhoea	root	The paste made out of root (1 to 2 g) is taken with butter milk (30 to 60 mL), 2 to 3 times a day
2	Dysentery, abdominal disorders, peptic ulcers, piles and improves appetite	root bark	The decoction prepared out of the root bark churnam is taken orally (30 to 60 mL) twice in day for about 1 to 2 weeks. In children the dosage should be limited to 5 to 10 ml in divided doses.
3	Hypercholostremia	root	The fine powder of the root is taken orally (2 to 5 g) with honey twice a day for a period of 3 months.
4	Abortifacient	root	Local administration of fine root paste (3–5 g) of chitraka into the vaginal track for a period of 3 to 5 days.
5	Anemia and improves blood formation	root	The fine powders of chitraka and *Abutilon indicum*(L.) Sweet. root in equal proportion is given in dosages of 1 to 3 g with milk ones in a day for 3 months .
6	Leucoderma and psoriasis	root	The fine powder of chitraka (1 part), dry zinger, *Piper longum*L. and *Piper nigrum*L. (1 part each) are taken orally 2 to 3 g with ghee or honey, twice a day for period of 3 months.

2.5. Phytochemistry

Early phytochemical investigations of *P. zeylanica* have revealed that the roots are rich in bioactive constituents, including *plumbagin*, 3-chloro*plumbagin*, 2,3-bi*plumbagin*, 6,6-bi*plumbagin*, zeylinone, isozeylinone, chitranone (3,3′-bi*plumbagin*), droserone, plumbagic acid, and plumbazeylanone. In addition, the roots contain carbohydrates such as glucose and fructose, as well as enzymes including protease and invertase. In contrast, the leaves and stems contain little or no *plumbagin*. The aerial parts of the plant are reported to contain naphthoquinones, sitosterol, lupeol, lupenyl acetate, hentriacontane, and various amino acids.

The plant is particularly characterized by the presence of naphthoquinones (Figure 2a), including *plumbagin* (Figure 2b), chloro*plumbagin*, droserone, zeylinone (Figure 2c), isozeylinone, plumbagic acid, plumba-zeylanone, naphthelenone, isonaphthelenone, and isoshinanolone [36]. Amino acids such as aspartic acid, tryptophan, tyrosine, threonine, alanine, histidine, glycine, methionine, and hydroxyproline have been isolated from the aerial parts of the plant [37].



(**a**) **Naphthaquinone** (**b**) ***Plumbagin*** (**c**) **Zeylinone**

Figure 2. Chemical structure of constituents of *Plumbago zeylanica.*

3. Materials and Methods

A comprehensive literature survey was conducted to compile and analyze published information on the antifertility potential of *P. zeylanica* Linn. Scientific databases and search engines, including Google Scholar, PubMed, Scopus, Web of Science, ScienceDirect, and Wiley Online Library, were systematically searched. Relevant data were collected from peer-reviewed research articles, review papers, theses, dissertations, and published floras. Publications focusing on phytochemistry, pharmacological activities, antifertility mechanisms, and toxicological aspects of *P. zeylanica* were critically evaluated and included in the present review.

4. Male Antifertility Activity

P. zeylanica is from the family *Plumbagin*aceae, which is well known to show remarkable antifertility activity, which is more related to its roots and leaves. *Plumbagin*, isoshinanolone, trans-cinnamic acid, vanillic acid, sitosterol, 4-hydroxybenzaldehyde, and plumbagic acid were some of the identified compounds that contribute towards the biological activity. Apart from its traditional uses for treating hemorrhoids, leukoderma,

and some skin disorders, it was also known to possess anti-Helicobacter pylori activity, antidiabetic activity, antioxidant, and antifertility properties. To evaluate the male antifertility potential of *P. zeylanica,* a study was conducted using the ethanol extracts, which were administered to male wister rats. Histological changes were observed at a dose of 159 mg/kg b.wt., including reduction of seminiferous tubular diameter and significantly decreased spermatocyte and spermatid number and quantity production. Immature and mature Leydig cell populations also reduced, and significantly degenerating cell numbers increased with a significant decrease of testicular cell concentration. The results indicate that *P. zeylanica* derived from plants shows good male antifertility activity and also antifertility properties [38].

