A PROSPECTIVE OPEN LABELLED PHASE-II NON RANDOMIZED CLINICAL TRIAL DRUG ON HERBAL FORMULATION OF "NANNARI VER OORAL KUDINEER" FOR THE TREATMENT OF "VALI AZHAL KEEL VAYU" (RHEUMATOID ARTHRITIS)

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A PROSPECTIVE OPEN LABELLED PHASE-II NON RANDOMIZED CLINICAL TRIAL DRUG ON HERBAL FORMULATION OF NANNARI VER OORAL KUDINEER FOR THE TREATMENT OF VALI AZHAL KEEL VAYU (RHEUMATOID ARTHRITIS) "** is a bonafide work done by **Dr. E.MALARVIZHI (Reg.No.321611004)** Govt. Siddha Medical College, Palayamkottai in partial fulfilment of the University rules and regulations for award for **MD (S), BRANCH-I POTHU MARUTHUVAM** under my guidance and supervision during the academic year **OCTOBER 2016-2019.**

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Certified that I have gone through the dissertation entitled **"A PROSPECTIVE OPEN LABELLED PHASE-II NON RANDOMIZED CLINICAL TRIAL DRUG ON HERBAL FORMULATION OF NANNARI VER OORAL KUDINEER FOR THE TREATMENT OF VALI AZHAL KEEL VAYU (RHEUMATOID ARTHRITIS)"** submitted by **Dr.E.MALARVIZHI (Reg. No.321611004) a student of final year MD (S), Branch-I, Department of Pothu Maruthuvam** of this college and the dissertation work has been carried out by the individual only. This dissertation does not represent or reproduce the dissertation submitted and approved earlier.

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DECLARATION

I declare that the dissertation entitled **"A PROSPECTIVE OPEN LABELLED PHASE-II NON RANDOMIZED CLINICAL TRIAL DRUG ON HERBAL FORMULATION OF NANNARI VER OORAL KUDINEER FOR THE TREATMENT OF VALI AZHAL KEEL VAYU (RHEUMATOID ARTHRITIS)"** submitted for the degree of MD in Siddha Medicine of Government Siddha Medical College, Palayamkottai, Tirunelveli, Tamil Nadu (The Tamil Nadu Dr. M.G.R. Medical University, Chennai) the record of work carried out by me under the supervision of **Prof.Dr.A.Manoharan, MD (S), (Ph.D.**) Head of the Department of Pothu Maruthuvam, and guidance by **Dr. G.Subash Chandran , MD (S), Ph.D.,** Lecturer, Govt. Siddha Medical College, Palayamkottai. This work has not formed the basis of award of any degree, diploma, associateship, fellowship or other titles in the university or any other university or institution of higher learning.

Place : Palayamkottai

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Date :

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LIST OF ABBREVIATIONS

%	-	Percentage
i.e.,	-	That is
RA	-	Rheumatoid Arthritis
ESR	-	Erythrocyte Sedimentation Rate
ASO	-	Anti-Streptolysin 'O' factor
TJC 28	-	Tender Joints 28
SJC 28	-	Swollen Joints 28
DAS 28	-	Disease Activity Score 28
VAS	-	Visual Analog Scale
gms	-	Grams
kg	-	Kilogram
mg	-	Milligram
dl	-	Decilitre
Ml	-	Milli litre
Cm	-	Centimeter
S E M	-	Structural Equation Modelling
ANOVA	-	Analysis Of Variance
Hb	-	Haemoglobin
TC	-	Total Count
DC	-	Differential Count
P	-	Polymorphs
L	-	Lymphocytes
E	-	Eosinophils
CRP	-	C-Reactive Protein
WBC	-	White Blood Corpuscles
RBC	-	Red Blood Corpuscles
HLA	-	Human Leukocyte Antigen
MHC	-	Major Histo Compability Complex
ACPA	-	Anti-Citrullinated Peptide Anti bodies
TNF	-	Tumour Necrosis Factor
IL	-	Interleukin
Anti-CCP	-	Anti-cyclic Citrullinated peptide

MMPs	-	Matrix Metalloprotases
ANA	-	Anti Nuclear Anti body
PIP	-	Proximal Interphalangeal Joint
DIP	-	Distal Inter Phalangeal Joint
MCP	-	Metacarpo Phalangeal Joint
MTP	-	Metatarsal Phalangeal Joint
CMC	-	Carpometacarpal Joint
Ref	-	Reference
CT	-	Computerized Tomography
MRI	-	Magnetic Resonance and Imaging
SLE	-	Systemic Lupus Erythematous
NVOK	-	Nannari Ver Ooral Kudineer

ABSTRACT

Vali Azhal Keel Vayu (Rheumatoid Arthritis) is now becoming a common disease now-a-days with numbers of suffers increasing day by day. The evidence of the disease was derived from "Sabapathy Manuscript" Noi Naadal Noi Mudhal Naadal Thiratu Part-II" 2nd Edition, compiled by Dr. M. Shanmugavelu, B.H.I.M [Page No: 623]. The signs and symptoms mentioned in the Literature of Siddha closely resembles with "Rheumatoid Arthiritis" in modern medicine. Totally 40 patients were selected and treated with the trial medicine "NANNARI VER OORAL KUDINEER" 90 ml Thrice a day for 30 days. Reference for trial medicine was taken from Gunapadam Mooligai Vaguppu, Pg.No.562,Dr.K.S.Murugesa Mudaliyar. The trial drug was subjected to biochemical, anti-micribial, phytochemical , pharmacological & toxicological analysis. At the end of the trial study, the majority of the cases showed good clinical improvement. All the relevant reports were statistically analysed and found to be significant.

CHAPTER I
INTRODUCTION

1.1 BACKGROUND:

The Siddha medicine is one of the traditional medical system originated during pre-vedic period in Southern India. It was founded by a set of people with tremendous supernatural powers called "*Siddhars*". This system had been developed with "Philosophy" or ''*Thathuvam''* as its base. *Siddhars* had given equal importance to *'Vedhanta'* and '*Sidhanta*'. The siddha system includes various sciences such as philosopy, yoga, astrology, anatomy, physiology & psychology. The treatment goal focusses on body and the mind simultaneously.

Health is the state of complete well being of physical, psychological, social and spiritual components of the body. But onset of diseases causes intervention to this state of well being.

"உடம்பா ரழியின் உயிரா ரழிவர்
திடம்பட மெய்ஞானஞ் சேரவு மாட்டார்
உடம்பை வளர்க்கும் முபாய மறிந்தே
உடம்பை வளர்த்தே னுயிர்வளர்த் தேனே''

\- திருமூலர் திருமந்திரம்

The ultimate aim of *Siddhars* was to attain eternal bliss. Human body is considered to be the media for that purpose. Thus the media must be protected from undesired effects such as degenerative changes, diseases and untimely death .For that sole purpose*, siddhars* followed specific type of life style including dietary habit which was also clearly mentioned in this system medicine.

According to *siddhars* theory, human body is constituted by 5 basic elements which also constitute the universe viz .Earth,fire,air,water and ether. The three humors are derived from *pancha bootham*. By the combination of earth and water, *kabham* is produced. Fire alone forms *pitham* and union of air and ether forms *vatham* .The normal functioning of human body is based on homeostasis of 3 forces or 3 humors called *Vatham,Pitham And Kapham*.

Among these three ,*vatham* is placed first .It can be provided by the following line,

''வாதமலாது மேனி கெடாது''

Any derangements in this homeostasis lead to pathological condition called *PINI* Or *NOI*. This is what that ***Thiruvalluvar*** says,

"மிகினும் குறையினும் நோய் செய்யும் நூலோர்
வளிமுதலா எண்ணிய மூன்று"

By observing the signs and symptoms of the patient we could find the disordered humor and the particular aliment could be diagnosed through the specific sets of diagnostic methods called *Envagai thervugal* in which the *naadi* examination is the principal method. According to *Yugimunivars Vaidhya Chindamani-800, vatha* diseases were classified into 80 types . Some authors say that there are 84 *vatha* diseases .*Keel vayu* comes under of 80 types of *vatha* diseases . *Keel vayu* was further divided into 10 types in the text of *Siddha Maruthuvam*. Vali azhal keel vayu is one among the 10 sub division. The Vali azhal keel vayu [*Noi Nadal Noi Muthal Nadal Thirattu*-II (Pg No .623) can be correlated in modern medicine as Rheumatoid Arthritis (RA).

RA is a chronic inflammatory multi systemic disease characterized by symmetric polyarticular joint involvement in association with extra articular manifestation .The disease affects approximately 1% of the world wide population and occurs in women 2 to 3 times more frequently than in men.The most common age of onset is between 30 and 50 years. The inflammation of the synovium typically of the small joints of the hands [MCP and PIP],wrists and feet. The symptoms includes pain, swelling, stiffness and can lead progressive joint damage resulting in deformities and loss of function, associated organ damage also contributes to severe disability.In the management of RA, herbs contribute approximately 50% of currently used crude drugs and another 25% is derived from chemically altered natural products. Thus, Siddha medicines possess a potential role as the definite alternative therapy in curing rheumatoid arthritis.

So, I have chosen my clinical trial drug as ''*NANNARI VER OORAL KUDINEER*'', mentioned in Gunapadam Mooligai Vaguppu Pg.NO.562, Dr.K.S.Murugesa Mudaliyar in the management of VALI AZHAL KEEL VAYU [*Noi Nadal Noi Muthal Nadal Thirattu*-II (Pg No .623)].

1.2 AIM AND OBJECTIVE

AIM:

To document the clinical therapeutic efficacy of *NANNARI VER OORAL KUDINEER* [Internal] in the treatment of VALI AZHAL KEEL VAYU.

OBJECTIVE

Primary Objective

To evaluate the clinical therapeutic efficacy of *NANNARI VER OORAL KUDINEER* [Internal] in the treatment of VALI AZHAL KEEL VAYU (RHEUMATOID ARTHRITIS)

Secondary objective

1. To adjudge the Bio-chemical, Phyto chemical, Anti microbial analysis of the trial drug..
2. To evaluate pharmacological parameters such as Analgesic, Anti-inflammatory and Immunomodulatory actions.
3. To evaluate acute and sub-acute toxicity activities of the trial medicine.
4. To evaluate additional effects and siddha parameters [*Envagai Thervugal*] changes in Vali Azhal Keel Vayu.
5. To explore the apt definition, aetiology, clinical features, pathology, diagnosis, complication and treatment for Vali Azhal Keel Vayu in Siddha literatures and correlation with modern science.
6. To survey the incidence of the diseases according to age, occupation, socio economic status, habits, family history, *paruva kaalangal*, thinai and three vital humours.
7. To divulge how the *mukkutram* and seven *udal kattugal* are deranged in this disease.
8. To have a detailed clinical investigations.
9. To use modern parameters to confirm the diagnosis and prognosis of the disease.
10. To rule out any adverse effect of the drug.

1.3 JUSTIFICATION OF RESEARCH:

Over the past two decades, the treatment of RA has been revolutionized by advances in the understanding of its pathologic mechanism and the development of drugs which target them.These newer medications have shown great promise at improving disease outcomes but they come up with notable side effects which can pose long term treatment, difficulties in the perioperative arena and also with significant financial cost, of which medication has been a major contributor.As a disease that affects primarily women, RA has a major impact on family life and child rearing. So consideration for strategies to improve diagnosis, treatment and implement more cost effective care was taken before and during the trial.Therefore, current therapy of "NANNARI VER OORAL KUDINEER" for RA served the role which reduced the impact of diseases in a way by extending the benefits beyond the patient himself/herself.

CHAPTER II

LITERATURE REVIEW

2.1 FROM SCIENTIFIC JOURNAL:

TAXONOMY:

Kingdom : Plantae
Division : Magnoliophytina
Sub-division : Magnoliophytina
Class : Magnoliopsida
Sub-class : Magnoliodae
Order : Gentianales
Sub-order : Gentianineae
Family : Asclepiadiaceae
Genus : Hemidesmus
Species : Hemidesmus indicus

Macroscopic features of Nannari :

The roots are dark brown in color with 30 centimeter length and 3-8 millimeter in diameter on average. Usually,it is thick cylindrical, hard, sparsely branched and are provided with few thick rootlets along with secondary roots. Cortical layer is present in the wood. Bark is light brownish and showed the transverse crack & longitudinal fissure and highly aromatic in nature.(Bonvicini et al. 2018).

Microscopic features of Nannari :

Transverse section of roots shows periderm consisting three layers of tissues, secondary cortex cork and cork cambium.

- Cork cells are rectangular, filled with dark brown contents and radially flattened.
- Cork cambium is 2 or 3 layered is filled with deep brown contents which are compressed.
- Secondary cortex contains little 3-4 layers of cells.
- Secondary phloem ray cells along with several scattered laticiferous ducts and sieve elements are also present.

- ❖ Parenchyma cells contain prismatic crystals of calcium oxalate which are filled with starch grain.
- ❖ Cambium is extremely narrow.
- ❖ Xylem is tranverse with narrow medullary rays.
- ❖ Patted marks are seen in vessels and trachieds with absence of piths in central area which is occupied by woody tissues (Parthipan et al. 2011).

Chemical constituents :

Roots of H.indicus are reported to contain chemical constituents like

- ➢ Pregnane glycoside viz.Hemindicusin
- ➢ Coumarinolignoids viz.Hemidesmin-1 and H-hemidesmin-2 .
- ➢ Others – β-amyrin acetate ,α-amyrin, β-amyrin, lupeol acetate,β-sitosterol, hexadecanoic acid, hexatriacontane, lupeol octasonate.

Essential oil founds to contain the following constituents:

- ➢ 80% of crystalline matter.
- ➢ Glucose
- ➢ Hemidesmol.
- ➢ Hemidesterol.
- ➢ 2-hydroxy 4-methoxy benzaldehyde.
- ➢ Others - resin acid, glucoside, α-amyrin triterpene, β-amyrin triterpene, and benzaldehyde.(Sethi A et al, 2006 &Austin A 2008)

Pharmacological screening:

Hemidesmus indicus is a widely used shrub in Indian traditional medicines. For wide range of medicinal properties of the H.indicus, considerable efforts have been made to verify its efficacy as a curative agent through pharmacological investigations. Different experiments in vitro and vivo models convincingly demonstrated the ability of H.indicus exhibiting various actions due to its remarkable biological activity and bioactive constituents are as follows(Sneha Dandekar et al.(2018), Lalrinpuia et al.(2017)

- Analgesic
- Anti-arthritic
- Anti-inflammatory
- Antipyretic
- Antioxidant
- Hepatoproductive
- Immunomodulatory
- Diuretic
- Anti-carcinogenic activities
- Anti-hyperlipidaemic
- Anti-ulcer
- Anti-leprotic
- Antimicrobial
- Anti-diabetic

Analgesic activity:

Farook SM et al.(2011), study showed the hydro-alcoholic extract of H,indicus at different doses (100,200 and 300 mg/kg,p.o) in swiss albino mice significantly inhibitis writhing response,decrease the licking response in acetic acid induced writhing response and Eddy's hot plate method.A maximal effect was observed at 300mg/kg which was comparable to 10 mg of piroxicam per kg body weight [b.w] . **Gupta et al.(2011**)studies of the aqueous extract of above preparation found to possess analgesic property with very low ulcerogenicity and toxicity in animal model. **Magaji MG et al. (2008)** evaluated the hydro –alcoholic extract of 100,200 and mg/kg b.w in adult wister rats showed significantly reduces the licking response in Eddy's hot plate method [55-56ºc]. The analgesic effect of the extract may therefore be due to either its action on the inhibition of the production of algogenic substance or the inhibition at the central level of the transmission of painful message. **Verma PR et al.(2005),** studied Oral administration of ethanolic extract [25,50,100 mg/kg],prior to pain induction ,produced dose-dependent antinociceptive effects and blocked neurogenic eand inflammatory pain in the acetic acid (writhing),formalin (paw licking) and hot plate tests in mice.

Anti arthritic activity:

Mehta A et al.(2012), found that H.indicus root has protective activity against arthritis and the activity is might be attributed by presence of terpens,sterols and phenolic compounds in hydroalcoholic root extract as well as in ethyl acetate fraction.The protective effects of hydroalcholic (450mg/kg BW,p.o),ethyl acetate (75mg/kg,BW,p.o),Chloroform (60 mg/kg BW,p.o) extact and residual fraction (270mg/kg BW,p.o)from roots of *H*.indicus on arthritis in vitro model in rats were studied.There was significant decrease in physical and biochemical parameters

supported by good tissue architecture in histopathological analysis. The hydroalcoholic extract and ethyl acetate fraction protective effects were coparable with methotrexates which were used as positive control.

Anti-inflammatory activity:

A.Guerrini et al.(2014) Anantamul has demonstrated anti-inflammatory activity in laboratory studies mediated by the inhibition of the transcription factor,NF-kB ,reduction of pro-inflammatory IL-8 exprssion. **Shaikh (2011)** determined ethanolic extracts (100,200 mg/kg) exhibited dose dependent inhibition in various subchronic and chronic models of inflammation,and delayed type hypersensitivity using egg white iysozyme as an antigen. **Vijayalakshmi K et al.(2010)** Study observed a hydro-alcoholic extract of anantamul at a dose level of 100mg/kg/b.w demonstrated good anti-inflammatory activity than indomethacin (a non-steriodal anti-inflammatory drug) in a carrageenan –induced hind paw rodent model. **Lakshman K et al.(2006)** observed in carragenan induced paw odema method that methanolic roots extract also exhibited significant reduction in volume between 2-4 hr after treatment. **Periyanayagam K et al.(2004)** aqueous extract of H.indicus showed significant anti-inflammatory activity when compared to diclofenac sodium gel. **Jain and Basal et al. (2003),** reported that polymorphonuclear leukocytes (PMNL) and monocytes treated with Propionnibacterium acnes in the presence or absence of H. indicus (5-50 µg/ml) showed a significant suppression of ROS and pro- inflammatory cytokines ,two inflammatory mediators in acne pathogenesis. **Joseph P et al.(1918),** studied a saponin from the H.indicus and found to have anti inflammatory activity against formalin induced edema. **Dutta MK et al.(1982),** revealed that ethyl acetate extract of H. indicus root shows much anti-inflammatory effect in acute and subacute inflammation .Oral administration of H.indicus root extract blocked both neurogenic and inflammatory pains.

Anti –pyretic activity:

Farook MG (2011) , study showed the anti-pyretic [brewer's yeast induced pyrexia] effect in Wister albino rats (measured as % reduction in body temperature) was compared with paracetomol [100 mg/kg orally] .Hydro –alcoholic extract of Hemidesmus indicus at the dose of 300 mg/kg caused significant decrease in body temperature of rats. **Lakshman et al.(2006)** determined the standard drug

paracetamol 100 mg/kg b.w and H.indicus extract at a dose of 100,200 and 400 mg/kg BW reduced the yeast elevated rectal temperature compared to control group. **Gupta M et al.(2010),**observed that aqueous extract of root showed anti-pyretic –analgesic property with very low ulcerogenicity and toxicity in animal model.

Antioxitant activity:

Zarei M and Javarappa K.M et al. [2012] ,determined H.indicus root extract for its antioxidant properties & found out significant reduction in the oxidative stress and thereby toxicity induced by doxorubicin. **Santheesh Kumar D et al.(2013),** paper revealed the aqueous extracts of whole plant of H.indicus showed significant free radical scavenging activity which indicates that the plants extracts has antioxidants. **Kumar G et al.(2008)** ,observed that administration of H. indicus extract 500 mg/kg /day for 30 days of experiment significantly reduced the level of serum –urea,uric acid, creatinine and kidney –thiobarbituric acid reacting substances [TBARS],lipid peroxidase and conjugated dienes. **Nadana S et al.(2007),** studied and postulated that in rats with ethanol induced nephrotoxicity, ethanolic extract of H. indicus showed potent antioxidant effect and provided protection against free radical mediated oxidative stress in kidney.

Hepatoprotective activity:

Ashaa S et al.(2011), Observed Methanolic root extract of H.indicus (500 mg/kg ,p.o) showed a remarkable hepatoprotuctive activity against paracetamol induced hepatotoxicity. **Mookan P et al.(2000),** observed that Ethanolic extract of H.indicus roots showed protective effect against Rifampicin and Isoniazid [INH] induced liver toxicity. **Prabakaran M et al.(2000),** reported that Oral administration of 50% ethanolic extract of H.indicus significantly prevented rifampicin and isoniazid induced hepatotoxicity in male wister rat.

Immunomodulatory effects :

Kainthla RP et al.(2006), reported that H.indicus extract (1 mg/ml) stimulated the proliferation and viability of peripheral blood lymphocytes (PBLs) ,increased IgG production and adenosine deaminase activity ,and suppressed both cell-mediated and humoral components of the immune system.

Diuretic activity:

Kotnis M.S et al.(2004), reported that aqueous extract of H. indicus root extract to diabetic rats,reduced level of glycogen content in muscle tissues was significantly improved. **Gadge and Jalapure (2011),** reported that the aqueous extract (400 mg/kg), which caused a marked increase in urinary Na+ and k+ levels over 5 hr,was comparable to that of frusimide and hydrochlothiazide.

Anti –cancerous activity:

Zarei M and Javarappa KM (2012) observed it significantly enhanced antitumor activity of three commonly used chemotherapeutic drugs –methotrexate ,6-thioguanine,cytarabine. **Hiremath SP et al since (1997)**, study showed the roots decoction of H.indicus showed cytotoxic on HepG2 cells.**Pasumarthi S et al.(2011)**, The roots methanolic extractsshowed inhibition on colon adenocarcinoma cell line with IC 50 60 µg /ml by MTT assay and this may be due to the presence of saponins ,tannins steroids.**Zarei M and Javarappa K.M [2012]**, reported that H.indicus have remarkable anticancer potentials against MCF7 Breast cancer cell lines.H. indicus methanolic root extract showed a significant cytotoxic activity against Ehrlich Ascities Tumor too. **Sultana S et al.(2003)** studied extract inhibited tumor growth in mouse skin and hence can be considered as a potent chemopreventive agent.

Anti hyperlipidaemic activity:

Bopanna KN et al.(1997) ,evaluated Cell culture extracts of H.indicus [CCH] administered at a dose of 16 mg/kg showed decreased low density lipoproteins [LDL] and very low dencity lipoproteins [VLDL] ,Cholesterol and significantly increased high density lipoproteins [HDL] :cholesterol ratio. **Saravanan and nalini (2007),** HMBA (200 µg/kg) showed antihyperlipidaemic activity in ethanol (5 g/kg p.o) induced antihyperlipidaemia significantly decreasing plasma and hepatic lipids ,and increasing plama Low –density lipoprotein (LPL) concentrations.

Anti- ulcer activity:

Austin A et al.(2008), studied established the anti ulcer activity of H. indicus. It acts by mucoprotective action and selectively inhibiting prostaglandins .Even standard drugs,like- omeperazole, rantidine have less mucoproductive activity than H.indicus have.**Vishali et al.(2011**), the ethonal extract (200,400 mg/kg) showed

ulcer production comparable to that of omeprazole in the indimethacin (20 mg/kg) induced ulcer in rat ,possibly due to cytoproductive action or strengthening of vgstric mucosa. **Nadana S et al (2007),**observed Aqueous ethanolic extracts decreased formation of gastric and duodenal ulcers by various ulcerogenic procedure and cytodestructing agent.

Anti leprotic activity:

Gupta PN et al.(1981), paper revealed that aqueous extract of H.indicus root orally administered at 2% concentration in mice infected with Mycobacterium leprae showed delayed in cutaneous hypersensitivity stimulation.

Antimicrobial activity:

Pandey KK and Dwivedi M et al.(2001),determined that the drug was found to be safe and effective against E.coli ,Bacillus sp ,proteus sp,Klebsiella sp and Pseudomonas sp. **Hiremath SP et al.(1997)**, study showed that chloroform and 95% ethanolic extracts of roots of H. indicus posses antifungal activity against Aspergillius niger. **Das and Devaraj (2006)**, was evaluated the chloroform and methanol extracts (500-1000 µg/ml) were effect against S.flexineri and other enterobacterial strains,except for Shigella dysenteriae.

Anti diabetic activity:

Subramaniyan et al.(2012), study have reported antihyperglycemic, antioxidant and anti dyslipidemic properties of H,indicus root extract in Alloxan – induced experimental diabetic in rats.The dry powdered roots were extracted with petroleum,ether,then soxhletted with ethanol. The level of lipid peroxides in the plasma and pancreatic tissues of diabetic rats were elevated significantly and were normalized by the administration of the extract. **Banerjee and Ganguly et al.(2014)** , paper revealed upon treatment with H.indicus root extract to diabetic rats ,reduced level of glycogen content in muscle tissues was significantly improved. Treatment with H. indicus root extract showed a significant decrease in the glycosylated hemoglobin level, which could be due do improvement in glycemic control. **Mahalingam and Kannabiran (2009)**, studied the crude aqueous extract (500 mg/kg),and HMBA (500µg/kg),produced hypoglycemic and hypocholesterolemic effects in steptozotocin-induced diabetic rats.

2.2 SIDDHA LITERATURE:

As per the below verse, a physician can plan the line of treatment accurately and will be able to provide maximum benefit to the patient

"கூர்பாரு தாதனிலக் கணமும் பாரு
கோள்பாரு நாள்பாரு குணமும் பாரு
நேர்பாரு தேசபே தங்கள் பாரு
நிலைபாரு கிரகவுச்ச நீசம் பாரு
பேர்பாரு இவனைநீ பிறகு பாரு
பேரதிலே கீர்த்தியின் றன்மை பாரு
வேர்பாரு தழைபாரு மிஞ்சினக்கால்
மெல்லமெல்ல பற்பசெந் தூரம் பாரே"

- சித்த மருத்துவாங்கச் சுருக்கம் (473)
- க.சு.உத்தமராயன்

It is clearly evident that physician should preferrably start with herbal medications initially using underground part like root,then by aerial parts like leaves/flowers/fruits etc.If these medications does not yield any result, it is advised to use higher order medicines like parpam or chendooram.

The underground part like root absorbs the various nutrients and minerals from the land it grows. So collection of roots in correct time is required to maintain the quality of roots. Such roots with active phyto-chemicals after processing into finished drugs found to be more beneficial in the management of Vali azhal keel vayu.

2.3 GUNAPADAM ASPECT OF NANNARI:

Botanical name	**:**	***Hemidesmus indicus***
Tamil	**:**	***Nannari,Ankari mooli, Chariyam,Krishnavalli, Paathala mulli***
English	**:**	Indian sarsaparilla
Hindi	**:**	Salsa
Telugu	**:**	Suganthi
Bengali	**:**	Anantmul
Sanskirit	**:**	Dhawala Shariva, Gopavalli
Part used	**:**	Root

Properties of nannari

- *Suvai : Inippu*
- *Thanmai : Tatpam*
- *Pirivu : Inippu*

Action :

- Alternative
- Tonic
- Demulcent
- Diuretic,
- Diaphoretic

Ingredients and Medicinal uses of Nannari Ver Ooral Kudineer:

(***Gunapadam Mooligai vaguppu Muthal pagam*** pg no.562 ,

(***Pathartha gunapadam*** pg no.210)

TAMIL NAME	**PHARMACOLOGICAL ACTIONS**	**THERAPEUTIC USES IN SIDDHA**
Nannari	• Analgesic, • Anti-inflammatory • Immunomodulatory • Anti pyretic • Anti oxitent • Anti ulcer • Anti canceros • Diuretics	• Chronic rheumatism • Fever • Edema • Loss of appetite, • Diseases of the vatham and pitham • Syphilis • Skin diseases • Leucorrhoea • Diabetes, • Indigestion

2.4 SIDDHA ASPECT - VALI AZHAL KEEL VAYU:

According to the siddha system, the individual is a microcosm of the universe.The human body consists of the five primordial elements & the three humours. In state of imbalance, they vitiate the structural and functional elements known as Udal Thathus. The equilibrium of humours is considered as health and its disturbance or imbalance leads to a diseased state.

Reflecting this theory of cosmic oneness, the five senses are said to correspond with the five elements.

- Ether [*veli*] is responsible for hearing
- Air [*katru*] for sense of touch
- Fire [*thee*] for sight
- Water [*neer*] for taste
- Earth [*mann*] for the sense of smell.

VATHAM:

Vatham is the primal constituent of the living body whose structure is Vayu+Agayam. Among the three humours, vatham is called as king of all sort of ailments . Vayu plays a relavant role in the function of joints. Features of increased vatham in the body are as follows.

"வாதம் வந்துற்ற போது வயறது பொருமி கொள்ளும்
தாதவிழ்ந்திடுப்பு கைகால் சந்துகள் கடுப்புத் தோன்றும்
சீதொரு மலமும் நீருந் சிறுத்துடன் கடுத்து விழு
மாதவமரை மேல் வந்த வாதத்தின் குணமிதாமே"
- யூகி முனிவர் பெருநூல் வைத்திய காவியம் (1000)

- Abdominal discomfort
- Pain in the hip joint and in the joints of upper and lower limbs
- Decreased quantity and painful voiding of urine
- Constipation

The Vatha dosha quoted in various Siddha Literature are as follows

According to Agasthiyar,

"காணப்பா வாதமீறில் கால்கைகள் பொருத்து நோவும்
பூணப்பா குடல் புரட்டும் மலசலம் பொருமிக்கட்டும்"

அகத்தியர் வைத்திய காவியம் 150
(பாடல் எண்.10, பக்கம் எண்.2)

According to Thirumoolar,

‘எறிய நல்வாதம் எறிக்கும் குணங்கேளு
குறியெனக் கைகால் குளைச்சு விலாச் சந்து
புறியென நொந்துடல் பச்சைப்புண் ஆகுமே”

திருமூலர் கருக்கிடை வைத்தியம்-600
(பாடல் எண்.36,பக்கம் எண்.11)

CHARACTERS OF VATHAM:

- ❖ Hardness
- ❖ Dryness
- ❖ Lightness
- ❖ Coldness
- ❖ Mobility
- ❖ Subtleness

OPPOSITE QUALITIES OF VATHAM:

- ❖ Softness
- ❖ Unctuousness
- ❖ Heaviness
- ❖ Hotness
- ❖ Stability
- ❖ Solid

DWELLING PLACES OF VATHAM:

“உண்டி சமைத்துடற் கூட்டுங் குடற்பகுதி
திண்டிலென்பு செவிகுறங்கு விண்ட
தொடுணர்வு தோற்றுவிக்கும் தோலிருப் பிவ்வாறும்
வடுவிலிடமாம் வளிக்கு”

“அறிந்திடும் வாதம் அடங்கு மலத்தினில்”

“நாமென்ற வாதத்திற்கு கிருப்படமே கேளாய்
நாபிக்குக் கீழென்று நவில லாகும்”

(நோய் நாடல் நோய் முதல் நாடல் முதல் பாகம்)

Abanan	Idaikalai
Undhiyin Keezh moolam	Bones
Ear	Thigh
Skin	Hip region
Muscle	Nerve
Joints	Hair follicles

FUNCTIONS:

"ஒழுங்குடன் தாது ஏழ் மூச்சோங்கி இயங்க
எழுச்சிபெற எப்பணியுமாற்ற – எழுந்திரிய
வேகம் புலன்களுக்கு மேவச் சுறுசுறுப்பு
வாகளிக்கும் மாந்தர்க்கு வாயு"

மருத்துவத்தனிப் பாடல்

- Giving briskness
- Respiration
- Maintenance of body and mind in a balanced state
- Regulation of reflexes[14 urges]
- Enhancement of functioning of seven Udal Thathukal
- Protection and strengthening of sense organs

DISTURBANCE IN VATHAM:

- Body ache
- Pricking pain
- Nerve weakness
- Shivering
- Numbness in feet
- Joint pain
- Cramps in calf muscles
- Increased thirst
- Weakness of organs
- Breaking pain in the joints
- Pain in the leg and thigh
- Unable to do flexion & extension of the limbs
- Pilo-erection
- Dryness
- Polydypsia
- Excess salivation
- Anuria and constipation
- Astringent taste perception in all food
- Darkness of skin, eyes and urine

RELATIONS WITH FIVE ELEMENTS:

Vatham – Air + Sky

Pitham – Fire

Kabham - Water + Earth

Vatham has ''Air'' and ''Sky'' as its elemental constituents. If ''Air'' and "Sky'' or any one of them is decreased [or] increased from the normal level, it will surely lead to pathological state of vatham.Regarding diet, bitter,pungent and astringent taste contain air and bitter alone contains sky. So if these are consumed in large amounts ,they result in the vitiation and eventually vatha diseases.

VATHAM & SUVAIGAL:

Siddha system explains about six types of tastes, which are formed by the combination of two boothams. They are sweet, salt, sour, bitter, pungent and astringent. some tastes will aggrevate vatham and some tastes will neutralize vatham. Futher if the thodam (thodam) is increased, it will cause an alteration of taste in tongue, which is appreciable by the patient. So suvaigal holds a separate place in diagnosing.

"மாத்திய புளிப்பு மீறில் வந்திடும் வாதமாகும்"

- அகத்திய நாடி

"வாதமே புளிப்பு வேண்டும் வன்பித்தம் கசப்பு வேண்டும்"

-இரத்ன சுருக்க நாடி

"புளிதுவர் விஞ்சுங்கறி யாற்பூரிக் கும்வாதம்"

The above versions denotes that sour, astringent and pungent tastes hold its part in raising vatham

"வாதம் மேலிட்டால் மதுரம் புளி உப்பு"

- கண்ணுசாமியம்

Exaggerated vatham can be neutralized by tastes like sweet ,sour and salt. The basic concept behind this is,among the panchabootham, Vin and Vayu forms vatham. So tastes formed by other boothams are advisable to neutralize it. It is noted that, in the formation of sweet tastes vayu and vin doesn't takes part.

KEEL VAYU

சித்த மருத்துவத்தில் எண்பது வகை வளி நோய்கள் பற்றிக் கூறப்பட்டுள்ளது. வளி அழல் கீல் வாயு என்பது, கீல் வாயு என்ற தலைப்பின் கீழ்க் கூறப்பட்ட பத்து வகைகளுள் ஒன்று. கீல்வாயு என்பது மூட்டு மற்றும் அதனைச் சுற்றியுள்ள பகுதிகளில் ஏற்படும் நோய்க ளைக் குறிப்பதாகும்.

According to Agasthiar in Agasthiyar Gunavagadam,

தானாக கீல்வாத ரோகம் பேரை
.....நோய் தனக்கு பாகியாய் வாதரோக மென்பார்
நுட்பமுள்ள வாதரோக மெண்பதுந் தான்
ஆய்ந்தெடுத்து இதற்குள்ளே அடக்கம் பாரு.....

