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Research Article

Assessment of effective dose and tolerability of an herbal formulation *Phalatrikadi Ghana Vati* in patients of Non-Alcoholic Fatty Liver Disease through Dose Escalation

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is a rapidly growing public health concern with limited treatment options. Ayurveda offers plant-based remedies, which have been traditionally used since centuries but lack scientific evidence. The reverse pharmacology (RP) approach provides a framework for their scientific evaluation. This study aimed to determine the best effective and tolerable dose of *Phalatrikadi Ghana Vati* (PGV) for NAFLD management. Methods: A dose escalation study was conducted on 36 participants with NAFLD. Participants were randomly allocated to three groups receiving 500mg, 1000mg, or 1500mg of PGV twice daily for four weeks. Clinical symptoms (abdominal pain, nausea, indigestion), liver function tests (ALT, AST), and tolerability were assessed. Results: PGV significantly reduced abdominal pain (*udarshula*) compared to baseline, with the 1000mg dose showing the most significant improvement (p=0.002). Improvements in liver function tests were also observed, with the 1000mg dose again demonstrating the most significant reduction in ALT levels ($p<0.01$). PGV at 500mg and 1000mg was well-tolerated, but two patients in the 1500mg group reported mild gastrointestinal side effects. Discussion: This study suggests that PGV at a dose of 1000mg twice daily is safe, effective, and well-tolerated for managing NAFLD symptoms and improving liver function. The individual ingredients of PGV possess documented hepatoprotective properties, which may contribute to its therapeutic effect. Conclusion: RP offers a promising approach for evaluating Ayurvedic medicines. PGV at 1000mg twice daily demonstrates potential as a safe and effective treatment for NAFLD. Further research is needed to confirm these findings and explore the underlying mechanisms of action.

Keywords: *Ayurveda,* Dose Escalation Study, NAFLD, *Phalatrikadi Ghana Vati,* Reverse Pharmacology.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is rapidly emerging as a significant health concern. Characterised by excessive fat accumulation in the liver in the absence of alcohol consumption, NAFLD has become the leading cause of chronic liver disease globally.(1) The prevalence of NAFLD is alarmingly high, with estimates suggesting it affects 6-35% of the adult population worldwide as well as in India(2,3). This number is projected to rise further, driven by factors such as the increasing prevalence of obesity, type 2 diabetes, and metabolic syndrome.

Despite its growing prevalence, NAFLD often goes undiagnosed due to its asymptomatic nature in the early stages. This scenario underscores the need for a deeper understanding of NAFLD pathogenesis, effective diagnostic tools, and therapeutic interventions. In absence of any specific pharmacological agent available for its effective management, the focus is rapidly shifting to develop a plant-based remedy(4,5). Ayurveda is a rich source of plant-based medicines and several of its drugs can be evaluated for their effective use in patients with NAFLD. The scientific validation of such drugs can be performed through

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Reverse Pharmacology (RP), which generally follows a bedside-to-bench approach.

Considering this novel RP process, along with a less time-consuming approach, a study was undertaken to evaluate *Phalatrikadi Ghana Vati* (PGV) for its effect in patients with NAFLD.(4) The formulation composition of the drug is shown in Table 1. This dose escalation study of PGV was undertaken to find out the best effective and tolerable dose in patients of NAFLD. The assessment was done in a limited number of patients.

Table 1: Formulation composition of *Phalatrikadi Ghana Vati*(6)

S.No.	Botanical Name	Sanskrit Name	Part used	Ratio
1	*Phyllanthus emblica* L.	*Amalaki*	Pericarp	1 part
2	*Terminalia bellerica* Roxb.	*Haritaki*	Pericarp	1 part
3	*Terminalia chebula* Retz.	*Bibhitaki*	Pericarp	1 part
4	*Tinospora cordifolia* Miers.	*Vasa*	Whole Plant	1 part
5	*Adhatoda vasica* Nees.	*Guduci*	Stem	1 part
6	*Andrographis panniculata* Nees.	*Katuka*	Root	1 part
7	*Azadirachta indica* A. Juss.	*Kalmegha*	Whole plant	1 part
8	*Picrorrhiza kurroa* Royale ex Benth.	*Nimba*	Stem Bark	1 part

Material and Methods

A dose escalation study was undertaken to decide the best effective and safe dose in patients of NAFLD as per the sequence shown in Figure-1(7). This pilot study was conducted on 36 patients diagnosed with NAFLD, divided randomly among three groups. The patients in group one were administered dose of 500mg PGV, second group was given 1000 mg dose and the third group 1500 mg dose twice a day for a duration of four weeks.

