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EVALUATION OF ANTI-ARTHRITIC ACTIVITY OF *VYOSHADI GUGGULU* AND *NAGARADI QWATHA*

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ABSTRACT

The present study was undertaken to evaluate the Anti-arthritic effect of *Vyoshadi Guggulu* (VG) and *Nagaradi Qwatha* (NQ) in albino rats. The Anti-arthritic action experimental models were studied by Freund's adjuvant induced Arthritis Method. Forty eight adult Wistar rats were divided into eight groups of six each and maintained under uncontrolled conditions. Group I was taken as control and Group II treated with the standard drug Ibuprofen 100mg /kg. Groups III and IV were administered with *Vyoshadi Guggulu* 270 mg/kg and *Nagaradi Qwatha* 8.1ml/kg respectively. Group V was administered with combination of *Vyoshadi Guggulu* 270 mg/kg and *Nagaradi Qwatha* 8.1ml/kg. Groups VI and VII were administered with 540mg /kg of Vyoshadi *Guggulu* and 16.2ml/kg of *Nagaradi Qwatha* respectively. Group VIII was administered with combination of both *Vyoshadi Guggulu* at dose of 540mg /kg and *Nagaradi Qwatha* 16.2ml/kg. In the present study, both *Vyoshadi Guggulu* and *Nagaradi Qwatha* and their combination caused significant increase in the anti-inflammatory activity with different dose levels and showed the spleen weight also significantly decreased by the trial drugs. The percentage of increase in the anti-inflammatory activity as well as the reduction in the spleen weight, are dose-dependent and differed significantly among the groups of rats receiving different dose levels of *Vyoshadi Guggulu* and *Nagaradi Qwatha.*

Keywords: *Vyoshadi Guggulu, Nagaradi Qwatha*, Freund's adjuvant induced Arthritis**,** Anti-arthritic Activity

INTRODUCTION

Inflammation is a universal host defense process involving a complex network of cell-cell, cell-mediator and tissue interactions. It occurs in response to a variety of harmful stimuli viz. physical, chemical, traumatic, antigen challenge, infectious agents and ionizing radiations etc. Apart from *exogenous factors* (physical, chemical, mechanical, nutritional and biological etc.) *endogenous factors* (immunological reactions, neurological and genetic disorders) also contribute to inflammatory response.

Inflammation most commonly occurs when microbial invasion or tissue injury overcomes the body's

non-specific defense mechanisms. Subsequent to infection, immune system gets activated, communication and coordination occurs between different classes as well as actions of immune cell to produce inflammation is tightly regulated by the body and is the starting point of the body's self-repair process initiated by body's defense system to thwart pathologic assaults but occasionally it runs amok, leading to physiological chaos and death[1].

The inflammation could be acute, sub-acute or chronic in nature. The acute inflammation is short lasting whereas chronic inflammation may persists for weeks, months or years. There are 3 principle components of an inflammatory response ***a***. increased blood flow, ***b***. increased capillary permeability and ***c***. Increased migration of leucocytes into the affected area[2].

The inflammatory diseases cover a broad spectrum of conditions including auto immune diseases (e.g. Rheumatoid Arthritis), Osteo-Arthritis, Inflammatory Bowel Diseases, Multiple Sclerosis, Asthma, Chronic Obstructive Pulmonary Disease, Allergic Rhinitis, Infectious Diseases, various types of cancers and cardiovascular diseases etc. In the recent years there has been increased focus on the component III of inflammatory response, the leukocyte migration[3]

Rheumatoid Arthritis (RA), one of the commonest autoimmune diseases, is a chronic, progressive, systemic inflammatory disorder affecting the synovial joints and typically producing symmetrical arthritis that leads to joint destruction, which is responsible for the deformity and disability. The consequent morbidity and mortality has a substantial socio-economic impact[4].

