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Comparison Of Anti-Inflammatory Effect Of Withania Somnifera(Ashwagandha) With Tinospora Cordifolia (Guduchi) In Male Albino Wistar Rats.

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Abstract:
Introduction:Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. The importance of inflammation in progression of casual disease is one of the factors for the use of anti-inflammatory drugs in clinical medicine. The main aim of this study is to assessthe anti-inflammatory properties of herbal plants. In this context, comparative study regarding anti-inflammatory effect of Withania somnifera and Tinospora cordifolia in rats using plethysmograph has been initiated.Objectives:1) To study the anti-inflammatory effect of Withania somnifera and Tinospora cordifolia in male albino wistar rats. 2) To compare anti inflammatory effect of Withania somnifera (ashwagandha) with Tinospora cordifolia (guduchi) in male albino wistar rats by using plethysmographMethodology: A Randomized controlled trial was conducted in the Dept. of Pharmacology, Dr Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation (Dr.PSIMS), Chinoutapalli, Krishna District, Andhra Pradesh with the institutional ethical committee clearance. All male albino wistar rats weighing between 250-300gm were selected for the study andrats were randomly divided into 3 groups (Control, Test-1 & Test-2).0.2 ml of normal saline was administered to Control group rats, Withania somnifera in a dose of 25.69mg/kg BW was administered to test-1 group rats, Tinospora cardifolia in a dose of 25.69 mg/kg BW was administered to test-2 group rats, as single oral dose half an hour before injecting 0.1ml of 1% carrageenan to the sub-plantar region of hind paw and the paw edema of each rat was measured at 3hours.Conclusion: The results showed that found that the Withania somnifera has more effective anti-inflammatory activity than tinospora cordifolia. However the above preclinical experiments only give us an idea about the anti-inflammatory activity of Withania somnifera and Tinosopra cordifolia but large scale clinical trials are necessary for final assessment.

Introduction:

Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a complex reaction in tissues that consists mainly of response of blood vessels andleukocytes. It is a series of host responses directed as a protective

attempt by the organism toremove the injurious stimuli as well as initiate the healing process for the tissue[1]. The term inflammation is derived from the Latin word "inflammare" meaning to burn. Inflammation is a protective response, designed to get rid the organism of both the initial cause of cell injury (e.g. microbes, toxins) & the consequences of such injury (e.g. necrotic cells and tissues).The vascular and cellular reactions of inflammation are triggered by soluble factors that are produced by various cells (or) derived from plasma proteins and are generated (or) activated in response to the inflammatory stimulus. The clinical features of inflammation were described in an Egyptian papyrus dated as early as around 3000 BC,

The first four cardinal signs of inflammation were first enunciated by Celsus, a Roman writer and includeRubor(Redness),Tumor(Swelling),Calor(Heat),Dolor (Pain)[2]. The fifth sign; Functio laesa (loss of function) was added by Rudolf Virchow in the 19th century. These signs are more prominent in acute inflammation than in chronic inflammation[1].Inflammation may contribute to a variety of diseases that are not thought to be primarily due to abnormal host responses. For instance, chronic inflammation may play role in atherosclerosis, type-2 diabetes, degenerative disorders like Alzheimer disease and in cancer. In recognition of the wide-ranging harmful consequences of inflammation, the lay press has rather melodramatically referred to it as "the silent killer"[1].

The importance of inflammation in progression of casual disease is one of factor for use of anti-inflammatory drugs in clinical medicine. More research on antiiflammatory activity is done on allopathic drugs than on herbal drugs even though the herbal drugs are claimed to have less adverse effects. Withania somnifera is having anti-inflammatory property and acts by inhibition of cyclooxygenase[3]

Withania or Ashwaganda is one of the most utilized herbs in Ayurvedic medicine holding a position of importance similar to that of ginseng in China. Ayurvedic practitioners consider Ashwaganda a powerful 'rasayana' herb or potent tonic to promote greater vitality and longevity. Ashwaganda is believed to balance 'vata' and 'kapha' in Ayurvedic medicine. Several medicinal properties of Withania or Ashwaganda includes- Osteoarthritis, Anxiety, Type 2 Diabetes, Cancer, Anti-Oxidant, Provide energy, General tonicetc.

