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The Efficacy of A-4 Tablets in Rheumatoid Arthritis (Amavata)

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Abstract R.A. is a progressive and disabling auto-immune disease. The available treatment in modern science if continued for a longer time they are having systemic side effects. So goals of Ayurvedic treatment aim at giving significant relief with no adverse side effects. Also the treatment is integrated towards preventing the long term damage to articular structures, maintaining proper function and control of systemic involvement. So present study was undertaken with A-4 tablet on 30 patients for a period of 3 months. During this period symptomatic parameters and investigations were observed. A significant relief in the symptoms like joint pain and swelling were noted and the working ability of the patients improved.
Keywords *Amavata; Rheumatoid Arthritis; A-4 Tablets*

1. Introduction

Rheumatoid arthritis is characterized by inflammation of the lining at the joints. This Inflammation of joints can lead to long term damage, chronic pain and restricts daily activity [1]. Rheumatoid arthritis has a worldwide distribution with an estimated prevalence of 1 to 2%. Prevalence increases with age, approaching 5% in women over age 55. Although rheumatoid arthritis may present at any age, patients most commonly are first affected in the third to sixth decades [2; 3].

The Spread occurs within months to years to other joints and almost any joint may be involved. Spontaneous remission can occur (after acute onset). The life expectancy is reduced by 7 years in men and 3 years in women [4].

Rheumatoid arthritis which is described as "Amavata" in Ayurveda. It has been described as -

"SaKashtahaSarvarogaanaamyadaaprakupitoBhavet |
Hasthapaadashirogulphatrikajaanuurusandhishu ||
Karotisarujamshophamyatradoshahaprapadyate |
Sadeshorujateatyathamvyaviddhaivavrishchkaihi ||"

(Madhavnidanamavatanidanam 25/7-9)

This means "If the disease "amavata" (rheumatoid arthritis) becomes chronic the joints (sandhi) of hands (Hastha), feet (paada), ankles and elbow (gulpha), low back trika), knee (jaanu), and hip (uru) become inflamed and painful. The pain in affected joints resembles the pain of a scorpion's sting" [5].

1.1. Need of Study

The commonly used drugs are NSAIDs, Corticosteroids, Methotrexate, Hydroxychloroquine, Leflunomide, Tumor Necrosis Factor Inhibitors, T-cell Costimulatory Blocking Agents, Interleukin-1 (IL-1) Receptor Antagonist Therapy, Intramuscular Gold etc. But they are having certain side effects like Hepatic cirrhosis, Interstitial pneumonitis, Severe myelosuppression, Stomatitis and oral ulcers, Mild alopecia and hair thinning, GI upset etc. The goals of therapy of RA are relief of pain, Reduction of inflammation, Protection of articular structures, Maintenance of function, and Control of systemic involvement [6; 7].

2. Aims & Objectives

1) To evaluate the efficacy of A-4 Tab. in Rheumatoid Arthritis [Amavat]
2) To establish an Ayurvedic formulation the constituents of which are freely available, free from adverse effects and cost effective.
3) To put forth the effect of A-4 Tab in Rheumatoid Arthritis [AMAVAT] in such way that it should be convincing and acceptable globally.

3. Materials & Methods

- Study type – Open uncontrolled phase II clinical study;
- Study centre – Dr. D.Y. Patil college of Ayurved, Hospital and Research institute. Nerul, Navi Mumbai, Maharashtra, India;
- Sample size -30 for pilot study with A-4 Tab;
- Study duration- 3 months;
- Statistical evaluation-The statistical evaluation of study was conducted with appropriate statistical test.

3.1. Selection of Patients

Uncomplicated patients with characteristic symptoms and signs of Amavat (Rheumatoid Arthritis), irrespective of age, sex, religion, education, occupation etc were selected.

Inclusive Criteria

- Age Group- 20 to 60 years
- Sex –Both sexes
- Physical examination & clinically significant abnormal laboratory investigation at the prestudy.
- Availability of subjects for entire period of study.
- Ability to understand & communicate with the Investigator & staff.

