AYUSHDHARA

An International Journal of Research in AYUSH and Allied Systems

Research Article

A CLINICAL STUDY OF MARKET SAMPLES OF *NAGAKESARA* IN THE MANAGEMENT OF POLY CYSTIC OVARIAN DISEASE (PCOD)

Nikath. S[1]*, Sitaram Bulusu[2], Suneela.P[3]

*[1]P.G.Scholar, [2]Professor, [3]Associate Professor, Department of Dravyaguna, S.V. Ayurvedic College, Tirupati, A.P, India.

*Address for correspondence
Dr Nikath. S
P.G.Scholar, Department of Dravyaguna, S.V. Ayurvedic College, Tirupati, A.P, India.
Email: drnikhath90@gmail.com
Ph: 9000885785

ABSTRACT

This study was conducted to evaluate the efficacy of different market samples of *Nagakesara* in cases of PCOD. In this study 30 patients were divided into 3 groups. Group 1: MF Group (*Mesua ferrea* Linn*. powder with milk), Group 2: OL Group (*Ochrocarpus longifolium* Benth & Hook. f; powder with milk), Group 3: CT Group *(Cinnamomum tamala* Nees & Ebern powder with milk) and advocated the trial drug with a dosage of 40-50mg/kg body weight per day for a duration of 3months with a follow up of every 15days. Subjective parameters like duration of menstruation, gap between two cycles, pain during menstruation, quantity of menstrual bleeding, Acne, Hirsutism, Acanthosis nigracans, Obesity are taken and results were analyzed statistically before and after treatment. Group 1 showed that 10% of the patients recovered completely, 55.09% recovered moderately and 35% remains unchanged. Group 2 showed that 10% of the patients recovered completely, 45.66% moderately and 44% remains unchanged. Group 3 showed that 0% of the patients recovered completely, 52% recovered moderately and 48% remains unchanged. *Mesua ferrea* showed extremely significant result i.e., $P<0.001$ in duration of menstruation (67.85%), gap between two cycles (65.62%), quantity of menstrual bleeding (66.66%). All the observations related to the total effect of therapy suggests that patients of Group 1 were well responded to the therapy than the patients of Group 2 and Group 3. **Conclusion:** The present comparative clinical study shows that the *Amapachana* property, the capacity to induce ovulation and reduction in the clinical features are more clearly observed in *Mesua ferrea* Linn. than in others.

INTRODUCTION

Ayurveda is the oldest system of life science, health care and cure, its antiquity goes back to the Vedas. Traditional medicinal literature appreciated their value as nature's gift to mankind for the healing of illnesses.

Diseases of longevity often referred as "lifestyle disorders" are posing a great threat to the overall health of the society. Among those, Poly Cystic Ovarian Disease (PCOD) is considered as one of the major burning issue with symptoms like irregular menstruation, oligomenorrhoea/ amenorrhea, infertility, obesity, hirsutism and acne vulgaris. PCOD is one of the most common reasons for menstrual irregularities of women of

reproductive age with 4-12% (12-45yrs old). Women develop PCOD during their teenage or child bearing years with 5-10%. Worldwide PCOD affects up to 6-7% of the total population.[1]

Nagakesara mentioned in classical works has become controversial because of improper identification, using the drug with different names in different areas and many other contributing factors like cheating trade.

As it is not a single disease it is not possible to correlate PCOD with any one of the condition explained in the classics. But PCOD can be understood with clinical condition like *Artava Kshaya, Anartava, Nastartava, Kshinartava, Vandhya*

Yonivyapat, Pushpaghni-Jataharini, Sthoulya and *Prameha.* Recently, there has been an increased in interest in the field of PCOD research. Thousands of articles were published in the past five years concerning the different aspects and relationships regarding PCOD. Despite the high and increasing incidence of PCOD among the population, there are several aspects that remain ambiguous.[2]

Aims and Objectives

Initially this study is aimed at finding out a feasible solution in resolving the controversy of *Nagakesara* through its clinical use in PCOD.

- To procure different market samples of *Nagakesara*.
- To identify pharmacognostically the source plants of the samples.
- To evaluate the efficacy of samples in cases of PCOD.

