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Integrative Approach to PCOS: Pharmacological Insights from Siddha Formulations

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Abstract: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine and metabolic disorder affecting up to 20% of women in India. Conventional therapies often fail to address its multifactorial etiology and have limitations due to side effects. Siddha medicine, an ancient South Indian system, offers multimodal interventions that target hormonal, metabolic, and inflammatory pathways. This review aimed to evaluate the pharmacological basis, clinical evidence, and integration prospects of Siddha formulations in PCOS management.We conducted a scoping review of Siddha formulations commonly used in PCOS, such as *Ashokarishtam*, *Karisalai Karpam*, *Amukkara Choornam*, and *Keezhanelli*, analyzing preclinical and clinical evidence, proposed mechanisms of action, and safety considerations. Data were extracted from published experimental and clinical studies, Siddha classics, and pharmacological reviews. Siddha medicine offers a promising, culturally sensitive adjunct in PCOS management, addressing its complex pathophysiology. Well-designed trials and standardization are needed to substantiate efficacy and ensure safety for wider clinical adoption.

Keywords: *Polycystic Ovary Syndrome; Siddha Medicine; Herbal Therapy; Integrative Healthcare; Insulin Resistance*.

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I. INTRODUCTION

Due in large part to shifting lifestyles and environmental factors, the prevalence of PCOS, a widespread and complex hormonal condition that affects 8–13% of women worldwide who are of reproductive age, is continuously increasing [1]. The disorder seems to be considerably more common in India, particularly in metropolitan areas, where studies indicate that up to 20% of women may exhibit PCOS symptoms [2]. Excess testosterone, enlarged ovaries with numerous tiny follicles, and irregular or nonexistent menstrual periods are common symptoms of PCOS in women. These reproductive symptoms are often associated with more general metabolic problems, including obesity, high cholesterol, insulin resistance, and an elevated risk of heart disease and type 2 diabetes [3,4].

Currently available treatments for PCOS usually include insulin-sensitizing medications like metformin, hormonal contraceptives, anti-androgens, and ovulation-inducing substances like clomiphene citrate. Despite their potential to alleviate symptoms, these drugs do not often deal with the underlying reasons of the illness. Also, their use is frequently restricted by side effects, contraindications, and long-term safety concerns [5]. Consequently, alternative and complementary therapies, such as Siddha and other traditional Indian medical systems, are gaining popularity.

One of the oldest traditional treatment systems still in use in South India, Siddha medicine approaches health and illness holistically. Mukkutram (the three essential humors—Vali, Azhal, and Iyyam) and Udal Thathukkal (the seven structural components of the body) serve as its foundation. According to Siddha theory, the body's natural harmony may be disrupted by imbalances in Vali and Iyyam, which could lead to reproductive problems like PCOS [6]. Siddha practitioners boost fertility, detoxify the reproductive system, and restore this balance using a range of herbal and herbomineral compositions. It is noteworthy that a number of these conventional treatments are currently being investigated for their pharmacological characteristics, such as hormone regulation, enhanced insulin sensitivity, antioxidant benefits, and anti-inflammatory activity—elements that closely correspond with the onset and progression of PCOS [7].

The scientific and pharmacological underpinnings of Siddha formulations used to treat PCOS are examined in this article. In addition to discussing their mechanisms of action, we highlight important herbs and chemicals and look at the preclinical and clinical data that currently supports their use as complementary medicines.

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II. SIDDHA MEDICINE: CONCEPTUAL FRAMEWORK

Originating in South India, Siddha medicine is a traditional therapeutic system based on a deep integration of physiological and metaphysical principles. The notion of Pancha Bootham, which holds that the five basic elements—earth (prithvi), water (appu), fire (thee), air (vayu), and ether (akasham)—are the foundation of both the cosmos and the human body, is at the heart of its philosophy [8].

The Mukkutram, or the three vital humors—Pitta, Kapha, and Vata—that regulate all physiological functions in the human body are the manifestation of these elemental forces. According to this concept, disease arises when these humors are out of balance (mukkutra nilai maaruthal), whereas health is defined as the balanced functioning of these humors [8,6].

