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A COMPARATIVE STUDY ONANTICONVULSANT EFFECT OF KSHEERA BALA TAILA- AN AYURVEDA FORMULATION MADE WITH TWO SOURCE PLANTS OF BALA (Sida cordifolia,Linn. and Sida retusaLinn.)

Nimmy V S[1], P. Jayasreee[2], M. S Deepa[3]

[1]P G Scholar, [2]MD (Ayu), Former Professor Dept. of Dravya Guna Vijnana, Govt. Ayurveda College, Thiruvananthapuram, Kerala, India

[3]MD(Ay)Asso. Professor Dept. of Dravya Guna Vijnana, Govt. Ayurveda College, Kannur, Kerala, India

Email:drvsnimmy@gmail.com

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ABSTRACT

Members of *Sida* species including *Sida cordifolia* Linn. and *Sida retusa* Linn. are considered the source plants of the herbal drug *"Bala"*. The plant is the key ingredient of *Ksheerabala Taila*- an Ayurveda formulation which is being used successfully in neurological disorders including Epilepsy. Ayurveda Formulary of India has accepted *Sida cordifolia* Linn. of Malvaceae family as "*Bala*". *Sida retusa* Linn. is used as source plant of *Bala* in Kerala. Hence in this study 2 samples of *Ksheerabala taila* were prepared with either of the source plants and both were tested for anticonvulsant effect by Maximal Electroshock Seizure Test in Wistar Albino rats both male and female (150- 200gm.). The experiment was carried out with 8 groups having 6 albino rats per group. "Phenytoin" was given to the standard group. Control group was kept on distilled water and Group III to VI comprised of 2 groups each for testing *Ksheerabala Taila* made with *Sida cordifolia* Linn. and *Sida retusa* Linn. (KBT-SC and KBT-SR) respectively in half effective dose and Effective dose for chronic test. Group VII and VIII were for testing the acute effect in effective dose. The frequency and severity of seizures, time in various phases of convulsion and general animal behavior were the outcome variables. Protection was defined as complete abolition or reduction of hind limb extension. At the end of trial KBT-SC and KBT-SR showed significant anticonvulsant action in effective dose and half effective dose in chronic model. Thus the use of *Ksheerabala taila* as *rasayana* in epilepsy is justified. The study drugs KBT-SC and KBT-SR had no significant anti-convulsant effect in single dosing. In chronic dosing KBT-SC and KBT-SR have shown 67.76% and 80.638% protection against Tonic Hind Limb extension in MES induced seizures in effective dose. Statistical analysis of the results was done by ANOVA followed by post hoc test. The results showed that KBT-SC and KBT-SR is equally effective pharmacologically as anti- convulsant. Hence for preparation of *Ksheerabala taila*, *Sida cordifolia* Linn. And *Sida retusa* Linn. can be used as the source plant of *Bala*.

Keywords: Anti-convulsant, *Ksheera Bala taila*, *Sida cordifolia* Linn., *Sida retusa* Linn.

INTRODUCTION

"*Bala*" is a highly valuable drug in Ayurveda and the fact that it is one amongst the "three most utilised raw drugs"[1] in the Ayurveda pharmaceutical industry justifies the claim. Presently many *Sida* species are employed as *"Bala"* throughout the country. *Sida cordifolia* Linn. is proposed as source plant of *Bala* in Ayurveda Formulary of India[2]. *Sida retusa* Linn. or *Sida alnifolia* Linn. is abundant in Kerala and is widely accepted as the source plant of '*Bala*'- locally known as 'Kurunthotti'[3,4,5]. Also *Bala* is widely used in the production of different Ayurveda formulations like *Ksheerabala taila, Dhanvantharamkasaya, Balaristam, Rasnadikasayam, Aswagandhadilehyam* etc. Hence the relevance of identifying the source plants of *Bala* cannot be neglected. The importance of the present study too lies on the fact that the primary objective of this study is to compare the pharmacological efficacy of *Sida cordifolia* Linn. and *Sida retusa*, Linn. and providing evidence for the same.

