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REVIEW ARTICLE

Exploring the Therapeutic Potential of *Caesalpinia bonducella* for Male and Female Reproductive Health: A Comprehensive Review

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Abstract

This review explores the potential of *Caesalpinia bonducella* Linn., particularly its seeds, known as '*bounducella*' or 'little ball', and its impact on diverse pharmacological activities. Its use in treating various illnesses, including male and female reproductive health, has been investigated. The data, gathered from reliable sources worldwide, transcend language barriers and align with Indian Ayurvedic and Siddha Pharmacopoeias. This article has compiled the pharmacognostic and phytochemical profiles of the seeds, emphasizing their influence on reproductive health, potentially aiding in PCOS management and addressing hyperandrogenism. Additionally, the seed extract of this plant has abortifacient and anti-fertility effects, suggesting that it is a potential alternative to Mifepristone. Nevertheless, further *in vivo* and *in vitro* research on seed constituents is essential for developing lead molecules for use in allopathic treatment.

Keywords: Anti-progesterogenic, Anti-spermatogenic, *Caesalpinia bonducella,* Male Contraceptive, Neuroprotective, PCOS, Testosterone Booster

1. Introduction

Around the globe, herbs play a considerable role in the health sector for both humans and animals. Herbal ingredients in nutraceutical supplements are not only consumed for diseased states but also used to maintain health. Therefore, one should be familiar above all with the chemical constituents that give medicinal herbs their therapeutic effects. Plant-based research is more advanced than ever before, and plant-related knowledge is employed in numerous traditional systems of medicine. Herbal medicinal plants are widely used because "greenery medications" are harmless and more trustworthy than man-made drugs; they are expensive and can produce adverse effects. Additionally, herbal medicine or plant medicines, extracts, and isolated biomolecules have their pharmacological activities and values. As a result, these medicinal plants are used to treat and prevent a variety of diseases and disorders[1-3].

Figure 1 shows *Caesalpinia bonducella* Linn., (Fabaceae/Caesalpiniaceae) and the synonyms are *C. bonducella* Linn., Flem., *Caesalpinia crista,* Prowazek., *Caesalpinia sogerensis,* Baker f., and *Caesalpinia sepiaria* Auct. non Roxb., and *Caesalpinia bonducella,* Griseb., are generally known as Bonduc nut, nicker nut, and fever nut[4]. It is a prickly shrub that grows in tropical

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regions around the world, especially in Sri Lanka, India, and the Andaman and Nicobar Islands. The portions of fever nut plant portions have significant medicinal value, so they have been used in traditional medicine. The word '*bounducella*' derived from the Arabic word '*bounduce*' is also called 'tiny ball' and it determines that the seeds of this plant are spherical. This seed is grey and resembles eyeballs. This plant also has been used in *Siddha* medicine. The seeds are used to treat psoriasis in the Malabar region of Kerala and Pakistan[5].

Bonduc nut plants have been reported to contain secondary metabolites such as glycosides, alkaloids, saponins, tannins, flavonoids, and terpenoids. Earlier studies have shown that it has the following pharmacological activities; adaptogenic, anthelmintic, anti-inflammatory, antipyretic, analgesic, anti-amyloidogenic, anti-filarial, antioxidant, nootropic, immunomodulatory, hypoglycemic, hepatoprotective, antimalarial, neuroprotective, diuretic, antifertility, antiviral, antifungal, and anticancer activities[6-8]. This review aims to disseminate updates on the potential of Bonduc nuts for treating communicable and noncommunicable illnesses, including male and female reproductive health. The present investigation also identified future research requirements. All the relevant data were compiled from various web sources such as Google, PubMed, the Wiley Online Library, Science Direct, Springer, Reaxys, Sci Finder, and Taylor and Francis. Furthermore, data on therapeutic usage were crosschecked against the *Ayurvedic* and *Siddha* Pharmacopeias of India without any language boundaries.

2. Description of Plant

2.1 Taxonomy[6,7]

Kingdom: Plantae
Phylum: Magnoliophyta
Division: Magnoliopsida
Class: Angiospermae
Order: Fabales
Family: Fabaceae
Genus: *Caesalpinia*
Species: *bonducella*

Figure 1. *Caesalpinia bonducella* Linn.

