

**Review Article**

**A REVIEW ON SCOPES, METHODS AND RATIONALE OF INTEGRATIVE APPROACH IN SIDDHA MEDICINE WITH BIOMEDICINE**

**S. RAJALAKSHMI<sup>1\*</sup>, P. SATHIYARAJESWARAN<sup>2</sup>, K. SAMRAJ<sup>3</sup>, K. KANAGAVALLI<sup>4</sup>**

<sup>1,3</sup>Siddha Clinical Research Unit (SCRU), Tirupati, Andhra Pradesh, India, <sup>2</sup>Director, Siddha Central Research Institute (SCRI), Chennai, Tamilnadu, India, <sup>4</sup>Director General, Central Council for Research in Siddha (CCRS), Chennai, Tamilnadu, India  
Email: dr.rajibsms23@gmail.com

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**ABSTRACT**

In India, according to WHO 2018 statistics, there were 63% of death occurred due to Non-communicable diseases (NCDs), in which Cardiovascular diseases were leading cause of death 27%, followed by Cancer 9%, Chronic respiratory disease 11%, Diabetes 3% and other NCDs 13%. This indicates that NCDs needs to become a priority in controlling and preventing. Therefore, the only effective intervention may be at controlling and preventing NCDs disease is Integrative Medicine. Integrative Medicine is a medical practice synthesizing Traditional medicine and Biomedicine preventive measures and treatment interventions. Autonomy of patients may end in no benefit out of their ignorance to select between the treatment options available in a country like India where Seven Recognized medical systems are available as a platter. Siddha system of medicine is one of the traditional medicines of India, practiced in the southern part of the country. This study aims at providing Health care system under one roof, in order to save public money, time and health as an existing model as co-location in Tamil Nadu. This can be achieved through assessing feasible areas of integration in the Siddha system of medicine with biomedicine. So the study deals with the utilization of Siddha system of medicine, scientific validation of Siddha medicines, Siddha medicine research undertaken by biomedical practitioners and some government policies supporting mainstreaming of Siddha.

**Keywords:** Complementary medicine, Integrative medicine, Medical pluralism, Siddha, Traditional medicine

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**INTRODUCTION**

Definition of integrative medicine (IM) is healing-oriented medicine that takes account of the whole person, including all aspects of lifestyle. It emphasizes the therapeutic relationship between practitioner and patient, is informed by evidence and makes use of all appropriate therapies [1]. Based on the review and close reading of medical peer-reviewed journals and government health statistics, Null *et al.* [2] show that the number of people having In-hospital, adverse drug reactions (ADR) to prescribed medicine in the US is 2.2 million per year. The most stunning statistic, however, is that the total number of deaths caused by conventional biomedicine is 783,936 per year, far higher than the number of deaths attributable to heart disease in 2001 that was 699,697 and cancer that was 553,251. In India, neither do we have any statistics of damages caused by medicine, nor a procedure to record damages due to medical errors and iatrogenic effects. The increase in the prevalence of non-communicable diseases, drug resistance and pharmaceutical complications; growing dissatisfaction with the outcomes of certain biomedical treatments; and the gaps provide conventional health care to several segments of the population, have directed much attention to traditional,

complementary and alternative medical (TCAM) systems [3]. This has led global population to conceive the idea of integration of Biomedicine with Traditional Medicine as it may mutually benefit both the medical systems in the form of filling up the gaps.

Indian traditional medicine is prevalent around the globe and integration exists scatterly with modern medicine for different health needs [4]. Siddha system of medicine is one of the traditional medicines of India, practiced in the southern part of the country. It is a primordial system of medicine that existed in the world. Siddhars are the spiritual scientists; they are well versed in Metallurgy, Geology and Phytochemistry. They have used all kinds of herbs, metals, minerals and animal products vastly. In spite of their popularity, the rational design, proper standardization, and careful monitoring of traditional Indian formulations, along with tough scientific evidence, are essential for their promotion [4]. In our time, there are lots of research are undertaken to bring out the scientific validation of Siddha medicine and they are published in national and international peer-reviewed journals. In AYUSH research portal around 1153 Siddha research articles, some of the research articles for various diseases are listed below (table 1).