Polycystic Ovary Syndrome (PCOS) is largely viewed as a condition of Vata and Kapha imbalance from a Siddha perspective [9]. Menstrual flow, hormonal regulation, and fertility are thought to be disrupted by a derangement of Vata, namely Abana Vayu, which controls downward movement in the body. At the same time, metabolic slowness, toxin buildup (silaithathu), and cystic follicle production are all caused by an intensified Kapha dosha [9,10].

The Udal Thathukkal, or the seven basic physical components that comprise the body, is another key idea in Siddha medicine:\

- Saaram (lymph/plasma)
- Cheneer (blood)
- Oon (muscle)
- Kozhuppu (fat)
- Enlumbu (Bone)
- Moolai (nervous tissue and bone marrow)
- Suronitham/Sukkkilam (ovum/semen)

Gynecological conditions like PCOS are especially linked to disturbances in the quality or balance of Saaram, Cheneer, and Suronitham. The condition's clinical manifestations may be influenced by these abnormalities, which may impact blood flow, hormone function, and the integrity of reproductive tissues [11].

In Siddha medicine, diagnosis is made via a thorough and comprehensive process called Ennvagai Thervu, or the eightfold way of examination, which consists of the following:

- Nadi (pulse analysis)
- Sparisam (palpation)
- Naa (tongue observation)
- Niram (skin and complexion)
- Mozhi (speech)
- Vizhi (eye appearance)
- Malam (stool characteristics)
- Moothiram (urine examination)

In order to guide a customized treatment plan, practitioners can identify the precise humor imbalance in each patient with the use of this comprehensive evaluation [8].

The complete approach to PCOS management in Siddha focuses on addressing the underlying causes of the disorder. The following are important elements of treatment:

- Pathiyam (dietary regulations tailored to humor balance)
- Sodhana (purification and detoxification therapies)
- Use of herbal and herbo-mineral formulations

All of these methods work together to improve hormonal and metabolic function, balance humor, control the menstrual cycle, and get rid of built-up pollutants. Resolving the underlying disharmony causing the ailment is the ultimate objective, in addition to alleviating its symptoms [10,12].

III. KEY SIDDHA FORMULATIONS AND THEIR PHARMACOLOGICAL ACTIONS

Siddha medicine uses plant-based, herbo-mineral, and holistic formulations to address the physiological imbalances at the root of illness. Several formulations have demonstrated possible therapeutic effectiveness in the context of PCOS through processes that resemble contemporary pharmaceutical objectives, including oxidative stress reduction, insulin sensitization, androgen management, and ovulation support. This section outlines the main Siddha formulations that have historically been used to treat PCOS, along with information on their pharmacological effects, phytochemical profiles, and supporting data.

A. Karisalai Karpam (Eclipta alba)

- *Phytochemistry:*

Karisalai Karpam is derived from *Eclipta alba*, a plant rich in bioactive compounds such as wedelolactone, ecliptine, luteolin, β-amyrin, stigmasterol, and various flavonoids [13].

- *Pharmacological Actions:*

- Anti-androgenic: It has been demonstrated that wedelolactone inhibits 5α-reductase, which lowers dihydrotestosterone (DHT) levels and helps to relieve symptoms including acne and hirsutism [14].
- Insulin sensitization is essential for lowering insulin resistance, which is frequently shown in PCOS, because it increases glucose absorption and insulin receptor sensitivity [15].
- Hepatoprotective: Promotes liver function by lowering oxidative stress and enhancing hepatic enzyme profiles, which helps with steroid hormone metabolism [16].

- *Clinical Evidence:*

- It was demonstrated that Eclipta alba extract dramatically decreased ovarian cysts and restored hormone levels in a rat model of PCOS produced by letrozole [17].

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- Karisalai Karpam is recommended in traditional Siddha scriptures to treat liver failure and irregular menstruation linked to PCOS [11].

B. Amukkara Choornam (Withania somnifera)

➢ *Phytochemistry*:

Commonly known as Ashwagandha, *Withania somnifera* contains pharmacologically active withanolides, withaferin A, sitoindosides, and various alkaloids [18].

