REVIEW ARTICLE

# Malaysian *Phyllanthus sp*: An Updated Review of Their Impacts on The Reproductive Functions and Fertility

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**ABSTRACT**

*Phyllanthus* belong to the Phyllanthacea family, which consists of 60 other genera and about 2000 species. *Phyllanthus* contains numerous active compounds, such as alkaloids, flavonoids, coumarins, polyphenols, tannins, triterpenes, and sterols. Several studies have shown that *Phyllanthus* species have pharmacological effects. These include the properties of antioxidants, antimicrobials, anti-diabetic, anti-cancer, anti-hyperglycemic, antispasmodic, and anti-hepatotoxic. In Malaysia, there are about 20 species of *Phyllantus* plants. However, only nine species were scientifically proven to improve health, mainly reproductive functions, and fertility. This review aims to summarize the current literature regarding Malaysian *Phyllanthus* species and discuss how they impact reproductive functions and fertility.
**Keywords:** : Malaysian *Phyllanthus*, Health impacts, Reproductive functions, Fertility

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## INTRODUCTION

Malaysia's rainforest is one of the richest tropical rainforests globally, with various species of flora and fauna. Its green biodiversity has allowed many plant species to grow. These include herbs, lichens, flowers, fruits, shrubs, and many more. Among them are numerous species of medicinal plants that possess high medicinal value. One of the genus that possesses excellent diversity of secondary metabolites is the genus *Phyllanthus*. A number of plants in the genus *Phyllanthus* have long been used in herbal formulations. Traditionally, herbs are used to treat various health conditions such as digestive problems, kidney stones, liver diseases, viral infection, genitourinary infections, hypertension, respiratory illnesses, and skin conditions (1,2). In recent years, several studies on the ability of different bioactive components in *Phyllanthus* have been undertaken. Some of the potentials reported are antioxidant activity, anti-diabetic, anti-cancer, anti-mutagenic, anti-viral, and anti-obesity properties (3–5). However, little scientific evidence currently supports the use of *Phyllanthus* on reproductive functions and fertility.

Humans are exposed to dozens of chemicals and pollutants, which can perturb homeostatic imbalances and alter normal biological functions. Exposure to environmental pollutants is suggested to be one of the causes of chronic diseases such as cardiovascular diseases (CVD), neurodegenerative diseases, autoimmune disorders, musculoskeletal diseases, reproductive problems, and infertility (6). More interestingly, stress has also been a significant cause of infertility by exhibiting testosterone suppression, reducing spermatogenesis and libido, contributing to sexual dysfunction (7). Medication and surgery are both used in treating sexual dysfunction. Herbal therapies, however, are a plausible solution for individuals who seek to increase their sex drive due to the existence of reliable contemporary treatments. In many countries, alternative medicine utilizes various trees and shrubs as reproductive stimulants to enhance couples' reproductive performance. These include *Eurycoma longifolia, Terminalia catappa, Lepidium meyenii, Tribulus terrestris, Montanoa tomentosa, Allium sativum, Alpinia galangal, Anacardium occidentale, Anacyclus pyrethrum, Butea frondosa, Caesalpinia benthamiana, Cannabis sativa, Chlorophylum borivilianum, Citrullus lanatus, Ginkgo biloba, Hibiscus sabdariffa,* and *Fadogia*

*agrestis* (8). In recent years, studies reported that some of the active compounds obtained from the *Phyllanthus* contribute to improving reproductive functions and enhancing fertility in males and females (9). Therefore, this review focuses on Malaysian *Phyllanthus* species and their impacts on male and female reproductive functions and fertility.

Botanical perspectives of Malaysian *Phyllanthus* and its common active compounds

*Phyllanthus* are a very diverse genus of flowering trees, shrubs, and spurge family herbs (Euphorbiaceae). The plants are deciduous and floriferous with flattened green roots, which acts as leaves called phyllodes. Some species have leafy twigs, with white or reddish flowers cover the stalk (1). It has been shown that most herbs of the genus *Phyllanthus* contain different secondary metabolite combinations. Phytochemicals synthesized from all these plants include flavonoids, polyphenols, and lignans (10).

