Research Article

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A RANDOMISED OPEN-LABELLED COMPARATIVE CLINICAL STUDY TO EVALUATE THE EFFICACY OF DARUHARIDRA VATI WITH NISHAMALAKI VATI IN THE MANAGEMENT OF PCOS WITH RESPECT TO INSULIN RESISTANCE

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder characterised by hyperandrogenism, oligo/anovulation, and polycystic ovarian morphology. Insulin resistance contributes significantly to its reproductive and metabolic manifestations. In Ayurveda, PCOS with insulin resistance may be understood through conditions such as Anartava, Artavakshaya, Vandhya, and Pushpaghni Jataharini, involving Kapha-Meda Dushti, Agnimandya, Ama, Srotorodha, and Avarana of Vata, leading to Artava Dushti and metabolic disturbances. Aim: To evaluate and compare the efficacy of Daruharidra Vati and Nishamalaki Vati in managing PCOS with respect to insulin resistance. Materials and Methods: A randomised clinical study was conducted on 30 patients diagnosed with PCOS with insulin resistance. Participants were randomly allocated into two groups of 15 each. Group A received Daruharidra Vati, while Group B received Nishamalaki Vati. Participants received treatment for two months, followed by one month of follow-up without medication. We assessed clinical, anthropometric, dermatological, and biochemical parameters before and after treatment. Phytochemical analysis of the drugs and monitoring for adverse drug reactions were also undertaken. Results: Within-group analysis demonstrated statistically significant improvement in several clinical, anthropometric, dermatological, and biochemical parameters in both groups. However, between-group comparison showed no statistically significant differences. Conclusion: Statistically, we accepted the null hypothesis, indicating no significant difference between the two interventions. However, clinically, Nishamalaki Vati showed a relatively superior trend in improving menstrual irregularities, anthropometric parameters, glycemic control, and dermatological manifestations associated with insulin resistance.

Keywords: PCOS, Nishamalaki Vati, Daruharidra Vati, Insulin Resistance, Ayurveda.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common hormonal condition that affects women of reproductive age. It usually starts during adolescence, but symptoms may fluctuate over time.[1] Polycystic ovary syndrome (PCOS) affects an estimated 8-13% of reproductive-aged women.[2] (In 2022, 11.34% was the prevalence of polycystic ovarian syndrome in India).[3] According to the Rotterdam criteria, it is defined by at least two of the following abnormalities: Clinical or biochemical hyperandrogenism, evidence of oligo-anovulation, polycystic-appearing ovarian morphology on ultrasound, with exclusion of other relevant disorders.[4] In PCOS, patients experience irregular menstrual periods, insulin resistance, hirsutism, acne and impotence.[5] The cause of PCOS is unknown but women with a family history or diabetes are at higher risk.[2] Several ideas have been provided to explain the etiology of PCOS. Insulin Resistance (IR) plays a significant role.[6] IR is a prominent feature of PCOS with a prevalence of 35%-80%. It is usually defined as a pathological condition characterised by a decreased responsiveness or sensitivity to the metabolic actions of insulin. IR in women with PCOS is associated with hyperinsulinemia, which causes erratic gonadotropin absorption and androgen biosynthesis from the adrenal glands and ovaries due to elevated insulin levels. Ovarian follicle growth is constrained, leading to irregularity of menstrual cycles. In women with PCOS, IR plays an important role in the development and persistence of this disorder and is recognised to lead to many of the metabolic abnormalities associated with metabolic syndrome. PCOS patients with IR are likely to have chronic subclinical inflammation and impaired fasting plasma glucose levels, which in turn enhance the prevalence of cardiovascular diseases and dyslipidemia.[7] Given this high prevalence, the need for accurate screening and management of insulin resistance in women with PCOS is obvious. In Ayurvedic classics, conditions mentioned under headings such as Anartava, Nashtartava, Artavakshaya, Vandhya Yonivyapat (infertility), Pushpaghni Jataharini, and Granthibhuta Artavadushti can, to some extent, be compared with PCOS symptoms.[8] The symptoms of PCOS with Insulin resistance can be included under Santarpanajanya Vikaras (Metabolic abnormalities/disorders), Rasa and Medo Pradoshaja Vikara. The Medo Dhatwagni is affected by Ama created in the body by excess Kapha Dosha, which in turn leads to increased Medas Dhatu or fat, in the body; this causes obstruction in the Strotas (micro-channels) of the body. Kapha Medo Vriddhi along Agnimandya (impaired metabolism) results in Bahudrava Shleshma. As Ama reaches Medo Dhatu, it enters deeper into the body and feeds the Artava Dhatu; it increases tissue formation within the reproductive system, creating cysts. Also, accumulated Kapha in the Artava Vaha Strotas manifests as cysts on the ovary and results in subsequent absent menstruation.[9] Daruharidra[10], Nisha[11] and Amalaki[12] have anti-microbial, anti-inflammatory, hypoglycaemic, anti-spasmodic, hypo-lipidemic, anti-oxidant, anti-tumour properties along with their classical indication in

symptoms resembling PCOS with respect to insulin resistance, which suggests their probable mode of action and therapeutic application in the same. Vati Kalpana is one among the Kalpanas (Formulation) mentioned by Sharangdhara Acharya. It is easy to take, has a long shelf life, and is more acceptable than Churna, Kashaya Kalpana, and many others.[13] Hence Daruharidra Vati and Nishamalaki Vati has been selected for the study.

Aim: To study and clinically evaluate the efficacy of Daruharidra Vati and Nishamalaki Vati in managing PCOS with respect to insulin resistance.