The prevalence of arthritis is approximately in the West. The prevalence of RA in India subcontinent is 1.5-2 percent of population. The epidemiological ratio of arthritis in female: male is 3:1 and the prevalence is 1% of the world population. Adjuvant Induced Arthritis (AIA) in rats, a chronic inflammatory disease characterized by infiltration of synovial membrane in association with destruction of joints resembles RA in humans.[5]

It has reported that the increase in edema of hind paw after adjuvant infection in rat is paralleled by increased extra cellular activities of lysosomal enzymes. These enzymes are involved in the degradation of structural macromolecules in connective tissue and cartilage proteoglycans. They are also capable of destroying extra cellular activities by increased extra cellular activities of lysosomal enzymes. They are also capable of destroying extra cellular structures and may participate in mediating tissue injury in rheumatic diseases.[6]

Amongst the various experimental animal models of arthritis, induction of arthritis by Freund's Adjuvant is one of the standardized methods which mimics the human patho-physiological state including chronic swelling in multiple joints due to accumulation of inflammatory cells, joint cartilage erosion, bone destruction and used to investigate the activity of various potent anti-inflammatory and anti-arthritic agents.[7]

Presently many non-steroidal, steroidal and immunosuppressive drugs are used to control inflammatory symptoms and pain**,** they are associated with certain undesirable side effects.[8] With these difficulties, the field of arthritis research has progressed exponentially towards herbal therapies that have been considered safe and effective in all elevating chronic pain associated with arthritis.[8]

There are many studies available on single drugs about their pharmacological effects. *Vyoshadi Guggulu* and *Nagaradi Qwatha* are the formulations with minimal in number easily available herbal ingredients, with no information regarding their pharmacological activity, attracts pharmacological importance. In this term, it is planned to evaluate the Anti-inflammatory activity of both ***Vyoshadi Guggulu*** and ***Nagaradi Qwatha*** individually and synergistically and to compare it with a standard NSAID, through **Freund's adjuvant induced Arthritis Method.**

MATERIALS AND METHODS

Trial Drugs:

- ***Vyoshadi Guggulu (VG)***[9] a poly Herbal formulation containing *Trikatu*, *Triphala*, *Trimada* and *Guggulu* as the main ingredient with a quantity equal to the quantity of all other ingredients **(Table 1)**, is explained by *Vagbhata* as a *shamanaushadhi* in the treatment of *Amavata* as these ingredients possesses both *Amapachaka* and *Vatanulomana* actions. The drug was specially prepared at *Rajashree Ayurveda pharmacy – Udupi* for this study.
- ***Nagaradi Qwatha (NQ)***[10] is an herbal formulation containing the extracts of the medicinal plants viz. *Nagara*, *Harithaki* and *Amritha* **(Table 2)**. These constituents are possessing the *deepana,pachana* and *vatanulomana* qualities. The trial drug is prepared in *S.D.M.Ayurveda Pharmacy – Udupi.*

Determination of drug dose [11]

The rat dose was calculated from the human dose of 3 g/day with the ***Conversion Factor 0.018***. Hence the calculated dose of *Vyoshadi Guggulu* for the rat of 200 g body weight is 54 mg (i.e. 270mg /kg body weight). The dosage form of the pill was prepared as a suspension in distilled water and used for all the experimental purposes

Selection of animals, caring and handling:

A total of 48 healthy Wistar rats (180–240 g), of either sex, bred locally in the animal house of ***S.D.M. Centre for Research in Ayurveda and Allied Sciences, Udupi***, were selected for the study. They were housed in normal uncontrolled conditions individually in polypropylene cages containing sterile paddy husk (procured locally) as bedding throughout the experiment.

All animals were fed with sterile commercial pelleted rat feed supplied by ***VRK Nutritional Solutions (Sangli - India)*** and had free access to water. Animals were kept under fasting for overnight and weighed before the experiment. The study was commenced after obtaining approval ***(Letter No. SDMCAU /ACA-49/EC–A/10-11; Dt. 09th July 2010)*** of Institutional Animal Ethics Committee.

Study design:

The rats were randomly allocated into eight groups of six rats each for evaluation of Anti-Arthritic activity of both ***Vyoshadi Guggulu*** and **Nagaradi Qwatha** by **Freund's adjuvant induced Arthritis Method**

Group I served as normal control and received normal tap water. **Group II** was taken as Standard group and served with **Ibuprofen** (*Cipla ltd, Mumbai)* 100mg/kg as standard drug. Group III was administered *Vyoshadi Guggulu* 270mg/kg. Group IV was administered *Nagaradi Qwatha* 8.1 ml/kg. Group V was administered with combination of *Vyoshadi Guggulu* 270mg/kg & *Nagaradi Qwatha* 8.1 ml /kg.