There are approximately 20 species of *Phyllanthus* in Malaysia, namely *Phyllanthus albidiscus, Phyllanthus emblica, Phyllanthus niruri, Phyllanthus debilis Phyllanthus amarus, Phyllanthus chamaepeuce, Phyllanthus gracilipes, Phyllanthus columnaris, Phyllanthus elegans, Phyllanthus filicifolius, Phyllanthus gomphocarpus, Phyllanthus columnaris, Phyllanthus oxyphyllus, and Phyllanthus pachyphyllus* (2,11). Only two of *Phyllanthus*'s described species, *Phyllanthus filicifolius* and *Phyllanthus watsonia*, are endemic to Malaysia (11). Of the twenty species described, the nine species are *Phyllanthus amarus, Phyllanthus niruri, Phyllanthus columnaris, Phyllanthus emblica, Phyllanthus recticulatus, Phyllanthus debilis, Phyllanthus urinaria, Phyllanthus watsonii,* and *Phyllanthus pulcher* have been thoroughly investigated. Researchers attempt to unravel the plants' medicinal properties, exposing their hidden potential, followed by claims of additional beneficial health effects.

a. *Phyllanthus amarus*

*Phyllanthus amarus* has been found in the Bahamas, Brazil, China, Ghana, India, Malaysia, Nigeria, the Philippines, Thailand, and West Africa. It's locally referred to as Dukung Anak (12). *Phyllanthus amarus* has been commonly used as an ethnomedicine in different countries such as India to treat jaundice, malaria, prevalent diseases, in Nigeria for stomach pain treatment, and in Brazil to treat fever and kidney problems (13,14). It is used to treat diabetes, hypertension, diarrhea, and poisonous insect bite antidote in Malaysia (2). Alkaloids, dihydrosecurinine, tetrahydrosecurinine, securinine, securinol, phyllanthine, allosecurin, norsecurinine, quercetin, quercetin, 4-hydrosecurinine, 4-methoxydihydrosecurinine, 4-methoxytetrahydrosecurinine, epibubbialine, and isobubbialine are some of the active compounds found in *Phyllanthus amarus* (15).

b. *Phyllanthus emblica*

*Phyllanthus emblica* is also known as Pokok Melaka and can be found in China, Malaysia, India, and Indonesia. It has been widely used in many local herbal medicines due to its anti-inflammatory and antipyretic effects. The fruit is used as a tonic beverage, infertility treatment, and cancer (3,10). Gallic acid, D-fructose, C-fructose, myo-inositol, coumarins, ellagic acid, gibberellin, kaempferol, astragalin, leucodelphinidin, quercetin, isoquercitrin, rutin, and lipids are active compounds present in *Phyllanthus emblica* (10).

c. *Phyllanthus niruri*

*Phyllanthus niruri* is native to the Amazon rainforest, including South East Asia, Southern India, China, and other tropical regions. It is known locally as Dukung Anak. It is historically used as anti-hyperglycemic, antispasmodic, anti-hepatotoxic, anti-viral, anti-bacterial, laxative, diuretic, carminative, antimalaria, jaundice, hepatitis B, cough, pneumonia, diarrhea, vaginitis, tumors, and kidney stones (2,16). Some of the active compounds present in *Phyllanthus niruri* are nirurine, securinine, phyllanthine, gallic acid, corillagine, ellagic acid, quercetin, quercitrin, isoquercitrin, rutin, astragalin, nircetin, hypophyllanthin, niranthin, niretralin, lintetalin, hydroxynirathin, isolintetralin, linnanthin, nirphyllin, ricinoleic acid, catechin, epicatechin, gallocatechin, epigallocatechin, gallate, lupeol, phyllantenol, phyllathenone, and phyllantheol (1,4).

d. *Phyllanthus reticulatus*

*Phyllanthus reticulatus* is present in Africa, Bangladesh, China, Southeast Asia, Thailand, India, and Northern Australia. Locally, it's known as Kayu Darah belut. Traditionally, *Phyllanthus reticulatus* has been used as a diuretic to encourage fertility in women, treat piles and hemorrhoids, remedy hookworms, toothache, venereal sores, and smallpox syphilis, asthma, and sore throat (17). 1-octacosanol, 1-teracosanol, 1-tricosanol, pyrogallic acid, gallic acid, ellagic acid, coumaric acid, tricin, pirorisinol, beta-sitosterol, daucosterol, stigmasterol, friedelin, 21-hydroxyfriedelin, friedelanol, and epi-friedeol are some of the active compounds present in *Phyllanthus reticulatus* (1,17).

