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Non-surgical management of uterine fibroids with a classical siddha formulation, *Rasaganthi Mezhugu* - an open pilot trial

Shyamala Rajkumar[*1], A. Faridha[2], Eugene Wilson[3], M. Kannan[4], S. Vinayak[5]

[1*] *Siddha Regional Research Institute, Puducherry, India*

[2] *Pothigai Siddha Speciality Centre, Puducherry, India*

[3] *Central Council for Research in Siddha, Chennai, Tamil Nadu, India*

[4] *Siddha Central Research Unit, Bengaluru, India*

[5] *Siddha Central Research Institute, Chennai, Tamil Nadu, India*

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Abstract

Uterine fibroids are the most common non-cancerous growth among women of reproductive age and elderly women, and this is highly concerned with affecting women's quality of life. The treatment procured in conventional medicine is of either medicinal management or surgical, which may lead to several complications. As a matter of considering the limitations of other conventional management, *Rasaganthi Mezhugu* (RGM), a classical Siddha formulation, has been selected to validate its clinical role in the management of *Karuppai Sathai Kattigal/ Karuppai Naarthasai Kattigal* (Uterine Fibroids). The objective of this study was to determine the safety and efficacy of RGM in patients with uterine fibroids. The study was designed as an open pilot single-arm clinical trial with a sample size of 20 patients. Women aged 25-55 years with clinical symptoms of uterine fibroids and the presence of fibroids confirmed with Trans-vaginal Ultra sonogram were included in the study. The trial drug, RGM was administered orally in 500 mg capsule twice a day for a period of 90 days and followed up at month 6 and month 9. Among 20 patients, complete disappearance of Intramural fibroids was noted in 7 patients (35%) and there was a positive significant difference in the size of fibroids from baseline compared to day 90, month 6 and month 9 at a 5% level of significance. The patients were also symptomatically relieved. Also, there were no significant differences observed in the haematological indexes of the recruited subjects, substantiating the safety profile.

* **Corresponding Author:** Dr. Shyamala Rajkumar ✉ shyamalasiddha@gmail.com

Introduction

Uterine fibroids are benign tumors of smooth muscle cells and fibrous connective tissue that develop within the walls of the uterus (Geethamala *et al.,* 2016). In other words, it is known as non-cancerous uterine growths, commonly seen in women of childbearing age and referred to as uterine leiomyoma, fibromyoma, myoma, or fibroids. It is one of the most common tumors of the uterus, with an estimated incidence of 20%–40% in the reproductive age group (Khan T *et al.,* 2014). Sabry and Al-Henry in 2012, reported that Leiomyomas are the reason behind one-third of all hospital admissions to gynecology services and one of the commonest indications for hysterectomy. Fibroid uterus is more common among older nulliparous and obese women, particularly the ones with a family history of this disease. The true prevalence of uterine fibroids is unknown because most of these tumors are asymptomatic (Stewart *et al.,* 2017).

Uterine fibroids may occur in single but most often are multiple and vary in size, ranging from a few millimeters to over 20 centimeters in diameter, significantly enlarged, occupying the abdominal cavity. They are named according to their location. Intramural fibroids lie wholly within the uterine walls, sub-mucosal fibroids protrude into the uterine cavity and sub-serosal fibroids project to the outer surface of the uterus (DC Dutta, 2013).

Among the Traditional systems of medicine, Siddha medicine finds a significant place in the health care system of South India, Sri Lanka and Malaysia mentioned by Sabry M and Al-Hendy A in 2012. Siddha system of medicine assures a cure for certain disease conditions that are found to be complicated to treat by contemporary medical systems. Fibroid uterus, which is a pressing concern for many Indian women, can be well managed with Siddha regimen according to various traditional literatures, whereas contemporary management is by surgical intervention. Literary review reveals that the estimated rate of leiomyosarcoma was 0.51 per 1000 procedures or approximately 1 in 2000 (Elizabeth A *et al.,*2015). Another study reveals the total incidence of uterine sarcoma among patients operated for uterine leiomyoma is extremely low (0.23%). Therefore, there is the very least chance for the fibroid to present as a leiomyosarcoma (Tanos V *et al.,*2017).

