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Unveiling of *Citrullus colocynthis*. Linn medicinal formulations in Siddha system of medicine and its therapeutic role in reproductive health: A review

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ABSTRACT:

Women experience reproductive health issues at least once in their life time. In India, the prevalence of gynecological disorders has increased significantly, affecting approximately 43-92% of women with reproductive morbidities. This highlights the urgent need for effective and minimally invasive treatments. Women seek guidance to maintain their well-being, as their health is vital to the welfare of their families and society. Siddha medicine offers management for health issues from childhood to postmenopausal stages. The Herbal and Herbo-mineral formulations of *Citrullus colocynthis* Linn (CC) were indicated for treating various gynecological disorders like menstrual irregularities, infertility, hormonal imbalances, and even postpartum issues especially, *Kumatti mezhugu* and *Navauppu mezhugu* were commonly used to treat infertility, uterine fibroids respectively in the Siddha System of Medicine. The present review focuses on the composition, indications, therapeutic applications, and scientific work done on herbal and herbo-mineral formulations of CC. CC-based Siddha formulations were obtained from prehistoric Siddha books and their recent research evidence from electronic databases such as Science Direct, Pubmed, Cochrane, and Google Scholar. The study results indicated that *Kalingathy Thailam* and *Kalingathy Kadugu* have scientifically proven efficacy in treating female reproductive conditions like PCOS, infertility, irregular menstruation, and cervical cancer. Additionally, research studies revealed that the pharmacological properties of CC and its phytochemicals, including vitexin, cucurbitacins, and L-arginine, positively impact reproductive health.

Keywords: *Citrullus colocynthis* Linn, *Kalingathy thailam*, Siddha formulations, Reproductive health

INTRODUCTION:

Reproductive health encompasses the well-being of the male and female reproductive systems throughout all stages of life. These systems comprise essential organs and hormone-secreting

glands, including the pituitary gland in the brain. In both females and males, the ovaries and testicles play a crucial role in producing and releasing hormones.[1] Gynecological conditions significantly affect the quality of life in various aspects, especially when combined with issues like infertility, obesity, metabolic disorders, chronic pain, or mood disturbances.[2] These diseases contribute to approximately 4.5% of the global disease burden.[3] Gynecological morbidities are comparatively more common, accounting for about 43-92% of the disease burden among women.[4] In recent decades, there has been growing interest in finding effective alternatives with minimal adverse effects for treating female reproductive tract disorders.

In India, nearly 95% of medications are derived from herbal-based formulations and 80% of the world's population relies on traditional herbal medicine for primary healthcare.[5] Siddha therapeutics focuses on treating the core of ailments with various Siddha formulations, including herbal, polyherbal, and herbo mineral formulations, which have shown potential therapeutic value with scientific validations. *Citrullus Colocynthis* Linn (*CC*), commonly known as bitter apple or bitter cucumber, has a long history of use in traditional medicine across various cultures. *CC* fruit contains an abundance of bioactive proteins and organic compounds, making it clinically significant.[6] However, its toxicity is directly proportional to the increase in the dosage.[7] Within the Siddha pharmacopeia, *CC* is classified as a scheduled E1 herb, represented as scheduled under the Drugs and Cosmetics Act of 1940. Before using *CC* in medicines, it requires purification following Siddha traditional methods to neutralize or reduce the toxic components.[8] *CC* serves as a key ingredient in numerous Siddha medicinal formulations indicated for both internal and external use. Its inclusion underscores its efficacy and safety profile, as well as its integral role in Siddha therapeutic interventions. By delving into its rich historical legacy and contemporary relevance, we aim to unravel the holistic healing potential of this esteemed herb and shed light on its significance in the broader landscape of traditional medicine.

This review aims to provide a comprehensive overview of the polyherbal and herbo-mineral formulations of *CC*, focusing on their composition, traditional uses, therapeutic applications, and scientific research. Additionally, the review elucidates the role of these formulations of *CC*, emphasizing its therapeutic role in the reproductive system.

MATERIALS AND METHODS:

Study design: Review

Research type: Literature review

Research period: 3 months

Literature collected from: A comprehensive review of these formulations and research data was obtained from prehistoric Siddha books and their research evidence from electronic databases such as Science Direct, PubMed, Cochrane, and Google Scholar.