e. *Phyllanthus urinaria*

*Phyllanthus urinaria* can be found in subtropical and tropical regions such as China, India, Thailand, Trinidad and Tobago, and South America. The plant was used to treat liver damage, hepatitis, jaundice, kidney diseases, enteritis, diarrhea, and dropsy in traditional oriental medicine. Experimentally, some of the active compounds found in *Phyllanthus urinaria* are hexacosanoic acid, phyllanthin, phyllanthidine, alkanols; triacontanol, gallic acid, phyllurine, ellagic acid, methybrevifolin carboxylate, trimethyl ester dehydrochebulic acid, astragalin, quercetin, quercitrin, isoquercitrin, rutin, kaempferol, lactone glycosides, phyllanturinolactone, and lignanolactone (1,18).

f. *Phyllanthus watsonii*

A small shrub that grows to about 15 cm in height, *Phyllanthus watsonii* is usually found near fast-flowing rivers. The species is native to Rompin Endau, Malaysia. It has been used to treat cancers, including cancers of the cervix, liver, lungs, macrophages, uterus, stomach, breast, and colon. β-Sitosterol-β-D-Glucoside, β-sitosterol, lupeol, friedelin, glochidone, and glochidonol are some of the active compounds present in *Phyllanthus watsonii* (1,19).

g. *Phyllanthus columnaris*

*Phyllanthus columnaris* is a deciduous tree commonly found in low-lying inland forests in India (Andaman Islands), Bangladesh, Myanmar, Thailand, and Malaysia. The plant is used for various ailments, including smallpox, syphilis, asthma, and diarrhea. Some of the compounds that have been isolated from *Phyllanthus columnaris* are taraxerol, taraxerone, friedelin, lupanyl acetate, lupeol, stigmasterol, lupeol acetate (1,20,21)

h. *Phyllanthus debilis*

*Phyllanthus debilis* can be found in a waste spot area. It is distributed in Thailand, India, Sri Lanka, Indonesia, and Malaysia. Traditionally, it is used to treat various diseases, including diabetes, jaundice, sickle-cell anemia, diarrhea, wounds, inflammation, intestinal worms, scabies, gall stones, and kidney stones. The compounds isolated from *Phyllanthus debilis* are hypophyllanthin, furosin, geranin, rutin, β-sitosterol, and gallic acid (1,22).

i. *Phyllanthus pulcher*

*Phyllanthus pulcher* is an ornamental plant that has been used for problems with the stomach. It is known as Naga Buana as well. Historically, it is a cure for eye infections, nasal ulcers, abscesses, pruritus, problems with fever and kidneys, stomach pain, and hypertension. Terpenoids, glochidone, glochidonol, and lupeol are some of the compounds isolated from *Phyllanthus pulcher* (1,23).

**The mechanism involved in reproductive functions and fertility**

Some medicinal plants have been shown to have an aphrodisiac activity that can enhance desire for sex, boost libido, improve sexual performance and reproductive functions, and increase sexual duration. Interestingly, the reason behind this is that the central nervous system controls and regulates sexual desire. The mechanism involves incorporating tactile, olfactory, and mental stimuli. In some cases, it provides immediate actions to consumers by improving sexual performance and libido. It may affect blood flow across the genital region, for instance, and then increase the duration of sexual activity. Besides, other types of aphrodisiac plants consist of psychopharmacological compounds that cross the *blood-brain's barriers* and induce some regions of sexual arousal. These include the compounds' interference with neurotransmitters, hormones, pheromones, and drugs (8,24).

