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Evaluation of Analgesic and Antipyretic Activity of Kankshi in Albino Rats- Retrospective Analysis

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Introduction :

Ayurveda is intimately connected with Vedas. Our Acharyas describe Ayurveda as upaveda of atharvaveda and as upang of Rigveda. According to Acharya Charaka, Ayurveda is source from which the knowledge of 'Ayu' is derived. Sensation of pleasure and pain are the inherent feelings of all living organisms in the world.

While mentioning the origin of disease , we can see a psychosomatic approach in which one or the other might have upper hand. According to Acharya Charaka , Jwara is supposed to be present both during the time of birth and death. Depending upon the causative factors, periodicity and severity , various types of Jwara are described by Acharya Charaka, Sushruta and Vagbhata. Generally, in Jwara, pitta is main dosha for the cause of santapa in sarira.[1] Amatva is root cause for Jwara. Irregular food habits and regimen's result in vitiation of doshas which get mixed up with jatharagni. The resulting rasa dhatu , which is in vikrut condition obstructs the channel of its own & that of sweda and suppress the activities of agni. Thus dispelling the heat from the site of digestion. The ahar rasa thus produced in circulation spreads the heat all over the body resulting in Jwara[2].

Modern science also gives importance to Jwara (fever). Fever is one of the most misunderstood symptom in all of medicine. Fever can be defined as a regulated elevation in body temperature above the customary set point of the hypothalamic thermostat, which means the body temperature above the usual range of normal. Fever, serves as one of the body's natural defence against the bacteria and viruses , which can not live at higher temperature. Also the defense mechanism seem to work more effectively at a higher temperature. But improper monitoring of this mechanism may lead to heat stroke. So drugs which bring about cure are necessity.

Rasashastra is pharmaceutical science of Ayurveda and as such it deals with mainly with the drugs of mineral origin, their varieties, characteristics , processing techniques , properties and their therapeutic use along the description of different apparatuses. Today, most of the world's population still continues to depend on the plant based herbal medicines; and all of us knows the existence of multiple side effects in consumption of artificially manufactured chemicals or medications. Synthetically prepared drugs face multiple health risks as we will not find a single drug without side effects warnings. So there is an urgent need of an alternative system of medicines and for this, Ayurveda is as golden treasury to the modern scientists for providing clues for the prevention and management of common and complicated diseases.

Now days, single drug therapy is becoming popular. Many single drugs are screened to understand their pharmacological action. The main advantage of a single drug therapy over a compound preparation is that it is very easy and convenient from the point of processing, it is economical and will produce specific action of the drug. It becomes simple, easy and convenient for the patient and the physician to fulfill the purpose of the treatment. Due

to this, single drug Kankshi is selected to evaluate its antipyretic and analgesic property. In the present study, an attempt had been made to establish antipyretic and analgesic property of the trial drug Kankshi.

Material And Methods :

Jwara –

The disease which produces 'santapa' to the body, indriyas and manas is called as Jwara. Improper Ahara, vihara, Asatmendriyartha samyoga, prajnaparadha, parinama or aganthuka karana causes vitiation of doshas. These vitiated doshas are responsible for Jwara. While describing Jwara, Acharya Charaka, says that it appear in the human body due to eight causes namely Vata, Pitta, Kapha, Vata- Pitta, Pitta – Kapha, KaphaVata, Vatapittakapha, and Aganthuka. Jwara is manifested due to some disturbance in the digestive tract. The site of pitta is amashaya. The vitiated pitta by its own physiological factors cause mandagni. There will be agnimandya in amashaya. From amashaya, it replaces agni along with rasadhatu, it circulates all over the body resulting in the rise of somatic temperature and then produces srotorodha. Predormal symptoms (Poorvarupa) of Jwara are dyspepsia, heaviness of limbs, agitation of eyes, lacrimation, hypersomnia, giddiness , yawning, flexion, tremors, fatigue etc. Three cardinal symptoms of Jwara namely:

1.Swedavarodh
2.Santapa
3. Sarvangagraha ,

Other Acharyas have described various symptoms according to the variety ofthe disease. In a person having strong physique (bala) , if Jwara occurs by the vitiation of less amount of doshas and if there is no complications, then it is easily curable and vice versa.[3]

Symptoms of relief of Jwara-[4]

1. Laghuta
2. Sweda Darshana
3. Kandu
4. Mukha paka
5. kshavathu
6. Anannabhilasha

Fever:

Hyperthermia is elevation of body temperature beyond hypothalamic set point due to physiological or pathological conditions. Few factors responsible for disturbance of hypothalamic thermoregulatory function are- Brain lesions, toxins, infections, environmental conditions.[5] Human body temperature is not constant throughout the day. It fluctuates in a typical manner which is called as 'circadian temperature rhythm'. The normal 24 hour circadian temperature rhythm varies to 0.5 °C to 1° C between AM & PM. Generally human body temperature is 37 °C or 98 °F. If AM temperature is more than 37.2 °C (98.9 °F) and PM temperature is more than 37.6 °C (99.9°F), it is considered as fever.