Exclusive Criteria

- Age Below 20 and above 60
- HIV
- HbsAg
- Bone malignancy
- Tuberculosis
- Cardiac Disorders,
- Liver Disorders,
- Neurological or Psychiatric disease,
- Pregnant & lactating women.

3.2. Subjective Parameters [8, 9]

Table 1: *Subjective Parameters*

Symptoms	No	Mild	Moderate	Severe
	0	**+**	**+ +**	**+ + +**
Agnimandya (Loss of Appetite)	Normal appetite	Mild loss of appetite	Moderate loss of appetite	Severe loss of appetite
Jwara (Fever)	Absence of fever	Occasional low grade fever	Persisting low grade fever	Continuous moderate fever
Vida-vibandha (Constipation)	Normal bowel movements	Occasional constipation Not using medicine	Constipation with occasional use of medicine	Chronic constipation with regular use of laxative
Gaurav (Heaviness in body)	Active without heaviness	Slight heaviness without any problem	Routine work & activity mildly hampered	Routine work & activity moderately hampered
Sarujasandhi (Pain in joints)	Absence of pain in joints	Short duration pain in joints	Continuous mild pain in joints	Continuous unbearable pain in joints
Sandhishotha (Odema in joints)	Absence of oedema in joints	Mild oedema in joints	Moderate oedema in joints	Severe oedema in joints
Pidanasahatva (Tenderness in joints)	No pain on putting pressure	Mild pain	Patient winces	Patient winces and withdraw the affected part.

3.3. Laboratory Investigations

CBC**,** ESR**,** RA Factor**,** ASO titre**,** Urine R/M**,** X-Ray of affected joint [10]

SOP OF ‘A- 4’ TAB. Contains

1. Anantamula (Hemidesmusindicus) 2. Abhaya (Terminaliachebula)
3. Amruta (Tinosporacardiofolia) 4. Arushka (Semicarpusanacardium)

The raw material for study is purchased from the recognized Ramesh Ayurvedic Aushadhalay. Certified by Dravyaguna Dept. of Dr. D.Y. Patil College of Ayurved. (Authentification certificate).
1 to 3 ingredients were cleaned and powdered separately.
4 *A*rushka (Semicarpusanacardium) - Shodhan

Purification done by standard Ayurvedic Granth and powdered separately.
*Ref-Rasa Tarangini 24/477-478-479

All powders are mixed in equal quantity. After homogeneous mixing, sufficient quantity of gum acacia is added for binding purpose. Full mixed material is sent for manufacturing of tablets. All the manufacturing procedure was conducted in Rasashastra Dept. of Dr. D.Y. Patil College of Ayurved

Nerul. Tablets are packed and stored in air tight containers. Each container having 115 tablet for 7 days with batch no & mfg date and only for clinical trial.

Phytochemical evaluation of raw material and end product A-4 tablet was done at UICT University of Mumbai.

- Each 500mg tablet contains 125 mg of each herb
- Dose ---2gm (4 tab)
  - QID (Four times) in a day
  - With warm water for three months.

3.4. Assessment of Total Effect of Therapy

Table 2: *Criteria for assessment*

Result	Criteria for assessment
Cured	Complete relief(100%) in signs & symptom of disease amavata, was taken as cured
Moderate relief	Patients with improvement of more than 60% in sign & symptoms, were taken as moderately relieved
Mild relief	Patients with improvement in between 30-60% in sign & symptoms were considered as mild relief.
Unchanged	No change or less than 30% improvement insigns & symptoms were considered as unchanged.

Observations and Results

- 30 patients of either sex in the age group of 20-60 years of R.A. (AMAVAT) were selected as per the selection criteria, underwent physical and pathological examination. Patients -received A-4 tab dose of 2gm (4 tablets) four times daily, for 3 months.
- Patients were followed up every 15 days for 3 months and Laboratorial Investigation done on initial day, 45 and end of 3 months.

3.5. The Symptoms Score was Compared Before and After Treatment

Relief in the pain other subjective symptoms were considered as the criteria for efficacy.