**Positive impacts of Phyllanthus on reproductive functions and fertility**

A brief report of current research on *Phyllanthus* on reproductive functions and fertility potential is described as follows. Ojezele et al. (25) reported that treatment with *Phyllanthus amarus* seed extract showed a substantial increase in serum and semen testosterone levels, sperm parameters, and morphology in *Plasmodium bergheii* treated mice. In another study by Obianime and Uche (26), the methanol extracts of *Phyllanthus amarus* caused a non - significant enhancement in the levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thereby increasing libido and male reproductive function. Moreover, Azubuike et al. (27) reported that the *Phyllanthus amarus* extracts could increase serum testosterone levels, epididymal sperm concentration, and sperm motility. Phyllanthin, a significant lignan derived from *Phyllanthus amarus*, demonstrated strong apoptosis activation in cervical cancer cells (28).

In addition, Priya and Islam (3) stated that *Phyllanthus emblica* increases the number of sperm and produces an aphrodisiac effect in males. At the same time, it preserves normal and stable menstruation in females, improves the reproductive tissue and ovaries, strengthens the uterus, prevents white discharge, relieves vaginitis, and protects the reproductive system. Iamsaard et al. (29) demonstrated that *Phyllanthus emblica* significantly improved testicular weight, increased levels of testosterone hormone and sperm concentration, and mitigated testicular impairment in valproic acid-treated rats. On another note, *Phyllanthus emblica* was found to protect the genotoxicity caused by cyclophosphamide in mice germ cells by substantially increasing the percentage of defects of the sperm head (30).

In a study performed by Pryuttma and Parimal (31), they emphasized that *Phyllanthus emblica* extract treatment was found to mitigate endosulfan's toxic effects by improving testicular weight, protecting seminiferous tubules, germinal epithelium, Sertoli cells, and spermatogenic cells from injury. The effects of *Phyllanthus emblica* on males were also studied by Arun et al. (32). Their study reveals that *Phyllanthus emblica* has significantly increased sperm concentration, testosterone levels, and StAR protein expression. Besides, *Phyllanthus emblica* altered the tyrosine-phosphorylated protein in the testis, decreased corticosterone and MDA levels, reduced head defects in sperm, and acrosome-reacted sperm in rats.

Data from Madhavi et al. (33) also revealed that a significant reduction in the number of sperm head defects had been recorded in heavy metal-treated animals, suggesting that *Phyllanthus emblica* contributes to modulating heavy metal mutagenesis in mammalian animals. In another research (10), the estrogenic and gonadotropic activities of *Phyllanthus emblica* fruits affecting females' reproductive parameters

were reported. The petroleum ether showed the most potent estrogenic and follicle-stimulating hormone-like activity, and *Phyllanthus emblica* chloroform fractions demonstrated strong luteinizing hormone-like [LH] activity. In addition, neither estrogenic nor gonadotropic activities were seen in the ethyl acetate fractionated extract.

According to Giribabu et al. (34), the treatment of *Phyllanthus niruri* leaf aqueous extract to rats in the diabetic group could mitigate oxidative stress in the kidneys and testes, preventing reduced amounts of endogenous antioxidant enzymes. In another *Phyllanthus niruri* study, Jia et al. (4) showed that corilagin derived from *Phyllanthus niruri* serves as a natural, promising therapeutic agent against the growth of ovarian cancer cells by targeting the TGF-β/AKT/ERK/Smadad/Smad/Smad/TGF signaling pathways.

Young et al. (35) have shown that phyllanthusmins from *Phyllanthus poilanei* serve as an inhibitor of late autophagy and primary antitumor efficacy through the autophagic pathway against ovarian cancer. Other than that, Ndeingang et al. (36) stated that by decreasing cystic follicles, luteinizing hormone (LH), and testosterone levels, *Phyllanthus muellerianus* could alleviate reproductive functions, hormonal levels, and structural changes in PCOS rats, increase estradiol, and restore the estrus cycle after 14 days of treatment. In another scenario (5), the administration of *Phyllanthus fraternus* aqueous extract increased lipid peroxidation levels. It showed a protective action against cyclophosphamide-mediated antioxidant depletion as restoring male mice's histopathological architecture.