- அகத்தியர் குணவாகடம்

From this we understood Keel Vayu is one the *Vatha* Disease.

வேறு பெயர்கள்:(Synonyms)

Santhuvali, Muttuvali, Megasoolai, Mudakku vayu, Santhu vatham, Soolai kattu, Vayu rogam, Santheega silaeshma rogam , Aamavatham .

‘தானான கீல்வாத ரோக பேரை
சாற்றுகிறேன் நீயறிய விபரமாக
மானான வாய்வுரோகம் வாத ரோகம்
மகத்தான முடக்குவாயு முடக்கு வாதம்
தேனான சந்தீக சிலேட்டும ரோகம்
தெளிவான கைகாலில் பிடிப்பு ரோகம்
ஊனான ரசவாதம் சூலைக்கட்டு
உத்தமனே சந்திவாதம் வாதசூலை யாமே
ஆமென்ற இத்தனையும் அதற்குப் பேராம்”

- அகத்தியர் குணவாகடம்

Thus the terms of the diseases are named according to the Cause, Tridhosa principle ,kurigunam, site of lesion, complication etc.

Cause	:	*Mega Soolai*
Tridhosa principle	:	*Vatha soolai,Santheega silaeshma rogam*
Kurigunam	:	*Soolai kattu*
Site of lesion	:	*Muttu vali ,Santhu vali ,Aama vatham, Santhu vatham*
Complication	:	*Mutakku vatham*

Description of the nomenclature:

Vali Azhal Keel Vayu	**=**	***Vali+ Azhal+ Keel+ Vayu***
Vali	**=**	***Vatham***
Azhal	**=**	***Pitham***
Keel	**=**	**Joint**
Vayu	**=**	***Vatham***

Initially the joints are affected by the vitiated ***Vatham***. Then, other two Humours will be affected. Mostly it is affected in ***Pitha Kaalangal*** (Middle 1/3 of the life span).

DEFINITION:(இயல்)

‘வளியு மையுந் தன்னிலை கெட்டு
வலியுடன் வீக்கச் சுரமும் காய்ந்து
மூட்டுக டோறும் முடுக்கியே நொந்து
மூட்டுக டன்னின் நீரும் சுரந்து
தாங்கொணா வலியுடன் நொந்திடு மம்மே”

- ***சபாபதி கையேடு***

Keel vayu is a vatha diseases characterized by pain and swealing of the joint stiffness of the muscles and joints with tenderness frequently associated with fever,anorexia,insomnia etc.It may be accompanied by emaciation ,anemia and restriction of joint movements can also occur.

AETIOLOGY: (நோய் வரும் வழி)

According to Siddha system, any modifications (or) disturbances in Uyir thathugal, especially Vatham which plays a major role to produce Keel Vayu. There are various number of factors that can play its role in modification of Vatham. They are:

1. Environmental factors
2. Physical factors
3. Factors of kanmam

1) Environmental factors:

‘ஆடியாதியாய் ஐப்பசி ஈறாய்
ஆனிலமதற் கோரரசியல் காலம்”

சதகநாடி (நோய் நாடல்)
(பாகம்.1, பக்கம் எண்.167,168)

Sathaganaadi describes that the Vatha diseases are predominant in the months of Aadi to Iypasi (July to November).

‘வாத வர்த்தனை காலமேதோ வென்னில்
மருவுகின்ற ஆனி கற்கடகமாகும்
ஆதவைப் பசியோடு கார்த்திகை தன்னில்
அருடமே.....”

- **யூகி வைத்திய சிந்தாமணி-800**
(பாடல் எண்.245, பக்கம் எண்.76)

In Yugi Chinthamani, Yugimuni says that the Vatham provokes in its own site in Aani and Aadi (தன்னிலை வளர்ச்சி). But it provokes and spread beyond its site in the month of Iypasi and Karthigai (வேற்றுநிலை வளர்ச்சி) and reassumes normal in the rest of the months (தன்னிலை அடைதல்).

According to this Poem,

‘பதுமத்தைப் பூக்க வைக்கும் பானுமிக்க காயும்
முதுவேனி லிற்பு விநீர் முற்றும் - கதுமென
வற்றும் கபகும் வாயுமிகும்.....”

- மருத்துவர் தனிப்பாடல்

முதுவேனிற் காலத்தில், சூரிய வெப்பத்தின் காரணமாக பெருவாரியாக நீர் ஆவியாக்கப்பட்டு பூமியில் வறட்சி நிலவும். அதுபோல் நமது உடலில் வறட்சி ஏற்பட்டு வளிநோய் வருவதற்கு ஏதுவாகிறது.

2. Physical factors:

1. According to Sabapathy Manuscript,

‘வளிதரு காய்கிழங்கு வரைவிலா தயிலல் கோழை
முளிதரு போன்மிகுக்கு முறையிலா வண்டி கோடல்
குளிர்தரு வளியிற் தேகங்குனிப்புற வுலவல் பெண்டிர்
களிதரு மயக்கம் பெற்றோர் கடிசெயல் கருவியாமால்”

சபாபதி கையேடு - சித்த மருத்துவம் (பொது)
(பக்கம் எண்.624)

Excessive intake of rhizomes and vegetables that can increase Vatha diseases. Irregular food intake, prolonged exposure to cold air, staying in hilly area, excessive sexual activity and hereditary factors produce Keel Vayu.

2.According to Agasthiyar in Agasthiyar Gunavagadam,

“தானான கீல் வாத ரோகம் பேரை…….
போமே தான்ரச தூஷியத் தினாலே
பொல்லாத இந்த நோய் காணும் பாரு”

- அகத்தியர் குணவாகடம்;

Keel Vayu occurs due to dietary substances which degrade the quality of chyle (அன்னரசம் – chyle).

3.According to Yugi Muni in Yugi Vaithya Chinthamani,

‘பகரவே வாதமது கோபித்தப்போ
பண்பாக பெண்போகம் அதுதான் செய்யில்
நகரவே வெகுதூர வழிநடக்கில்
நளிரான காற்றுமே பனிமேல் பட்டால்
மிகரவே காய்கள் கனிகிழங்கு தன்னை
மிகவருந்தி மீறியே தயிர்தான் கொண்டால்
முகரவே முதுகெலும்பை முறுக்கி நொந்து
முழங்காலும், கணுக்காலும் கடுப்புண்டாமே”

யூகி வைத்திய சிந்தாமணி-800
(பாடல் எண்.215, பக்கம் எண்.89)

Excessive sexual activity (or) desire, walking for a long distance, prolonged exposure to cold, harmful consumption like taking excessive curd after eating fruits, vegetables and tubers produces toxic factors which affects bones and muscles, produce Vatha disease.

4.According to Theraiyar in Theriyar Vagadam text,

‘வெய்யிலில் நடக்கையாலும் மிகத் தண்ணீர் குடிக்கையாலும்
சேய்யிழை மகளிரைச் சேர்ந்தன பவிக்கையாலும்
பையனே உண்மையாலும் பாகற்காய் திண்கையாலும்
தையலே வாதரோகம் சனிக்கு மென்றறிந்து கொள்ள”

தேரையர் வாகடம்
(பாடல் எண்.16, பக்கம் எண்.5)

Excessive walking in hot Sun, excessive intake of water, excessive sexual activity, intake of bitter guard etc…, may disturb the normal functions of Vatham.

5. According to Pararasa sagaram,

Improper Dietary habits and Sleep pattern causes Vatha disease.

‘தொழில்பெறு கைப்புக் கார்த்தல் துவர்த்தல் விஞ்சுகினுஞ் சோறும்
பழையதாம் வரகு மற்றைப் பைந்திணை யருந்தி னாலும்
எழில்பெறப் பகலு றங்கி இரவினி லறங்கா தாலும்
மழைநிகர் குழலி னாளே வாதங்கோ பிக்குங் காணே”

- பரராச சேகரம்

‘காலங்கண் மாறி யுண்ணுங் காரியத் தாலுந் தண்ணீர்
சாலவே யருந்தி னாலுஞ் சந்தியி லுட்கார்ந்தாலும்
வாலவார் முலைநல் லாளே வாதமுற் பவிக்குங் காயே”

- பரராச சேகரம்

3. Factors of Kanmam (Genetics):

In Siddha system, many diseases are said to be precipitated by Kanmam, which means the deeds good (or) bad committed, by an individual in his / her previous and the present births. According to **Agasthiyar Kanma Kandam-300,** Vatha diseases may also be precipitated by Kanmam.

Vatha Kanma Varalaru says,

‘நூலென்ற வாதம் வந்த வகைதானேது
துண்மையாய்க் கன்மத்தின் வகையைக் கேளு
காலிலே தோன்றியது கடுப்பதேது
கைகாலில் முழக்கியது வீக்கமது
கோலிலே படுகின்ற விருட்சமான
குழந்தை மரந்தனை வெட்டல் மேல்தோல்சீவல்
நூலிலே சீவஜந்து கால் முறித்தல்
நல்லகொம்பு தழைமுறித்தல் நலித்தல் தானே”

அகத்தியர் கன்மகாண்டம்

(பாடல் எண்.56, பக்கம் எண்.23)

Psychological factors such as removing the bark of living trees, injuring the animals, cutting the branches in the living trees and plucking the leaves may produce Vatha disease.

As per Karmic Law:

‘அந்தணர் கற்பு மாதர் அருளிய சாபத்தாலும்
முந்திய வினையாலும் முதிர்கர்ப்ப மேகத்தாலும்
சிந்தையிற் கொடுமையாலும் சிவகுரு நிந்தையாலுந்
தொந்தமாம்வியாதியாலும ் தோன்றிடும் சூலைதானே”

- அகத்தியர்

Soolai may occur by the curse of well characterized people and ladies or due to evil deeds in the previous births or due to megam produced by their parents or due to bad thoughts and curse of Guru.

Prodromal symptoms of Keel Vayu:(முற்குறிகுணங்கள்)

Nasal block, running nose, hoarseness of voice, low grade fever, painful arthralgia are prodromal symptoms of Keel vayu.

Individual derangements in Mukkutram :

- Abanan and Viyanan were affected in Vatham.
- In Pitham, Sathaga Pitham is affected.
- In Kapham, Santhigam is affected.

Classification of Keel vayu:

According to **Sabapathy manuscript** the Keel vayu is classified into 10 types.They are:

1. Vali keel vayu
2. Azhal keel vayu
3. Iya keel vayu
4. Vali azhal keel vayu
5. Vali iya keel vayu
6. Azhal vali keel vayu
7. Azhal iya keel vayu
8. Iya vali keel vayu
9. Iya azhal keel vayu
10. Mukkutra keel vayu

General clinical features of keel vayu:

1. Painful joints
2. Swelling
3. Restricted joint movements
4. Stiffness
5. Fever
6. Loss of appetite
7. Synovial effusion

VALI AZHAL KEEL VAYU:

- Vali Azhal Keel Vayu is one among the ten of keel vayus.
- When the Vatha dosham is in vitiated condition, some untold activity, food stuffs, kanmam provoke the Pitha dosham which is the causative factor of Vali Azhal Keel Vayu.

The normal structure and functions of **Vatham** (வடிவத்தன்மை)

- **Dry (வறட்சி)**
- **Cold (குளிர்ச்சி)**
- **Rough (கடினம்)**
- **Motion (அசைதல்)**
- **Light(லகு)**

The normal structure and functions of **Pitham** (வடிவத்தன்மை) is:

- **Heat (வெப்பம்)**
- **Sharpness (கூர்மை)**
- **Lubrication (நெய்ப்பு)**
- **Relaxation (நெகிழ்ச்சி)**
- **Motion (இயக்கம்)**

வாத மிகு குணம்:

‘அறியவிம் மூன்றின் தன்மை சொன்னார்நந்தி
ஏறிய நல்வாத மெறிக்குங் குணங்கேளு
குறியெனக் கைகால் குளைச்சு விலாச்சந்து...”

- திருமூலர் கருக்கிடை வைத்தியம் 600

‘வாதவீறு அன்னமிறங் காது கடுப்புண்டாம் வண்ணமுண்டாம்
மோதுகட்கு ரோகம் சுரமுண்டா மிருமலுமா முறங்காதென்றும்
ஓதுதரிய வாதமனலாகு நடுக்கமுண்டாம் பொருள் களயர்ந்த
தீதெனவே நரம்பித்து சந்துகள் தோறுங் கடுக்குந் தினமுந்தானே”

தேரையர் வாகடம்

(பாடல் எண்.210, பக்கம் எண்.58)

‘தக்க வாயு கோபித்தால் சந்துளைத்து சூலைநோவா
மிக்க கொட்டாவி விட்டங் கெரியு மலங்கெட்டும்
ஒக்க நரம்பு தான் முடங்கு மலர்ந்து வாய் நீரூறிவரும்
மிக்க குளிரும் நடுக்கமாய் மேனி குன்றி வருங்கானே”

- தேரையர் வாகடம்

(பாடல் எண்.43, பக்கம் எண்.13)

வாதம் மிகும்போது பசியின்மை, உடல் கடுப்பு, சுரம், இருமல், உறக்கமின்மை, உடல் நடுக்கம், நரம்புத் தளர்ச்சி, சந்துகள் தோறும் குடைதல், விலாச்சந்துகள் நோதல், வயிறு பொருமல், குடலிறைச்சல், மலச்சிக்கல், மிகுந்த கொட்டாவி போன்ற குறி குணங்கள் தோன்றும்.

பித்தம் மிகு குணம்:

கண், மலம், சிறுநீர், தோல் இவைகள் மஞ்சள் நிறம் அடைதல், பசி, நீர்வேட்கை மிகுதிப்படல், உடல் முற்றும் எரிச்சல் உண்டாதல், குறைந்த தூக்கம் போன்ற குறி குணங்கள் தோன்றும்.

So, thus Vali Azhal Keel Vayu is the deranged Vatha Pitha dosham which produce stiffness, swelling, restriction of movements in the affected joints.

‘தானான கீல்வாத ரோகம் பேரை

.....

பொல்லாத இந்த நோய் காணும் பாரு

நாமேதான் முழங்கால் பெரியகீல்கள்

நன்மையுடன் அதைச் சுற்றி இருக்கும் சவ்வின்

.....”

- அகத்தியர் குணவாகடம்

According to *Agasthiyar Gunavagadam*, keel vayu affects all joints and their periarticular surface. So, I compared Vali Azhal Keel Vayu, the disease affecting major, minor joints and produce disability.

CLINICAL FEATURES OF VALI AZHAL KEEL VAYU:

According to Sabapathy Manuscript,

‘வாத பித்தக் கீல் வாயுவின்

வருங்குறிச் சாற்றக் கேளாய்

ஏதமார் மந்த மேப்பம்

இரைச்சலும் வயிற்றிற் காணும்

ஓதருங் குத்தல் வீக்கம்

ஓய்தலில் எரிச்ச லுண்டாம்

காதறு முறக்க மின்மை

காய்ச்சலுங் காணுங் கண்டாய்”

- உணவு செரியாமல் புளியேப்பம் (Dyspepsia).
- அடிக்கடி காற்றுப் பரிதல் (Flatulence).
- மலச்சிக்கல் (Chronic constipation).
- உடல் பெருத்தல் (Morbid obesity)
- மணிக்கட்டு, கணுக்கால், விரல்கள் இவற்றில் கீல்கள் சிவந்து எரிச்சலையும்,வலியையுமுண்டாக்கும; (Painful proximal interphalangeal joints,
- distal inter phalangeal joints).
- அக்கீல் கரடு கட்டி நீட்டவும், நன்றாய் மடக்கவும் முடியாமல் நிலைத்து நிற்கவும் செய்யும். தூக்கமின்மை, படுக்கையிற் புரளல், சிறுசுரம் ஆகியவை ஏற்படும; (Stiffness, insomnia, low grade fever).

Review of literature about the disease of joints implies that the clinical features more or less correlates with Vali Azhal Keel Vayu.

i) According to Yugi Muni,

‘வைகிதமாய்க் கணைக்காலு முழங்கால் தானு
மற்கடஞ் சந்துபுற வடியும் வீங்கிச்
செய்கிதமாஞ் சிறுவிரல்கள் மிகவு நொந்து
சிந்தைதடு மாறியே சலிப்புண்டாகும்
பைகிதமாய் பயித்தியத்தில் வாத மிஞ்சிப்
பாரமா யுற்பவித் தழலுண்டாகும்
உய்கிதாம மசனமது தானும் வேண்டா
உதிரவாதச் சுரோணிதத்தி னுணர்ச்சி யாமே”

சித்தமருத்துவம் (பொது) (பக்கம் எண்.609)

Uthira Vatha Surothinam, one of the 80 Vatha disease characterized by swellings especially in ankle, knee and in all major and minor joints. Secondarily it can produce depression, fatigueness, anorexia. This is due to the deranged (or) altered Vatha and Pitha dosham.

ii) According to Theriyar in Theriyar Vagadam,

‘மொழி வாதம் மொழிகடோறுங் கரணைகட்டும்
.....மிசிந்து நோகும்”

தேரையர்வாகடம் மூலமும் உரையும்
(பாடல் எண்.215, பக்கம் எண்.59)

Theriyar, here defines **Mozhi Vatham** the one among 81 Vatham, has a characteristic features of joint pain, erosion and fusion of joints, causing deformity leading to inability to use the joints.

iii). According to Panditharathna Dr. S. Chidambarathanu Pillai, Siddha Medical Literature Research Centre,

‘உடலது வெதும்பி கை கால்கள்
உளைவுடன் கடுத்து நொந்து
கடலலை தான் பிரண்டாப் போலே
கனத்துமே அயர்ந்து காணும்
சடமது விழுந்து தாகம்
சஞ்சலம் தோஷம் உண்டாய்
முடமதாம் கைகால் தன்னை
முடக்கிய வாதமென்றே”

மேலும்,

‘முறிந்த வாதம் வந்தால்
எழுந்ததுமே நடக்க வொட்டாது”

வாதநோய் மருத்துவம் (பக்கம் எண்.164)

‘வாரிநீர் பெருகும் போலே உலர்ந்திடும் மூடடும், காலும்
பாகுற சந்து தோறும் பரந்துடல் சுளித்துக் குத்தும்
காரிகை உதிரமெல்லாம் நயந்துமே வருந்திவாடும்
கூரிய வாதமென்று கொற்றவர் வருத்தார் தாமே...”

- வாதநோய் மருத்துவம்(பக்கம் எண்;.168)

Kooriya Vatham is one among the 80 types of Vatha disease. It is characterized by painful interphalangeal joints and swelling. All the above features described in various texts closely resembles the clinical features of Vali Azhal Keel Vayu (Rheumatoid Arthiritis).

DIAGNOSIS IN SIDDHA:

a) Piniyari Muraigal (Methods of Diagnosis) is based upon three main topics namely,

- Poriyal Aridhal (Physical Examination, Perception)
- Pulanal Aridhal (Palpation)
- Vinnadhal (Interrogation)

1.Poriyal Aridhal (Inspection)

Poriyal Aridhal means examining the “Pori” of the patient by the “Pori” of the physician for proper diagnosis. Pori is considered as the five sensory organs of perception namely.

- Mei (Skin)
- Vai (Tongue)
- Kan (Eye)
- Mooku (Nose)
- Sevi (Ear)

ஞானேந்திரியங்களின் ஆய்வு

புலன்கள்	தொழில்கள்	வளி அழல் கீல் வாயு நோயில் பாதிப்பு
1.செவி	ஒலியை அறிய செய்தல்	இயல்பு
2.மெய்	உடலில் ஊற்றை அறிதல்	மூட்டுக்களில் வலி, வீக்கம்
3.கண்	ஒளியை அறியச் செய்தல்	இயல்பு
4.நாக்கு	சுவையை அறியச் செய்தல்	இயல்பு
5.மூக்கு	வாசனையை நுகரச் செய்தல்	இயல்பு

கன்மேந்திரியங்களின் ஆய்வு

புலன்கள்	தொழில்கள்	வளி அழல் கீல் வாயு நோயில் பாதிப்பு
1.வாய்	பேசச் செய்யும்	இயல்பு
2.கை	இடுதலும், ஏற்றலும் செய்யும்	பாதிப்பு
3.கால்	நடக்கச் செய்யும்	மூட்டுக்களில் வலி, நடக்கச் சிரமம்
4.எருவாய்	மலத்தைக் கழிக்கும்	மலச்சிக்கல்
5.கருவாய்	கரு, சுக்கிலத்தைக் கழிக்கும்	இயல்பு

2. Pulanal Aridhal (Palpation):

The five sense are given below:

- Smell
- Taste
- Vision
- Sensation of touch
- Hearing

By examining the Pulan of the patient the physician can diagnose the disease.

3. Vinnadhal (Interrogation):

Vinnadhal is questioning and gathering information regarding the previous history of disease and clinical features which is much essential for diagnosis.

b) Envagai Thervugal (Eight Diagnostic Tools):

The excellent and unique method in the Siddha system is the Envagai Thervugal. They are,

‘நாடி ஸ்பரிசம் நா நிறம் மொழி வழி

மலம் மூத்திரம் மருத்துவராயுதம்”

நோய் நாடல் நோய் முதல் நாடல்

முதல் பாகம் (பக்கம் எண்.270)

1.Naadi (Pulse):

Among the Envagai Thervugal Naadi is most important. Naadi is felt as Vatham, Pitham and Kapham with the tip of the index, middle and ring fingers respectively over the end of the radius.

Normally Vatham, Pitham and Kapham are held in the ratio of 1:1/2:1/4. Derangement in this will reflect as disease. Naadi Nadai in Keel Vayu is,

‘திருத்தமாம் வாதத் தோடே தீங்கொடு பித்தஞ் சேரில்
பொருத்து கள்தோறும் நொந்து போதவே பிடிக்கும்

நோயின் சாரம் - சித்தமருத்துவம் (பொது)
(பக்கம் எண்.634)

‘காணப்பா வாத மீறில்
கால்கைகள் பொருத்து நோகும்”

காவியநாடி - சித்த மருத்துவம் (பொது)
(பக்கம் எண்.634)

‘சொல்லிய வையத்தோடு பித்தமுங் கூடிற்றானால்
வல்லியம் போலக் குத்தும் மைந்தனே எலும்பு தோறும்”

காவியநாடி - சித்த மருத்துவம் (பொது)
(பக்கம் எண்.634)

‘அறிந்துபார் வாதமே தனித்தானதால்
சரிந்திடவே கால் முடக்கும்”

அகத்தியர் ரத்தினச் சுருக்கம்
(பக்கம் எண்.634)

‘வாதத்தில் சேத்துமமாகில் வலியோடு வீக்கமுண்டாம்”

- அகத்தியர் நாடி

In Vali Azhal Keel Vayu the following Naadi nadai are commonly felt.

- Vatham
- Vatha Pitham
- Pitha Vatham

2. Sparisam (Sensation to touch):

In Vali Azhal Keel Vayu heat is noticed over the affected joints.

3. Naa (Tongue):

In Vali Azhal Keel Vayu no abnormality is seen in Naa.

4. Niram (Color):

In Vali Azhal Keel Vayu some skin colour changes seen in affected area due to inflammatory mechanism.

5. Mozhi (Voice):

In Vali Azhal Keel Vayu no abnormality is seen.

6. Vizhi (Eyes):

In Vali Azhal Keel Vayu Eye pallor is reported in some cases.

7. Malam (Faeces):

In Vali Azhal Keel Vayu Constipation is reported in some cases.

8. Moothiram (Physical appearance of Urine):

In urine, Neer kuri and Nei kuri examinations are done.

Nei kurai :

"அருந்து மாறிரதமும் அவிரோதமதாய்
அ.ஃகல் அலர்தல் அகாலஊண் தவிர்ந்தழற்
குற்றளவருந்தி உறங்கி வைகறை
ஆடிக் கலசத் தாவியே காது பெய்
தொரு முகூர்த்தக் கலைக்குட்படு நீரின்
நிறக்குறி நெய்க்குறி நிருமித்தல் கடனே" - தேரையர்

Prior to the day of urine examination the patient is instructed to take a balanced diet and quantities of food must be proportionate to his / her appetite. The patient should get good sleep. After waking up in the morning, the first urine voided is collected in a clear wide mouthed glass dish or china clay bowl and is subjected to analysis of "Neer kuri'' and "Nei kuri'' within one and a half an hour of its collection. The collected urine specimen is kept in a glass dish or china clay container and observed under direct sunlight without shaking the vessel. Then add one drop of gingelly oil and observe the spreading pattern and conclude as follows:

Character of vatha neer:

'அரவென நீண்டின அ.ஃதே வாதம்'

When the drop of oil lengthens like a snake, it indicates 'Vatha Neer'.

Character of pitha neer :

'ஆழிபோற் பரவின் அ.ஃதே பித்தம்'

When the oil drop spreads like a ring , it indicates 'pitha Neer'

Character of kabha neer :

'முத்தொத்து நிற்கின் மொழிவ தென் கபமே'

When the oil drop remains that of pearl, it indicates 'Kabha Neer'

Character of Thontha neer:

‘அரவிலாழியும் ஆழியில் அரவும்
அரவின்முத்தும் ஆழியில் முத்தும்
தோற்றில் தொந்த தோடங்களாமே’

Thontha neer appears as the combination of above patterns.

When the oil drop gets immersed in urine,it indicates ‘Mukkutra Neer’.

In ‘Vali Azhal Keel Vayu’ ,the Neikuri appears to be thontha neer indicating patterns of aravil aazhi and aazhiyil aravu . Few cases showed patterns that the snake indicating vatha neer.

Thinai : (land and place)

The geographical distribution of land is classified into the five groups. Vatha diseases is predominantly affected in peoples who are living in Mullai & Neidhal places.

- Kurinji - Mountain and its surroundings
- Mullai - Forest and its adjacent areas
- Marutham - Field and its surroundings
- Neithal - Sea and its surroundings
- Paalai - Desert and its surroundings

Paruvakaalam (Seasonal variations):

State of Kuttram		**Kaalam**
Vaatham thannilai adaithal	-	Munpani Kaalam
		Pinpani Kaalam
		Koothir Kaalam
		Elavenil Kaalam
Vatham thannilai valarchi	-	Muthuvenil Kaalam
Vatham vetrunilai valarchi	-	Karakalam

முதுவேனிற் காலத்தில் நமது உடலில் வறட்சி ஏற்பட்டு வளிநோய் வருவதற்கு ஏதுவாகிறது.

ஏழு உடல் தாதுக்களின் ஆய்வு (Seven Udal Thathukal Examinations):

Seven Thathus

Saaram - Strenthens the body and mind

Senner - gives power, knowledge and boldness to the mankind

Oon - It strengthens the body

Kozhuppu - It lubricates the joints

Enbu - It protects all the internal organs and gives the structure the body

Moolai - It is present in the bones

Sukkilam and suronitham - Mean for reproduction (male and female respectively)

Table: Seven Udal Thathukal Examinations

SI. No.	Udal Thathukal	Increased conditions	Decreased condition
1	**Saaram**	Loss of appetite excessive salivation	Tiredness, fatigue, diminished activity of the sense organs.
2	**Senneer**	Boils and tumours in different parts of the body, spleenomegaly, colic pain, increased blood pressure, reddish eyes and skin, jaundice, leprosy,	Tiredness lassitude, anemia.
3	**Oon**	Tumours or extra growth around the neck, face, abdomen, thigh, genitalia etc., with dyspnoea.	Muscle wasting
4	**Kozhuppu**	Tumours or extra growth around the neck, face, abdomen, thigh with dyspnoea and loss of activity	Joint Pain, Emaciation, Spleenomegaly
5	**Enbu**	Extra growth of bone and teeth	Weak bones , teeth , nails and hair.
6	**Moolai**	Heaviness, swollen eyes, swollen phalanges, oliguria and non healing ulcers.	Osteoporotic changes, Blurred vision.
7	**Sukkilam or Suronitham**	Increased sexual activity and symptoms as that of urinary calculi.	Infertility, pain in genitalia.

In Vali Azhal Keel Vayu: Saaram, Seener, Kozhuppu, Enbu, Moolai thathukal are commonly affected.

- **Saaram** : Weakness, pain in all major and minor joints
- **Seneer** : Tiredness, anemia
- **Kozhuppu** : Early morning stiffness occurs in affected joints
- **Enbu** : Joint space narrowing, marginal erosions and deformities
- **Moolai** : Joint effusion and oedema are seen in the joints.

MUKKUTRAM:

Uyir thathukal i.e., Vatham, Pitham and Kapham responsible for normal physiological conditions of the body. Vatham is mainly responsible for proper locomotor functions. Bones and joints are the major site of Vatha.

Vatham:-

Locations : ln abana vayu , faeces , idakalai , spermatic cord , pelvic bone , skin nerves, joints etc.,

Types of vatham

1. **Piranan (uyirkkal)**

This controls knowledge mind and five objects of senses which are helpful for breathing and digestion

2. **Abanan (Keezh Nokkukal)**

This is responsible for all downward movements such as passing of urine stools, sperm menstrual flow etc.,

3. **Samanan (Nadukkal)**

This Aids for proper digestion

4. **Viyanan (Paravukkal)**

Responsible for movements of all parts of the body

5. **Uthanan (Mel Nokukkal)**

Responsible for all upward visceral movenments such as cough, hiccup, vomiting, nausea etc.,

6. **Nagan**

Responsible for opening and closing of the eyes

7. **Koorman**

Responsible for vision and yawning

8.Kirukaran

Responsible for salivation, nasal secretion and appetite

9. Dhevathathan

Responsible for laziness, sleep and anger

10.Dhananjeyan

Produces bloating of body after death and escapes on the third day bursing the cranium

In vali azhal keel vayu abanan, viyanan, samanan, koornan and kirukaran are affected and they produce symptoms as follows

- Affected abanan produces constipation,
- Affected samanan produces loss of appetite and indigestion
- Affected viyanan produces pain and restriction of movements of the affected joints
- Affected koorman produces disturbed sleep
- Affected kirukaran produces loss of appetite

Pitham

Locations of Pitham: In pirana vayu, bladder, molakini, heart, umbilical, region, abdomen, stomach, sweat glands. Eyes, saliva, blood etc.,

Types of pitham

1) **Anilapitham** - It gives appetite and helps digestion
2) **Pirasagapitham** - It gives complexion to the skin
3) **Ranjagapitham** - It gives colour to the blood
4) **Alosagapitham** - It brightens the eye
5) **Sathagapitham** - it controls the whole body

In vali azhal keel vayu, anilapitham, Pirasagapitham, Ranjagapitham, and Sathagapitham maybe affected.

- Affected anilapitham produces loss of appetite
- Affected ranjagapitham produces anemia
- Affected sathagapitham produces disability to carry out regular works
- Affected Pirasagapitham produces pallor of skin

Kabam

Locations: In samana vayu , sperm, head, tongue, vulva etc.,

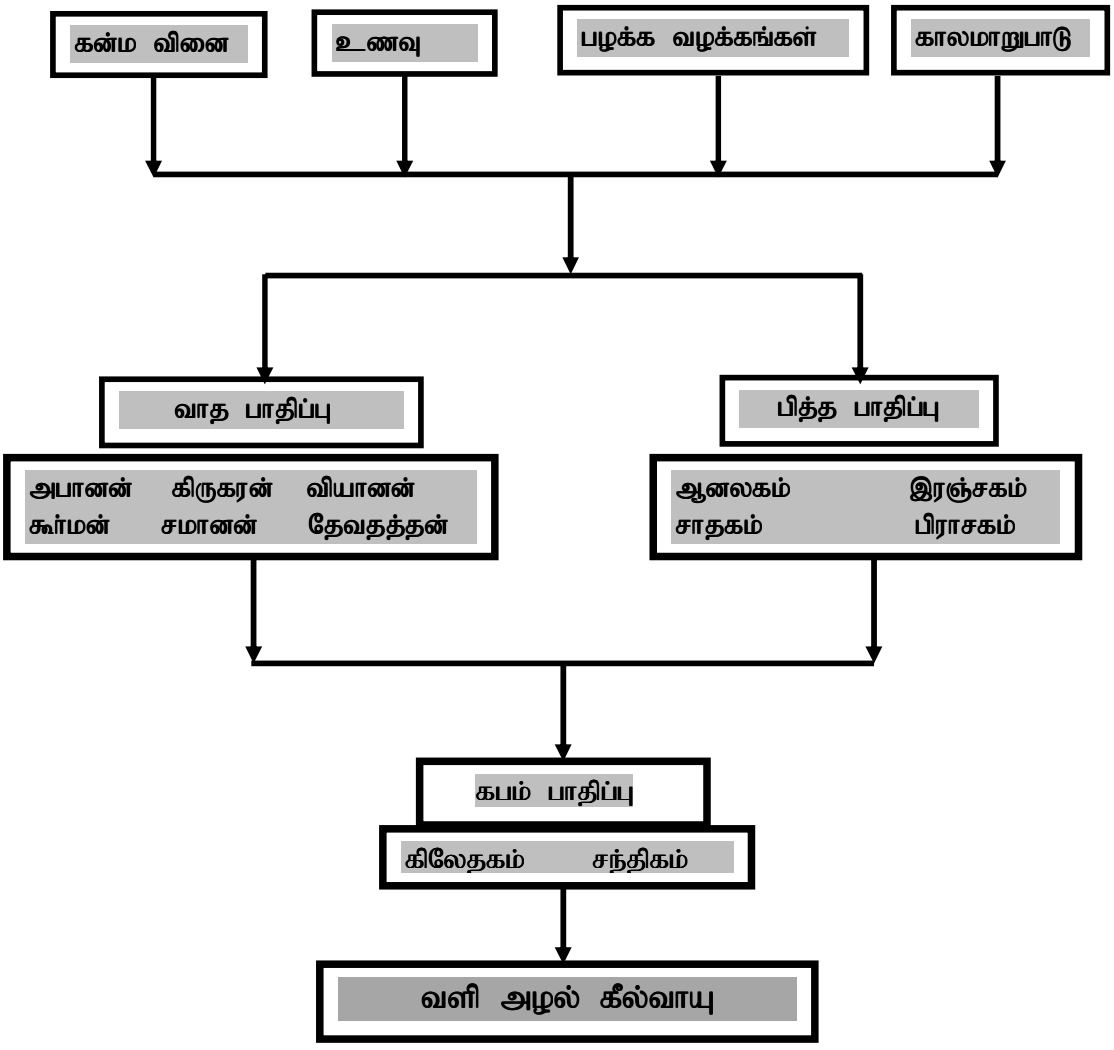
Types of Kabam

1. **Kilethagam** – Lies in stomach, makes food soft and helps in digestion
2. **Avalambagam** – Lies in lungs, controls the heart and other kabas,
3. **Pothagam** – responsible for indentifying tastes
4. **Tharpagam** – present in the head and responsible for the coolness of both eyes
5. **Santhigam** – responsible for the lubrication and free movement of the joints.