Materials and Methods

Drug

1. Sample collection

The three market samples of *Nagakesara* will be collected from three different places i.e., Hyderabad, Chennai and Bangalore and they will be processed separately for internal administration at Srinivasa Ayurveda Pharmacy, Tirupathi, into 500mg tablets each.

2. Processing of the drug

- Drying of the drug
- Making powder by using Pulveriser
- Making tablets by using tablet making machine

Plan of Study

1) Criteria for selection of patients
2) Criteria for diagnosis
3) Method of research
4) Criteria for assessment

Criteria for Selection of Patients

Inclusion criteria

- Female patients suffering from PCOD diagnosed through Ultrasonography.
- Age between 18-40 years.
- Both married and unmarried females.

Exclusion criteria

- Age below 18 years and above 40 years.
- Primary PCOS.
- Pituitary abnormalities.
- Hyper and Hypo Thyroidism.
- Patients with other disorders of serious consideration.

The Drug

- The market samples were collected separately and powdered well. They were made into

tablets weighing 500mg each and stored with separate marks.

Criteria for Diagnosis

All the patients confirming the above said inclusion criteria were taken for the study and subjected to thorough interrogation, general, systemic examinations and investigations and the data obtained from them were noted in the specially prepared research proforma. Patients were selected on the basis of their clinical presentation particularly related to Poly Cystic Ovarian Disease. The compulsory criteria is being the presence of PCOD in Ultrasonography.

Investigations [3]

Laboratory investigations were carried out before and after treatment to rule out any other pathological conditions as well as to record any specific change by the treatment.

Haematological

Routine haematological examinations like,

- Hb%, TLC, DLC, E.S.R.
- F.B.S. and P.P.B.S.
- Thyroid profile.

Urine

- Routine and microscopic examination.

Other Blood Tests

i) Lipid profile
ii) Glucose Tolerance Test

Special Investigations

- Ultrasonography (USG)
- If necessary, Hormonal Assay likes Serum Estrogen, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Testosterone etc.

Method of Research

The method adopted in the present study is a randomized open label clinical trial before and after the treatment. The study had a due clearance from the Institutional Ethics Committee.

Informed Consent

The purpose of the study, nature of the study, drugs, the procedures to be carried out and the potential risks and benefits were explained to the patients in detail in non-technical terms and trilingual. Thereafter their written consent was taken before starting the procedure.

Diagnostic Criteria

Patients were examined clinically and details regarding disease starting from history taking, physical examination, signs and symptoms as mentioned in our classics and allied sciences and relevant lab investigations were recorded in a specially prepared proforma.

Special clinical proforma for the assessment of subjects was prepared, based on criteria of selection and parameters. Special grading was given to chief symptoms/signs of PCOD. Informed consent of all the registered subjects was taken.

Criteria for Assessment

Patients were assessed before and after treatment for subjective and objective parameters.

Subjective Parameters

Subjective criteria

Assessment was totally based on the changes in the clinical features of Poly Cystic Ovarian Disease and improvement in scoring index of Duration of menstruation, gap between two cycles, pain during menstruation, acne, hirsutism, etc.[6] For all these symptoms, the following symptom scores were given depending upon the changes seen before and after the treatment.

Table 1: Showing PCOD grading scale for subjective parameters

Parameters	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
A) Duration of Menstruation					
a) Menorrhagia	3–5 days	6 – 8 days	9 – 12 days	12 – 14 days	>15 days
b) Hypomenorrhea	3–5 days	2 – 3 days	1 – 2 days	<1 day	Spotting
B) Gap between two cycles					
a) Oligomenorrhea	25- 35 days	36 – 60 days	61 – 90 days	91 – 120 days	>120 days
b) Epimenorrhea	25 -35 days	20 – 25 days	15 – 20 days	10 – 15 days	<10 days
C) Pain during Menstruation	No pain (not disturbing the normal activities)	Bearable pain	Requirement of oral analgesics	Requirement of injectable Analgesics	__
D) Quantity of Menstrual bleeding					__
a)Heavy bleeding	2 pads/ day	3 – 4 pads /day	5 – 6 pads/day	7 pads and above	
b) Scanty bleeding	2 pads/ day	1 pad/day	<1 pad/ day	Just appears	
E) Acne	No acne	1 or 2 acne seen only on face (on & off)	Appears on face before periods and subsides after periods	Persistent acne on face	Spreading of acne in other parts of the body
F) Hirsutism	Normal distribution of hair	Mild coverage (Thin distribution hair on chin, cheeks and moustache)	Moderate coverage (Thick distribution of hair on chin, cheeks and moustache)	Heavy coverage (Thick distribution of hair on chin, cheeks and moustache and other parts of body and grows rapidly)	__
G) Acanthosis Nigracans	Nil	Mild	Moderate	Severe	__
H) Obesity (BMI)	20 – 25 kg/m²	25 – 30 kg/m²	30 – 40 kg/m²	More than 40 kg/m²	__
I) Ultrasonography					
i) Rt Ovarian volume	5 – 10 ml	11 – 15ml	16 – 20ml	20 – 25ml	__
ii) Lt Ovarian volume	5 – 10 ml	11 – 15ml	16 – 20ml	20 – 25ml	
iii) Number of follicles	<3	4 - 8	9 – 10	11 – 12	>12