2.2 Regional Name

Tamil name: *Kalarciver*, *Kalarcikkolunthu*, *Kalarcipparuppu*, *Avil*, *Kazarchi*, *Kalarchikai*, *Kazharchikkaai*; Telugu name: *Gaccakayai*, *Mulluthige*; English name: Niker nut, Niker seed, fever nut, Bounduc nut; Hindi name: *Sagar Gota*, *Kantikaranja*, *Kantkarej*; Bengali name: *Nata*; Urdu name: *Akitmakit*; Marathi name: *Gajaga*; Sanskrit name: *Valli*, *Vita Palaranja*, *Kantakini*, *Kakachika*, *Latakaranja*, *Kuberaksah*, *Puttikah*; Persian name: *Khayabe-i-iblas*; French name: *Bois*[6,7].

2.3 Habit and Habitat

Bonduc nut grows to a height of 10 metres in shadow as well as in open space. This plant may be found up to 1000m in the Himalayas and the wild throughout India's plains on wastelands, sea sides, or watersides. This plant may also be found in the delta areas of southern, western, and eastern India, especially in the coastal regions of the sea throughout the hotter parts of India. This species grows in Bangladesh, Burma, China, Sri Lanka, Vietnam and Myanmar[6,7].

2.4 Growth and Cultivation

Caesalpinia bonducella Linn., develops quickly at all stages of its life. The seedlings will reach a height of approximately 26 cm after 40 days. Every year, older individuals grow 1 metre or more. This species typically lives along the coast and needs light shade, but it prefers full sun. It can flourish in a broad range of soil pH values, from moderately acidic to alkaline, and can withstand salt sprays, salty soils, and intermittent floods with seawater. Typically, found in coastal vegetation and at better-drained mangrove forest borders, it climbs into the peaks of low vegetation and does well in grassy and herbaceous areas[7].

2.5 Propagation

The plant reproduces naturally and spreads through seeds. Sandy loamy soil provided an ideal environment

for growth. Dormancy can be disturbed by concentrated sulphuric acid and acid-treated seeds germinate completely. As soon as the seeds are planted, irrigation is needed. Seedlings protrude within 3-4 weeks and reach their full height at 2-12 m[7].

2.6 Pharmacognostic Studies

2.6.1 Macroscopic Features

The botanical descriptions are as follows: evergreen foliage; deep and tap roots; and hard and woody stems. Leaves: Bipinnate compound; ovate shaped; alternate arranged; green in colour; glossy surface. The seed type is dicot, which is a characteristic odour and bitter in taste[7].

2.6.2 Leaves and Leaflets

The leaves of this plant are large, branched, leafy and basal appendages; with a length of 30-60 cm; and a prickly leaf stalk. As a result, pinnae are 6-8 pairs of 5-7.5 cm long, and a set of hooks is changed near the base of the primary leaf axis equipped with strong, recurved spines, that are sharp, and separated into 4 to 8 pairs of secondary branches. There were 6-9 pairs of leaflets, 2-3.8 by 1.3-2.2 cm, elliptic-oblong, membranous, obtuse, highly mucronate, glabrous above, and puberulous underneath; the petiolules were extremely pointed, and the stipels contained short hooked spines[6,9].

2.6.3 Seeds

The seeds are very dry and round in shape; the seed coat is too hard, shiny, and smooth and the hue ranges from greenish to ash grey, as shown in Figure 2. As a result, the plant is pierced by circular and vertical weak crack markings, generating a consistent rectangle to square all over the surface of the seed, which appears oblong and has a length of 1.3 cm. At the receding edge of the seeds, an enlarged hilum with stalk remnants lay in the heart of the black patch. There is an absence of endosperm in seed (exalbuminous). The seed kernel surface is wrinkled and flattened, measuring approximately 1.23 to 1.75 cm in diameter. A micropyle scar can be found at the tip of the kernel, separating the embryo's two cotyledons (Figure 3).As a result, the plemule radical axis is cylindrical, straight and thick. The flavour of the seed is extremely bitter, and the odour is sickening and repulsive[6].

Figure 2. Fresh seed pod of *Caesalpinia bonducella* Linn.

Figure 3. Fresh seed kernels of Bonduc nut.

Figure 4. Fresh seed with a pod of Bonduc nut.

2.6.4 Flowers

As shown in Figure 5, flowers in terminal and supraaxillary racemes are dense at the top and lax downwards, 15-25 cm long; pedicels are exceedingly short in the bud, elongating to 5 mm in bloom and 8 mm in fruit (Figure 5). As a result, the plant begins flowering in August-mid and continues until the 2nd week of April. Flowering occurs mostly between August and September, and it is modestly common from January to mid-April. Flowering has ceased from the latter week of April to the first week of August[6].