RESULTS:

FORMULATIONS OF CC IN THE SIDDHA SYSTEM OF MEDICINE:

Totally 10 formulations of CC were retrieved from the authenticated Siddha literature. Out of these 3 were polyherbal formulations and 7 were herbo-mineral formulations. (fig.1)

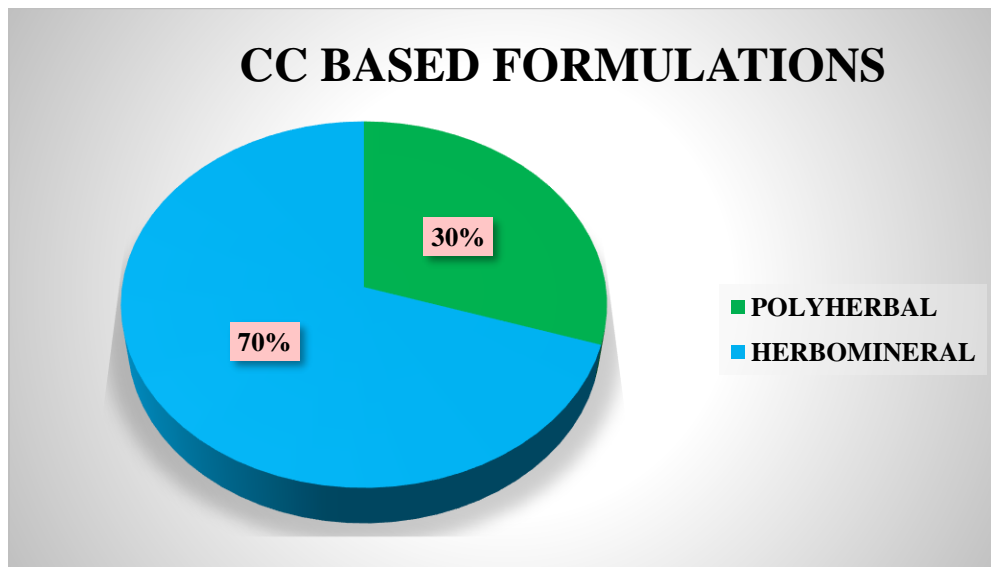


Figure 1: CC based formulations

THE POLYHERBAL FORMULATIONS OF CC:

Table 1: Polyherbal formulations of CC

S. No	Polyherbal formulation	Reference books
1.	Visha amirtha chooranam	Pathartha guna vilakkam [9]
2.	Kumatti ennai	Ravana mangayar maruthuvam [10]
3.	Kalingathy thailam	Siddha vaithiya thirattu [11]

1. Visha Amirtha Chooranam (VC):

The ingredients of visha amirtha chooranam are as follows:

Table 2: Drug profile of VC

S.NO	Name of the drug		Quantity
	Siddha name	Scientific name	
1.	Periya kumattikai	CC	Equal amount
2.	Siru kumattikai	<i>Cucumis trigonus</i>	Equal amount
3.	Pei surai	<i>Lagenaria siceraria</i>	Equal amount
4.	Pei pudalai	<i>Trichosanthes cucumerina</i>	Equal amount
5.	Pei peerkku	<i>Luffa cylindrical</i>	Equal amount

Dosage

2 g of visha amirtha chooranam twice a day with hot water

Indications:

All types of toxins

Dietary instructions

No diet instructions were found [9]

2. Kumatti ennai (KE)

The formulation of KE contains the following ingredients

Table 3: Drug profile of KE

S.no	Name of the drug		Quantity
	Siddha name	Scientific name	
1.	Kummattikai juice	CC	1100 g
2.	Pachai manjal	<i>Curcuma longa</i>	480 g
3.	Nervalam	<i>Croton tiglium</i>	20 g
4.	Castor oil	<i>Ricinus communis</i>	750 ml

Dosage

16 ml on an empty stomach during the first 3 days for 3 months of the menstrual phase, it has purgative action

Indications:

This medicine is known to treat polycystic ovarian syndrome, dysmenorrhea, and infertility.

Dietary instructions

No diet instructions were found [10]

Earlier research data on KE

No research studies were done on KE

3. Kalingathy thylam (KT):

Kalingathy thailam contains the following ingredients,

Table 4: Drug profile of KT

S.no	Name of the drug		Quantity (g)
	Siddha name	Scientific name	
1.	Kummattikai juice	<i>CC</i>	1500
2.	Malai vembu leaf juice	<i>Melia dubia</i>	1500
3.	Onion juice	<i>Allium cepa</i>	1500
4.	Lemon juice	<i>Citrus limon</i>	1500
5.	Castor oil	<i>Ricinus communis</i>	1500

Dosage

15-30 ml in the morning only with old rice water during the first 3 days of the menstrual period

Indications:

Amenorrhea, Menorrhagia, and 3 types of infertility cases. This medicine is not advised during the pre-puberty and post-partum period.

