‘A study of Ayurvedic Pharmacoepidemiology and therapeutics of *Madhumeha* (Type 2 Diabetes mellitus): An Untapped potential for new drug discovery’

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THE UNIVERSITY OF TRANS-DISCIPLINARY HEALTH SCIENCES AND TECHNOLOGY

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DOCTOR OF PHILOSOPHY

BY

DR MRS NUTAN SHAM NABAR
under the guidance of

DR ASHOK DB VAIDYA

COGUIDE
DR CHETHALA VISHNUPRASAD

The University of Trans-disciplinary Health Sciences and Technology
#74/2, Jarakabande Kaval, Post Attur via Yelahanka,
Bengaluru. PIN: 560 064 INDIA.

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THE UNIVERSITY OF TRANS-DISCIPLINARY HEALTH SCIENCES AND TECHNOLOGY

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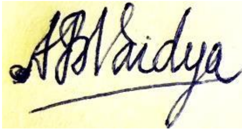
CERTIFICATE

This is to certify that the work incorporated in this thesis **"A study of Ayurvedic Pharmacoepidemiology and therapeutics of *Madhumeha* (Type 2 Diabetes mellitus): An Untapped potential for new drug discovery"** submitted by Dr Mrs Nutan Sham Nabar was carried out under my supervision. No part of this thesis has been submitted for a degree or examination at any university. References, help and material obtained from other sources have been duly acknowledged. I hereby confirm the originality of the work and that there is no plagiarism in any part of the dissertation.

Research Supervisor



Dr Ashok DB Vaidya
Research Director, Kasturba Health Society's Medical research Centre
17. KD Road, Vile Parle West, Mumbai 400056, INDIA

Emeritus Professor, The University of Trans-disciplinary Health Sciences and Technology,
#74/2, Jarakabande Kaval, Post Attur via Yelahanka,
Bengaluru. PIN: 560 064 INDIA.

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Abstract

Introduction

The Center for Drug Evaluation and Research- Food and Drug Administration (CDER-FDA 2011) report shows that, on an average, 22- 24 different modern drugs are approved per year. Several drugs are withdrawn couple of years after marketing because of severe adverse drug reactions (ADRs) and sometimes deaths. There is a general trend towards using natural products and nutraceuticals due to fear of ADRs. Globally, as many as 50-60 % people are inclined to use traditional medicines. Self-medication and Over the Counter (OTC) drugs are fairly common practice in India. Such utilization is higher in chronic diseases, musculo-skeletal illnesses and skin-related ailments. However, there is a relative paucity of usage data of Ayurvedic medicines in the community. The potential of drug-drug or herb-drug interactions is of concern for safety and reduced/enhanced therapeutic activity. It is important and relevant to investigate the extent and the nature of the field usage of Ayurvedic medicines.

Pharmacoepidemiology (PE) is the branch of science which studies the use and effects of the drug in a large number of people . PE covers the field-studies of drug-usage, safety (ADRs), efficacy, acceptability and interactions of drugs. PE, can also be a source of novel beneficial effects of a drug, which may open up a path to new drug discovery or repositioning of a drug. In Ayurveda, *Janapada* is a word that has been ascribed to large population. *Janapadadhwansa* implies the determinants of diseases, in large populations as such as polluted air, water, soil and *Adharma* (unjust or evil) .

Ayurvedic Pharmacoepidemiology (AyPE) is a new inter-discipline proposed by Vaidya RA et al for the study of the usage, acceptability, efficacy, compatibility, interactions and cost-effectiveness of Ayurvedic drugs in a large number of people. Alarming headlines about the toxicity of Ayurvedic medicines in newspapers, journals and media, without appropriate scientific studies can have an adverse impact on a system of health used for centuries.

Ayurvedic formulations marketed in India are manufactured at 7,910 manufacturing units. Several preclinical and clinical studies, as a part of MD PhD theses, have explored the anti-diabetic potential of some of the selected plants and formulations. Their mechanisms of actions and biological plausibility are also being investigated. Despite these studies it is essential to have proper AyPE evidences for safety and efficacy of Ayurvedic anti-diabetic drugs. In view of diabetes mellitus (Type II) being a major challenge in India, due to cardiovascular, renal, retinal and neural complications such a study with AyPE was

contemplated. Diabetic patients often consume Ayurvedic medicines for controlling diabetes, reducing side-effects, complementary use and prevention of complications. The data on exact nature of usage of Ayurvedic and other traditional medicine for diabetes are scarce.

Objectives:

1. To enlist commercially Marketed Ayurvedic Antidiabetic Formulations (MAAF) and study the labels and patient inserts.
2. Compare biological plausibility of medicinal plants from MAAF with respect to *Dravyaguna* (pharmacological) rationale from classical texts of Ayurveda
3. To study the utilization patterns of MAAF, OHA as mono system antidiabetic drugs as well as concurrent use of both amongst known diabetic patients.
4. To assess Knowledge, Attitude and Practices (KAP) of diabetes amongst diabetic patients and doctors prescribing these drugs.
5. To study the pharmacological activity and safety of selected Ayurvedic formulations using conventional laboratory based techniques by Reverse Pharmacology

Methodology:

Ancient and current Literature survey:

The classical ancient but still relevant literature was accessed at several libraries for - all the *sutras* and *tikas* on diverse aspects of *Madhumeha*. Textbook of medicines, endocrinology, national international journals, sites of various diabetic association viz IDF, ADA, etc. WHO, and various online sources were searched to get most recent description of diabetes, management guidelines, new oral hypoglycemic agents, paradigm shift in antidiabetic targets.

