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Analyses of action of Saindhavadya ghruta W.S.R. to its anti-convulsant activity

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Abstract

Ancient acharyas of Ayurveda had an excellent knowledge of the properties and action of the single drugs. Through their deep insight they formulated enumerable yogas by the combination of these single drugs. Various research studies have proved the efficacy of these formulations. This article attempts to analyze the action of one such formulation Saindhavadya Ghruta, indicated for Apasmara and Graha Doshas in Yogaratnakara. In an experimental study undertaken, Saindhavadya Ghruta showed good anti-convulsant activity. It proves to be an excellent drug designing by the author. Previous studies indicated that all the ingredients of the preparation are independently having anti-convulsant action. Even the drugs used for murcchana have been studied to have anti-convulsant activity individually. Hence, it proves the synergistic action of the drugs combined in the formulation judiciously to pronounce the total action of the yoga.

Keywords: Saindhavadya Ghruta; Anti-convulsant activity; Apasmara; PTZ Kindling in mice; Blood brain barrier

1. Introduction

Ayurvedic classics are rich sources of various kinds of formulations starting from primary formulations like Swarasa to secondary preparations such as Sandhana, Sneha, etc. These yogas which were formulated by ancient scholars seem to have strong scientific basis and rationality. Ayurveda has relied on a combination of drugs rather than a single drug. Administration of drugs in combinations may either enhance or antagonize the response of the individual component. Hence in compounding a formulation, incompatibilities between the constituents are also considered.

Another important aspect of drug action is its delivery to the site of action. The formulations have to be designed in such way as to get delivered to the target organ. Ghruta and taila are one of the techniques described in Ayurveda which use the process of incorporating drugs in lipid media to target them to their site of action. Similar pharmaceutical principles are utilized in formulating preparations for topical use for their action on different layers of skin.

For the treatment of diseases related to brain like Unmada, Apasmara etc. most of the yogas are in the form of ghruta. Ghruta is an important dosage form in Ayurveda. There are approximately 650 Ghruta preparations described in Charaka Samhita and similarly in other Ayurvedic texts. Even recent studies have proven the fact that medicine administered in the lipid form is effective in crossing the blood brain barrier. A study by Divya Kajaria et al [1], explained the action of Ghruta as follows – "Cell membranes are biologic barriers that selectively inhibit passage of drug molecules. The membranes are composed primarily of a bimolecular lipid matrix, which determines membrane permeability characteristics. Therefore, drug in lipid soluble form is more permeable than water soluble form. Substance with high

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lipid solubility may move across the blood- brain barrier by simple diffusion. The rate of entry of compounds that diffuse into the brain depends on their lipid solubility." The study concluded that drug in fat soluble form is more permeable than water soluble drug.

Hence, Saindhavadya ghruta being a lipid-based media is found to be opt in the treatment of convulsions.

The formulation SAINDHAVADYA GHRUTA for present study was selected from the text "Yogaratnakara" – Apasmara chikitsa.[2]

Kalka made from Saindhava Lavana, Hingu and Pippali, Murcchitha Go Ghruta and Gomutra was taken in the ratio of 1:4:16 and subjected to Ghruta Paka procedure. Thus, prepared Saindhavadya Ghruta can be used to relieve Apasmara and Graha Dosha.

2. Materials and Methods

2.1. Ingredients

- Kalka dravya:
  - Pippali
  - Hingu
  - Saindhava lavana
- Sneha dravya: Murcchitha Go Ghruta
- Drava dravya: Gomutra

2.2. Analysis of mode of action of *Saindhavadya Ghruta* – individual ingredients

2.2.1. Gomutra

Cow's urine in Ayurveda is claimed to be Apasmarahara and is well known for its anticonvulsant property. Cow's urine is rich in volatile free acids which are very potent antioxidant agents. [3, 4] Also there are enough evidences to suggest the role of oxidants in the causation of epilepsy. [5,6] Cow urine distillate as a bio-enhancer was granted a US patent [7]. The presence of anti-oxidant activity could be one of the contributing factors for the observed efficacy during kindling induced convulsion.