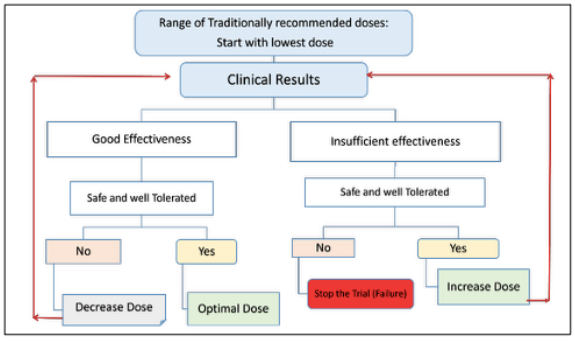
Informed Consent

The participants were informed about the study. Those willing to participate were randomly allocated into different groups using a computer-generated random sequence. Informed written consent was obtained from each participant prior to the study.

Ethical Approval & Registration

Ethics approval vide no MGACHRC/IEC/July-2021/321 dated 31.07.2021 was obtained from the Institutional Ethics Committee of the study center and registered with CTRI/2022/06/043428.

Figure 1: Methodology of Dose Escalation Study



Inclusion Criteria

Participants of either sex in the age group 30-60 years, non-alcoholic presenting with clinical features of *udarashula* (pain in the right upper quadrant/epigastric region of the abdomen), *utklesha* (feeling of nausea and vomiting), *Agnimandya* (impaired digestion), ultrasonography (USG) of the abdomen suggestive of non-alcoholic fatty liver disease and having elevated liver enzymes, namely alanine transaminase (ALT) and/or aspartate transaminase (AST), above the normal limit of 40 IU/L and up to three times the upper normal limit were included in the study.

Exclusion Criteria

Participants unwilling to participate in study, having a history of alcohol intake exceeding 20 g/day and those testing positive for markers of other viral hepatitis were excluded from the study.

Statistical Analysis: The obtained data was analyzed statistically and expressed in terms of mean and standard deviation (± SD). Chi-square and F-tests were applied to observe the significance of results obtained after treatment. The data was analysed using the "spss software" of statistics.

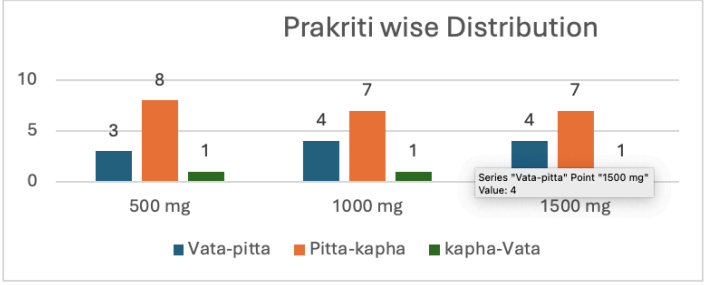
Observations

A total of 36 participants fulfilling the inclusion criteria were randomly allocated in to either of the three groups, i.e. 500mg, 1000mg or 1500mg group of 12 each and all completed the study. The mean age of the participants was 44.44 ± 9.424 found non-significant as F-value resulted at 0.272 a p-value 0.763 ($p>0.05$) as shown in table 2. Across the three groups, the number of males participants were seven (58.3%) in each group and five female participants (41.7%) showing a homogenous population. Prakriti analysis of the participants revealed that the majority of them were *pitta-kaphaja prakriti,* with eight (66.67%) in the 500mg group, seven (58.33%) in the 1000mg group and seven (58.33%) in the 1500mg group as shown in figure 2.