The substance that induce the fever are called pyrogen. Endogenous pyrogens are the proteins released from degenerating tissue, released from injured cells, Polypeptide, produced by variety of cells. Exogenous pyrogens are those, which are produced by invading organisms. The temperature of the body is regulated almost entirely by nervous feedback mechanism and almost all of these operate through temperature regulating centres located in the hypothalamus. The principal area in the brain in which heat affects body temperature control, consists of the preoptic and anterior & posterior hypothalamic nuclei of the hypothalamus. Pathologically pyrexia may be divided into three types based on duration of affection such as:

1. Continuous fever – when the fever does not fluctuate more than it during 24 hrs. But at no times, touches normal , it may be described as continuous fever.
2. Intermittent fever – when the fever is present only for several hours during the day, it may be called as intermittent fever.
3. Remittent fever – When the daily fluctuation exceeds 2°F, it may be known asremittent fever.

Vedana –[6,7]

In shareera sthana of Charak Samhita, Acharya Charaka has used the word Vedana in the sense of sensation. (C.S.Shareer 1/56). According to him, Vedana is of two types, sukhatmaka vedana and dukhatmaka vedana. Dukhatmaka Vedana is considered as Roga and needs treatment. Impairment of intellect, retention power and memory, maturity

of kala & karma and unwholesome contact with objects of sense organs are considered to be the causative factors of dukha. Among tridosha, vata is responsible for pain. The intensity and character of it depends upon the involvement and characteristics of other doshas.

According to ancient Indian scholars, dukha (Pain) has been divided into three main types ; which are as follows ,

I. Adhyatmika (psycho somatic pain)
II. Adhibhautika (Pain due to animals / non animals)
III. Adhidaivika (Pain due to desire, evil, sources)

Further adhyatmika variety has been subdivided into two types

1. Sareera (physical) perceived through Sparshenendriya.
2. Manasa (Psychic) felt only by manas.

The drug which is used to control the unpleasant sensation of a particular part of the body and which restores the normal state is known as vedanasthapana.

Pain-[8,9,10]

A complex experience consisting of a physiological (bodily) response to a noxious stimulus followed by an affective (emotional) response to that event. Pain is a warming mechanism that helps to protect an organism by influencing it to with drawfrom harmful stimuli. It is primarily associated with injury or the threat of injury , to bodily tissues. Analgesics are drugs that selectively relieve pain by acting in the CNS or on peripheral pain mechanism, without specifically altering the consciousness. Pain is interpreted and perceived in the brain. The sensation of pain is modulated by two types of CNS active drugs known as analgesics and anesthetic. The term analgesics refer to a drug that depresses the CNS. It is characterized by the absence of all perception of sensory modalities including loss of consciousness without loss of vital function.

Material and Methods-[11,12,13,14]

Material:

I. Kankshi (test drug)
II. Paracetamol (standard drug)
III. Wister strain albino rats – 24 nos
IV. Bakers yeast (to induce pyrexia)
V. Normal saline 0.9 % (to prepare yeast solution

Equipments and glass wares :

1. Digital tele thermometer (to record the rectal temperature of albino rats)
2. Glass breakers
3. 18 G needles
4. Disposable syringes
5. Stop watch
6. Hand gloves
7. Glass rod.

- **Preparation of Shuddha Kankshi-**
  1) 100 gm of Ashuddh Kankshi was powdered in khalva yantra.
  2) 100 gm Ashuddh kankshi is taken in to iron pan.
  3) Bharjan (frying) process was carried out on pan till all water evaporates.
  4) All impurities and dust were separated.
  5) Shodhit Kankshi was of white colour.
  6) The total time taken for shodhana was 5 minutes.

- **Method**:

1. Healthy male adult albino rats (wister strain) of 90 -120 days old, weighing from 150 – 200 gms was taken for the experimental study.
2. The animals were maintained under strict laboratory condition with controlled environment of temperature, humidity, light and dark cycles.
3. Rats were fed with balanced pellet diet as prescribed by CFTRI, Myrore (Central food technological research institute) and water as libitum.
4. Maximum number 03 animals per cage were maintained. Animals under different groups of experiments were caged separately.
5. The study is conducted at BLDEAS AVS Post Graduate cum Research Centre, Vijayapur and rats were selected considering inclusive and exclusive criteria.
6. One rat is marked at head region, one at body region and one at tail region for identification in each cage.