Ksheerabala taila is a simple formulation consisting of only three drugs: *Ksheera* (cow's milk), *Bala* (*Sida cordifolia* Linn. or *Sida retusa* Linn.) and *tilataila* (sesame oil)[6]. The formulation has proven to be effective in the management of arthritis, insomnia and neurological disorders like facial palsy and trigeminal neuralgia. *Ksheerabala Taila* is said to pacify all the eighty chronic conditions of *Vata* origin (*Vata nanatmajavikara*) like convulsions (*aksepaka*), tremor (*vepathu*), fatigue *(srama),* malaise *(glani*), depression (*visaada*), insomnia (*aswapna*) and behavioural disorders (*anavasthithachitata*)[7]. These symptoms can be widely equated to generalised convulsions. *Ksheerabala Taila* is being utilised as a *rasayana* drug in conventional Ayurveda treatment for epilepsy. But till date no experimental studies or other pre-clinical studies have been conducted to validate this knowledge.

A recent research on *Ksheerabala Taila* has showed that it reduced the oxidative stress in rat brain and hence has proven effect on neurotoxicity[8]. Another similar study shows that *Ksheerabala* (101) significantly protects brain cells and reduces the severity of damage caused by alcohol intoxication[9]. Thus the preparation has proven effect on neurons. Epilepsy is a chronic disorder requiring long term medication. So *Ksheerabala taila* was tested separately in different animals for chronic effect (15 days) and acute effect (single day).

Epilepsy is a chronic neurological disorder that is characterised with recurrent seizures[10]. According to World Health Organisation, around 50 million people suffer from epilepsy worldwide[11]. Nearly 80% of the people with epilepsy are found in developing countries. The risk of premature death and threat to the quality of life has led to the search for a solution that is effective and consistent. *Ksheerabala taila* which is being used successfully in neurological disorders as both internal and external medication could have a wider therapeutic area.Hence the study could help to determine whether using *Sida cordifolia* Linn. (as accepted by AFI) or *Sida retusa* Linn. (as used in Kerala) in the preparation is therapeutically more effective. If the anti-convulsant action of *Ksheera Bala taila* is proven by this study, then it will help justify the use of *Ksheerabala taila* as *rasayana* (tonic) in generalised seizures. *Ksheerabala taila* is being utilised as a long term medication for prevention of neurological complaints. Thus if the anti-convulsant effect of the drug is proven by the study then it can yield a safe and ideal Ayurvedic medication for chronic disorder like epilepsy.

Materials and Methods:

Sida cordifolia, Linn. was collected from *Neyyatinkkara*, Thiruvananthapuram district Kerala in the months of May to June 2016. *Sida retusa* Linn. was collected from natural surroundings from

Nedumangadu Thiruvananthapuram district, Kerala and Aluva, Ernakulam district, Kerala in the months of March to June 2016. Both the plant species were collected at the time of flowering and the 2 species of *Sida* were identified by taxonomist of Pharmacognosy Unit, Govt. Ayurveda College Thiruvananthapuram and a herbarium of the same has been deposited to the Department of *Dravyaguna Vijnana* Govt. Ayurveda College Thiruvananthapuram. The roots of both source plants were thoroughly cleaned and were used freshly for *taila* preparation.

Tilataila of Agmark standard (*Swarnam* brand gingelly oil, manufactured by United Oil Industries, Aluva, Batch no.R23) was used. The cow's milk was collected fresh from a household near Thirumala, Thiruvananthapuram just before the preparation of the *taila. Ksheerabala taila* was prepared as per the classical procedure in *Sarngadhara Samhita*. Dose was calculated using the table constructed by Paget G.E & Barnes T.M considering the human dose of *Taila* as 12 ml as per AFI.

Standard drug: Phenytoin Sodium Injection (Eptoin), 2ml ampule (50mg/ml) , of Abbot Health care Pvt Ltd. The medicine was procured from a local pharmacy near General Hospital junction, Thiruvananthapuram Dose: 25mg/kg intraperitonially

Animals:

48 adult healthy Wistar albino rats of both sex and weight 150-200 gm. were obtained and the experimental study was conducted as per the protocol accepted by the Institutional Animal Ethical Committee (29/IAEC/AVC/2015) and the animals were handled as per CPCSEA guidelines. The anticonvulsant effect was evaluated by Maximal Electroshock Seizure test (MES) for the acute effect and after chronic dosing (15 days) in Albino rats in the Department of *Dravyaguna Vijnana*, Government Ayurveda College, Thiruvananthapuram, Kerala.