Table 2: Descriptive statistics for age amongst three groups 500 mg, 1000 mg, 1500 mg

Doses	N	Mean	Std. Deviation	Minimum	Maximum	F-value	P-value
500 mg	12	43.333	10.289	32.00	60.00	0.272	0.763
1000 mg	12	46.083	8.938	33.00	58.00		
1500 mg	12	43.916	9.605	32.00	56.00		
Total	36	44.444	9.424	32.00	60.00		

Figure 2: Graphical representation of frequency distribution of prakriti analysis amongst three groups 500 mg, 1000 mg, 1500 mg



Effect on *Udarshula*

The chi square value 6.052 found non-significant with p=0.417 (p<0.05) representing the groups at homogeneous similarity in *udarshula* before the intervention. The chi-square value 6.052 indicate a statistically significant association between the intervention dose and the grade of abdominal pain. Thus, doses reflect the observable impact on the distribution of abdominal pain grades. That said, 1000 (mg) reflects the best dose per the analysis for degrading abdominal pain (*Udara Sula*). The results are shown in Table 3.

Effect on *utklesha*

Statistical assessment of observations before treatment showed that the chi-square value ($\chi2 = 5.934$, $p = 0.431$) was found to be non-significant, suggesting that both groups are at equilibrium for the feeling of nausea (Utklesa). After the treatment, the Chi-square test indicated no statistically significant association between the intervention dose and the *Utklesa* grade (Feeling of nausea)($\chi2 = 2.483$, $p = 0.289$), signifying that there was no statistical improvement as shown in Table 4.

Effect on *Agnimandya*

Statistical assessment of observations before treatment showed that the Chi-square value ($\chi2 = 3.596$, $p = 0.731$) resulted in no statistically significant association between the dose of intervention and the grade of the *Agnimandya* (impaired digestion) suggesting that the at pre-intervention distribution of *Agnimandya* (impaired digestion) grades across different doses were at the equilibrium position After the treatment, the Chi-square test indicated value = 9.273 found non-significant as p-value =0.054633 > P=0.05 as shown in table 5.

Effect on Alanine transaminase (ALT): The mean ALT levels before intervention in 500mg group were recorded at 77.892±6.486, in 1000 mg group 78.500 ± 4.583, and in 1500 mg group with mean value 75.667 ± 4.334. ANOVA analysis showed an f-value of 0.979, found non-significant as the p-value recorded at 0.387 > P=0.05. At the post-intervention, for the 500 mg group, consisting of 12 participants, the mean ALT level was 70.750 ± 7.338. For the 1000 mg group, the mean ALT level was 49.333 ± 2.270 and in 1500mg group, it was 71.250 ± 4.975. ANOVA showed the F-value was 67.297, p <0.01, indicating a statistically significant difference among the three doses with best response in the 1000mg dose group. The results are also shown in Tables 6 and figure 3.

Effect on Aspartate aminotransferase (AST): The mean AST levels before intervention in The 500 mg group, was 68.658±8.508 in the 1000 mg group, 63.942±8.544, in the 1500 mg group, it was 68.658± 8.508. ANOVA showed an F-value of 1.226 and a corresponding p-value of 0.307, indicating no significant difference among the dosage groups. At post-intervention, the mean AST level in 500mg group was 59.800± 8.034, in 1000mg group 48.517 ± 7.488 and in 1500mg group, 59.800 ± 8.034. The F-value was 8.251, with p-value was 0.001, indicating a statistically significant difference. The results are also shown in Tables 6 and figure 4.

Table 3: Comparative evaluation of Udara Sula (Pain in Abdomen) in three dose administration at before and after treatment

***Udarashula* (Pain Abdomen) B.T.**		**500 mg**	**1000 mg**	**1500 mg**	**Total**	**Chi Sq**	**P-value**
Grade Zero	Frequency	0	1	0	1	6.052	0.41737
Grade One	Frequency	8	5	10	23		
Grade Two	Frequency	3	5	2	10		
Grade Three	Frequency	1	1	0	2		
Total	Frequency	12	12	12	36		
A.T.		**500(mg)**	**1000(mg)**	**1500mg**	**Total**	**Chi Sq**	**P-value**
Grade Zero	Frequency	2	10	2	14	16.571	0.002341
Grade One	Frequency	9	2	10	21		
Grade Two	Frequency	1	0	0	1		
Total	Frequency	12	12	12	36		