In vali azhal keel vayu, kilethagam and santhigam may be affected

- ❖ Affected kilethagam causes loss of appetite
- ❖ Affected santhigam causes pain in the joints

வளி அழல் கீல்வாயு நோயில் முக்குற்ற வேறுபாடுகள்



In Vali Azhal Keel Vayu, the Vatha kutram and Pitha kutram is mainly affected. This produces the following signs and symptoms.

- ❖ Deranged Viyanan leads to painful stimuli and difficulty in movements with early morning stiffness.
- ❖ Deranged Abanan leads to constipation.
- ❖ Inflammatory changes of the joints, heat, redness and swelling are developed due to altered Pitham. Ranjaga Pitham – reduced haemoglobin level. Sathaga Pitham –hindering of the locomotor functions.
- ❖ Along with Vatham, Kapham is also deranged, Santhigam is affected and this leads to abnormality in joint movements.
- ❖ Erosion, loss of joint space, increased secretion of synovial fluid may lead to synovial effusion due to increased Kapham.

S.NO	Name	Location	Physiological function
1	Abanan	Lower abdomen and extremitis	Responsible for urination, defecation, parturition, menstruation and ejaculation of the sperm.
2	Viyanan	Heat	Responsible for movements of all parts of the body and sensation.
3	Samanan	Stomach	Responsible for proper digestion.

NOI KANIPPU VIVATHAM (Differential Diagnosis):

Vali Azhal Keel Vayu is differentiated from the following diseases,

சந்து வாதம்(Santhu Vatham)

"செய்கை தான் சந்துகளு மிகத் திமிர்ந்து
சடமெங்கும் நொத்துமே மிகவ ழற்றி
நைகையாய் நலுத்துமே மயிர்க் கூச்சலிட்டு
நாணியே முன்போல் நடை கொடாது
மைகைதான் மயக்கமொடு வாய் நிருறும்
வரண்டிடுமே நாவுதானடிக்க டிக்குக்
கைகால்தான் தரணிதனிற் றரிக் கொணாது
சஞ்சரிக்குஞ் சந்துவாம் வாதங் கேளே".

Pain in joints, body pain, pilo erection, inability to walk, giddiness, dryness of togue, excessive salivation and unable to keep the limbs in floor are the features of the disease.

அழல் கீல் வாயு (Azhal Keel Vayu):

"பித்தக்கல் வாய்வு தன்னாற் பிறங்குகீன் மூட்டு வீங்கிச்
சித்தர் செய் மருத்து வத்துஞ் சீரபடாத் தன்மைத் தாகித்
தத்தறு காய்ச்சல் கண்டு சாலவே தனைதான் தந்தே
மெத்தறு சிகிச்சை தன்னால் மென்மேல் நீங்கு மப்பா"

- சபாபதி கையேடு சித்த மருத்துவம் (பொது)
(பக்கம் எண்.626)

It is characterized by swelling of joint associated with severe pain and fever. In later stages joints gets fused to one another and result in inability to using joints leading to deformities.

ஐய கீல் வாயு (Iya Keel Vayu):

"கருதருங் கபக்கில் வாயு கண்டிடின் உடலிளைக்கும்
உருமெலிவாக்குங் கொள்ளும் உண்டியைச் சுருக்கு மினபந்
தருதுயில் நீங்கு முட்டிற் றாங்கொணா வலுவையாக்கும்
இருமலே விக்கல் வாந்தி, சோபை பாண்டெழுப்பும் பாரே"

சபாபதி கையேடு சித்த மருத்துவம் (பொது)
(பக்கம் எண்.627)

It is characterized by severe pain in the joints associated with loss of weight, anorexia, insomnia, cough, hiccough, vomiting, anemia and dropsy. The common sites are spinal cord, hip joint and knee joints.

நரித்தலை வாதம் (Narithalai Vatham)

"முர்க்கமாய் முயன்று முழங்கால்தான் விங்கி
முதிர்ந்துரத்த முந்திரண்டு முயற்சி யாகி
நிக்கமாய் தின்றிடவொ ணாமற் றானும்
நிமிர்ந்திடுகில் சந்துந்தான் முடக் கொணாமல்
தீர்க்கமாய்த் துண்டித்து மிக சிக்கென்று
செழுமை நரித் தலை போல மிகவே வீங்கி
நார்க்கமாய் நாடியுமே படபடக்கும்
நரித்திலையின் வாதமென்றே நவில லாமே".

Swelling of the knee joint with hyperemia, difficulty to stand, palpitation will be seen, the swelling looks like the head of the fox are the features of this disease.

வளி ஐயக் கீல் வாயு (Vali Iya Keel Vayu):

"வயங் வாதக் கபக்கீல் வாயுவான் வலி மிகுந்தே
உயங்கு நீர் கோத்து கீல்கள் ஒரியின் தலைபோற் காணும்
நயங்கொள்ள முடக்கல் நீட்டல் நண்ணிடாமெய் யுங்காயும்
மயக்குறு முறக்கமின்னாம் மன்னிய நெரிக்கட் டாமே"

சபாபதி கையேடு சித்த மருத்துவம் (பொது)
(பக்கம் எண்.628)

It is characterized by pain in the joints associated with effusion of joint, swelling, restricted joint movements, pyrexia, fainting, insomnia, asymmetrical presentation lymphadenopathy, generalized malaise, atrophy of the affected limb etc.,

TREATMENT : (*Pini neekkam / parikaram)*

The aim of *pini neekam* is,

- To bring the three doshas in equilibrium
- Treatment of disease and topical application of medicated oils, *ottradam* (Fomentation) thokkanam (Message) etc.
- Diet and prevention of the diseases.

Since siddha system of medicine is based on mukkutra theory ,the treatment is mainly aimed to bring down the increased dosha to its equilibrium state and thereby restoring the physiological condition of various thathus.

"விரேசனத்தால் வாதந் தாழும்"

Vali Azhal Keel Vayu is a vatha diseases. Therefore laxatives or mild purgatives are to be administered on the first day or in the early morning respectively according to patient's tolerance to the drug .

Thokkanam may be advised in case of atrophy or wasting of muscle.

PATHIYAM :

During the course of treating according to the drug administered to the patient and nature of the diseases, the patient is advised to follow certain precautions regarding diet and physical activities. This form of medical advice in siddha system of medicine is termed as ***'pathiyam'***.

Pathiyam for vatha diseases as mentioned in 'Patharthaguna Chinthamani' is as follows

"செங்கழு நீர்கோட்டந் தேன்மிளகு நல்லெண்ணெய்
தங்குபெருங் காயந் தழுதாழை – எங்கெங்கும்
கூட்டுசிறு முத்துநெய் கோதில் உழுந்திவைகள்
வாட்டுமணி லத்தை மதி"

Root of water lily, costus root, honey collected on branches of trees, black pepper, gingelly oil, asafoetida, leaves of clerodendron phlomoides, caster oil black gram etc cure vatha diseases.

நீக்க வேண்டியவை:

புளிப்பு, துவர்ப்புச் சுவையுள்ள உணவுகள்.

In ***Theraiyar venba***, under the heading Itcha pathiyam mentioned to avoid

பாகற்காய், மாங்காய், கத்தரிக்காய், கொத்தவரங்காய், கல்யாணப்பூசணிக்காய், அகத்திக்கீரை, மந்தமுள்ள பதார்த்த வகைகள் and also underground tubers , coconut, mustard and sexual intercourse should be avoided.

2.5. MODERN ASPECT:

RHEUMATOID ARTHRITIS

Definition :

Rheumatoid Arthritis is a chronic inflammatory systemic disease characterized by persistent inflammatory synovitis, usually involing peripheral joints in a symmetric distribution. The potential after effect of the synovial inflammation includes cartilage damage, bone erosions and subsequent changes in joint integrity which are the hallmarks of the disease.

Epidemiology:

In worldwide, the annual incidence of RA is approximately 3 cases per 1000 population and the prevalence rate is approximately 0.8-1.0% increasing with age. It peaks between the age of 35 and 50 years. Women are affected 3 times more often than men but sex differences diminish in older age groups (Pg.No.2083)

Causes and Risk factors:

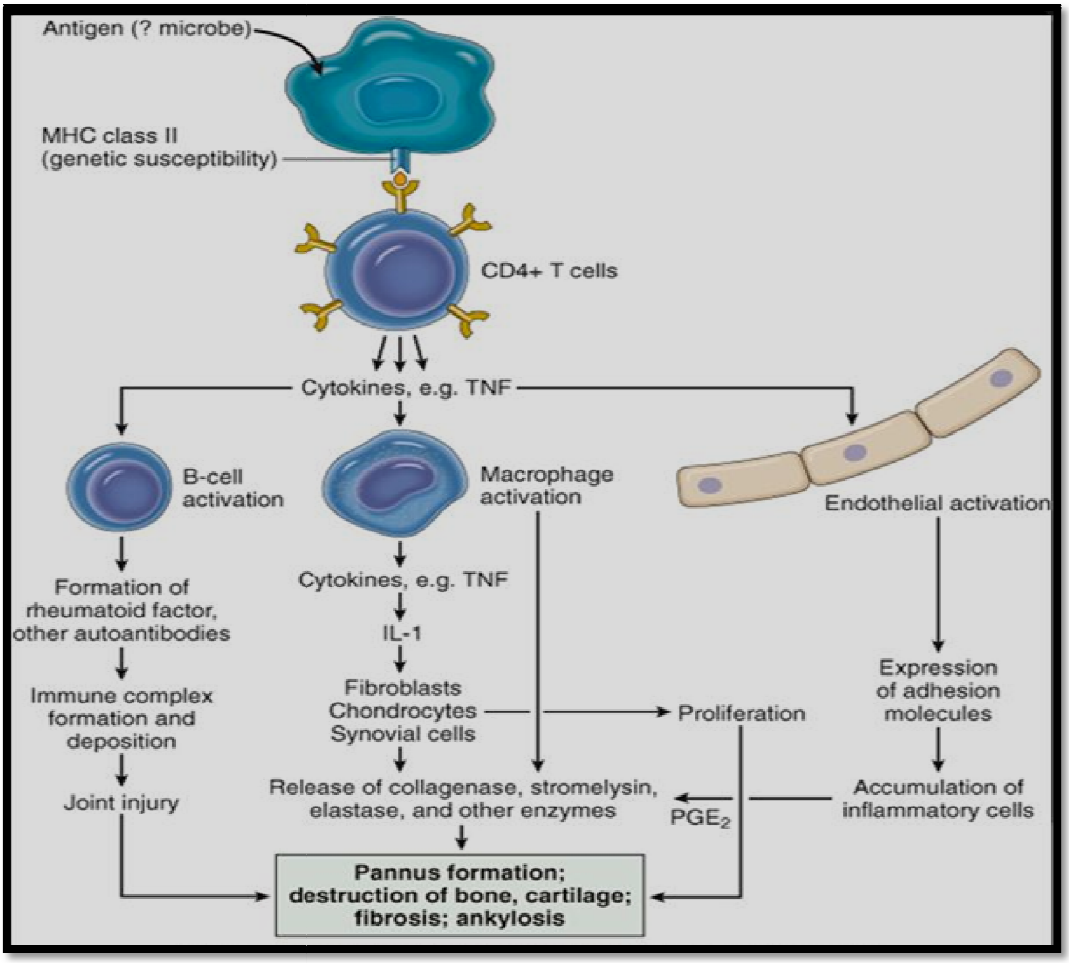
The cause of rheumatoid arthritis is unknown. The risk factors may be:

- Infectious agents.
- Hereditary
- Environmental factors
  - Smoking
  - Tobacco chewing
  - Exposure to Silica Mineral
- Periodontal diseases

The tendency to develop rheumatoid arthritis may be genetically (hereditary) related. Certain genes have been identified that increase the risk for rheumatoid arthritis. It is also revealed that various environmental factors might trigger the activation of the immune system in susceptible individuals. The misdirected immune system acts as self antigens and leads to inflammation in the joints and sometimes in various organs of the body.

In RA, immune cells called lymphocytes gets activated and chemical messengers (cytokines, such as tumor necrosis factor/TNF, interleukin-1/IL-1, and interleukin-6/IL-6) are expressed in the inflammed areas.

PATHOGENESIS: (https://images.app.goo.gl/fcomp9tqcGwVuFw36)



Changes in Synovium :

The synovium is a thin delicate lining that serves as an important source of nutrients for cartilage since cartilage itself is avascular.Synovial cells also synthesize joint lubricants that constitute the structural framework of the synovial interstitium.

1. ***Synovial lining or intimal layer:***

- This layer is only 1-3 cells thick usually.
- In RA, this gets highly hypertrophied (8-10 cells thick) & primary cell populations includes fibroblasts and macrophages.

2. Subintimal area of synovium:

- The synovial blood vessels are located here & this area normally has very few cells.
- In RA, the area is heavily infiltrated with inflammatory cells that differentiate into multinucleated osteoclasts.

- The intense cellular infiltrate is accompanied by new blood vessel growth (angiogenesis).
- The hypertrophied synovium (also called pannus) invades and erodes contiguous cartilage and bone.

Changes in Cartilage:

Composed primarily of type II collagen and proteoglycans, this is normally a very resilient tissue that absorbs considerable impact and stress.

- In RA, cartilage damage appears to be due to action of proteolytic enzymes (collagenase, stromelysin) in synovial lining cells and by chondrocytes themselves.
- Cytokines including IL1, 6 and TNF generates reactive oxygen & nitrogen species , increases chondrocyte catabolic pathways and matrix destruction.It also inhibit new cartilage formation.
- Polymorphonuclear leukocytes in the synovial fluid may also contribute to this degradative process.

Changes in Bone:

Primarily composed of type I collagen.

- Bony destruction is a characteristic of RA occuring by the activation of osteoclasts.
- Osteoclasts differentiate under the influence of cytokines especially the interaction of RANK with its ligand.
- The expression is done by the action of cytokines including TNF and IL1, IL-17 & mediators derived from activated synovial cells.

Changes in Synovial Cavity:

The synovial cavity is a space with 1-2ml of highly viscous fluid with few cells. In RA, large effusions occur which are filtrates of plasma. In synovial fluid the predominant cell is neutrophil.

Disease Initiation:

a) Genetic Susceptibilities:

- Class II MHC on the surface of an antigen presenting cell interacts with a T cell receptor in the context of a specific antigen. The hypervariable region of HLA-DR4 remains the largest genetic risk factor described for RA.It is

estimating that 30% of the genetic risk accounts by HLA-DR4 for this disease.

- A triggering peptide (or peptides) formed by these residues is an early event leading to the activation of T lymphocytes. Modified citrullinated peptides also have significant binding specificity for shared epitope alleles. Citrullinated sequences from different proteins are associated with allelic restriction.
- Other genetic susceptibilities include peptidyl arginine deiminase-4 (PAD-4) which may lead to increased citrullination, PTNP22, STAT4, and CTLA4 which may be involved in T cell activation & TNF receptors.
- In research studies the concordance rates between twins were higher in monozygotic twins ranging from 15-35% compared with dizygotic twins in which the concordance was in the 5% range. Even the dizygotic RA prevalence was higher than the general population estimates of approximately 1%. It is important to emphasize however that even in twins with nearly identical DNA, there was far from perfect correlation of the development of RA, implicating many other factors related to the development of disease than genetic factors.

b) Citrullination:

- Citrullination is a normal process required for normal skin formation and other physiologic functions. The triggering factors of RA results in increase citrullination of Proteins. However, in rheumatoid arthritis an autoimmune response develops against citrullinated peptides detected as anti-citrullinated peptide antibodies (ACPA).
- A polymorphism in the PAD4 gene leads to increased citrullination. In RA patients, autoantibody responses also develop against the PAD4 protein, associated with a more aggressive disease course.
- One species of oral bacteria *Porphyromonas gingivalis* has a PAD enzyme. Given the relationships described with periodontal disease and RA, it has been hypothesized that these bacteria may also serve to initiate citrullination in the preclinical phases of RA.

c) Propagation of Disease:

- **T cell activation**

Upon encounter with antigen in the context of MHC on an antigen presenting cell, a T lymphocyte is positioned for 3 possible fates:

- Activation
- Anergy /Tolerance
- Apoptosis (Death).

T cell activation is only possible if the T cell receives a "second signal" through engaging additional cellular receptors. The second signal is delivered through the CD28 molecule on the surface of the T cell but many other second signals are also involved. Upon engagement of these receptors, a T cell usually becomes activated. Failure to engage the stimulatory receptors, or engagement of a down-regulator receptor will cause the cell to become tolerant to the antigen or to undergo programmed cell death through apoptosis.

Activated T cells will proliferate and begin to secrete additional cytokines which furthers their proliferation depending on exposures to cytokines such as IFN-γ, TNF, and IL-4. Due to effect of the cytokines that additional cells become activated. T cells also directly interact through surface receptors with other cells to generate additional activation signals.

- **B Cell Activation and Autoantibodies**

B cells become activated through interactions with T cells and through cytokines that enhance their proliferation and differentiation. B cells express a number of receptors on their surfaces during their differentiation, including the molecule CD20. B cells and plasma cells can be found in rheumatoid synovium sometimes as lymphoid aggregates in the subsynovium.

The B cells plays roles in forming plasma cells including cytokine production, direct cellular interactions and they themselves serve as antigen-presenting cells to T lymphocytes.

Autoantibodies known as rheumatoid factors (RF) and anti-citrullinated peptide antibodies (ACPA) present in RA are directed against native antibodies most classically described as IgM antibodies that recognize the Fc portion of IgG molecules. RF may also be of the IgG or IgA isotypes.

❖ **Effector Cell Activation**

Most of the damage from the disease occurs through effector cells and their products. The synovial lining in RA represents an expansion of fibroblast like cells and macrophages.

Macrophages are one of the principal factor for the effector damage in RA. Macrophages are major producers of pro inflammatory cytokines including TNF, IL-1, IL-6, IL-8, and GM-CSF. These cytokines further stimulate the macrophage, fibroblastsand osteoclasts. Macrophages are also producers of prostaglandins and leukotrienes, nitric oxide, and other pro-inflammatory mediators with local and systemic effects. The synovial fibroblast also secretes cytokines including IL-6, IL-8 and GM-CSF, and other mediators including destructive proteases and collagenases.

Neutrophils are present abundantly in rheumatoid cavity & can be confirmed by examing the synovial fluid. The recruitment of neutrophils to the joint is carried by IL-8, leukotriene B4, and localized complement activation through C5a. Neutrophils in the synovial fluid are in an activated state, releasing oxygen-derived free radicals that depolymerize hyaluronic acid and inactivate endogenous inhibitors of proteases. So it leads to damage of the joint.

Chondrocytes like synovial fibroblasts, are activated by IL1 and TNF to secrete proteolytic enzymes. They may contribute to the dissolution of their own cartilage matrix, thus explaining the progressive narrowing of joint spaces seen radiographically in this disease.

d) Inflammatory Mediators in RA:

e) Cytokines:

One of the most important group of mediators in RA are cytokines. The most prominent of these are **TNF, IL-1, and IL-6**. These cytokines, released in the synovial microenvironment have autocrine, paracrine, and endocrine effects .It accounts for many systemic manifestations of disease. There are many shared functions of TNF, IL-1, and IL-6, and these cytokines in turn upregulate the expression of the others. Among the important effects of these cytokines are:

- Induction of cytokine synthesis
- Upregulation of adhesion molecules
- Activation of osteoclasts

- Induction of other inflammatory mediators including prostaglandins, nitric oxide, matrix metalloproteinases
- Induction of the acute phase response
  (Increased C-reactive protein, increased ESR)
- Systemic features (Fatigue, fever, Cachexia)
- Activation of B cells (IL-6)

Soluble mediators of inflammation that may diffuse in from blood and/or be formed locally within the joint cavity include prostaglandins, leukotrienes, matrix metalloproteinases. Prostaglandins are involved in pain sensitization, localized inflammation and some effects on bone. Leukotrienes play roles in vascular permeability and chemotaxis. Matrix metalloproteinases (MMPs) are potent in their ability to enzymatically degrade the collagen matrix of cartilage. Kinins cause release of prostaglandins from synovial fibroblasts, and are also potent algesic (pain-producing) agents.Complement may be available for interaction with immune complexes to generate additional chemotactic stimuli. The neuropeptide substance P is a potent vasoactive, pro inflammatory peptide that has also been implicated in RA.

SIGNS AND SYMPTOMS:

RA symptoms come and go, depending on the degree of tissue inflammation. When body tissues are inflammed, the disease is active. When tissue inflammation subsides, the disease is inactive (in remission). Remissions can occur spontaneously or with treatment and can last weeks, months, or years. During remissions, symptoms of the disease disappear, and people generally feel well. When the disease becomes active again (relapse), symptoms return. The return of disease activity and symptoms is called a Flare. The course of rheumatoid arthritis varies among affected individuals, and periods of flares and remissions are typical.

When the disease is active, RA symptoms can include

- ❖ Fatigue
- ❖ Insomnia
- ❖ Lack of appetite.
- ❖ Low-grade fever
- ❖ Muscle and joint pain
- ❖ Stiffness

Muscle and joint stiffness are usually most notable in the morning and after periods of inactivity. This is referred to as morning stiffness and post-sedentary stiffness. Arthritis is common during disease flares. Also during flares, joints frequently become warm, red, swollen, painful, and tender. This occurs because the lining tissue of the joint (synovium) becomes inflammed, resulting in the production of excessive joint fluid (synovial fluid). The synovium also thickens with inflammation (synovitis) Rheumatoid arthritis usually inflammes multiple joints and affects both sides of the body. In its most common form, therefore, it is referred to as a symmetric polyarthritis. Early RA symptoms may be subtle. The small joints of both the hands and wrists are often affected. Symptoms in the hands with rheumatoid arthritis include difficulty with simple tasks of daily living, such as turning door knobs and opening jars. The small joints of the feet are also commonly involved, which can lead to painful walking, especially in the morning after arising from bed.

Chronic inflammation can cause damage to body tissues, including cartilage and bone. This leads to a loss of cartilage and erosion and weakness of the bones as well as the muscles, resulting in joint deformity, destruction, and loss of function. Rarely, rheumatoid arthritis can even affect the joint that is responsible for the tightening of our vocal cords to change the tone of our voice, the cricoarytenoid joint. When this joint is inflammed, it can cause hoarseness of the voice. Symptoms in children with rheumatoid arthritis include limping, irritability, crying, and poor appetite.

ARTICULAR MANIFESTATIONS:

HANDS AND WRISTS:

There is a predilection for:

- PIP and MCP joints (especially 2nd and 3rd MCP)
- Ulnar –Styloid Process
- Triquetrum
- As a rule, the DIP joints are spared.

  Late changes include:
- Subchondral cyst formation: Destruction of cartilage presses synovial fluid into the bone

- Subluxation causing: Ulnar deviation of the MCP joints
- Deformities
  - Boutonniere deformity
  - Swan neck Deformity
  - Hitchhiker□s thumb deformity or " Z " deformity
- Carpal instability: Scapholunate dissociation, Ulnar translocation
- Ankylosis

FEET:

Similar to the hands, there is a predilection for the PIP and MTP joints (especially 4th and 5th MTP).

- Involvement of Subtalar joint
- Posterior Calcaneal tubercle erosion
- Hammer toe deformity
- Hallux valgus

SHOULDER:

- Erosion of the distal clavicle
- Marginal erosions of the Humeral head: The superolateral aspect is a typical location
- Reduction in the Acromiohumeral distance: "High-riding shoulder" due to Subacromial-Subdeltoid bursitis and high incidence of rotator cuff tear

HIP:

- Concentric loss of joint space where there is a tendency for superior loss of joint space
- Acetabular protrusion

KNEE:

- Joint effusion
- Typically involves the lateral or non-weight bearing portion of the joint
- Loss of joint space involving all three compartments
- Lack of subchondral sclerosis and osteophytes, compared with OA
- Baker's cyst (Popliteal cyst) - rare
- Prepatellar bursitis
- Vulgus deformity

IN SPINE:

The Cervical spine is frequently involved in RA , where as a Thoracic and Lumbar involvement are rare. Findings include

- Erosion of the dens
- Atlantoaxial subluxation-atlantoaxial distance in more than 3 mm on a flexion radiograph Atlantoaxial impaction (cranial settling): cephalad migration of C2
- Erosion and fusion of uncovertebral (apophyseal joints) and facet joints
- Osteoporosis and osteoporotic fractures
- Erosion of spinous processes

EXTRA ARTICULAR MANIFESTATIONS:

SYSTEMIC:

1.Fever
2.Fatigue
3. Weight loss
4.Susceptability to infection

MUSCULO SKELETAL

1.Muscle Wasting
2.Bursitis
3.Tenosynovitis
4.Osteoporosis

HAEMATOLOGICAL

1.Anemia
2.Eosinophilia
3.Thrombocytopenia

LYMPHATIC

1.Splenomegaly
2.Felty's syndrome

NODULES

1.Sinuses
2.Fistulae

OCULAR:

1.Scleritis
2.Episcleritis
3.Scleromalacia
4.Keratoconjuctivitis Sicca

VASCULITIS:

1.Digital Arteritis
2.Mononeuritis Multiplex
3.Venous ulcers
4.Visceral Arteritis
5.Pyoderma gangrenosum

CARDIAC:

1.Pericarditis
2.Myocarditis
3.Endocarditis
4.Conduction defect
5.Coronary Vasculitis
6.Granulomatous Aortitis

PULMONARY:

1.Nodules
2.Bronchiolitis
3.Pleural Effusion
4.Caplan's syndrome
5.Fibrosing alveolitis

NEUROLOGICAL

1.Cervical cord compression
2.Peripheral neuropathy
3.Compression neuropathies
4.Mononeuritis Multiplex

Amyloidosis is a rare complication of prolonged active disease and usually presents with Nephrotic syndrome.

Subcutaneous Rheumatoid Nodules

Subcutanneous and intracutaneous nodules are the hall mark of the disease. It develop in 20 to 30% of patients with Rheumatoid Arthritis.

They are usually found on peri articular structures, extensor or other areas subject to Mechanical pressure.

Common locations include a olecranon bursa, the proximal ulnar, the achilles tendon, the occipital bone etc., They are also found in the flexor tendon,the scalar,with in the aortic value,myocardium,larynx and vocal cord.

Histologically, the nodules consist of a central zone of necrotic material,including collagen fibrils,non-collagenous filaments and cellular debris,mid zone of palisading macrophages that express HLA-DR antigens and an outer zone of granuloma tissue.

Rheumatoid vasculitis

It can affect nearly any organ system and is seen in patients with severe from and high titres of circulating rheumatoid factors. Neurovascular disease presenting either as distal sensory neuropathy or as mononeuritis multiplex may be the only sign of vasculitis. Custaneous vasculitis usually presents as crops of small brown spots in the nail bed, nail folds and digital pulp,large ischaemic ulcers especially in the lower

extremity may also develop. Vasculitis also involves the lungs, bowel, liver, spleen, pancreas, lymphnodes and testes.

Renal Involvement

Renal papillary necrosis and interstitial nephritis occasionally occur IgA nephropathy associated with elevated serum levels of IgG and IgA is described in RA.

Liver Involvement

This is evident in about 10% of patients with active disease.

There may be mild hepatospleenomegaly and asympatamatic elevation of the serum alkaline phosphatase.

Kupffer cell hyperplasia and lymphocytic infilteration of the portal tracts may be seen.

Pulmonary Manifestations

Pleuro pulmonary nodule may occur as singly or in clusters when they appear in individual with the pneumoconiosis and diffuse nodular fibrotic nodules 0.5-5 cm in diameter are seen mainly in the periphery of the lung fields. This association is known as Caplan's syndrome. These nodules may produce pneumothorax or broncho pleural fistula.

Interstitial fibrosis.

- Pleurisy and pleural effusion produce frank synovitis.
- Pulmonary fibrosis is common in rheumatoid arthritis but is often subclinical.
- Pulmonary hypertension due to vasculitis.
- Obliterative bronchiolitis is a rare but rapidly progressive and fatal process
- Cardiovascular Manifestations
- Asymptamatic pericarditis
- Pericardial effusion
- Constructive pericarditis
- Cardiomyopathy
- Coronary artery occlusion
- Acute aortic regurgitation
- Valvulitis

STAGES OF RHEUMATOID ARTHIRITIS

The American College of Rheumatology has developed a system for classifying rheumatoid arthritis that is based upon the X-ray appearance of the joints. It describes the severity of rheumatoid arthritis with respect to cartilage, ligaments, and bone.

Stage-I

- No damage seen on X-rays, although there may be signs of bone thinning

Stage-II

- On X-ray, evidence of bone thinning around a joint with or without slight bone damage
- Slight cartilage damage possible
- Joint mobility may be limited; no joint deformities observed
- Atrophy of adjacent muscle
- Abnormalities of soft tissue around joint possible

Stage-III

- On X-ray, evidence of cartilage and bone damage and bone thinning around the joint
- Joint deformity without permanent stiffening or fixation of the joint
- Extensive muscle atrophy
- Abnormalities of soft tissue around joint possible

Stage-IV

- On X-ray, evidence of cartilage and bone damage and osteoporosis around joint
- Joint deformity with permanent fixation of the joint (referred to as ankylosis)
- Extensive muscle atrophy
- Abnormalities of soft tissue around joint possible.

CRITERIA:	
JOINTS AFFECTED	**SCORE**
1 Large joint	**0**
2-10 Large joints	**1**
1-3 Small joints	**2**
4-10 Small joints	**5**
SEROLOGY	
Negative RF and ACPA	**0**
Low Positive RF or ACPA	**2**
High Positive RF or ACPA	**3**
DURATION OF SYMPTOMS	
<6 weeks	**0**
>6 weeks	**1**
ACUTE PHASE REACTANTS	
Normal CRP and ESR	**0**
Abnormal CRP or ESR	**1**

Patient with a score greater than or equal 6 are considered to have definite Rheumatiod Arthritis.

Criteria for the Diagnosis of Rheumatoid Arthritis:

1. Morning Stiffness for more than 1 hour
2. Arthritis of 3 or more joint
3. Arthritis of hand joints
4. Symmetrical distribution of arthritis
5. Rheumatoid Nodules
6. Rheumatoid Factor
7. Radiological findings

Dignosis of Rheumatoid Arthritis made with 4 or more criteria

By using the above criteria Rheumatoid Arthritis can be differentiated from other types of arthritis.

INVESTIGATIONS

HAEMATOLOGICAL INVESTIGATIONS:

- Haemoglobin Concentration
- Total WBC count
- Differential count
  - Polymorphs
  - Lymphocytes
  - Eosinophils
  - Monocytes
  - Basophils
- ESR
- Blood sugar
- Total Cholesterol
- Urea
- Creatinine
- Uric acid .

URINE

- Albumin
- Sugar
- Deposits

SPECIFIC INVESTIGATIONS

- **CRP**
- **ASO Titre**
- **Antinuclear antibody (ANA)**
- **Rheumatoid factor (RF):** Designed to detect and measure the level of an antibody that acts against the blood component gamma globulin, this test is often positive in people with Rheumatoid arthritis.
- **Anti-cyclic citrullinated peptide (anti-CCP)**: Also called anti-citrullinated protein antibodies (ACPA)
- **HLA tissue typing –** This test, which detects the presence of certain genetic markers in the blood, can often confirm a diagnosis of ankylosing spondylitis (a disease involving inflammation of the spine and sacroiliac joint) or reactive arthritis (a disease involving inflammation of the urethra,

eyes and joints). The genetic marker HLA-B27 is almost always present in people with either of these diseases.

- **Lyme serology –** This test detects an immune response to the infectious agent that causes Lyme disease and thus can be used to confirm a diagnosis of the disease.
- **Skin biopsy**
- **Muscle biopsy**
- **Joint fluid tests**

RADIOLOGICAL INVESTIGATIONS:

The radiographic hallmarks of Rheumatoid arthritis are:

- **Soft tissue swelling:** Fusiform and Periarticular; it represents a combination of Joint Effusion, Oedema and Tenosynovitis
- **Osteoporosis:** initially juxta-articular, and later generalised.
- **Joint space narrowing:** Symmetrical or Concentric
- **Marginal Erosions:** Due to erosion by pannus of the bony "bare areas"

Ultrasound:

Sonography can assess the soft tissue manifestations of RA. In particular:

- Synovial proliferation and inflammation of the superficial joints
- Tenosynovitis: Extensor carpi ulnaris tendon involvement is common in early disease and may lead to erosion of the ulnar styloid 2
- Bursitis

CT:

CT is not routinely used in the evaluation of peripheral RA. It has applications in imaging of the spine, and peri-operative assessment.

MRI

MRI is particularly sensitive to the early and subtle features of RA.

Features of RA best demonstrated with MRI include:

- Synovial hyperaemia: indication of acute inflammation
- Synovial hyperplasia (rice bodies)
- Pannus formation
- Decreased thickness of cartilage
- Subchondral cysts and erosions
- Juxta-articular bone marrow oedema
- Joint effusions

DIFFERENTIAL DIAGNOSIS

The differential for the skeletal manifestations of RA includes

- **Osteoarthritis** involving the: DIPs, PIPs, 1st CMC joints, Nonuniform joint space loss, subchondral sclerosis and osteophyte, soft tissue swelling, Heberdon's node (DIPs) and Bouchard node (PIPs), no Erosions and no anklylosis.
- **Erosive osteoarthritis**: Clinically an acute inflammatory attacks (swelling, erythema, pain) in postmenopausal woman typically includes the DIPs, PIPs 1st CMC joint 6, but not the metacarpophalangeal (MCP) joints and large joints. Classic central erosions, possible ankylosis.
- **Psoriatic arthritis (PsA):** Commonly involves the hands and there is an interphalangeal predominant distribution in PsA . MCP joint predominance in Rheumatoid arthritis (RA) starts with erosions in the margins and eventually involves the whole joint.

  Classic: **"pencil in cup"** and bone proliferation (unlike RA).

  Osteoporosis not a feature in PsA. MRI dynamic enhancement pattern may differentiate PsA from RA at 15 minutes
- **Reactive arthritis (Reiter's syndrome):** Predilection for the lower limb Osteopenia and then Osteoporosis, uniform joint space loss, subchondral cyst formation, subluxations, marginal erosions but no bone formation, symmetrical involvement of the: PIPs, MCPs, and carpal bones.
- **Systemic lupus erythematosus (SLE)/Jaccoud arthropathy:** Joint space loss, subchondral sclerosis, osteophyte, and ulnar deviation of the phalanges without erosions
- **Calcium pyrophosphate dihydrate (CPPD) arthropathy:** usually only affects the MCP's: symmetric joint space narrowing, subchondral cysts, and osteophytes. unlike RA: chondrocalcinosis and no erosions.
- **Gout** usually in older men : Punched out erosions usually with a sclerotic border and overhanging edges, tophi, most commonly involves the 1st MTP known as podagra.