Dietary instructions

salt-free diet [11]

Earlier research data on KT

1. A pharmacological study of *Kalingathy thailam* revealed that KT induces ovulation in hormone-induced PCOS female rats and also found that KT increased the levels of luteinizing hormone and follicle-stimulating hormones at a dose of 100 and 200 mg/kg.[12]
2. Preclinical safety evaluation of KT demonstrated that there was no sign of toxic effects or mortality after single or repeated administration at varying doses of 20,100, and 200 mg/kg/day for 28 days.[13]
3. An open, non-randomized clinical trial using KT in patients with polycystic ovarian syndrome (*Soothaga vayu*), the trial produced dominant follicle induction and menstrual

regulation. Out of 40 cases, 27 (67.5%) had favorable results, 8 (20%) had moderate results, and 5 (12.5%) had unfavorable outcomes. There were no side effects noted while the treatment was being administered.[14]

- Through Insilico computational screening, KT was found to exhibit significant binding against CYP-17 α -hydroxylase. The computational analysis showed that the bioactive substances (Cucurbitacin B, Linolenic acid, Protocatechuic acid) inhibit the target enzyme, suggesting that KT might be used as a potential therapeutic agent to treat PCOD.[15]

HERBO MINERAL FORMULATIONS OF CC IN THE SIDDHA SYSTEM OF MEDICINE:

The Herbo mineral formulations are listed below

Table 5: Herbo mineral formulations of CC

S.no	Herbomineral formulation	Reference books
1.	Kumattikai chooranam	Ravanar mangayar maruthuvam[10]
2.	Navamula guru chunnam	Noigaluku Siddha parigaram[16]
3.	Navauppu mezhugu	Siddha vaidhiya thirattu[11]
4.	Kumatti mezhugu	Agathiyar vaithiya kaviyam 1500 [17]
5.	Kalingathy kadugu	Agathiyar vaidhiya vallathy 200 [18]
6.	Kumatti kulambu	Agathiyar vaidhiya vallathy 200 [18]
7.	Kumatti uppu chooranam	Siddha vaidhiya thirattu,[11] Nam nattu vaithiyam [19]

1. Kumattikai chooranam (KC):

The composition of KC is as follows:

Table 6: Drug profile of KC

S.no	Name of the drug		Quantity
	Siddha name	Scientific name	
1.	Kummattikai	CC	10 nos
2.	Nayuruvi uppu	<i>Achyranthes aspera</i>	30 g
3.	Indhuppu	<i>Himalayan salt</i>	30 g
4.	Porigaram	<i>Purified Borax</i>	15 g

Dosage

200 to 260 mg twice a day with a sufficient amount of palm jaggery for 10 days

Indications:

This formulation is known to cure uterine infections, gastric ulcers, and dysmenorrhea and also to treat infertility.

Dietary instructions

No diet instructions were found [10]

Earlier research data on KC

No research studies were done on KC

2. Navamula Guru Chunnam (NMC)

Ingredients of NMC are as follows

Table 7: Drug profile of NMC

S.no	Name of the drug		Quantity
	Siddha name	Scientific name	
1.	Kummattikai juice	CC	1lb
2.	Kovai leaf juice	<i>CoCCinia grandis</i>	¼lb
3.	Murungai tender leaves juice	<i>Moringa oleifera</i>	¼lb
4.	Induppu	<i>Rock salt</i>	70g
5.	Sodium bicarbonate	-	70g
6.	Valayaluppu	<i>Glass gale</i>	70g
7.	Kariuppu	<i>Sodium chloride</i>	70g
8.	Paraiuppu	<i>Halite</i>	70g
9.	Puneer	<i>Fuller's earth</i>	70g
10.	Common salt	-	70g
11.	Kalluppu	<i>Crystal salt</i>	70g
12.	Vediuppu	<i>Potassium nitrate</i>	70g

Dosage

2 to 5 grains (65 to 325 mg) may be given with suitable adjuvants twice a day for 3 to 7 days.

Indications:

This medicine serves as a catalytic agent for preparing parpam, chenduram and chunam by adding about 20 grains. NMC is used to treat various conditions such as peptic ulcer, abdominal pain, stricture urethra, amenorrhea, and dysmenorrhea. For amenorrhea and dysmenorrhea, NMC is taken with the juice of *Phyla nodiflora*, garlic, and pepper twice a day for 7 days. It is also used for cholera and dyspeptic disorders. Additionally, it can be used for insect bites and scorpion stings when mixed with the latex of *Calotropis gigantea* and applied locally or used as snuffing in poisonous bites.