Table 4: Comparative evaluation of *Utklesa* (Feeling of nausea) in three dose administration at before and after treatment

Utklesa (Feeling of nausea) B.T.		**500(mg)**	**1000(mg)**	**1500(mg)**	**Total**	**Chi Sq**	**P-value**
Grade Zero	Frequency	7	3	4	14	5.934	0.431
Grade One	Frequency	3	4	6	13		
Grade Two	Frequency	2	4	2	8		
Grade Three	Frequency	0	1	0	1		
Total	Frequency	12	12	12	36		
Utklesa (Feeling of nausea) A.T.		500(mg)	1000(mg)	1500(mg)	Total	Chi Sq	P-value
Grade Zero	Frequency	10	11	8	29	2.483	0.288
Grade One	Frequency	2	1	4	7		
Total	Frequency	12	12	12	36		

Table 5: Comparative evaluation of *Agnimandya* (impaired Digestion) in three dose administration at before and after treatment

***Agnimandya* (impaired Digestion) B.T.**		**500(mg)**	**1000(mg)**	**1500(mg)**	**Total**	**Chi Sq**	**P-value**
Grade Zero	Frequency	1	0	0	1		

Grade One	Frequency	5	5	7	17	3.596	0.731212
Grade Two	Frequency	5	6	5	16		
Grade Three	Frequency	1	1	0	2		
Total	Frequency	12	12	12	36		
***Agnimandya* (impaired Digestion) A.T.**		500(mg)	1000(mg)	1500(mg)	Total	Chi Sq	P-value
Grade Zero	Frequency	2	8	2	12	9.273	0.054633
Grade One	Frequency	9	4	9	22		
Grade Two	Frequency	1	0	1	2		
Total	Frequency	12	12	12	36		

Table 6: Comparative assessment of outcome parameters (Quantitative) at pre and post intervention amongst three doses using ANOVA

At Pre-Intervention		**N**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**	**F-value**	**P-value**
ALT	500 mg	12	77.892	6.486	66.30	90.00	0.979	0.387
	1000 mg	12	78.500	4.583	69.00	83.00		
	1500 mg	12	75.667	4.334	67.00	81.00		
	Total	36	77.353	5.220	66.30	90.00		
AST	500 mg	12	68.658	8.508	52.20	78.10	1.226	0.307
	1000 mg	12	63.942	8.544	51.60	78.00		
	1500 mg	12	68.658	8.508	52.20	78.10		
	Total	36	67.086	8.575	51.60	78.10		
At Post-Intervention		N	Mean	Std. Deviation	Minimum	Maximum	F-value	P-value
ALT	500 mg	12	70.750	7.338	58.000	82.000	67.297	<0.01
	1000 mg	12	49.333	2.270	45.000	54.000		
	1500 mg	12	71.250	4.975	62.000	80.000		
	Total	36	63.778	11.561	45.000	82.000		
AST	500 mg	12	59.800	8.034	44.000	72.000	8.251	0.001
	1000 mg	12	48.517	7.488	40.000	64.000		
	1500 mg	12	59.800	8.034	44.000	72.000		
	Total	36	56.039	9.343	40.000	72.000		

Figure 3: Graphical representation of ALT at pre-post evaluation comparing their mean values

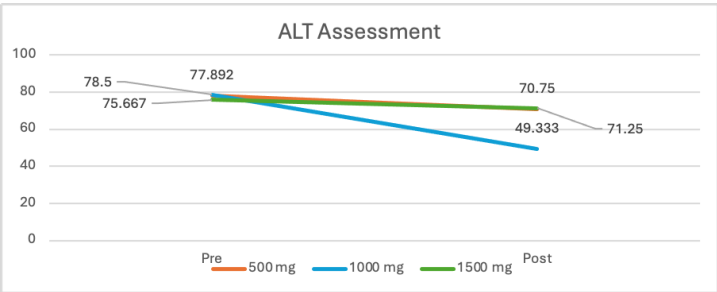
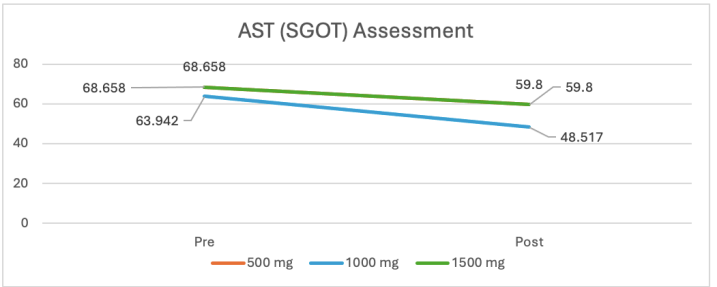