Analysis and interpretation: Assessment is made according to gradation given in case sheet, later the result is analysed and interpreted into the hypothesis.

Treatment protocol

After the proper diagnosis, patients were divided into 3 groups irrespective of their age, socio-economic status, religion etc. All the patients were given *Deepana, Pachana* drugs for 7 days. During this period, the investigations were carried out and there after the drugs were administered

Grouping and posology

Patients were divided randomly into three groups each consisting of ten members.

- ❖ Group 1: MF Group (*Mesua ferrea* Linn**.**)
- ❖ Group 2: OL Group (*Ochrocarpus longifolium* Benth & Hook. f)
- ❖ Group 3*:* CT Group (*Cinnamomum tamala* Nees & Ebern)
- ❖ Dose : "40-50 mg/kg (1-3gms app per day) body weight" per day[4]
- ❖ Dosage form : Tablet form
- ❖ *Anupana* : Milk
- ❖ Duration : 3 months
- ❖ *Aushadasevanakalam* : *Abhaktam*

Follow Up

Total days of treatment follow up visits: 6 visits

Post treatment follow up   : 2 visits

Observation and Results

Table 2: Statistical Significance of Group 1 (*Mesua ferrea)*

	Mean		Sd			Sem	Df	T value	P Value	Significance
	BT	AT	BT	AT	BT	AT				
Duration of menstruation	2.80	0.90	1.32	0.32	0.42	0.10	9	5.0186	0.0007	Extremely Statistically significant
Gap between two cycles	3.20	1.10	1.03	0.88	0.33	0.28	9	4.8462	0.0009	Extremely Statistically significant
Pain during menstruation	2.80	1.00	1.32	0.94	0.42	0.30	9	4.3235	0.0019	Very Statistically significant
Quantity of menstrual bleeding	1.50	0.50	0.79	0.50	0.25	0.17	9	1.96	0.002	Extremely Statistically significant
Acne	0.50	0.30	0.97	0.67	0.31	0.21	9	1.5	0.167	Statistically not significant
Hirsutism	0.80	0.70	1.03	1.06	0.33	0.33	9	1	0.34	Statistically not significant
Acanthosis Nigracans	1.10	0.80	1.29	1.14	0.41	0.36	9	1.96	0.081	Statistically not significant
Obesity	0.40	0.20	0.84	0.42	0.27	0.13	9	1.5	0.16	Statistically not significant
Mood Changes	0.40	0.20	0.84	0.42	0.27	0.13	9	1.5	0.16	Statistically not significant
U/S Rt Ovary	1.60	0.90	0.84	0.74	0.27	0.23	9	4.5	0.0013	Very Statistically significant
U/S Lft Ovary	1.70	1.30	0.82	0.82	0.26	0.26	9	2.44	0.036	Statistically significant
Number of follicles	2.10	2.00	0.57	0.94	0.18	0.30	9	0.3612	0.726	Statistically not significant

Table 3: Statistical Significance of Group 2 (*Ochrocarpus Longifolius*)