Tinospora cordifolia (common name: Guduchi), is an herbaceous plant of the family Menispermaceae indigenous to the tropical areas of India, Nepal and Sri Lanka. The plant is a climbing shrub found throughout India, typically growing in deciduous and dry forests. It is one of the most valuable traditional Indian medicinal herbs and has been used in ayurvedic preparations for the treatment of various ailments throughout the centuries.Several medicinal properties of Tinospora cordifolia includes- Anti-allergic, antipyretic, analgesic, anti-inflammatory,antispasmodic,Anti-cancer, antineoplastic,antioxidant, anti-stress, anti-ulcer, Immunomodulatory, Hepatoprotective and Hypoglycaemic etc.

The main aim of this study is to assess the anti-inflammatory properties of herbal plants. In this context, comparative study of anti-inflammatory effect of Withania somnifera and Tinospora cordifolia in rats using plethysmographwas conducted.

Materials & Methods:

A Randomized controlled trial was conducted in the Dept. of Pharmacology, Dr Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation (Dr.PSIMS), Chinoutapalli, Krishna District, Andhra Pradesh with the institutional ethical committee clearance.

All male albino wistar rats weighing between 250-300gm were selected for the study andrats were randomly divided into 3 groups (Control, Test-1, Test-2) each group contains 6 rats.A mark is made at the ankle joint (tibio-tarsal joint) of each rat and Initial paw edema of each rat was measured before giving drug carrageenan[4] by using plethysmograph[5].Control group rats 0.2 ml of normal saline was administered orally half an hour before injecting 0.1ml of 1% carrageenan to the sub-plantar region of the hind paw and the paw edema of each rat was measured at 3hours.Test-1 group rats *Withania somnifera* 25.69mg/kg BW was administered as single oral dose half an hour before injecting 0.1ml of 1% carrageenan to the sub-plantar region of hind paw and the paw edema of each rat was measured at 3hours.Test-2 group rats *Tinospora cardifolia* 25.69 mg/kg BW was administered as single oral dose half an hour before injecting 0.1ml of 1% carrageenan to the sub-plantar region of hind paw and the paw edema of each rat was measured at 3hours.

Carrageenan induced paw edema model:

To study the acute and sub acute phases of inflammation in rats. Carrageenan is a widely used irritant or inflammogen or a phlogistic agent. Chemically, it is a sulphated polysaccharide obtained from sea weed (rhodophyceae)[6]. The experimental tissue injury caused by this irritant initiates a cascade of inflammatory events leading to formation of exudates. The inflammation induced by it is biphasic in nature.The first phase is attributed to the release ofhistamine, 5-hydroxy tryptamine (serotonin) and kinin while the second phase is related to the release of prostaglandins.

The well-recognized method of winter et al, 1962 is followed[7].A 1% w/v suspension of carrageenan is prepared freshly in normal saline and injected into sub planter region of left hind paw (usually 0.1ml in rats).In control group animals only vehicle is injected. Test drug is usually administered intraperitoneally (or) orally, according to body weight, half an hour before the carrageenan challenge.A mark is made at the ankle joint (tibio-tarsal joint) of each rat. Paw edema volume up to the ankle joint is measured in drug treated and untreated groups at 0 and at 3hours following carrageenan challenge by using mercury Plethysmograph filled with mercury[8]. Percentage (%) of reduction in edema is calculated using the following formula.

Chemicals and Solutions:-Carrageenan[5], Double distilled water, Normal saline, *Withania somnifera* (ashwagandha), *Tinospora cordifolia* (guduchi)

Animals:- Male Albino wistar rats weighing about 250-300gm.

Equipments:- Plethysmograph (MKM)[6], Mercury, Insulin syringes, Tuberculin syringes, Infant feeding tube, Hypodermic syringe, Measuring jar, Glass beakers, Animal weighing balance, Animal cages and water bottles, Cotton, Spirit, Stopwatch, Glass rod, Disposable needles.