Figure 5. Flower of *Caesalpinia bonducella* Linn.

2.6.4 Fruits

The fruits of this plant are inflated pods with strong spines. The pods are rectangular, short-stalked, and measure 5.0 to 7.5 cm by approximately 4.5 cm. terrorizingly equipped with wiry prickles.1-2 seeds per pod[6] (Figure 4).

2.6.5 Microscopical Features

The plant has elongated testa in the outer single row, which are very slender, transparent, and compactly organized cells that form palisade layers. The cells of this plant are hexagonal on the surface and have thick walls that are pectin-rich. The subepidermal zone is made up of two or three layers of thick-walled cells. The outer layer of these osteo-sclereids may contain brown-coloured substances; elongated vascular tissue is also observed in the bottom portion of this zone. The cells near the inner vascular elements gradually condense and are thus rounded at the inner edge; cotyledons represent an outer single epidermal layer of small, isodiametric cells and inner parenchymatous ground tissue cells in solid oils with evenly distributed empty cavities[10-12].

The seed is made up of several layers of vertical, columnar luminal cells. As a result, the columnar palisade cells seemed to be powdery, but parenchyma cells were black in colour, with strong bone-moulded walls and starch-loaded granules inside the cells. The seed powder is light yellow to mustard brown in colour, gritty and free-flowing, and has a bitter flavour and tamarind-like odour. As a result, scalar form thickenings and groups of thin, palisade cells with a light line are present; the height of the groups of cells ranges from 150 to 250µm, squarish cells and up to 150µm long osteosclereids; cotyledon cells (up to 35µm) are present when installed in Sudan III, displaying fixed oil[10-12].

2.7 Traditional Uses

Various plant parts, such as stem, seeds, nuts, bark and roots, are used for medicinal purposes. The seeds of *Caesalpinia bounducella* are used for styptic, anthelmintic, purgative and useful control of colic, inflammation, malaria, leprosy, and hydrocele. Powdered seed ointment and castor oil are used topically to treat hydrocele and orchitis. The seeds are tonic, febrifuge, and antihemorrhagic and the seed oil is used to treat convulsions and paralysis. Powdered *Caesalpinia bounducella* seeds are given orally for the treatment of malaria and patients who are sufferers consume equal amounts of seed powder and pepper powder. The seeds are also taken for snake bite. The seed is combined with powdered pepper, which may work as an expectorant. The burned seed, along with the burnt areca nut and alum, is used as a superior dentifrice to cure spongy gums. The roasted seed is used to treat diabetes in the West Indies[6,7,9].

The seed kernel is used to treat fever, similar to black pepper; it should be taken three times per day, with a dose of 15 - 30 grains for adults; and 3 - 4 grains for children. This roasted kernel decoction is used to treat asthma. Kernel extract, along with ginger, salt, and honey, is given to young people to improve the digestibility of maternal milk because it has a stomachic effect. Kernel paste is prepared to relieve inflammation and boils. The kernel cakes are constructed of 30 grains that have been burned in ghee and are consumed twice a day. They serve as excellent remedies for acute orchitis, ovaritis, and scrofula. The roots of this plant are used to treat fever and anthelmintics in Madagascar. As a result, the bark of the root is used to treat amenorrhoea and cough, and it works as an anthelmintic. The flowers are used to cure urinary problems, Leucorrhoea, piles, and wounds. Leaves and twigs have long been used to treat tumours, inflammation, and liver disorders, as well as toothache. Leaf juice has historically been used to treat elephantiasis and smallpox. *C. bonducella* plant powder was approved by the Indian Pharmaceutical Codex[16]. The suggested amount of powder to decrease fever is 15-18 grains. When taken internally, kernel powder plus goat milk may be useful for treating liver diseases[6,7].

2.8 Used in *Ayurvedic* Medicine and Valuable Parts of the Plants

Rasa (taste): *Tikta* (bitter), *Kashaya* (astringent); *Guna* (properties): *Laghu* (light), *Ruksha* (dry), *Tikshna* (sharp); *Veerya* (potency): *Ushna* (hot); *Dosha*: Pacifies *tridosha; Vipak*: *Katu* The nuts, seeds, bark, leaves, stem, and roots are used for medicinal purposes[6].