COMPLICATIONS:

Since rheumatoid arthritis is a systemic disease, its inflammation can affect organs and areas of the body other than the joints.

Inflammation of the glands of the eyes and mouth can cause dryness of these areas and is referred to as **Sjögren's syndrome**. Dryness of the eyes can lead to corneal abrasion. Inflammation of the white parts of the eyes (the sclerae) is referred to as **scleritis** and can be very dangerous to the eye. Rheumatoid inflammation of the lung lining **(pleuritis)** causes chest pain with deep breathing, shortness of breath, or coughing. The lung tissue itself can also become inflammed and scarred, and sometimes nodules of inflammation (rheumatoid nodules) develop within the lungs.

Inflammation of the tissue (pericardium) surrounding the heart, called **pericarditis,** can cause a chest pain that typically changes in intensity when lying down or leaning forward. Rheumatoid arthritis is associated with an increased risk for **heart attack**. Rheumatoid disease can reduce the number of red blood cells **(anemia)** and white blood cells. Decreased white cells can be associated with an enlarged spleen referred to as **Felty's syndrome** and can increase the risk of infections.

The risk of lymph gland cancer **(lymphoma)** is higher in patients with rheumatoid arthritis, especially in those with sustained active joint inflammation. Firm lumps or firm bumps under the skin, subcutaneous nodules called **rheumatoid nodules** can occur around the elbows and fingers where there is frequent pressure. Even though these nodules usually do not cause symptoms, occasionally they can become infected.Nerves can become pinched in the wrists to cause **carpal tunnel syndrome**. A rare, serious complication, usually with longstanding rheumatoid disease, is blood vessel inflammation **(vasculitis)**. Vasculitis can impair blood supply to tissues and lead to tissue death **(necrosis)** leading to leg ulcers.

CHAPTER-III

MATERIALS AND METHODS

3.1 STUDY AREA AND SETTING

The study period was covered from June 2017 to July 2019 at the Govt. Siddha Medical College and Hospital, Palayamkottai- 627 002, Tirunelveli, Tamil Nadu. All procedures were carried out before getting the permission from Institutional Ethical Committee (**GSMC-IV-IEC/2017/Br.-I/04/29.05.2017**).

3.2 STUDY DESIGN:

STUDY TYPE : A open labelled Phase II non - randomized clinical trial

STUDY PLACE : OPD & IPD of Govt.Siddha Medical College and Hospital, Palayamkottai.

STUDY PERIOD : 24 Months

SAMPLE SIZE : 40 Patients (20 OPD &20 IPD)

3.3 SELECTION OF PATIENTS

Patients with symptoms mentioned in inclusion criteria reported in P.G.Dept of Pothu Maruthuvam, GSMC, Palayamkottai was subjected to screening test and documented using screening proforma.

3.3.1 INCLUSION CRITERIA

- Age : 18 – 50 years
- Sex : Both male and female
- Symmetrical joint involvement
- Arthritis of 3 or more joints
- Florid Morning stiffness and swelling that lasts for few hours or days
- Pain, Joint swelling especially in the interphalangeal joint.
- Patients who are willing for admission and stay in IPD for minimum 20 – 30 days or willing to attend OPD.
- Patient who are willing to undergo radiological investigation and give blood and urine samples for laboratory investigation.
- Pain criteria score should be greater than or equal to 6.

3.3.2 EXCLUSION CRITERIA

- Age : Below 18 and above 50 years
- Gouty arthritis
- Psoritatic arthritis
- Mixed Connective Tissue Disorders (MCTD)
- SLE
- Extra pulmonary Tuberculosis
- Other auto-immune disease
- Chronic kidney disease
- Pregnant women and lactating mothers

3.3.3 DIAGNOSIS

The Siddha diagnostic procedure were included this study, which are,

- Poriyal Arithal
- Pulanal Arithal
- Vinathal
- Mukkutra nilaigal
- Envagai thervugal
- Nilam
- Kaalam & Udal kattugal

3.3.4 INVESTICATIONS:

The following investigations were done in modern medicine aspects.

Haematological aspects

- Total RBC count
- Hb%
- Total WBC count
- Differential count
- ESR
- Blood sugar
- Serum cholesterol
- Serum urea
- Serum creatinine
- Serum uric acid

Urine analysis:

- Albumin
- Sugar
- Deposits

Specific investigations:

1. CRP
2. RA factor
3. ASO titre
4. Anti-CCP (In selective cases)

Radiological investigations (for selected cases):

- X-ray of affected joints (AP and lateral view)

Assessment of results:

The results were assessed on the basis of symptomatic relief and DISEASE ACTIVITY SCORE OF 28 JOINTS (DAS 28).The difference in the score before and after treatment represents the improvement in the treatment.

3.4 The preparation of Trial Medicine (Annexure I)

The selected clinical trial drug was **NANNARI VER OORAL KUDINEER**

Reference : Gunapadam Mooligai Vaguppu, Pg. No. 562

Author : Dr. K.S. Murugesa Mudaliyar

Dose : 90 ml (thrice a day)

Duration : 30 days.

All the paients admitted for the study were provided with regular hospital diet.

After discharge all the patients were advised to attend the Out patient Department of Pothu Maruthuvam, Government Siddha Medical College and Hospital, Palayamkottai for further follow–up.

3.5. Collection and authentication of trial medicine (Annexure VI):

The required drug for preparation of **NANNARI VER OORAL KUDINEER** (Internal) was purchased from a well reputed country shop and authenticated by Botanist, Department of Medicinal Botany, Govt. Siddha Medical College,

Palayamkottai. The drug was purified and the medicine was prepared in the Gunapadam practical hall of Govt.Siddha Medical College, Palayamkottai.

3.6 Preclinical analysis of trial medicine

All the preclinical studies of the study drug including bio-chemical and pharmacological studies were carried out and results were cross checked before starting the treatment.The bio-chemical analysis was carried out in Dept. of Biochemistry, GSMCH, Palyamkottai..

The relevant pharmacological activities - Anti inflamatory, Analgesic, Immunomodulatory Activity, Anti microbial, Phytochemical and Acute and sub-acute toxicity activities were carried out in this study. Studies were done in K.M. College of Pharmacy, Madurai -625107.

3.7 Ethical review

The study was conducted in accordance with the ethical principles that are consistent with Good Clinical Practice guidelines and obtained prior approvals before start of the trial from the Institutional Ethical Committee of GSMCH, Palayamkottai (**GSMC-IV-IEC/2017/Br.-I/04/29.05.2017**) and Institutional animal ethical committee (IEAC) of K.M. College of Pharmacy, Madurai (**TNMGRMU/KMCP/IEAC/26/2018**). The trial was applied and approved by the Clinical Trial Registry of India **(CTRI/2018/06/014450[Registered on: 07/06/2018]).** Trial was registered prospectively as per the norms.

3.8 Study enrolment

Patients reported at the OPD & IPD of Pothu Maruthuvam Govt. siddha medical college and hospital, palayamkottai with the clinical symptoms of pain in three or more joints, swelling of small joints, morning stiffness was examined clinically for enrollment in the study based on the inclusion and exclusion criteria.

The patients who were to be enrolled were informed about the study, trial drug, possible outcomes and the objectives of the study in the language and terms understandable to them.

During the visit, various parameters like body weight, blood pressure, cardiovascular, neurological and respiratory system were clinically recorded. During the treatment any adverse reaction or side effects of patients, immediately to inform

patient and pharmacovigilence committee. At the end of the study period, all the patients were instructed to follow diet control, and to monitor relevant parameters. They were also advised to pursue the further treatment in the PG, Pothu Maruthuvam OPD for the follow up study.

WITHDRAWAL CRITERIA:

- Intolerance to the drug and development of adverse reactions during drug trial.
- Poor patient compliance and defaulters.
- Patient turned unwilling to continue in the course of clinical trial.
- Occurrence of any serious illness.

3.9 Statistical Analysis

All data were analysed using the SPSS 20.0 (IBM). Data were expressed as means and standard deviation. The significance of the difference between the means of the baseline and the final examinations was tested using the paired 't' test. A probability value of <0.05 was considered to be statistically significant.

CHAPTER-IV

OBSERVATION AND RESULTS

4.1.PRE CLINICAL STUDY OF NANNARI VER OORAL KUDINNER

4.1.1.BIO-CHEMICAL ANALYSIS OF NVOK

PREPARATION OF THE EXTRACT:

5 gm of the drug was weighed accurately and placed in a 250ml clean beaker. Then 50ml of distilled water was added and dissolved well. It was boiled well for about 10 minutes and allowed to cool. Mixture was filtered in a 100ml volumetric flask and then it is made into 100ml with distilled water and taken for analysis.

QUALITATIVE ANALYSIS

Table;4.1.1.a.BIO-CHEMICAL ANALYSIS OF NVOK

Sl. No.	EXPERIMENT	OBSERVATION	INFERENCE
1.	**TEST FOR CALCIUM** 2ml of the above prepared extract is taken in a clean test tube. To this add 2ml of 4% Ammonium oxalate solution	A white precipitate is formed	**presence** of **calcium**
2.	**TEST FOR SULPHATE** 2ml of the extract is added to 5% Barium chloride solution.	A white precipitate is formed	**presence** of **sulphate**
3.	**TEST FOR CHLORIDE** The extract is treated with silver nitrate solution	No white precipitate is formed	**Absence** of **Chloride**
4.	**TEST FOR CARBONATE** The extract is treated with concentrated Hcl.	No brisk effervescence is formed	Absence of Carbonate
5.	**TEST FOR STARCH** The extract is added with weak iodine solution	Blue colour is Formed	**presence** of **starch**
6.	**TEST FOR FERRIC IRON** The extract is acidified with Glacial acetic acid and potassium ferro cyanide.	No blue colour is formed	Absence of ferric iron

7.	**TEST FOR FERROUS IRON** The extract is treated with concentrated Nitric acid and Ammonium thiocyanate solution	Blood red colour is formed	**presence** of **ferrous Iron**
8.	**TEST FOR PHOSPHATE** The extract is treated with Ammonium Molybdate and concentrated nitric acid	No yellow precipitate is formed	Absence of Phosphate
9.	**TEST FOR ALBUMIN** The extract is treated with Esbach's reagent	No yellow precipitate is formed	Absence of Albumin
10.	**TEST FOR TANNIC ACID** The extract is treated with ferric chloride.	No blue black precipitate is formed	Absence of tannic acid
11.	**TEST FOR UNSATURATION** Potassium permanganate solution is added to the extract	It gets decolourised	**presence** of **unsaturated compound**
12.	**TEST FOR THE REDUCING SUGAR** 5ml of Benedict's qualitative solution is taken in a test tube and allowed to boil for 2 minutes and add 8-10 drops of the extract and again boil it for 2 minutes.	No colour change Occurs	Absence of reducing sugar
13.	**TEST FOR AMINO ACID** One or two drops of the extract is placed on a filter paper and dried well. After drying, 1% Ninhydrin is sprayed over the same and dried it well.	Violet colour is Formed	**presence** of **amino acid**
14.	**TEST FOR ZINC** The extract is treated with Potassium Ferrocyanide.	No white precipitate is formed	Absence of Zinc

Inference:

- Indicates the **presence** of calcium, sulphate, starch, ferrous iron, unsaturated compound and amino acid.

4.1.2.ANTIMICROBIAL ANALYSIS OF NANNARI VER OORAL KUDINEER

Figure .4.1.2.1.ANTIMICROBIAL ANALYSIS OF NVOK

fig. 4.1.2.1.a. *Staphylococcus aureus*

fig.4.1.2.1.b. *E.Coli*

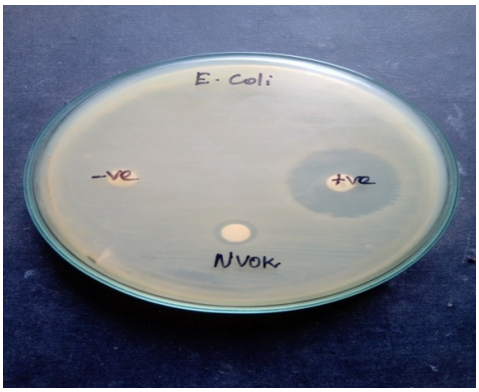


fig.4.1.2.1.c. *Bacillus subtilius*

fig.4.1.2.1.d. *Klebsiella pneumoniae*

Fig.4.1.2.1.e. *Streptococcus mutans*

ANTIMICROBIAL RESULTS

Sample Code	Bacteria Strains Name				
	***Staphylococcus aureus* (G+)**	***Streptococcus mutans* (G+)**	***Bacillus subtilis* (G+)**	***Klebsilla pneumo nia* (G-)**	**E – coli (G-)**
NVOK	**12**	**-**	**-**	**10**	**11**
PC	**22**	**16**	**26**	**28**	**18**
NC	**-**	**-**	**-**	**-**	**-**

Keys

PC - Positive Control (Streptomycin)

NC - Negative Control

- - No Zone

Mm - Millimetre

G+ - Gram Positive Organism

G- - Gram Negative Organism

Trial drug showed the anti- microbial activity against (MIC) both Gram positive (S*taphylococcus aureus*) and Gram negative bacteria *(Klebsiella pneumoniae, E.coli)*

4.1.3.PHYTOCHEMICAL STUDY OF NANNARI VER OORAL KUDINEER

The word “phytochemicals” are generally used to describe plant compounds that are under research with unestablished effects on health and are not scientifically defined as essential nutrients. These are chemicals produced by plants through primary or secondary metabolism. For the standardization purpose, islosation of specific compounds, determining their structures and identifying what specific phytochemical is primarily responsible for specific biologic activity should be carried out.

The Nannari Ver Ooral Kudineer was subjected to qualitative phytochemical investigation. Details of the various test performed for the presence of the phyto constituents is shown in Table.4.1.3.a.

Table 4.1.3.a: Phytochemical Results of Nannari ver ooral kudineer.

Phytochemical tests for *NVOK*	**Tests**	***Inference***
Alkaloids	Mayer's test	Positive
	Dragendroff's test	Positive
	Hager's test	Positive
Carbohydrates and glycosides	Molisch test	Positive
	Legal's test	Positive
	Borntrager's test for anthraquinones	Positive
Phytosterols	Liebermann-Burchard test	Positive
	Salkowski test	Positive
Flavanoids	Shinoda test Magnesium turnings and hydrochloric acid (Presence of red color)	Positive
	Fluorescence test	Positive
Tannins	Ferric chloride test	Positive
	Potassium dichromate test	Positive
	Lead acetate test	Positive
Proteins	Millon's test	Positive
	Biuret test	Positive
	Ninhydrin test	Positive
Fixed oils and fats	Spot test	Negative
	Saponification test	Negative
Lignin	Phloroglucinol test	Positive
Saponins	Frothing test	Negative

Positive indicates the presence of phyto-chemical constituents.

Negative indicates the absence of phyto-chemical constituents .

Results:

The qualitative phytochemical analysis of *nannari ver ooral kudineer* has showed the presence of flavonoids, Carbohydrates, glycosides, alkaloids, phytosterols, Tanins, proteins and lignin. Fixed oils and saponins are absent .

4.1.4. PHARMACOLOGICAL ACTIVITIES:

4.1.4.1 Analgesic activity:

Acetic acid - induced writing test:

The acetic-acid writhing test was performed as per the following procedure:

24 adult male albino mice (25-35g) were divided into 4 groups. Groups of rats (n=6) were administered with 100 mg/kg and 200 mg/kg of nannari ver ooral kudineer, 10 mg/kg/. Diclofenac was taken for positive control group and 1ml distilled water as negative control group respectively. After 30 minutes , the animals were administered with i.p injection of 0.1ml acetic acid 0.6 % .Then the count of abdominal contractions of animals during 30 minutes after acetic acid injection was reported and the percentage activity (PAA) was calculated by using the following formula

$$PAA = (C-CD)/ CD) X 100$$

C=mean of contractions count in animals treated with different doses of Nannari Ver Ooral Kudineer and diclofenac sodium

lCD=Mean of contractions count in animals served as negative control.

Table 4.1.4.1.a Effects of Nannari Ver Ooral Kudineer on acetic acid induced writhing response (N-6 in each group)

Groups	Treatment	(Number of writhing movements) (Mean ±SEM)	Percentage %
Group I	Distilled water	34.00±2.75	
Group II	Diclofenac Sodium 100 mg / kg	6.55±1.02*b	80.73%
Group III	100mg/kg NVOK	15.30±1.68*b	55.00%
Group IV	200mg/kg NVOK	13.15 ± 1.28*b	61.32%

Values are expressed as mean ± SEM

*(b) Values are significantly different from Toxic control G2 at P<0.01

Discussion

Acetic acid increases the PGE2 and PGEα in peritoneal fluid. The results of Nannari ver ooral kudineer when administered at the doses of 100 and 200 mg / kg showed significant antinociceptive activity in mice models and comparable with the effect of diclofenac sodium in analgesic activity. The analgesic activity shown in models of pain is indicative that nannari ver ooral kudineer might possess centrally and peripherally mediated antinociceptive properties.

4.1.4.2Anti-inflammatory activity

I. Carrageenan induced paw edema assay:

Paw swelling or footpad edema, is a convenient method for assessing inflammatory responses to antigenic challenges and irritants.

The Albino Wister rats (180 + 5g) were used. The rats were divided into 5 groups of 5 animals each.

- Rats of group I were given normal saline and treated as negative control.
- Rats of group II were treated with carrageenan (1%w/v) in saline in the sub-plantar region of the right hind paw.
- Rats in group III were administered Indomethacin(10 mg/kg, bw) and considered as standard.
- Rats from group IV and V were given two doses siddha formulation (100 and 200 mg/kg bw) respectively.

Method:

Acute paw edema was induced by injecting 0.1 ml of 1% (w/ Carrageenan solution, pre-pared in normal saline. After 1 hr, 0.1ml, 1 % Carrageenan suspension in 0.9% NaCl solution was injected into the sub-plantar tissue of the right hind paw.The linear paw circumference will be measured at hourly interval for 4hr.The perimeter of paw was measured by using vernier callipers. Measurements were taken at 0-4hr after the administration of carrageenan.

The anti-inflammatory activity was calculated by using the relation

$$\%\text{inhibition of edema} = \frac{T-T0}{T} \times 100$$

T= Thickness of paw in control group

T0= Thickness of paw edema in the test compound treated group.

Table 4.1.4.2.a. Effect of NVOK on carrageenan induced rat paw edema.

Treatment	Dose (mg/kg, p.o.)	Mean increase in paw volume (ml)	% Decrease in paw volume
Normal control	10ml/kg saline	1.12 ± 0.11	
Toxic control	0.1 ml. 1% Carrageenan	3.48 ±0.32*a	
Standard control	10 mg/kg Indomethacin	1.25 ±0.14*b	64.08%
Treatment control	100mg/kg NVOK	1.46 ± 0.19*b	58.04%
Treatment control	200mg/kg NVOK	1.36 ±0.16*b	60.91%

Values are expressed as mean ± SEM.

Values were compared by using analysis of variance (ANOVA) followed by Newman-Keuls multiple range tests

(a) Values are significantly different from normal control G1 at P<0.01

(b) Values are significantly different from Toxic control G2 at P<0.01.

Results

The results obtained indicate that the Nannari ver ooral kudineer had significant anti-inflammatory activity in rats. The kudineer reduced carrageenan induced edema by 58.04% and 60.91% on oral administration of 100 and 200 mg/kg, as compared to the untreated control group .Indomethacin at 10 mg/kg inhibited the edema volume by 64.08%.

II. Carrageenan Induced Pleurisy In Rats

The animals were divided into five groups of five rats each as described in the carrageenan induced paw edema model and each were pretreated with siddha formulation (100 and 200 mg/kg. p.o.), Indomethacin (10 mg/kg, p.o.) or normal saline (0.1 ml).One hour later all the animals were received 0.25 ml of an intra-pleural injection of carrageenan on the right side of the thorax.

The animals were sacrificed 3 h after carrageenan injection by ether inhalation. One ml of heparinized Hank's solution was injected into the pleural cavity and gently massaged to mix its contents. The fluid was aspirated out of the cavity and the exudates were collected. The number of migrating leukocytes in the exudates was determined with Neubauer chamber . The values of each experimental group were expressed as mean SEM and compared with the control group.

Table4.1.4.2.b.Effect of NVOK on carrageenan induced pleurisy in rats.

Treatment	Dose(mg/kg, p.o.)	Pleural exudates (ml)	Leukocytes ($X10^3$cells / ml)
Normal control	10ml/kg saline	0.17 ±0.07	0.39 ± 0.06
Toxic control	0.1 ml. 1% carrageenan	0.45 ±0.16*a	4.23 ±0.39*a
Standard	10 mg/kg Indomethacin	0.18 ±0.08*b	0.48 ±0.08*b
Treatment control	100mg/kg Nannari ver Ooral kudineer	0.23 ±0.10*b	0.56 ± 0.11*b
Treatment control	200mg/kg Nannari ver Ooral kudineer	0.19 ± 0.09*b	0.52 ± 0.10*b

Values are expressed as mean ± SEM.

Values were compared by using analysis of variance (ANOVA) followed by Newman-Keuls multiple range tests

(a) Values are significantly different from normal control G1 at P<0.01

(b) Values are significantly different from Toxic control G2 at P<0.01.

Results

The volume of pleural exudates in the toxic control group was 0.45+0.16 ml. Animals treated with the nannari ver ooral kudineer (100 and 200 mg/kg, p.o.) decreased the pleural exudates to 0.2340.10 ml and 0.19 0.09.Treatment with Indomethacin (10 mg/kg,p.o.) produced the exudates of 0.18+0.08 ml. The leukocyte count for the control group was found to be $4.23+0.39x10^3$ cells/ml. Animals treated with the Nannari ver ooral kudineer and standard produced a leukocyte migration of $0.56+0.11x10^3$,$0.52+0.10X10^3$and $0.48+0.08X10^3$cells/ml, respectively.

4.1.4.3 IMMUNOMODULATORY ACTIVITY

The immunomodulatory study of Nannari ver ooral kudineer was conducted in wistar albino rats (180-220g) of either sex. It was tested on cyclophosphamide-treated immune suppressed rat models. The wistar albino rats were divided into seven groups and each group contained 6 animals.

The groups are as follows:

- **Group I** served as a **control,** which received saline solution.
- **Group II** served as an **immunosuppressant group**, which received cyclophosphamide at the dosage of (30 mg/kg, i.p.)
- **Group III** served as a **parse control** which received Nannari ver ooral kudineer (100 mg kg, i.p.)
- **Groups IV and V** served as the **test groups** which were immune-suppressed with cyclophosphamide (30 mg/kg, i.p) and treated with Nannari ver ooral kudineer (50 and 100 mg/kg, i.p), respectively.

Group VI served as the **positive control** which received cyclophosphamide (30 mg/kg,i.p) along with Standard drug-levamisole hydrochloride (LH) (10 mg/kg bw, i.p) All the groups treated with Siddha Preparation Nannari ver ooral kudineer and levamisole hydrochloride were injected on daily basis for 11 days, while cyclophosphamide was given on 4, 5 and 6^{th} days of the experiment.

At the end of the experiment, the animals were sacrificed by cervical dislocation and the blood was collected using heart puncher in 3% citrate containing tubes. The organs namely liver, spleen, heart and kidney were immediately collected, weighed and stored at 8°C.

Body weight and relative organ weight determination: -

Body weight and relative organs (Spleen, liver, Heart, Kidney) weight were measured for all animals and the results were expressed as mg of organ weight/g body weight of animal,

Organ weight index= $W1/W0 \times 100$,

where W1 is the weight of Organ and W0 is the weight of body

Hematological analysis

The level of WBC, RBC, platelet and heamoglobin level were determined using an automatic cell counter

Delayed type Hypersensitivity reaction

The cell mediated immune response was assessed by footpad reaction test. On the 10^{th} day, 5µg of hepatitis B vaccine was injected in the right paw and saline was injected in the left paw. On the 11th day after 24hr, the paw volume was measured using plethysmometer and the results were expressed as % of increase in the paw volume.

Phagocytic response

The phagocytic response was determined according to the method of Wang et al (2012). On the 7th day of the experiment, the animals were injected with 100 µl of Indian ink via intravenous injection. 50µl of blood was collected with 5µl of 3% citrate by retro-orbital puncher at an interval of 2 and 30 minutes after the injection of ink. Then 25 µl of citrated blood was added to 3 ml of 0.1% sodium carbonate solution to lyse the RBC. The concentration of ink in the blood was read at A675nm using spectrophotometer.

The carbon clearance rate (κ) and phagocytic index (α) were calculated by using the following formula:

Rate of carbon clearance (κ) = $(logOD1 - \log OD2)/(T1 - T2)$

where OD1 is the absorbance at 2 minutes; OD2 is the absorbance at 30 minutes; T1 is the time of blood collection at 2 minutes; T2 is the time of blood collection at 30 minutes

Phagocytic index α =$(\sqrt[3]{k \times A})/(B+C)$

where A is the body weight, B is the liver weight, and C is the spleen weight.

Total glutathione level

Estimation of the reduced glutathione (GSH) level was done according to the method of Ellman (1959). Briefly, 400µl of the tissue homogenate was treated with 400µl of 5% sulphosalicylic acid and mixed well with vortex. Then the mixture was centrifuged at 1000 x g for 10 minutes at 4°C. 100 µl of the supernatant was mixed with 400 µl of 0.3 M phosphate buffer (pH 8.4) and 400 µl of distilled water. Then 100 µl of 0.001 M freshly prepared DTNB (5,5-dithiobis (2-nitrobenzoic acid)) was added and kept in room temperature for 10 minutes. The formation of yellow coloured product was measured at 412nm. The amount of glutathione present in the tissue homogenate was calculated by constructing standard graph with glutathione and the results were expressed as µM/mg of protein.

Lipid peroxidation

The amount of lipid peroxide present in the tissue was estimated according to the method of Stocks and Dormandy (1971). Briefly, 400 µl of the tissue homogenate was mixed with an equal volume of 10 % Trichloro acetic acid and kept in 4°C for 30 minutes. The proteins were removed by centrifugation at 2000 × g for 10 minutes at 4°C. 500 µl of of 1% thiobarbituric acid was added to 500 µl of the supernatent and the mixture was kept in boiling water bath for 30 minutes. The reaction mixture was cooled and centrifuged at 2000 × g for 10 minutes at 4°C. The absorbance of the supernatant was measured at 532 nm using a spectrophotometer. The concentration of lipid peroxide was calculated using molar extinction coefficient of MDA-thiobarbituric chromophore (1.56 x 10-5/M/cm) and the results were expressed in terms of nmoles MDA/mg of protein.

Carbonyl protein

The level of protein damage was determined by carbonyl protein estimation according to the method of Reznick and Packer (1994). Briefly 200µl of the tissue homogenate was treated with 200µl of 1% trichloro acetic acid and was kept at 4°C for 30 minutes. The mixture was centrifuged at 2000 x g for 15 minutes and the pellet was re-suspended in 10 mM 2,4-dinitrophenylhydrazine in 2N HCl or with 2N HCl as a control blank. This mixture was kept in room temperature for 1 hour and then centrifuged at 2000 x g for 10 minutes.

The pellet was washed three times with 1:1 ethanol/ethyl acetate solution. Finally, the carbonyl protein containing the pellet was dissolved in 6 M Guanidine. The protein hydrazones were measured at A370 nm using spectrophotometer. The amount of carbonyl protein was calculated from molar extinction coefficient of 22,000 M−1 cm−1 and the results were expressed as µg/mg of protein.

Superoxide Dismutase activity

The level of superoxide dismutase in the tissue was estimated according to the method of McCord and Fridovich (1969). This method is based on the ability of the enzyme to inhibit the auto-oxidation of pyrogallol. Briefly, 100µl of the tissue homogenate was added to 700 µl of 100 mm of Tris-HCl buffer (pH 8.2) containing 30 mm EDTA. Then, 200µl of 2 mm of pyrogallol was added to the solution and measured at 420nm for 60 sec using spectrophotometer. A blank was run without the addition of homogenate. One unit of SOD activity is the amount of enzyme capable of

inhibiting 50% of the rate of autoxidation of pyrogallol compared with the blank and are expressed as units'/mg protein/min

Catalase activity

The catalase level in the tissue homogenate was estimated according to the method of Sinha (1972) with minor modification. Briefly, add 100 µl of tissue homogenate to 300 µl of 50 mM phosphate buffer pH-7. Then, 100 µl of 200mM H_2O_2 was added to the mixture, mix well and placed it in room temperature for 30 sec. Immediately, after 30 secs, add 500 µl of 1.5% potassium dichromate / acetic acid (weight/volume). The mixture was kept in boiling water bath for 10 minutes and cooled. The absorbance was read at 590 nm against blank using spectrophotometer. The different concentration of H_2O_2 (1-50 µM) was used for construct the standard graph and The catalase activity was calculated from the standard graph of H_2O_2 (1-50 µM) and results were expressed as µmole of H_2O_2 consumed/ mg of protein/ minute.

Table no. 4.1.4.3.a Effect on Siddha Preparation NVOK on Haemoglobin level

Groups	Haemoglobin (g/dl)
Group I	13.85 ± 0.34
Group II	10.95 ± 0.24
Group III	12.83 ± 0.30
Group IV	12.92 ± 0.31
Group V	13.02 ± 0.33
Group VI	13.24 ± 0.36

Table no. 4.1.4.3.b Effect on Siddha Preparation NVOK on RBC level

Groups	RBC (10^6/µL)
Group I	7.89 ± 0.17
Group II	6.74 ± 0.09
Group III	8.12 ± 0.13
Group IV	7.62 ± 0.12
Group V	7.56 ± 0.15
Group VI	7.77 ± 0.16

Table No 4.1.4.3.c Effect of Nannari ver ooral kudineer on WBC level

Groups	WBC (10^6/ml)
Group I	7.32 ± 0.24
Group II	3.48 ±0.12
Group III	6.56 ± 0.19
Group IV	6.92 ± 0.21
Group V	7.08 ± 0.22
Group VI	6.82 ± 0.20

Table 4.1.4.3.d Effect of Nannari ver ooral kudineer on Platelets level

Groups	Platelets count (103/µl)
Group I	842.44 ± 10.55
Group II	562.94 ± 6.35
Group III	831.13 ± 9.66
Group IV	792.24 ± 8.28
Group V	806.28 ± 8.48
Group VI	803.45 ± 7.88

Table no: 4.1.4.3.e Effect of Siddha Preparation Nannari ver ooral kudineer on enzymatic and non-enzymatic antioxidant status of liver tissue

GROUPS	Catalase U/mg	SOD U/mg	Glutathione U/mg	MDA ηM/mg of protein	PCO ηM/mg of protein
Group I	**4.97±0.38**	**63.28±3.82**	**36.64±1.40**	**7.38±0.42**	**3.22±0.17**
Group II	**1.34±0.22**	**40.25±2.62**	**20.52±1.08**	**14.82±0.88**	**6.54±0.30**
Group III	**3.88±0.34**	**56.25±2.88**	**32.45±1.32**	**12.62±0.68**	**5.42±0.21**
Group IV	**3.63±0.29**	**56.62±2.98**	**30.28±1.12**	**12.82±0.75**	**5.68±0.24**
Group V	**4.07±0.33**	**59.32±3.15**	**33.57±1.40**	**13.35±0.79**	**5.92±0.28**
Group VI	**4.20±0.35**	**61.22±3.28**	**33.82±1.42**	**13.82±0.84**	**6.12±0.32**

The protective effect of Siddha Preparation Nannari ver ooral kudineer on hematopoietic function against CYP induced immune-toxicity was evaluated by counting the level of hematological parameters like (Haemoglobin) Hb, RBC, WBC and platelet cells. The results of hematological analysis showed that the level of Hb, RBC, WBC and platelet cells were significantly reduced in negative control group of animals (G2- CYP alone treated) when compared to normal control group of animals (G1-Saline alone) ($P<0.01$) However, these levels were raised significantly in Siddha Preparation Nannari ver ooral kudineer treated group of animals (G4 =50 (mg/kg b.w.), and G5 = 100 (mg/kg b.w.) in a dose dependent manner.

Myelo suppression is the process of decreasing the production of immune cells (leukocytes), oxygen carrying cells (erythrocytes) and the cells responsible for blood clot (thrombocytes) (Urabe 2003). The results of this study showed that the groups treated with Siddha Preparation Nannari ver ooral kudineer have improved the production of hematopoietic cells like RBC, WBC, platelets and hemoglobin. The **hematological results** reveal that the Nannari ver ooral kudineer has protective effect against CYP induced myelo suppression.

The **cell mediated immune response** was determined by delayed type hypersensitivity reaction(DTH) by measuring their footpad thickness. The group of animals treated with Nannari ver ooral kudineer alone (G3) showed 33% higher footpad volume than the control group. In this study, Nannari ver ooral kudineer has enhanced the cell mediated immune response through the activation of T-cell.

The **phagocytic test** is used to evaluate the non-specific immunity of the system. The phagocytic index is calculated from the rate of clearance of colloidal carbon particles from the circulatory system. The results carbon clearance test indicates that Siddha Preparation Nannari ver ooral kudineer can enhance non-specific immune response against CYP induced immunosuppression

The **weight index** of organs like spleen, liver, kidney and heart reflects the health of the organism. The toxic metabolite produced from CYP is initially metabolized in liver and produces toxic metabolite which is further transferred to other organs. The results of organ weight index showed that the suppressed health due to CYP induced oxidative stress have recovered to normal after Siddha Preparation Nannari ver ooral kudineer treatment.

The **non-enzymatic antioxidant** status plays a major role in maintaining the innate antioxidant status. Reduced glutathione level is a suitable indicator for overall antioxidant defense which maintains alpha-tocopherol and ascorbic acid and is also a coenzyme for glutathione S-o transferases and glutathione peroxidases. Nannari ver ooral kudineer treatment on cyclophosphamide-treated intoxicated group of animals (G4 and G5) directly decreased the glutathione level significantly based on the dose concentration in liver organs.

Superoxide dismutase (SOD) and catalase (CAT) maintain the **enzymatic antioxidant status** of tissue. The Siddha Preparation Nannari ver ooral kudineer treatment to animal (G4 and G5) significantly restored the decreased CAT level to an equal or above the CAT levels of normal control group of animals in a dose-dependent manner. The CAT levels in liver of Siddha Preparation Nannari ver ooral kudineer alone treated group of animals (G3) was found high by 12.8 % than that normal control group of animals (G1).