The clinical features of fibroid uterus are well correlated to those of Siddha medical term "*Karppa Vippuruthi*", featured by the presence of uterine mass, pelvic pain, menorrhagia followed by amenorrhea, headache and the associated pressure symptoms like the fullness of lower pelvis region, abdominal distention and constipation (*Yugi Vaidya Chinthamani, 1998).* One of the lexicons of Siddha medicine describes "*Vippuruthi*" as tumors characterized by the formation of connective tissue connecting the epithelial cells (*Sambasivam Pillai T.V*, 1994). Hence, *Karppa Vippuruthi*, a classical Siddha terminology mentioned in *Yugi Vaidya Chinthamani,* could be rightly equated with *Karuppai Sathai Kattigal* (KSK), presenting the features of the fibroid uterus.

There is insufficient evidence to recommend any medical treatment in the management of fibroids based on the Systematic Review and Network Meta-Analysis of 47 Randomized Controlled Trials (Gurusamy K S *et al.,* 2016). Moreover, Cochrane Reviews on the use of Chinese herbal preparations and aromatase inhibitors inferred that there was no evidence to support the use of herbal preparations or aromatase inhibitors as medical therapy for treating myomas(Song H *et al.,*2013). The usefulness of acupuncture for the treatment of uterine fibroids also remains indefinite (Zhang Y *et al.,* 2010).

Hysterectomy is one of the common major surgeries in relation to non-pregnancy, uterine and ovarian tumors (Kalaiselvi R, Brundha MP, 2016). Hysterectomy should be considered only when other treatment options have failed or if there are any complications (Donnez J, Dolmans M M, 2016). Most importantly, a hysterectomy has some serious risk factors like damage to the bladder, ureter, bowel,

hemorrhage, venous thrombosis, or pulmonary embolism. The aftermath of hysterectomy is the surgical menopausal symptoms, which in turn psychologically affect the woman (Taylor M, 2001). Based on the Cochrane Database of Systematic Reviews that evaluated seven RCTs comparing Uterine artery embolization (UAE) and surgery (abdominal hysterectomy or myomectomy) concluded that the studies lack precision due to wide confidence intervals, failure to clearly report methods, and the absence of blinding for subjective outcomes. They also estimated that between 15% and 32% of subjects would require further surgery within two years of UAE (Lethaby A *et al.,* 2001).

Keeping the above hazards in the conventional treatment, the investigator selected a Siddha classical compound preparation *Rasaganthi Mezhugu* (RGM) (*Pulippani Vaithiyam -500*, 1999), which has been in safe practice for more than many hundred years with noticeably no adverse effects for uterine fibroid management. The treatment aims to relieve the symptoms and shrinkage or disappearance of the fibroid. RGM, a compound formulation consisting of 48 ingredients of herbal, metal, mineral and animal origin, is indicated in treating such conditions (*Pulippani Vaithiyam -500*, 1999). In clinical practice, many practitioners have successfully observed the shrinkage of fibroids after the administration of RGM. This compound formulation is included in "The Siddha Formulary of India", Part - I (English), 1992, which is enlisted under Drugs and Cosmetics Act, 1940(The Siddha Formulary of India, Part I,1992). The synergistic effect of ingredients in RGM also revealed its potency in the treatment of uterine fibroids (Shyamala Rajkumar, 2015). Management of fibroid uterus by classical Siddha preparation may benefit the patient to avoid the risk of surgery, thereby reducing the cost of treatment and improving the patient's quality of life. So, a maiden attempt has been put forth to validate RGM for the management of fibroid uterus.