Group VI was administered *Nagaradi Qwatha* 16.2 ml/kg. Group VII was administered with *Nagaradi Qwatha* 16.2 ml/kg and Group VIII was administered with combination of *Vyoshadi Guggulu* 540 mg /kg & *Nagaradi Qwatha* at 16.2 ml /kg body weight/rat/day for 21 days.

Instruments & Chemicals:

1. Weighing Scale
2. Mortar & pestle
3. Syringes
4. Surgical gloves
5. Freund's Adjuvant
6. Anaesthetic ether
7. Intra Gastric tube
8. Digital Plethysmometer

Procedure[12]

The method according to Pearson and Wood has been adopted for evaluation of anti-arthritic property. Arthritis was induced by a single intra-dermal injection (0.1 ml) of Freund's adjuvant containing 1.0 mg dry heat-killed *Mycobacterium tuberculosis* per milliliter sterile paraffin oil into a foot pad of the left hind paw of albino rats. Drug treatment was started from the initial day i.e. from the day of adjuvant injection (0 day), 30 minutes before adjuvant injection and continued till 21st day. Paw volume was measured on 4th, 8th, 14th and 21st day by using Digital Plethysmometer.

Evaluation

The mean paw oedema for each treated group was determined and compared with that obtained for the control group. Inhibition percentage of inflammation (**I%**), was derived, using the formula

$$I\% = \frac{\{N0 - N_1\}}{N_0} \times 100$$

Where N1 = the mean paw size for each group after adjuvant injection, and N0 = the mean paw size obtained for each group before Freund's adjuvant injection.

Blood samples were collected by puncturing the retro-orbital plexus into heparinised vials and analysed for blood parameters. Rats were sacrificed by cervical dislocation and spleens were removed. All the spleens of rats were weighed immediately after dissection.

Statistical Analysis

- Statistical analysis was performed with Computer statistical package ***SIGMASTAT (Version 3.5).*** The results were analyzed for statistical significance using **one way ANOVA** followed by Dunnet's test. Data was presented as **mean ± SEM**. A **P-value<0.050** was considered significant.

OBSERVATIONS

- In ***Freund's adjuvant induced Arthritis model***, both *Vyoshadi Guggulu* (VG-SD) 270 mg/kg and *Nagaradi Qwatha* (NQ-SD) 270 mg/kg and 8.1ml/kg and their combination (VG&NQ – SD) 270 mg/kg and 8.1ml/kg caused significant increase in the anti-arthritic activity. **(Table 3).** The percentage of increase in the anti-inflammatory activity was dose-dependent and differed significantly among the groups of rats receiving different dose levels of Vyoshadi Guggulu and Nagaradi Qwatha. **(Chart 1).**
- The percentage of increase in the inhibition of inflammation caused by the Vyoshadi Guggulu in single dose (*270mg/kg*) was significantly detectable on 4th day (71%) on 8th day **(6**7%) and on 14th day (46%). Nagaradi Qwatha (8.1ml/kg) also showed a significant increase in the inhibition of inflammation with 50% at early intervals of the study.
- The Double Dose of Vyoshadi Guggulu (540 mg /kg) has showed highly significant increase in the anti- arthritic activity (75%) on 4th, (57%) on 8th, (52%) at 14th and (45%) at 21st days of the study. Nagaradi Qwatha in double dose (16.2 ml / kg) also showed significant increase of anti-arthritic activity at all intervals of the study i.e. (71%) at 4th, (50%) at 8th, (46%) at 14th and 39% of inhibitory activity of inflammation of joints.
- The combination of Vyoshadi Guggulu and Nagaradi Qwatha in single doses (270mg/kg + 8.1ml/kg) showed a significant change on 4th and 8th days with 61% and 49% of inhibition of inflammation respectively, but the double doses (540 mg /kg &16.2 ml /kg) showed their peak of activity of inhibition at all intervals by 84%, 57%, 54% and 49% respectively.
- Standard drug (Ibuprofen100mg/kg) showed a significant change on comparison with trial drugs. At all intervals of the study, there is significant (P<0.001) increase in anti-inflammatory activity by Vyoshadi Guggulu and Nagaradi Qwatha when compared to the control group.