**Table 1: Some important clinical trials, pre-clinical trials done in Siddha system of medicine (scientific evidence)**

First author/year	Diseases	Study type/Sample size	Siddha Intervention	References
Carlo Calabrese/2008	Cognitive performance, Anxiety, Depression	Randomized, Double-Blind, Placebo-Controlled Trial (48)	Bacopa monnieri	[5]
Thanikachalam Sadagopan/2014	Diabetes	Open, non-comparative, non-randomized, phase IV clinical trial (95)	Madhumeega choornam (Internal)	[6]
G. S. Lekha/2018	Dengue	Cohort study (100)	Nilavembu Kudineer (Internal)	[7]
Arul Mozhi P/2016	Cerebral palsy	Phase II Clinical trial (210)	Brahmi nei (Internal)	[8]
Sugunthan s/2017	Cervical spondylosis	Phase II Clinical trial(60)	Vilvaver kudineer (Internal), Varmam (Physical manipulation)	[9]
Velpandian V/2013	Osteoarthritis	Phase II Clinical trial (50)	Gowri chinthamani chendhuram (Internal medicine)	[10]
Rajalakshmi S/2019	Psoriasis	Open, Comparative clinical trial (40)	Panchamuga chendhuram (Internal) Kundavaathi thailam (External oil)	[11]

P. Kamalasoundaram/2018	Dysfunctional uterine bleeding	Phase II Clinical trial (40)	Perumbadukku pittu (Internal)	[12]
Karthik nagarajan	Male infertility	Open, Comparative Clinical trial (40)	Thetran ilagam (Internal) and Yoga therapy	[13]
Subramanian Sridhar/2018	Osteoarthritis	Phase II Clinical trial (30)	Suttigai (Cauterization)	[14]
Kingsley j/2018	Rheumatoid arthritis	Phase II Clinical trial (20)	Seendhil Chooranam (Internal)	[15]
Siva josyaa s/2018	Urticaria	Phase II Clinical trial (20)	Serankottai Nei Nilavagai Chooranam (Internal)	[16]
Bapat RD/1998	Varicose ulcer	Phase II Clinical trial (20)	Sanjeevi Thylam (External)	[17]
G. Ridhambaradevi/2018	Cerebral palsy	Phase II Clinical trial (10)	Attai vidal (Leech therapy)	[18]
P. Mirunaleni/2018	Diabetes	Phase II Clinical trial (10)	Brahmi nei (Internal medicine)	[19]
K. Samraj/2017	Benign Prostate Hypertrophy	Case series (10)	Podithimirthal (Dry powder massage)	[20]
R. Gayatri/2019	Renal calculi	Case series (2)	Yoga therapy	[21]
Natrajan/2019	Acute avulsion of posterior cruciate ligament of knee with bone fragment	Case study	Nilavembu Kudineer (Internal)	[22]
Lalitha sivasankaran/2019	Tennis elbow	Case study	Varmam (Physical manipulation)	[23]
L. Janani/2018	Insomnia	Case report	Attai vidal (Leech therapy)	[24]
G. S. Lekha/2018	Tinea infection	Case study	Varmam (Physical manipulation)	[25]
Sivakkumar S/2018	Varicose ulcer	Case study	Sivanaramritham (Internal)	[26]
Aruna devi R/2018	Diabetic Ulcer	Preclinical study	Thriphala chooranam (Internal)	[27]
Kumaravel Appavoo/2019	Peptic ulcer	Preclinical study	Karbogi paste (External)	[28]
ChristianGJ/2014	Peptic ulcer	Preclinical study	Pugai (Fumigation)	[29]
Sivaranjani K/2016	Musculoskeletal disorders	Review	Matthan thailam (External)	[30]
S. Bhavani/2017	Hepatitis-B	Review	Sirucinni Uppu (Internal)	[31]
Dharani/2016 M	Hemorrhoids	Review	Anda leghyam (Internal)	[32]
Chitra, Beyaril/2015	Senile Dementia	Review	Varmam (Physical manipulation)	[33]
B K Priya/2018	Sinusitis	Review	Nasiyam (Nasal instillation)	[34]
Ananthalakshmi ramamoorthy/2015	Oncology	Review	Internal medicine	[35]
Jeeva gladys. R/2013	Oncology	Review	Internal medicine	[36]

Table 2: Utilization of siddha system of medicines in siddha OPDs around Tamil Nadu