Marketed Antidiabetic Ayurvedic Formulations (MAAF):Study of labels, patient information and packaging of the formulations Information provided on the labels was analyzed according to dosage formulation, dosage strength/schedules, vehicle, timing of administration, parts of the plant used, and number of ingredients and concentrations of MAAF. Labels of first consecutive 100 formulations were evaluated for regulatory compliance as per the standard format of the rules (1945) of the Drug and Cosmetics Act 1940 (XVII, 161) . Package inserts were analyzed as per WHO guidelines for evaluating package inserts of traditional medicine.

Drug utilization Study:

Swadeshi Arogya Mela in Mumbai: Known type 2 diabetic patients voluntarily visited to the assigned booth. Predesigned survey form was used to record the demographic data, history of duration of diabetes, information regarding pharmacological and nonpharmacological

modalities (diet and physical activity, Yoga and others) as well as random blood sugar at the booth site on the same day.

Drug Utilization Survey at a Tertiary Health Care center in Mumbai: A survey was conducted at Endocrine out-patient department of a tertiary health care centre- NAIR Hospital in Mumbai. Prescriptions and the patient's health records were reviewed simultaneously during the interview of the patient.

Retrospective survey of clinical case records at Ayurvedic Hospital of FRLHT

Clinical case records of all diabetic patients, who have completed follow ups of 6 months till December 2016 (January 14 to December 16- Last 3 years) were reviewed. All available data for each patient was recorded in EXCEL sheets and analyzed to evaluate usage, safety and efficacy of the Ayurvedic Antidiabetic

Knowledge, Attitude and Practices (KAP) Survey:

KAP survey of Diabetic patients for the management of their disease: It was a cross sectional survey of type 2 diabetic patients visiting Integrative Diabetes clinic at MRC-KHS. Information based on structured interview was recorded.

Knowledge and practices of Ayurvedic Physicians towards diabetic management:

Ayurvedic Physicians were surveyed with a pre designed questionnaire. All the information recorded in questionnaire was analyzed by SPSS software. Student's t test for significant difference between two means and Chi 2 test was used for association of knowledge and practices. $P<0.05$ was considered as statistically significant.

Clinical studies of selected Ayurvedic Antidiabetic formulations under the project CSIR NMITLI Diabetes: Two formulations *NishaAmalaki* (combination of *Curcuma longa* Linn and *Phylanthus emblica* Linn in 2:3 proportion) and *Mamejava Ghana vati* (formulation made by evaporation of decoction of Plant *Enicostemma littorale* Blume as per Ayurvedic Methodology*) were* studied for safety, antidiabetic activity in healthy volunteers and diabetic patients as well as for drug interaction in healthy volunteer also. Reverse Pharmacology path was followed for these clinical trials. Exploratory study for complementary effect of *NishaAmalaki and* Mamejava Ghana vati were conducted in treated uncontrolled type 2 diabetes mellitus patients with GCP guidelines.

Alpha Glucosidase inhibition activity:

Market samples of *NishaAmalaki* (Combination of *Curcuma longa* Linn and *Phyllanthus emblica* Linn), *Mamejava Ghana (Enicostemma littorale* Blume) and phytoactives of E. Littorale (Phytoactives viz, Swartiamarine, Apigenin, sweroside, stigmasterol) were screened for α glucosidase inhibition activity by standard protocol.

Results

Literature search: Ayurveda has described the rationale of use of medicines in the Classical Texts Brihattrayi and laghuttrayi. Pathophysiology and Symptomatology have been discussed vividly. Complete management as per the doshik dominance with medicinal plants, herbo-mineral preparations and the detail assessment of dietary articles have discussed in detailed.

Marketed Ayurvedic Antidiabetic Formulations: Labeling, Drug Information

One hundred and eighty Marketed Ayurvedic Antidiabetic Formulations (MAAF) purchased and analyzed. They were in the form of capsules (n=66), tablets (n=65), powders (n=37), liquids (n=8), granules (n=3) and one herbal wooden cup of *Pterocarpus marsupium*. They were packaged in diverse forms like plastic bottles, glass bottles for liquids, plastic sachets, paper cartons with plastic bags, silver foil bags, blister strips. Majority formulations found to have 10-20 ingredients. Study of labels reveals that basic 3 components i.e. manufacturing license number, manufacturing date, and batch number were printed on the labels in all 100 formulations. None of the labels either indicated contraindications or any information about anupan and aushadhi kala.. Some of the brand names appear to reflect that the products are meant to “completely cure diabetes”.

Drug utilization Study

***Swadeshi Arogya Mela* : Pilot study in Mumbai**

Two hundred & twenty seven diabetic patients (166 men + 61 women) visited the counter during 4 days of *Swadeshi Arogya mela* (age range of 35-75 yrs*)*. The pharmacological antidiabetic management included only allopathic medicines (45.4%), only Ayurvedic (8.4%), both Ayurvedic and allopathic concomitantly (32.6%) and others (3 %) and 10.6% diabetic patients were not taking any drug. Among the oral hypoglycemic agents (OHA) glibenclamide (28.2%) was the most frequently consumed agents followed by Metformin (23.6%), Insulin (8%) and glimepiride (7.5%). Forty one % diabetic patients were consuming traditional Ayurvedic medicine. The most common MAAF were *Lokmanya Churna, Madhumehari Dane, Tablet Diabecon,* Capsule *Karnim and* Capsule *Karela*. Besides MAAF, diverse combinations of Ayurvedic medicinal plants also were taken by the patients. Within the nonpharmacological management a restricted diet was followed by 72.7% patients in terms of reduced sugar & oil. Walking was the most prevalent physical activity followed by 72.7% diabetics.