Materials and methods

The open pilot single-arm clinical trial was approved by the Institutional Ethics Committee, Siddha Regional Research Institute (SRRI), Puducherry, India (IEC No: CCRS/SRRI-1/2011-12/02). As per the inclusion and exclusion criteria of selection, 72 subjects were screened and 26 patients were recruited for the trial. After getting the written informed consent, the trial drug *Rasaganthi Mezhugu,* 1 capsule (500 mg) was given orally twice a day after food for a period of 45 days, followed by 15 days of drug holiday and then 45 days of medicine. 20 patients completed the trial as per the original sample size calculation. A follow-up period of 6 months after the completion of 90 days of treatment was also observed to look for any recurrence of uterine fibroids. This trial was also registered in the Clinical Trial Registry of India (CTRI No: CTRI/2018/05/014338). The drug RGM (500 mg capsules) was purchased from a GMP-certified firm namely IMPCOPS Ltd. The study was conducted at OPD (Out-patient department) level of SRRI, Puducherry.

The Inclusion criteria were as follows: a) Clinical signs and symptoms of fibroid uterus for 6 months or more, b) Women in the age group of 25–55 years, c) Presence of Fibroid confirmed by Trans-vaginal Ultra Sonogram, d) Ambulatory and Co-operative. The exclusion criteria were as a) If underwent any previous procedure for fibroid uterus, b) History of malignancy in any part, c)Metabolic disorders like Diabetes Mellitus, d) Other chronic disease involving vital organs like Heart, Liver, Kidney, or lung diseases, e) HIV/AIDS and f) Chromosomal abnormality. The primary objective was to evaluate the efficacy in reducing the size of fibroids and to ease the clinical symptoms. The secondary objective was to evaluate the safety of the trial drug and to look for the recurrence of fibroids after the study period.

Haemopoietic parameters were taken before (Baseline) and after the treatment (after 90 days). Safety parameters viz Liver Function Test (LFT) and Renal Function Test (RFT) were done before treatment (Baseline), during the treatment (after 45 days) and after the treatment period (after 90 days).

Trans-vaginal ultrasonogram was done at baseline, after 90 days, i.e., 6th month (1st follow-up) and at 9th month (2nd follow-up). In addition, the clinical assessment was done before, during and after the treatment, taking into consideration the following symptoms: low back pain (Visual Analogue Scale - VAS), painful menstruation (dysmenorrhea), excessive bleeding (Menorrhagia), constipation, frequent urination, and dyspareunia. To evaluate the safety of the drug, LFT, RFT and haemopoietic parameters were done.

Results and discussion

Twenty (20) women, aged 25 to 55 years, with uterine fibroids confirmed by Trans-vaginal ultra-sonogram were enrolled and completed the study (N=20). The prevalence was also higher in women of 35-45 years (Table 1). Parity 2 was observed in 40% of patients, 25% showed Parity 1, 20% showed Parity 3 or above and 10% were nulliparous (Table 2). Out of 20 patients, 7 patients had complete disappearance of the Intramural fibroid (35%), 9 patients had a reduction in the size of the intramural and sub-mucosal fibroid (45%), 1 patient (5%) had a minimal increase in the size of the sub-serous fibroid and 3 patients (15%) did not show any difference in the size of the fibroid (Table 3). Reduction in size of the fibroid was prominent in peri-menopausal age and less reduction in size of the fibroid was observed in reproductive age.

Table 1. Age-wise distribution of uterine fibroid cases.

S. No	Age Range	Number of cases (N=20)	Percentage
1.	Between 25 - 35years	4	20 %
2.	Between 36 – 45 years	9	45 %
3.	Between 46 – 55 years	7	35 %

Amongst 20 patients, 15 patients had low back pain ranging from 4 to 8 in the Visual Analogue Scale. After 90 days of treatment, 12 patients reported no pain and in the rest of three patients, pain was reduced to 1-3 in VAS. Painful menstruation (Dysmenorrhea) was also assessed by VAS. 8 patients reported dysmenorrhea, 2 patients had severe dysmenorrhea of 8-9 in the VAS and 6patients reported to have pain in the midrange of 4 to 6.