Data was collected, compiled and analysed using SPSS-V19. Statistical tools applied were means, SD, Percentages and t-Test.

Results:

Table-1: Volume of paw edema in (ml) in three different groups i.e Normal saline,Withania somnifera, Tinospora cordifolia at 0 and 3hrs

Group	Drug	Dose	Paw edema in ml		Paired t-value	P-value	Inference
			At 0 Hrs Mean ± SD	At 3 Hrs Mean ± SD			
Control	Normal Saline	0.2ml	4.11±0.04	4.37±0.08	7.32	<0.01	HS
Test-1	Withania Somnifera	6.42mg/kg	4.12±0.04	4.23±0.05	7	<0.01	HS
Test-2	Tinospora Cordifolia	6.42mg/kg	4.13±0.05	4.3±0.06	7.9	<0.01	HS

HS-Highly Significant

In case of normal saline, the volume of paw edema at 0 Hrs was 4.11 ml and increased to 4.37 ml after 3 Hrs,

in case of Withania Somnifera, the volume of paw edema at 0 Hrs was 4.12 ml and increased to 4.23 ml after 3 Hrs but In case of Tinospora Cordifolia, the volume of paw edema at 0 Hrs was 4.13 ml and increased to 4.3 ml after 3 Hrs.

Table-2: Increase in mean paw edema volume after 3 Hrs

Group	Mean	SD
Normal saline	0.25	0.08
Withania somnifera	0.12	0.04
Tinospora cardifolia	0.16	0.05

Increase in mean paw edema volume after 3 Hrs in case of normal saline was 0.25 ml, with withania somnifera was 0.12 ml and with Tinospora cardifolia was 0.16 ml.

Table-3: Comparison between the groups regarding paw edema volume inhibition.

Comparison	% Decrease	Independent t-value	P-value	Inference
Normal saline vs Withania somnifera	52	2.90	0.009	HS
Normal saline vs Tinospora cardifolia	32	2.07	0.03	S
Withania somnifera vs Tinospora cardifolia	25	1.86	0.04	S

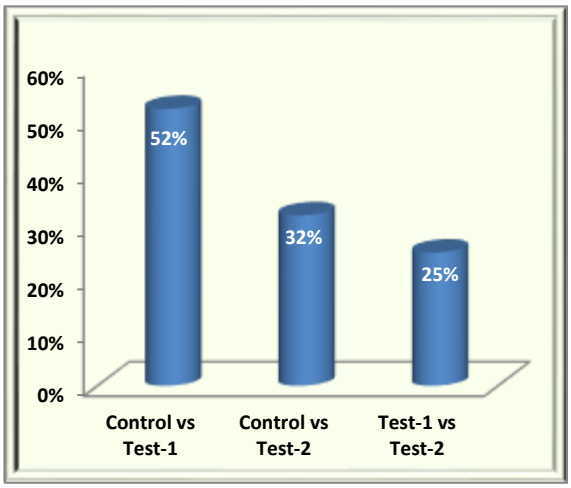
HS-Highly Significant, S-Significant

The percentage inhibition of paw edema in rats treated with Withania somnifera was 52% in comparison with normal saline.
The percentage inhibition of paw edema in rats treated with Tinospora cordifolia was 32% in comparison with normal saline.

The percentage inhibition of paw edema in rats treated with Withania somnifera was 25% in comparison with Tinospora cordifolia.

Hence it shows that Withania somnifera is more effective anti-inflammatory agent than Tinospora cordifolia.
The present study suggests the possible potential role withania somnifera as a anti-inflammatory drug, however further research is required to establish it's use.

Fig-3: Percentage of paw edema inhibition



Discussion:

In spite of the availability of various anti-inflammatory agents, we were interested in evaluating the herbal drugs which can be widely used for different therapeutic purposes.The herbal formulations are relatively free from any adverse effects and more are less drug dependence forming.
The study comprises,comparison of anti-inflammatory effect of Withania somnifera (ashwagandha) with Tinospora cordifolia (guduchi) in rats using one of the acute methods i.e. Rat paw edema.