Inclusive and Exclusive criteria

INCLUSIVE CRITERIA

a. Adult healthy male albino rats.
b. Albino rats weighing 150 – 200 gms.
c. Albino rats between 90 – 120 days.

EXCLUSIVE CRITERIA

a. Unhealthy albino rats.
b. Weight range below 150 gms and above 200 gms
c. Female albino rats.
d. Albino rats of age below 90 days and above 120 days.

Experimental protocol Antipyretic study-

(on yeast produced pyrexia in albino rats)

Sample size - 12 albino rats were taken for the experimental study, distributed 6 in each group. Three groups were taken for antipyretic study. Study group:

Group I: Test drug (Kankshi)
Group II: Standard drug (Paracetamol)

Dosage and Mode of drug administration:

Animal dose = Human dose × 0.0181.

1.Kankshi- Dose - (6.75 mg /200 gm rat)
Dosage form – Suspension (with cmc)
Route – oral

2.Paracetamol Dose – 9 mg/ 200 gm rat
Dosage form – Suspension
Route- oral.

Method :

1. The animals were stored for 24 hrs and water ad libitum.
2. The digital tele thermometer cord was lubricated with borax glycerine and initial temperatures of the chosen animals were recorded.
3. Preparation of 15 % yeast solution => For 15 gm of freeze dried baker's yeast (prestige yeast manufactured by SAF yeast Co. Ltd. Mumbai) 100 ml of 0.9 % normal saline was added and triturated thoroughly to make homogenous solution . Every time fresh yeast solution was prepared and used.
4. Induction of pyrexia- Pyrexia was induced by the parental administration of 2 ml of yeast solution atthe nape region.
5. The medicines (test drug, standard drug) were administered, after 18 hrs of administration of pyrogen.
6. Before inducing yeast temperature was recorded and after 18hrs of yeast inducing temperature was recorded.
7. Rats shown more than 100.40F (380 c) were used to experimental study.
8. After drug administration, rectal temperature was recorded consecutively at 30min, 60min, 90min, 120min, 150min, 3hr, 4hr, 5hr, 6hr, and 7hr.

Experimental protocol: Analgesic study:

Sample size: 12 albino rats were taken for the experimental study, distributed 6 in each group. Two groups were taken for analgesic study.

Study group:

Group I: Test drug (Kankshi)
Group II: Standard drug (Paracetamol)

Dosage and Mode of drug administration:

Animal dose = Human dose × 0.0181.

1.Kankshi- Kankshi (6.75 mg /200 gm rat)
Dosage form – Suspension (with cmc)
Route – oral

2. Paracetamol – 9 mg/ 200 gm rat
Dosage form – Suspension
Route- oral.

Method: Tail Flick method

1. The animals were held in left hand with tail extended.
2. Lower 5 cm portion of tail is marked.
3. Then the marked portion is dipped in a beaker of water maintained with 55 + or – 0.5°C.
4. Reaction time recorded with stopwatch.
5. Determination of reaction time periodically after oral administration of test drug doses at 0, 1, 2 , 3, 4, 5, 6 hrs.

Notes:

1. After recording the time, tail is carefully dried.
2. Cut off time of the immersion is 15 seconds, to avoid injury to the tail.

Results-

After the induction of bakers yeast solutions, all the albino rats were closely observed for their behavior and symptoms. The observations noted are mentioned below;

1. Increase in temperature was noted in all the rats.
2. Trembling was noted in all the rats after an hour

of induction of bakers yeast.

3. Fur erected.
4. Face of all the rats bent downwards. They were less active.

All these symptoms found in albino rats confirmed that they were suffering from hyperpyrexia

Table : Showing the results of antipyretic activity of group I and Group II (n=6)

	Before inducing Pyrexia	After drug administration (Temperature in °F)									
		0 min.	30 min.	60 min.	90 min.	120 min.	150 min.	180 min.	4 hr	5 hr	6 hr	7 hr
Test Group	98.73	103.69	103.12	102.29	100.63	99.92	99.72	99.47	98.68	98.54	98.09	**99.66**
Standard Group	**98.23**	**103.66**	**103.09**	**101.71**	**100.81**	**100.37**	**99.95**	**99.81**	**99.22**	**98.67**	**98.84**	**99.79**

Table : Showing comparison between Group I and Group II

Comparison between	Paired t test
Before vs after before inducing pyrexia	**p= 0.001***
Before vs after after inducing pyrexia	**p=0.001***
Before vs after 30 min.	**p=0.001***
Before vs after 60 min.	**p= 0.566**
Before vs after 90 min.	**p=0.001***
Before vs after 120 min.	**p=0.001***
Before vs after150 min.	**p=0.847**
Before vs after 180 min.	**p=0.001***
Before vs after 4 hr	**p=0.001***
Before vs after 5 hr	**p=0.001***
Before vs after 6 hr	**p=0.001***
Before vs after7 hr	**p=0.001***

After the drug administration (test and standard) all the albino rats were closely observed for their behavior and symptoms.