1 <sup>st</sup> Author	Sample size Male/Female n (%)	Place/Duration of the study	Morbidities n (%)	References
Kanna et al.	1511 Male 1070 (73) Female 411 (27)	Special Geriatric Clinic, Siddha Central Research Institute, Chennai/January to December 2009	Skin diseases	113 (7.4)
			Genital Disorder	3 (0.2)
			Fever	4(0.26)
			Musculoskeletal disorders	300 (20)
			Alimentary Canal diseases	50 (3.3)
			Respiratory Diseases	119 (7.88)
			Diabetes	84 (5.56)
			Cardiac Diseases	10 (0.66)
			Eye diseases	2 (0.13)
			Arthritis	345 (45.2)
Selva Raj k et al.	763 Male 445 (58.3) Female 318(41.7)	2 Siddha OPD (Andhiyur and Bhavani Government Hospitals), Erode District, Tamil Nadu, India./June-July 2014	Neuritis	67 (8.8)
			Diabetes	50 (6.6)
			Bronchial Asthma	40 (5.2)
			Hemiplegia	28 (3.7)
			Eczema	25 (3.3)
			Acid peptic Ulcer	22 (2.9)
			Lumbar Spondylosis	19 (2.5)
			Ulcer	16 (2.1)
			Allergy	15 (2)
			Fungal Infection	65 (24.2)
M M Reddy et al.	227 Males 138 (60.8) Female 89 (39.2)	2 Siddha OPD (Andhiyur and Bhavani Government Hospitals), Erode District, Tamil Nadu, India, 2015	Primary Complex	49 (21.6)
			Bronchitis	29 (10.1)
			Diarrhoea	13 (8.4)
			Arthritis	362 (21)
V. Duraisamy et al.	1720 Male 807 (46.9) Female 913 (53.1)	2 Siddha OPD, (Andhiyur and Bhavani Government Hospitals), Erode District, Tamil Nadu, India/February, 2014.	Neuritis	172 (10)
			Fungal diseases	116 (6.7)
			Bronchitis	114 (6.6)
			Acid peptic diseases	109 (6.3)

### Utilization of siddha system of medicines

In a study Shalini Rudra *et al.* explore the out-of-pocket expenditure on AYUSH treatment. The result shows that, the average expenditure on AYUSH medicines is Rs 270 in rural and Rs 378 in urban areas and is lower than average expenditure on non-AYUSH (allopathic) medicine [37]. This study focuses on AYUSH and lacks individual System wise which is warranted. To explore the integrative medicine, it is vital to understand the feasibility, efficacy and acceptability of Siddha interventions among the public. Some of the studies in Siddha OPDS around Tamil Nadu are listed below (table 2). The common use of Siddha medicines is for skin diseases, musculoskeletal disorder, diabetes, Respiratory diseases, gastrointestinal diseases.

### Various siddha medicine research conducted by biomedicine practitioners

1. Thanikachalam *et al.*, conducted a study to evaluate the clinical efficacy and safety of the polyherbal compound MMC in the management of type 2 diabetes. This pilot study was an open, non-comparative, non-randomized, phase IV clinical trial, conducted at the PURSE-HIS research station, at Sri Ramachandra University, Porur, Chennai, India from January 2008-2010. The trial included 95 patients; the results revealed that the fasting, postprandial blood glucose, HbA1c showed significant reduction after MMC intervention. The liver, renal functions, along with the hematological parameters were well within the normal range [6].

2. Govindan *et al.* conducted a study on the clinical efficacy of *Solanum xanthocarpum* and *Solanum trilobatum* in bronchial asthma at Madras medical college; the results revealed that improvement in Peak expiratory Flow rate (PEFR) and the reduction in other symptom scores clearly show a bronchodilator effect, a decrease of edema and secretions in the airway lumen. The response to these herbs, equal to that of deriphylline but less than salbutamol [42].

3. P. M. Murali *et al.*, conducted a randomized, double-blind study with Plant-based formulation (DCBT1234-Lung KR) in the management of chronic obstructive pulmonary disease, result revealed that, Improved PaO<sub>2</sub> was observed in 15.4% of DCBT1234-Lung KR patients while no improvement was seen with patients in any other arms. Symptoms like dyspnoea, wheezing, cough, expectoration, disability and sleep disturbances also considerably reduced in DCBT1234-Lung KR and the biomedical group patients, but not in the placebo arm. DCBT1234-Lung KR was alike, but not better than the present-day treatment with salbutamol, theophylline and bromhexine combination in COPD patients and this was ascertained using FEV<sub>1</sub> and ABG values [43].