In the study done by Siddalingapa et,al, evaluated the anti-inflammatory activity of aqueous extract of Tinospora cordifolia (AECT) in rodents, as we were interested in anti-inflammatory property to relate with our study. The material used was the powdered leaves extracted with distilled water and method followed to evaluate the anti-inflammatory activity of leaves of Tinospora cordifolia is carrageenan induced paw edema in rats. In study five groups of rats taken and drugs administerd orally, Distilled water, (control), 5mg Diclofenac, 100mg Tinospora cordifolia, 200 mg Tinospora cordifolia, and 100mg Tinospora cordifola plus 5mg Diclofenac respectively were used as standard and control, respectively for anti inflammatory activity.The result showed that Tinospora cordifola in doses of 100mg/kg , 200mg/kg, 100mg/kg with 5mg/kg of Diclofenac (after 30,60,90 minutes of administraion). Tinospora cordifola showed 32.63%, 36.63%, and 40.5% inhibition of paw edema respectively at the end of three hours. With diclofenac the the percentage inhibition was 35.64%.They concluded that study has shown Tinospora cordifola has significant anti-inflammatory activity. The results indicate that identification of active principle from the leaves may add a new, potential anti-inflammatory drug to treat acute conditions of inflammation[9].The present study using 25.69mg/kg of Tinospora cordifilia in capsule form manufactured by Himalaya Company (Guduchi) trade name, but the above study used Tinospora cordifolia 100mg in the form of leaf

exctract..Both the studies show similar results. There is slight variation in the results is due to formulation.

In another study by Sangita Chandra,evaluated anti-inflammatory effect of Ashwagandha.
The methodsused in this study to test extract at different concentrations was incubated with egg albumin in controlled experimental conditions and subjected to determination of absorbance and viscosity to assess the anti-inflammatory property. Diclofenac sodium was used as the reference drug.resultsexhibited a concentration dependent inhibition of protein (albumin) denaturation by the ashwagandha extract.The effect of diclofenac sodium was found to be less when compared with the test extract. Form the present findings it can be concluded that ashwagandha possessed marked anti-inflammatory effect against denaturation of protein *in vitro*. The effect was plausibly due to the alkaloid and withanolide contents of ashwagandha[10].

Another study by Anbalagan et al, found Withania somnifera caused dose-dependent suppression of α2-macroglobulin (an indicator for anti-inflammatory drugs) in the serum of rats inflamed by sub-plantar injection of carrageenan suspension. The doses of Withania somnifera were 500, 1000, 1500, or 1200 mg/kg given as suspension orally 3-4 hours prior to induction of inflammation. Maximum effect (about 75%) was seen at 1000 mg/kg. Actual measurements of inflammation were not conducted[11].

Experimental studies reveals that extracts of Sphaeranthus indicus, Ashwagandha (at dose 100 mg/kg) produced an anti-inflammatory action by decreasing the paw volume in the model of carrageenan-induced paw edema in mice. Both chloroform and petroleum ether extracts of Ashwagandha (at dose 100mg/kg) exhibits strong anti-inflammatory activity as compared to methanolic extracts (100mg/kg). Standard drug diclofenac sodium showed maximum anti-inflammatory action. Further studies are needed to isolate the active principles of the plant extract.

Summary and Conclusion:

At a dose of 25.69mg/kg body weight, both the drugs showed the anti-inflammatory property, but when compared with each other the *withania somnifera* (ashwagandha) showed more anti-inflammatory effect which is statistically highly significant. The percent of decrease of the edema in Withania somnifera treated rats was 52% were as for Tinospora cordifolia treated rats the decrease of edema is 35% only. It shows that the withania somnifera was more efficant than the tinospora cordifolia, However the above preclinical experiments only give us an idea about the anti-inflammatory activity, of withania somnifera and Tinosopra cordifolia but large scale clinical trials are necessary for final assessment.

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