1. The marked portion is dipped in a beaker of water maintained with 55 + or – 0.5°C.
2. Reaction time (tail flick) recorded with stop watch.

Table: Showing the results of analgesic activity of group I and Group II (n=6)

	Initial reaction time (in sec)	After drug administration reaction time interval (sec) at time (hr)						
		0.5 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Group I	2.62	3.17	3.99	4.54	5.59	5.70	4.52	**2.91**
Group II	**2.81**	**3.12**	**3.72**	**4.24**	**5.47**	**3.87**	**3.54**	**2.84**

Table : Showing comparison between Group I and Group II

Comparison between	Paired t test
Before vs after Initial reaction time	**p= 0.001***
Before vs after 0.5 hr	**p=0.001***
Before vs after 1 hr.	**p=0.001***
Before vs after 2 hr.	**p= 0.589**
Before vs after 3 hr.	**p=0.001***
Before vs after 4 hr.	**p=0.001***
Before vs after 5 hr.	**p=0.478**
Before vs after 6 hr.	**p=0.001***

Discussion-

Kankshi is a single drug categorized as a uparasa and its references are in Rasa Tarangini and Rasa Ratna Samucchaya. Experimental study on albino rats was carried out to assess the antipyretic activity. The statistical analysis was done with student 't' test. The antipyretic study was carried out in albino rats by using yeast induced Hyperpyrexia method. 12 male albino rats were selected & distributed 6 in each group and maintained at constant room temperature of 24 – 25°C for 24 hours before the experimental study.

Initial rectal temperature was recorded individually before inducing pyrexia. Pyrexia was induced by subcutaneous injection of 2 ml of 15 % Bakers yeast solution in 0.9 % normal saline. After 18 hours of yeast solution administration, rise in temperature was recorded in group I (Test dose) from 98.73 to 103.69 °F and in Group II (Standard drug) from 98.23 to 103.66 °F. Then rectal temperature was recorded every half hour for three hours and hourly for next five hours.

In Group I (Test dose) , gradual reduction in temperature was started from 103.69 (0 min) to 98.09 °F (6 hr). Further gradual increase in body temperature was noted from 6th hour. In Group II (Standard drug) , gradual reduction in temperature was started from 103.66 (0 min) to 98.67 °F (5th hr). Further gradual increase in body temperature was noted from 5th hour. A standard drug Paracetamol may bring down the temperature to normal level but Kankshi has demonstrated antipyretic activity and contributed for promotion of positive health.

The analgesic study was conducted in two groups , with 12 albino rats , 06 animals in each group ,by Tail Immersion Method described by fuckawa et al. The tail was immersed up to 5 cm in hot water at 55°C. The time taken for the animal to withdraw the tail completely out of the hot water was considered as reaction time. After oral drug administration, pain threshold reaction time was recorded at 0.5, 1, 2, 3, 4, 5, 6 hour intervals in Test Group and Standard Gorup. Kankshi has Snigdha guna and mitigates all three vitiated doshas. This might have attributed for analgesic activity.

Conclusion-

- Kankshi has shown significant antipyretic activity from 30 minutes to 6th hour of drug administration.
- Paracetamol (Standard drug) has shown significant antipyretic activity from 30 minutes to 5th hour of drug administration.
- In Test and standard groups, antipyretic activity was observed from 30 minutes of drug administration. In Test group, antipyretic activity was continued up to 6th hour but in Standard group, it was up to 5th hour.
- Kankshi has Katu – Tikta and Kashaya rasa and Vishaghni (mitigation of Visha dosha), so rats were active in Test Group than Standard.
- This study has given scope for further clinical research.
- The test Group has shown analgesic activity from 0.5 hour and it was up to 6th hour after drug administration.
- Significant & Sustained analgesic activity was from 0.5 hour to 4 hour after drug administration.
- The Standard Group has shown analgesic activity from 0.5 hour and it was it was up to 6th hour after drug administration. Significant and Sustained analgesic activity was from 0.5 hour to 4 hour after drug administration.
- In Test group, highly significant and peak level a nalgesic activity was observed at 2nd hour to 4th hour.
- In Standard Group, highly significant and peak level analgesic activity was observed at 2nd hour to 4th hour.
- Both the Test Group and Standard Group has shown sustained and significant analgesic activity.

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