Effect on Weight of Spleen:

- Standard drug (Ibuprofen100mg/kg) showed maximum activity by reducing the weight (67.8%) on comparison with control group. The percentage of reduction in the weight of spleen is significantly observed by the Vyoshadi Guggulu in single doses was significantly detectable (61.2%) and Nagaradi Qwatha with 57.2%.The combination of Vyoshadi Guggulu and Nagaradi Qwatha in single doses showed a significant change in the percentage (59.8%) of reduction in weight of spleen.
- The Double Dose of Vyoshadi Guggulu has showed highly significant increase in the anti-inflammatory activity (62.9%). Nagaradi Qwatha in double dose showed highly significant reduction (61.2%) and the combination showed a sig-

nificant change in the percentage (65.8%) of reduction in weight of spleen.

DISCUSSION AND CONCLUSION

- Numerous experimental methods for evaluation of anti-inflammatory drugs have been developed over the last few years. These methods help not only understanding the pathogeneses of inflammation but also explore the anti-inflammatory mechanisms as well as to identify the suitability of drugs for specific inflammatory diseases.
- Inflammatory response protects the body by triggering innate and acquired immunity under conditions such as tissue damage and infections, but chronic inflammatory responses can result in diseases such as cardio-vascular disease, diabetes, pulmonary disease and Rheumatoid Arthritis[14].
- Freund's Adjuvant- induced arthritis model is well established rat model and has been widely used from many years for evaluation of anti-inflammatory and anti-arthritic potential of various agents. An array of changes occurred after the administration of Adjuvant in rats including joints swelling, infiltration of inflammation cells, bone destruction, joint cartilage erosion and remodeling which results in the destruction of joint integrity and function disability[15]
- Freund's adjuvant is inactivated and dried mycobacteria which are mainly responsible for stimulation of cell-mediated immunity which ultimately increased the production of certain immunoglobulins. Adjuvant induced arthritis is a primary and secondary chronic arthritis[16].
- Primary is inflammatory phase where generation of prostaglandin occurs and secondary immunological state in which autoantibodies is generated. Release of various inflammatory mediators including cytokines (IL-1B and TNF-alpha), MCSF, interferon's and Platelet derived growth factor (PDGF) are responsible for the initiation of pain along with swelling of the limbs and joints, bone deformations and disability of joint function[17].
- Significant increase in the paw thickness after sub-plantar administration of Freund's adjuvant is reflecting the status of arthritis. In the present study, both *Vyoshadi Guggulu* and *Nagaradi Qwatha* and their combination caused significant increase in the anti-inflammatory activity with different dose levels and showed the spleen weight also significantly decreased by the trial drugs.
- The percentage of increase in the anti-inflammatory activity as well as the reduction in the spleen weight, are dose-dependent and differed significantly among the groups of rats receiving different dose levels of Vyoshadi Guggulu and Nagaradi Qwatha.

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Table 1: Ingredients of *Vyoshadi Guggulu*

Sl.No	Name	Botanical Name	Part Used	Quantity
1.	***Shunti***	*Zingiber officinale Rosc.*	Rhizome	1 Part
2.	***Maricha***	*Piper nigrum Linn.*	Fruit	1 Part
3.	***Pippali***	*Piper longum Linn.*	Fruit	1 Part
4.	***Haritaki***	*Terminalia chebula Retz.*	Fruit pulp	1 Part
5.	***Vibhitaka***	*Terminalia belerica Roxb.*	Fruit pulp	1 Part
6.	***Amalaki***	*Emblica officinalis Gaertn.*	Fruit pulp	1 Part
7.	***Chitraka***	*Plumbago zeylanica Linn.*	Root	1 Part
8.	***Musta***	*Cyperus rotundus Linn.*	Rhizome	1 Part
9.	***Vidanga***	*Embelia ribes Burm.*	Fruit	1 Part
10.	***Guggulu***	*Commiphora mukul Engl.*	Gum oleo-resin	9 Parts