Df - 9	Mean		Sd		Sem		T value	P Value	Significance
	BT	AT	BT	AT	BT	AT			
Duration of menstruation	1.10	0.70	0.74	0.67	0.23	0.21	2.4495	0.0368	Statistically significant
Gap between two cycles	1.60	1.10	0.70	0.57	0.22	0.18	1.7556	0.0962	Statistically not Significant
Pain during menstruation	1.20	0.60	0.63	0.52	0.20	0.16	2.3238	0.0320	Statistically significant
Quantity of menstrual bleeding	1.80	1	0.42	0.47	0.13	0.15	4.0000	0.0008	Very Statistically significant
Acne	1.20	0.70	0.92	0.67	0.29	0.21	1.3868	0.1825	Not Statistically significant
Hirsutism	1.00	0.80	1.25	1.14	0.39	0.36	0.3750	0.7120	Statistically not significant
Acanthosis Nigracans	1.20	0.50	1.14	0.85	0.36	0.27	1.5609	0.1360	Statistically significant
Obesity	1.50	1.00	1.08	1.25	0.34	0.39	0.9583	0.3506	Statistically significant
Mood Changes	1.00	0.80	0.82	0.79	0.26	0.25	0.5571	0.5843	Statistically not significant
U/S Rt Ovary	1.50	1.30	0.85	0.95	0.27	0.30	0.4966	0.6255	Statistically not significant
U/S Lft Ovary	1.30	1.00	0.67	0.82	0.21	0.26	0.8955	0.3823	Statistically not significant
Number of follicles	1.90	1.50	0.32	0.53	0.10	0.17	2.0580	0.0544	Statistically Not Significant

### Table 4: Statistical Significance of Group 3 (*Cinnamomum Tamala*)

Df-9	Mean		Sd		Sem		T value	P Value	Significance
	BT	AT	BT	AT	BT	AT			
Duration of menstruation	1.20	0.60	1.32	0.84	0.42	0.27	2.7136	0.0239	Statistically significant
Gap between two cycles	2.00	1.30	0.82	0.67	0.26	0.21	3.2796	0.0095	Very Statistically Significant
Pain during menstruation	0.70	0.40	0.95	0.52	0.30	0.16	1.9640	0.0811	Statistically not significant
Quantity of menstrual bleeding	1.30	0.50	0.95	0.53	0.30	0.17	4.0000	0.0031	Very Statistically significant
Acne	0.50	0.30	0.53	0.48	0.17	0.15	1.500	0.1679	Statistically not significant
Hirsutism	1.00	0.70	1.05	0.95	0.33	0.30	1.9640	0.0811	Statistically not significant
Acanthosis Nigracans	1.10	0.50	1.10	0.53	0.35	0.17	2.2500	0.0510	Statistically not significant

Obesity	1.30	1.00	0.95	0.82	0.30	0.26	1.1523	0.2789	Statistically not significant
Mood Changes	1.20	0.80	0.92	0.79	0.29	0.25	1.5000	0.1679	Statistically not significant
U/S Rt Ovary	1.40	1.20	0.52	0.79	0.16	0.25	1.500	0.1679	Statistically not significant
U/S Lft Ovary	2.20	1.70	0.63	0.67	0.20	0.21	3.000	0.0150	Statistically significant
Number of follicles	1.70	1.50	0.48	0.53	0.15	0.17	1.5000	0.1679	Statistically not significant

Table 5: Overall result of the study – % of relief parameters wise result in Group 1, Group 2 & Group 3