Objectives

Primary Objective

- To clinically evaluate the efficacy of Daruharidra Vati in managing PCOS with respect to insulin resistance, based on disease-related subjective and objective parameters in the institution's clinical setting.
- To clinically evaluate the efficacy of Nishamalaki Vati in managing PCOS with respect to insulin resistance, based on disease-related subjective and objective parameters in the institution's clinical setting.
- To compare the efficacy of Daruharidra Vati and Nishamalaki Vati in managing PCOS with respect to insulin resistance, based on disease-related subjective and objective parameters in the institution's clinical setting.

Secondary Objectives

- A literature review of PCOS and insulin resistance will be done.
- To clinically evaluate the efficacy of Daruharidra Vati and Nishamalaki Vati in managing the clinical course of PCOS.
- Recording and reporting of any adverse drug reaction will be done.
- Phytochemical analysis of the drugs will be done.

MATERIALS AND METHODS

This open-labelled, controlled clinical study used a pre- and post-test design, and 30 subjects with PCOS and insulin resistance were selected for the study. As this exploratory postgraduate dissertation was conducted within a defined study period, 30 eligible participants were included. The selected 30 patients were divided into 2 equal groups of 15. Participants were randomly allocated into two groups using a lottery method. A detailed proforma was prepared to cover all study-related points. The study parameters were scored based on standard methods and analysed statistically.

Ethical approval and Informed consent

The study was conducted in accordance with the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants and applicable ICH-GCP guidelines. Written informed consent was obtained from all participants before enrolment, and participant information was kept confidential.

Inclusion Criteria

- Subjects between the ages of 18 and 45 years, irrespective of Marital Status.
- Subjects with irregular cycles and regular cycles.
- Subjects willing to sign the consent form.
- Subjects diagnosed with PCOS and Insulin Resistance.

Exclusion Criteria

- Subjects with Primary amenorrhea, Congenital anomalies and Structural anatomical abnormalities like cryptomenorrhea.
- Subjects on Insulin therapy and Oral hypoglycaemic drugs.
- Subjects on Oral Contraceptive Pills and intrauterine contraceptive devices.
- Subjects with known case of Uncontrolled Chronic Systemic Illness and known case of malignancy.
- Subjects who are Lactating and Pregnant.

Diagnostic Criteria

- Based on Classical symptoms of PCOS and Insulin resistance.
- ICD-11 [Jan 2024] for PCOS is Code: 5A80.1 and Insulin resistance is Code: 5A44.[14]
- Based on laboratory investigations.

Table 1: Investigations Planned

Pre-study/Diagnostic assessment (0^{th} day)	Assessment on 30^{th} day	Assessment on 60^{th} day	Post-Study assessment on (90^{th} day)
USG- abdomen and pelvis	FBS	FBS	FBS
FBS			HbA1C
OGTT			
HbA1C			

Table 2: Study Design For Intervention

	Group A	Group B
Medication	Daruharidra Vati	Nishamalaki Vati
Duration of Drug administration	60 days	60 days
Study duration	90 days (On medication 60 days Observation period 30 days without medication)	90 days (On medication 60 days Observation period 30 days without medication)
Dosage	2 Tab (500 mg each) TID After food	2 Tab (500 mg each) TID After food
Route of Administration	Oral	Oral
Anupana	Koshna Jala (Warm Water)	Koshna Jala (Warm Water)

Assessment Criteria

- Assessment done based on clinical symptoms of PCOS and Insulin resistance.
- Based on Rotterdam criteria.[15]
- NIH Insulin Resistance criteria/MetS criteria.[16]

Parameters

Table 3: Grading of Interval of Cycle [17]

Interval between cycles	Grade
21-35 days	0
36-45 days	1
46-60 days	2
61-180 days	3
181-365 days	4

Table 4: Grading of BMI [18]

Classification	BMI	Grade
Normal range	18.50-24.99	0
Pre-Obese	25.00-29.99	1
Obese Class-1	30.00-34.99	2
Obese Class-2	35.00-39.99	3
Obese Class-3	≥40.00	4

Table 5: Grading of Duration of Bleeding [17]

No. of days	Grade
4-5 days	0
2-3 days	1
1 day	2

Table 6: Grading of Acanthosis Nigricans scoring table [19]

Skin Color Score	Skin Color Description	Skin Texture Score	Skin Texture Description
1	Very fair	1	Normal skin texture appearance without skin thickening
2	Fair	2	Slightly pronounced skin markings without skin thickening
3	Fair to yellow	3	Moderately pronounced skin markings with slight skin thickening
4	Light brown	4	Exaggeration of skin markings with moderate skin thickening
5	Brown	5	Velvety plaque with marked skin thickening
6	Dark brown	6	Bark-like skin with marked skin thickening
7	Black brown	-	-
8	Black	-	-

Table 7: Grading of Hirsutism FG score grading

Level	Score	Grade
Normal	Absent	0
Mild	Up to 8	1
Indicative of androgen excess	8-15	2
Severe Hirsutism	>15-36	3

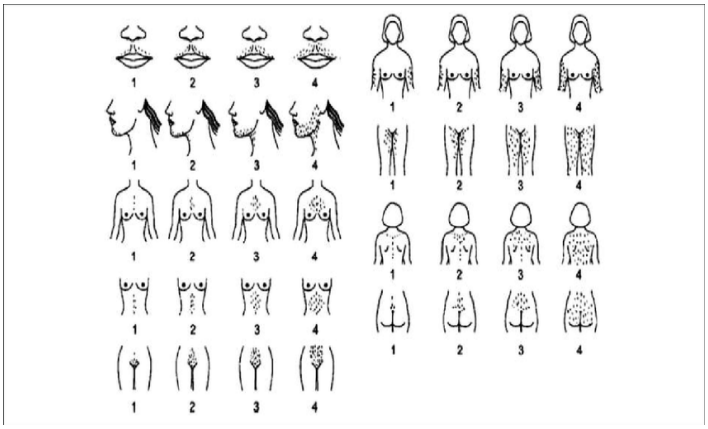

Figure 1: Hirsutism FG score

Table 8: Grading of Indian Diabetic Risk Score: Waist circumference [20]