➢ *Pharmacological Actions:*

- Adaptogenic: Adjusts the hypothalamic-pituitary-adrenal (HPA) axis, which aids in cortisol regulation and lessens hormonal imbalance brought on by stress [19].
- Anti-inflammatory: Reduces chronic inflammation associated with PCOS pathogenesis by downregulating pro-inflammatory cytokines like TNF-α, IL-6, and NF-κB [20].
- Antioxidant: Preserves and promotes the growth of ovarian follicles by neutralizing reactive oxygen species (ROS) [21].
- Hormonal Modulation: Improves the LH/FSH ratio and reduces increased testosterone levels, which aids in the restoration of ovulation [22].

➢ *Clinical Evidence:*

- Randomized controlled research found that women with PCOS treated with Withania somnifera had significantly improved insulin resistance, testosterone levels, and menstrual regularity [23].
- Preclinical investigations in PCOS animal models demonstrated the restoration of normal ovarian shape and hormonal profiles [24].

C. Ashokarishtam (Saraca asoca)

➢ *Phytochemistry*:

This classical formulation contains key phytonutrients such as luteolin, kaempferol, procyanidin B2, tannins, saponins, and glycosides [25].

➢ *Pharmacological Actions:*

- Aromatase Inhibition: Flavonoids such as luteolin regulate estrogen levels by inhibiting aromatase, which balances the LH/FSH ratio [26].
- Uterine tonic and anti-inflammatory: Promotes uterine health by increasing endometrial tone and decreasing ovarian inflammation [27].

➢ *Clinical Evidence:*

- In animal investigations, extracts of Saraca asoca decreased cystic follicles and restored hormonal balance in PCOS models [28].
- Clinically, Ashokarishtam is commonly used to treat PCOS symptoms such as menorrhagia, amenorrhea, and cycle irregularities [29].

D. Keezhanelli (Phyllanthus niruri)

➢ *Phytochemistry:*

Phyllanthus niruri contains bioactive compounds including phyllanthin, hypophyllanthin, ellagitannins, flavonoids, and various alkaloids [30].

➢ *Pharmacological Actions:*

- Hepatoprotective: Improves liver detoxification and steroid metabolism by increasing antioxidant enzymes [31].
- Anti-inflammatory and antidiabetic properties: Reduces systemic inflammation and improves insulin sensitivity by activating AMP-activated protein kinase (AMPK) pathways [32].
- Endocrine Modulation: Helps to restore hormonal balance by increasing follicular maturation and ovulation [33].

➢ *Clinical Evidence:*

- In preclinical models, P. niruri treatment has been shown to improve insulin sensitivity, decrease cystic ovaries, and improve ovarian histology [34].
- In traditional Siddha practice, Keezhanelli is prescribed for conditions such as insulin resistance, liver dysfunction, and menstrual irregularities, which are symptoms frequently associated with PCOS [12].

IV. MECHANISMS OF ACTION IN PCOS MANAGEMENT

PCOS is characterized by a complex interaction of metabolic, inflammatory, and endocrine dysfunctions. In order to tackle this complexity, siddha formulations are typically made up of herbal and herbo-mineral constituents that work in concert to target several underlying pathophysiological pathways. As a reflection of Siddha medicine's holistic ethos, these formulations seek to restore systemic balance rather than just alleviate symptoms.

A. Hormonal Regulation

➢ One of the main causes of PCOS is hormonal imbalance, specifically in the hypothalamic-pituitary-ovarian (HPO) axis. Through a number of methods, siddha formulations support hormonal equilibrium.
➢ Gonadotropin Modulation: Some phytochemicals affect the hypothalamus's pulsatile release of gonadotropin-releasing hormone (GnRH), which helps to balance levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Ovulation and proper follicular development depend on this balance [26].
➢ Enzyme Inhibition: Components such withanolides and flavonoids prevent the conversion of testosterone into the more powerful dihydrotestosterone (DHT) by inhibiting

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enzymes like 5α-reductase. Hirsutism and acne are examples of androgenic symptoms that can be lessened by blocking this route [14, 35]. In a similar vein, aromatase inhibition helps maintain estrogen balance by avoiding unopposed estrogen effects such as irregular bleeding and endometrial hyperplasia [26].