2.9 Chemical Constituents

Caesalpinia seeds made with 25.3% protein contained amino acids such asleucine, lysine, isoleucine, threonine, and methionine but tryptophan was absent from the seeds. Amylase, catalase, peroxidase, oxidase, and protease are seed-containing enzymes, and lipase and invertase are missing[7]. The phytosterols found in seed kernels include sitosterol; heptocosane is noncrystalline, bitter glycoside, bonducin, and neutral saponin[9]. The hexane extract of seed kernel oil which contains α-tocopherol (460.21 mg/kg), followed by β-sitosterol, stigmasterol, campesterol, δ-tocopherol, Δ5-Δ7-stigmastenol and avenasterol were found to be major sterols. Linoleic acid is abundant in kernel oil, are as oleic, stearic and palmitic acids[13]. The 32 components that were isolated from the seeds were as follows: α-caesalpin, β-caesalpin, γ-caesalpin, ζ-caesalpin, δ-caesalpin, ε-caesalpin, Casalpinia-F, Bonducellin, Caesalpinin, Neocaesalpin H, Eocaesalpin-P, Cordylane A, Caesalpinin B, Bonducellpin-E, Caesalpinolide-A, 17-Methylvouacapane-8(14), -9(11)-diene, Caesal-A, Caesall-B, Caesall-C, Caesall-D, Caesall-E, Caesall-F, Caesall-G, Norcaesalpinins MC, Caesalpinins-D, and Bonducellpin-D, Caesall H to M[7].

3. Pharmacological Activity

Early research on the seed extract's acute toxicity in albino mice were conducted. The extract's LD_{50} was found to be greater than 2000 mg/kg. and no alterations in the mice's behavioral characteristics were noted[14].

3.1 Antioxidant Activity

Caesalpinia bonducella Linn., seed ethanolic concentrations were used for repression, to quench free radicals to terminate the radical chain reaction and to function as reducing agents. These compounds also contained a good level of phenolic constituents. DPPH was used to confirm that the ethanol leaf extract of *C. bonducella* exhibited potential antioxidant activity. Additionally, the chloroform extract of the seeds has antioxidant properties. These findings showed that antioxidant activity may contribute to plant cytotoxicity, suggesting a possible area for further investigation[15-17].

3.2 Anti-cancer Activity

The pet ether fraction of the ethanolic extract of *C. bonducella* seeds exhibited substantial anticancer activity in the *invitro* anticancer MTT experiment[18].

3.3 Anti-inflammatory, Analgesic and Antipyretic Properties

Treatment with different concentrations of ethanolic seed extract produced substantial ($p<0.05$) antipyretic, anti-inflammatory, and analgesic effects on animal models, which indicates that the ethnomedicinal potential of fever nuts is important for curing pain and swelling-related disorders, supporting its effectiveness as a natural analgesic, antipyretic and anti-inflammatory agent[19].

3.4 Antifungal Activity

Aqueous and ethyl acetate seed extracts were screened for antifungal activity against *Alternaria solani, Candida albicans, Fusarium oxysporum* and *Aspergillus niger*. *C. bonducella* has been reported to be able to manage significant fungal pathogens[20].

3.5 Antifilarial and Antimalarial Activities

Microfilaricidal, macrofilaricidal, and female sterilising effects against *Litomosoides sigmodontis*, as well as female sterilising effects against *Brugiamalayi*, were demonstrated in the *C. bonducella* seed part. It also served as a potential springboard for the creation of new anti-filarial tranquilizers. *Plasmodium falciparum* growth was significantly inhibited by the use of seed extracts[21].

3.6 Neuroprotective Activity

This plant extract reportedly possesses marked acetylcholinesterase, butyrylcholinesterase, Monoamine Oxidase (MAO), and Na^+/K^+ATPase inhibitory activities. The ethanolic and hexane extracts of these plants inhibited acetyl and butyrylcholinesterase (43.32 – 69.94 %), equivalent to the traditional drug donepezil, at a concentration of 50 µg/ml[22].

3.7 Diuretic Activity

Aqueous and methanol extracts of *Caesalpinia bonducella* seeds were tested for diuresis effectiveness in rodents. According to the findings, both the aqueous and methanol extracts significantly increased the amount of urine produced compared to that in the control group, which received the study's standard medication, Furosemide. When taken in greater quantities, both extracts increased potassium elimination while also increasing sodium excretion. Evidence of a dose-dependent increase in urine output suggested that *C. bonducella* seed extracts have diuretic properties[23].

3.8 Antidiabetic Activity

The seed is endowed with antihyperlipidemic and antidiabetic effects. It is used as a form of conventional medicine to treat diabetes; most tribal groups use it to manage blood sugar. A decoction prepared from seed kernel powder is used for the treatment of diabetes in Assam. Seed extract has been shown to demonstrate both hypoglycaemic and hypolipidaemiceffects[24].