Waist circumference	Grade
<80 cm	0
80-90 cm	1
>90 cm	2

Table 9: Skin Tag: Acrochordons

Description	Size of skin tag	Grade
Absent	0	0
Small skin tags furrowed papules appearing on neck and axillae	1-2mm in width and height	1
Mid-Sized skin tags solo or multiple filiform skin tags that on other sites of the body	5mm long and 2mm wide	2
Large sized skin tags pedunculated lesions on lower part of the body(groin)	Bag like appearance	3

Table 10: Grading of Gradings of Acne (Pillsbury's)

Acne	Grade
Absent	0
Comedones, Occasional small cysts confined face	1
Comedones, with occasional small pustules and small cysts confined to the face	2
Many Comedones and small and large inflammatory papules and pustules, more extensive but confined to face.	3
Many Comedones and deep lesions tending to coalesce and canalize, and involving the face and upper aspects of the trunk	4

Table 11: Grading of Alopecia: Ludwig visual score

Description	Grade
Absent	0
Perceptible thinning of hair on the crown, limited in front by a line situated 1-3 cm behind the frontal hair line	1
Pronounced rarefaction of the hair on the crown within the area seen in grade 1	2
Fill baldness (total denudation) within the area seen in grades 1 and 2	3

As per Centres for Disease Control And Prevention Criteria [21]

Table 12: Levels of FBS

Stage	FBS Value
Normal	<99 mg/dl
Prediabetic	100-125 mg/dl
Diabetic	>126 mg/dl

Table 13: Levels of OGTT

Stage	OGTT Value
Normal	140 mg/dl
Prediabetic	140-199 mg/dl
Diabetic	>200 mg/dl

Table 14: Levels of HbA1C

Stage	HbA1C Value
Normal	5.7%
Prediabetic	5.7-6.4%
Diabetic	>6.5%

Table 15: Table for follow-up assessment

Pre assessment	0^{th} day
1^{st} assessment	On 30^{th} day
2^{nd} assessment	On 60th day
Follow up (On observation, without medicines Assessment)	On 90^{th} day

Table 16: Qualitative Analysis and Phytochemical Analysis for Daruharidra Vati and Nishamalaki Vati Done at a GMP-certified Company

Daruharidra Vati		Nishamalaki Vati	
Test	**Results**	**Test**	**Results**
Physical Description	Brown, circular tablet with characteristic Odor	Physical Description	Yellow, circular tablet with characteristic odour
Phytochemical Constituents		Phytochemical Constituents	
Iodine Test (Starch)	Positive	Iodine Test (Starch)	Positive
Biuret Test (Protein)	Negative	Biuret Test (Protein)	Positive
Salkowski Test (Steroids)	Positive	Salkowski Test (Steroids)	Positive
Shinoda Test (Flavonoids)	Positive	Shinoda Test (Flavonoids)	Positive
Foam Test (Saponins)	Positive	Foam Test (Saponins)	Positive
Dragendorff's Test (Alkaloids)	Positive	Dragendorff's Test (Alkaloids)	Positive
Salkowski Test (Triterpenoids)	Positive	Salkowski Test (Triterpenoids)	Positive
Ferric Chloride Test (Polyphenols and Tannins)	Negative	Ferric Chloride Test (Polyphenols and Tannins)	Negative

RESULTS AND OBSERVATIONS

A total of 30 patients fulfilling the inclusion criteria were registered for the study,
Total number of patients screened - 30
Number of participants registered for the study- 30
Number of participants who completed the study- 30

Observation Based On Demographic And Personal Data

- Age: 57% of participants were aged 24-31 years, followed by 30% aged 32-39 years and 13% aged 18-23 years.
- Education: 93% of participants were graduates, while 7% had completed high school education.
- Socioeconomic status: 57% belonged to the middle socioeconomic class, followed by 23% from the upper class and 20% from the lower class. The corrected distribution is based on 17, 7 and 6 participants, respectively.
- Locality: 97% of participants were from urban areas, while 3% were from rural areas.
- Dietary pattern: 57% followed Vishamashana, followed by 30% with Adhyashana, 10% with Samashana, and 3% with Anashana.
- Appetite: 56% had poor appetite, 40% had moderate appetite, and 3% had good appetite.
- Agni: 80% had Manda Agni, 20% had Teekshna Agni, and none had Samagni.
- Sleep pattern: 73% reported disturbed sleep, 20% had delayed sleep, while 3% each reported sound sleep and insomnia.
- Bowel habits: 50% had irregular bowel habits, 40% had constipation, and 10% had regular bowel habits.
- Lifestyle: 60% had a poor lifestyle, 37% had a moderate lifestyle, and 3% had an excellent lifestyle.
- OGTT: 43% had OGTT values between 180-199 mg/dL, while 17% each had values <140 mg/dL and >200 mg/dL. A further 13% had values between 141-159 mg/dL, and 10% between 160-179 mg/dL.
- Prakruti: Pittakapha Prakruti - 27%, Vatapitta - 23%, Vatakapha constituted 17%, while pure Vata, Pitta, and Kapha Prakruti were less common

- Vikruti: Vatakapha Vikruti - 73%, Kapha Vikruti - 13% and Vatapitta Vikruti - 7%.