At the end of treatment in the 90th day, 5 patients reported to have mild pain of 1-2 in the VAS. Menorrhagia was reported by only 25% of the patients in the VAS in the range of 5 to 9. All the subjects benefitted from the treatment as reported in the VAS of 1-2 after the course of the medication. 2 patients reported constipation during the initial assessment, with one patient reporting mild constipation of 3 in the VAS and another patient with severe constipation of 8 in the VAS respectively. On the 90th day, the latter patient informed reduction of the severity of constipation. Regarding frequent urination in the subjects, frequency was increased in 20 % of patients of 3 in the VAS. During the interim analysis conducted on the 45th day, all patients were relieved of the increased frequency of urination.

Table 2. Division of Uterine Fibroids in Participants according to Parity.

S. No	Parity	Number of cases (N=20)	Percentage
1	Nullipara	2	10 %
2	Parity 1	5	25 %
3	Parity 2	8	40 %
4	Parity 3 or above	4	20 %
5	Parity was not mentioned	1	5 %

Only 2 patients were admitted to suffer from dyspareunia that, too moderately of 5 in the VAS. After the completion of the course, 1 patient stated of having mild dyspareunia of 1 in the VAS. Regarding the hematological picture and safety parameters (Liver Function Test and Renal Function Test) of all the recruited subjects, there is no significant difference statistically obtained (P value >0.05) before and after the treatment (Table 4, 5, 6), hence proving the safety of the drug.

Table 3. Status of Uterine Fibroids in Participants after RGM Therapy.

S. No	Status	Number of cases (N=20)	Percentage
1	Cured	7	35 %
2	Improved	9	45 %
3	Not Improved	3	15 %
4	Size Increased	1	5 %

The anterior and posterior fibroid uterus values in centimeters were summed together and analyzed using the generalized linear model-dependent test for repeated measurements at a 5% level of significance. The subjects with no fibroids either at the anterior or posterior wall was considered as zero and patients who did not turn up for follow-up visit was treated as missing values and those missing values were imputed using LOCF (Last Observation Carried Forward). A general analysis with non-missing observation for all four visits was done and as an exploratory analysis, missing values were imputed using the LOCF method (missing value placed with last visit's available observation) and then analysis was done (Table 7, 8 & Fig. 1). The baseline values have not been carried forward.

Table 4. Haematological Parameters (N= 20).

Parameters with Unit	Before Treatment (Baseline)	After Treatment (After 90 days)
*Hb (g/dl)	9.33 ± 1.63	8.69 ± 2.03
*TC(10^3 /µL	7180.00 ± 1749.16	6440.50 ± 1516.21
Neutrophils(%)	59.85 ± 7.94	60.55 ± 8.12
Lymphocytes(%)	31.05 ± 5.00	31.95 ± 6.57
Eosinophils(%)	9.05 ± 6.10	7.35 ± 3.13
Monocytes(%)	0 ± 0	0.10 ± 0.30
*ESR ½ Hour (mm/hr)	8.35 ± 5.49	9.20 ± 5.54
ESR 1 Hour (mm/hr)	16.80 ± 11.07	17.60 ± 8.76
Sugar - Random (mg/dl)	115.10 ± 18.87	118.30 ± 17.80
Cholesterol(mg/dl)	169.20 ± 12.66	164.16 ± 18.62

*Hb= Haemoglobin, TC=Total Count, ESR=Erythrocyte Sedimentation Rate
P value >0.05=Not Significant.