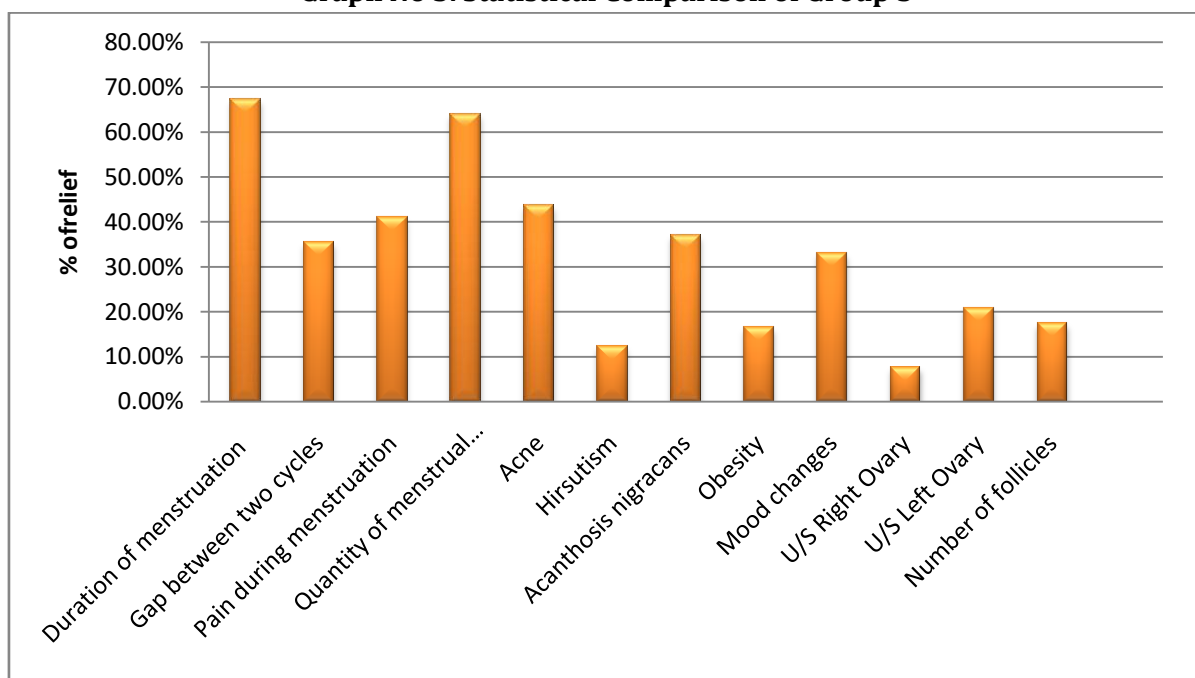| Parameters	Group 1	Group 2	Group 3
Duration Of Menstruation	67.85%	36.36%	50%
Gap Between Two Cycles	65.62%	31.25%	35%
Pain During Menstruation	64.28%	50%	42.8%
Quantity of Menstrual Bleeding	66.66%	44.44%	61.53%
Acne	40%	41.6%	40%
Hirsutism	12.5%	20%	30%
Acanthosis Nigracans	27.2%	58.3%	54.5%
Obesity	50%	33.33%	23%
Mood Changes	50%	20%	33.3%
U/S Right Ovary	43.75%	13.33%	14.2%
U/S Left Ovary	23.52%	23%	22.7%
Number Of Follicles	4.76%	21%	11.7%