Based On Assessment Parameters
Overall Assessment Within The Group

Table 17: Overall Assessment with Group A

Parameters	BT-AT1(30th day)	AT1-AT2 (30th-60th day)	AT2- FU (60th-90th day)	BT-FU (0-90th day)	BT-AT2 (0-60th day)	AT1-FU (30th- 90th day)
Interval between cycles	0.0063-NS	0.102 -NS	0.180-NS	0.052-NS	0.0024-S	0.680-NS
DOB	1.000-NS	1.000-NS	1.000-NS	1.000-NS	1.000-NS	1.000-NS
BMI	0.005-HS	0.332-NS	0.102-NS	0.004-HS	0.007-HS	0.233-NS
Hirsutism	1.00-NS	0.157 -NS	1.000 -NS	0.157 -NS	0.157 -NS	0.157 –NS
AN-skin colour	0.317-NS	0.125-NS	0.317-NS	0.016-NS	0.063-NS	0.031-S
AN-Skin texture	0.317-HS	0.157-NS	0.317-NS	0.034-S	0.083-NS	0.059-NS
Waist Circumference	0.001-VHS	0.003-HS	0.005-HS	0.001-VHS	0.001-VHS	0.001-VHS
Alopecia	0.157-NS	0.158-NS	0.317-NS	0.046-S	0.059-NS	0.083-NS
Skin tag	1.000-NS	0.317-NS	1.000-NS	0.317-NS	0.317-NS	0.317-NS
Acne	0.157-NS	0.157-NS	0.157-NS	0.046-S	0.059-NS	0.157-NS
FBS	0.001-VHS	0.001-VHS	0.001-VHS	0.001-VHS	0.001-VHS	0.001-VHS
HbA1C	-	-	-	0.001-VHS	-	-

BT: Before Treatment, AT: After Treatment, FU: Follow-up, DOB: Duration of bleeding, AN: Acanthosis Nigricans, FBS: Fasting Blood Sugar

Table 18: Overall Assessment with Group B

Parameters	BT-AT1(30th day)	AT1-AT2 (30th-60th day)	AT2- FU (60th-90th day)	BT-FU (0-90th day)	BT-AT2 (0-60th day)	AT1-FU (30th- 90th day)
Interval between cycles	0.071-NS	0.236 -NS	0.157-NS	0.026- S	0.0042- S	0.121-NS
DOB	0.034-S	0.317-NS	0.317- NS	0.015- S	0.0233-S	0.157-NS
BMI	0.003-HS	0.018- S	0.007- HS	0.001- VHS	0.001- VHS	0.005- HS
Hirsutism	0.317-NS	1.000-NS	1.000- NS	0.317- NS	0.317-NS	1.000-NS
AN-skin colour	0.157-NS	0.008-HS	0.046-S	0.016-S	0.007-HS	0.001-VHS
AN-Skin texture	0.157-NS	0.038-S	0.157-NS	0.010-HS	0.014-S	0.008-HS
Waist Circumference	0.001-VHS	0.001-VHS	0.001-VHS	0.001-VHS	0.001-VHS	0.001-VHS
Alopecia	0.317-NS	0.317-NS	1.00-NS	0.157-NS	0.157-NS	0.317-NS
Skin tag	1.00-NS	0.317-NS	1.000-NS	0.317-NS	0.317-NS	0.317-NS
Acne	0.157-NS	0.157-NS	0.317-NS	0.023-S	0.046-S	0.157-NS
FBS	0.001-VHS	0.001-VHS	0.001-VHS	0.001-VHS	0.001-VHS	0.001-VHS
HbA1C	-	-	-	0.001-VHS	-	-

BT: Before Treatment, AT: After Treatment, FU: Follow-up, DOB: Duration of bleeding, AN: Acanthosis Nigricans, FBS: Fasting Blood Sugar

- Within-group analysis demonstrated statistically significant improvement in several clinical, dermatological, anthropometric, and biochemical parameters in both Group A and Group B following treatment.
- Daruharidra Vati significantly improved the interval between cycles, acanthosis nigricans skin colour and texture, alopecia, acne, BMI, waist circumference, fasting blood sugar, and HbA1c levels.
- Nishamalaki Vati showed statistically significant to very highly significant improvements in bleeding duration, interval between cycles, acanthosis nigricans skin colour and texture, acne, BMI, waist circumference, fasting blood sugar, and HbA1c levels.

Overall Assessment Between the Groups

Table 19: Overall Assessment between the groups

Parameters	Mann Whitney p-value (BT, 30th day, 60th day, 90th day)	Inference
Duration of menstrual bleeding	BT- 0.001-VHS 30th day- 0.073-NS 60th day- 0.150-NS 90th day- 0.317 -NS	Intergroup comparison using Mann–Whitney U Test showed a statistically significant difference at baseline ($p = 0.001$), while post-treatment and follow-up comparisons were non-significant ($p > 0.05$), indicating comparable efficacy in both groups. Although Group B showed greater percentage improvement than Group A, the intergroup difference after treatment was statistically non-significant, suggesting relatively better clinical improvement with Nishamalaki Vati
Interval between two cycles	BT- 0.030-S 30th day- 0.120-NS 60th day- 0.121-NS 90th day- 0.0430-S	Intergroup comparison using Mann–Whitney U Test showed statistically significant differences at baseline ($p = 0.030$) and follow-up assessment ($p = 0.043$). Group B demonstrated greater percentage improvement and lower mean rank scores compared to Group A, indicating relatively better efficacy of Nishamalaki Vati in improving interval between menstrual cycles. However, comparisons at 30th and 60th day were non-significant ($p > 0.05$).
BMI	BT- 0.295-NS 30th day- 0.404-NS 60th day- 0.283-NS 90th day- 0.189-NS	Intergroup comparison using Mann–Whitney U Test showed non-significant differences between Group A and Group B at all assessment intervals ($p > 0.05$). However, Group A demonstrated comparatively higher mean rank values throughout the study period, indicating minimal intergroup difference in BMI reduction between the two interventions.