2.3. Purana ghruta

Purana ghruta alone is indicated in *Apasmara* in the classics (Su.su.45, Ch.ci.8, Y.R) [8,9,10]. Apart from this *Ghruta* may act in the following ways.[11]

- Ghruta because of its Samskarasya Gunanuvartana (Ch.su.13/13) [12] property i.e., the peculiar adaptability in pharmaceutical preparation, ghee is considered the best among the Snehas. The blood brain barrier is permeable to lipid soluble substances (Guyton, 1996).[13] Thus, the ghee containing the active principles of the ingredients of the Saindhavadya Ghruta easily crosses the blood brain barrier delivering them at the specific sites of their action.
- Ghruta may induce ketosis due to the presence of fats in the form of cow's ghee and various amino acids are present in the protein content of cow's urine. The ketone bodies produced in turn may alter the blood brain barrier (BBB) properties making the active principles of the Ghruta to enter the brain.
- The Rasayana effect of Ghruta may play a major role. A part of its action may be explained on the basis of the theory that the drug accelerates the rate of sugar transport (Gilbert 1971). It is proposed that the antiepileptic effect of the drug is due to the increase in brain glucose level.
- Drug delivery of Ghruta is comparable with liposomal drug delivery system. Solid lipid nanoparticles are formed which have better bioavailability and transdermal absorption. Drugs encapsulated in liposomes are expected to be transported without rapid degradation and minimum side effects to the recipients. (Neetu Singh, Anand Chaudhary) [14]
- Ghruta can also be used as a bio enhancer for the drugs which have poor bio availability like Curcumin. [15]

2.3.1. Hingu

Hingu is the best Sanjna sthapana dravya, thereby it acts as Akshepahara dravya. Hingu is mentioned by Bhavaprakasha as 'Apasmarahara dravya' i.e., drug of choice in Apasmara.[16]

Alcohol and aqueous extracts of Hingu were tested to screen anti-epileptic effect on albino rats by using MES method. Aqueous extract showed statistically significant anti-convulsant activity.[17]

2.3.2. Pippali

Pippali in Ayurveda is said to be Medhya Rasayana, Deepana and Pachana. Moreover, it removes the Srothorodha at the cellular level. Pippali is known to have a potent bio-enhancer activity. Piperine, a major alkaloid of Pippali was found to enhance the bioavailability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics due to its easy partitioning and increase in permeability of other drugs.[18] Researchers showed that piperine may serve as a potential functional food to improve brain function.[19] Studies at Regional Research Lab CSIR Jammu, have established that it is piperine that affects the bioavailability of drugs. The doses of many potent drugs can be drastically reduced when mixed with piperamides. [20]

2.3.3. Saindhava lavana

It is the compound of NaCl, hence may help in influx of Na+ ion across the membrane and opening up of chloride channels which is the function of GABA, inhibitory neuro transmitter.[21]

2.4. Analysis of mode of action of drugs used for *Murcchana* –

2.4.1. Haridra

The anticonvulsant activity of bisabolene sesquiterpenoids of *Curcuma longa* Linn in Zebrafish and mouse seizure models were noticed during a study by Orella Pauchar *et al*. [22] Jithendra Chimakurthy *et al* [23] showed the significant effect of Curcumin on the maximal electro shock induced generalized tonic clonic seizures when studied against sub therapeutic doses of phenytoin and sodium valproate as well as has effect on memory retention in seizure induced rats.

Animal studies have indicated that *Curcumin* can enhance the adult hippocampus neurogenesis process by increasing the number of newly generated cells in the dentate gyrus region of hippocampus. [24] *Curcumin* also enhances the level of neurotrophic factors such as brain derived neurotrophic factor (BDNF). [25] Apart from its neuroprotective action *Curcumin* has also shown powerful antioxidant and anti-inflammatory properties. [26]

2.4.2. Musta – Cyperus rotundus Linn

Porwal Mayur *et al* [27] suggested that *Cyperus rotundus* Linn roots and rhizomes showed anticonvulsant effect against PTZ and PTX induced convulsions which may be mediated, at least partly, through GABA A- benzodiazepine receptor complex. Shivkumar SI *et al* [28] found the flavonoids present in ethanol extract could be responsible for the observed anticonvulsant activity. Mohsen Khalili *et al* [29] also concluded that *Cyperus rotundus* Linn rhizome extract, probably via its antioxidant properties could have exerted a potent antiepileptic effect.

2.4.3. Amalaki – Emblica officinalis Gaertn

Hydroalcoholic extract of *Emblica officinalis* Gaertn administered to rats was evaluated on pentylenetetrazol (PTZ) induced seizures, cognitive deficit and oxidative stress markers and results in completely abolished generalized tonic seizures and improved the retention latency in passive avoidance task as well as ameliorated the oxidative stress induced by PTZ. [30]

2.4.4. Hareetaki - Terminalia chebula Retz

The ethanolic extracts of *T. chebula* Retz produced anticonvulsant activity against MES and PTZ induced seizures in rats. [31] The antioxidant and free radical scavenging properties of *Hareetaki* have been well proven in different studies. The leaves, bark and fruit of *T. chebula* Retz possessed high antioxidant activity and phenolics were found to be responsible for this activity. [32]

3. Results

In a study conducted by Shilpa. S.N. et al [33], Saindhavadya Ghruta in its therapeutic dose showed presence of moderate anti-convulsant activity in PTZ model.