Hospital Based Drug Utilization study: NAIR Hospital

A total of 279 type 2 diabetic patients (136 men and 143 women) were interviewed during the period of 8 months. Only 33 (21 men and 12 women) of 279 diabetic patients were consuming Ayurvedic Medicine concurrently with conventional Antidiabetic medicine for the

management of the disease. Most of them (21/33) consumed Ayurvedic medicines on empty stomach with water. Controlled sugar was found in 51 diabetic patients as judged by normal glucose values (fasting <110 mg% and PP < 140 mg %.). Reduced blood sugar (13/33) was the commonest benefit of taking Ayurvedic medicines reported. All the patients were agreed upon to continue the Ayurvedic Medicines in future.

Retrospective study of case record forms at FRLHT, Bengaluru

Case record of diabetic patients visiting *Swasthavritta* department were reviewed. *Vasant kusumakar ras* was most frequently prescribed (39.3% visits) medicine followed by *Nishaamalaki vati* (37% visits), D-nil capsules (28 %) and Diabecon DS (28%) tablets. Seventy two % patients were already receiving various concurrent conventional antidiabetic medications. Most common two drug combination consumed was Glimepiride-Metformin combination (25%). Among single drugs; Metformin alone (19.5%) glimepiride (17 %), insulin injections (17%), Gliptins (17 %) and Voglibose (12.2 %),were common. No adverse events were found during 6 months of therapy, except for one patient reporting loose motion after *Nisha Kathakadi Kashay* which was then discontinued.

Knowledge Attitude and Practice survey

KAP survey of Diabetic patients at integrative clinic of diabetes at MRC KHS in (168 men and 125 women): Thirty four % diabetic patients did not know what diabetes (nature of the diseases) is. Significant association was noted with education (p=0.005), occupation (p=0.001) and gender (0.003). Regarding the causes of diabetes hereditary was significantly associated with education (0.01) and occupation (0.02).Knowledge of complications was poor; however retinopathy (74%) was the most frequently selected followed by cardiovascular diseases (CVD-69%). Diet modification (p= 0.00) and yoga (p= 0.02) were significantly associated with education. Majority patients (95.6%) think that blood sugar control is important for the health and education regarding the disease will help for better control. Seventy one % diabetics perceived that Ayurveda can be used to control the diabetes. Physical activity (47 %) and diet modifications (44%) were the most common modalities used to manage the diabetes. Sixty one % patients are regularly having medical advice which are significantly associated (p= 0.02) with their education.

Knowledge and Practices of Ayurvedic Physicians for the management of diabetes

Data of 143 (99 men and 44 women) Ayurvedic physicians were analyzed. More than half (57.3%) participants felt that Fasting and PP glucose test is the best test to diagnose diabetes and 44% felt that HbA1C is the best test to monitor the glucose control. These physicians use F&PP sugar test (79%) to diagnose diabetes followed by Ayurvedic Nidan (53%). Lipids

(83.2%) and eye check-up (51%) are the two investigations which are additionally carried out with sugar test. Amongst the drug modality, Ayurvedic medicines (74.1%) and Oral Hypoglycemic Agents (61.5%) are prescribed by the physicians. Among the non-drug modality of managing diabetes; walking is advised by 71% physicians followed equally by exercise (67.8%), yoga (66.4%) and diet(63.6%). Among all physicians, 50.4% and 29.4 % physicians had ≥ 75 percentile of knowledge, and practice points respectively.

Clinical studies of selected medicinal plants in type 2 Diabetes under CSIR NMITLI diabetes project:

1. Exploratory study for complementary effect of Nisha amalaki in treated uncontrolled type 2 diabetes mellitus:

Neither antihyperglycemic nor hypoglycemic and hypolipidemic activity were observed. However, insulin sensitization was observed in 2 out of 4 hyperinsulinimic and insulin resistant individuals. Reduction in glycated hemoglobin (HbA1c) was also observed in 4 out of 13 patients. Maintenance of the HbA1c was noticed in the other 6 patients. Remaining 3 patients showed the worsening of the HbA1c. Hence the study with experimental design was planned to find out activity in newly detected patients with type-2 diabetes

2. Study in newly detected diabetic patients

There was a definite lowering of blood sugar level (OGTT values) in the patients with Medical Nutritional Therapy (MNT) with DM FN-01 as compared to only MNT at the end of 30 days of therapy. HbA$_{1}$c values decreased at the end of 30 days of therapy in the MNT + DM FN-01 group as compared to MNT only. It was of interest to observe that HbA$_{1}$c values of MNT group also decreased at the end of 60 days when DM FN-0 1 was added for last 30 days. No effect was seen on lipid profile as well as CRP values. Improvement in energy level was observed clinically.

3. Exploratory study for complementary effect of Mamejava Ghana vati in treated uncontrolled type 2 diabetes mellitus

Mamejabva Ghana vati was found to be safe with good tolerability and acceptability. Significant reduction in HbA1c ($p<0.0001$), in postprandial plasma glucose ($p<0.003$) and in high triglycerides ($p<0.002$) was observed. Directionality in CRP reduction suggests the anti-inflammatory potential. Average weight loss of 1.5 kg at the end of 2 months of therapy was observed. Clinically beneficial effects were seen as sense of well- being, increase in energy and decrease in false hunger.