Hirsutism	BT- 0.637-NS 30th day- 0.502-NS 60th day- 0.750-NS 90th day- 0.750-NS	Intergroup comparison using Mann–Whitney U Test showed non-significant differences between Group A and Group B at all assessment intervals ($p > 0.05$). Although Group A showed relatively greater reduction in hirsutism scores, both Daruharidra Vati and Nishamalaki Vati demonstrated comparable efficacy in improving hirsutism in PCOS with insulin resistance.
AN-skin colour	BT- 0.314-NS 30th day- 0.301-NS 60th day- 0.706-NS 90th day- 0.981-NS	Intergroup comparison using Mann–Whitney U Test showed non-significant differences between Group A and Group B at all assessment intervals ($p > 0.05$). However, Group B showed comparatively greater improvement in acanthosis nigricans skin color, suggesting relatively better clinical efficacy of Nishamalaki Vati, though the intergroup difference was statistically non-significant.
AN-skin texture	BT- 0.086-NS 30th day-0.080-NS 60th day- 0.338-NS 90th day- 0.558-NS	Intergroup comparison using Mann–Whitney U Test showed non-significant differences between Group A and Group B at all assessment intervals ($p > 0.05$). However, Group B showed comparatively greater improvement in acanthosis nigricans skin texture, suggesting relatively better clinical efficacy of Nishamalaki Vati, though the intergroup difference was statistically non-significant
Waist circumference	BT- 0.256-NS 30th day- 0.289-NS 60th day- 0.328-NS 90th day- 0.200-NS	Intergroup comparison using Mann–Whitney U Test showed non-significant differences between Group A and Group B at all assessment intervals ($p > 0.05$). Group A demonstrated comparatively higher mean rank values, indicating minimal intergroup difference in waist circumference reduction between the two interventions
Skin tag	BT- 0.695-NS 30th day-0.695-NS 60th day- 1.000-NS 90th day-1.000-NS	Intergroup comparison using Mann–Whitney U Test showed non-significant differences between Group A and Group B at all assessment intervals ($p > 0.05$). Both groups showed minimal improvement in skin tag scores; however, Group B demonstrated comparatively greater reduction, suggesting relatively better clinical improvement with Nishamalaki Vati, though statistically non-significant.
Alopecia	BT- 0.422-NS 30th day- 1.000-NS 60th day- 0.695-NS 90th day- 1.000-NS	Intergroup comparison using Mann–Whitney U Test showed non-significant differences between Group A and Group B at all assessment intervals ($p > 0.05$). However, Group A showed comparatively greater improvement in alopecia, suggesting relatively better efficacy of Daruharidra Vati, though the difference was not statistically significant.
Acne	BT- 0.750-NS 30th day- 0.845-NS 60th day- 0.666-NS 90th day- 0.476-NS	Intergroup comparison using Mann–Whitney U Test showed non-significant differences between Group A and Group B at all assessment intervals ($p > 0.05$). However, Group B showed comparatively greater improvement in acne scores, suggesting relatively better efficacy of Nishamalaki Vati, though the difference was not statistically significant.
FBS	BT- 0.706-NS 30th day- 0.426-NS 60th day- 0.168-NS 90th day- 0.049-S	Intergroup comparison using Mann–Whitney U Test showed non-significant differences at baseline, 30th day, and 60th day ($p > 0.05$), while a significant difference was observed at follow-up ($p = 0.049$). These findings indicate comparatively better reduction in fasting blood sugar in Group B, suggesting relatively superior efficacy of Nishamalaki Vati.
HbA1C	BT- 0.844-NS 90th day- 0.066-NS	Intergroup comparison using Mann–Whitney U Test showed non-significant differences between Group A and Group B before and after treatment ($p > 0.05$). However, Group B showed comparatively greater reduction in HbA1c levels, suggesting relatively better efficacy of Nishamalaki Vati in improving long-term glycemic control.

Intergroup comparison using Mann–Whitney U Test demonstrated statistically non-significant differences between Group A and Group B for most parameters throughout the study period. However, fasting blood sugar showed a statistically significant intergroup difference at follow-up, indicating comparatively greater improvement in Group B.

Anthropometric parameters such as BMI and waist circumference decreased progressively in both groups during treatment and follow-up assessments. Group B showed a greater reduction in BMI and waist circumference than Group A. Biochemical parameters, including fasting blood sugar and HbA1c, improved markedly in both groups, indicating that both interventions benefited insulin resistance and long-term glycaemic control.

Table 20: Overall Assessment Significance

Significance Level	Group A	Group B	Between Groups
Very Highly Significant (VHS)	36.4%	54.5%	4.5%
Highly Significant (HS)	31.8%	18.2%	0%
Significant (S)	13.6%	9.1%	9.1%
Not Significant (NS)	18.2%	18.2%	86.4%

Group A - Group A improved, though the pattern was less consistent than in Group B.

Group B - There was progressive and statistically significant improvement across most time points.

Between Group A and Group B - No statistically significant difference.

Although Group B has good statistical significance, as per the overall assessment,

As there is no statistically significant difference between the two groups, the null hypothesis (H0) is accepted; that is, Daruharidra Vati and Nishamalaki Vati have no effect on PCOS management with respect to Insulin resistance.