Its therapeutic and double dose showed mild anti-convulsant activity in MES model.

In the study, Saindhavadya Ghruta suppressed development of kindled seizures in mice. Further, it protected against a sub convulsant dose of PTZ in kindled mice, suggesting that it not only inhibits the development of epilepsy (epileptogenesis) but also seizure severity even when the disease state was fully developed. The protection afforded by test drug was comparable to the standard antiepileptic drug Sodium valproate. In therapeutic dose, it showed high anti-convulsant activity in PTZ induced kindling in mice.

Overall, it was concluded that, Saindhavadya Ghruta showed moderate anti-convulsant activity.

4. Discussion

Akshepaka is a Vata predominant disease associated with Kapha, where the Sanjnavaha srotas is blocked and the patient goes into unconscious condition. The ingredients of Saindhavadya Ghruta i.e., Gomutra, Pippali and Hingu have Katu Rasa, Ushna Virya and Katu Vipaka which remove the margavarodha created by Kapha. Similarly, Tikshna Guna of Gomutra, Pippali and Hingu helps to regain Smruti by acting on Sanjnavaha srotas and removing Sanga. Hingu is said to be best Sajna sthapana dravya. Hingu is best Anilahara Dravya and hence helps in subsiding the aggravated Vata. Ghruta is known for its Medhya and Rasayana action. The Chikitsa of Apasmara includes mainly Sroto shodhana followed by Samana. The Medhya Rasayanas are particularly advocated in chronic and intractable conditions. The site of action of Saindhavadya Ghruta is not limited to central nervous system but it also influences the entire metabolic process, and the concentration of electrolytes thus influencing the seizure threshold.

By the synergistic action of individual ingredients, Saindhavadya Ghruta may show its efficacy in the following ways,

- Since the Na+, K+ and Ca2+ ions are important in the development and conduction of action potential, the decrease in the activities of respective ATPases may alter the rate of influx and efflux of cations correlating with altered membrane permeability properties.[34] In a study done by Vajragupta et al, it has been shown that Curcumin present in Haridra plays neuroprotective role by elevating Na+, K+ ATPase activity in all the brain regions of rat. [35]
- Saindhava Lavana, an ingredient of the drug being NaCl compound may also act in a similar way by elevating the Na+ ATPase. In this way, the bioactive factors present in the ingredients of Saindhavadya Ghruta may offer neuroprotection by directly or indirectly modulating the activities of ATPases and thus may be helpful in the treatment of seizures.
- Gomutra, Goghruta, Amalaki etc. ingredients in the test drug are potential anti oxidants. Free radicals have been suggested to be the most likely candidate responsible for producing the neuronal changes mediating the behavioral deficits in neurodegenerative disorders. [36] Gupta et al have demonstrated that antioxidants are effective in the rodent models of epilepsy, stroke and Alzheimer's disease.[37]
- Free radicals have been implicated in the development of seizures by Sejima et al., 1997. [38] However, when the production of free radicals increases or the defense mechanism of the body decreases, they cause cellular dysfunction by attacking at the polyunsaturated sites of the biological membranes leading to lipid peroxidation as shown by Gupta and Sharma, 1999. [38] Some antioxidants have been shown to be effective in reducing the oxidative stress in the models of epilepsy [40,41,42,43, 44]
- By overall analysis, it shows that, Saindhavadya Ghruta may act as anti-convulsant through one of these probable mechanisms –

4.1. By increasing the concentration of natural inhibitor GABA in CNS

- synapses
- By facilitation of GABAergic neurotransmission
- By reducing N-methyl-D-aspartate (NMDA)-receptor mediated glutamate excitation
- By increasing serotonergic inhibition and attenuation of neurogenic inflammation
- By inhibition of the voltage-dependent sodium channels
- Through anti-oxidant property

Even though the experimental study has proved its efficacy, analyzing the exact mechanism of action is not possible as it requires other tests like EEG, cross sectional studies of brain, estimation of GABA level in the brain etc. Hence it provides scope for further studies in this field.

5. Conclusion

Our ancient seers were able to formulate excellent combination of drugs by their insight and deep knowledge. But in the present era even with the advanced techniques of drug research we are lacking in the drug designing aspects. With the increase in newer diseases, there is always a need to explore the formulations mentioned in our classics and evaluate them for their actions in various conditions. It is essential to update the science of Ayurveda with rational drug combinations in order to suit the present-day challenges like unavailability of some drugs, short supply etc. The basic fundamental principles of drug manufacturing mentioned in Ayurveda which are definitely having scientific basis should be adopted by the present-day drug industry.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

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