From Tables 7 and 8, p-value we could say that there is a significant statistical difference from baseline to month 6 for analysis done with non-missing observation (N=15) at a 5% level of significance and there is a significant statistical difference from baseline compared to day 90, month 6 and month 9 at 5% level of significance for LOCF analysis (N=19). Patients who completed the treatment period of 90 days were N=20 and follow-up visits were considered for the recurrence of fibroids (N=19 at month 6 follow-up and N=15 at month 9 follow-up). Uterine fibroids remain the main cause of morbidity in women of reproductive age and occasionally even after menopause. There are numerous factors that are responsible for the growth and occurrence of these common tumors, but this supports their relatively unknown etiology. The symptomatology of fibroid uterus is correlated in Siddha pathology as '*Karppa*

Vippuruthi', commonly called as '*Karuppai Sathai Kattigal/ Karuppai Naarthasai kattigal* featured by abdominal distension, lower abdominal pain, weight loss, the proliferation of uterine tissue with blood clots which gives a mass like structure and produce symptoms similar to rolling of the fetus during pregnancy, constipation, headache and ulceration of the uterus (*Yugi Vaidya Chinthamani*, 1998).

Table 5. Liver Function Test (N= 20).

Parameters with Unit	Before Treatment (Baseline)	During Treatment (After 45 days)	After Treatment (After 90 days)
Total Bilirubin(mg%)	0.74 ± 0.17	0.81 ± 0.10	0.78 ± 0.15
Direct Bilirubin(mg%)	0.20 ± 0.18	0.15 ± 0.05	0.13 ± 0.07
*AST(U/lit)	31.60 ± 17.27	35.95 ± 12.98	29.10 ± 8.92
*ALT(U/lit)	35.45 ± 11.88	47.80 ± 17.60	37.26 ± 8.31
*ALP(U/lit)	191.10 ± 23.06	213.90 ± 21.02	199.47 ± 28.71

*AST=Aspartate Transaminase, ALT= Alanine Transaminase, ALP=Alkaline Phosphatase

P value >0.05=Not Significant.

Table 6. Renal Function Test (N= 20).

Parameter	Before Treatment (Baseline)	During Treatment (After 45 days)	After Treatment (After 90 days)
Urea (mg%)	27.45 ± 5.02	27.37 ± 3.20	29.50 ± 3.81
Creatinine(mg%)	0.84 ± 0.16	0.89 ± 0.13	0.98 ± 0.12
*BUN(mg/dl)	14.40 ± 3.77	14.69 ± 3.07	14.78 ± 2.87
Total Protein(gm%)	6.37 ± 1.38	6.76 ± 0.48	6.41 ± 0.47
Albumin(gm%)	3.94 ± 0.48	4.13 ± 0.24	3.91 ± 0.41
Globulin(gm%)	2.74 ± 0.47	2.50 ± 0.46	2.45 ± 0.45
Uric acid(mg%)	4.59 ± 0.62	4.60 ± 0.78	4.68 ± 0.51
Calcium(mg%)	8.89 ± 0.63	9.24 ± 0.64	8.95 ± 0.96
Bicarbonate(mEq/L)	21.70 ± 3.49	21.23 ± 3.19	21.05 ± 3.98

*BUN=Blood Urea Nitrogen

P value >0.05=Not Significant.

According to the Siddha concept, any growth in the body is attributed to the phlegm humor called *Iyyam*. The five elemental theory of Siddha science describes the constitutional generation of phlegm humor as composed of the basic elements of Earth and Water responsible for the growth and nourishment of all cellular entities. Therefore, an abnormal growth or mass development within the body is purely the result of vitiation of phlegmatic humor due to various reasons, including diet, lifestyle variations and hereditary influences (Dr. Shanmugavel M, 2006). The science of six tastes plays a vital role in Siddha pharmacology, and those tastes that nullify the deranged *Iyyakutram* promote the shrinkage of any type of abnormal growth (Dr. M. Shanmugavel, 2006).

Table 7. Descriptive statistics of anterior + posterior fibroid size (cm) visit-wise – LOCF.