4. A study of plasma levels of Metformin with or without oral Antidiabetic formulations.

In the part one study, volunteers with simultaneous administration of DMFN 01 showed a reduction in the mean C-max from 1577 ± 520 SD ng/ml to 712 ± 206 SD ng/ml (decrease of 55 %) , and of AUC (0-24 h) from 10066 ± 3405 SD ng.ml.h to 4936 ± 1389 SD ng.ml.h (decrease of 51 %) of metformin (Student's t test ; P <0. 002). There was no significant reduction in the mean C-max (1419.8 ± 189 SD ng/ml vs 1345.9 ± 401 SD ng/ml) , and in the mean of AUC $_{0\text{-}24\ hr}$,(8377.7 ± 2105 SD ng.ml.h vs 7769.6 ± 1775 SD ng.ml.h) of Metformin without or with DMFN 02(Paired t test; P=0.645). None had any side effect due to administration of either drug except one volunteer reported stomatitis after 2 days of cross over after Metformin, which was not drug related.

Alpha Glucosidase (α G) inhibition

Alpha Glucosidase inhibition by *Mamejava* (*Enicostemma littorale* Blume): Four samples of MAMEJAVA marketed formulations inhibited α-G activity in a concentration dependent manner. *Mamejawa* Lion has higher potency EC 50 (16.37) in inhibiting the alpha glucosidase followed by *Mamejawa* Powder (17.73), SDM (21.69) and Chaithanya (22.72).

Alpha Glucosidase inhibition by selected phytoactives of *Mamejava*: These compounds showed marginal activity

Discussion and Conclusions

Ayurveda do have information regarding frequent urination i.e. *Prameha* which has been described in many classical Ayurvedic texts such as *Brihattrayi* and *laghuttrayi*. Various herbal and herbominaral formulations have been recommended as a therapy for various conditions of *Prameha* and *madhumeha*. Rational thinking behind the therapeutic guidelines as a whole and the formulations specifically reveals the reversal of pathophysiology (shatkriyakalas). Thousands of Ayurvedic drug manufacturing units are producing and marketing these formulations, and are available for diabetic patients without need of prescriptions as well as with scarcity of patient information leaflets. If sufficient Pharmacoepidemiological evidence is collected safety and efficacy can be generated. Study of labels of these marketed formulations shown that the labels follow mandatory instructions; however the specific information of *bheshaj kala* (time of administration) , *anupan* (vehicle), and indication - contraindication as per Ayurvedic therapy were not displayed. Our study is of first of its kind as no studies are reported in literature regarding Ayurvedic Antidiabetic drug usage by Diabetic patients.The drug utilization study in diabetic patients noted varied percentage of using Ayurvedic medicines for diabetes. As these were pilot studies, conducted

for the first time adopting the conventional method; the results can't be applied to the community.

KAP survey of diabetic patients presented better knowledge score than the attitude and practice.In KAP survey of Ayurvedic physicians among all physicians reveals good knowledge compare to practice. The potential drawback of our study is a report from a single study hence cannot be generalized to the diabetic population of Mumbai

Alpha Glucosidase inhibition study by MAAF and phytoactives showed dose dependent inhibition of the enzyme suggesting a new target for antidiabetic drug discovery. AyPE needs triple competence in clinical pharmacology, medicine, and epidemiology or a team with such diverse expertise. This is because as per WHO estimates, almost 80% of population of many Asian and African countries relies on traditional medicine for primary health care. Ayurvedic pharmacoepidemiology approach can provide early evidence of the safety, efficacy and acceptability of Ayurvedic drugs. Such an endeavor may precede Observational Therapeutics and Reverse Pharmacology.

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Private University Established in Karnataka by ACT 35 of 2013

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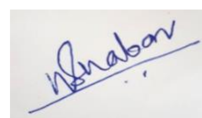
DECLARATION BY THE CANDIDATE

I declare that this thesis entitled "**A study of Ayurvedic Pharmacoepidemiology and therapeutics of *Madhumeha* (Type 2 Diabetes mellitus): An Untapped potential for new drug discovery'** submitted for the awardm of Doctor of Philosophy to THE UNIVERSITY OF TRANS-DISCIPLINARY HEALTH SCIENCES AND TECHNOLOGY, Bengaluru, is my original work, conducted under the supervision of my guide Dr Ashok DB Vaidya and co-guide, Dr Chetala Vishnuprasad. I also wish to inform that no part of the research has been submitted for a degree or examination at any university. References, help and material obtained from other sources have been duly acknowledged.
I hereby confirm the originality of the work and that there is no plagiarism in any part of the dissertation.



Place: Bengaluru **Signature of the Candidate**

Date: February 2021

Name of candidate: Dr Mrs Nutan Sham Nabar
Reg. No.: 21015030110
February 2021

Acknowledgement

Emotions can’t be adequately expressed in words as than emotion are transformed into formalities. Nevertheless formalities have to be completed. My acknowledgement is many more than what I am expressing here.

My journey for PhD program started way back in 1993!! On my day of final examination of MD Ayurveda Kayachikitsa (Internal Medicine), Head examiner, Dr SP Sardeshmukh (Director, Integrated Cancer Treatment and Research Centre, Wagholi,) had offered me his studentship for PhD. I politely denied the offer as I was mother of a 4 months old child. I thought I might not justify the research work during that period; however I thank him for ploughing the seed for further education.