- Hormone Receptor Modulation: The active ingredients in Siddha herbs also improve progesterone receptor expression and control estrogen receptor activity, which promotes endometrial receptivity and luteal phase sufficiency, both of which are essential for menstrual regularity and fertility [27].

B. Insulin Sensitization

- PCOS's metabolic and reproductive problems are largely caused by insulin resistance. Herbs used in siddha have insulin-sensitizing properties through:
- Insulin Signaling Enhancement: Bioactives increase the activity of the insulin receptor substrate (IRS) and downstream signaling via the Akt and phosphoinositide 3-kinase (PI3K) pathways. This facilitates GLUT4's translocation to cell membranes, improving glucose absorption and lowering hyperinsulinemia, both of which suppress the generation of androgens by the ovaries [15, 34].
- AMP-activated protein kinase (AMPK), a crucial energy regulator that promotes lipid oxidation, boosts mitochondrial efficiency, and inhibits the generation of glucose by the liver, is triggered by herbs such as Phyllanthus niruri. This lowers insulin resistance and aids in weight management [32].
- Restoring Sensitivity Associated with Inflammation: Insulin signaling is hampered by chronic inflammation. By enhancing insulin receptor sensitivity, reducing pro-inflammatory cytokines like TNF-α and IL-6, and disrupting the inflammation-insulin resistance loop, siddha herbs help to mitigate this [20].

C. Anti-inflammatory and Antioxidant Effects

- Chronic low-grade inflammation and oxidative stress are now known to have a major role in the development of PCOS. Siddha medications have two functions by taking care of both:
- Cytokine Suppression: By suppressing inflammatory indicators such as TNF-α, IL-1β, IL-6, and NF-κB, polyherbal formulations lower systemic inflammation. This promotes follicular development and improves the intra-ovarian environment [21].
- Enhancement of Antioxidant Defense: Flavonoids and other antioxidants improve the body's natural enzyme systems, such as glutathione peroxidase (GPx), catalase, and superoxide dismutase (SOD), which neutralize reactive oxygen species (ROS) and shield ovarian tissues from oxidative damage [36].
- Mitochondrial Protection: By stabilizing mitochondrial membranes and enhancing mitochondrial bioenergetics, some Siddha ingredients lower follicular apoptosis and increase oocyte survival [36].

D. Ovarian Function Restoration

- Multiple immature ovarian cysts are the outcome of missed ovulation and disturbed folliculogenesis in PCOS. Siddha medicines aid in the reversal of this process:
- Follicle Support: Through the overexpression of growth factors including insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), bioactive chemicals stimulate the proliferation and differentiation of granulosa cells. Timely ovulation and the development of dominant follicles are promoted by these effects [37, 38].
- Resorption of cystic follicles and re-establishment of ovulatory cycles are facilitated by Siddha treatments, which also reduce inflammation and restore hormonal and metabolic balance [28,38].
- Apoptosis Regulation: Follicle survival depends on the equilibrium between apoptotic (like Bax) and anti-apoptotic (like Bcl-2) proteins. Premature follicular atresia is decreased by siddha herbs' modulation of these apoptotic pathways [37].
- Hepatoprotective Effects: The liver is essential for the metabolism of hormones, especially the detoxification of estrogen. Eclipta alba and Phyllanthus niruri-containing formulations preserve liver tissues and improve hepatic enzyme performance, which indirectly supports hormonal balance [16,39]

V. SAFETY, PHARMACOKINETICS, AND DRUG INTERACTIONS

Many traditional formulas are regarded as safe when used properly under the supervision of trained Siddha practitioners. Studies on both humans and animals have confirmed the low toxicity profiles of herbal substances often used in Siddha medicine, including Saraca asoca, Eclipta alba, and Withania somnifera [40,41,57]. But there are still legitimate safety concerns, particularly when it comes to preparations that contain metals like arsenic, lead, or mercury. Traditional Bhasma processes, which need for exact purification methods, are sometimes used to include these. These formulations have the potential to cause major side effects, including toxicity to the liver, kidneys, or nervous system, if improperly made [42,43,59,60]. Standardized processing, quality control, and frequent safety monitoring are therefore crucial, especially for susceptible populations like expectant mothers or people with liver or renal diseases [44,64].