Comparatively, Nishamalaki Vati demonstrated relatively superior clinical efficacy in improving menstrual irregularities, anthropometric measures, glycaemic control, and dermatological manifestations associated with insulin resistance. Hence, from a clinical perspective, the alternative hypothesis is accepted that Nishamalaki Vati has a greater effect than Daruharidra Vati in managing PCOS with respect to Insulin resistance.

Special Observation

- A positive family history of diabetes mellitus was common in both groups, being slightly higher in Group B (maternal DM: 12 vs. 11; paternal DM: 9 vs. 6), indicating a strong hereditary predisposition to insulin resistance.
- Premenstrual symptoms and disturbed bowel habits improved in most patients in both groups, suggesting overall improvement in metabolic and gastrointestinal function after treatment.

- Symptoms associated with hyperglycaemia, including polyuria, nocturia, hasta-pada suptata, and kara pada daha, showed noticeable improvement in both groups after treatment.
- Associated metabolic comorbidities such as dyslipidemia, hypertension, and fatty liver were observed in a few patients, reflecting the metabolic nature of PCOS with insulin resistance.
- An LH:FSH ratio >3:1 was observed in three patients before treatment, and clitoromegaly was noted in one patient, indicating underlying hyperandrogenism in a subset of participants.
- Overall, these findings indicate a positive trend toward improved glycemic control and metabolic function in both groups. Although the change in glycaemic parameters was modest, it was clinically meaningful and accompanied by favourable changes in associated metabolic manifestations, with comparatively better outcomes in Group B.

DISCUSSION

The Polycystic Ovary Syndrome with respect to Insulin Resistance: PCOS, now globally known as PMOS (polyendocrine metabolic ovarian syndrome and previously known as Polycystic Ovary Syndrome (PCOS), is one of the most common endocrine disorders affecting women of reproductive age and is frequently associated with insulin resistance (IR), irrespective of obesity. Increasing evidence suggests that insulin resistance plays a central role in the development and progression of PCOS. Compensatory hyperinsulinemia enhances ovarian androgen production, suppresses sex hormone-binding globulin (SHBG), and disrupts normal follicular development, ultimately resulting in chronic anovulation, menstrual irregularities, and hyperandrogenic manifestations such as acne, hirsutism, and alopecia. If left untreated, these metabolic disturbances increase the long-term risk of impaired glucose tolerance, type 2 diabetes mellitus, dyslipidaemia, and cardiovascular disease.

Since insulin resistance forms the common link between the reproductive and metabolic abnormalities seen in PCOS, therapies targeting insulin sensitivity are likely to provide broader clinical benefits than treatments directed only at symptomatic relief. Based on this concept, this study evaluated the role of Daruharidra Vati and Nishamalaki Vati in improving insulin resistance and the associated clinical manifestations of PCOS.

PCOS Through Ayurveda Principles And Samprapti: Although PCOS is not described as a distinct disease in the Ayurveda classics, its clinical presentation closely resembles conditions such as Artava Kshaya, Nashtartava, Pushpaghni Jataharini, Vandhyatva, Sthoulya, and Prameha. Rather than considering it as a single disease, Ayurveda understands it as a complex disorder resulting from multiple derangements involving Dosha, Dhatu, Agni, and Srotas. Improper dietary habits, excessive intake of Guru, Snigdha, and Madhura Ahara, lack of physical activity, stress, and a sedentary lifestyle lead to Agnimandya. Impaired digestion leads to the formation of Ama, which then aggravates Kapha and Meda. The accumulation of these pathological factors causes Srotorodha, particularly in the Medovaha and Artavavaha Srotas. Obstruction in these channels disturbs the normal function of Apana Vata, leading to defective Artava Utpatti and Artava Pravritti, manifesting clinically as irregular menstruation and anovulation. As the disease progresses, persistent Kapha-Meda Dushti resembles the pathogenesis of Prameha, explaining insulin resistance and metabolic abnormalities.

The pathology can be understood as Santarpanotha Nidana Janya Vikara involving Kapha and Meda Dhatu Dushti, with impaired Jatharagni, Dhatwagni, and Panchabhutagni, leading to Ama formation; Srotorodha; and increased Kleda and Drava Guna of Kapha and Meda. Increased Abaddha Medas cause Vata Dushti and Avarana of Vatavaha Strotas by Kapha. Kaphavruta Vyana Vata causes impaired Rasa Paribhramana, Uttarottara Dhatu Dushti, and Kaphavruta Apana causes Artava Dushti, hampers Artava Utpatti and Pravrutti leading to conditions like Anartava, Nashtartava or Artavakshaya, Vandhya, Pushpaghni Jataharini along with Granthibhuta Artava Dushti at the ovarian level, Dhatupradoshaja Vikara Lakshana, further leading to Prameha and manifestation of metabolic symptoms. Acharya Charaka and Sushruta say that, in the concept of Avarana, Vyana Vata and Apana Vata Vaha Strotoavarana by Kapha Dosha leads to Prameha, Shukra, and Artava Dushti. Thus, PCOS with insulin resistance represents a complex interplay of many Vyadhis that culminate in ovarian dysfunction and systemic metabolic derangement, manifesting clinically as menstrual irregularities, anovulation, and features of Prameha, with potential progression to full-fledged metabolic syndrome if the underlying Nidana continue unabated.