4. P. M. Murali *et al.*, conducted a controlled clinical trial to compare plant-based formulation (DCBT4567-Astha-15) efficacy with oral salbutamol and theophylline for Bronchial Asthma, the results revealed that DCBT4567-Astha-15 was as efficacious as salbutamol (12 mg/day) in combination with theophylline (200 mg/day) treat reversible asthmatics. Quality of life of patients also improved with DCBT4567-Astha-15 drug treatment [44].

5. Chidambaram s. babu *et al.*, conducted a trial on Venthamarai chooranam, a polyherbal Siddha medicine, alleviates hypertension via AT (1)R and eNOS signaling pathway in 2K1C hypertensive rats, 2014 in Ramachandra University, Porur, Chennai, India. The result shows, Venthamarai chooranam potentially interacts with renin-angiotensin components and endothelial functions, and antihypertensive action [45].

6. Chidambaram s. babu *et al.*, conducted a study on Polyphenols in madhumeega chooranam, a Siddha medicine, ameliorates carbohydrate metabolism and oxidative stress in type II diabetic rats in Ramachandra University, Porur, Chennai, India. The results revealed that Madhumeega chooranam mediates its anti-diabetic action through the inhibition of gluconeogenesis and activation of glycolytic pathways in type II diabetic rats. Increased GLUT4 and PPAR $\gamma$  expressions provide more information on its glucose uptake/sensitising and hypolipidemic potential [46].

7. KR Subash *et al.* conducted the study in Sri venkateshwara institute of medical science, tirupati, Andhra Pradesh, India. They

evaluated the analgesic activity of *Alpinia galanga* extract in mice models and TNF-alpha receptor computational docking analysis on its leads with pharmacokinetics prediction. The results showed *Alpinia galanga* extract had significant antinociceptive activity and followed by computational analysis of 20 compounds with known chemical structure predicted Galanal B as a lead compound with best in-silico pharmacokinetic and drug-like features [47].

8. R. V. Ramanarayana Reddy *et al.* conducted the study at Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research, Tamil nadu, India. Evaluation of the antidiabetic activity of polyherbal formulation of Seenthil churnam in Alloxan induced diabetic rats. Administration of alcohol extract of Seenthil Churnam produced a dose-dependent decrease in blood glucose levels in Alloxan induced rats. There was a significant fall in blood sugar level in the dose of 300 mg/kg; this is comparable to the effect of Glibenclamide [48].

9. Thyagarajan SP *et al.* conducted a trial in CMC Hospital, vellore, India. 24 healthy long-term HBV carriers were treated with phyllanthus amarus and placebo; the result shows HBsAg clearance and HBV-DNA levels were significantly reduced [49].

10. J. Saikarthik *et al.* conducted the trial in Saveetha medical college and hospital, Chennai, Tamilnadu, India. Phytochemical analysis of methanolic extract of seeds of *Mucuna pruriens* by gas chromatography-mass spectrometry; the analysis reveals the presence of 5 major compounds namely, pentadecanoic acid, 14-methyl-, methyl ester, dodecanoic acid, 9,12-octadecadienoic acid (z,z)-, methyl ester, 9,12-octadecadienoic acid and 2-myristynoyl-glycinamide which are therapeutically potential [50].

These examples show how the benefits of Siddha medicines could be brought into the mainstream health care where they are balanced to play an increasingly important role.

### Government health policies for mainstreaming of siddha

Several policies which may help to integrate Siddha medicine for health care system are listed below,

1. Udupa Committee in its report published in 1958 recommended that there is a need for integrated system of medicine in India [51].

2. The National Population Policy 2000, National Health Policy 2002, and the National Commission on Macroeconomic and Health—2005 of the Ministry of Health and Family Welfare, Government of India, emphasized on reorientation and prioritization of research in Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) and to confirm therapy and drugs in chronic and lifestyle-related diseases [52,53].

3. The National Health Policy (NHP) 2017 has strongly advocated mainstreaming the potential of AYUSH within a pluralistic system of integrative health care. The NHP 2017 uses a new language of 'medical pluralism' and re-emphasizes the need for integrating AYUSH in the National Health Mission, research and education. Indeed, the NHP 2017 is the most powerful policy expression of integrative healthcare since independence for which the Ministry of Health and Family Welfare must be congratulated. NHP 2017 highlights strategies to meet national health goals through protocol driven integrative practices [54].