Figure 4: Graphical representation of AST at pre-post evaluation comparing their mean values



The drug was well tolerated in the doses of 500mg and 1000mg, and none of the patients reported any side effects or untoward incidents upon taking the drug. In the 1500 mg group, two patients reported heaviness in the abdomen after medicine intake, which subsided gradually within two hours of the intake. One patient reported sour eructations within this duration, hence their dose was reduced to the lower level.

Discussion

Reverse Pharmacology has emerged as the most suitable tool for validating the efficacy of Ayurveda medicines in an accelerated way. This study forms the part of second stage of RP, which is dose escalation study. The main focus in this stage is to find the best effective and tolerable drug dose, with each patient receiving at least the minimum therapeutic dose.

Literature search revealed that a common dose of *ghana vati* is not clearly mentioned in the classical texts. Extending the search for the dose of various other *ghana vati* like *guduchi ghana*, *sarpagandha ghana* and *kutaja ghana vati,* it is observed that these are prescribed in doses from 500mg to 1gm at least twice a day (8). A case study on the management of Hepatitis B reported the use of *Phalatrikadi ghan vati* (PGV) in a dose of 1000mg twice a day (9). These studies showed that the drug was well tolerated without any side effects. Thus, based on the literature review, an optimum dose of 500mg was decided as base dose of PGV.(7) Thus, in the dose escalation study, which is second stage

of RP, an initial dose of 500mg, a next higher dose of 1000 mg and another higher dose of 1500 mg were undertaken for evaluation.

The statistical evaluation of the observations showed that the drug was effective in lowering the symptoms of *udarshula* and the levels of ALT and AST. This effect was more pronounced in the 1000mg dose group. The first group, i.e. 500mg dose group was safe and tolerable, however the effect on lowering of levels of elevated liver enzymes was statistically not significant. Moreover, in the 1500 mg group, since patients reported heaviness in the abdomen and sour eructations post medicine intake, their dose was reduced to one step lower. This may be the reason for the insignificant effect of the drug in this group. The higher dose of 1500mg was also not well tolerated by all patients, and 3 patients (25%) reported gastrointestinal side effects. Though these were minor in nature, the drug in a dose of 1000 mg only was considered the most effective and tolerable to the patient.

The individual ingredients of PGV have shown a potent hepatoprotective effect in different animal models.

Phyllanthus emblica L. has shown significant antioxidant activity and reduces body weight, epididymal fat and peritoneal fat in rats fed with a high-fat diet, along with a reduction in serum ALT and AST.(10,11) The three myrobalans, together (*triphla*), mitigate inflammatory markers in hepatocytes, thus preventing the development of NAFLD in rats fed with a high-fat diet(12).

Tinospora cordifolia Miers. and *Adhatoda vasica* Nees. also show significant hepatoprotective action causing a reduction in hepatic biochemical parameters.(13–15) *Picrorrhiza kurroa* Royale ex Benth. is a proven hepatoprotective agent that suppresses the activity of Kupffer cells activated liver injury and exhibits regeneration in hepatocytes.(16) The therapeutic action of *Phalatrikadi Ghana Vati* on NAFLD may be attributed to its active phytoconstituents which have individually been proven as potent hepatoprotective agents in different studies.

Conclusion

Reverse Pharmacology is the most appropriate methodology for evaluating Ayurveda drugs for their safety and effectiveness. The dose escalation study conducted in stage two of RP provides a scientific pathway for finding out the best effective and tolerable dose of the drug. The drug *Phalatrikadi Ghana Vati* is safe and effective in managing NAFLD at a dose of 1000mg, which is also the best tolerated dose.

Ethics Statement: The authors undertake full responsibility for the contents of the study.

Conflict of Interest: The authors declare no conflict of interest

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