	Baseline	Day 90	1st Follow-up (Month 6)	2nd Follow-up (Month 9)
N	19	19	19	19
Average	12.05	6.92	5.28	5.13
SD	12.654	9.789	9.198	7.940
Min	1.1	0	0	0
Median	9.18	2.4	1.96	1.68
Max	48.28	32.3	29.6	29.49

The drug, which pacifies the vitiated phlegm humor, has a direct or indirect effect on tumour cells. *Rasaganthi Mezhugu* (RGM) is a classical poly herbo-mineral formulation with 48 ingredients of Herbal, Metal, Mineral and Animal origin. Most of the herbal sources used in this preparation possess astringent, bitter, pungent and sour tastes and the combined cumulative effects support the six-taste concept in tumorous conditions (Murugesa mudhaliyar K.S, 2008). All the ingredients were subjected to a specific Standard Operating Procedure (SOP) of detoxication mentioned in the Siddha classical texts. Likewise, the toxicities of metals and minerals may be antagonized by the active principles of the herbs. A literary review reveals that the classical preparation RGM is indicated for the management of tumors (*The Siddha Formulary of India*, 1992). Earlier, many clinical trials and pharmacological studies with RGM had been conducted. The safety of the RGM has been established through various research conducted earlier. An acute toxicity study indicated that 1.5 g/kg body weight RGM given orally to rats did not induce any mortality, revealing the safety profile of the drug. This concentration is almost 150 times higher than the therapeutic dose and 75 times higher than the therapeutic dose for 60 days in a chronic toxicity study that revealed no significant organ damage or haematological toxicity in animals.

Table 8. Efficacy of RGM from baseline compared with a follow-up visit.

Visit	N	Mean	Mean Difference From Baseline	p-value
Non-Missing Observation				
Baseline	15	12.60		
Day 90	15	8.15	4.457	0.054
Month 6	15	6.16	6.448	0.000
Month 9	15	5.97	6.637	0.051
LOCF				
Baseline	19	12.05		
Day 90	19	6.92	5.131	0.021
Month 6	19	5.28	6.771	0.000
Month 9	19	5.13	6.919	0.011

Administration of RGM for one year in HIV patients found that RGM did not alter the haematological and serum parameters and also the hepatic and renal function parameters (Tharakan S T, 2010).

Chloroform fraction of RGM (CRGM) demonstrated that it inhibits the proliferation and induces apoptosis in HPV- Positive cervical cancer cells. Also, it has been concluded that apoptosis is through the mitochondria-mediated pathway. The comet assay results revealed that CRGM breaks strands in the DNA of cervical cancer cells had been reported (Riyasdeen A, *et al.,* 2012).

Implications for policy and/or practice

A maiden attempt has been put forth to validate the traditional Siddha compound formulation for the management of uterine fibroids, which is a consequential healthcare implication on women's health. According to an epidemiological study, fibroids account for 29% of gynecologic hospitalizations and surgical interventions (Pavone D, *et al.,* 2018). Therefore, this Siddha medicine is a viable option for women who opt for complementary and integrative treatments. This herbo-mineral intervention is a safe and effective regimen that possesses Cytotoxic, Immuno-modulatory, Anti-tumor and Antioxidant activity. Based on the preliminary results obtained, Central Council for Research in Siddha (CCRS), Ministry of AYUSH, Govt of India, an apex body for research in Siddha will be conducting multicentric studies on non-surgical management of "*Karuppai Sathai Kattigal*" (fibroid uterus) with classical Siddha formulation RGM.