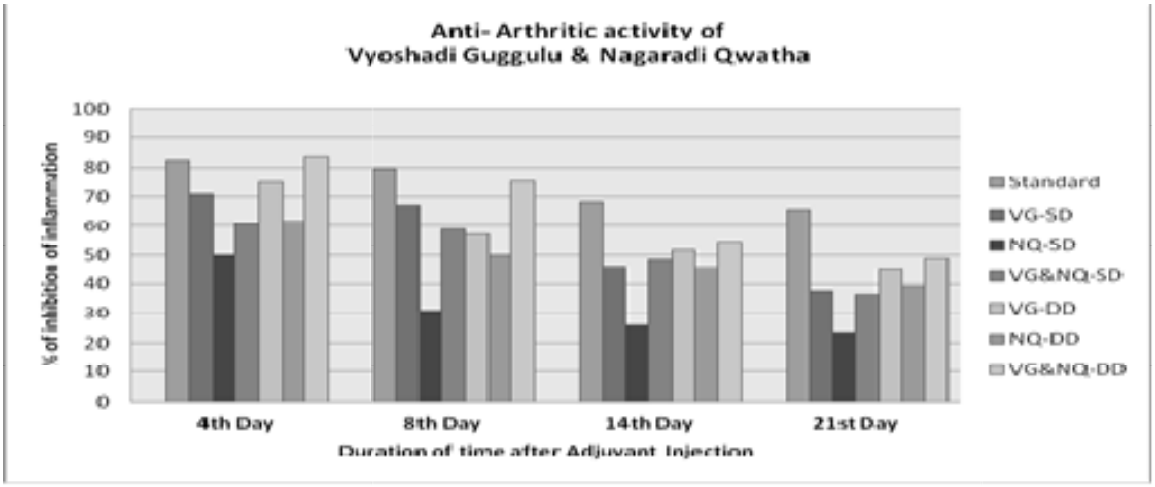
Table 2: Ingredients of *Nagaradi Qwatha*

Sl.No	Name	Botanical Name & Family	Part Used	Quantity
1.	***Nagara***	*Zingiber officinale Rosc.*	Rhizome	2 parts
2.	***Haritaki***	*Terminalia chebula Retz.*	Fruit pulp	4 parts
3.	***Amrita***	*Tenospora cardifolia (willd.) Miers*	Stem	6 parts

Table 3: Anti- Arthritic activities of Vyoshadi Guggulu and Nagaradi Qwatha by Fruend's Adjuvant Induced Arthritis in Albino Rats

Group	Drug & Dose	Fruend's adjuvant induced Arthritis (Mean ± SEM) with % of Inhibition				
		0th Day	4th Day	8th Day	14th Day	21st Day
I.	Control	0.75± 0.027	-	-	-	-
II.	Standard Ibuprofen 100mg /kg	0.705 ± 0.017	1.093±0.034 (82.5)	1.072± 0.031 (79.7)	0.993±0.010 (68.4)	0.973±0.026 (65.6)
III.	VG-SD 270mg /kg	0.810 ±0.023	1.167±0.046 (70.9)*	1.202±0.065 (67.1)*	1.027±0.021 (46.2)*	0.955±0.195 (37.5)
IV.	NQ–SD 8.1ml/kg	0.787 ± 0.015	1.018±0.0487 (50.1)*	0.867±0.0476 (31.1)	0.832±0.040 (26.1)	0.810±0.034 (23.5)
V.	VG&NQ-SD 270mg/kg + 8.1ml/kg	0.753 ± 0.018	1.023±0.027 (61)*	0.927±0.019 (49)*	0.863±0.021 (35.7)*	0.792±0.010 (47.7)
VI.	VG-DD 540mg /kg	0.726 ± 0.011	1.080±0.032 (74.9)*	0.948±0.035 (57.1)*	0.905±0.030 (51,7)*	0.855±0.024 (44.8)*
VII.	NQ–DD 16.2 ml/kg	0.707± 0.009	1.047±0.0265 (71.3)*	0.933±0.0126 (50.1)*	0.827±0.010 (45.9)*	0.777±0.011 (38.9)*
VIII.	VG&NQ-DD 540mg/kg+16.2ml/kg	0.747 ± 0.017	1.057±0.014 (83.7)*	1.000±0.009 (57.0)*	0.968±0.011 (54.3)*	0.930±0.011 (49)*

*Results expressed as mean ± SEM from six observations; * P<0.050; ** P<0.01*
VG=Vyoshadi Guggulu; NQ=Nagaradi Qwatha; SD= Single Dose; DD= Double Dose



VG=Vyoshadi Guggulu; NQ=Nagaradi Qwatha; SD= Single Dose; DD= Double Dose

Chart 1: Anti- Arthritic activities of *Vyoshadi Guggulu* and *Nagaradi Qwatha on Freund's adjuvant induced Arthritis*

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