There were 16 males 14 females. Almost all the patients have bilateral knee joint involvement with a few of them having additional joint involvement. All the patients were examined clinically at every follow up, and analysis was carried out at 3 months. The average score for the symptomatic evaluation before the treatment was 18.56 in the score was reduced from 8.02 it indicates 55.96 % relief in various symptoms.

Table 3: *Symptomatic Evaluation*

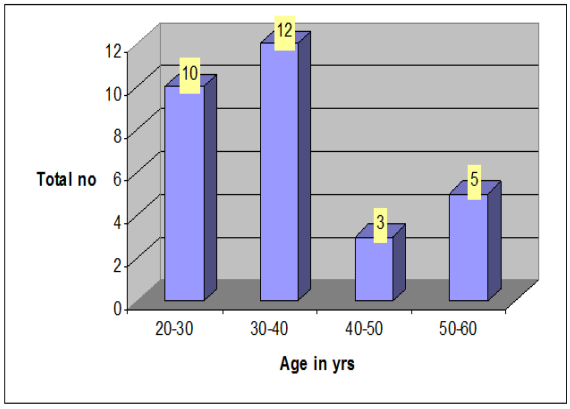
	Before treatment	After treatment
Mean	18.56	8.02
SEM	0.29	0..40
% of inhibition	55.96 %	

The average score for the number of the joints involved before the treatment was 3.44 in the score was reduced from 3.44 to 1.16.

Thus, there was 66.28% reduction in the number of joint involvements.

Table 4: *Average Number of Joints Involved*

	Before treatment	After treatment
Mean	3.44	1.16
SEM	0.14	0.14
% of inhibition	66.28 %	



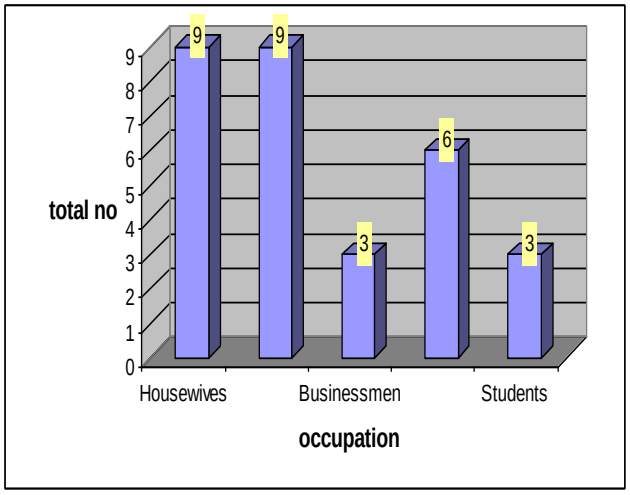


Table 5: *Age*

Age	Total
20-30	10
30-40	12
40-50	3
50-60	5

Table 6: *Occupation*

Occupation	Total
Housewives	9
Labourers	9
Businessman	3
Employees	6
Students	3

The Laboratory evaluations for safety (CBC, ESR, SGPT, S. Creatinine& Urine routine) did not indicate any significant change compared to baseline

Table 7: *Vitals*

Vitals	Mean ± Std. Dev.	
	Baseline	Day 90
Hb	13.5 ± 1.89	13.55 ± 1.48[b]
Total RBC	5.21 ± 0.69	5.22 ± 0.69[b]

Total WBC	7447.78 ± 1970.92	6177.5 ± 1185.65 [b]
Neutrophils	60.88 ± 6.71	60.9 ± 5.97 [b]
Lymphocytes	34.11 ± 3.41	33.87 ± 3.23 [b]
Eosinophils	3.78 ± 4.44	2.46 ± 2.04 [b]
Monocytes	1.17 ± 1.87	2.31 ± 2.76 [b]
Basophils	0.07 ± 0.2	0.33 ± 0.71 [b]
ESR	13.56 ± 8.73	9.37 ± 4.31 [b]
SGPT	30.49 ± 23.03	28.41± 20.30 [b]
S. Creatinine	0.86 ± 0.15	0.89 ± 0.14 [b]
Lipid profile	180 ± 184	178 ± 180
Blood Urea	34.25± 32.20	34.10± 31.20