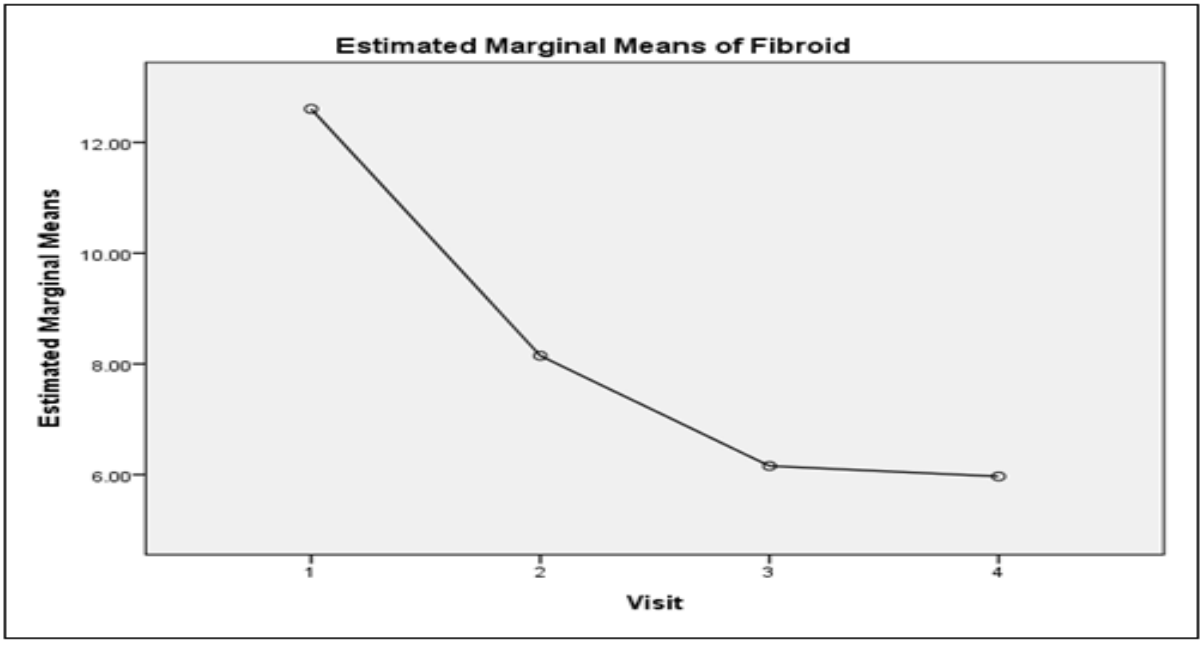

Fig. 1. Estimated Marginal Means of Fibroid.

This multicentric study is being conducted in four centers across the country as per AYUSH Good Clinical Practice (GCP) guidelines. Moreover, this drug RGM is used widely by Siddha practitioners, particularly for fibroid and various clinical manifestations, as mentioned in the official gazette publication Siddha Formulary of India, Part -I.

Conclusion

The clinical trial conducted was reported to be beneficial in the non-surgical management of fibroid uterus with the classical Siddha formulation RGM. Based on this preliminary result, RGM is found to be safe and effective as a single drug therapy in *Karuppai Sathai Kattigal*. On the other side, the clinical trial with RGM in fibroid uterus cases throws light on several areas to be focused on in the future by conducting a multicentric trial. Since it is an observational, open pilot clinical trial with a sample size of 20 and with a satisfactory outcome, a multicentric study with a larger sample size in four centers of CCRS institutes/units is in progress so as to obtain statistically significant data which will enable the researchers to generalize the effectiveness of RGM for the fibroid uterus patients.

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Author's contribution

The mentioned authors are eligible to be an author as per the guidelines of the International Committee of Medical Journal Editors (ICMJE).

Conflict of interest

None declared.

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References

Donnez J, Dolmans MM. 2016. Uterine fibroid management: From the present to the future, Human Reproduction Update **22(6)**, 665–686.

Dr. Shanmugavel M. 2006. *Noinaadal Noi muthalnaadal Thirattu*. Directorate of Indian Medicine and Homeopathy, Chennai, India, Part **2**.

Dutta DC. 2013. Dc Dutta's Textbook of Gynaecology. Jaypee Brothers Medical Publishers (P) Ltd, 6th Edition.

Elizabeth AP, David JV, Jonathan SB, William P, Ronald F, Jacqueline F, David LO. 2015. The prevalence of occult leiomyosarcoma at surgery for presumed uterine fibroids: A meta-analysis. Gynecological Surgery **12,** 165–177.

