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A Pharmaceutico - Analytical and Experimental Study to Evaluate Kaphaketu Rasa on Hypothyroidism

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ABSTRACT

Background: Hypothyroidism refers to the common pathological condition of thyroid hormone deficiency. It is the most common disorder after Diabetes Mellitus. The prevalence of hypothyroidism in India is 11% and 4-5% in worldwide. It is a hypometabolic clinical state resulting from inadequate secretion of thyroid hormones for prolonged periods or rarely from resistance of the peripheral tissues to the effects of thyroid hormones. Generally, hypothyroidism, a metabolic disorder can consider as agnimandya. All signs and symptoms of hypothyroidism are kaphapradhana. Kaphaja galaganda can be considered as hypothyroidism based on lakshnas and sthana. Kaphaketu rasa is one such yoga explained in Rasendra Chintamani containing Shuddha tankana, shankha bhasma, Shuddha vatsanabha and Shuddha pippali with three ardraka swarasa bhavana with indication in all kaphaja rogas like swasa kasa galarogas peenasa etc Objective- the aim of study was to evaluate anti-hypothyroid effect Of Kapha Ketu Rasa in PTU induced hypothyroid rat models. **Materials & methods** Hypothyroidism was induced by giving Propyl Thio Uracil to rats on daily basis. After one hour of giving inducing medicine, test drug is given for 30 days continuously. The effect of drug on body weight and thyroid hormones were quantified at 30th day. On 30th day animals were sacrificed and thyroid gland is dissected out and screened for histopathological study. **Result & conclusion** Experimental study Data showed decrease in TSH, and improvement in T3 and T4 hormone levels compared to diseased group. Histopathological values showed reduced congestion of blood vessels, reduction in follicular cell hyperplasia reduced inflammation, and no inflammatory infiltrate in test drug group.

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KEYWORDS: *Kaphaketu Rasa, shankha Bhasma, Hypothyroidism, kaphaja galaganda*

INTRODUCTION

Kaphaketu rasa is a herbo-mineral *khalviya rasayana*, which is effective in *kaphapradhana vyadhis* especially *urdwajathru rogas*. It is indicated in *galaroga, galagraha, swasa, kasa, karnaroga, nasaroga.* It also corrects *agni* because it's ingredients have *deepana, pachana* property. Hypothyroidism refers to the common pathological condition of thyroid hormone deficiency. It is the most common disorder after Diabetes Mellitus. The prevalence of hypothyroidism in India is 11% and 4-5% in worldwide.

Hypothyroidism is a hypometabolic clinical state resulting from inadequate secretion of thyroid hormones for prolonged periods or rarely from resistance of the peripheral tissues to the effects of thyroid hormones. Generally, hypothyroidism, a metabolic disorder can consider as *agnimandya*. All signs and symptoms of hypothyroidism are *kaphapradhana. Kaphaja galaganda* can be considered as hypothyroidism based on *lakshnas* and *sthana*. Almost all ingredients of *Kaphaketu rasa* have *katu rasa, laghu ruksa guna, ushna veerya, kaphapittahara* properties which helps in *kapha nissaraka* and thereby cures hypothyroidism.

METHODOLOGY

Test drug

Kaphaketu rasa preparation

Test drug kaphaketu rasa was prepared as per the classical text reference in the department of Rasashastra and Bhaishajya Kalpana, Taranath

Government Ayurvedic Medical College and Hospital, Ballari.

- Ingredients are purchased from khalvachaya ayurvedic retail shop, Ballari.

Method of preparation

- Fine powders of *shuddha Tankana, shuddha Vatsanabha, Shankha Bhasma* and *shuddha Pippali* are taken in clean khalvayantra.
- Bhavana is given with *Ardraka swarasa* for 3 times.

EXPERIMENTAL STUDY

Study was conducted in SDM research center, Udupi.

The animals were acclimatized and maintained with 24ºC ± 2ºC,70%RH and 12/12h light and dark cycle throughout the study at animal house, department of pharmacology, S.D.M. centre for Research in Ayurveda and Allied Sciences, Udupi, as per the protocol outlined in publication of the committee for the purpose of control and supervision of experiment on Animal standard guidelines (CPCSEA) and approval was obtained from Institutional Animal Ethical Clearance Committee (IAEC) Approval No: SDMCRA/IAEC/TB-R-13.

18 healthy wistar albino rats were selected and grouped into 3 groups. Selected animal was grouped by randomisation method. 6 animals in each group. The individual rat was weighed and rats with weight around 200-250 only taken for study and marked with picric acid for identification.