Housing and feeding conditions

All the animals were maintained in appropriate environmental and nutritional circumstances through the experiment. The rats were maintained under standard laboratory conditions with natural dark and light cycle. They were provided with free supply of standard dry rat diet and water. Animals were acclimatized for 7 days prior to experimentation. 2 animals were housed in each cage made of polypropylene with stainless steel top grill. The bedding was changed on alternate days. Bedding provided in rat cages was in sufficient quantity to cover the whole floor.

Grouping of animals:

The acclimatised animals were weighted and randomly divided into 8 groups having 6 animals in each group. The random selection ascertained unbiased distribution of animal with regard to sex, age, weight etc. in each group. The animals were marked for proper identification and kept in separately labelled cages. The dose of each animal was calculated according to the body weight and was put in tables for further reference.

Group I – Negative Control group – no active treatment received. The animals were on normal rat diet and water. **Group II** – Standard group /positive control – Phenytoin (20 to 25 mg/kg) **Group III**- Effective dose for testing Ksheera Bala Taila made with *Sida cordifolia* Linn. **Group IV**– Half effective dose for testing *Ksheera Bala Taila* made with *Sida cordifolia* Linn. **Group V** - Effective dose for testing *Ksheera Bala Taila* made with *Sida retusa* Linn.

Group VI – Half effective dose for testing *Ksheera Bala Taila* made with *Sida retusa Linn.*

Group VII- for testing *Ksheera Bala Taila* made with *Sida cordifolia* Linn. in Effective dose for its immediate effect **Group VIII-** for testing *Ksheera*

Bala Taila made with *Sida retusa* Linn. in Effective dose for immediate effect

Procedure of MES test:

The Albino Rats were restrained by hand and subjected to electric shock through their ear pinna using ECT (Electro Convulsant Unit). Lignocaine gel was applied on the ear pinna before applying the electrodes. The rats were released immediately following electrical stimulation to permit observation of maximal seizure. The maximal seizure typically consists of a short period of initial tonic flexion and prolonged period of tonic extension followed by clonic convulsions and stupor. The maximal electro shock that induced 100% maximal seizures is found to be 150mA alternating current of 100Hz frequency for 0.2 sec duration. Protection is defined as complete abolition or reduction of hind limb extension.

Results:

The drug is supposed to have anti-convulsant effect if it reduces the duration of Tonic Hind limb Extenion (THE) or abolishes the same. The statistical analysis of time (in seconds) over the tonic extensor phase of MES convulsions in each group was carried out to establish the effect of the study drug in each group.Data and percentage change of average Tonic Hind Limb Extension (THE) time in seconds among the various groups has been given in Table no. 1. The Significance of the data across all groups were analysed by ANOVA. As ANOVA showed significance at $p<0.05$, then post hoc test was applied for finding the pair of group having statistical significance.

Table 1: Data and percentage change of average Tonic Hind Limb Extension (THE) time in seconds among the various groups

GROUP	Arithmetic mean	Standard deviation	Percentage protection compared to control	Significance
Group I	10.33	1.1055	-	-
Group II	0	0	100%	Highly Significant $p<0.001$
Grou VII	9.5	0.957	8.73%	Not Significant $p>0.05$
Group VIII	10	0.957	3.19%	Not Significant$p>0.05$

In the acute study that is in single dose administration of the study drug the therapeutic dose of KBT-SC and KBT-SR in Group VII and VIII showed no anti-convulsant effect. Though there was 8.73% and 3.19% reduction in time of THE compared to control group, it proved to have no statistical relevance. The standard drug (Phenytoin) treated group showed 100% abolishment of THE time, exhibiting maximum anti-convulsant effect.