Dietary instructions

No diet instructions were found. [16]

Earlier research data on NMC

No research studies were done.

3. Navauppu mezhugu (NUM)

The composition of NUM is as follows

Table 8: Drug profile of NUM

S.no	Name of the drug		Quantity
	Siddha name	Scientific name	
1.	Induppu	<i>Himalayan salt</i>	10 g
2.	Sotru uppu	<i>Sodium chloride</i>	10 g
3.	Vediuppu	<i>Potassium nitrate</i>	10 g
4.	Kalluppu	<i>Crystal salt</i>	10 g
5.	Navaacharam (amuriuppu)	<i>Ammonium chloride</i>	10 g
6.	Mungiluppu	<i>Bambusa arundinaceae</i>	10 g
7.	Punneeru	<i>Fuller's earth</i>	10 g
8.	Valayaluppu	<i>Glass gale</i>	10 g
9.	Paraiuppu	<i>Types of sodium chloride</i>	10 g
10.	Purified veeram	<i>Hydrargyrum perchloride</i>	40 g
11.	Purified rasa karpooram	<i>Mercuric chloride</i>	20 g
12.	Milagu	<i>Piper nigrum</i>	12 g
13.	Chukku	<i>Zingiber officinale</i>	12 g
14.	Thippilli	<i>Piper longum</i>	12 g
15.	Purified nervalam	<i>Croton tiglium</i>	10 g
16.	Attruthumattikai juice	CC	1 lit
17.	Thiripalai kudineer	-	Required amount
18.	Thai pal	<i>Mother's milk</i>	Required amount
19.	Pasumpall	<i>Cow milk</i>	1 lit

Dosage

56 – 200 mg with palm jaggery once a day for 12 days

Indications:

Navauppu mezhugu is indicated for throbbing pain (Soolai), Ascites (Mahotharam), Lymphadenitis (Kiranthi), Venereal diseases (Megam), Rhinitis (Neerkovai), Flatulence (Uthara vayu), Virulence (Vida vatham), Hydrocele (Anda vatham), Rheumatism (Vali vatham), Arthritis (Mudaku vatham), chest pain (Thamar vatham), soothagavayu (Dysmenorrhea), 8 types of gastric ulcer (envagai gunmam), Parisavatham (Paralysis).

Dietary instructions

Salt-restricted diet. Hot water, rice, cow milk, buttermilk, amaranth, drumstick, brinjal, broad beans, legumes, and green gram are also added to the pathyam.[11]

4. Kumatti mezhugu (KM)

KM is composed of the following ingredients

Table 9: Drug profile of KM

S.no	Name of the drug		Quantity
	Siddha name	Scientific name	
1.	Kumattikai juice	<i>CC</i>	2 litres
2.	Lemon juice	<i>Citrus limon</i>	2 litres
3.	Garlic juice	<i>Allium sativum</i>	2 liters
4.	Notchy leaf juice	<i>Vitex negundo</i>	2 litres
5.	Ginger juice	<i>Zingiber officinale</i>	2 litres
6.	Purified rasam	<i>Elementary mercury</i>	4 g
7.	Purified lingam	<i>Mercuric sulphide</i>	4 g
8.	Perungayam	<i>Ferula assa-foetida</i>	4 g
9.	Induppu	<i>Rock himalayan salt</i>	4 g
10.	Vengaram	<i>Sodium baborate</i>	4 g
11.	Kadugu	<i>Brassica nigra</i>	4 g
12.	Manjal	<i>Curcuma longa</i>	4 g
13.	Vendhayam	<i>Trigonella foenum-graecum</i>	4 g
14.	Milagu	<i>Piper nigrum</i>	4 g
15.	Purified kaantham	<i>Magnetic oxide of iron</i>	4 g
16.	Purified nervalam	<i>Croton tiglium</i>	4 g

Dosage

200 – 500 mg with palm jaggery or sugarcane jaggery once in the morning for 3 to 5 days.

Indications

KM is used for treating peptic ulcers, ascites, ovarian tumors, chronic fever, hepatomegaly, splenomegaly, anemia, dysmenorrhea, and PCOS.