Experimental design

Wistar albino rats were randomly divided into 3 groups.

Group 1-normal control

Group 2-disease control

Group 3-test drug group

Experimental induction of hypothyroidism

Hypothyroidism was induced to rats by oral administration of propyl thio uracil oraly on daily basis for 30 days. Dose was calculated according to individual rat weight. PTU was given by diluted in distilled water.

Dose fixation

The dose for Rats was calculated by referring the table of Paget and Barnes:

i,e Rat Dose =Human Dose mg/kgbw X $K_m$ratio/kgbw.

Dose of PTU drug:

To induce hypothyroidism PTU was administered orally in the dose of 50mg/kgbw in humanbody.

Rat dose- 1 mg/kgbw

Dose of test drug

The therapeutic Human dose of *Kaphaketu Rasa* is 125 mg per day. Therefore, Rat Dose =Human Dose X 0.018 X 5 = 11.25 mg/kgbw.

ROUTE OF DRUG ADMINISTRATION:

The dosage form of *Kaphaketu Rasa* was administered through the oral route by intragastric tube using 5 ml syringe fitted with number 18 gauze gavaging needle with round tip made of steel, prescribed dose of suspended drug was loaded in the syringe and the tube was inserted into the oesophagus and drug was administered.

DOSAGE FORM:

The Dosage of *Kaphaketu Rasa* (125mg/kgbw) was administered in the form of suspension by adding 20ml of *Ardraka Swarasa* which is the *Anupana* mentioned.

DRUG DOSING SCHEDULE

To induce hypothyroidism 1 mg of PTU is administered orally by diluting in distilled water daily. Test drug *Kaphaketu Rasa* along with *Ardraka Swarasa* as *anupana* is administered after one hour of PTU administration to the same group. To another group only PTU is given to induce hypothyroidism.

STATISTICAL ANALYSIS

The data obtained was analyzed by using analysis of variance (ANOVA) followed by Dunnett's 't' test for determining the level of significance of the observed effects. A 'P' value of less than 0.05 was considered statistically significant.

- **EVALUATION OF ANTIHYPOTHYROID ACTIVITY**

A number of experimental models are employed to assess antihypothyroid activity. When the rats are exposed to multiple doses of PTU, it causes lowering of T3,T4 and TSH levels. Administration of drug *Kaphaketu Rasa* is done to make the thyroid hormone levels in normal level. Also, the histopathological changes also evaluated. This fact has been used to design experimental models for assessing hypothyroid activity.

In the present study evaluation of *Kaphaketu Rasa on hypothyroidism* was carried out using PTU induced Hypothyroid models in rats.

Treatment protocol:

Group	Group name	Treatment	Dose	Frequency	Duration
1.	Normal control	Vehicle	-	Daily	30 days
2.	Positive control	(PTU)	1 mg/kg BW	Daily	30 days
3.	Induced HYPOTHYROIDISM Test drug: *KKR* with *Ardraka Swarasa as anupana*	PTU	1 mg/kg BW	Daily	30 days
		KKR with *Ardraka Swarasa* as *anupana*	11.25mg/kg BW	Daily	30 days

Group 1 Vehicle treated: animals received tap water.

Group 2 POSITIVE CONTROL-: animals received PTU (1 mg/kgbw), and distilled water.

Group 3 Test drug: animals received *Kaphaketu Rasa* (11.25mg/kgbw,p.o.), in addition to PTU.

The Test drug *Kaphaketu Rasa* were administered orally in test group after one hour of giving PTU daily for 30 consecutive days. One group (vehicle) is treated only with water and food. Another group is given only PTU, no test drug given (Positive control). All the animals were sacrificed by cervical dislocation after ether anesthesia. Blood withdrew to check biochemical parameters. And thyroid organ is dissected out and cleaned to remove extraneous tissues, blotted to remove blood stain. Thyroid organ was preserved in 10% formalin for histopathological processing.

Serum was separated and serum level of biochemical parameters namely TSH, T3 and T4. were estimated as per standard procedure prescribed by manufacturer.

Observation and results of experimental study

Effect of test drug (Kaphaketu rasa) on Biochemical Parameters

Results of test drug (Kaphaketu Rasa) on TSH:

Groups	mean ± SEM	% Change
Normal control	0.173±0.04	-
Positive control	33.106 ± 6.00 **	↑19036@
Test	40.523± 1.56 ns	↑28.444#

Data; MEAN ± SEM, **P<0.0001, ns- **P Value >0.05**

@-compared with normal control

#-compared with positive control

The effect of test drug on TSH hormone in PTU induced hypothyroidism has been depicted in above table

The data shows there is drastic increase in TSH level in disease control group, due to negative feedback mechanism in hypothyroidism, when compared to the normal control group, the observed increase was found to be statistically very significant.