Time flew very fast. I started my research carrier after almost 10 years in 2001 at Bhavan’s Swami Prakashananda Ayurveda Research Centre (SPARC), Juhu, Mumbai as Senior Research fellow for the project on the study of *Panchvalkal* in vaginal infections under the guidance of Dr Jayashree Joshi from whom I acquired skills of thorough gynaecological examination including colposcopy and PAP smears. I would like to thank her for the encouragement that she gave me in stepping up in clinical research as per GCP guidelines.

In the year 2003, I was involved as Research Associate for a major nationwide project of CSIR NMITLI Diabetes (New Millennium Indian Technology Leadership Initiative) led by Dr Ashok Vaidya and Dr Rama Vaidya. It focused on a development of Ayurveda Inspired herbal product for one of the NCDs i.e. type 2 Diabetes mellitus (T2DM). During the research work I was fascinated by the multifaceted personalities of Dr Ashok Vaidya and Dr Rama Vaidya. She lovingly ordered me to register for PhD program which I could not deny.

I feel immense pleasure to express sincere thanks and deepest sense of gratitude towards her, for constant inspiration, vast guidance, constructive criticism, parental affection, scholastic encouragement throughout the course of investigation right from selection of problem to shaping manuscript of this thesis. I have no idea without her whether I could complete the program.

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I am indebted from bottom of my heart to thank my Guide Dr Ashok Vaidya. He has opened my vision and widened the horizons of my knowledge which help me in interpreting Ayurvedic *sutras* as well as conventional medicines. I was exposed to both clinical diabetology and dimensions of experimental diabetes and metabolic syndrome, and the field reality of usage of Ayurvedic drugs by diabetic patients. Influenced by these thought I was motivated to do Pharmacoepidemiological work under the guidance of Dr Rama Vaidya. He extracted best of me out as a Guru and took me on his shoulder while travelling through the *dnyanganga*. I would like to be in their debt throughout my life and reciprocate my feelings about them by offering my duties towards them and serving them devotedly. I would like to dedicate my work to them.

During CSIR and HIP 2 projects I had an opportunity to discuss multifactorial Diabetes disease with multidisciplinary experts like Clinical Pharmacologists (Dr Ashok Vaidya, Dr MUR Naidu, Dr Urmila Thatte), *Dravyagunadnya* (Dr S D Kamat, Dr Tanuja Nesari), Endocrinologists (Dr Rama Vaidya, Dr Prema Vartakavi), Diabetologists (Dr V Mohan, Dr Sanjiv Shah, Dr Vijay Ajgaonkar), Phytochemists (Dr Ashok Amonkar, Dr Vahalia, Dr Chandrashekhar), and Ayurvedic Experts (Dr Nitin Kamat, Dr Manoj Nesari). I would like to acknowledge their influence on my thinking process.

No words or phrase can convey my exact feelings towards my parents (Kulkarni family) for their boundless love and sacrifice in educating me at the cost of their comfort and consolation.

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Lately I express my grateful thanks to all those who indirectly influenced my success.

Mangirish !!

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    2. Nabar NS, VaidyaRA, Vishnuprasad CN, Iyer SR, Godse CS, Amonkar AJ, Vaidya ADB. Enicostemma axillare subsp. littorale (Blume) A.Raynal for Type 2 Diabetes mellitus: An overview Annals Ayurvedic Med. 2020; 9 (4) 279-290.

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1.Introduction

“The doctor of the future will give no medicine, but will involve the patient in the proper use of food, fresh air and exercise.”

– Thomas Edison

Introduction

1.1 Ayurveda: pluralistic health care systems

India is a country, where seven pluralistic health care systems are officially available to whole population. Ayurveda is one of the most ancient and widely prevalent health care systems. It was the mainstream health care system even thousands of years before the British occupation (1679) of this country[1,2]. One of the most important objectives of Ayurveda is maintenance of health and management of disease. Diet and behaviour in daily and seasonal regimes have been given the utmost importance for maintenance of health as well as in management of disease(s), as these are considered to be major causative factors that alter the harmony between the *Doshas* and *dhatus* leading to the development of disease[3]. One can maintain one’s health if *pathyapathya* (intake of beneficial /desirable food)is followed. In modern system of medicine also, importance of a healthy diet has been appreciated more in the last few decades. The benefits of combined therapy of following a healthy diet and physical activity have been studied reported after Dean Ornish provided evidence that it is possible to reverse heart disease[4]. Besides diet, sleep is one of the important components of the triad (*Trayopstambha*- ‘pillars’) of health) and is considered as important as diet in balancing *dosha* and *dhatu*. Sleep deprivation causes hyperinsulinemia and insulin resistance,

leading to obesity with a higher risk of type 2 diabetes mellitus and metabolic syndrome [5]. In Ayurveda, dietary modification, exercise and other lifestyle modifying measures have been well delineated for each health condition/disease.