The level of SOD significantly increased upon the dose dependent manner treatment with Siddha Preparation Nannari ver ooral kudineer and attained the level of normal control group of animals at the concentration of 100mg/kg. in liver tissues showed 22% higher SOD level than the normal control group of animals (G1).

The important **markers of macromolecular damage** is due to oxidative stress by lipid and protein damage which produce lipid peroxide (MDA) and carbonyl protein (PCO). The increase levels of MDA and PCO indicate that toxic metabolite produced from CYP induced oxidative stress damage the lipids and proteins present in the organ tissue. CYP treatment significantly elevated the levels of macromolecule damage (MDA and PCO) and decrease the levels of enzymatic (SOD and CAT), non-enzymatic (GSH) antioxidant status in Liver. At the same time, Siddha Preparation Nannari ver ooral kudineer treatment at the concentration of 100mg/kg b.w. reverse the effect of CYP induced damage via increasing CAT, SOD and GSH levels and thus protecting macromolecular damage and decrease MDA and PCO level. The morphological analysis also supports above study and shows the ability of Siddha Preparation Nannari ver ooral kudineer to repair the damage caused by CYP induced oxidative stress.

DISCUSSION

According to above Table no 4.1.4.3 (1-5) In this study, CYP is given to the wistar albino rats to suppress the immune system and induce oxidative stress. The cyclophosphamide effect is expected to reduce the activity of hematological parameters, cell mediated immune responses and macrophage production. Moreover, CYP impaired the organs through its toxic metabolites and caused oxidative stress. The effect of Siddha Preparation Nannari ver ooral kudineer on CYP induced immune-toxicity was examined through myelo suppression, immune suppression and oxidative damage.

4.1.5. Toxicity study of Nannari ver ooral kudineer

Acute toxicity:

Female Wister albino rats weighing 180 ± 20 g were used in acute toxicity study. The total no: of 18 animals were divided into three groups of six animals in this study.

- The Group I animals were administered with a single daily dose of 0.5 ml of Tween 80 orally for 15 days.
- In Group II are administered with (300 mg.kg-1b.w.NVOK) once a day for 15 days.
- The Group III are fed 2000 mg.kg-1b.w. once daily for 15 days for acute toxicity studies.

HPE revealed no acute toxic symptoms were observed after 15th day All test animals were subjected to gross necropsy.

Table. 4.1.5.a Acute toxicity study of Nannari ver Ooral kudineer

	Dose (mg.kg-1)	**Sign of Toxicity (ST.NB-1)**	**Mortality (D.S-1)**
Group I	0	0/3	0/3
Group II	300	0/3	0/3
Group III	2000	0/3	0/3

Table.1 showed ,the acute toxicity of Nannari Ver Ooral kudineer on experimental rats were tested using OECD -423 guidelines, where ST-sign of toxicity ,NB- normal behaviour, D- died, S-survive. Values are expressed as number of animals (n=3).

RESULTS

- The acute toxicity of Nannari ver Ooral kudineer has showed no mortality or morbidity in animals through the 15-days period following single oral administration at all selected dose levels of the NVOK (Table- 4.1.5.a).
- The morphological characteristics and physical appearance of all animals seems to normal. The physical appearance and motor nervous system was normal.
- On comparison, Group I ,II and III showed no toxic effects for the doses upto 2000/kg/bw.

Sub-acute toxicity:

The sub acute toxicity were performed in Male and female Wistar rats weighing 180 ± 10 g. The animals were divided into five groups of six animals each. The administration of dose is calculated based on the body weight of the animal.

- The animals in Group I were administered with a single daily dose of 0.5 ml of Tween 80 orally for 20 days.
- The animals in Group II were administered with 50 mg.kg-1 b.w. of the NVOK once in daily for 20 days.
- The animals in Group III were administered with 100 mg.kg-1 b.w. of the NVOK orally once daily for 20 days.
- The animals in Group IV and V were administered 200 and 400 mg.kg-1 b.w. once in daily for 20 days.

The animals were weighed during every five days starting from commencement of the study to record the weight variations. At the end of the treatment, blood samples were taken for biochemical analysis. The serum plasma was analyzed for

- Total cholesterol
- Total triglyceride
- HDL-cholesterol levels
- LDL-cholesterol
- Plasma glucose
- Alanine aminotransferase (ALT) &Aspartate aminotransferase (AST)
- Creatinine and urea level.

Effect of Nannari ver Ooral kudineer(NVOK) on internal organs

According table no **4.1.5.b**. no toxic effects found in kidney, heart, liver and brain of the rats were observed. From the study it was clear that, significant ($p<0.01$) changes in the weights of various organs of the animals with higher doses of NVOK (400 mg.kg-1 bwt). The group I was compared with other group II, III, IV, and V.

Table: 4.1.5.b The effects of NVOK on kidney, heart, liver and brain of the rats

Treatment	Heart	Kidney (gms)	Liver (gms)	Brain (gms)
Control	**0.35 ± 0.05**	**0.65± 0.03**	**3.33± 0.05**	**0.68± 0.06**
NVOK 50 mg.kg-1	**0.36± 0.02**	**0.81± 0.03**	**3.45± 0.03**	**0.71± 0.4**
NVOK 100 mg.kg-1	**0.37± 0.06**	**0.79± 0.04**	**3.76±0.02**	**0.69± 0.3**
NVOK 200 mg.kg-1	**0.36± 0.04**	**0.74± 0.02**	**3.65± 0.02**	**0.76± 0.06**
NVOK 400 mg.kg-1	**0.35± 0.03**	**0.75± 0.03**	**3.87± 0.03**	**0.78± 0.06**

The values are expressed as mean ± S.E.M. n=6. The results of group I were compared with other groups such as II, III, IV, and V. The statistical analysis was carried out using one way ANOVA method, where **P<0.01.

Effect of biochemical profiles of rats

Table no 4.1.5.c.The effect of NVOK on biochemical parameters

Treatment	Glucose (mg.dl-1)	Cholesterol (mg.dl-1)	Triglyceride (mg.dl-1)	HDL (mg.dl-1)	LDL (mg.dl-1)
Control	94.65± 0.62	39.62± 0.56	28.25± 0.45	135.25± 0.55	83.15±1.72
NVOK 50 mg.kg-1	92.50± 0.56	25.85± 0.25*	13.22± 0.23*	175.28± 0.65*	71.59±1.28
NVOK 100 mg.kg-1	89.45± 0.47	26.74± 0.26*	15.42± 0.28*	165.18±0.78*	69.84±1.10
NVOK 200 mg.kg-1	90.25± 0.55**	33.18± 0.30	17.84± 0.38*	184.30± 0.84*	48.60±1.30
NVOK 400 mg.kg-1	86.25± 0.45**	32.78± 0.28	19.28± 0.34*	182.2± 0.85*	46.50±0.84

Above Table no 4.1.5.c Showed that nannari ver ooral kudineer has significantly decreased ($p<0.05$) the plasma glucose level in treated rats especially at higher dose (400 mg.kg-1) compared with control groups. **P<0.01 *P<0.05. Significant decrease ($p<0.05$) in the plasma total cholesterol (TC), triglyceride (TG) and LDL-cholesterol levels were also noted. There was no evidence of severe toxicity associated with the administration of higher concentration of NVOK.

Change noted in the hepatic enzymes:

In table.4.1.5.d.comparison of AST, ALT, ALP, TP and Albumin values between Group I and groups II, III, IV, and V were demonstrated.

Table. 4.1.5.d The effects of NVOK on hepatic enzymes in rats.

Treatment	AST (IU.l-1)	ALT (IU.l-1)	ALP (IU.l-1)	TP (g.l-1)	ALBUMIN (g.l-1)
Control	328.5±12.0	70.5± 3.18	253.58± 8.80	69.85± 3.32	37.15±2.35
NVOK 50 mg.kg-1	317.0±9.50	68.5±2.20**	266.10±2.75**	70.30± 2.32	34.30±2.65
NVOK 100 mg.kg-1	318.3±7.20	66.1± 3.15**	260.18±6.70**	80.15± 2.82	36.30±3.05
NVOK 200 mg.kg-1	313.4±7.95	61.4± 2.90	265.00± 5.20	69.25± 3.32	38.20±2.75
NVOK 400 mg.kg-1	323.2±8.20	63.3± 3.52	269.40± 4.40	74.05± 2.58	37.48±2.70

Effect of Nannari Ver Ooral Kudineer on haematological parameters in rats:

From the study it was evident that, a significant increase ($p<0.01$) were observed in the hemoglobin contents and RBC count in the group treated with 200 mg.kg-1 / body weight. There was no significant change in the calcium level in all the treated animals compared to the control.

Table. 4.1.5.e. The effect of Nannari Ver Ooral Kudineer on haematological parameters & calcium in rats

Treatment	Haemoglobin (mg.dl-1)	RBC (106 /mm3)	WBC (106 /mm3)	Calcium (mg.dl-1)
Control	11.3± 0.25	9.15± 0.02	11.45± 0.05	9.44 ±0.02
NVOK 50 mg.kg-1	12.5± 0.26*	9.50± 0.04*	9.55± 0.01*	9.20 ±0.02
NVOK 100 mg.kg-1	12.3± 0.15*	9.55± 0.02*	8.35± 0.32*	9.26 ±0.20
NVOK 200 mg.kg-1	10.7± 0.20*	8.30± 0.12*	11.45± 0.03*	9.61 ±0.13
NVOK 400 mg.kg-1	11.5± 0.35*	8.48± 0.45*	10.55± 0.13*	9.75 ±0.02

Effect of Nannari ver Ooral kudineer on body weight in rats:

The effect of NVOK was observed for their effect on the body weight changes was observed ,significant increased ($p<0.05$) in body weight. The results are described in **Table. 4.1.5.f** The values are expressed as Mean ± S.E.M. n=6. The results of group I were compared with other group II, III, IV, and V (**P<0.01 *P<0.05).

Table. 4.1.5.f.The effects of NVOK on body weight changes in rats

Treatment	Day1	Day 5	Day 10	Day 20
Control	187.15±6.8	189.45 ±6.20	198.15 ±6.35	196.75±6.60
NVOK 50 mg.kg-1	196.30 ±6.4	195.30 ±6.30	200.25 ±6.70	198.35±6.76*
NVOK 100 mg.kg-1	188.35 ±5.7	191.30 ±6.40	198.55 ±7.10	197.40±6.36*
NVOK 200 mg.kg-1	197.30 ±7.2	200.15±6.50	200.90 ±7.20**	206.50±7.30**
NVOK 400 mg.kg-1	187.65 ± 6.05	194.15 ±5.60	197.60 ±6.35**	207.63±7.42**

DISCUSSION

In **acute toxicity**, the limit dose of 2000 mg/ kg (NVOK) did not result in mortality or any clinical sign of acute toxicity in animals in the short-term (48 hours) and longterm (14 days) observatory periods, suggesting that no toxic effects upto 2000 mg/kg in rats.

Sub acute toxicity study showed that the extract did not affect the normal growth of the animals as evidenced by comparing the body weight gain in both control and treated animals over the 28-day treatment periods. There were no significant changes in liver enzymes (ALT,AST,ALP and IP) .The significantly increased in the level of RBC,WBC and hemoglobin was found in treatment with Nannari ver Ooral kudineer (400mg.kg-1). The extract caused no undesirable effect on the all organ of the animals making it safe for consumption by human health and it was non hemotoxic.

4.2 Clinical study:

The results were observed regarding the following criteria by clinical trial study on 40 patients: Out of forty, 20 In patients and 20 Out patients of both sex.

The criteria were:

1. Sex Distribution
2. Age Distribution
3. Kaalam
4. Constitution of body
5. Gunam
6. Religion
7. Paruva Kaalam
8. Thinai
9. Socio – Economical status
10. Food habits
11. Family History
12. Occupation
13. Clinical Manifestation
14. Duration of Illness
15. Kanmenthiriyam
16. Gnanendrium
17. Condition of Mukkutram
    a). Condition of Vatham
    b). Condition of Pitham
    c). Condition of Kapham
18. Involvement of Udal Kattugal
19. Conditions of Envagai Thervugal
20. Neer kuri
21. Nei kuri
22. Assessment of outcome
23. Gradation of results
24. Laboratory Investigations
    a). Out patients b). In patients
25. Diseases activity pain score
    a). Out patients b). In patients
26. Case summary
    a). Out patients b). In patients

1.**SEX DISTRIBUTION:**

Table-1 Illustrates the Distribution of Sex and its percentage.

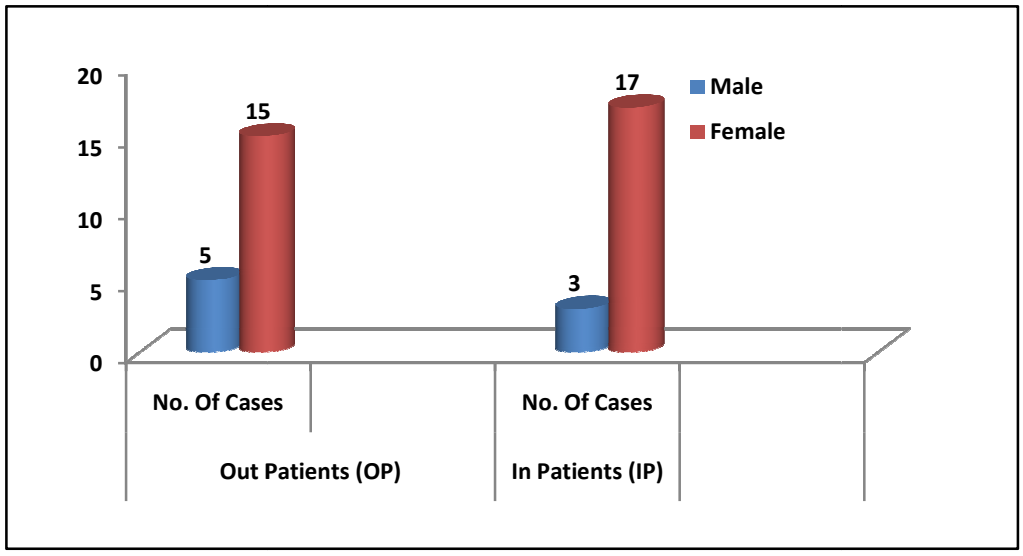
TABLE-1 DISTRIBUTION OF SEX

Sl. No.	Sex	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Male	5	25%	3	15%
2.	Female	15	75%	17	85%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients 25% were Male and 75% were Female.

Among 20 In patients, 15% were Male and 85% were Female.

FIGURE-1 DISTRIBUTION OF SEX



2.AGE DISTRIBUTION:

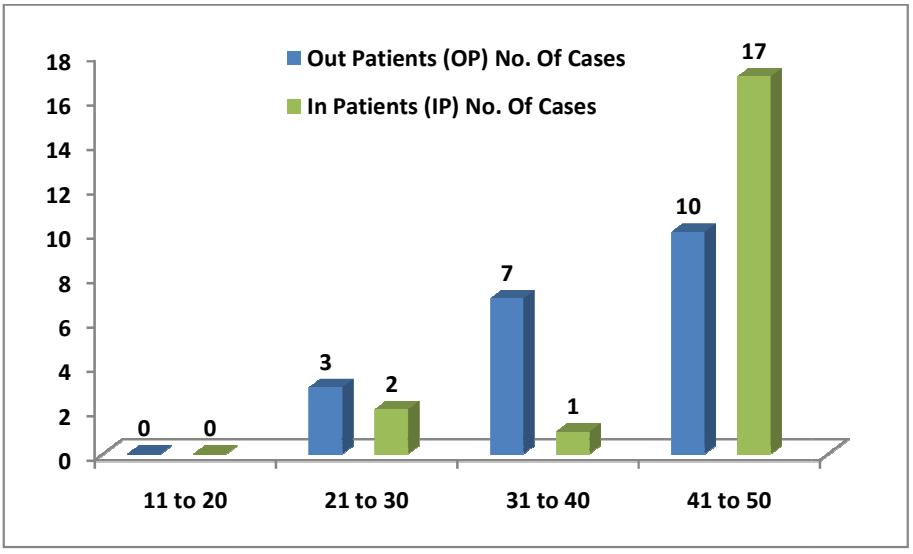
Table-2 Illustrates the Distribution of Age and its percentage.

TABLE-2 DISTRIBUTION OF AGE

Sl. No.	Age group in years	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	11 to 20	0	0%	0	0%
2.	21 to 30	3	15%	2	10%
3.	31 to 40	7	35%	1	5%
4.	41 to 50	10	50%	17	85%
	Total	**20**	**100%**	**20**	**100%**

From the above table it is observed that the highest incidence of Vali Azhal Keel Vayu in Out patients is among the age group of 41 to 50 with 50% and 31 to 40 with 35%, 15% were in the age group of 21 to 30 years. Among 20 In patients 10% were in the age group 21 to 30 years , 05% were in the age group of 31 to 40 years , 85% with the highest incidence in the age group of 41 to 50 years.

FIGURE-2 DISTRIBUTION OF AGE



3.KAALAM DISTRIBUTION:

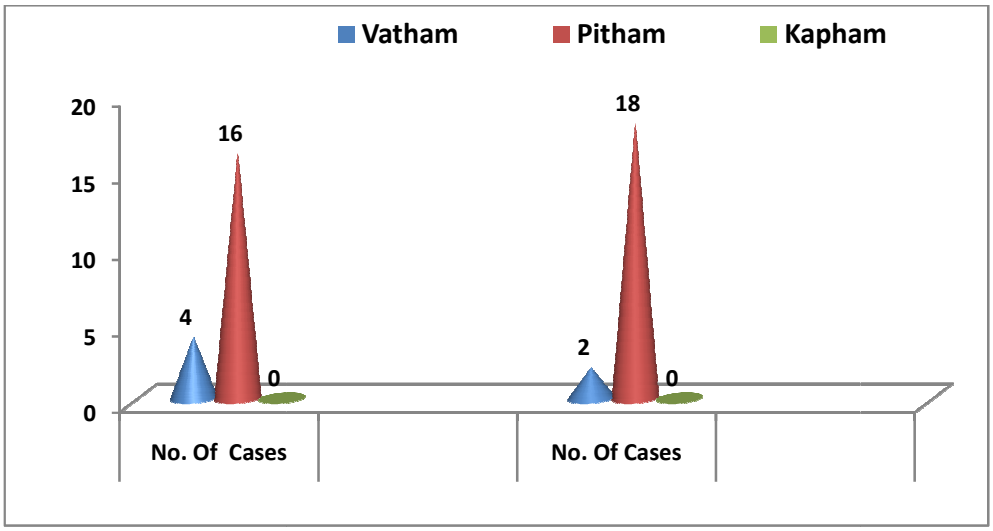
Table-3 Illustrates the Distribution of Kaalam and its percentage.

TABLE-3 DISTRIBUTION OF KAALAM

Sl. No.	Kaalam	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Vatham	4	20%	2	10%
2.	Pitham	16	80%	18	90%
3.	Kapham	0	0%	0	0%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 20% were affected in Vatha Kaalam and 80% were affected in Pitha Kaalam. Among 20 In patients, 90% were affected in Pitha Kaalam and 10% were affected in Vatha Kaalam.

FIGURE-3 DISTRIBUTION OF KAALAM



4.CONSTITUTION OF BODY:

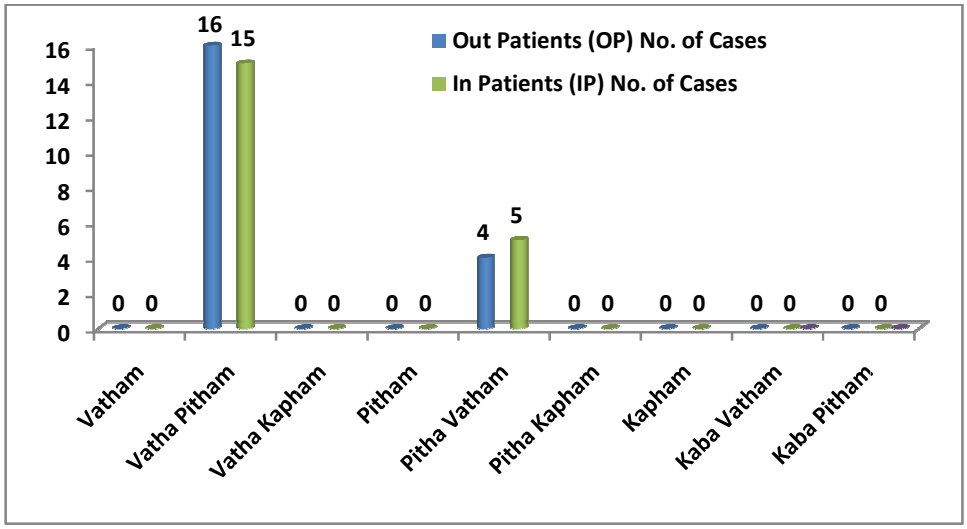
Table-4 Illustrates the Distribution of Constitution Body and its percentage.

TABLE-4 DISTRIBUTION OF CONSTITUTION OF BODY

Sl. No.	Constitution of body	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Vatham	0	0%	0	0%
2.	Vatha Pitham	16	80%	15	75%
3.	Vatha Kapham	0	0%	0	0%
4.	Pitham	0	0%	0	0%
5.	Pitha Vatham	4	20%	5	25%
6.	Pitha Kapham	0	0%	0	0%
7.	Kapham	0	0%	0	0%
8.	Kaba Vatham	0	0%	0	0%
9.	Kaba Pitham	0	0%	0	0%
	Total	**20**	**100%**	**20**	**100%**

Vatha Pitha Thegi register high incidence of Vali Azhal Keel Vayu with 80% OP and 75% IP. Remaining Pitha Vatha Thegi of 20% OP and 25% IP.

FIGURE-4 DISTRIBUTION OF CONSTITUTION OF BODY



5. GUNAM:

Table-5 Illustrates the Distribution of Gunam and its percentage.

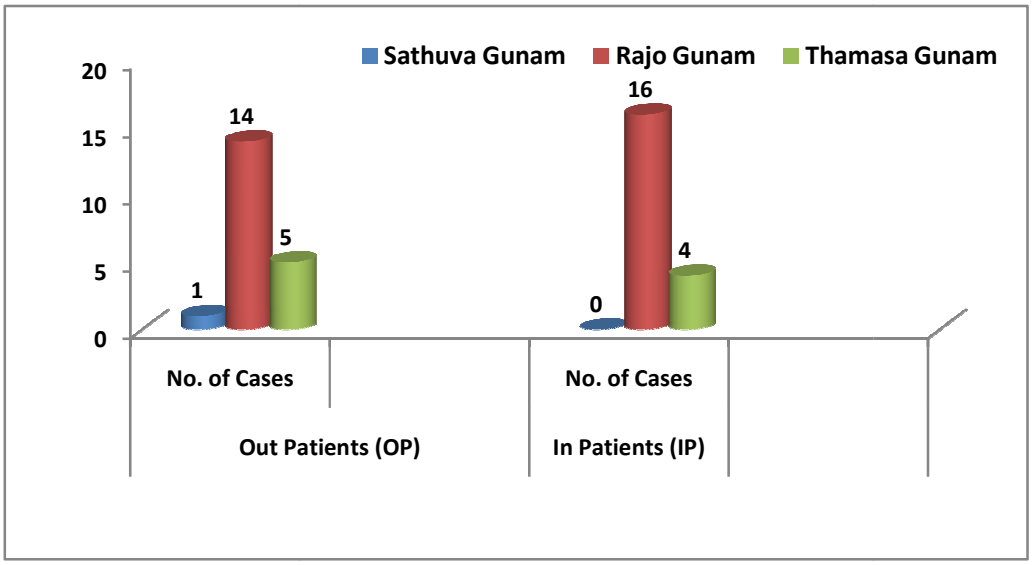
TABLE-5 DISTRIBUTION OF GUNAM

Sl. No.	Gunam	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Sathuva Gunam	1	5%	0	0%
2.	Rajo Gunam	14	70%	16	80%
3.	Thamasa Gunam	5	25%	4	20%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 5% were Sathuva Gunam, 70% were Rajo gunam and 25% were Thamasa gunam.

Among 20 In patients, 80% were Rajo gunam and 20% were Thamasa gunam.

FIGURE -5 DISTRIBUTION OF GUNAM



6. RELIGION:

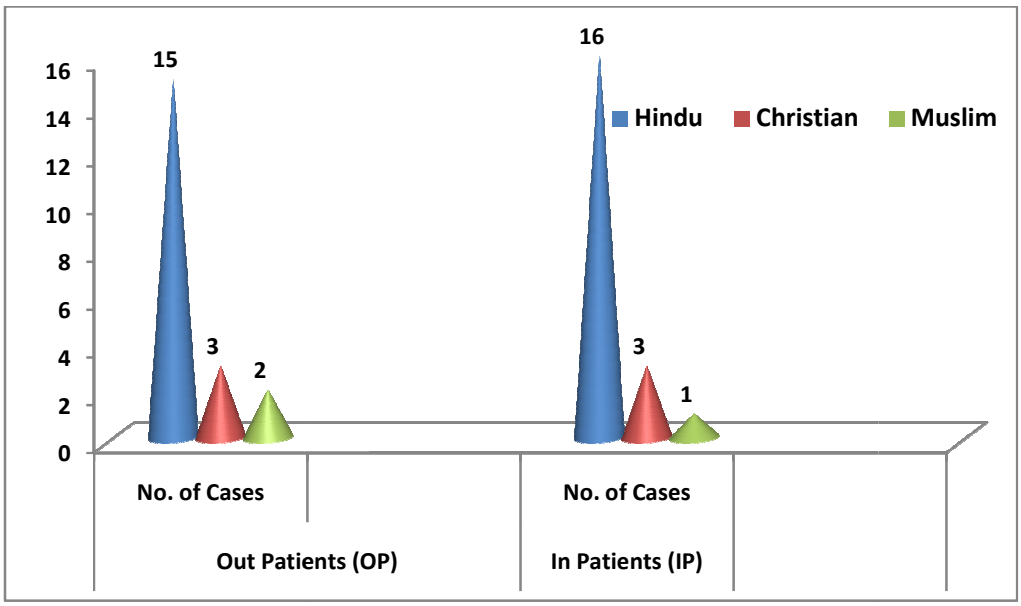
Table-6 Illustrates the Distribution of Religion and its percentage.

TABLE-6 DISTRIBUTION OF RELIGION

Sl. No.	Religion	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Hindu	15	75%	16	80%
2.	Christian	3	15%	3	15%
3.	Muslim	2	10%	1	5%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 75% were Hindus, 15% were Christians.10% were Muslims. Among 20 In patients, 80% were Hindus,15% were Christians and 5% were Muslims .

FIGURE-6 DISTRIBUTION OF RELIGION



7. PARUVA KAALAM:

Table-7 Illustrates the Distribution of Paruva Kaalam and its percentage.

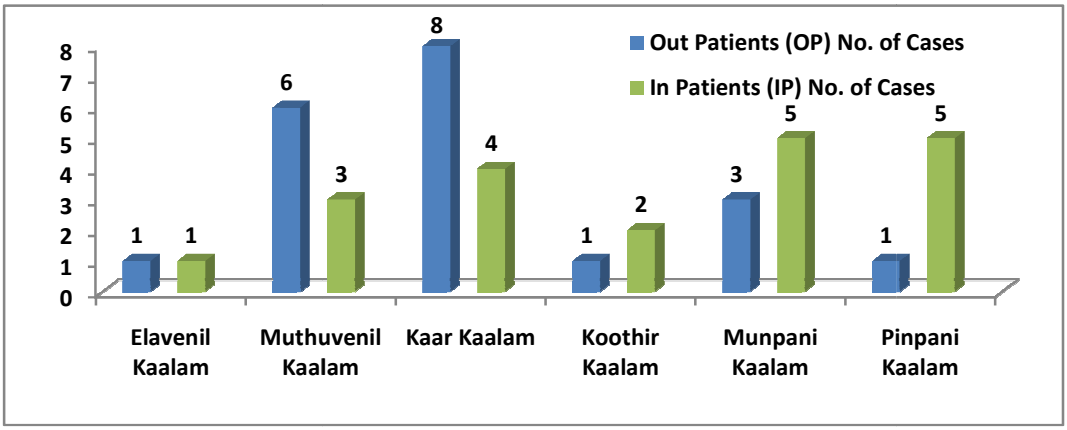
TABLE-7 DISTRIBUTION OF PARUVA KAALAM

Sl. No.	Paruva Kaalam	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Elavenil Kaalam	1	5%	1	5%
2.	Muthuvenil Kaalam	6	30%	3	15%
3.	Kaar Kaalam	8	40%	4	20%
4.	Koothir Kaalam	1	5%	2	10%
5.	Munpani Kaalam	3	15%	5	25%
6.	Pinpani Kaalam	1	5%	5	25%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 05% of cases were in Elavenil Kaalam, 30% of cases were in Muthuvenil Kaalam ,40% of cases were in Kaar Kaalam ,05% of cases were in Koothir Kaalam, 15% of cases were in Munpani Kaalam and 05% of cases were in Pinpani Kalam.

Among 20 In patients, 05% of cases were in Elavenil Kaalam, 15% of cases were in Muthuvenil Kaalam ,20% of cases were in Kaar Kaalam ,10% of cases were in Koothir Kaalam, 25% of cases were in Munpani Kaalam and 25% of cases were in Pinpani Kalam.

FIGURE-7 DISTRIBUTION OF PARUVA KAALAM



8. THINAI:

Table-8 Illustrates the Distribution of Thinai and its percentage.

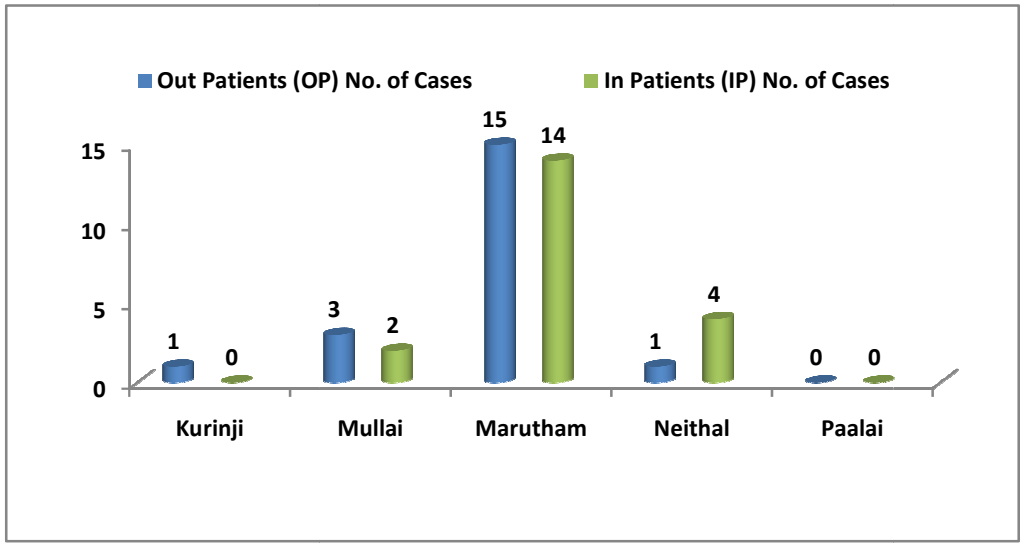
TABLE-8 DISTRIBUTION OF THINAI

Sl. No.	Thinai	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Kurinji	1	5%	0	0%
2.	Mullai	3	15%	2	10%
3.	Marutham	15	75%	14	70%
4.	Neithal	1	5%	4	20%
5.	Paalai	0	0%	0	0%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 5% were from Kurinji, 15% were from Mullai, 75% were in Marutham and 5% were in Neithal.

Among 20 In patients, 70% were in Marutham , 20% were in Neithal ,10% were in Mullai,

FIGURE-8 DISTRIBUTION OF THINAI



9. SOCIO - ECONOMICAL STATUS:

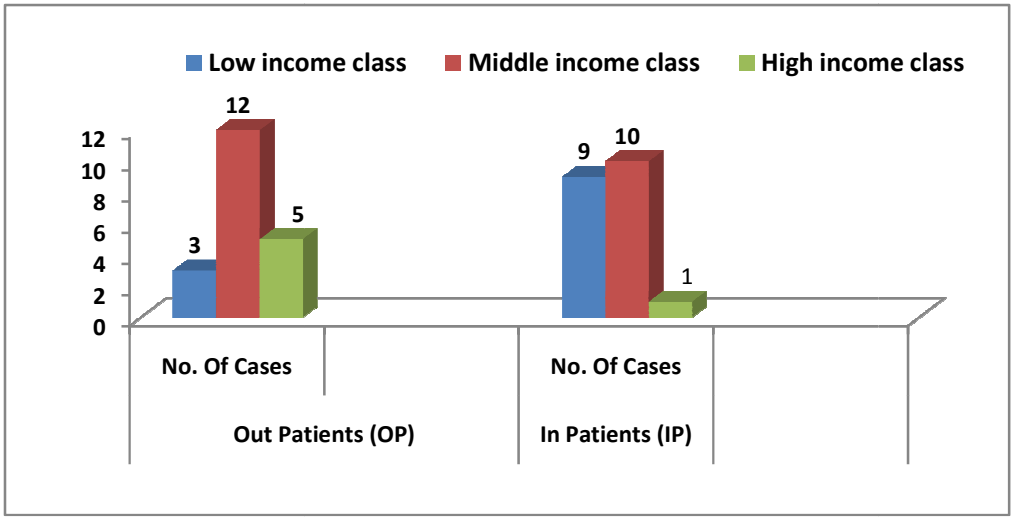
Table-9 Illustrates the Socio – Economical Status of patients and its percentage.

TABLE-9 SOCIO – ECONOMICAL STATUS

Sl. No.	Socio – Economical Status	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Low income class	3	15%	9	45%
2.	Middle income class	12	60%	10	50%
3.	High income class	5	25%	1	5%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 15% were in Low income class, 60% were in Middle income class and 25% were in High income class. Among 20 In patients, 45% were in Low income class, 50% were in Middle income class and 5% were in High income class.

FIGURE-9 SOCIO – ECONOMICAL STATUS



10. FOOD HABITS:

Table-10 Illustrates the Distribution of diet among the patients and its percentage.