Even though Siddha formulations have been used for a long time, there are still no thorough pharmacokinetic studies that examine how the body absorbs, distributes, metabolizes, and gets rid of these substances. Their intricate, multi-ingredient nature presents a problem. The therapeutic benefits of important bioactive substances like flavonoids and withanolides may be limited by their rapid breakdown in the liver and low water solubility [46,65]. By blocking specific liver enzymes and transporters, the combination of these herbs with natural bioavailability enhancers such as Piper nigrum (black pepper) has demonstrated potential in enhancing absorption [48,67]. After entering the body, these substances are believed to be mainly broken down by liver

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enzymes, particularly those belonging to the cytochrome P450 family, which also breaks down a lot of contemporary medications [49,68].According to certain studies, these substances may even preferentially accumulate in organs such as the ovaries, which could explain why they are beneficial in PCOS [50,69]. However, to better understand these pathways, we need to do more thorough research using contemporary methods like metabolomics [51,70,71].

The possibility of interactions with traditional drugs is another crucial factor to take into account. Many PCOS-afflicted women are already on anti-androgens, hormonal contraceptives, or metformin. Certain Siddha herbs may increase the glucose-lowering impact of metformin and have insulin-sensitizing properties, which could raise the risk of hypoglycemia if not carefully controlled [61,81]. Similarly, by altering liver enzymes like CYP3A4 and CYP2D6, many herbal ingredients can either accelerate or slow down the breakdown of pharmaceuticals, which may result in decreased efficacy or more adverse effects from prescription drugs [62,73,75]. Drug absorption and distribution within the body may become even more complicated if drug transport mechanisms, such as P-glycoprotein, are interfered with [54,65]. The significance of exercising caution and regular monitoring is emphasized by reports of herb-induced liver and kidney damage, especially when taken with pharmaceutical medications [55,67]. Open communication and cooperation between traditional and contemporary healthcare practitioners are essential to providing individualized, high-quality care when combining Siddha and allopathic treatments successfully [68].

VI. CLINICAL EVIDENCE AND EFFICACY

The therapeutic benefits of Siddha formulations in the treatment of Polycystic Ovary Syndrome (PCOS) have been emphasized by an increasing number of clinical studies. These trials show quantifiable changes in a number of fundamental clinical indicators, such as improved insulin sensitivity, hormonal regulation, monthly regularity, and ovarian cyst reduction.

Particularly positive outcomes have been observed using Karisalai Karpam (Eclipta alba). It supports the normalization of menstrual cycles and, according to clinical evaluations, helps decrease the size and quantity of ovarian cysts. The reproductive endocrine axis appears to be influenced by its anti-androgenic and hepatoprotective qualities, which improve ovarian function and significantly lessen hyperandrogenic symptoms including acne and hirsutism [69,70].

In randomized controlled studies, Amukkara Choornam (Withania somnifera), which is recognized for its adaptogenic qualities, has shown notable advantages. After taking this mixture, women with PCOS saw improvements in their hormonal profiles and ovulatory function. In particular, it was found to have regulatory effects on the hypothalamic-pituitary-ovarian (HPO) axis, as evidenced by decreases in luteinizing hormone (LH) levels and stabilization of the FSH:LH ratio, two important endocrine indicators that are frequently disturbed in PCOS [71,72].

Clinical studies have connected Ashokarishtam, a formulation that mostly contains Saraca asoca, to benefits in hormone management, namely in balancing the levels of progesterone and estrogen, as well as a reduction in cystic follicles. The flavonoid components in it are thought to reduce inflammation in the ovarian microenvironment and decrease aromatase activity, which helps regular ovulatory cycles to resume [73,74].

A possible supplementary treatment for PCOS is keezhanelli (Phyllanthus niruri), especially because of its metabolic advantages. Improvements in insulin sensitivity and decreased ovarian cyst development have been demonstrated in both preclinical and clinical investigations. It is relevant in controlling the metabolic elements of PCOS because of its capacity to modulate glucose metabolism and lower inflammatory biomarkers [75,76].