1.2 Drug usage :Current scenario

The report of The Center for Drug Evaluation and Research- Food and Drug Administration (CDER-FDA USA 2011) shows that, on an average, 22- 24 different modern drugs are approved per year However, several drugs are withdrawn a few years after they have been introduced into the market because of severe adverse drug reactions (ADRs) and sometimes evendeath associated with use of the drug(s)[6]. Examples of newly approved drugs which had to be withdrawn (or repurposed for other indications) are Valdecoxib (Bextra), Pemoline (Cylert) , Bromfenac (Duract), Levamisole (Ergamisol), Rofecoxib (Vioxx), Isotretinoin (Accutane), Sibutramine (Meridia), Terfenadine (Seldane). These were withdrawn within a few years after marketing because of severe adverse drug reactions (ADRs) associated with high mortality. Consequently, there is a general trend towards use of natural products and nutraceuticals with beneficial pharmacological activity and with a good safety profile. Globally, as many as 50-60 % people are inclined to use traditional medicines [7-9]. In India, in spite of the heritage of traditional medicines, conventional medicine is recognized as mainstream medicine because of the dramatic cures in acute illnesses. However, it is observed that self-medication and Over the Counter (OTC) drugs/preparations from traditional (often Ayurveda) health care systems is fairly a common practice. This is because there is a general belief among lay persons that such drugs/preparations are safe and there is likely to be no risk of adverse reactions.

Medicines from diverse health care systems are available for people in India. People do consume these medicines concurrently with conventional medicines. A national representative health survey (2014) reported that use of traditional medicines is less among the middle-income households than in rich and poor households. Such utilization is higher for chronic diseases, musculo-skeletal illnesses and skin-related ailments [10.] However, there is a relative paucity of data regarding usage of Ayurvedic medicines in the community.

Recently MHRA (Medicines and Healthcare products Regulatory Agency (MHRA/UK and EU) accepted that long term (>30 years) uses of any herbal preparation, in the country of

origin or more than 15 years' use in the country of import would indicate its usage safety [11] [12]; however unfortunately documentary evidence is meagre in general.

In India, the Ministry of AYUSH (Ayurveda, Yoga, Unani, Siddha, and Homeopathy) governs traditional medicinal practices and research. In India, there are around 300 Ayurveda colleges, 2000 hospitals and 13000 dispensaries wherepatients are treated with Ayurvedic medicines. Ayurvedic formulations marketed in India are manufactured in approximately 8000 manufacturing units[13]. Several preclinical and clinical studies, as a part of MD and PhD theses, have explored the potential of selected plants and formulations[14]. Their mechanisms of actions and biological plausibility are also being investigated[15]. However, it is essential to have evidence from epidemiological studies to document usage as well as safety and effects of Ayurvedic medicine.[16] This requires study of drug utilization at various levels. 'Ayurvedic Pharmacoepidemiology' (AyPE) has been proposed to address several aspects of safety, effectiveness and drug usage for Ayurvedic medicines which is the need of the hour and which requires collective efforts.

1.3 Pharmacoepidemiology:

Pharmacoepidemiology (PE) studies use and effects of drug(s) in large population[17,18]. "Pharmacoepidemiology is the study of the utilization and effects of drugs in large numbers of people; it provides an estimate of the probability of beneficial effects of a drug in a population and the probability of adverse effects. It can be called a bridge science spanning both clinical pharmacology and epidemiology. Its scope includes drug-usage, safety, efficacy, acceptability and interactions of drugs. Besides providing the numerical data on adverse events, it can also be a source of novel beneficial effects of a drug, which may open up a path to new drug discovery or repositioning of a drug.

Pharmacoepidemiology concentrates on clinical patient outcomes from therapeutics by using methods of clinical epidemiology and applying them to understanding the determinants of beneficial and adverse drug effects, effects of genetic variation on drug effect, duration-response relationships, clinical effects of drug-drug interactions, and the effects of medication non-adherence.

In Ayurveda, the word *Janapada* has been used to refer to large population or kingdom or realm [19]. *Janapadadhwansa* suggests the demolition of community. Whilst in general it could

mean destruction of a population due to war, or natural disasters like earthquakes and floods, in Ayurved .The word denoted the study the determinants of diseases, such as polluted air, water, soil and *Adharma* (unjust or evil) in large populations in ancient times[19].

Ayurvedic Pharmacoepidemiology (AyPE) is a new discipline proposed by Vaidya RA et al for the study of the usage, acceptability, efficacy, safety compatibility, interactions and cost-effectiveness of Ayurvedic drugs in a large number of people [20].

Alarming reports about the toxicity of Ayurvedic medicines in newspapers, journals and other media sometimes made without serious investigation have led to wariness about the use of Ayurvedic medicines particularly in foreign countries. Without appropriate and adequate scientific evidence, such reports can have an adverse impact on the system of medicine (health) that has been used for centuries and is still alive [21,22]. The need for introducing Ayurvedic Pharmacoepidemiology discipline was keenly felt due to increasing domestic turnover of traditional medicines in India, publications regarding usage of traditional medicines in the country and outside as well as perturbing media headlines about unacceptable heavy metal content in Ayurvedic medicines in media reference.

Such a discipline is required at this time in view of present circumstances. Estimates given by the World Health Organization (WHO) indicate that almost 80% of the population in many Asian countries relies on traditional medicine for primary health care [23]. AyPE needs competence and expertise in diverse areas like clinical pharmacology, medicine, epidemiology and Ayurveda in an individual or a team. AyPE can provide early evidence of the safety, efficacy and acceptability of Ayurvedic drugs. Such an endeavor may precede Observational Therapeutics and Reverse Pharmacology[24,25] .

On similar lines, Debnath et al have proposed Ayurpharmacoepidemiology as a new field that requires collaboration of three fields viz, Ayurveda, Clinical Pharmacology and Epidemiology[26].