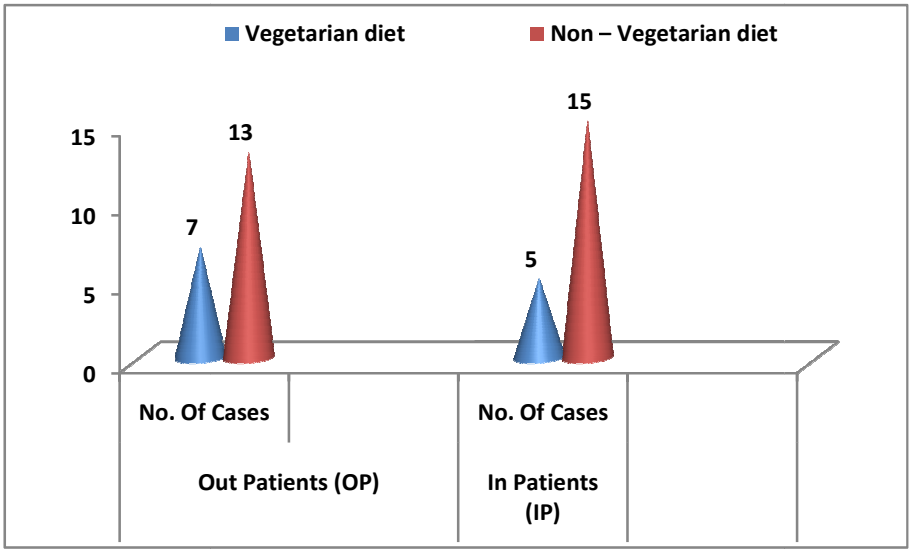
TABLE-10 FOOD HABITS

Sl. No.	Food Habits	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Vegetarian diet	7	35%	5	25%
2.	Non – Vegetarian diet	13	65%	15	75%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 35% were Vegetarian and 65% were non – vegetarian.

Among 20 In patients, 25% were vegetarian and 75% were non – vegetarian.

FIGURE-10 FOOD HABITS



11. FAMILY HISTORY:

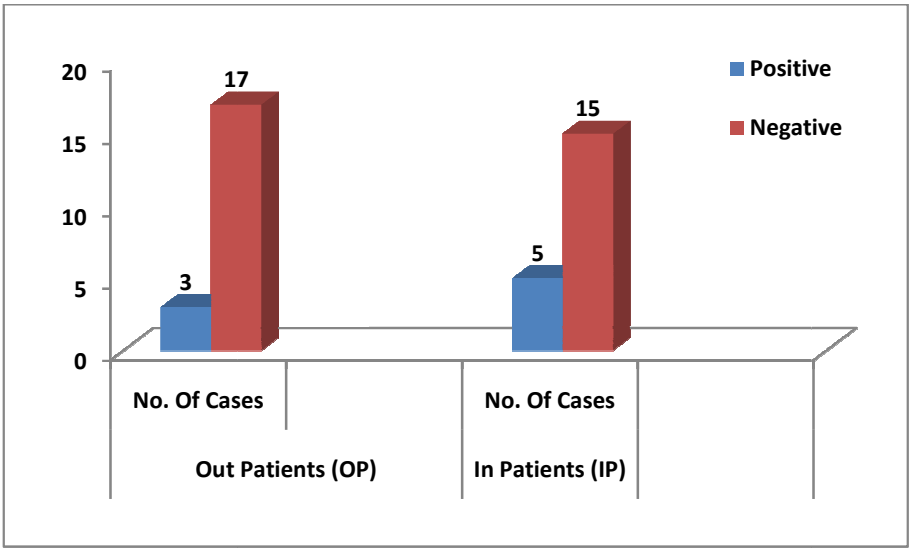
Table-11 Illustrates the Family History and its percentage.

TABLE-11 FAMILY HISTORY

Sl. No.	Family History	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Positive	3	15%	5	25%
2.	Negative	17	85%	15	75%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 15% have positive Family History and 85% don't have any positive Family History. Among 20 In patients, 25% have positive Family History and 75% don't have any positive Family History.

FIGURE-11 FAMILY HISTORY



12. OCCUPATION:

Table-12 Illustrates the Occupation and its percentage.

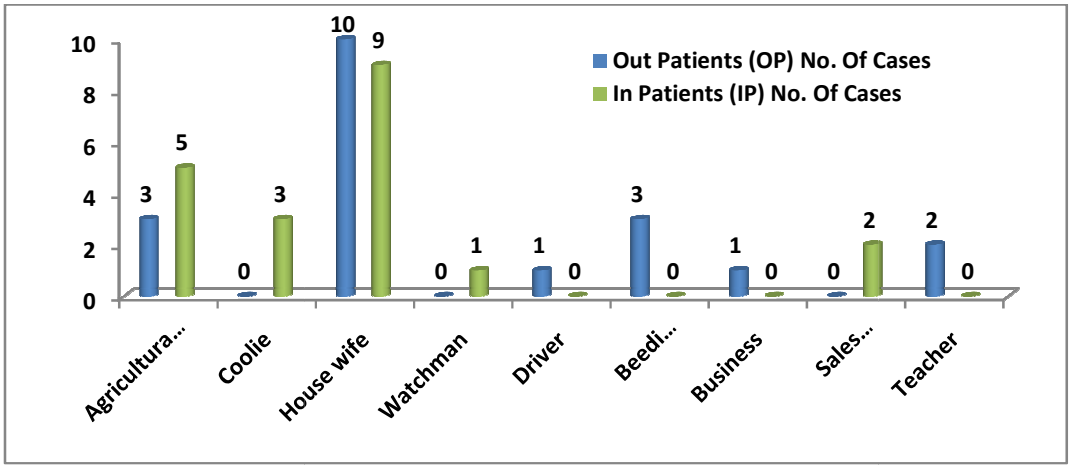
TABLE-12 OCCUPATION

Sl. No.	Occupation	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Agricultural labours	3	15%	5	25%
2.	Coolie	0	0%	3	15%
3.	House wife	10	50%	9	45%
4.	Watchman	0	0%	1	5%
5.	Driver	1	5%	0	0%
6.	Beedi Worker	3	15%	0	0%
7.	Business	1	5%	0	0%
8.	Sales Women	0	0%	2	10%
9.	Teacher	2	10%	0	0%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 15% Agricultural labours, 50% House Wife, 5% Driver, 1 5% Beedi worker, 5% Business and 10% Teacher.

Among 20 In patients, 25% Agricultural labours, 15% Coolie, 45% House Wife,5% Watchman, and 10% Sales women were observed.

FIGURE-12 OCCUPATION



13.CLINICAL MANIFESTATION:

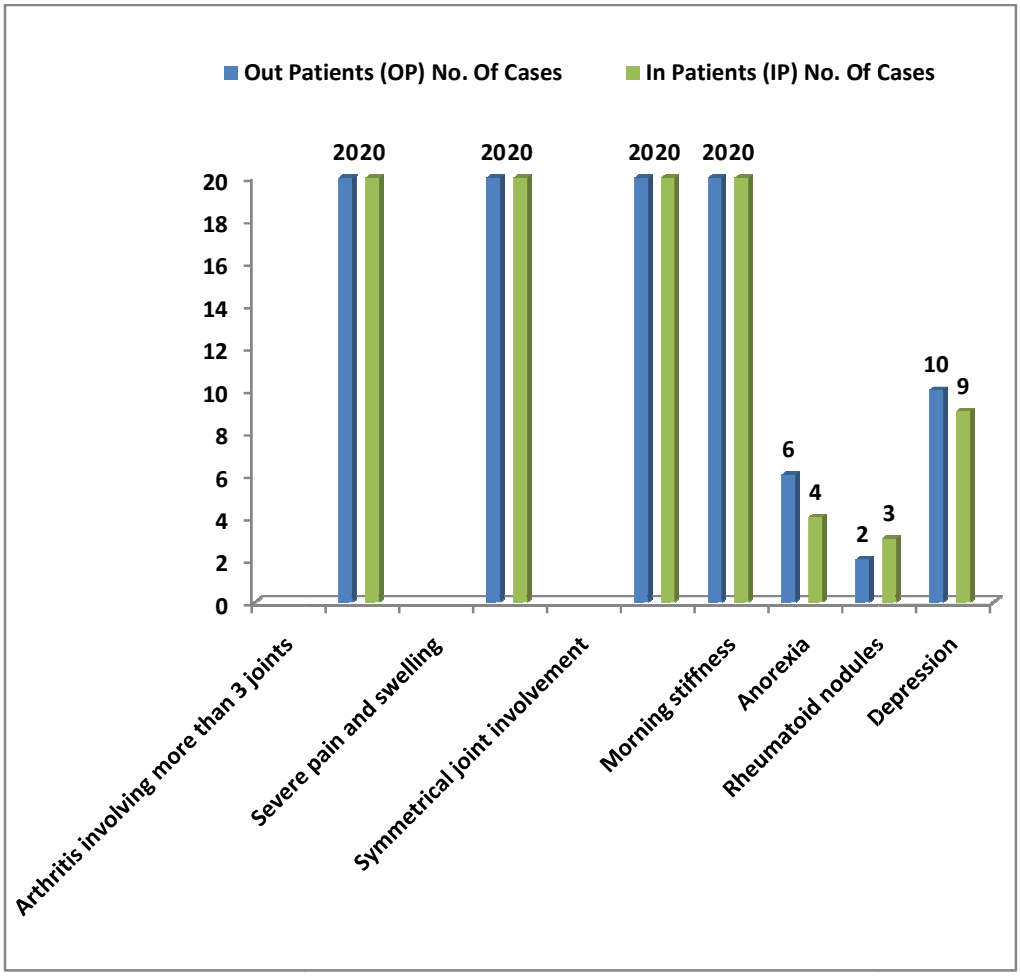
Table-13 Illustrates the Clinical Manifestation and its percentage.

TABLE-13 CLINICAL MANIFESTATION

Sl. No.	Symptoms	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Arthritis involving more than 3 joints	20	100%	20	100%
2.	Severe pain and swelling	20	100%	20	100%
3.	Symmetrical joint involvement	20	100%	20	100%
4.	Morning stiffness	20	100%	20	100%
5.	Anorexia	6	30%	4	20%
6.	Rheumatoid nodules	2	10%	3	15%
7.	Depression	10	50%	9	45%

Among 20 Out patients, 100% cases have arthritis involving more than 3 joints, severe pain and swelling, symmetrical joint involvement,100% have morning stiffness , 50% have depression, 30% have Anorexia, 10% have Rheumatoid nodules. Among 20 In patients, 100% cases have arthritis involving more than 3 joints, severe pain and swelling, symmetrical joint involvement,100% have morning stiffness, 45%have depression, 15% have rheumatoid nodules, 20% have anorexia.

FIGURE-13 CLINICAL MANIFESTATION



14. DURATION OF ILLNESS:

Table-14 Illustrates the Duration of Illness and its percentage.

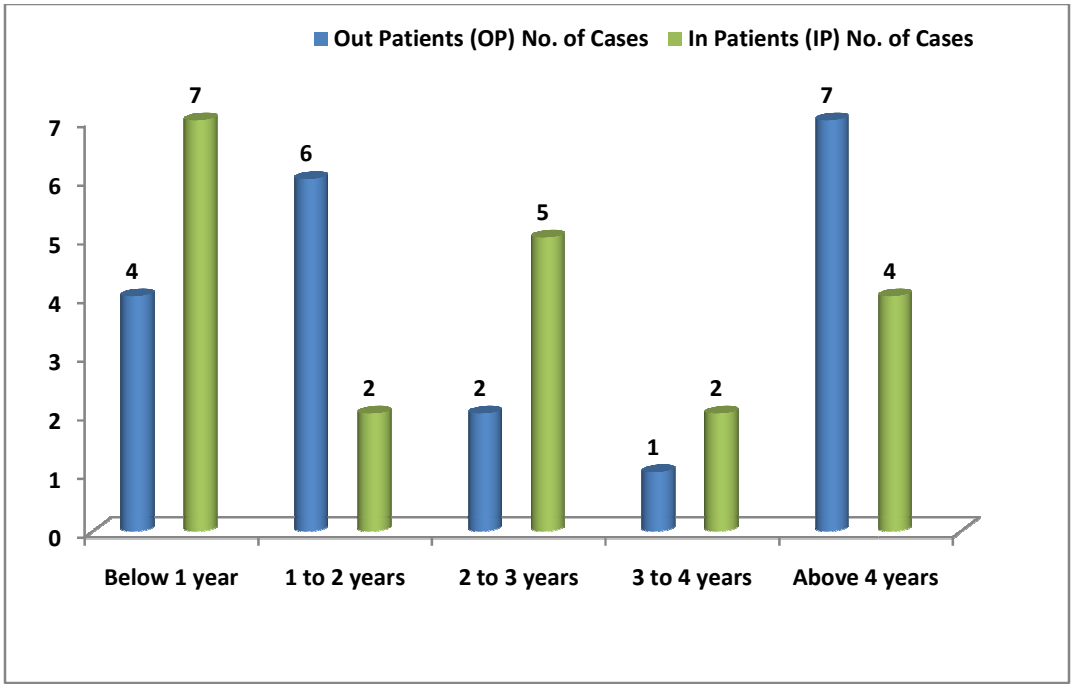
TABLE-14 DURATION OF ILLNESS

Sl. No.	Duration of illness	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Below 1 year	4	20%	7	35%
2.	1 to 2 years	6	30%	2	10%
3.	2 to 3 years	2	10%	5	25%
4.	3 to 4 years	1	5%	2	10%
5.	Above 4 years	7	35%	4	20%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, Duration of Illness was 20% below 1 year, 30% in 1 to 2 years ,10% in 2 to 3 years, 5% in 3 to 4 years and 35% in above 4 years.

Among 20 In patients, Duration of Illness was 35% below 1 year, 10% in 1 to 2 years, 25% in 2 to 3 years and 10% in 3to 4 years,20% above 4 year.

FIGURE-14 DURATION OF ILLNESS



15. KANMENTHIRIYAM:

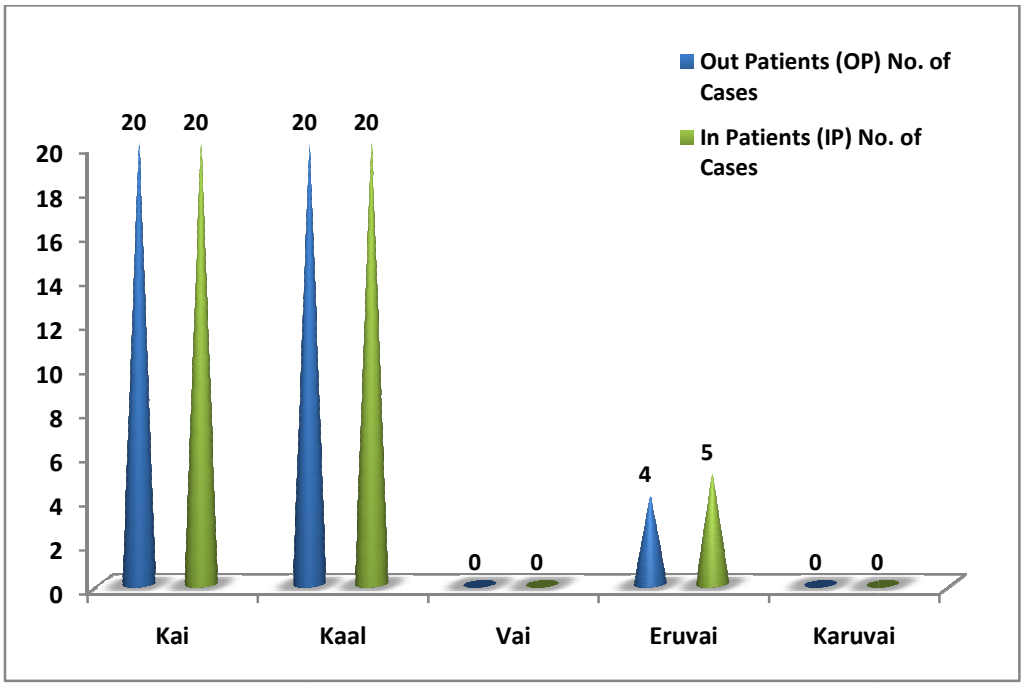
Table-15 Illustrates the Kanmenthiriyam and its percentage.

TABLE-15 KANMENTHIRIYAM

Sl. No.	Kanmenthiriyam	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Kai	20	100%	20	100%
2.	Kaal	20	100%	20	100%
3.	Vai	0	0%	0	0%
4.	Eruvai	4	20%	5	25%
5.	Karuvai	0	0%	0	0%

Among 20 Out patients, 100% cases were affected in Kai, Kaal, 20% cases were affected in Eruvai. Among 20 In patients, 100% cases were affected in Kai, Kaal, 25% cases were affected in Eruvai.

FIGURE-15 KANMENTHIRIYAM



16.GNANENDRIUM

Table-16 Illustrates the Gnanendrium and its percentage.

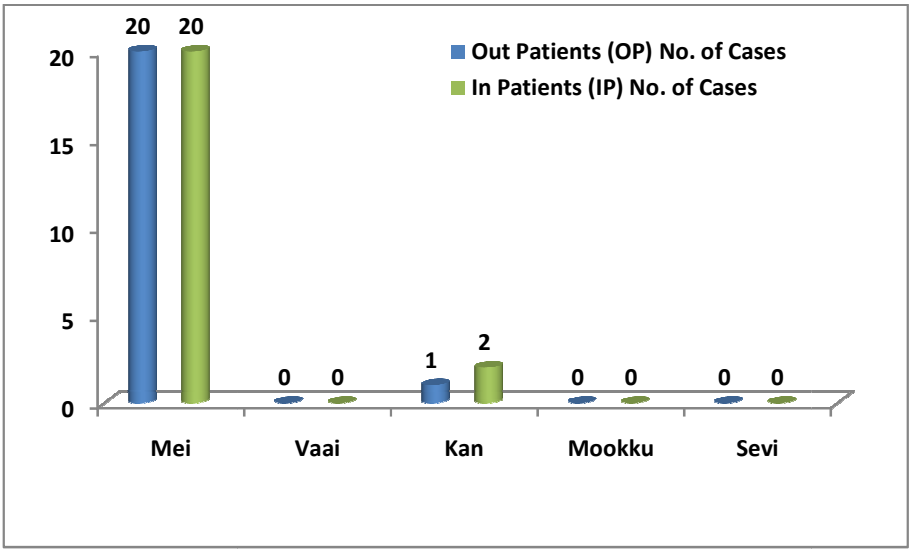
TABLE-16 GNANENDRIUM

Sl. No.	Gnanendrium	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Mei	20	100%	20	100%
2.	Vaai	0%	0%	0%	0%
3.	Kan	1	5%	2	10%
4.	Mookku	0	0%	0	0%
5.	Sevi	0	0%	0	0%

Among 20 Out patients, 100% of the patients were affected in Mei, 5% of the patients were affected in kan.

Among 20 In patients, 100% of the patients were affected in Mei, 10% of the patients were affected in kan.

FIGURE-16 GNANENDRIUM



17.CONDITION OF MUKKUTRAM:

17(a) Condition of Vatham.

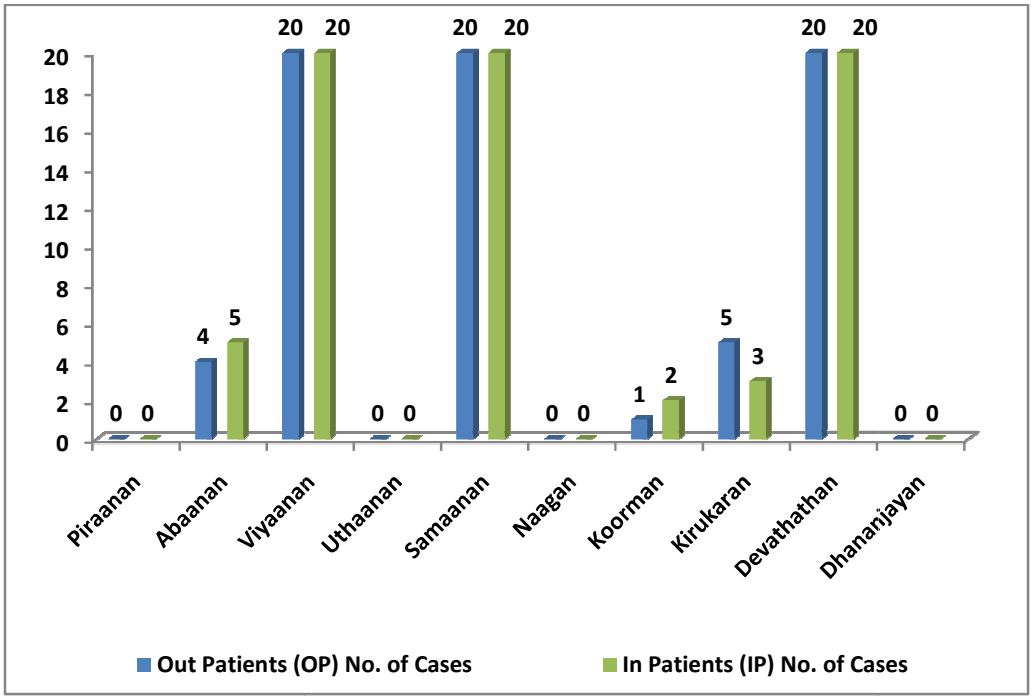
Table-17 Illustrates the Condition of Vatham and its percentage.

TABLE-17 (a) CONDITION OF VATHAM

Sl. No.	Condition of Vatham	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Piraanan	0	0%	0	0%
2.	Abaanan	4	20%	5	25%
3.	Viyaanan	20	100%	20	100%
4.	Uthaanan	0	0%	0	0%
5.	Samaanan	20	100%	20	100%
6.	Naagan	0	0%	0	0%
7.	Koorman	1	5%	2	10%
8.	Kirukaran	5	25%	3	15%
9.	Devathathan	20	100%	20	100%
10.	Dhananjayan	0	0%	0	0%

Viyaanan, Samaanan, were affected in 100% of both Out patients and In patients. Abaanan was affected in 20% of Out patients, and 25% of the In patients, Kirugaran was affected in 25% of Out Patients, and 15% of In patients. Devathathan was affected in 100% of Out patients, and 100% of In patients. Koorman was affected in 5% of Out patients and 10% of In patients,

FIGURE-17 (a) CONDITION OF VATHAM



17(b). CONDITION OF PITHAM

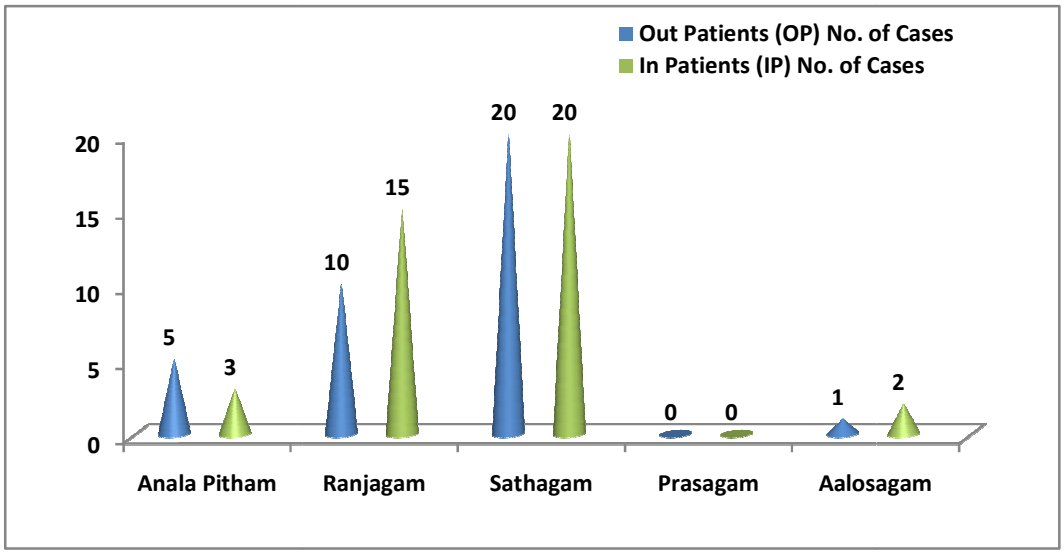
Table-17 (b) Illustrates the Condition of Pitham and its percentage.

TABLE-17 (b) CONDITION OF PITHAM

Sl. No.	Pitham	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Anala Pitham	5	25%	3	15%
2.	Ranjagam	10	50%	15	75%
3.	Sathigam	20	100%	20	100%
4.	Prasagam	0	0%	0	0%
5.	Aalosagam	1	5%	2	10%

Among 20 Out patients, 25% affected in Anala Pitham, 50% in Ranjaga Pitham and 100% in Sathiga Pitham, 5% in Aalosagapitham. Among 20 In patients, 15% affected in Anala Pitham, 75% in Ranjaga Pitham and 100% in Sathiga Pitham, 10% in Aalosagapitham.

FIGURE-17 (b) CONDITION OF PITHAM



17 (c) CONDITION OF KAPHAM

Table-17 (c) Illustrates the Condition of Kapham and its percentage.

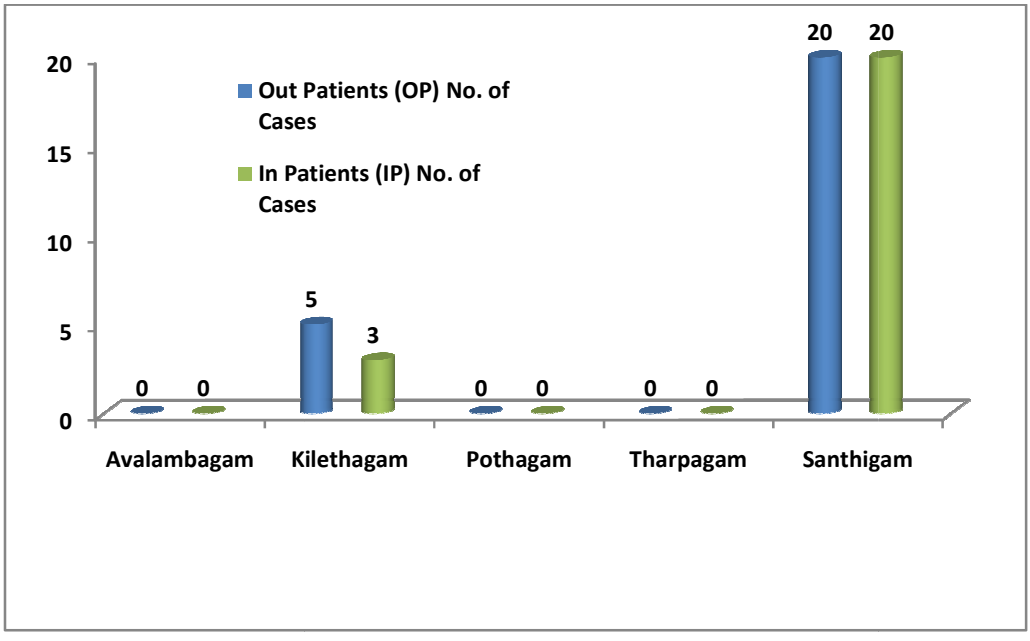
TABLE-17 (c) CONDITION OF KAPHAM

Sl. No.	Kapham	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Avalambagam	0	0%	0	0%
2.	Kilethagam	5	25%	3	15%
3.	Pothagam	0	0%	0	0%
4.	Tharpagam	0	0%	0	0%
5.	Santhigam	20	100%	20	100%

Kilethagam was affected in 25% of Out patients and 15% of In patients.

Santhigam was affected in 100% of both Out patients and In patients.

FIGURE-17 (c) CONDITION OF KAPHAM



18. INVOLVEMENT OF UDAL KATTUGAL

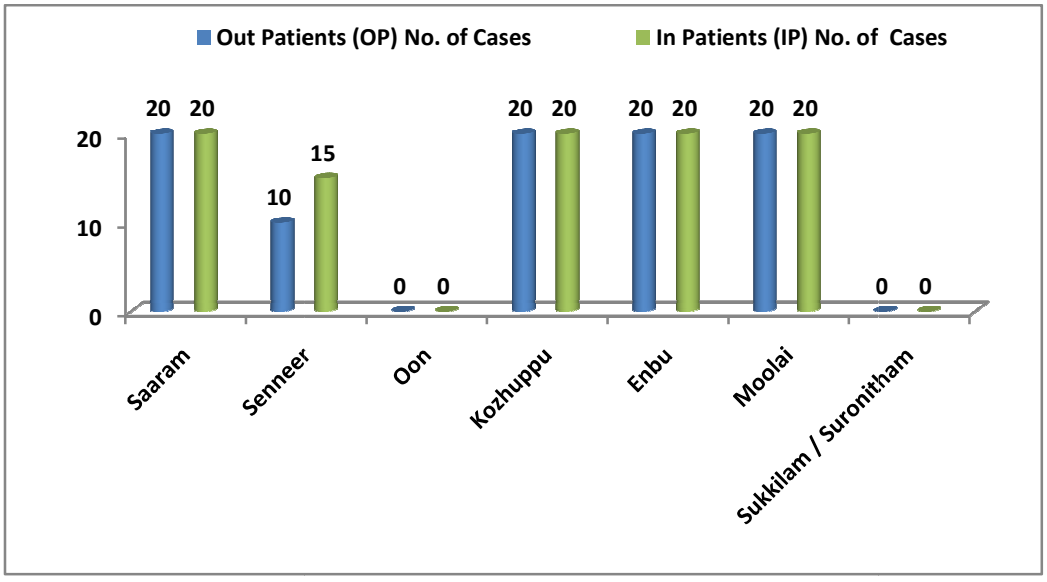
Table-18 Illustrates the involvement of Udal Kattugal (or) Udal Thathukal and its percentage.

TABLE-18 INVOLVEMENT OF UDAL KATTUGAL

Sl. No.	Udal Kattugal	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Saaram	20	100%	20	100%
2.	Senneer	10	50%	15	75%
3.	Oon	0	0%	0	0%
4.	Kozhuppu	20	100%	20	100%
5.	Enbu	20	100%	20	100%
6.	Moolai	20	100%	20	100%
7.	Sukkilam / Suronitham	0	0%	0	0%

Among 20 Out patients and In patients Saaram, Enbu,Kozhuppu, Moolai were affected in 100% of the cases. senneer was affected in 50% of OP and 75% of IP.

FIGURE-18 INVOLVEMENT OF UDAL KATTUGAL



19.CONDITIONS OF ENVAGAI THERVUGAL

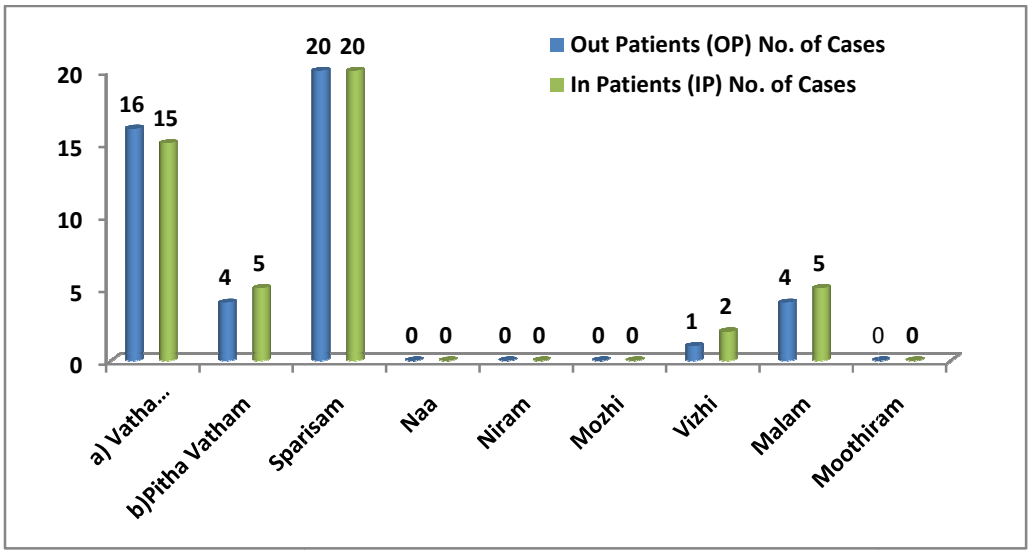
Table-19 Illustrates the conditions of Envagai Thervugal and its percentage.

TABLE-19 CONDITION OF ENVAGAI THERVUGAL

Sl. No.	Envagai Thervugal	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Naadi (Thontha Naadi)	20	100%	20	100%
	1). Vatha Pitham	16	80%	15	75%
	2). Vatha Kapham	0	0%	0	0%
	3). Pitha Vatham	4	20%	5	25%
	4). Pitha Kapham	0	0%	0	0%
	5). Kapha Vatham	0	0%	0	0%
	6). Kapha Pitham	0	0%	0	0%
2.	Sparisam	20	100%	20	100%
3.	Naa	0	0%	0	0%
4.	Niram	0	0%	0	0%
5.	Mozhi	0	0%	0	0%
6.	Vizhi	1	5%	2	10%
7.	Malam	4	20%	5	25%
8.	Moothiram	0	0%	0	0%

Among 20 Out patients, 5 % were affected in Vizhi, 20% were affected in Malam, 100% was affected in Sparisam, Naadi-80% with Vatha Pitham, 20% with Pitha Vatham . Among 20 In patients, 10% were affected in Vizhi, 25% was affected in Malam, 100% was affected in Sparisam, Naadi-75% with Vatha Pitham , and 25% with Pitha Vatham.