4. Ministry of AYUSH, along with Directorate General of Health Services (DGHS) is implemented NPCDCS (National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke) for health promotion, prevention and management of Noncommunicable diseases or Lifestyle related disorders [55].

### 5. Nilavembu kudineer

At the time of dengue epidemic 2012, the Tamil Nadu government distributed a Siddha herbal decoction, Nilavembu kudineer (NVK) at free of cost. Health and Family Welfare Department letter No. 41459/IM1(2)/2012, dated 21.11.2012 stated that "Nilavembu decoction, traditional Siddha drug is effective in the treatment of viral fevers like dengue". The Nilavembu kudineer has 9 ingredients they are Nilavembu (*Andrographis paniculata*), Vilamichai Ver

(*Plectranthus vettiveroides*), vetiver (*Vetiveria zizanioides*), Cukku (*Zingiber officinale*), Milagu (*Piper nigrum*), Korai kizhangu (*Cyperus rotundus*), Santanam (*Trichosanthes cucumerina*), Parpadagam (*Mollugo cerviana*). This is not only to treat diseases, but also to prevent diseases [56]. As a result, there is a reduction in morbidity and mortality of dengue fever. The antiviral activity of nilavembu kudineer was estimated by Jaspreet jain *et al.* [57], dengue and chikungunya virus through *in vitro* evaluation shows, NVK provides protection against CHIKV and DENV-2 during active infection and also help to prevent virus infection in the cells.

#### 6. Amma magapeeru sanjeev kit

For the first time, drugs of Siddha systems have been incorporated into the kits of ante-natal cases throughout the state of Tamilnadu. Health and Family Welfare Department Demand No.19 Policy Note 2016-17 stated that Amma mapeeru sanjeevi, at Rs. 10 crore scheme, which will have a bouquet of 11 siddha medicines for pregnant women and newborn." A kit contains Madhulai Manappagu, Karuveppilai Podi, Nellikkai Legiyam, Elathy tablet, Annabedhi tablet, Ulundhu thailam and Pinda Thailam (both for external application), Paavana Panchakula thailam, sathavari legium, kunthiriga thailam, Urai mathirai. These medicines will reduce nausea, vomiting, balancing iron deficiency, reducing false pain, improve immunity in infants. This helps the health systems to take care of many of women and children as a first line of care through the Siddha medicine [58].

#### Areas of focus in integration

##### Varmam (Physical manipulation)

In biomedicine, the treatment for musculoskeletal disorders are local injections of steroids, Nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, muscle relaxants are either ineffective or provide short-lasting benefits [59]. With this hitch the medical industry is in need of effective, long lasting benefits in musculoskeletal disorders. Siddha varmam therapy originated from the southern part of Tamilnadu, is now practiced in South Asian countries like India, Srilanka and Malaysia. Varmam specifies the therapeutic manipulation of certain points in which the life energy is found pooled. Handling on these points with a particular force for the definite time will release the life energy from these points and fetch relief to the affected individual by regulating the flow of life energy which is blocked due to attack on particular Varmam points or due to other causes [22]. It offers a conservative management approach to pain, Neuro-musculoskeletal disorders, metabolic disorders, sensory defects, gastrointestinal, respiratory diseases, endocrine disorders, pediatric diseases like autism and trauma [9,22,24,30]. The advantages of varmam are non-invasive technique, cost effective, easy to manipulate. Siddha varmam therapy may open new perspectives in the area of pain management. A national Guidelines to Practice varmam is available in India published by CCRS (Central Council for research in Siddha), Ministry of AYUSH, Government of India [60].

##### Karanool sigichai (Chemical cauterization)

Karanool sigichai is a unique para surgical treatment carried out for the management of fistula-in-ano. It is a method of chemical cauterization of fistula. *Achyranthus salt*, *Dalmia extensa salt* etc. are smeared on a surgical thread which is used to cut the tract. The major advantages of this procedure are, it will preserve the function of continence and prevents the recurrence of the condition and also cost effective [61,62]. This will open up a new scope of Siddha para-surgical procedure in Anal fistula.