The data shows the magnitude of increase in TSH level is less in test drug group, when compared to the normal control group, its due to less variation in thyroid hormones in test drug group. The observed decrease was found to be statistically nonsignificant.

Showing the result of test drug (KKR) on T3:

Group	mean± SEM	%change
Normal control	0.413± 0.075	-
Positive control	0.188± 0.014 *	↓54.48@
Test group	0.336± 0.072 ns	↑78.72 #

Data: MEAN ± SEM, *P<0.05, ns- **P Value >0.05**

@-compared with normal control

#-compared with positive control

The effect of test drug on T3 hormone in PTU induced hypothyroidism has been depicted in above table

The data shows there is decrease in T3 level in disease control group, due to induced hypothyroidism, when compared to the normal control group, the observed decrease is found to be statistically significant.

The data shows there is increase in T3 hormone level in test drug group, when compared to the disease control group. The observed increase is found to be statistically non-significant. Eventhough its statistically non-significant, the data shows more appreciable increase in T3 hormone level.

Showing the result of test drug (KKR) ON T4:

Group	Mean ± SEM	% change
Normal control	236.666 ± 33.384	-
Positive control	179.833 ± 10.901 ns	↓24.014@
Test group	268.166 ± 39.247 ns	↑49.119#

Data: MEAN ± SEM, ns- **P Value >0.05**

@-compared with normal control

#-compared with positive control

The effect of test drug on T4 hormone in PTU induced hypothyroidism has been depicted in above table

The data shows there is decrease in T4 level in disease control group, due to induced hypothyroidism, when compared to the normal control group, the observed decrease is found to be statistically non-significant.

The data shows there is increase in T4 hormone level in test drug group, when compared to the disease control group. The observed increase is found to be statistically non-significant. Eventhough its statistically non-significant, the data shows appreciable increase in t4 hormone level.

Histopathological Changes

Showing results of Histopathology

	Inflammatory infiltrate	Congested blood vessels	Follicular cell Hyperplasia
NC1	-	-	-
NC2	-	-	-
NC3	Thyroid tissue not seen in tissue section		
PC1	++	+++	+++
PC2	-	+	+++
PC3	-	+++	+++
T1	-	+	++
T2	-	+	+++
T3	Thyroid tissue not seen in tissue section		

NC(normal control)- All the tissue sections show round to oval thyroid follicles lined by cuboidal epithelial cells or thyrocytes. The lumen contains eosinophilic colloid.

PC(positive control)- All the tissue sections show severe diffuse follicular cell hyperplasia. Obliteration of lumina of most of the follicles is caused by hypertrophy and hyperplasia of the lining epithelium. Some follicles show very small lumina with reduced colloid material. The cells are overcrowded with nuclear pleomorphism (variability in size and shape of nuclei) in some areas. Chronic inflammatory infiltrate is seen in 1 slide. Severe congested blood vessels are seen in all the tissue sections. Tissue architecture is distorted

T(test group)- T1 and T2 shows diffuse follicular cell hyperplasia with nuclear pleomorphism in T2. Compared with PC group, all the tissue sections show reduced congestion of blood vessels. T1 shows slight reduction in follicular cell hyperplasia. Inflammatory infiltrate is not seen in any of the tissue sections.

Discussion

PTU induced hypothyroidism- Propyl thio uracil is an anti- thyroid drug used to manage Hyperthyroidism & grave's disease.

It inhibits the production of new thyroid hormone in thyroid gland. It acts by inhibiting the enzyme thyroid peroxidase, which usually converts iodide to iodine molecule and incorporates the iodine molecule into amino

acid Tyrosine. Hence Di iodo tyrosine and Mono iodothyronine does not get produced, which are main constituents in production of Thyroxine(T4) and Tri iodothyronine(T3). Peripherally, it acts by inhibiting the conversion of T4 to T3. It affects the existing thyroid hormones stored in the thyroid gland as well as circulating in the blood.

PTU can lead to Hypothyroidism- weight gain, constipation or drowsiness.

1. Physical parameter

Changes in % change in Body weight: Test drug at therapeutic dose administered groups showed decrease in the % change in body weight in comparison to Disease control group and was found to be statistically non-significant. Eventhough statistically non-significant there is reduction in weight of rats, which indicates the action of drug on weight gain seen in hypothyroidism.