1.4 Diabetes mellitus: disease burden globally and in India

India is one of the six countries of the International Diabetes Federation-South East Asia (IDF SEA) region. The estimated global prevalence of diabetes was 9.3% (463 million people), which will increase to 10.2% (578 million) by 2030 and will be 10.9% (700 million)

by 2045 as per the IDF Diabetes Atlas Committee [27]. Saeedi *et al* have reported the overall prevalence of diabetes in 15 states of India was 7·3%; and varied from 4·3% in Bihar to 10·0% in Punjab, but the prevalence was lower in rural areas than urban areas[28].

The ICMR-INDIAB Study report gives the national prevalence of type 2diabetes mellitus and pre-diabetes. Adults aged 20 years and above, of either sex, from all 28 states, National Capital Territory (NCT) of Delhi or 2 Union Territories (UTs) namely Chandigarh and Pondicherry were included. The study was conducted in four phases. Phase one study was done in three states namely Tamil Nadu, Maharashtra, Jharkhand and one Union Territory namely Chandigarh located in the south, west, east and north of the country.

The prevalence of diabetes (both known and newly diagnosed) was more in Chandigarh, (13.6%) followed by Tamil Nadu (10.4%), Maharashtra, (8.4%) and Jharkhand (5.3%). The prevalence of prediabetes was also high in Chandigarh (14.6%) followed by Maharashtra (12.8%), Tamil Nadu (8.3%) and Jharkhand (8.1%). Knowledge and awareness about diabetes in rural India, is very low. The prevalence of obesity, dyslipidemia and hypertension are higher in both urban and rural areas of India compared with earlier studies.[29]

Diabetes is often associated with hypertension and dyslipidemia. Agarwal RP (2014) et al reported the high prevalence of vascular complications in type 2 diabetic patients in northwest India. Retinopathy (32.5 %,) often leading to blindness and nephropathy (30.2 %,) were more prevalent followed by peripheral neuropathy (26.8%), and coronary heart disease (25.8%) [30].

Acharya LD *et al* (2016) reported that in India, the median cost of treatment for a diabetic patient with any complication is between 20 to 30 thousand rupees per anum [31] . Yesudian *et al* (2014) critically reviewed nineteen studies on the cost of illness for diabetes and its complications in India and concluded that middle and high-income groups had higher expenditure in absolute terms, whereas the costs constituted a higher proportion of income for the poor. The economic burden was highest among urban groups[32].

Diabetic patients in India have access to treatment from any one of the several systems of pluralistic health care available in our country. They often use Ayurvedic medicines as complementary to allopathic medications for controlling diabetes, reducing side-effects, and for preventing complications[33-34]. But, the possibility of drug-drug or herb-drug

interactions is of concern in terms of safety and reduced/enhanced therapeutic activity[35]. However, the data on the exact nature of usage of Ayurvedic and other traditional medicine for diabetes are scarce and warrant investigation.

1.5 Diabetes mellitus: Ayurvedic Perspectives of management of Prameha and madhumeha

Frequent urination as a symptom was known as *Asrava* vyadhi since Vedic times as evident in *Atharvaveda*[36]. The classical texts of Ayurveda contain a precise description of the disease and its complications [37-41]. Diverse herbal and herbo-mineral formulations are recommended for diabetes mellitus as along with yoga, exercise and specific diets (*vyayam and pathyapathya*)[42]. Combinations are recommended as per the doshik dominance in the classics; however, an Ayurvedic physician has the liberty to use any combination as per the patient's condition and requirements. The frequently mentioned medicinal plants for diabetes in classical texts are *Harda (Terminalia chebula), Behada (Terminalia belerica), Amalaki (Phyllanthus emblica), Haridra (Curcuma longa), Musta (Cyperus rotundus), Vidanga (Emblia ribes), Daruharidra (Berberis aristata), Arjun (Terminalia arjuna), Devdar (Cedrus devdara), and Guduchi (Tinospora cordifolia).* Ayurvedic Dravyaguna rationale for recommending use of these plants is to reverse the pathogenesis (*Samprapti*) of *prameha and madhumeha*. Pathogenesis literally means development. One can arrest development or one can reverse the disease like Dean Ornish talks about heart disease.

Scrutiny of medicinal plants is imperative, as these have been shown to have more than one beneficial effect through one or more mechanisms of action. Nazarian-Samani *et al* in a systematic review have pointed out that most medicinal plants have shown produce hypoglycemic effect by stimulating insulin secretion, augmenting peroxisome proliferator-activated receptors (PPARs), inhibiting α-amylase or α-glucosidase, glucagon-like peptide-1 (GLP-1) secretion, advanced glycation end product (AGE) formation, free radical scavenging plus antioxidant activity (against reactive oxygen or nitrogen species (ROS/RNS)), up-regulating or elevating translocation of glucose transporter type 4 (GLUT-4), and preventing development of insulin resistance. Besides this they may also be effective against various complications of diabetes mellitus [43]. This is particularly relevant vis-à-vis the pathophysiological mechanisms underlying type 2 diabetes mellitus. In modern medicine, numerous pharmacological agents are available, most of them aimed at glycemic control. However, side effects of several of these agents are well documented.