**The negative impacts on reproductive functions and fertility**

Besides having a good effect on reproductive functions and fertility, there are also studies on *Phyllanthus*, which bring about adverse effects to the reproductive functions of both men and women. Research by Bakare et al. (37) highlighted that by increasing the intensity of micronucleated polychromatic erythrocytes and sperm abnormalities, the aqueous extract of *Phyllanthus amarus* possessed metabolites that are able to cause systemic and damage to DNA in the mouse and rat. The results of Ataman and Sakpa (38) have generally established the anti-fertility effects of *Phyllanthus amarus* on ovarian morphology and functions, which involves no implantation, resorption, and litters. Other than that, the levels of estrogen, FSH, LH, and progesterone have significantly reduced, impaired folliculogenesis, increased follicles of the atretic ovary, and degenerative ovarian stroma.

More interestingly, a subchronic course of *Phyllanthus amarus* administration in rats possessed anti-fertility activity and has shown a substantial reduction in testes, epididymides weight, and sperm parameters (39). The findings are consistent with past work by Etta et al. (40), which stated that the extract of *Phyllanthus amarus* affects the count, morphology, and motility of epididymal sperm of animals treated with *Phyllanthus amarus*. On another note, the aqueous extract of *Phyllanthus amarus* was reported to have an abortifacient effect and decreased the implantation time frame (41). In the Ataman and Ikediashi study (42), the rats treated with ethanolic extract of *Phyllanthus amarus* showed various testicular degeneration degrees, with a significant reduction in total sperm count, sperm concentration, and survival, and unflattering spermatozoa in the lumen of seminiferous tubules. The results also showed the differentiation and production of germ cells were stopped in the lumen. Ronnie (43) discovered that oral treatment with *Phyllanthus amarus* aqueous extract lowered the fertility index, reduced testicular and prostate weight, reduced sperm parameters, impeded spermatogenesis, and have had an estrogen-like effect on male rats.

*Phyllanthus niruri* is another *Phyllanthus* species that exhibits anti-fertility properties. According to Ezeonwu (44), the treatment of *Phyllanthus niruri*'s aqueous crude extract contributed to a significant reduction in seminal fluid fructose level and sperm parameters. On another note, *Phyllanthus niruri* extract was found to decrease mature spermatozoa and cause harmful testes (16). Degenerative effects on sperms and a significant reduction in testosterone, estrogen, and progesterone levels were also reported in males treated with *Phyllanthus niruri* (45). Moreover, the extract of *Phyllanthus niruri* was demonstrated to alter somatic gonadal development, modified the corpus luteum function on synthesis and secretion of estrogenic hormones, reduced the number of embryos, and cause morphophysiological dysfunctions, which leads to miscarriage (46). Paula et al. (47) suggested that fetal macrosomia, excessive ossification areas, impaired maternal kidney weight, and morphology, and reduced offspring weight were influenced during fetal development by treating *Phyllanthus niruri* aqueous extract.

**Common active compounds in Phyllanthus that affect reproductive functions and fertility**

Interestingly, this review found three common active compounds in *Phyllanthus*, namely rutin, quercetin, and β-sitosterol, that have been actively studied and reported. However, there are other active compounds in the species that are yet to be discovered or studied on, such as phyllantine, phyllantidine, gallic acid, corrilagin, ellagic acid, kaempferol, astragalin, isoquercitrin, phyllanthin, hypophyllanthin, niranthine, niretraline, isolintetraline, phyllester, daucosterol, geranin, furosin, lupeol, and lupeol acetate.

**a. Rutin**

Rutin is a flavonol glycoside that is important to protect capillaries, prevent arteriosclerosis and high blood pressure. Studies confirmed that rutins are potent antioxidants that combat free radicals. Akondi et al. (48) found that rutin has shown protective effects on sperm against gentamycin, affecting sperm development, ototoxicity, and nephrotoxicity. In another study, rutin

mediated GSH and GSH-Px activities to blockade against oxidative stress in rats by elevating testicular GSH-peroxidase and GSH activities (49).