When taken as a whole, these results indicate that Siddha formulations have a great deal of potential as supplemental treatments for PCOS. Despite the strong preliminary findings, more extensive, well planned multicentric clinical trials are still necessary. In order to facilitate wider clinical acceptance, such research ought to focus on standardizing formulations, optimizing doses, and guaranteeing consistent therapeutic outcomes [77,78].

VII. RESEARCH GAPS AND FUTURE DIRECTIONS

While Siddha medicine's therapeutic potential in controlling Polycystic Ovary Syndrome (PCOS) is becoming more widely acknowledged, several major research gaps must be addressed before it can be fully integrated into clinical practice and regulatory systems.

A. Standardization

The absence of standardization is a significant barrier in the clinical application of Siddha formulations. Variability in raw herbal material sourcing, changes in traditional processing methods, and dose inconsistency all pose substantial challenges to reproducibility and safety. Without consistency, treatment effects can vary greatly among batches and methods. Establishing pharmacopeial standards, established manufacturing procedures, and effective quality control techniques is critical for ensuring consistency, safety, and efficacy, especially for commonly used remedies like Amukkara Choornam and Ashokarishtam [79,80].

B. Pharmacokinetic Studies

Despite centuries of practical use, most Siddha formulations' pharmacokinetic characteristics in humans remain completely unknown. Current research is frequently limited to basic in vitro or animal experiments, which provide only preliminary insights. Comprehensive investigations on the absorption, distribution, metabolism, and excretion (ADME) of important bioactive compounds as withanolides, flavonoids, and alkaloids are urgently required. Advanced

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methods, such as LC-MS/MS analysis, physiologically based pharmacokinetic (PBPK) modeling, and metabolomics, could provide a better knowledge of therapeutic windows and potential interactions with conventional medications [90,91].

C. Clinical Trials

Although preliminary research and anecdotal data suggest Siddha formulations' efficacy in PCOS, large-scale, multicenter randomized controlled trials (RCTs) are required to generate solid clinical proof. These trials should include different patient demographics, long-term follow-up, and direct comparisons to established allopathic treatments. Furthermore, using standardized outcome measures—such as hormone profiles, ovulatory response, and insulin sensitivity markers—would assist maintain consistency across studies and enable data synthesis [92-94].

D. Integration into Conventional Practice

An integrative strategy that integrates Siddha medicine with evidence-based allopathic treatments may provide a more holistic and patient-centered approach to PCOS management. These endeavors necessitate collaborative frameworks that bring together traditional healers, gynecologists, endocrinologists, and clinical pharmacologists. Pilot programs and real-world studies can aid in assessing the clinical advantages, safety, patient satisfaction, and cost-effectiveness of integrated care models [95,96].

It is imperative to fill these research gaps in order to validate the scientific foundation of Siddha medicine and to increase the number of safe and efficient treatment choices accessible to women with PCOS.

VIII. DISCUSSION

Polycystic Ovary Syndrome (PCOS) can be effectively managed with Siddha therapy, especially considering its multimodal therapeutic approach. The underlying hormonal, metabolic, and inflammatory abnormalities that define PCOS are addressed by Siddha formulations, which closely correspond with contemporary clinical objectives. Ashokarishtam, Karisalai Karpam, and Amukkara Choornam are among the remedies that have demonstrated promising outcomes in restoring hormonal balance, lowering insulin resistance, and enhancing ovulatory function.

Notwithstanding these positive results, widespread clinical use of Siddha treatments necessitates thorough scientific proof in addition to conventional wisdom. To verify efficacy and safety, standardized pharmacological research, carefully monitored clinical trials, and pharmacokinetic analyses are necessary. Additionally, incorporating Siddha concepts into modern healthcare systems—through patient-centered care models and interdisciplinary collaboration—may provide women with a more comprehensive and culturally appropriate choice for managing PCOS.

IX. CONCLUSION

In conclusion, Siddha medicine has a lot of promise as a component of an integrative PCOS treatment paradigm that embraces the rigor of contemporary science while honoring traditional wisdom.

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