Geethamala K, Murthy VS, Vani BR, Rao S. 2016. Uterine Leiomyomas: An ENIGMA. Journal of Mid-Life Health **7(1),** 22–27.

Gurusamy KS, Vaughan J, Fraser IS, Best LMJ, Richards T. 2016. Medical Therapies for Uterine Fibroids – A Systematic Review and Network Meta-Analysis of Randomised Controlled Trials. PLoS ONE, **11(2).**

Kalaiselvi R, Brundha MP. 2016. Prevalence of Hysterectomy in South Indian Population. Research Journal of Pharmacy and Technology **9(11).**

Khan AT, Shehmar M, Gupta JK. 2014. Uterine fibroids: Current perspectives. International Journal of Women's Health **6,** 95–114.

Lethaby A, Vollenhoven B, Sowter M. 2001. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. The Cochrane Database of Systematic Reviews **(2),** CD000547–CD000547.

Murugesa Mudhaliyar KS. 2008. *Gunapadam-Mooligai Vaguppu*, Directorate of Indian Medicine and Homeopathy, Chennai, 2nd Edition.

Pavone D, Clemenza S, Sorbi F, Fambrini M, Petraglia F. 2018. Epidemiology and Risk Factors of Uterine Fibroids. Best Practice & Research Clinical Obstetrics & Gynaecology **46,** 3–11.

Ramachandhiran SP (Ed.). 1999. *Pulippani Vaithiyam* -500 (1st Edition). Thamarai Noolagam, Chennai.

Riyasdeen A, Periasamy VS, Paul P, Alshatwi A, Akbarsha MA. 2012. Chloroform Extract of *Rasaganthi Mezhugu*, a Siddha Formulation, as an Evidence-Based Complementary and Alternative Medicine for HPV-Positive Cervical Cancers. Evidence-Based Complementary and Alternative Medicine, 1–10.

Sabry M, Al-Hendy A. 2012. Innovative Oral Treatments of Uterine Leiomyoma. Obstetrics and Gynecology International. Hindawi Publishing Corporation **2012,** Article ID 943635, 10 pages. http://dx.doi.org/10.1155/2012/9436351–10.

Sambasivam Pillai TV. 1994. Dictionary of Medicine, Chemistry, Botany and Allied Sciences, Madras, Govt. Central Press, **5.**

Shyamala Rajkumar, Vijaya Kumar V, Ponmuthu Rani C, Gopakumar K, Ramaswamy RS. 2015. Management of Fibroid Uterus with a Traditional Siddha Formulation – A Review. International journal of multidisciplinary health sciences **1(1).**

Song H, Lu D, Navaratnam K, Shi G. 2013. Aromatase inhibitors for uterine fibroids. In The Cochrane Library. John Wiley & Sons, Ltd.

Stewart E, Cookson C, Gandolfo R, Schulze-Rath R. 2017. Epidemiology of Uterine fibroids: A Systematic Review. BJOG: An International Journal of Obstetrics & Gynaecology **124(10),** 1501–1512.

Tanos V, Brölmann H, De Wilde RL, O'Donovan P, Symeonidou E, Campo R. 2017. Survey among ESGE members on leiomyosarcoma morcellation incidence. Gynecological Surgery **14(1).**

Taylor M. 2001. Psychological consequences of surgical menopause. The Journal of Reproductive Medicine **46(3),** 317–324.

Tharakan ST, Kuttan G, Kuttan R, Kesavan M, Rajagopalan K. 2010**.** Toxicity Studies of Siddha Medicine- Rasagandhi Mezhugu. The Open Toxicology Journal **4(1).**

The Siddha Formulary of India. 1992. 1st Edition, Govt. of India Press, Chennai. *Yugi Vaidya Chinthamani*, 1998, Directorate of Indian Medicine and Homeopathy, 1st Edition, Chennai.

Zhang Y, Peng W, Clarke J, Liu Z. 2010. Acupuncture for uterine fibroids. The Cochrane Database of Systematic Reviews **(1),** CD007221.