2. Blood parameters

A. TSH-

Thus, serum estimation of TSH which is fairly specific for assessing normal thyroid functioning. It is well established that level of TSH will gets elevated in Hypothyroidism by negative feedback mechanism. In the present study also remarkable but non-significant (due to variation) elevation was observed. This elevation was found to be reduced in test drug group. This can be considered as the first line of evidence for the action of test drug.

B. EFFECT ON TRI IODOTHYRONINE

In the present study, T3 hormone level is reduced in disease control group which means hypothyroidism is induced in that group. In test drug group the T3 value is increased to quite large amount, but statistically its shown as non-significant. Eventhough the elevation is not statistically significant; the effect of test drug in elevating T3 hormone is acceptable.

C. THYROXINE

In this study, the thyroxine value is reduced in disease control group, showing hypothyroidism is induced in that group. In test drug group it showed non-significant increase in thyroxine level. This may indicate the test drug's action on increasing thyroxine levels in blood and thereby curing Hypothyroidism.

Histopathology

Histopathological study reveals that the test drug reduces the inflammatory infiltration, necrosis, degeneration, cellular alteration and congestion in the thyroid tissue when compared with Disease control group. This proves the test drug can reduce the damages of tissue upto an appreciable extent.

Probable mode of action.

Thyroid hormone functions are similar to the functions of *agni (jataragni, dhatvagni, bhutagni)* in our body causing transformations/ tissue metabolism at various levels and thus maintaining the Basal Metabolic Rate. *Agnimandya* at any level is due to *kaphakara nidaana* results in increased *Dhatugata mala sanchaya*, resulting in *srotorodha* causing compromised *dhatu saara* leading to both physical and mental features in hypothyroidism. Vata acts as a *yogavahi* in aggravating the *kaphadushti*. Thus, it is a *vata kapha samsarga* condition.

Medicine having *Deepana, pachana, lekhana, ruksha, ushna, Sukshma, kaphachedhana, kaphashoshana* properties can boosts the body metabolism and can reduce the disease condition.

Kaphaketu rasa is such a potent *kaphahara* drug which contains *Shankha Bhasma, vatsanabha, tankana, Pippali* as ingredients and *ardraka swarasa* as *bhavanadravya*.

S*hankha Bhasma* works on deep seated *dushita kapha* by its scraping property and thus helps in improving *agni*. With pacification of *kapha*, *Ama* condition which is responsible for underlying inflammation in body is reduced. *Shankha Bhasma* is a very potent antacid, anti-inflammatory and good source of organic calcium. Being potent antacid, it will balance the more *teekshna* effect of *Pippali*, *vatsanabha* etc on git. Also, *shankha Bhasma* can regulate the body metabolic rate by correcting *dhatvagnis*.

It consists of 43% calcium carbonate. Calcium carbonate is indicated for low serum calcium conditions like osteoporosis, hypothyroidism, hypoparathyroidism, pseudo-hypoparathyroidism etc. Cytoprotective effects may occur through increased bicarbonate ion (HCO_3^-) and prostaglandins.

Vatsanabha with its *ushna, teekshna, vikashi, vyavayi* properties will act on *dooshita kapha.* It will help to remove the *avarana* of *kapha*. Being *visha* its action will be fast and penetrating. Also, aconitum alkaloids

present in *vatsanabha* have metabolism stimulating properties. Aconitum chasmanthum, a chemical constituent in *vatsanabha* has anti-inflammatory effects, by reducing IgE, monocyte chemo attractant protein -1, eosinophil, & lymphocytes which are important inflammatory mediators involved in auto immune hypothyroidism.

Immunomodulatory drugs have a major role in hypothyroidism, because auto immunity is the major cause for disease manifestation. The drugs like *Pippali* and *Vatsanabha* have *Rasayana* effect, which can reduce the autoimmune system attack of thyroid, in these cases body reduces selenium supply. But drugs like *Pippali* can increase the absorption of selenium and thus helps in proper thyroid functioning. Selenium is required for many enzymes known as selenoproteins. The chemical reaction which converts thyroxine to tri-iodothyronine is catalysed by these selenoproteins. Pippali have properties like *ushna*, *teekshna*, will helps to reduce the *kapha dushti* and thereby reduces the hypothyroid symptoms. The *Shodhana dravya* used for *Pippali* is *chitraka*, which is also helps in thyroglobulin formation while hormone synthesis

Tankana, which is a *kshara with lekhana, ushna, teekshna ruksha* properties will reduce the *kaphadushti* and clears the *margavarodha*. Also, it's an antidote to the potent ingredient *vatsanabha. Tankana* is anti - inflammatory in action, thereby it can inhibit the pro- inflammatory cytokines and reduces inflammation and swelling of thyroid tissues and thus helps in production of thyroid hormones properly.