Using Paired t test : a=significant (p< 0.05) as compared to baseline
b= not significant (p> 0.05) as compared to baseline

4. Results

A significant reduction was observed in joint pain and swelling (P<0.001) and the working ability of the individual was also improved. Tenderness was reduced (P<0.001). In haematological parameters reduction in ESR was significant (P<0.001).By this study it has become clear that Tab A-4 can be used effectively in the cases of Rheumatoid arthritis.

4.1. Statistical Analysis

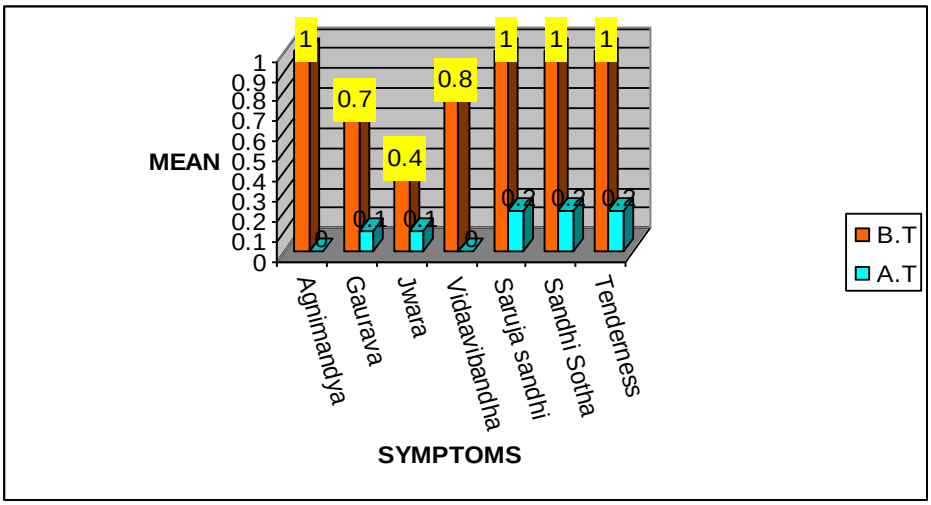


Figure 1: *Statistical Analysis*

Table 8: *Signs & Symptoms*

Signs & Symptoms	Mean		%	SD	SE	T value	P value
	B.T	A.T					
Agnimandya	1.0	0	100	0	0	-	-
Gaurava	0.7	0.1	86	0.51	0.16	3.67	0.01
Jwara	0.4	0.1	75	0.48	0.15	1.96	0.01
Vidaavibandha	0.8	0.0	100	0.42	0.13	6.0	0.001
Sarujasandhi	1.0	0.2	80	0.42	0.13	6.0	0.001
SandhiSotha	1.0	0.2	80	0.42	0.13	6.0	0.001
Tenderness	1.0	0.2	80	0.42	0.13	6.0	0.001

Table 9: *Variation in Symptoms Severity with Drug*

Day/visit	0 day	30 day	60 day	90 day
Symptoms				
Arthritis of 3 or more joint areas.	100%	100%	80%	60%
Duration of 6 weeks or more.	100%	100%	80%	60%
Morning stiffness > 1 hr.	>1 hr.	>1 hr.	>30 min	>15 min
Arthritis of hand joints.	3	3	2	2
Symmetrical arthritis.	3	3	2	1
Radiological changes.	100%	100%	100%	85%
Rheumatoid nodules.	3	3	2	2
R.A. factor +ve.	+ve.	-ve.	-ve.	+ve.
Low grade fever	100%	70%	50%	20%
Restricted movements	100%	100%	80%	60%
Inflammation of joints.	3	3	3	1
Insidious onset.	3	3	3	1
Weakness	100%	80%	80%	30%
Malaise	100%	80%	80%	60%
Complete ankylosis	100%	100%	100%	90%