Graph No 1. Statistical Comparison of Group 1
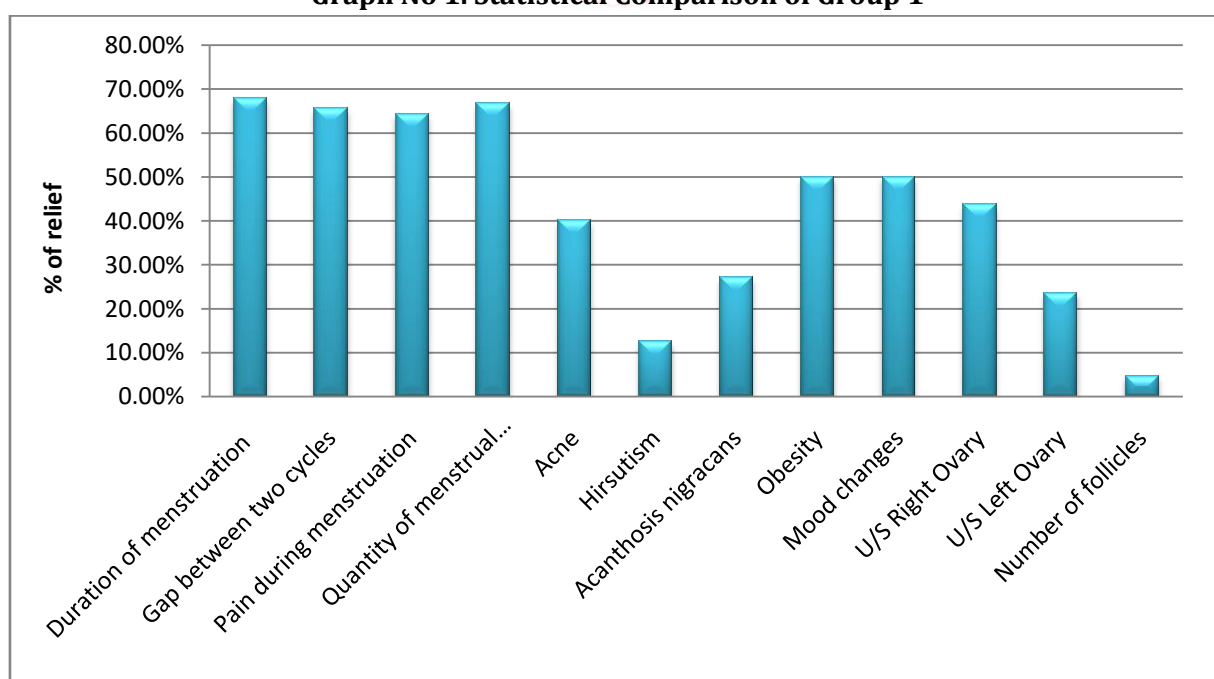
Graph No 2. Statistical Comparison of Group 2
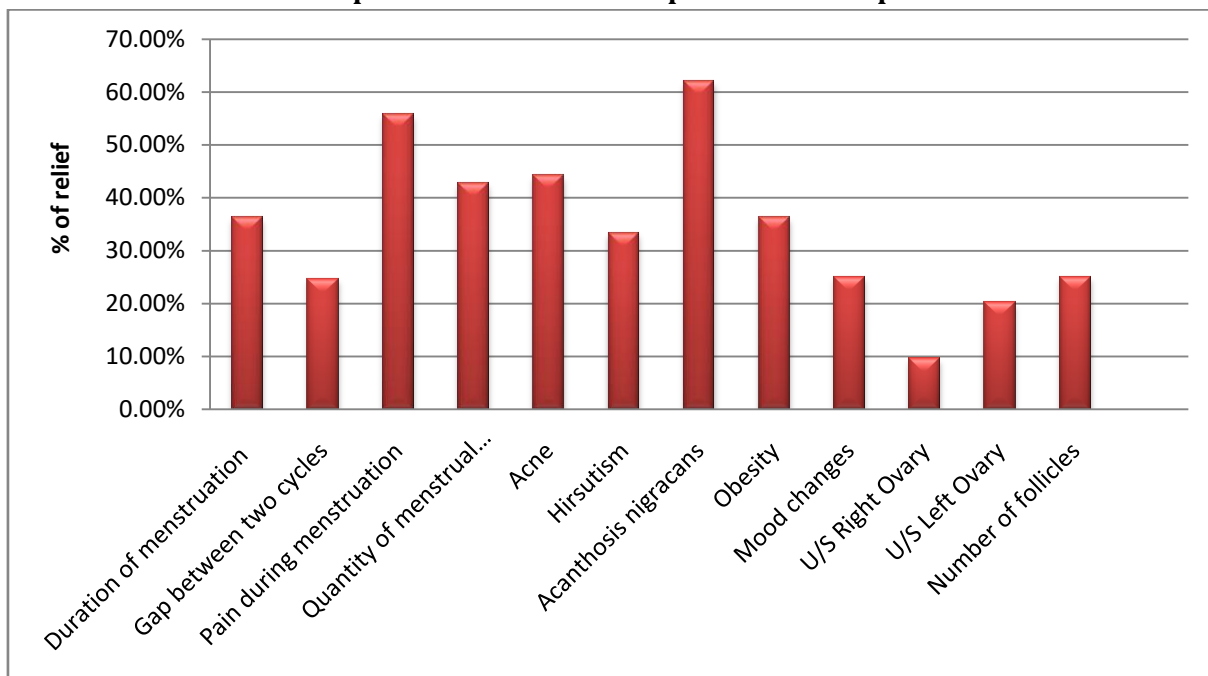
Graph No 3. Statistical Comparison of Group 3

Table 6: Improvement Wise Result in Group 1, Group 2 & Group 3

Overall Effect	Group 1	Group 2	Group 3
Completely relieved	10%	10%	0%
Moderately relieved	55.09%	45.66%	52%
Unchanged	35%	44%	48%

DISCUSSION

Interpretation of results in Group 1

Nagakesara in Group 1 (*Mesua ferrea* Linn with milk) has shown following results.