In the chronic test that is, after 15 days of drug administration, the entire Experimentally Drug Treated Groups displayed significant anti-convulsant effect. Data and percentage change of average Tonic Hind Limb Extension (THE) time in seconds among the various groups is given in Table no. 2

Table 2: Data and percentage change of average Tonic Hind Limb Extension (THE) time in seconds among the various groups

GROUP	Arithmetic mean	Standard deviation	Percentage protection compared to control	Significance
Group I	10.33	1.1055	-	-
Group II	0	0	100%	Highly Significant p<0.001
Group III	3.33	0.745	67.76%	Significant p<0.01
Group IV	5.666	0.745	45.15%	Significantp<0.01
Group V	2	1.914	80.638%	Significantp<0.01
Group VI	4.833	0.898	53.21%	Significantp<0.01

The therapeutic dose of KBT-SC and KBT-SR showed more effectiveness than the half dose. On statistical analysis the anti-convulsant effect between the therapeutic dose of KBT-SC and KBT-SR. were found to be equally effective. Similarly the half dose of KBT-SC and KBT-SR had no statistically significant difference in the anti-convulsant effect.

Thus even though all study groups showed anti-convulsant effect in chronic dosing, the therapeutic dose of KBT-SC and KBT-SR are found to be more effective at the end of the experimental study. None of the trial drug groups showed complete abolition of extensor phase of MES convulsions as that of the standard drug Phenytoin treated group.

In view of all these findings, it can be stated that both the study drug *Ksheerabala taila* made with *Sida cordifolia* Linn. And *Ksheerabala taila* made with *Sida retusa* Linn. possess significant Anti-convulsant effect on long term use as showcased by Maximal Electro-shock Seizure test in albino rats. Hence, either *Sida cordifolia* Linn. or *Sida retusa* Linn. can be used as source plants of *Bala* in preparation of *Ksheerabala taila*.

DISCUSSION

Epilepsy is a disease of the body and mind, in which all the three *dosas* are involved but the main *dosa* involved is *Vata*. An epileptic attack is nothing but an abrupt and excessive electric discharge of cerebral neurons. *Chesta* or movements are the effect of *Vata dosa*. The events of tonic clonic seizures or generalised seizures indicate the derangement of *Vata dosa* predominantly over the other *dosas*. Therefore an episode of epileptic seizure can be viewed as *Akshepaka* (convulsions). The chronic disease profile which involves repeated seizures along with affliction of body, mind, memory and consciousness may be viewed as *Apasmara*. This fact highlights the relevance of the *tailakalpana* which is the best for alleviation of *Vata dosa* in the management of *Apasmara*. *Ksheerabala taila* is predominantly *Vata nashana, balya, brimhana* and has *rasayana* properties which increase the strength and endurance of neurons against further seizures. The continuous administration of this *snehakalpana* prevents the release of abrupt electric discharges and improves the physical and mental condition of the patient.

Ksheerabala taila has profound soothing and relaxing effect on the mind. Acharya Charak says that the mind is continuously active, that is "*Chanchala"*. Therefore it cannot stay at one particular place. Any change in the quantity or quality of *Vata dosa* causes vitiation of *manovahasrotas* as *Vata* is said to be the regulator and controller of the "*Manas*" (*niyatapraneta cha manasa*). Thus the control of *Vata* could regulate the normal functioning of *Manas.*The probable mode of action of the preparation could be analysed by its *Rasa Panchaka*. All the 3 ingredients *Bala, Ksheera* and *Tilataila* possess *Madhurarasa* and *vipaka*. *Madhura* rasa mitigates both *Vata* and *Pitta dosa*. It

also endows maximum strength to the tissue (*dhatunaamprabalambalam*) and is good for sense organs and pleasing to mind (*Shadindriyaprasadaka*). Madhura rasa bestows unctuousness to the tissues (*snehana*), thus reducing Vata. It nourishes the body (*Tarpayati*), and plays a major role in promoting life (*jeevayati)*. *Tilataila* possesses *Tikta rasa* (Bitter taste) in addition to *Madhura rasa*. *Tikta rasa* is the most effective in mitigating *Pitta dosa* and *Kaphadosa*. *Tikta rasa* is effective in relieving fainting (*murchaprasamana*) and Promotes memory and intellect (*medhya*).