FIGURE-19 CONDITION OF ENVAGI THERVUGAL



20.NEER KURI

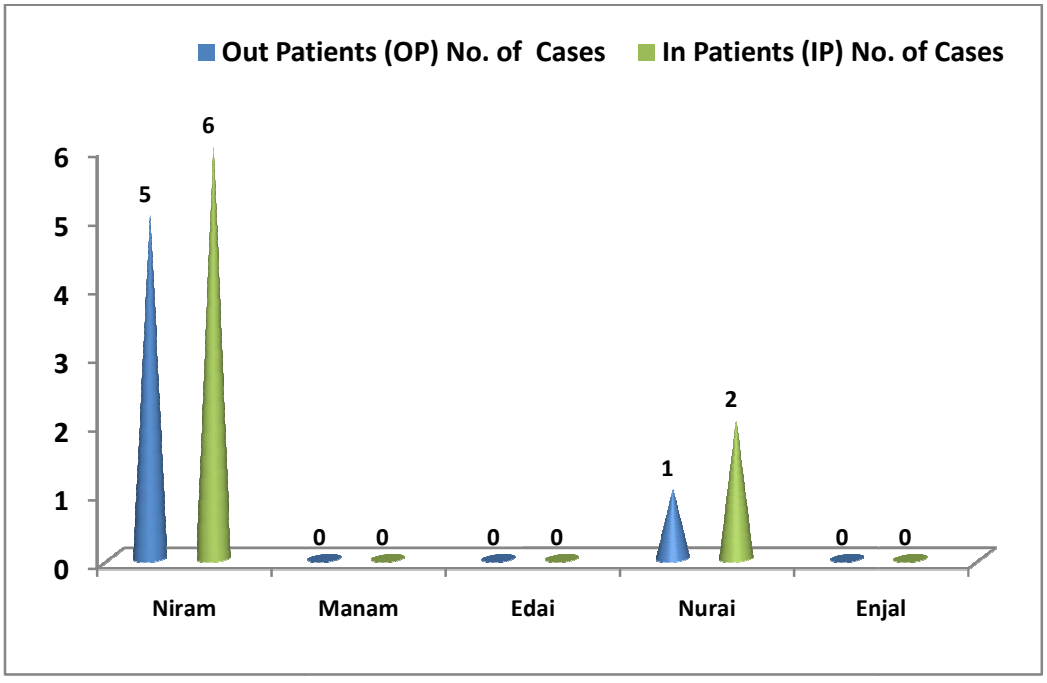
Table-20 Illustrates the Neer kuri condition and its percentage.

TABLE-20 NEER KURI

Sl. No.	Neer kuri	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Niram	5	25%	6	30%
2.	Manam	0	0%	0	0%
3.	Edai	0	0%	0	0%
4.	Nurai	1	5%	2	10%
5.	Enjal	0	0%	0	0%

Niram was affected in 25% of Out patients and 30% of In patients. Nurai was affected in 5% of Out patients and 10% of In patients.

FIGURE – 20 NEER KURI



21.NEI KURI

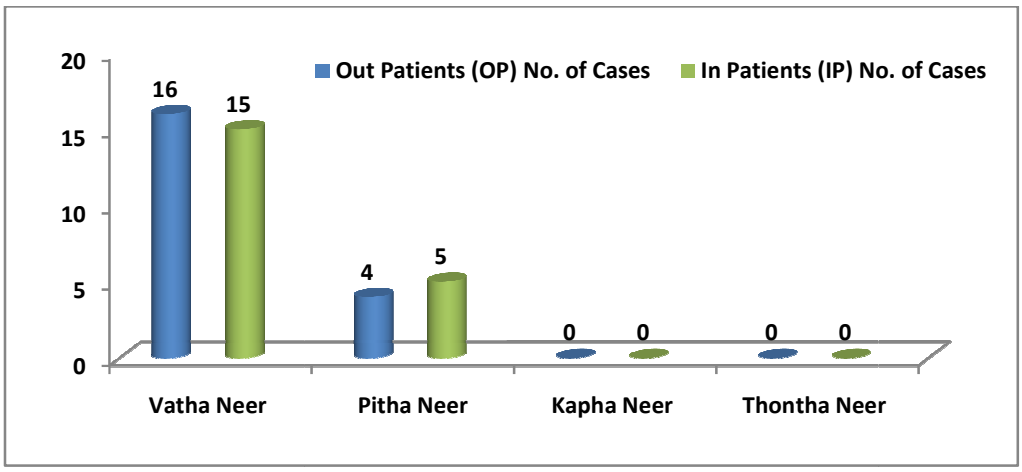
Table-21 Illustrates the Nei Kuri conditions and its percentage.

TABLE-21 NEI KURI

Sl. No.	Nei Kuri	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Vatha Neer / spreading like snake	16	80%	15	75%
2.	Pitha Neer / spreading like ring	4	20%	5	25%
3.	Kapha Neer / spreading like pearl	0	0%	0	0%
4.	Thontha Neer / Asthiya Neikurigal	0	0%	0	0%

Among 20 Out patients, 80% had Vatha Neer, 20% had Pitha neer. Among 20 In patients, 75% had Vatha Neer, 25% had Pitha Neer.

FIGURE-21 NEI KURI



22.ASSESSMENT OF OUTCOME:

Table-22 Illustrates the Assessment of Outcome and its percentage.

TABLE-22 ASSESSMENT OF OUTCOME

Sl. No.	Assessment of Outcome	Before Treatment				After Treatment			
		Out Patients (OP)		In Patients (IP)		Out Patients (OP)		InPatients(IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)	No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Low	0	0%	0	0%	11	55%	12	60%
2.	Moderate	0	0%	0	0%	6	30%	6	30%
3.	High	20	100%	20	100%	3	15%	2	10%

Lower disease activity 2.6<DAS28 ≤ 3.2

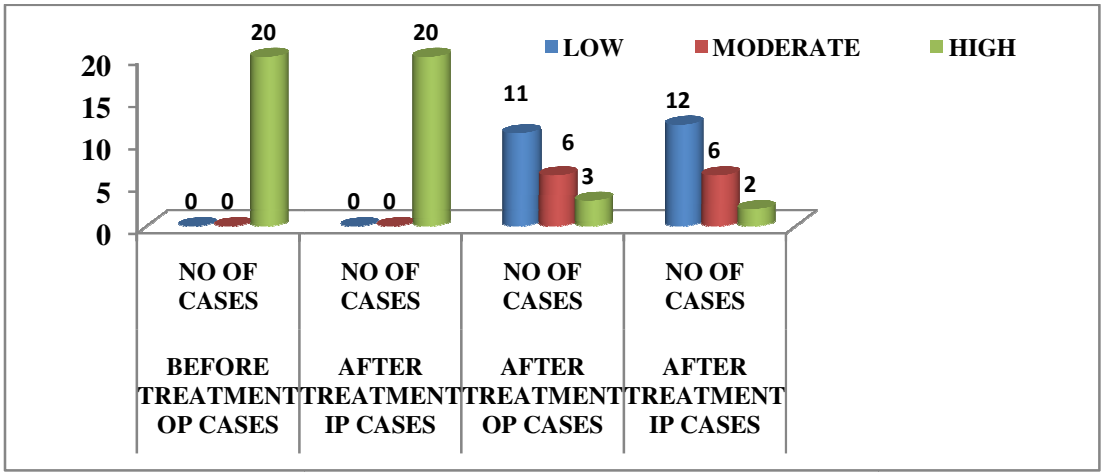
Moderate disease activity 3.2<DAS28 ≤ 5.1

High disease activity DAS28>5.1

Reference:

Prevoo ML, Van't Hof MA Kuper HH, Van Leeuwen MA, Van de Putte LB, Van Rie / PL (1995). "Modified disease activity scores that include twenty-eightjoints counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis". Arthritis Rheum. 38 (1):44-8.

FIGURE -22 ASSESSMENT OF OUTCOME



Before Treatment:

Among 20 Out patients, and 20 In patients 100% of cases were with High disease activity.

After Treatment:

Among 20 Out patients, 55% of cases with Low disease activity 30% of cases with Moderate disease activity and 15% of cases with High disease activity. Among 20 In patients, 60% of cases with Low disease activity, 30% of cases with Moderate disease activity and 10% of cases with High disease activity.

23. GRADATION OF RESULTS:

Table-23 Illustrates the Gradation of results and its percentage.

TABLE-23 GRADATION OF RESULTS

Sl. No.	Results	Out Patients (OP)		In Patients (IP)	
		No. of Cases	Percentage (%)	No. of Cases	Percentage (%)
1.	Good response	11	55%	12	60%
2.	Moderate response	6	30%	6	30%
3.	Poor response	3	15%	2	10%
	Total	**20**	**100%**	**20**	**100%**

Among 20 Out patients, 55% of cases showed Good response, 30% of cases showed Moderate response and 15% of cases showed Poor response.

Among 20 In patients, 60% of cases showed Good response, 30% of cases showed Moderate response and 10% of cases showed Poor response.

FIGURE-23 GRADATION OF RESULTS

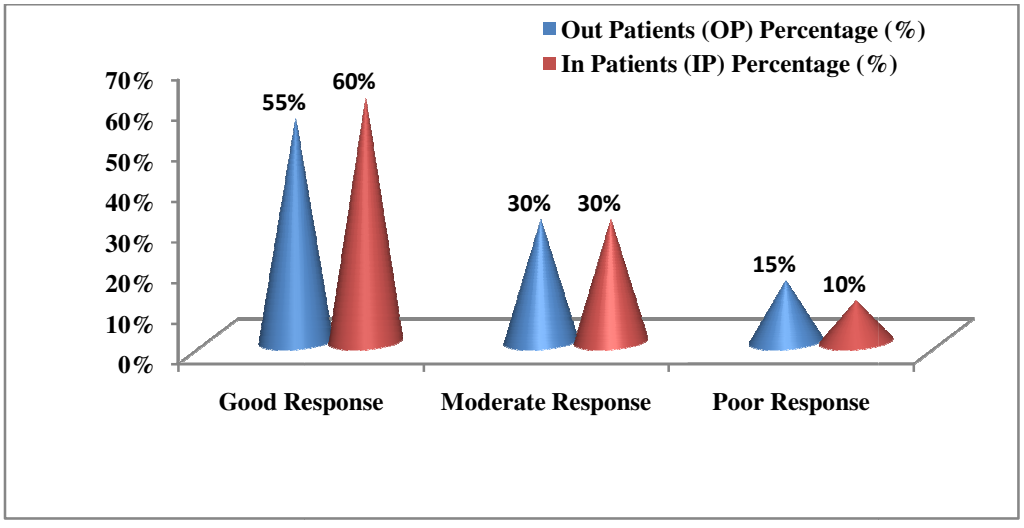


TABLE-24(a)

i) LABORATORY INVESTIGATION OF OUT PATIENTS

SL. NO	OP. NO	HAEMATOLOGICAL REPORT												URINE ANALYSIS					
		BEFORE TREATMENT						AFTER TREATMENT						BEFORE TREATMENT			AFTER TREATMENT		
		TC	DC			ESR (1hr)	Hb gms %	TC	DC			ESR (1hr)	Hb gms %	Alb	Sug	Dep – Epi cells/ Pus cells	Alb	Sug	Dep – Epi cells/ Pus cells
			P	L	E				P	L	E								
1.	**50264**	6000	63	35	2	70	10.7	6500	66	32	2	25	11.1	NIL	NIL	NAD	NIL	NIL	NAD
2.	**50813**	7300	70	27	3	30	12.4	7100	73	25	2	8	12.9	NIL	NIL	NAD	NIL	NIL	NAD
3.	**51145**	9600	68	27	5	53	10.5	7500	69	28	3	10	10.9	TRACE	NIL	3-8 pus cells	NAD	NIL	1-2 pus cells
4.	**51887**	8800	66	30	4	28	8.2	9600	71	27	2	7	11.9	TRACE	NIL	10-15pus cells	NIL	NIL	1-2 pus cells
5.	**53806**	9300	69	26	5	52	11.1	9500	72	25	3	25	11.0	NIL	NIL	NAD	NIL	NIL	NAD
6	**56271**	7400	69	29	2	35	13.5	7300	73	26	1	10	11.8	NIL	NIL	NAD	NIL	NIL	NAD
7.	**60797**	7400	65	29	6	45	12.0	7000	60	38	2	8	12.8	NIL	NIL	NIL	NAD	NIL	NIL
8.	**70311**	7900	78	19	3	50	9.4	7500	64	33	3	9	9.5	NIL	NIL	1-2 epi.cells	NIL	NIL	NAD
9.	**71246**	8900	68	28	4	40	11.4	8700	70	27	3	17	11.3	NIL	NIL	NAD	NIL	NIL	NAD
10.	**74409**	7800	58	36	6	26	12.8	7900	66	32	2	6	13.2	NIL	NIL	NAD	NIL	NIL	NAD
11	**74892**	7300	56	38	6	80	10.5	7400	64	32	4	42	11.8	TRACE	NIL	2-3 epi .cells	NIL	NIL	NAD
12.	**75542**	9900	67	30	3	50	12.7	9700	70	28	2	9	12.6	NIL	NIL	Few pus cells	NIL	NIL	NAD
13.	**75545**	7600	64	33	3	45	6.8	7800	67	31	2	7	7.0	NIL	NIL	NAD	NIL	NIL	NAD
14	**75662**	7300	57	40	3	58	12.1	7800	60	36	4	22	13.0	NIL	NIL	NAD	NIL	NIL	NAD
15.	**77398**	6000	58	40	2	50	13.8	6400	68	30	2	9	14.3	NIL	NIL	NAD	NIL	NIL	NAD
16.	**95880**	8600	66	31	3	44	14.3	8500	71	27	2	8	13.9	NIL	NIL	Few pus cells	NIL	NIL	NAD
17	**9175**	8500	62	31	7	38	9.7	8300	68	28	4	7	10.6	NIL	NIL	NAD	NIL	NIL	NAD
18	**14488**	6800	60	36	4	65	10.9	5400	68	29	3	27	12.8	NIL	NIL	NAD	NIL	NIL	NAD
19	**16486**	8900	63	29	8	55	10.4	8600	70	27	3	19	11.4	NIL	NIL	NAD	NIL	NIL	NAD
20	**40744**	7800	68	28	4	62	11.4	7600	72	25	3	24	11.2	NIL	NIL	1-2 puscells	NIL	NIL	NAD

TABLE-24(a)

ii). LABORATORY INVESTIGATION (OUT PATIENTS)

SI NO	OP NO	BEFORE TREATMENT				AFTER TREATMENT			
		Blood sugar(R)	Blood Urea	Serum cholestrol	Serum creatinine	Blood sugar(R)	Blood Urea	Serum cholesterol	Serum creatinine
1	**50264**	97	25	179	0.6	74	21	156	0.7
2	**50813**	84	25	213	1.0	66	30	180	0.8
3	**51145**	74	16	291	0.8	84	16	140	0.7
4	**51887**	123	10	169	0.6	87	28	143	0.6
5	**53806**	138	20	200	0.5	125	23	187	0.6
6	**56271**	85	27	157	0.9	76	24	130	0.8
7	**60797**	109	27	169	0.7	89	24	161	0.5
8	**70311**	122	14	186	0.7	82	20	179	0.8
9	**71246**	160	24	187	0.5	98	25	156	0.7
10	**74409**	98	24	131	1.0	72	26	124	0.8
11	**74892**	130	26	187	0.9	119	24	196	1.0
12	**75542**	182	28	170	0.8	154	26	148	0.9
13	**75545**	104	26	167	0.5	94	25	156	0.7
14	**75662**	250	24	196	1.0	208	20	180	0.9
15	**77398**	86	32	168	0.8	92	34	155	0.6
16	**95880**	64	15	166	1.0	67	23	148	0.9
17	**9175**	90	16	171	0.6	92	21	136	0.5
18	**14488**	108	25	148	0.6	100	23	140	0.6
19	**16486**	135	18	167	0.7	84	22	178	0.5
20	**40744**	102	20	201	0.8	96	26	160	0.7

Table-24(a)

iii). LABORATORY INVESTIGATIONS (OUT PATIENTS)

SI NO	OP NO	BEFORE TREATMENT				AFTER TREATMENT			
		RA Factor (IU/ml)	ASO Titre (IU/ml)	CRP (mg/dl)	Anti –CCP (U/ml)	RA Factor (IU/ml)	ASO Titre (IU/ml)	CRP (mg/dl)	Anti –CCP (IU/ml)
1.	**50264**	152.0	97.5	8.0	-	145	85.4	7.2	-
2.	**50813**	45	90.4	5.3	-	42.0	78.8	4.7	-
3.	**51145**	85.1	182	6.3	-	73.8	167.3	5.9	-
4.	**51887**	40.0	78.4	4.9	-	36.7	66.8	3.5	-
5.	**53806**	76.2	95.8	53.56	-	72.6	91.5	50.4	-
6	**56271**	22.4	69.3	4.0	-	17.5	54	2.9	-
7.	**60797**	52.0	114.7	6.8	26.9	48.2	103	5.7	24.3
8.	**70311**	35.7	135	3.5	-	26.8	124.5	2.6	-
9.	**71246**	63.6	65	6.2	-	58.3	61	5.7	-
10.	**74409**	25.9	63.5	4.2	-	20.4	57	3.9	-
11	**74892**	180	240	28.0	40.73	175.3	233.6	6.2	39.16
12.	**75542**	65.5	172	5.3	-	59.4	165	4.5	-
13.	**75545**	30.0	83.7	2.6	-	26.2	62	1.8	-
14	**75662**	68.9	54	36.0	73.18	61.5	46	27.3	72.4
15.	**77398**	39.25	70.6	6.7	-	34.4	58.2	5,4	-
16.	**95880**	40.0	124	5.9	-	32.9	113	4.3	-
17	**9175**	30.9	115	3.7	-	26.3	102	2.5	-
18	**14488**	52.0	153	9.6	-	47.6	147.2	9.1	-
19	**16486**	101.7	88.5	5.9	-	70.4	74	4.8	-
20	**40744**	163.7	140.7	6.9	-	157.5	126.4	5.7	-

Reference range:

Rheumatoid factor : Upto 20 IU/ml ASO titre : Upto 200 IU/ml

CRP : Upto 6 mg/dl Anti –CCP : Upto 20 U/ml

TABLE-24 (b) i). LABORATORY INVESTIGATION OF IN PATIENTS

SI. NO	IP NO	HAEMATOLOGICAL REPORT												URINE ANALYSIS					
		BEFORE TREATMENT						AFTER TREATMENT						BEFORE TREATMENT			AFTER TREATMENT		
		TC	DC			ESR (1hr)	Hb gms %	TC	DC			ESR (1hr)	Hb gms %	Alb	Sug	Dep – Epi cells/ Pus cells	Alb	Sug	Dep – Epi cells/ Pus cells
			P	L	E				P	L	E								
1.	**1681**	6500	62	31	7	70	10.7	6700	68	29	3	55	10.9	NIL	NIL	1-2pus cells	NIL	NIL	NAD
2.	**1732**	6900	65	30	5	26	11.1	7300	70	28	2	9	11.8	NIL	NIL	NAD	NIL	NIL	NAD
3.	**1761**	6700	65	31	4	30	12.0	7800	59	38	3	11	14.7	NIL	NIL	NAD	NIL	NIL	NAD
4.	**2242**	7800	60	36	4	30	10.6	7000	71	26	3	8	11.1	NIL	NIL	Few puscells	NIL	NIL	NAD
5.	**2246**	9900	78	19	3	24	9.4	9800	74	25	1	7	11.5	NIL	NIL	NAD	NIL	NIL	NAD
6	**2350**	8500	50	40	10	52	10.2	8700	57	38	5	15	10.9	NIL	NIL	NAD	NIL	NIL	NAD
7.	**2550**	5900	63	33	4	20	9.0	6000	58	40	2	6	9.3	NIL	NIL	NAD	NIL	NIL	NAD
8.	**2661**	7000	62	36	2	23	10.2	7300	64	35	1	7	10.3	Trace	NIL	5-6pus cells	NIL	NIL	1-3pus cells
9.	**2685**	8100	60	35	5	72	9.9	7000	65	31	4	40	10.8	NIL	NIL	NAD	NIL	NIL	NAD
10.	**3189**	8000	66	30	4	21	10.6	6200	58	38	4	6	12.1	NIL	NIL	NAD	NIL	NIL	NAD
11	**183**	10600	77	15	8	28	12.1	10500	69	28	3	8	12.0	NIL	NIL	NAD	NIL	NIL	NAD
12.	**255**	11200	72	25	3	23	11.2	8700	70	28	2	9	12.5	NIL	NIL	1-2 pus cells	NIL	NIL	NAD
13.	**274**	8100	70	26	4	20	8.4	7700	69	28	3	9	8.6	NIL	NIL	NAD	NIL	NIL	NAD
14	**285**	7500	62	36	2	39	11.2	7400	64	34	2	12	10.9	NIL	NIL	Few pus cells	NIL	NIL	NAD
15.	**530**	7000	55	40	5	35	10.3	7300	60	37	3	10	10.1	NIL	NIL	NAD	NIL	NIL	NAD
16.	**537**	9600	65	30	5	22	10.8	9400	63	35	2	10	10.6	NIL	NIL	NAD	NIL	NIL	NAD
17	**542**	7300	64	32	4	78	10.3	8600	70	28	2	21	10.9	NIL	NIL	NAD	NIL	NIL	NAD
18	**617**	6000	71	27	2	28	10.6	6400	70	29	1	7	10.5	NIL	NIL	NAD	NIL	NIL	NAD
19	**651**	8400	60	32	8	34	14.0	8600	66	31	3	9	13.8	NIL	NIL	Few pus cells	NIL	NIL	NAD
20	**1106**	9200	67	27	6	90	10.4	6400	66	30	4	24	10.9	NIL	NIL	NAD	NIL	NIL	NAD

Table. 24 (b)

ii). LABORATORY INVESTIGATION (IN PATIENTS)

SI NO	IP NO	BEFORE TREATMENT				AFTER TREATMENT			
		Blood sugar(R)	Blood Urea	Serum cholestrol	Serum creatinine	Blood sugar(R)	Blood Urea	Serum cholestrol	Serum creatinine
1.	**1681**	85	15	248	0.6	97	21	204	0.7
2.	**1732**	88	20	203	0.8	78	32	170	0.8
3.	**1761**	102	18	199	0.9	114	25	182	0.8
4.	**2242**	129	17	224	0.8	118	21	145	0.7
5.	**2246**	82	14	186	0.7	100	38	150	0.6
6.	**2350**	88	28	162	0.7	95	25	148	0.8
7.	**2550**	118	12	258	0.8	72	23	106	0.9
8.	**2661**	175	27	237	0.9	140	28	187	0.7
9.	**2685**	94	17	187	0.9	91	28	150	0.7
10.	**3189**	100	20	186	0.5	108	31	142	0.6
11.	**183**	119	15	195	1.2	110	26	153	0.9
12.	**255**	156	21	220	0.4	130	26	203	0.6
13.	**274**	111	34	207	1.1	103	24	152	0.9
14.	**285**	136	21	204	0.7	118	31	163	0.8
15.	**530**	76	25	218	0.9	92	30	180	0.7
16.	**537**	128	23	230	0.6	112	28	172	0.9
17.	**542**	171	17	161	0.8	126	19	146	0.6
18.	**617**	118	19	200	0.7	106	26	139	0.8
19.	**651**	94	19	162	0.6	115	34	142	0.7
20.	**1106**	125	20	200	0.7	100	18	165	0.6

Table 24(b)

iii). LABORATORY INVESTIGATIONS (IN PATIENTS)

SI NO	IP NO	BEFORE TREATMENT				AFTER TREATMENT			
		RA Factor (IU/ml)	ASO Titre (IU/ml)	CRP (mg/dl)	Anti –CCP (IU/ml)	RA Factor (IU/ml)	ASO Titre (IU/ml)	CRP (mg/dl)	Anti – CCP (IU/ml)
1.	**1681**	285	197	12.7	64	292.6	186	12.3	63
2.	**1732**	39.2	65.2	4.3	-	30.8	63	2.9	-
3.	**1761**	53	72.4	7.1	-	46.7	68.4	6.5	-
4.	**2242**	25.9	80.7	3.2	-	19.5	76.4	2.9	-
5.	**2246**	22.1	126.4	2.6	-	16.8	118.3	2.4	-
6	**2350**	68.29	213.5	20.1	32.40	61.0	176	17.6	30.8
7.	**2550**	30.34	138.91	14.6	-	24,5	129.80	13.5	-
8.	**2661**	20.0	96.2	2.4	-	16.4	93.0	2.1	-
9.	**2685**	449	98	9.7	-	454	94	8.5	-
10.	**3189**	26.0	79.6	2.9	-	14.3	71.2	2.0	-
11	**183**	24.8	65.4	2.8	-	16.7	60.3	2.3	-
12.	**255**	48.0	84.3	4.1	-	45.2	79.8	3.5	-
13.	**274**	36.2	107	3.7	-	34.6	102	3.5	-
14	**285**	37.3	89.4	3.4	-	34.8	74	2.8	-
15.	**530**	30.0	76.7	16.4	-	26.3	62.0	14.7	-
16.	**537**	27.6	88.2	3.2	-	23.2	82.4	2.9	-
17	**542**	166.0	114.2	56.0	-	160.2	93	53.8	-
18	**617**	22.7	65.7	1.9	-	18.3	61.5	1.5	-
19	**651**	29.6	76	2.5	-	21.7	72.1	2.3	-
20	**1106**	110.3	93.2	5.6	-	95.2	90.8	4.7	-

Reference range:

Rheumatoid factor : Upto 20 IU/ml ASO titre : Upto 200 IU/ml

CRP : Upto 6 mg/dl Anti –CCP : Upto 20 U/ml

TABLE 25(a)

DISEASE ACTIVITY PAIN SCORE (OUT PATIENTS)

SI NO	OP NO	Before Treatment					After Treatment				
		TJC 28	SJC 28	ESR mm/hr	VAS	DAS 28	TJC 28	SJC 28	ESR mm/hr	VAS	DAS 28
1.	**50264**	13	11	70	60	6.77	6	4	25	30	4.61
2.	**50813**	12	9	30	50	5.87	4	2	8	10	3.11
3.	**51145**	17	14	53	60	6.98	8	3	10	20	3.96
4.	**51887**	9	8	28	40	5.37	3	2	7	10	2.87
5.	**53806**	24	15	52	70	7.58	13	8	25	30	5.48
6	**56271**	10	8	35	40	5.62	3	2	10	10	3.12
7.	**60797**	11	9	45	50	6.07	4	3	8	10	3.2
8.	**70311**	10	8	50	70	6.29	3	2	9	20	3.18
9.	**71246**	12	8	40	50	6.02	6	5	17	10	4.12
10.	**74409**	12	10	26	40	5.67	3	2	6	10	2.76
11	**74892**	26	20	80	80	8.3	17	12	42	40	6.46
12.	**75542**	13	8	50	60	6.39	4	2	9	10	3.19
13.	**75545**	12	9	45	50	6.15	3	3	7	10	2.96
14	**75662**	16	9	58	50	6.62	10	4	22	20	4.77
15.	**77398**	14	11	50	60	6.61	4	2	9	10	3.19
16.	**95880**	13	8	44	50	6.16	4	2	8	10	3.11
17	**9175**	11	9	38	50	5.95	3	2	7	10	2.87
18	**14488**	25	18	65	70	7.9	16	10	27	30	5.85
19	**16486**	14	13	55	60	6.76	9	6	19	20	4.71
20	**40744**	20	15	62	70	7.46	9	7	24	30	5.07

Interpretation:

Low disease activity	$2.6 < DAS\ 28 \leq 3.2$
Moderate disease activity	$3.2 < DAS\ 28 \leq 5.1$
High disease activity	DAS 28>5.1
Reference range	ESR 5-15mm / hr.

TABLE 25

(b) DISEASE ACTIVITY PAIN SCORE (IN PATIENTS)

SI NO	IP NO	Before Treatment					After Treatment				
		TJC 28	SJC 28	ESR mm/hr	VAS	DAS 28	TJC 28	SJC 28	ESR mm/hr	VAS	DAS 28
1.	**1681**	25	23	70	80	8.25	14	10	55	40	6.35
2.	**1732**	12	8	26	50	5.72	4	2	9	10	3.19
3.	**1761**	24	8	30	60	6.76	12	5	11	20	4.52
4.	**2242**	10	9	30	60	5.84	3	2	8	10	2.96
5.	**2246**	12	8	24	60	5.8	3	3	7	20	3.1
6	**2350**	13	12	52	70	6.74	6	5	15	20	4.17
7.	**2550**	14	7	20	60	5.78	4	3	6	20	3.14
8.	**2661**	13	9	23	50	5.76	4	2	7	10	3.02
9.	**2685**	27	25	72	90	8.58	15	12	40	50	6.43
10.	**3189**	8	7	21	60	5.3	3	2	6	10	2.76
11	**183**	10	7	28	60	5.69	4	3	8	10	3.2
12.	**255**	9	6	23	50	5.27	3	3	9	10	3.13
13.	**274**	12	7	20	60	5.62	3	2	9	20	3.18
14	**285**	14	10	39	60	6.39	7	4	12	20	4.06
15.	**530**	16	9	35	60	6.41	8	3	10	20	3.96
16.	**537**	9	6	22	60	5.38	3	2	10	10	3.12
17	**542**	20	15	78	80	7.77	9	7	21	30	4.97
18	**617**	8	6	28	50	5.31	4	2	7	10	3.02
19	**651**	9	7	34	70	5.88	3	2	9	20	3.18
20	**1106**	18	13	90	70	7.52	8	6	24	30	4.92

Interpretation:

Low disease activity	$2.6 < DAS\ 28 \leq 3.2$
Moderate disease activity	$3.2 < DAS\ 28 \leq 5.1$
High disease activity	DAS 28>5.1
Reference range	ESR 5-15mm / hr

TABLE-26

(a) CASE SUMMARY - OUT PATIENTS

SI NO	OP NO	Name	Age/ Sex	Occupation	Duration of Illness	DOA	DOD	Total Days	Results
1.	**50264**	Eswari	38/F	Beedi worker	4 Years	13.6.18	13.7.18	30	Moderate
2.	**50813**	Mariyappan	45/M	Driver	1 Year	15.6.18	15.7.18	30	Good
3.	**51145**	Beaula	35/F	Teacher	8 Months	16.6.18	16.7.18	30	Moderate
4.	**51887**	Dhanalakshmi	41/F	Housewife	1 ½ years	19.6.18	19.7.18	30	Good
5.	**53806**	Kanjana	46/F	Housewife	1 Year	26.6.18	26.7.18	30	Poor
6	**56271**	Selvi	43/F	Housewife	5 Years	5.7.18	5.8.18	30	Good
7.	**60797**	Elango	36/M	Teacher	1 ½ Years	21.7.18	21.8.18	30	Good
8.	**70311**	Lincy	42/F	Housewife	7 Years	24.8.18	24.9.18	30	Good
9.	**71246**	Gomathi	38/F	Housewife	6 Years	27.8.18	27.9.18	30	Moderate
10.	**74409**	Muthulakshmi	28/F	Beedi worker	1 Year	7.9.18	7.10.18	30	Good
11	**74892**	Fathima	39/F	Beedi worker	5 Years	8.9.18	8.10.18	30	Poor
12.	**75542**	Joseph Thangaraj	39/M	Business	5 Months	11.9.18	11.10.18	30	Good
13.	**75545**	Maragatham	23/F	Housewife	1 Year	11.9.18	11.10.18	30	Good
14	**75662**	Indhira	42/F	Housewife	8 Months	11.9.18	11.10.18	30	Moderate
15.	**77398**	Bala Subramaniaan	45/M	Agricultural labour	2 Years	18.9.18	18.10.18	30	Good
16.	**95880**	Chella durai	45/M	Agriculture labour	6 Months	20.11.18	20.12.19	30	Good
17	**9175**	Shanmuga Devi	29/F	Housewife	4 Years	24.1.19	24.2.19	30	Good
18	**14488**	Mydheen Fathu	31/F	Housewife	2 Years	8.2.19	10.3.19	30	Poor
19	**16486**	Petchiyammal	44/F	Agricultural labour	3 Years	14.2.19	16.3.19	30	Moderate
20	**40744**	Kaaliyammal	42/F	Housewife	4 Years	3.5.19	3.6.19	30	Moderate

TABLE-26

(b) CASE SUMMARY - IN PATIENTS

SI NO	IP NO	Name	Age/ Sex	Occupation	Duration of Illness	DOA	DOD	Total Days		Total days	Results
								IP	OP		
1.	**1681**	S.Pappa	47/F	Housewife	6 Months	2.7.18	2.8.18	30	-	30	Poor
2.	**1732**	Salomi	36/F	Coolie	1 Year	6.7.18	6.8.18	30	-	30	Good
3.	**1761**	Michealammal	49/F	Housewife	2 Years	11.7.18	11.8.18	30	-	30	Moderate
4.	**2242**	Ramalakshmi	42/F	Agricultural labour	5 Months	1.9.18	1.10.18	30	-	30	Good
5.	**2246**	C.Madaththi	40/F	Coolie	7 Years	1.9.18	1.10.18	30	-	30	Good
6	**2350**	Jeyasakthi	26/F	Sales women	8 Years	17.9.18	18.10.18	30	-	30	Moderate
7.	**2550**	Rathika	28/F	Housewife	6 Months	11.10.18	15.11.18	30	-	30	Good
8.	**2661**	Poomani	45/F	Agricultural labour	2 Years	29.10.18	1.12.18	30	-	30	Good
9.	**2685**	Lakshmi	42/F	Agricultural labour	4 Years	2.11.18	28.12.18	25	5	30	Poor
10.	**3189**	Mydeen Nachiyar	40/F	Housewife	5 Months	29.12.18	27.1.19	30	-	30	Good
11	**183**	Subramanian	45/M	Agricultural labour	4 Months	29.1.19	1.3.19	30	-	30	Good
12.	**255**	R.Pappa	43/F	Housewife	2 Years	5.2.19	7.3.19	30	-	30	Good
13.	**274**	Pichumani	46/M	Watchman	2 Years	7.2.19	9.3.19	30	-	30	Good
14	**285**	S.Madaththi	45/F	Housewife	5 Months	8.2.19	10.3.19	30	-	30	Moderate
15.	**530**	Eswari	43/F	Agricultural labour	5 Years	1.3.19	3.4.19	30	-	30	Moderate
16.	**537**	Jeyalakshmi	47/F	Housewife	9 Months	2.3.19	4.4.19	30	-	30	Good
17	**542**	Pitchaammal	44/F	Sales women	3 Years	2.3.19	3.4.19	30	-	30	Moderate
18	**617**	Kuruvammal	40/F	Housewife	1 Year	9.3.19	10.4.19	30	-	30	Good
19	**651**	Maduraiveeran	47/M	Coolie	2 Years	13.3.19	15.4.19	30	-	30	Good
20	**1106**	Rejina Mary	41/F	Housewife	3 Years	1.5.19	3.6.19	30	-	30	Moderate

4.3 Bio –Statistical Analysis:

Statistical analysis has shown DAS 28 score among OP & IP was found to be highly significant at P < 0.01 from Statistical analysis is done using students's Paired 't' test using SPSS Software.The results were expressed as Mean, Standard Deviation, 't' value and P values < 0.01 was considered as statistically significant.