4.2. Clinically Proven to be Well Tolerated

No severe adverse events were noted during the study; A-4 was very well tolerated

Table 10: *Grade*

Grade	Percentage
Very Good: No side effects	66.7%
Good: Mild side effects	33.3%
Fair: moderate side effects	-
Poor: Severe side effects requiring withdrawal of therapy	-
Total	100%

4.3. Probable Mode of Action of A-4 Tablet – [11]

The probable mode of action of Tab.A-4 in the management of Amavat can be explained on the basis of Sampraptivightan i.e. elimination of Amadosha, correction of the state of Agnimandya (by Agni deepan) & Evacuation of Mal & Vat shaman resulting in Srotoshuddhi.

Table 11: *Probable Mode of Action of A-4 Tablet*

Name	Quality	Rasa	Vipaka	Virya	Action
Anantamula	Guru, Snigdha	Tikta, Madhura	Madhura	Sheeta	Deepan, Pachan, Anulomana, Raktashodhak,Shothahara, Kaphaghna, Jwaraghna, Dahaprashamana, Rasayana, Vishaghana.
Abhaya	Laghu, Ruksha	Kashaya, Katu, Tikta, Amla, Madhura	Madhura	Ushna	Sarvadoshaprasamana, Rasayan, Dipan, Pachana, Anuloman, Mrudurechana, Hrudya, Shothahara, Vedanasthapana, Kaphaghana, Srotah-shodhana, Rasayana.
Amruta	Laghu	Tikta, Kashaya	Madhura	Ushna	Balya, Dipan, Pachana, Rasayan, Raktasodhak, Raktavardhak, Pittasaraka, Jwaragna, Vedanasthapana, Kaphaghana, Anulomana, Hridya, Dahaprashamana.
Arushka	Laghu, Tikshna, Snigdha	Madhur, Katu, Tikta,	Madhura	Ushna	Vatahara, Kaphahara, Vishghana, Dipan, Pachana, Shothahara, Jwaraghana, Rasayana,

A-4 Tablet contains-

1) **Anantamula (Hemidesmusindicus)**

Bacteriostatic, anti-inflammatory, anticancer, antiviral antilithic, hypotensive, antifungal, antibacterial, spasmodic. [14; 15]

2) **Abhaya (Terminaliachebula)**

Immunomodulatory, potent antioxidant and a probable radioprotector cytoprotective activity, antistress, antispasmodic, cardiotonic activity, antimutagenic activity .Purgative antimicrobial, antibacterial and antifungal properties. [16]

3) **Amruta (Tinosporacordiofolia)**

Antimicrobial, anti-inflamatory, analgesic, antipyretic, immunomodulator antifungal, antibacterial, *antistress*, antispasmodic, *purgative.* [17]
Effective in rheumatoid arthritis.

4) **Arushka (Semicarpusanacardium)**

Immunomodulatory activity, Anticancer, antitumour, *antioxidant, anti-inflammatory, analgesic, antiarthritic, antispasmodic, cytotoxic, cytoprotective, moderate analgesic, immunomodulatory*. [18; 19