Furthermore, Mehfooz et al. (50) revealed that rutin significantly decreases the adverse effects of restraint stress by inducing the production in testes of cleaved PARP1 and cleaved Caspase-3. Other findings by Jahan et al. (51) showed that the effect of cisplatin on cellular damage and sperm parameters in male rats was alleviated by rutin co-therapy. Jamalan et al. (52) illustrated the impact of rutin treatment on the metals' adverse effects on sperm motility. Daim et al. (53) reported that animals' co-treatment with rutin enhances spermatogenesis, sperm count, motility, viability, and morphology. Interestingly, a study by Elsawy et al. (54) showed that rutin reversed the impaired sperm quality caused by $CCl_4$ through a decrease in the levels of sperm production-related hormonal mediators, including serum testosterone, LH, and FSH.

Other results indicated that the mitochondrial activity, which correlated with sperm motility maintenance, was stabilized and prevented following rutin administration (55). There is a significant improvement in male sexual activity and sperm parameters of the diabetic animal models after five weeks of intervention with rutin. Rutin was also attenuated by impaired serum testosterone and penile cGMP content, improved sexual functionality, and protected against diabetic-induced testicular injury (56). Taken together, the outcomes from Jianhua et al. (57) revealed that rutin alleviates $H_2O_2$-induced oxidative damage and apoptosis in Leydig cells by stimulating PI3K/Akt signal pathways and helping to reduce oxidative stress associated with male infertility.

**b. Quercetin**

The permeability of the blood vessels, including capillaries, can be improved and modulated by quercetin. This compound has anti-aggregant, anti-cancer, anti-fungal, anti-glaucoma, anti-inflammatory, antioxidant, antiseptic, and antispasmodic activities. Moretti et al. (58) have confirmed that quercetin's protective capacity for sperm motility and viability against lipid peroxidative damage in human ejaculated semen caused by tert-butyl hydroperoxide (TBHP). Mazroa (59) also demonstrated the protective effects of quercetin against BPA-induced damage on sperm and cauda. Another finding indicates that quercetin therapy significantly reduced MDA production and mediated the detrimental effects of metals on sperm (52).

Quercetin showed scavenger properties and a protective effect on human sperm against ultrastructural damage of lipid peroxidase, according to Mazzi et al. (58). Besides, quercetin inhibits the wobble of goat sperm in frozen semen experiments and increases linearity and straightness (60), enhances sperm motility and viability, decreases DNA fragmentation, and reduces the concentration of ROS in cryopreserved human semen (61). Supplementation with quercetin (15 mM) in red fowl extender has also been documented to enhance sperm motility, viability, the integrity of plasma membrane and acrosome, condensation of chromatin, and mitochondrial function during cryopreservation (62).

Diao et al. (63) stated that progesterone-induced sperm motility and acrosome reactions were improved by quercetin in male sperm leukocytospermia. Karabulut et al. (64) reported that quercetin enhanced sperm motility in asthenozoospermia cases. In other notes, quercetin treatment corrected the degree of male sexual activity and improved sperm parameters in rats with diabetes (56). Mehranjani (65) observed that quercetin could eliminate dexamethasone's adverse effects on sperm and biochemical parameters in mice.

**c. β-Sitosterol**

ß-Sitosterol is one of the phytosterols with similar chemical structures to that of cholesterol. It is white, dry, and waxy with a distinctive odor. Moreover, β-Sitosterol is alcohol-soluble and hydrophobic. β-Sitosterol demonstrated aphrodisiac ability in a study using sexually naive rats (66). Another study reported significant improvements in sperm viability, growth, spermatogonium, fertility index, litter size, Leydig cells, and spermatozoa in essential oils containing β-sitosterol (67).

## CONCLUSION

In conclusion, *Phyllanthus* plants possessed many beneficial effects on male and female reproductive functions and fertility. Despite the limited studies available and the challenges with human intervention treatments, there is a presumption that *Phyllanthus* plants will benefit from human intervention trials, especially on reproductive health, thus reflect a potential being used as a nutraceutical. Therefore, additional studies are needed to fully understand the mechanisms and complicated relationship between *Phyllanthus* active compounds with all reproductive parameters and other systems to corroborate any possible health benefits and adverse effects. Furthermore, more outcomes from pharmacological screenings, phytochemical studies, clinical studies, and epidemiological data are essential to confirm a substantial connection between the usage and health benefits of *Phyllanthus* plant extracts and to promote conventional uses, and to establish leading compounds.

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