5. Female Antifertility Activity

The antifertility activity of the leaf extracts of *P. zeylanica* has been explored by a number of studies on experimental animal models. From various studies on rats, it has been concluded that treatment with the acetone and ethanol extracts of the leaves of *P. zeylanica* in a dose of 200 and 400 mg/kg brought about significant disruptions in the estrous cycle of female rats. Effects included a prolonged estrous phase in animals with induced pseudopregnancy and a temporary block of ovulation and this return to the normal cycle after cessation of the treatment. This shows the reversible nature of the anti-ovulatory activity and the potential to be used as a fertility-regulating agent.

In further research, immature ovariectomised female wistar rats treated with hydroalcoholic extract of the leaves of *P. zeylanica* showed a marked antifertility effect in a dose of 200 mg/kg. The antifertility was due to the anti-estrogenic nature of the extract, which resulted in pronounced morphological and functional changes in uterine tissue [39]. Likewise, Edwin et al. (2009) [27] studied petroleum ether, chloroform, acetone, ethanol, and aqueous extracts of the leaves of *P. zeylanica* with doses of 200 mg/kg and 400 mg/kg, and it has been concluded that acetone and ethanol extracts showed a significant ($p < 0.05$) antifertility effect by interrupting the estrous cycle, prolonging the diestrous phase, and arresting the ovulation. Estrogenic and anti-estrogenic activity was observed.

Marked anti-implantation effects of hydroalcoholic extracts of leaves of *P. zeylanica* in immature ovariectomised female Wistar rats were found when given during the first 7 days post-mating [40]. An antiestrogenic activity was found at 200 mg/kg, which caused structural and functional changes of the uterus [39]. Furthermore, Azad Choudhary et al. (1982) [41] and Edwin et al. (2009) [27] again confirmed the arresting of the estrous cycle with acetone and ethanol extracts with a prolonged diestrous phase and temporarily blocked ovulation. Apart from that, the ethnomedicinal uses of the plant in humans for family planning [42] as an anti-implantation possibly through interference in the synthesis and metabolism of progesterone [43] were documented.

On the molecular level *P. zeylanica* treatment in the early days of gestation had depleted uterine proteins at molecular weights 13,000, 19,000, 26,000, and 75,000 D and resulted in pre-implantation loss; however, proteins of 55,000 and 65,000 D were absent in aborted rats treated by root powder from day 6 to day 17 of gestation [44]. *Plumbagin* in an inclusion complex with hydroxypropyl-cyclodextrin (HPCD) was prepared to increase its solubility and potency. Intraperitoneal administration of an inclusion complex in niosomes at a dose of 5 mg/kg increased antifertility potential as compared to control formulations [45].

The anti-implantation and abortifacient activity of *plumbagin* alone was effective at 1 mg/100 g body wt in albino rats, without teratogenic effect [46]. However, roots of *P. zeylanica* were found to be potentially toxic when given orally or applied vaginally, which causes termination of pregnancy [41]. Moreover, the hydroalcoholic extract of the leaves had displayed anti-implantation activity up to 95.17% because of its anti-estrogenic activity, where estrogenicity is nullified by anti-estrogenicity action leading to marked alterations in the uterus. The uterus exhibited a reduced amount of glycogen, a thinner endometrium and myometrium, a reduction in lumen size, and a reduction in the number/size of glands. Besides, it also leads to a reduction in vaginal cornification [40].

6. Toxicological Investigations

There have been comprehensive toxicity studies for the topical application of *P. zeylanica* extracts used in Ethiopian traditional medicine, which have been reported by Teshome et al. (2008) [47]. In the repeated dose toxicity tests, the animals of both sexes were found to have a significant increment in their relative testicle weight ($p < 0.05$) and higher blood urea nitrogen and potassium (K^+) levels ($p < 0.05$) after administering the highest tested dose of 1000 mg/kg; however, these biochemical changes were not associated with histopathological findings. Generally, the dermatotoxicity studies show that the effects of toxicity of *P. zeylanica* are mild and confined to mild skin irritation.