##### Attai vidal (Leech therapy)

In the Act of June 28, 2004, the Food and Drug administration (FDA) cleared for the first time the commercial marketing of medicinal leeches for medicinal purposes and determined that leeches are medical devices. In Siddha text leech therapy, especially indicated for edema, headache, abdominal pain caused by dysentery, whooping cough in children, inflammatory joint diseases, eye diseases. Bio-constituents in leech saliva have vasodilator, anesthetic, anti-inflammatory activity and also inhibits the blood

coagulation [63]. Leech therapy is used clinically for various diseases they are Osteoarthritis, Epicondylitis, varicose veins, and hematomata. It is also evident leech was used in dreadful condition, meningococcal purpura. As an integrative approach now leech is used in bone reconstruction surgery.

#### Yoga

The term 'Yogam' means 'union'. Siddhars have defined yogam as an art which controls the mind by preventing it from distracting through sense and sense organs and fuse it with the divinity. The eight steps or stages of yogam arelyamam (Learning discipline), Niyamam (Purity of action), Asanam (posture), Pranayamam (controlling one's breath), Prathyaharam (Controlling 5 senses), Dharanai (the practice of concentration), Dhyanam and Samadhi. Third step or stage of yogam is asanam, means posture or pose, it is also called as yogasanam. The perfect and scientific art of controlling one's breathing is called Pranayamam. It is also called as 'vasi' and 'vasiyogam' [64]. Yoga can be integrated with various diseases such as Musculoskeletal disorders, Bronchial asthma [65], hypertension [66], depression, insomnia etc [13,19]. It can also be used as an adjuvant therapy for many non-communicable diseases.

#### DISCUSSION

The concept of 'integrative' medicine has come up several times earlier and is not new. This, however is not a call for Siddha alone, but it is all about the direction of change. World Health Organization (WHO) has announced desirable doctor-population ratio as 1:1,000. In India as per current population, it gives a doctor (modern medicine) and a population ratio of 0.77:1,000 [65]. After considering AYUSH registered medical practitioners it counts, 1.33 billion of Indian population is being served by 1.8 million registered medical graduates during 2017. So, the ratio is 1.34 doctor for 1,000 Indian citizens as of 2017. This shows that India reached WHO norm by 1:1,000 doctor population ratio after considering AYUSH doctors. Besides this an assessment of the mainstreaming of AYUSH in Rajasthan, India [Society for Economic Development and Environmental Management (SEDEM) n. d.], revealed that AYUSH is popular and regularly accessed by the community. Approximately half the allopathic doctors studied reported never referring patients to AYUSH doctors<sup>3</sup> the lack of knowledge about traditional medicine in biomedicine practitioner is the reason behind this crisis; this can be rectified by including traditional medicine in the MBBS curriculum itself.

The Indian government also supports to promote the traditional medicine in India. The budget *al.* location for the Dept of AYUSH has increased gradually over the years. In the 12th Five Year Plan of India (2012-2017), the total allocation for AYUSH was INR. 10,044 crore, which was 235% more than the actual expenditure of 11th Plan [66]. Till date, AYUSH facilities have been co-located in 506 District Hospitals, 374 sub district Hospitals, 2871 CHCs, 8995 PHCs, and 5716 other healthcare centers. The Magnitude of AYUSH infrastructure in the country has reached 7,99,879 registered practitioners, said by the AYUSH minister on 19 July 2019 [67, 68].

Although we have proof of scientific validation, the utilization of Siddha medicines for various diseases, the data for Siddha Intervention as Add-on, limitations for Siddha intervention (Dislodgement of renal calculi of bigger size), areas where Siddha can compliment such as usage of Mathan thylam in diabetic ulcer without disturbing the contemporary treatment module, drug-drug interactions, drug food interactions and food based health benefits have to be documented. The discovery of complete integrative approach guidelines of Siddha medicine with biomedicine is the only approach to resolve this crisis. Both Siddha and biomedicine experts in a particular field should assemble and prepare the guideline to safeguard the public.

#### CONCLUSION

Hence, there has been a huge utilization of Siddha medicine and also proof of scientific validation of Siddha medicine its usage in both communicable and non-communicable diseases, Integrating Siddha medicine with biomedicine is essential to offer better health facilities to public. Integration of Siddha with the existing health care

system, not only helps in preventive and promotive health also focuses more in complementing Biomedicine by offering profound Siddha Varmam, Yoga therapy. Integrative approach is the only way to achieve the dream of health in an efficacious and cost effective manner.

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#### AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

#### CONFLICT OF INTERESTS

Nil

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