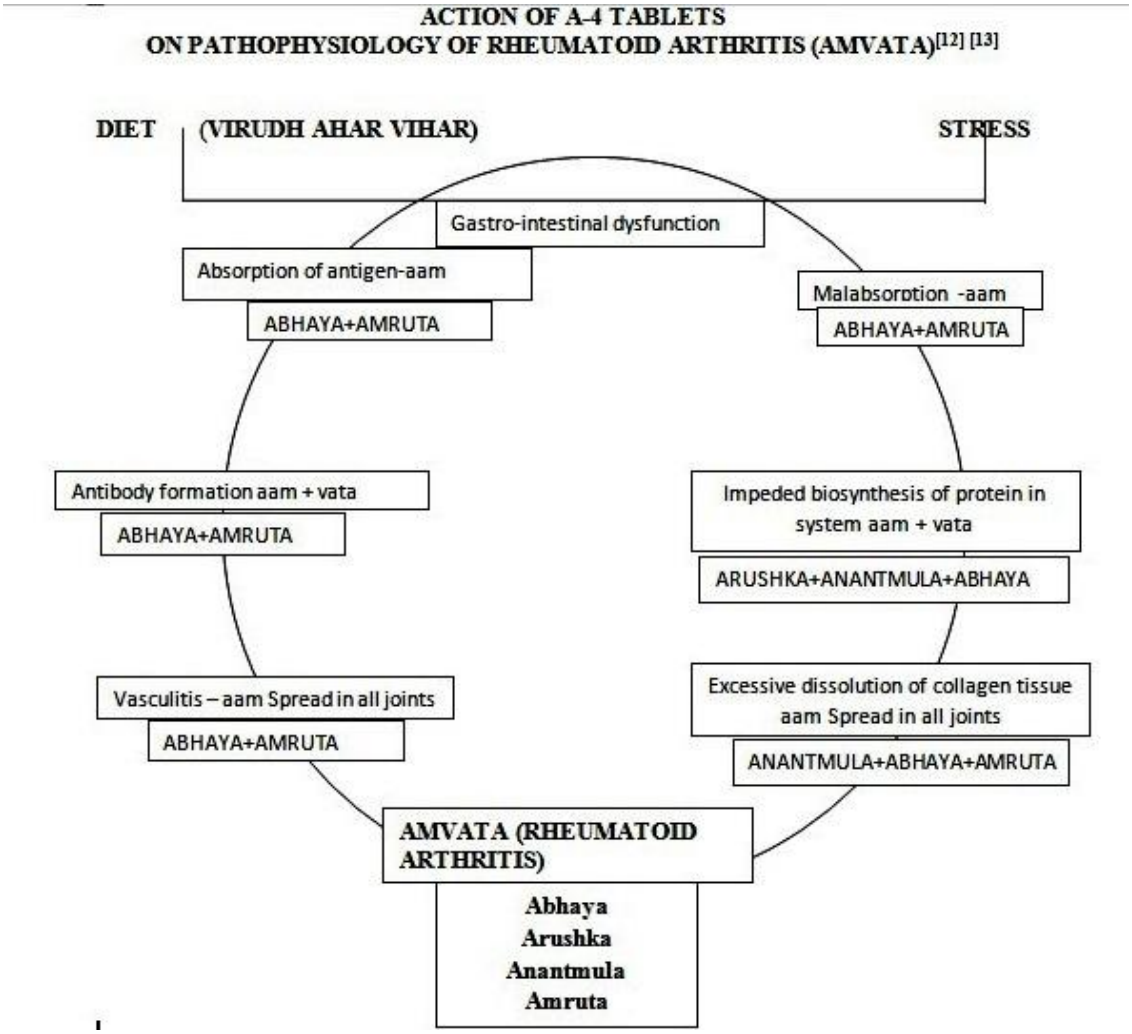


Figure 2: *Action of A-4 Tablet*

5. Conclusion

- In this study, most of the patients had a satisfactory outcome in terms of relief of pain and free mobility of the joints. No side effects were reported by any of the patients
- On observing the overall effect of the therapy it was found that, all the patients got relief, of them 27% of patients were Cured, 53% were Moderately relieved & 20% patients got Mild relief from the sign & symptoms of Amavat.
- The drug combination is safe and without any toxicity found.
- After observing the efficacy and safety of the trial drug in the management for Rheumatoid Arthritis (Amavat) is of paramount importance for the society.
- Long-term use of A-4TAB. Helps in the functional aspects of joints in R.A.(AMAVAT) patients, thereby improving the quality of life.

This disease is manifested by recurrent inflammation of joints. It is characterized by painful swelling of the joints of the body, which restricts the movements of patients. In chronic cases, the disease may cause deformity and total incapacitation.

Ayurveda has put forth a unique approach of its etiology assigning crucial role for the gastro-intestinal dysfunction. The treatment is also accordingly designed. The herbal, drugs has been successfully evaluated in the management of this disease.

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