Dietary instructions

No diet restrictions were found [17]

5. Kalingathy kadugu (KK)

Ingredients of KK are as follows

Table 10: Drug profile of KK

S.no	Name of the drug	Quantity
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	Siddha name	Scientific name	
1.	Kumattikai juice	CC	1.3 lit
2.	Kalluppu	<i>Sodium sulphate, sodium chloride, and sodium hydroxide</i>	1 kg
3.	Vediuppu	<i>Potassium nitrate</i>	17.5 g
4.	Valayaluppu	<i>Sodium chloride and sodium</i>	17.5 g
5.	Indhuppu	<i>Himalayan salt</i>	17.5 g
6.	Purified kaantham	<i>Magnetic oxide of iron</i>	17.5 g
7.	Chukku	<i>Zingiber officinale</i>	17.5 g
8.	Thippili	<i>Piper longum</i>	17.5 g
9.	Poondu	<i>Allium sativum</i>	17.5 g
10.	Perungayam	<i>Ferula assa-foetida</i>	8.75 g
11.	Purified nervalam	<i>Croton tiglium</i>	35 g
12.	Purified jathilingam	<i>Red sulphide of mercury</i>	35 g
13.	Illai kalli pal	<i>Latex of Euphorbia nivulia</i>	1.3 lit

Dosage

KK should be given at a dose of 4.16 gm.

Indications

Ascites, chronic fever, disease of the spleen, female sterility due to worm infections, gastrodynia, stomach ache due to constipation, irregular menstruation, uterine tumor, flatulency in the womb causing hysteria, amenorrhea, hepatomegaly, ovarian tumor, dyspeptic disorders, colic diarrheal pain.

Dietary instructions:

Hot rice porridge will be taken in the daytime. [18]

Earlier research studies on KK

The phytochemicals quantitative analysis of KK revealed that the presence of triterpenoids and tannins at RF values are 0.66, 0.89, 0.98, and 0.78, 0.91 respectively. The total quantity of triterpenoids is 0.25mg/g of dry weight and has potent anti-tumor activity through inhibition of transcription factor NF- κ B and STAT3 of cervical cancer cells, thus KK is prescribed in the management of cervical cancer.[20]

6. Kumatti kulambu

Kumatti kulambu is composed of 19 drugs listed in Table 11.

Table 11: Drug profile of kumatti kulambu

S.no	Name of the drug		Quantity
	Siddha name	Scientific name	
1.	Kumatti kai	CC	50 nos

2.	Komiyam	<i>Cow's urine</i>	10.7 lit
3.	Vellam	<i>Sugarcane jaggery</i>	437.5 g
4.	Chukku	<i>Zingiber officinale</i>	4.16 g
5.	Milagu	<i>Piper nigrum</i>	4.16 g
6.	Thippili	<i>Piper longum</i>	4.16 g
7.	Purified kaantham	<i>Magnetic oxide of iron</i>	4.16 g
8.	Poondur	<i>Allium sativum</i>	4.16 g
9.	Seenakaram	<i>Alum</i>	4.16 g
10.	Vengaram	<i>Sodium baborate</i>	4.16 g
11.	Vediuppu	<i>Potassium nitrate</i>	4.16 g
12.	Savukkaram	<i>Sodium hydroxide</i>	4.16 g
13.	Karunjeeragam	<i>Nigella sativa</i>	4.16 g
14.	Induppu	<i>Rock salt</i>	4.16 g
15.	Purified nervalam	<i>Croton tiglium</i>	2.08 g
16.	Thirugu kalli pall	<i>Latex of Euphorbia tirucalli</i>	125 ml
17.	Eranda ennai	<i>Ricinus communis</i>	125 ml
18.	Pasum pall	<i>Cow's milk</i>	1.3 lit
19.	Pasu nei	<i>Cow ghee</i>	125 ml

Dosage

100-200 mg with palm jaggery

Medicinal uses

Kumatti kulambu is used in the conditions of ascites, ovarian tumors through dropsy, uterine tumors, anemia, gastrointestinal disorders, and edema.

Diet

No diet restrictions were found [18]

Earlier research data on kumatti kulambu

No research studies were done

7. Kumatti uppu chooranam (KUC):

The ingredients are as follows

Table 12: Drug profile of KUC

S.no	Name of the drug		Quantity
	Siddha name	Scientific name	
1.	Kummattikai	CC	20 nos
2.	Valayaluppu	<i>Glass gale</i>	175 g
3.	Uppu	<i>Common salt</i>	1000g
4.	Pasum pall	<i>Cow's milk</i>	1.3 lit

Dosage

4-5 gm once in a morning time.