Ardraka, the *bhavana* dravya used will potencify the drug. The principal alkaloid Zingiberene results in decreasing lipid peroxidation and increasing the activity of anti-oxidant enzymes. It possesses anti-inflammatory, analgesic, carminative etc. its anti-inflammatory activity has been attributed to its ability to reduce pro-inflammatory mediators and due to anti-oxidant effect. It inhibits macrophages, neutrophils, monocytes and leukocyte migration to site of inflammation and thus can limit the extent of tissue damage.

Pippali and *ardraka* also exihibits bio enhancing properties which are useful in reducing the dose as well as duration of treatment.

Kaphaketu rasa altogether have properties *ruksha, lekhana, laghu, Sukshma guna, ushna veerya, katu vipaka, katu kashaya rasa*, having *Deepana, pachana, vatakaphahara, karma*. so effective in *kapha medo* disorders. Because of *Lekhana* is effective in management of hypothyroidism, it helps to reduce or breakdown deep seated *kaphadosha* and *meda dhatus* and clears the *srotorodha*. Thus, show significant action on sypmtoms like sudden weight gain, constipation, tiredness etc. in hypothyroidism.

Thus, *Kaphaketu rasa* acts on overall metabolism of body and helps to regulate the digestion and excretion process and reduces inflammation and enhance proper functioning of thyroid gland.

Conclusion

Kaphaketu Rasa is one yoga explained in Rasendra Chintamani, Kapha rogadhikara . It contains *Shuddha Tankana, Shuddha Pippali, Shankha Bhasma* and *Shuddha Vatsanabha. Vati is prepared after* three *Bhavana* in *Ardraka Swarasa* .it is indicated in *swasa kasa ,galarogas etc*. Almost all ingredients of *Kaphaketu Rasa*[1] possess *katu, tikta, kashaya Rasa, ushna veerya lekhana, kapha-vatahara,* properties.; hypothyroidism, by symptoms and clinical presentations, correlated as *kaphaja galaganda. Kaphaketu rasa* altogether have properties *ruksha, lekhana, laghu, Sukshma guna, ushna veerya, katu vipaka, katu kashaya rasa, having Deepana, pachana, vatakaphahara, karma*. so effective in *kapha medo* disorders. Because of *Lekhana* property it is effective in management of hypothyroidism, it helps to reduce or breakdown deep seated *kaphadosha* and *meda dhatus* and clears the *srotorodha*. Thus, show significant action on sypmtoms like sudden weight gain, constipation, tiredness etc. in hypothyroidism.

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Figures of animals study

Fig. no:1 -dosing of rats

Fig. no:2-collection of blood samples

Fig. no:3-dissection of rats

Fig. no:4- thyroid gland, along with portions of trachea

Normal group- Normal thyroid follicles

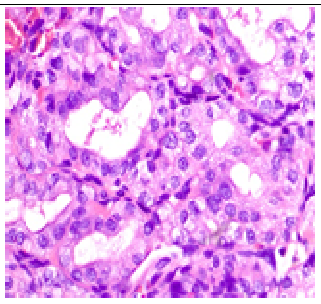

Fig no-1 positive control - chronic inflammatory infiltrate

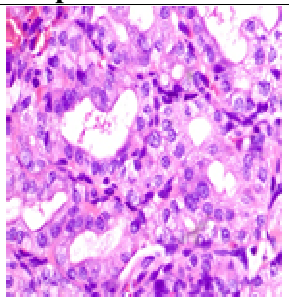

Fig no- 2 pc- follicular cell hyperplasia

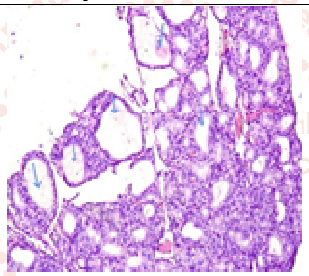

Fig. no. 4 Test group- reduced follicular hyperplasia

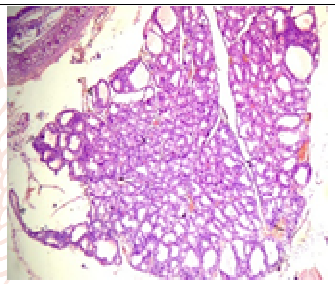

Fig. no.5 Test group- reduced hyperplasia, congestion

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