The roots of *P. zeylanica* have been shown previously as powerful poisons for oral administration and applied on the cervix in order to terminate pregnancy [27]. In contrast to the earlier report, methanolic extracts of *P.*

zeylanica root tested in rabbits show very few signs of dermal toxicity and have no observable dermal effect [48]. Moreover, it has a protective effect in vivo towards cyclophosphamide-induced oxidative stress and genotoxicity in Swiss albino mice [49].

For oral administration to albino rats, the acute toxicity studies found an LD_{50} of about 65 mg/kg body wt.; the autopsied dead rats showed severe haemorrhages in inner organs, suggesting systemic toxic effects in a higher dose [50]. Also, it has been reported that *plumbagin* from *P. zeylanica* has a potent biological activity, and this compound has been proposed to be one of the active constituents in the design of a new insecticide [48].

Genotoxic Effects

Plumbagin is the major naphthoquinone in roots of *P. zeylanica*. It was also reported to cause micronucleus formation in all tested doses (4, 8, and 16 mg/kg body weight) and showed toxicty towards the bone marrow cells of Swiss albino mice. Higher doses of *plumbagin* (8 and 16 mg/kg) caused a significant inhibition of GST activity, which shows oxidation-stress-mediated genotoxicity.

But interestingly, it is observed that isolated *plumbagin* is showing genotoxic effects, while alcoholic extract of roots of *P. zeylanica* exhibits protection against cyclophosphamide-mediated genotoxicity. Sivakumar et al. (2006) [49] showed that there was a marked decrease in the number of micronucleated polychromatic erythrocytes (MN PCE) and an increase in PCE/NCE ratio in bone marrow, and there was a decrease in lipid peroxidation and increased antioxidant profile in the animals treated with the extracts of roots. From these observations, we may conclude that the composite phytochemical content of the whole extract of the roots protects against the genotoxic effect of the isolated compound.

Another example for this dual role was provided by Demma et al. (2009) [51], where *plumbagin* at a non-DNA-damaging concentration inhibited both catechol-induced DNA damage with NQNO and catechol by acting as an antioxidant. Further toxicological studies of *plumbagin* by Teshome et al. (2008) [47] stated that the primary irritation index was 2.00 in rabbits. No sensitization was noted with *plumbagin* in mice even with 4 and 10 mg/mL, and there was no gross dermal toxicity in rats except a slight difference in the gain of body weight in female rabbits.

7.Conclusions

In this review, a documented medicinal perspective of *P. zeylanica* Linn., a promising plant with high antifertility efficacy (supported by traditional and scientific claims), is given. It is also documented by the presented studies that *P. zeylanica* possesses reversible anti-ovulatory, anti-implantation, and hormonal regulatory effects, which are primarily attributed to active constituents like *plumbagin* and other naphthoquinones. It has been strongly recommended to use botanically confirmed, authentic, and well-processed plant material and to use well-standardized plant extraction procedures and proper storing conditions of the extracts to ensure consistent and effective biological actions. This manuscript is concluded with the compilation of analytical methods available for detection and estimation of *plumbagin*, a significant phytochemical marker for the detection of the authenticity of the plant *P. zeylanica*. This compilation provides an organized overview of the antifertility efficacy of the plant from a scientific perspective and establishes the relevance of *P. zeylanica* to continued reproductive and other research. The review also pointed out that plant-derived fertility regulators provide simple and cost-effective means, particularly for developing countries where access and economic feasibility of modern contraceptive approaches still remain a significant problem. However, present data has only been shown by the experimental studies. Further studies of dose standardization, safety of the drug, toxicity of the drug, pharmacokinetic profile, and clinical investigation are required to explore the potential of *P. zeylanica* for fertility regulation.

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