Medicinal uses

Ulcers and gastrointestinal disorders such as indigestion, and flatulence.

Diet

No diet restrictions were found [11]

Earlier research data on KUC

No research studies were done.

Another method of **kumatti uppu (KU)** ingredients is as follows in Table 13,

Table 13: Drug profile of KU

S.no	Name of the drug		Quantity
	Siddha name	Scientific name	
1.	Kummattikai	CC	NA
2.	Indhuppu	Himalayan rock salt	NA

Dosage

130 - 390 mg with honey or ghee once in a morning time.

Medicinal uses

It serves as a laxative. For amenorrhea, KU is administered with honey; for dyspeptic disorders, it is taken with hot water; and for angina, it is given with ghee.

Diet

No diet restrictions were found. [19]

Earlier research data on KU

No research studies were done.

RESEARCH STUDIES OF CC ROLE IN THE REPRODUCTIVE SYSTEM:**Chemical composition of CC relating to reproductive health:**

The mature fruit of CC typically contains 90% moisture, along with approximately 30% protein, 10% carbohydrates, 4% ash, and 3% fiber.[21] Three flavone glucosides-isovitexin, isosaponarin, isoorientin, and the two cucurbitacin glucosides, 2-glucopyranosyl-cucurbitacin L and glucopyranosyl cucurbitacin were extracted and identified from the fruits of CC.[6] According to pharmacological research, vitexin or isovitexin dramatically improved sexual behavior, fertility, testicular pathological structure damage, reproductive organ weight, and sperm quality. Additional downstream analysis revealed that vitexin enhanced the secretion of serum testosterone, follicular-stimulating hormones, and luteinizing hormones.[22]

CC contains a specific bioactive compound named cucurbitacins (A, B, C, D, E, I, J, K, L, and Q) and colocynthosides (A & B), respectively, with wide-ranging pharmacological activities.[23] Cucurbitacins are triterpenoid compounds known for their toxicity and bitter flavor, which are useful in drug discovery because of their cytotoxic properties and showed anti-proliferative potential on human cancer cell lines and tumor xenografts, including breast, prostate, lung, uterine cervix, liver, skin, and brain cancers.[24] Owing to its high content of cucurbitacin, *CC* belongs to the list of toxic plants.[25]

CC seeds, pulp, and rind were subjected to an analytical study of amino acids, which showed that arginine was the most concentrated essential amino acid in all parts. *CC* pulp had a greater percentage of non-essential amino acids (59.33%) than essential amino acids (40.67%). L-arginine is one of ten essential amino acids that can alter pituitary function and increase blood flow to the reproductive tract. Besides, an experimental study also revealed that supplementing L-arginine in pre and postpartum mares increased uterine blood flow and improved fertility (fig.2).[26],[27]

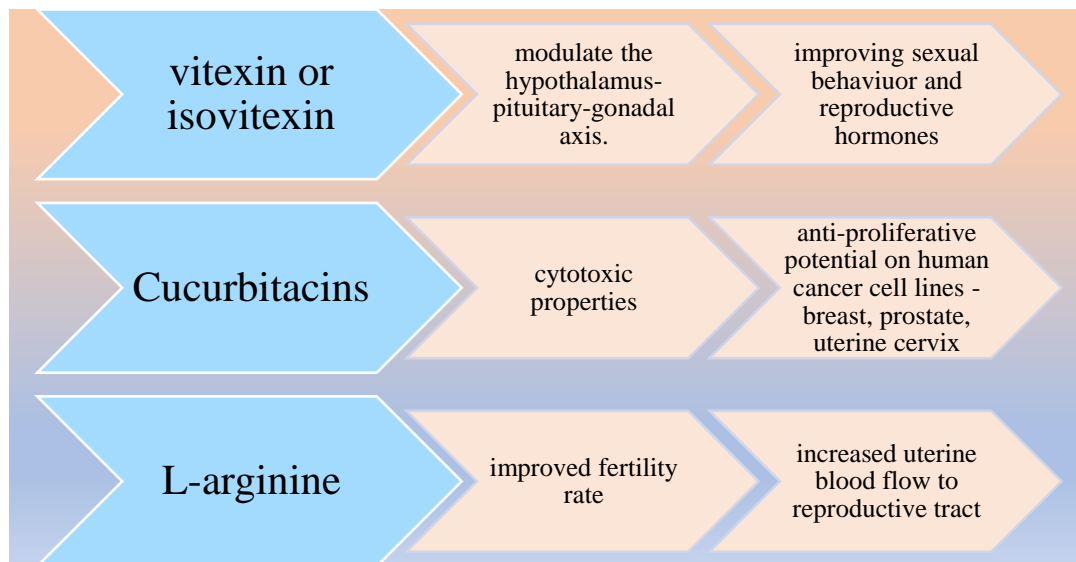


Figure 2: Presence of phytochemicals in *CC* related to reproductive health

Pharmacological properties of *CC* related to reproductive diseases:

Effect on PCOS:

- According to Barzegar MH 2017 et al., an experimental study in estradiol valerate-induced PCOS rats showed that marked improvement in hormonal and histological symptoms of PCOS may be due to *CC* (CCT) effects. There was a significant reduction in luteinizing hormone and testosterone in CCT extract-treated groups at a dose of 50mg/kg orally for 20 days whereas follicle-stimulating hormone was not significantly changed. Hence, CCT can potentially be considered an effective drug for the treatment of PCOS.[28]

Protective effect on the male reproductive system:

- Lately, cases of sexual dysfunction and fertility impairment have garnered attention as significant complications of diabetes. A study showed that *CC* pulp was found to have positive effects on diabetic mice, including increased testosterone and luteinizing hormone, decreased serum glucose, and testicular weight loss through the hypothalamus-pituitary-testis axis when given at a dose of 30 mg/kg of body weight for two weeks. These findings implied that *CC* had protective effects on the reproductive system.[29]

Effect on cervical cancer:

- *CC* showed anticancer activity against cervical cancer cells using the HeLa cell line. The whole fruit of *CC* exposed for 48 hours to varying concentrations up to 500 µg/ml of ethyl acetate (CCE) was three times more potently cytotoxic with an IC₅₀ value of 33.95 ± 3.39 (µg/ml) than methanol extracts (CCM) with an IC₅₀ value of 101.59 ± 24.37.10.[30]

Effects on the female fertility:

- A dose of 6mg/kg of an alcoholic extract of *CC* administered to adult Swiss albino female mice could accelerate the action of ovarian folliculogenesis and increase the rate of pregnancy, but an increase in *CC* concentration has a negative impact on fertility.[31]
- It seems that a study on the toxic effects of *CC* on the reproductive system in female Sprague-Dawley rats found that intraperitoneal administration of this substance at a dose of 400 mg/kg for two time periods, 4 and 12 weeks, did not significantly impact

reproductive health in the short term. However, longer-term exposure could lead to considerable reproductive toxicity.[32]

Effect on breast cancer:

- *CC* demonstrated strong anticancer activity against MCF-7 cells. According to the brine shrimp lethality assay, the alkaloid-rich fraction of *CC* fruits exhibited strong cytotoxic activity (LD-50 3.30µg/ml). The impact was observed on MCF-7 cells, which demonstrated a significant decline in cell viability in a dose-dependent manner (LC50 = 17.2µg/mL) at extremely low concentrations of 5µg/mL, 10µg/mL, and 20µg/mL. [33]

DISCUSSION:

Siddha medicine focuses on the preservation and maintenance of health, offering significant opportunities for Siddha practitioners in the field of gynecology.[34] Recently, there has been increasing interest in the therapeutic potential of this traditional system, especially through the use of herbo-mineral formulations.[5] These formulations, which blend the beneficial properties of herbs with essential minerals, have gained attention for their synergistic effects and enhanced therapeutic efficacy. Among these formulations, *CC* is a notable ingredient due to its rich phytochemical content and diverse pharmacological activities. When combined with other herbs and minerals, *CC* can further amplify its synergistic effects, increasing its potency and versatility in treating various gynecologic disorders such as menorrhagia, infertility, cervical cancer, and menstrual irregularities. *CC*-based Siddha formulations including polyherbal and herbo-mineral, 9 were indicated for female reproductive diseases, and the rest of the 1 formulation was indicated for toxins. The commonly used formulations such as "*Kalingathy thailam*," "*Kumatti mezhugu*," "*Navauppu mezhugu*," "*Navamula guru chunnam*," etc. were renowned for treating common gynecological disorders such as infertility (*Maladu*), amenorrhea (*soothagathadai*), menorrhagia (*Perumpadu*), polycystic ovarian syndrome (*Sinaipaineerkatti*), pelvic inflammatory disease (PID), leucorrhoea (*Vellainoi*), and dysmenorrhea (*Soothagavali*).[34]