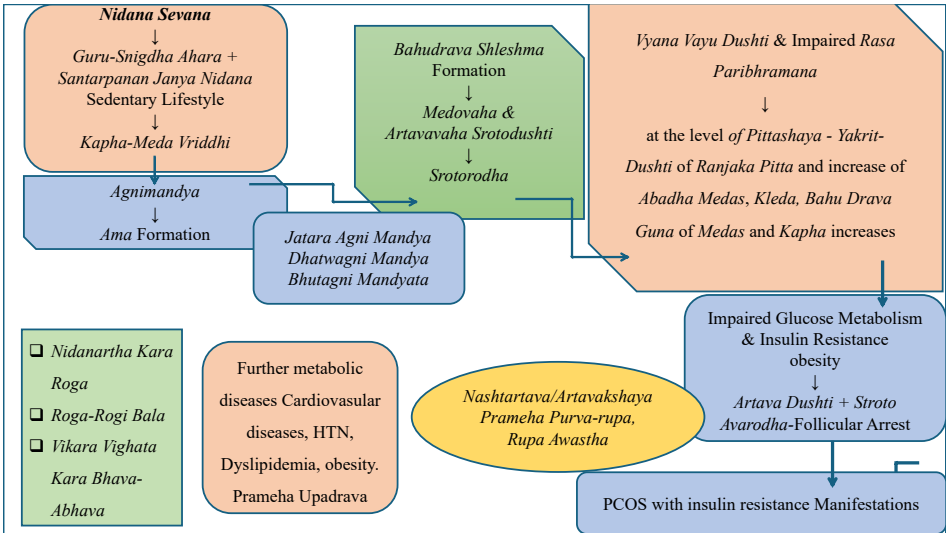

Chart 1: Samprapti for PCOS with reference to IR through Ayurveda Principles

Thus, PCOS associated with insulin resistance can be understood as a Kapha-Meda predominant Tridoshaja disorder involving Agnimandya, Ama, Srotorodha, and Apana Vata Vaigunya, producing both reproductive and metabolic dysfunction.

Chikitsa Siddhanta: Given the broad pathological spectrum, Chikitsa should focus on treating Agni, achieving Nirama Avastha, Srotoshodhana, relieving Avarana, balancing Tridosha, and Samprapti Vighatana of the Roga to prevent further complications. The treatment protocol in the present study was planned to address the disease at its root rather than merely alleviating symptoms.

The primary objective was to correct Agnimandya through Deepana and Pachana, thereby reducing Ama formation. Simultaneously, Kapha-Medohara and Pramehaghna therapies were employed to improve glucose metabolism and reduce the metabolic burden. Srotoshodhana was aimed at relieving obstruction within the Artavavaha and Medovaha Srotas, while restoration of normal Apana Vata function was expected to facilitate ovulation and regulate menstrual cycles. Since PCOS is a chronic metabolic disorder, Rasayana therapy was also considered important for improving tissue metabolism and preventing disease progression.

Under Vatavyadhi-Avaranajanya Vyadhi Chikitsa for Kaphavruta Vyana and Apana Vata Dushti-Kapha Medoja Roga, Prameha, and Shukra-Artava Dushti Lakshana, the classics mention Kapha-Medohara and Vatahara as the treatment line. Daruharidra and Nishamalaki are classically referred for the treatment of Kapha-medoja rogas; Prameha and Shukra-artavadushti can be understood to relieve PCOS with reference to insulin resistance, with improvement in all assessment parameters as discussed earlier under observation. Dietary regulation and lifestyle modification were advised to all participants, as these remain indispensable components of Ayurveda management of Prameha and metabolic disorders. Therefore, the observed clinical improvement may be considered the cumulative effect of the trial drugs together with appropriate Ahara and Vihara.

Rationale Behind Selecting Daruharidra Vati and Nishamalaki Vati: Daruharidra Vati and Nishamalaki Vati were selected based on both classical Ayurvedic principles and contemporary pharmacological evidence.

Daruharidra (Berberis aristata) contains berberine, a well-studied alkaloid known for its insulin-sensitising, antioxidant, and anti-inflammatory activities. Berberine activates AMP-activated protein kinase (AMPK), improves peripheral glucose uptake, suppresses hepatic gluconeogenesis, modulates the gut microbiota, and enhances lipid metabolism. These actions directly target insulin resistance, which forms the cornerstone of PCOS pathogenesis. From an Ayurveda perspective, Daruharidra possesses Kati-Tikta Rasa, Laghu-Ruksha Guna, and the formulation acts by Deepana-Pachana, Lekhana and Medohara, Srotoshodhaka relieves Avarodha of Vata-Vaha Strotas, Avarana of Vyana and Apana Vata by Kapha, Rasavaha, Medovaha, and Artavavaha Srotas and also has Varnya karma. Corrects Rasa Paribhramana and process of Uttara-Uttara Dhatu formation. Its Raktashodhaka and Kapha-Pitta Shamaka, Shothahara, Yakrit Vikara Hara actions help restore metabolic and hormonal balance by reducing inflammatory and metabolic disturbances and curing Sthoulya, Santharpanyotha Vyadhi Lakshana. Additionally, it shows Pramehaghna effect by reducing Kleda and Bahudrava Shleshma, thereby counteracting features of metabolic dysregulation. Overall, it reduces Kapha-Meda Dushti and corrects Ama-induced Srotorodha, enhances Dhatwagni and tissue metabolism, supports proper Rasa Paribhramana and Artava dhatu nourishment, and promotes normal Apana Vata function, ultimately improving Artava Pravritti, resulting in normalised menstrual cycles and restoring metabolic-reproductive balance.