- *Mesua ferrea* shown extremely significant result i.e., P<0.001 in duration of menstruation

(67.85%), gap between two cycles (65.62%), quantity of menstrual bleeding (66.66%). This proves that *Mesua ferrea* Linn. can be utilized to promote menstruation and correct the cycles.

- *Mesua ferrea* shown very significant result i.e., P=0.001 in Pain during menstruation (64.28%), U/S right ovarian volume (43.75%). As *Artava* is properly or timely formed which was proved by above result, so probably *Suddha artava lakshanas* are also associated.

- *Mesua ferrea* shown insignificant result i.e., P>0.05 in acne (40%), hirsutism (12.5%), *Acanthosis nigracans* (27.2%), obesity (50%), Mood changes (50%), number of follicles (4.76%). These all features occur due to increased androgen levels or *Sukradushti*. The drug might be effective in clearing the *Rasa-Raktavaha* channels only or dosage of drug and duration of course might be insufficient to bring complete relief in the above features.

Interpretation of results in Group 2

Surapunnaga in Poly cystic ovarian disease in Group - 2 (*Ochrocarpus longifolius* Benth & Hook f. with milk) has shown following results.

- *Ochrocarpus longifolius* has shown very significant result i.e., P=0.001 in quantity of menstrual bleeding (44.44%).

- *Ochrocarpus longifolius* has shown significant result i.e., P<0.05 in duration of menstruation (36.36%), pain during menstruation (50%), acne (41.6%), *Acanthosis nigracans* (58.3%), obesity (33.33%).

- *Ochrocarpus longifolius* shown insignificant result i.e., P>0.05 in gap between two cycles (31.25%), hirsutism (20%), mood changes (20%), U/S right ovary (13.33%), U/S left ovary (23%), number of follicles (21%). Though this has shown very significant result in quantity of menstruation, as this is not having the equivalent qualities like *Mesua ferrea,* it could not show significant improvement in other clinical features like interval between two cycles, duration of menstruation, pain etc.

Interpretation of results in Group 3

Tamalapatra in Poly Cystic Ovarian Disease in Group - 3 (*Cinnamomum tamala* Nees & ebern with milk) has shown following results.

- *Cinnamomum tamala* has shown very significant result i.e., P=0.001 in gap between two cycles (35.44%).

- *Cinnamomum tamala* has shown significant result i.e., P<0.05 in duration of menstruation (50%), quantity of menstrual bleeding (61.53%), U/S left ovary (20.85%).

- *Cinnamomum tamala* shown insignificant result i.e., P>0.05 pain during menstruation (42.8%), acne (40%), *Acanthosis Nigracans* (54.5%), obesity (23%), hirsutism (30%), mood changes (33%), U/S right ovary (13.33%), U/S left ovary (22.7%) number of follicles (11.7%).

- Cinnamomum could be able to show better efficacy only in the interval of menstrual cycle which is also very less i.e., 35.44%, but showed significant efficacy in duration and quantity of menstruation upto some extent. These results indicate that cinnamomum also has the property of in *Artavajanana*, but this is not equivalent to *Mesua ferrea.*

Overall effect of the clinical trial

- The overall effect of the clinical trial on Group 1 (*Nagakesara* with milk) shows that patients (10%) were completely cured, (31.8%) were cured moderately and (35%) were unchanged.

- The overall effect of the clinical trial on Group 2 (*Surapunnaga* with milk) (23.86%) were completely cured, (31.8%) were cured moderately, (44%) were unchanged.

- The overall effect of the clinical trial on Group 3 (*Tamalapatra* with milk) (19%) were completely cured, (32%) were cured moderately (48%) were unchanged.

Discussion on overall effect

As per the clinical study, there are very few completely relieved patients even in 1st and 2nd group. Though there is highly significant improvement in subjective parameters, as per ultrasound diagnosis, the improvement was non-significant. As ultrasound investigation is considered the main diagnostic criteria in the present study, this result was observed. In the 1st group, one patient conceived after the treatment. She was totally relieved from PCOD as observed through Ultrasonography. In the 2nd group also, in one patient, Ultrasound report appeared normal.

All the observations related to the total effect of therapy suggests that patients of Group 1 were well responded to the therapy than the patients of Group 2 and Group 3.

The present clinical study proved that *Nagakesara* is one of the best *Artavajanaka* and is effective in PCOD.