On surfing of these formulations, only 2 had undergone scientific evaluations such as *Kalingathy thailam*, and *Kalingathy kadugu*. Possession of ability in their 2 formulations to cure female-related reproductive diseases. Brunda et al., completed an open, non-randomized clinical trial

with *Kalingathy thylam* in PCOS patients and established authentic data to support the literature evidence of Siddha medicine. Moreover, pharmacological studies on *CC*'s role in reproductive health can also be described as informative, exploratory, and potentially groundbreaking. They delve into *Citrullus*'s effects on PCOS, hormonal imbalances in male and female fertility, breast cancer, cervical cancer, and other aspects of reproductive health, offering insights that could have significant implications for medical practice (**fig:3**). The reproductive toxicity of *CC* extract is influenced by both the dosage and the duration of exposure. A 12-week exposure can negatively impact fertility, whereas a shorter, 4-week exposure might accelerate ovarian folliculogenesis and potentially increase pregnancy rates.[31],[32] This suggests that the effects of *CC* extract on reproductive health can vary significantly depending on how long and at what dose it is used. An amino acid analytical study in *CC* found that L-arginine can modify pituitary function and enhance blood circulation to the reproductive system. [27]

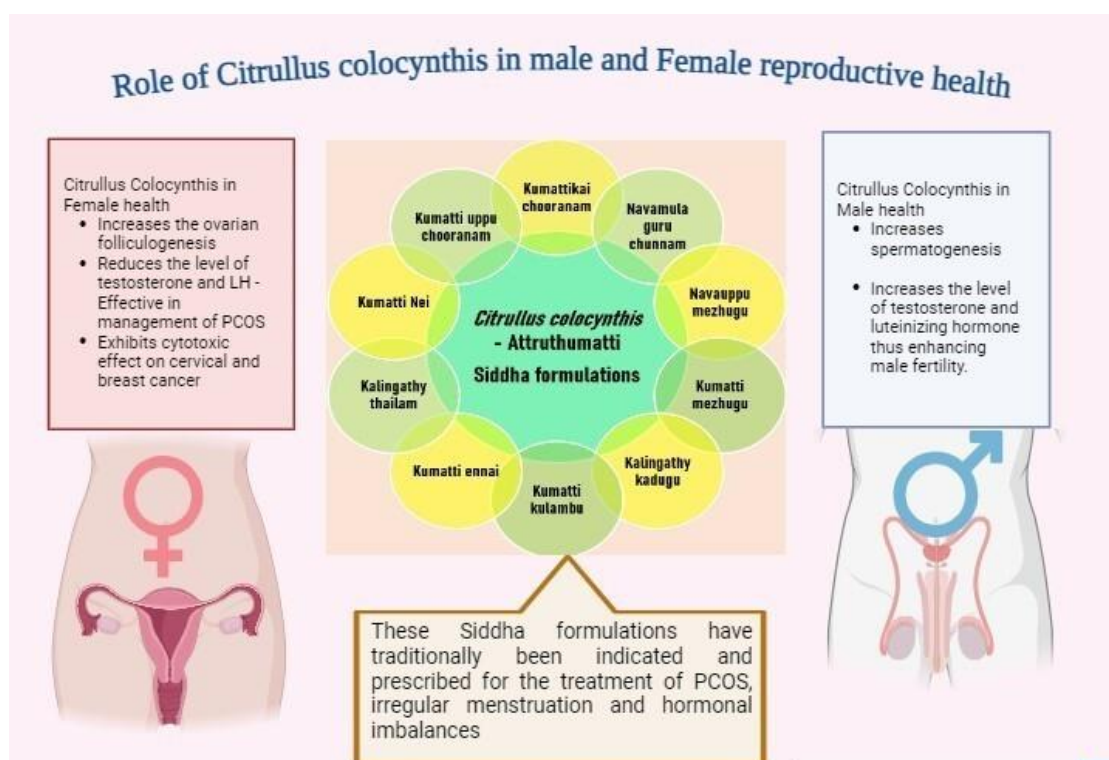


Figure 3: Role of *CC* in male and female reproductive health:

Additionally, In Ayurvedic system of medicine, *CC* is one of the ingredients in Kalyanaka Ghrta used for treating infertility. [35]

CONCLUSION:

As evident from this review, CC and CC based formulations has promising effect to treat gynecological disorders such as infertility, amenorrhea, menorrhagia, polycystic ovarian syndrome, pelvic inflammatory disease (PID), leucorrhoea and dysmenorrhea. This study's findings will help clinicians in patient care and guide future research to validate the therapeutic safety, efficacy, and clinical trials of these formulations, leading to high-quality documented evidence.

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