3.9 Myocardial Potency of Fever Nut

DOX-induced heart toxicity increased the level of CK-MB, LDH, Creatine Phospho Kinase (CPK), membrane-bound enzymes, nucleic acids, and troponin-T; decreased the lipid profile; and decreased the serum High Density Lipoprotein (HDL). After all the health hazards were perceived in the animal models, treatment with aqueous extract (150 - 300 mg/kg *b. w.*) of the aerial portion of Bonduc nut stopped the changes in the expression of seepage markers; altered the levels of protein, membrane-bound enzymes; and reduced the levels of VLDL, LDL cholesterol, and total cholesterol, with an increase in high-density cholesterol[25,26].

3.10 Anti-cataract Activity

The antioxidant and anticataract characteristics of the seed kernel ethanol extract may be effective at preventing or delaying the formation of cataracts. The extract showed Rat Lens Aldose Reductase (RLAR) inhibitory potential and exhibited antioxidant effects[27]. The hormonal modulation and therapeutic value of fever nuts are demonstrated in Figures 6 and 7.

3.11 Feminine Reproductive Health: Anti-esterogenic Activity, Abortifacient Activity and Anti-fertility Activity

3.11.1 Abortifacient Activity

Caesalpinia bonducella Linn., ethanolic seed extract was tested on pregnant rats from day 12 to day 18, the extract was given once daily, and the treatment had a significant abortifacient effect. The researchers also

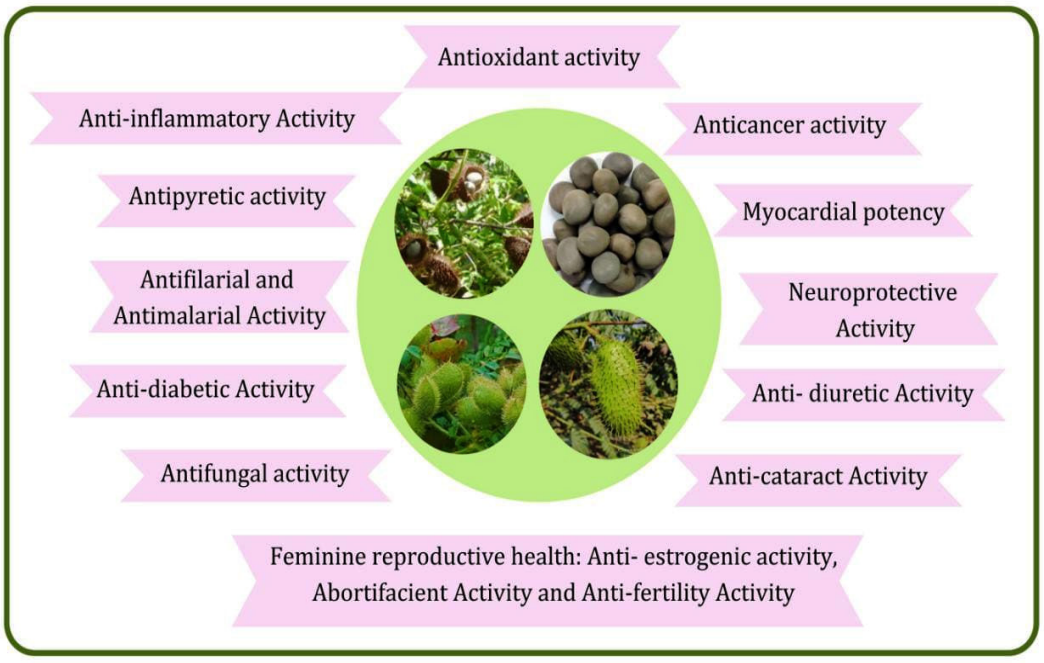

Figure 6. Pharmacological and therapeutic importance of the Boundac nut.

discovered a substantial decrease in maternal weight, number of implant sites, pup weight, implantation index, and number of living foetuses, placental weight, and percentage of foetuses that survived. Histology of the uteri in the seed extract group revealed larger myometrium and thinner endometrium, as well as uterine glands, degenerating cubic epithelial cells, and increased WBC infiltration. The corpora lutea shrank and degenerated in rats given extracts, which was observed in the ovaries. The placentas of rats given seed extract therapy demonstrated degeneration of the junction zone and the labyrinth. Deformed foetuses were observed in the extract treatment group. *C. bonducella* Linn., seeds were discovered to have an abortifacient effect[28].