*Usnavirya (*hot potency) of *Tilataila* reduces the *Vata* and *Kapha*. Since in this preparation *Tilataila* is processed by *sitavirya (*cold potency) drugs like *Bala* and *Ksheera;* its *usnatva* is altered. The *Vata* and *Kapha* undergo decrease without agitating *Pitta* which is also *usna*. Thus the *usna guna* of *Ksheerabala acts* without having adverse effect on *dhatus*. The alleviation of *Vata* and *Kapha* clears the channels, thereby allowing the action of rest of the properties like *snigdha, manda, sukshma* and *vyavayi*.

MES-induced convulsion model causes movement of Ca2+ and another positive ion like Na+ into the cells, and their blockade can prevent MES-induced tonic extension. The potentiation of GABA receptor may offer protection against MES-induced seizures. MES-induced seizure can be prevented either by drugs that inhibit voltage-dependent Na+ channels such as phenytoin and valproate or by drugs that block glutamatergic receptor such as felbamate. Both the samples of *Ksheera bala Taila* showed significant Anti-convulsant effect in MES test which could probably have been achieved by either of these mechanisms.

The presence of flavonoids in both the *Sida* species has been confirmed by phytochemical analysis. Furthermore, it is known that some flavonoids, as well as their glycosides, exert anxiolytic, sedative, and anticonvulsant effects on the central nervous systems (CNS)[16]. The drugs *Sida cordifolia* Linn. And *Sida retusa* Linn. possess “Flavanoids” and hence, could have exhibited the anti-convulsant effect by non- competitive inhibition of the GABA receptors.

The oxidative stress is the most prominent mechanism in the development and progression of epilepsy and other diseases, including Alzheimer’s disease, chronic degenerative diseases, stroke, rheumatoid arthritis, diabetes, and cancer. The constituents in this medicine that is Bala (*Sida cordifolia* Linn. and *Sida retusa* Linn.), milk and sesame oil are well demonstrated anti-oxidants. The presence of anti-oxidants prevents the possible damage of neurons occurring from repeated seizures. *Ksheerabala taila* has established to emolliate oxidative stress in rat brain[8,9].

Hence it can be stated that *Ksheerabala taila* possesses anti-convulsant activity when used continuously. *Sida cordifolia*, Linn. And *Sida retusa* Linn. have almost similar phytochemicals qualitatively. Both the samples showed statistically significant anti-convulsant effect also. Thus both source plants can be taken as *Bala* if the purpose is the preparation of *Ksheerabala taila*. The anticonvulsant action of the medicine could be by the synergistic action of its *rasapanchaka* or by the action of the phytochemicals like flavonoids and phenols that act by inhibition of GABA receptors. The formulation could also have the ability to prevent the occurrence of further seizures. The antioxidant potential of the preparation has significant role in its therapeutic efficacy as an anticonvulsive drug that prevents further occurrence of seizures.

CONCLUSION

The trial drugs *Ksheerabala Taila* made with *Sida cordifolia* Linn. And *Sida retusa* Linn. have a definite demonstrable anticonvulsant action in both effective dose and half effective dose in chronic dosing of 15 days as ascribed by the experimental study conducted on albino rats by MES test. The

therapeutic dose of both the samples showed maximum anti-convulsant effect after 15 days of drug administration compared to the half dose. Thus the use of *Ksheerabala taila* as *Rasayana* in *Apasmara* could be justified by the study. Both the study drugs KBT-SC and KBT-SR had no significant anti-convulsant effect in single dosing. The standard drug abolished the Tonic Hind Limb Extension (THE) phase, while the trial drugs KBT-SC and KBT-SR significantly reduced its duration when compared with the control group. KBT-SC and KBT-SR have shown 67.76% and 80.638% protection against Tonic Hind Limb extension in MES induced seizures in effective dose. On comparison the difference in the therapeutic efficacy of the 2 samples was statistically insignificant. From this point of view KBT-SC and KBT-SR is equally effective pharmacologically. If the requirement is for preparation of *Ksheerabala taila*, *Sida retusa* is equally effective to the source plant *Sida cordifolia.* The study justifies the use of *Sida retusa* as *Bala* in Kerala. Thus along with revealing the anti-convulsant effect of *Ksheerabala taila*, the present study also contributes *Sida cordifolia,* Linn and *Sida retusa* Linn. as source plants of *Bala*.

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