Out patients - DAS 28 Score comparison through statistical analysis

SI. No	Parameters	Mean	Standard Deviation	t value	P value	Results
1.	Before Treatment	6.5270	0.78874	22.232	< 0.01	Significant
2.	After Treatment	3.9295	1.13210			

In patients - DAS 28 Score comparison through statistical analysis

SI. No	Parameters	Mean	Standard Deviation	t value	P value	Results
1.	Before Treatment	6.2885	1.00868	43.819	< 0.01	Significant
2.	After Treatment	3.8190	1.10324			

CHAPTER-V

DISCUSSION

Vali Azhal Keel Vayu, described in Sabapathy manuscript is nearly correlated in modern science with Rheumatoid Arthritis (RA). In this clinical trial study totally 40 patients were selected, 20 were treated as Out patient and 20 were treated as In patients with clinical trial drug ***'NANNARI VER OORAL KUDINEER'.***

Professor, Associate Professor, Lecturers of the Department of Pothu Maruthuvam had supervised the entire clinical study, its observation and results.

The observed results were discussed below:

1.Sex Distribution:

Among 20 Out patients 25% were Male and 75% were Female.

Among 20 In patients, 15% were Male and 85% were Female.

2.**Age Distribution:**

It is observed that the highest incidence of *Vali Azhal Keel Vayu* in Out patients is among the age group of 41 to 50 with 50% and 31 to 40 with 35%, 15% were in the age group of 21 to 30 years. Among 20 In patients 10% were in the age group 21 to 30 years, 5% were in the age group of 31 to 40 years, 85% with the highest incidence in the age group of 41 to 50 years.

3. Kaalam:

Among 20 Out patients, 20% were affected in Vatha Kaalam and 80% were affected in *Pitha Kaalam.* Among 20 In patients, 90% were affected in *Pitha Kaalam* and 10% were affected in *Vatha Kaalam.*

4. Constitution of body:

Vatha Pitha Thegi register high incidence of *Vali Azhal Keel Vayu* with 80% OP and 75% IP. Remaining *Pitha Vatha Thegi* of 20% OP and 25% IP.

5. Gunam:

Among 20 Out patients, 5% were Sathuva Gunam, 70% were Rajo gunam and 25% were Thamasa gunam .

Among 20 In patients, 80% were Rajo gunam and 20% were Thamasa gunam.

6.Religion:

Among 20 Out patients, 75% were Hindus, 15% were Christians.10% were Muslims. Among 20 In patients, 80% were Hindus, 15% were Christians and 5% were Muslims .

7. Paruva Kaalam:

Among 20 Out patients, 05% of cases were in Elavenil Kaalam, 30% of cases were in Muthuvenil Kaalam, 40% of cases were in Kaar Kaalam ,05% of cases were in Koothir Kaalam, 15% of cases were in Munpani Kaalam and 05% of cases were in Pinpani Kalam.

Among 20 In patients, 05% of cases were in Elavenil Kaalam, 15% of cases were in Muthuvenil Kaalam ,20% of cases were in Kaar Kaalam, 10% of cases were in Koothir Kaalam, 25% of cases were in Munpani Kaalam and 25% of cases were in Pinpani Kalam.

8. Thinai:

Among 20 Out patients, 5% were from Kurinji, 15% were from Mullai, 75% were in Marutham and 5% were in Neithal.

Among 20 In patients, 70% were in Marutham, 20% were in Neithal ,10% were in Mullai,

9. Socio – economical status:

Among 20 Out patients, 15% were in Low income class, 60% were in Middle income class and 25% were in High income class. Among 20 In patients, 45% were in Low income class, 50% were in Middle income class and 5% were in High income class.

10. Food habits:

Among 20 Out patients, 35% were Vegetarian and 65% were non – vegetarian.

Among 20 In patients, 25% were vegetarian and 75% were non – vegetarian

11. Family History:

Among 20 Out patients, 15% have positive Family History and 85% don't have any positive Family History. Among 20 In patients, 25% have positive Family History and 75% don't have any positive Family History.

12. Occupation:

Among 20 Out patients, 15% Agricultural labours, 50% House Wife, 5% Driver, 15% Beedi worker, 5% Business and 10% Teacher.

Among 20 In patients, 25% Agricultural labours, 15% Coolie, 45% House Wife, 5% Watchman, and 10% Sales women were observed.

13. Clinical Manifestation:

Among 20 Out patients, 100% cases have arthritis involving more than 3 joints, severe pain and swelling, symmetrical joint involvement, 100% have morning stiffness , 50% have depression, 30% have Anorexia, 10% have Rheumatoid nodules.

Among 20 In patients, 100% cases have arthritis involving more than 3 joints, severe pain and swelling, symmetrical joint involvement, 100% have morning stiffness, 45% have depression, 15% have rheumatoid nodules, 20% have anorexia.

14. Duration of Illness:

Among 20 Out patients, Duration of Illness was 20% below 1 year, 30% in 1 to2 years ,10% in 2 to 3 years, 5% in 3 to 4 years and 35% in above 4 years.

Among 20 In patients, Duration of Illness was 35% below 1 year, 10% in 1 to 2 years, 25% in 2 to 3 years and 10% in 3to 4 years,20% above 4 year.

15. Kanmenthiriyam:

Among 20 Out patients, 100% cases were affected in Kai, Kaal, 20% cases were affected in Eruvai. Among 20 In patients, 100% cases were affected in Kai, Kaal, 25% cases were affected in Eruvai.

16. Gnanendrium:

Among 20 Out patients, 100% of the patients were affected in Mei, 5% of the patients were affected in kan.

Among 20 In patients, 100% of the patients were affected in Mei, 10% of the patients were affected in kan.

17. Condition of Mukkutram:

a) Condition of Vatham:

Viyaanan, Samaanan, were affected in 100% of both Out patients and In patients. Abaanan was affected in 20% of Out patients, and 25% of the In patients, Kirugaran was affected in 25% of Out Patients, and 15% of In patients. Devathathan was affected in 100% of Out patients, and 100% of In patients. Koorman was affected in 5% of Out patients and 10% of In patients,

b) Condition of Pitham:

Among 20 Out patients, 25% affected in Anala Pitham, 50% in Ranjaga Pitham and 100% in Sathiga Pitham, 5% in Aalosaga pitham. Among 20 In patients, 15% affected in Anala Pitham, 75% in Ranjaga Pitham and 100% in Sathiga Pitham, 10% in Aalosaga pitham.

c) Condition of Kapham:

Kilethagam was affected in 25% of Out patients and 15% of In patients. Santhigam was affected in 100% of both Out patients and In patients

18. Involvement of Udal Kattugal:

Among 20 Out patients and In patients Saaram, Enbu,Kozhuppu, Moolai were affected in 100% of the cases. senneer was affected in 50% of OP and 75% of IP.

19. Conditions of Envagai Thervugal:

Among 20 Out patients, 5 % were affected in Vizhi, 20% were affected in Malam, 100% was affected in Sparisam, Naadi-80% with Vatha Pitham, 20% with Pitha Vatham. Among 20 In patients, 10% were affected in Vizhi, 25% was affected in Malam, 100% was affected in Sparisam, Naadi-75% with Vatha Pitham, and 25% with Pitha Vatham.

20. Neer kuri:

Niram was affected in 25% of Out patients and 30% of In patients. Nurai was affected in 5% of Out patients and 10% of In patients.

21. Nei kuri:

Among 20 Out patients, 80% had Vatha Neer, 20% had Pitha neer. Among 20 In patients, 75% had Vatha Neer, 25% had Pitha Neer.

22. Assessment of outcome:

Before Treatment:

Among 20 Out patients, and 20 In patients 100% of cases were with High disease activity.

After Treatment:

Among 20 Out patients, 55% of cases with Low disease activity 30% of cases with Moderate disease activity and 15% of cases with High disease activity. Among 20 In patients, 60% of cases with Low disease activity, 30% of cases with Moderate disease activity and 10% of cases with High disease activity.

Result :

The before and after treatment mean value of DAS 28 score of Out Patients was respectively 6.5270 & 3.9295 ,In patients was 6.2885 & 3.8190.

The before and after treatment standard deviation of DAS 28 score of Out Patients was respectively 0.78874 & 1.13210 ,In patients was 1.00868 & 1.10324.

The ‘t’value of the DAS 28 Score of the OP & IP patients were 22.232,43.819.

That all the above details derived from biostatistical analysis showed that DAS 28 Score is significant ($P < 0.01$)

23. Gradation of results:

Among 20 Out patients, 55% of cases showed Good response, 30% of cases showed Moderate response and 15% of cases showed Poor response. Among 20 In patients, 60% of cases showed Good response, 30% of cases showed Moderate response and 10% of cases showed Poor response.

All the 40 patients were treated with the clinical trial medicine **NANNARI VER OORAL KUDINEER** for 30 days. Thus, at the end of the result, the clinical trial drug showed good clinical improvement of the disease

CHAPTER-VI
SUMMARY

A Prospective open labelled phase II Non- randomized clinical study on 'VALI AZHAL KEEL VAYU' with reference to its aetiology, pathogenesis, clinical features, diagnosis, investigations and treatment was conducted at Department of Pothu Maruthuvam, Government Siddha Medical College and Hospital, Palayamkottai.This clinical study was done on the basis of reference mentioned in Sabapathi manuscript in Noinadal, Noi mudhal naadal Thiratu Part-II, Pg.no.623. The disease can be correlated with Rhematioid arthritis.

The trial drug chosen for the clinical study – NANNARI VER OORAL KUDINEER (Ref.Gunapadam (Mooligai Vaguppu) K.S.Murugesu Mudaliyar,Pg. no.562)

The literature review of the disease were collected from a number of literatures both in Siddha system as well as in modern system of medicine. During the study, Out of 40 patients, 20 patients were admitted in the In patients ward and treated with trial medicine. Another twenty patients were treated in Out patients facility.

Routine blood examinations, Urine analysis, other specific investigations and radiological investigations were done by modern scientific methods. The same methods were considered for diagnosis and further follow up of the patients.Siddha diagnosis was made with the aid of Ezhu Udal Kattugal, Envagai Thervugal and other important criterias belonging to 96 thathuvams.Since, Vali Azhal Keel Vayu is a chronic disease, it requires treatment for minimum thirty days to minimize the severe pain, tenderness and swelling with slight disappearance of stiffness. The patient was advised to follow up the treatment in Out patient Department.

From this study, the following datas were collected.

- Disease was more common in female than male.
- Maximum incidence was in Pitha Kaalam.
- Clinically marked reduction in the symptoms along with increased sense of well being
- Decrease in ESR
- Decrease in the DISEASE ACTIVITY PAIN SCORE OF 28 JOINTS was noted.

Bio-chemical analysis of NANNARI VER OORAL KUDINEER showed the presence of **calcium, sulphate, ferrous iron, starch, amino acids and unsaturated compound.**

Anti- Microbial test shows NANNARI VER OORAL KUDINEER is highly sensitive to both gram positive and gram negative bacteria viz ***Staphylococcus aureus, E.coli and Klebsiella pneumoniae* .**

Phytochemical analysis of NANNARI VER OORAL KUDINER showed the presence of **flavonoids, carbohydrates, glycosides, phytosterols, alkaloids, tannis, proteins and lignin**.

The pharamacological evaluation of NANNARI VER OORAL KUDINEER showed significant anti inflammatory, analgesic and Immunomodulatory activity. No toxicity effects were noted during the treatment.

CHAPTER-VII

CONCLUSION

The Sabapathy Manuscript has mentioned Vali Azhal Keel Vayu under the main heading of keel vayu. Treatment was planned and given on the basis of Mukkutra & Suvai theories. In all cases, vitiation of vatha kutram was noticed. The trial medicine Nannari ver ooral kudineer has the taste of *inippu.*

According to *arusuvai* theory*, Inippu suvai* has the ability to neutralize the vitiation of *Vatham* and *Pitham.* Thus the trial drug acts as effective agent in the reduction of pain and swelling.

In pre-clinical studies, bio-chemical, phytochemical, pharmacological, anti-microbial and toxicological studies were carried out and obtained relevant results.

In all cases, considerable improvements were noticed after the trial. Reduction in pain and swelling along with improvement in joint flexibility was seen in majority of cases. So, I conclude that, NANNARI VER OORAL KUDINEER has improved the clinical symptoms of the RA and assured them a better standard of living.

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ANNEXURE - I

PREPARATION AND PROPERTIES OF TRIAL MEDICINE

நன்னாரி வேர் ஊறல் குடிநீர்

(***Reference;-****Gunapadam mooligai vaguppu*,Pg.No .562*, Dr K.S. Murugesa Mudaliyar*)

நன்னாரி பொதுகுணம்:

சலதோடம் பித்தமதி தாகம் உழலை
சலமேறு சீதமின்னார் தஞ்சூ-டுலகமதிற்
சொன்னமது மேகம் புண்சுரமிவையெ லாமொழிக்கும்
மென்மதுர நன்னாரி வேர்

இதனால் அழல் நோய், வண்டுகடி, போம். மேலும் நீரேற்றம், நீர்வேட்கை, வாய்நீர்ச்சுரப்பி, புணர்ச்சியின் சூடு, நீரிழிவு, கிரந்தி, சுரவேட்கை இவை தணியும்.

TABLE: 1 Details of *Hemidesmus Indicus*

Tamil Name	Botanical Name	Family	Part Used	Phyto chemicals	Action
Nannari	*Hemidesmus indicus*	Asclepiadiaceae	Root	Flavonoids, Steroids, Terbinoides, Glycosides, Tannins, Triterbinoids	Analgesic, Anti- Inflammatory, Immunomodulatory, Anti –Pyretic, Diuretic.

PURIFICATION OF RAW DRUGS:

The roots washed with pure water to remove the impurities and allowed it to dry.

METHODS OF PREPARATION:

Fresh roots of Nannari were cleaned and dryed in shade then it made into coarse powder.10gms of powder added to 100ml of hot water and waited for one hour till the powder infuse and then filtered it.

Dose : 90 ml (Thrice a day)

Duration : 30 days

PREPARATION OF NANNARI VER OORAL KUDINEER

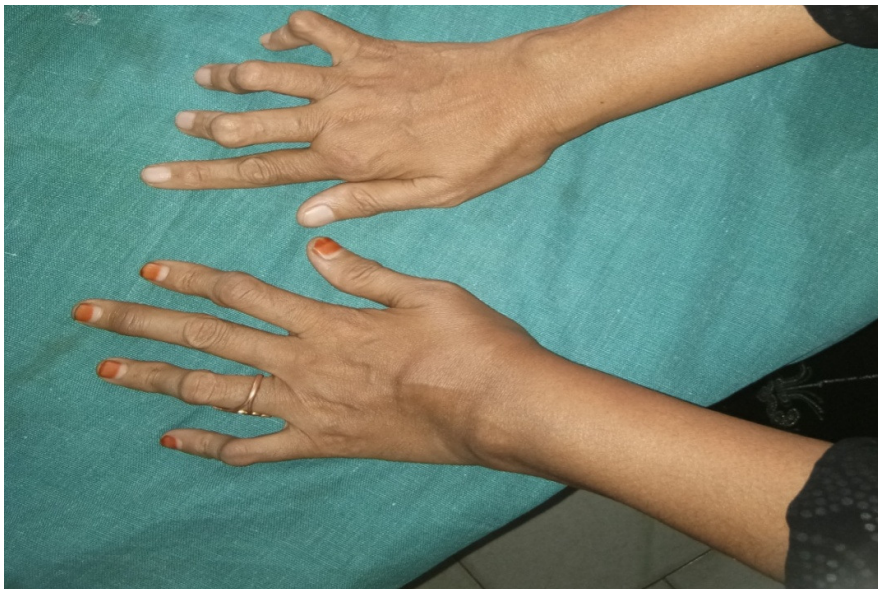
Dried Roots

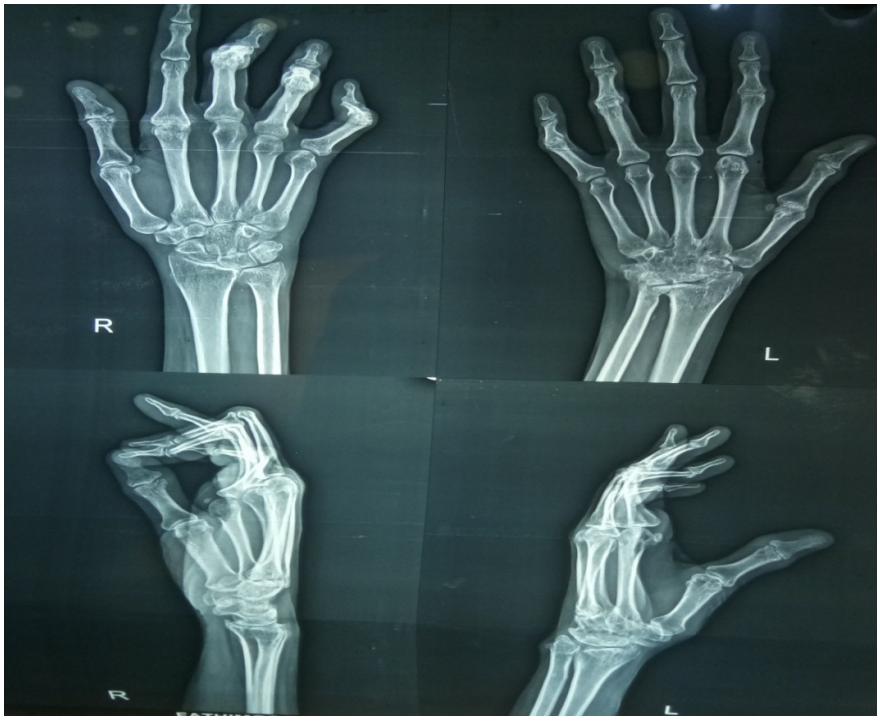
Kudineer Chooranam

Nannari Ver Ooral Kudineer

ANNEXURE - II

DEFORMITIES OBSERVED IN THE PATIENTS





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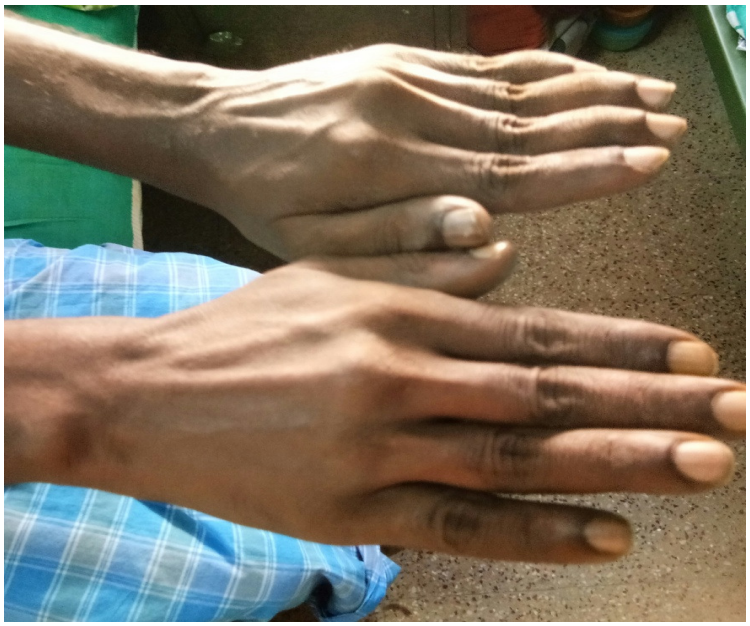

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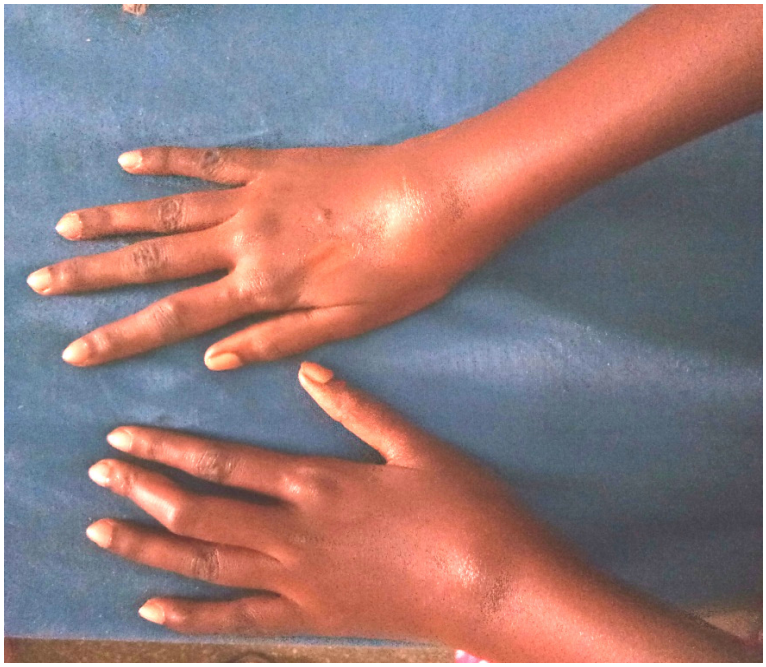

IP.NO : 2550 NAME : RATHIKA 28/F

ANNEXURE - III

SCREENING COMMITTEE CERTIFICATE

GOVERNMENT SIDDHA MEDICAL COLLEGE PALAYAMKOTTAI

SCREENING COMMITTEE

Name of the Candidate : Dr. E. MALARVIZHI

Registration No.: .....

DEPARTMENT OF POTHU MARUTHUVAM

This is to certify that the dissertation topic A Prospective open labelled phase- II Non Randomized Clinical trial on herbal formulation of **"*Nannari Ver Ooral Kudineer*"** for the treatment of **VALI AZHAL KEEL VAYU** (Rheumatoid Arthritis)has been approved by the screening committee.

Branch	Department	Name	Signature
1	Pothu Maruthuvam	Dr.A.Manoharan. MD(S)., Professor	
2	Gunapadam	Dr.A.Kingsly MD(S)., Associate Professor	
3	Sirappu Maruthuvam	Dr.A.S.Poongodi kanthimathi MD(S)., Professor	
4	Kuzhandhai Maruthuvam	Dr.D.K.Soundararajan. MD(S)., Professor	
5	Noi Nadal	Dr.S.Victoria MD(S)., Professor	
6	Nanju Nool Maruthuvam	Dr.M.Thiruthani. MD(S)., Professor	

Place : PALAYAMKOTTAI

Date : 26-5-2017

PRINCIPAL
Govt. Siddha Medical College
Palayamkottai.

ANNEXURE - IV

INSTITUTIONAL ETHICAL COMMITTEE CERTIFICATE

INSTITUTIONAL ETHICAL COMMITTEE,
GOVERNMENT SIDDHA MEDICAL COLLEGE,
PALAYAMKOTTAI, TIRUNELVELI- 627002,
TAMIL NADU, INDIA.

Ph: 0462-2572736/2572737/2582010 Fax: 0462-2582010
Email ID: gsmc.palayamkottai@gmail.com

R.No.GSMC/5676/P&D/Res/IEC/2014 **Date: 29.05.2017**

CERTIFICATE OF APPROVAL

Address of Ethical Committee	Government Siddha Medical College, Palayamkottai-627002, Tirunelveli district.
Principal Investigator	**Dr.E, Malarvizhi, M.D(s),** First year, Department of PothuMaruthuvam, Reg. No: Not yet registered.
Supervisor	**Prof.Dr.A.Manoharan, M.D$_{(s)}$.,** Head of the Department, Department of PothuMaruthuvam, Government Siddha Medical College and Hospital, Palayamkottai - 627002, Tirunelveli District. drmanoharan25@gmail.com
Guide	**Dr.G.Subash Chandran, M.D(s)., Ph.D.,** Lecturer Department of PothuMaruthuvam, Government Siddha Medical College and Hospital, Palayamkottai - 627002, Tirunelveli District. siddhadrgs21@gmail.com
Dissertation Topic	AProspective open labelled phase- II Non - Randomized Clinical trial on herbal formulation of ***"Nannari Ver Ooral Kudineer"*** for the treatment of **VALI AZHAL KEEL VAYU** (Rheumatoid Arthritis)
Documents Filed	(1)Protocol (2)Data Collection Forms (3)Patient Information Sheet (4)Consent Form (5)SAE (Pharmacovigilance)
Clinical/Non Clinical Trial Protocol (Others-Specify)	Clinical Trial Protocol-yes
Informed Consent Document	Yes
Any other Document	Case Sheet/Investigation Documents
Date of IEC Approval & its Number	GSMC IV-IEC/2017/Br-I/ 04/29.05.2017

We approve the trial to be conducted in its presented form.

The Institutional Ethical Committee expects to be informed about the process report to be submitted to the IEC at least annually of the study, any SAE occurring in the course of the study, any changes in the protocol and submission of final report.

Chairman

(Prof. Dr. Murugesan M.D(s).,)

Member Secretary

(Prof.Dr.R.Neelavathy MD(s).,Ph.D.,)

ANNEXURE - V

INSTITUTIONAL ANIMAL ETHICAL COMMITTEE CERTIFICATE

K.M. COLLEGE OF PHARMACY – MADURAI

IAEC – CERTIFICATE

This is to certificate that the project title A PROSPECTIVE, OPEN LABELLED, NON - RANDOMIZED, PHASE II CLINICAL TRIAL ON **"VALI AZHAL KEEL VAYU"** (RHEUMATOID ARTHRITIS) WITH TRIAL DRUG **"NANNARI VER OORAL KUDINEER"** has been approved by the **IAEC/E. MALARVIZHI /TNMGRMU/MD(S)/ 321611004/KMCP/26/2018.**

Dr. N. Chandrasekaran
Name of the Chairman / Member Secretary IAEC:

Signature with Date

I. A. E. C. CHAIRMAN
INSTITUTIONAL ANIMAL ETHICAL COMMITTEE
K. M. COLLEGE OF PHARMACY
MADURAI-625 107.

Dr. P. Thiyagarajan
Name of the CPCSEA Nominee

CPCSEA NOMINEE
INSTITUTIONAL ANIMAL ETHICS COMMITTEE
K.M. COLLEGE OF PHARMACY
MADURAI-625 107

Chairman / Member Secretary of IAEC

CPCSEA Nominee

(Kindly make sure that minutes of the meeting duly signed by all the participants are maintained by office).

ANNEXURE - VI

BOTANICAL AUTHENTICATION CERTIFICATE

GOVERNMENT SIDDHA MEDICAL COLLEGE
PALAYAMKOTTAI

Certificate of Botanical Authenticity

Certified the following plant drug used in Siddha formulation (Internal) **"NANNARI VER OORAL KUDINEER"** for **VALI AZHAL KEEL VAYU** (RHEUMATOID ARTHRITIS) taken up for Post-Graduation Dissertation Studies by Dr. E. MALARVIZHI, PG Scholar MD siddha, Department of Pothu Maruthuvam, are correctly identified and authenticated through Visual inspection / Organoleptic Characters / Experience, Education & Training Morphology Microscopically and Taxonomical methods.

Table 1: Ingredients of Nelli Kudineer

S.N	Drug	Botanical Name	Family	Parts Used
01	NANNARI	*Hemidesmus indicus*	Asclepiadaceae	Root

Station: Palayamkottai

Date : 24/1/2018

Authorized Signature

Dr. S. SUTHA, M.Sc.,M.Ed.,Ph.D.,
Associate Professor
Dept. of Medicinal Botany
Govt. Siddha Medical College
Palayamkottai, Tirunelveli - 2.

ANNEXURE - VII

RESEARCH METHODOLOGY & BIOSTATISTICS CERTIFICATE

ANNEXURE - VIII

CLINICAL TRIAL REGISTRY OF INDIA

Clinical Trial Details (PDF Generation Date :- Mon, 11 Jun 2018 03:24:09 GMT)

CTRI Number	CTRI/2018/06/014450 [Registered on: 07/06/2018] - **Trial Registered Prospectively**
Last Modified On	06/06/2018
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Siddha
Study Design	Single Arm Trial
Public Title of Study	A clinical trial to study the effect of drug NANNARI VER OORAL KUDINEER in VALI AZHAL KEEL VAYU(Rheumatoid arthritis)
Scientific Title of Study	A prospective open labelled phase II Non randomized clinical trial on herbal formulation of NANNARI VER OORAL KUDINEER for the treatment of VALI AZHAL KEEL VAYU(Rheumatoid arthritis)

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	Malarvizhi E
Designation	PG Student
Affiliation	Govt Siddha Medical College and Hospital Palayamkottai
Address	PG Second Year Department of Pothumaruthuvam Govt Siddha Medical College and Hospital Palayamkottai Tirunelveli Tamilnadu India Tirunelveli TAMIL NADU 627002 India
Phone	8807183465
Fax	
Email	malarvizhielumalai90@gmail.com

Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
Name	G Subash Chandran MD Siddha PhD
Designation	Lecturer
Affiliation	Govt Siddha Medical College and Hospital Palayamkottai
Address	Department Of Pothumaruthuvam Govt Siddha Medical College and Hospital Palayamkottai Tirunelveli TAMIL NADU 627002 India
Phone	9443358271
Fax	
Email	siddhadrgs21@gmail.com

Details Contact Person (Public Query)

Details Contact Person (Public Query)	
Name	G Subash Chandran MD Siddha PhD
Designation	Lecturer
Affiliation	Govt Siddha Medical College and Hospital Palayamkottai
Address	Department Of Pothumaruthuvam Govt Siddha Medical College and Hospital Palayamkottai Tirunelveli TAMIL NADU 627002

ANNEXURE - IX

CME PROGRAMME CERTIFICATE - I

GOVERNMENT SIDDHA MEDICAL COLLEGE

PALAYAMKOTTAI, TIRUNELVELI – 627 002

CONTINUING MEDICAL EDUCATION PROGRAMME

Conducted by

Post Graduate Department of Pothu Maruthuvam

This certificate is awarded to Dr / ~~Mr~~ / ~~Mrs~~.....MALARVIZHI...E.....
has participated in the CME Programme held on 05.12.2018 at Conference Hall, Special Therapy Wing, Government Siddha Medical College, Palayamkottai, Tirunelveli. This programme is focused on "HIV / AIDS"

Prof .Dr.A.MANOHARAN , M.D (s) , (Ph.D)
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GOVERNMENT SIDDHA MEDICAL COLLEGE& HOSPITAL
PALAYAMKOTTAI

CME PROGRAMME

Conducted by
SIRAPPU MARUTHUVAM
DEPARTMENT
GSMCH - PALAYAMKOTTAI

Organised by
ASHTAVAIDYAN THAIKKATTU MOOSS
VAIDYARATNAM

Supported by
PG Student Council

S.No: 139

CERTIFICATE

This Certifies that

Dr. E. Malarvizhi

has participated in Continuing Medical Education on "**AYUSH External Therapies-II**" held at GSMCH, Palayamkottai on Dec, 4 2018

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VAIDYARATNAM

Dr. R. Neelavathy MD (s), Ph.D.,
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ANNEXURE - X

JOURNAL PUBLICATION CERTIFICATE - I

FIRST PAGE OF JOURNAL PUBLICATION - I

International Journal of Reverse Pharmacology and Health Research (IJRPHR)

Research article

Toxicity study of a Siddha drug Nannari ver Ooral kudineer

Malarvizhi.E[1]*, Manoharan A[2], subash chandran G[3]

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Abstract

Background:

The root decoction of Nannari ver, *Hemidesmus indicus* (Linn) from Asclepiadaceae family has been using in traditional medicine for a long period. In Tamilnadu and even in Kerala people are more using *Hemidesmus indicus,* (Linn) Commonly in siddha this medicine used as diuretic and to reduce body heat.

Objective:

To evaluate the acute and sub-acute toxicity of Nannari ver Ooral kudineer (NVK) on experimental in Wister albino rat models.

Materials and Methods:

Acute toxicity study was carried out in female Wister albino rat. Administration of a single dose of 4000mg/kg of Nannari ver Ooral kudineer by gavages to five rat were found no mortality. In 1/20th dose was used as the highest therapeutic dose. In sub acute toxicity analysis male and female Wister albino rats has received daily 50 to 200mg/kg /bwt for 28 days.

Results:

No significant changes in WBC, RBC were observed between control and test groups following repeated administration of Nannari ver Ooral kudineer. The animals treated with NVK showed normal growth pattern and body weight compared with control rats . There was a slight decrease in plasma glucose level and increased in Hb levels,after administration of NVK (400 mg.kg-1).

Conclusion:

At the end of study there was no an undesirable effect of all organs and safe for consumption by human health.

Keywords

Siddha medicine, Nannari ver Kudineer, acute & sub acute studies.

Introduction

Plant based medicine is a traditional medicine, from time immemorial has been the main stay of health care need for the treatment of various types of diseases. Despite improvement in science and technology in medicine, greater numbers of the population are still following herbal medicine to resolve their primary health problems (Shetty Akhila et al . 2007). According to World Health Organization, more than 80% of the world's population have been used in traditional medicine for their primary healthcare needs .

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JOURNAL PUBLICATION CERTIFICATE II

RESEARCH ARTICLE

Journal of Research in Biomedical Sciences (JRBMS)
A Peer reviewed Indexed International Journal (IF 0.92)
An Official Publication of BioSci Group of Research

Phyto-chemical analysis of Siddha herbal preparation *Nannari Ver Ooral Kudineer*

Malarvizhi E*[1], Manoharan A[2]
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ABSTRACT

Introduction: In tamil *Hemidesmus indicus Linn* is commonly known as *Nannari (Indian Sarsaparilla).It* belongs to the family *Asclepiadaceae*. In Siddha system Nannari is used for treating pitha related disorders, it was based on three dhosa theory. The Pitha means heat related illness. So, it is used for the treatment of summer associated symptoms.

Objective: The main objective of this study is the phytochemical analysis of Siddha medicinal plant (*Hemidesmus indicus). Nannari ver*, this is *based on decoction, namely (Nannari ver ooral kudineer Linn)*

Methods: The phytochemical analysis was performed in *Nannari ver ooral kudineer*, for the qualitative estimation of constituents like, Alkaloids, Flavanoids, Carbohydrates, Phytosterols, tannins, Proteins, lignins, and saponins.

Results: The qualitative phytochemical analysis of *nannari ver ooral kudineer was* showed the presence of phenols, flavonoids, glycosides, steroids and Fixed oils and saponins are absent were observed from this study. Since this is a volatile based compound, it provides clinical efficacy of *Nannari ver ooral kudineer* .

Conclusion: From this study indicated nannari ver ooral kudineer is a important source of antioxidant, which is used to prevent the oxidative stresses. The presence of alkaloids, Phenols and flavanoid compounds are boon for human immunity.

KEYWORDS

Hemidesmus indicus, Phytochemical screening, Siddha Medicine, Antioxidant

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ANNEXURE - XI

PLAGIARISM REPORT

URKUND

Urkund Analysis Result

Analysed Document:	MALARVIZHI.docx (D54158846)
Submitted:	6/26/2019 9:54:00 AM
Submitted By:	jeromstat@gmail.com
Significance:	9 %

Sources included in the report:

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