3.11.2 Polycystic Ovary Syndrome (PCOS)

Many researchers tested the use of the seed extract of *Caesalpinia bonducella* (L.) Roxb., in PCOS-induced animal models[29]. An earlier study showed that female albino rats were used to study the effects of *C. bonducella* (L.) Roxb., extract on letrozole-induced PCOS. Researchers observed that *C. bonducella* could successfully restore hormone levels of testosterone, estrogen, and progesterone to perform self-protective regulation. The levels of triacylglycerides, LDL, VLDL, and TC in PCOS rats treated with plant extracts significantly decreased, while the levels of high-density lipoproteins increased[8,26].

In PCOS-induced albino female Wistar rats, which are animal models, there was a decrease in testosterone volume and an increase in the efflux of female hormone ingredients, which promoted ovarian development and helped to manage menses. The seed extract of *C. bonducella* produced significantly lower levels of testosterone while also exhibiting superior anti-androgenic effects[30,31].

The *C. bonducella* seed kernels have been found to contain more than 50 different substances. Researchers are investigating the antipyretic, anti-neoplastic, hypoglycemic, and anti-oxidant effects of seed kernel extracts that are high in active chemicals such caesalpinin, cassane furanoditerpenes, flavonoids, bonducellin, terpenoids, and sterols. Recent research has suggested that this plant has anti-androgenic and anti-estrogenic properties, and may be useful in controlling hyperandrogenism, the primary risk factor contributing to several additional clinical symptoms of PCOS[8].

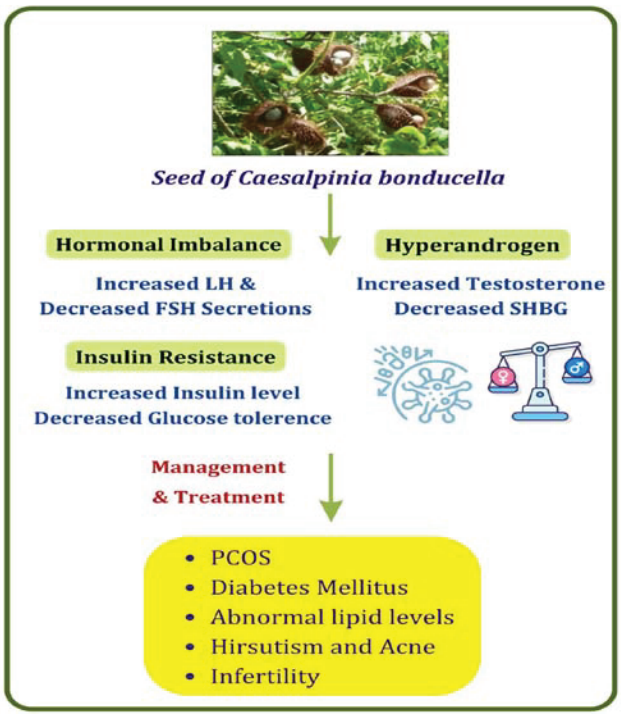

Figure 7. Illustrates how the male and female reproductive hormonal systems are regulated by *C. bonducella* seeds.

3.11.3 Reproductive Health of Males: Anti-spermatogenic Effect of Seeds

Researchers have shown that *C. bonducella* seeds have superior anti-androgenic efficacy over albino female Wistar rats. After the animals were pretreated with a hydroalcoholic seed extract of *C. bonducella* their hormonal levels were monitored. The efflux of female hormone components increases, and the amount of testosterone decreases, which improves ovarian growth and helps regulate the menstrual cycle in female rats[30].

The growth of Benign Prostatic Hyperplasia (BPH) was slowed by *C. bonducella* seed extracts because of their potential to inhibit the action of Testosterone Propionate (TP), which was demonstrated in an animal model by significantly decreased absolute and relative prostate weights. The decreases in the blood levels of Prostate-Specific Antigen (PSA) and Dihydrotestosterone (DHT), as well as in the serum, further corroborated these findings[32].

4. Conclusion

In conclusion, the findings of the antiandrogenic potential of *C. bonducella* seeds which increase the

efflux of female hormone components coupled with a reduction in testosterone levels in animal models open new avenues for exploring their applications in addressing hormonal disorders and reproductive health issues. As further investigations delve into the underlying mechanisms, these findings offer promising prospects for the development of novel lead interventions aimed at restoring hormonal equilibrium and promoting overall well-being in both animals and potentially human subjects.

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