Nishamalaki Vati, comprising Haridra and Amalaki, possesses complementary properties that may be beneficial in PCOS associated with insulin resistance. Haridra, with its Katu-Tikta Rasa, Laghu-Ruksha Guna, Ushna Virya and Katu Vipaka, exhibits Kapha-Pitta Shamana, Medohara, Deepana-Pachana and Srotoshodhana actions, which may help in correcting Agni Mandya, Ama and Kapha-Meda dushti. Amalaki, with its Pancharasa (except Lavana), Guru-Ruksha Guna, Sheeta Virya and Madhura Vipaka, along with Rasayana, Pramehahara and Yoni Doshahara properties, may support tissue nourishment and metabolic balance. Their combined actions may help reduce Kleda and Meda, clear Srotorodha and support normal Vyana and Apana Vata function, thereby contributing to restoration of Artava Utpatti and Pravritti.

From the phytochemical perspective, the constituents of Haridra and Amalaki, particularly curcumin and gallic acid, may contribute to improved insulin sensitivity, glucose utilisation, enhances pancreatic β-cell function, lipid metabolism and reduction of oxidative stress. Modulation of PPAR-γ and other metabolic pathways may further support correction of metabolic disturbances associated with insulin resistance. The formulation's antioxidant and anti-inflammatory properties may also contribute to improvement in associated clinical manifestations. Thus, the combined Ayurvedic and phytochemical actions of Nishamalaki Vati may contribute to Samprapti Vighatana of PCOS with insulin resistance, particularly through Pramehaghna, Kapha-Medohara, Deepana, Pachana, Raktaprasadana, and Rasayana properties, thereby addressing both the metabolic and reproductive aspects of PCOS.

Discussion of Results: The findings indicate that Daruharidra Vati and Nishamalaki Vati effectively improved the clinical and metabolic manifestations of PCOS associated with insulin resistance. Fasting blood sugar, HbA1c, body mass index, waist circumference, menstrual cycle regularity, acne, and acanthosis nigricans improved significantly. These improvements suggest that correcting insulin resistance positively influences ovarian function and systemic metabolic health.

Among the two treatment groups, Nishamalaki Vati demonstrated comparatively greater improvement in fasting blood sugar, HbA1c, menstrual regularity, acne, and acanthosis nigricans. This may be attributed to the complementary actions of Haridra and Amalaki on glucose metabolism, oxidative stress, inflammation, and insulin sensitivity. Daruharidra Vati also significantly improved glycaemic control and anthropometric parameters, supporting its role as an effective insulin-sensitising formulation.

In contrast, changes in hirsutism, alopecia, and skin tags were relatively modest in both groups. These clinical features usually represent chronic hyperandrogenic changes that develop over several years, and therefore may require a longer duration of treatment before substantial improvement becomes clinically evident.

Overall, the results suggest that interventions aimed at correcting insulin resistance can simultaneously improve both metabolic abnormalities and reproductive dysfunction in women with PCOS.

Samprapti Vighatana and the probable mode of action based on the Results: The beneficial effects observed in the present

study appear to be primarily mediated through improvement in insulin sensitivity. Better insulin utilisation reduces compensatory hyperinsulinemia, thereby decreasing ovarian androgen production and improving follicular maturation. This may explain the improved menstrual regularity and normalisation of cycle intervals.

Reduced fasting blood sugar and HbA1c indicate improved glucose metabolism and sustained glycaemic control. Simultaneously, reduced BMI and waist circumference reflect improved lipid metabolism and decreased central adiposity, both of which further enhance insulin sensitivity and interrupt the vicious cycle of insulin resistance.

Improvement in acanthosis nigricans probably reflects correction of chronic hyperinsulinemia, while improvement in acne may be attributed to reduced androgen excess together with the anti-inflammatory and antioxidant actions of the trial drugs. The relatively smaller changes observed in hirsutism and alopecia are understandable because these androgen-dependent manifestations generally respond slowly and often require prolonged therapy due to the long hair growth cycle.

From an Ayurvedic perspective, these findings may be explained by correcting Agnimandya, eliminating Ama, Kapha-Meda Dushtihara Karma, relieving Srotorodha and Avarana, Tridoshahara (predominantly Kapha-Vatahara) Karma, and restoring normal Vyana-Apana Vata function. Together, these actions facilitate normal Artava Utpatti and Artava Pravritti while simultaneously improving systemic metabolism by Samprapti Vighatana and Pramehahara Karma. Thus, the observed clinical improvements support the Ayurveda principle that correcting the underlying metabolic imbalance can restore both reproductive and endocrine homeostasis.

Because dietary and lifestyle modifications were advised to both groups, the observed improvements may reflect the combined effect of the interventions and these supportive measures. Both groups showed statistically significant improvement in several parameters, with Group B showing greater significance and a better clinical response. Several clinical parameters were assessed using ordinal grading systems. Consequently, statistically significant changes may reflect relatively small shifts between severity categories and should not necessarily be interpreted as large differences in absolute clinical magnitude. Therefore, although Group B showed significant improvement across more parameters, the difference between the two interventions remained modest for several outcomes.

CONCLUSION

This randomised, open-labelled comparative clinical study suggests that both Daruharidra Vati and Nishamalaki Vati were beneficial in managing PCOS with respect to insulin resistance, with improvements in menstrual, anthropometric, dermatological, and glycaemic parameters.

The improvements in menstrual pattern, BMI, waist circumference, and dermatological manifestations should be interpreted as the combined effect of the respective interventions and the dietary and lifestyle modifications advised to both groups. FBS and HbA1c improved consistently in both groups, supporting a favourable effect on glycaemic control, the study's primary metabolic focus. Group B, with Nishamalaki Vati intervention, showed a relatively greater clinical response in several parameters, particularly menstrual, anthropometric, dermatological, and glycaemic outcomes; however, the overall intergroup statistical difference was not substantial for most parameters.

Additionally, Nishamalaki Vati and Daruharidra Vati were well tolerated, with no significant adverse effects reported.

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