As per classics, *Nagakesara* is the best *Amapachaka* and it is used clinically as an ovulation inducing drug. The *Nidana* of PCOD also gives an inference that *Vata* and *Kaphadushti* are more in this disease which results in *Amotpatti* and there by the disease PCOD is manifested.[5]

As the disease PCOD is a syndrome complex, it is very difficult to assess the efficacy with single Ayurvedic drug. But the present drug *Nagakesara*

has proved that it has significant efficacy in the management of PCOD.

The present comparative clinical study shows that the *Amapachana* property, the capacity to induce ovulation and reduction in the clinical features are more clearly observed in *Mesua ferrea* Linn. than in others.

In context to induction of ovulation or PCOD, it is better to use *Mesua ferrea* Linn. Along with this drug, if other drugs that have synergetic action in induction of ovulation are combined, the efficacy may be enhanced.

On par with *Mesua ferrea* Linn. the remaining two drugs cannot be considered as substitutes, particularly in induction of ovulation or in the management of PCOD. But *Surapunnaga* (*Ochrocarpus longifolius* Benth & Hook f.), can be used as an adjuvant to *Mesua ferrea* Linn. in *Acanthosis nigracans*. The synergetic action of these two are proved, the combination may give a better result in PCOD.

CONCLUSION

- PCOD consists of gross symptoms like *Anartava, Sthoulya, Vandhyatwa, Yavana Pidaka* etc.
- The total number of patients was divided into three groups adjusting each 10 in a Group. They were grouped into Group 1, 2 & 3.
- The patients of Group 1 were administered the powdered drug of *Mesua ferrea* Linn. The 2nd Group was given *Ochrocarpus longifolius* Benth & Hook.f, and the 3rd Group was given the Buds of *Cinnamomum tamala* Nees & Ebern.
- The treatment continued for all the groups for a period of 3 months with a follow up of one more month and the results were tabulated.
- In the present study Group 1 (*Mesua ferrea* Linn. with milk) shows that 10% of the patients recovered completely, 55.09% recovered moderately and 35% remains unchanged.
- Group 2 (*Ochrocarpus longifolius* Benth & Hook, f. with milk) shows that 10% of the patients recovered completely, 45.66% moderately and 44% remains unchanged.

- Group 3 (*Cinnamomum tamala* Nees & Ebern with milk) shows that 0% of the patients recovered completely, 52% recovered moderately and 48% remains unchanged.
- On proper evaluation of the results, *Mesua ferrea* Linn. is proved to be more effective clinically in cases of *Artava vikara*, which we have equated with PCOD.
- Hence the final conclusion depending up on both, the literature study and clinical study, the exact source of *Nagakesara* can be equated with the flowers of *Mesua ferrea* Linn. The next place in case of non availability of the above drug goes to *Ochrocarpus Longifolius* Benth & Hook.f, finally the flower buds of *Cinnamomum tamala* Nees & Ebern, which is known as black variety in the markets may be used in any case of bleeding disorders like *Krchrartava*, *Arshas* and *Pradara*.

REFERENCES

1. Erin K.Bathemless, Rajesh K.Naz.Polycystic Ovarian Syndrome-Current Status and Future Perspective, HHS Public Acess, Front Biosci (Elite Ed)2014, 6:104-119.
2. Erin K.Bathemless, Rajesh K.Naz.Polycystic Ovarian Syndrome-Current Status and Future Perspective, HHS Public Acess, Front Biosci (Elite Ed) 2014, 6:104-119.
3. Andrew R Houghton and David Gray's Chamberlin's Symptoms and Signs in Clinical Medicine-An introduction to Medical Diagnosis, 13th edition 2010 Edward Arnold Ltd.
4. Acharya Chunekar K.C. Bhavaprakasha Nighantu of Sri Bhavamisra, Varanasi: Chaukhambha Bharathi Academy, 2015, p.221.
5. Acharya Chunekar K.C. Bhavaprakasha Nighantu of Sri Bhavamisra, Varanasi: Chaukhambha Bharathi Academy, 2015, p.220.
6. D.C. Dutta's, Textbook of Gynaecology including Contraception, sixth edition, West Bengal, New Central Book Agency,, 2012, p.440.Page No 1111.