Vaidya ADB et al studied at least ten medicinal plants in diabetic patients and established the safety and efficacy of these selected medicinal plants. Selection of these plants was done systematically by studying the literature related to Ethnobotany, study of the classical Ayurvedic texts, interviews and discussions with Vaidyas as well as field surveys. Based on this the medicines/plants that were most commonly used for treatment of diabetes in Ayurveda were identified. The list was then finalized by consensus after detailed discussions among clinical pharmacologists, phytochemists as well as Ayurvedic clinicians.
Antidiabetic activity of the medicinal plants was documented Studies on safety and tolerability were conducted. Novel studies using animal models of diabetes and insulin assessment were conducted at CIBA Research Centre. This study gave the hints to conduct exploratory studies in diabetic patients [44]. A paradigm shift has been occurred in the research on potential of antidiabetic plant materials/phytoactives. Biological plausibility and mechanism (s)of action of some medicinal plants with antidiabetic potential have been reported earlier [45]. Besides hypoglycemic activity, antioxidant, hypolipidemic, anti-inflammatory activities are studied, as diabetes is viewed in current times as a chronic inflammatory disease associated with dyslipidemia, oxidative damage and endothelial dysfunction[46].

This formed the basis of Reverse Pharmacology approach which was applied to the national CSIR-NMITLI diabetes project (2002-2007) under the leadership and guidance of Dr Ashok Vaidya. The multidisciplinary team of experts included clinical pharmacologists (Dr Ashok Vaidya, Dr MUR Naidu, Dr Urmila Thatte), *Dravyagunadnya* specialists(Dr S D Kamat, Dr Tanuja Nesari), endocrinologists (Dr Rama Vaidya, Dr Prema Vartakavi), diabetologists (Dr V Mohan, Dr Sanjiv Shah, Dr Vijay Ajgaonkar), phytochemists (Dr Ashok Amonkar, Dr Vahalia, Dr Chandrashekhar), and Ayurvedic experts (Dr Nitin Kamat, Dr Manoj Nesari). Based on this consensus the following plants were selected. *Nisha(Curcuma longa) Amalaki (Phyllanthus emblica) , Mamejava (Enicostemma littorale) Meshshringi (Gymnema sylvestre), Bimbi (Coccinia indica) and Chakshushya (Casia absus)*

Exploratory clinical investigations of these plants and the formulations were conducted with diabetic patients. The results of these studies provided leads to undertake experimental studies. *in-vitro* and *in-vivo* studies were conducted concurrently with the aim of to determining the mechanism(s) of action. Results of a study of use of *Nisha amalaki* formulation in treated uncontrolled type 2 diabetic patients suggested is the possibility of

drug interaction with metformin. This instigated the study on drug interaction for two formulations (*Nisha amalaki and Mamejava ghana vati*) in healthy volunteers, when simultaneously administered with prevalently used oral hypoglycemic agent (OHA) metformin[35].

These studies with *Mamejava ghana vati* resulted in identifying *Mamejava* as a candidate drug especially in diabetic patients with hypertriglyceridemia. Also para clinical studies on *Mamejava* were conducted by collaborating institutes with using various models of diabetes. These studies have shown that *Mamejava* possess several properties - antiinflammatory, antioxidant and DNA repair . This process of drug discovery was more economical, with fewer bottlenecks and needed less time to identify a potential drug candidate. This approach has provided a worthwhile strategy that can be used to conduct more studies for natural products and traditional medicines, through reverse pharmacology. Involvement as a research associate in these research efforts motivated me to undertake the present study using a multi-pronged approach.

Several herbal and herbominaral preparations and minerals such as *Chandraprabha vati* [47], *Jambadyarista*[48], *Navratna rasa* [49], *Arogyavardhini vati* [50], *Vasaguduchyadi Kwatha* [51] and arsenic containing Ayurvedic drug *Haratal Bhasma*[52] have been have been studied for safety/ animal toxicity. Ram Manohar has discussed this issue from the ancient and modern perspective in his paper. He states that protocols and practices to check for toxicity and safety of drug sources as well as formulations are described in classical texts, which are in practice even in the present times. This author has discussed and evaluated the available evidence in support of these viewpoints, pointed out the gaps and given and suggestions for further research[53].

Chandra (2016)[54] has stated that many a times, Ayurvedic preparations/medications may be viewed as being safer than modern medicines. However, a closer look at this shows that often claims regarding their effectiveness and safety is based on the justification that in the classical texts and that the formulations have been in use for hundreds of years rather than on scientific evidence and clinical data. It is well known that names of the plant materials used are in Sanskrit a language that most persons are unfamiliar with. Thus consumers may not understand what is easily purchased/ sold as an OTC. The need for harnessing Ayurvedic knowledge is keenly felt often, but needs to be backed by sound biomedical research.

Presently, no studies are available regarding the frequency of the usage of (OTC) medicines of different systems of healthcare, leave alone Ayurveda.

Thus, it is important and relevant to investigate the extent and the nature of the field usage of Ayurvedic medicines. In view of diabetes mellitus (Type II) being a major challenge in India, and because of the cardiovascular, renal, retinal and neural complications of diabetes, it was deemed worthwhile to undertake such a study with AyPE [55] .Quality, safety and effectiveness of Ayurvedic drugs can be ensured if scientific documentation, process validation along with other important aspects such as standardization and providing through biomedical research is required. Data on efficacy and effectiveness also need to be generated for general acceptance, promotion and development of Ayurvedic medicines and realization of their potential [56] . It is in this context that undertaking studies in the area of pharmacoepidemiology become increasingly relevant in order to document and provide the much needed evidence.
In this context, the overall aim of the present research was to study the usage of drug and non-drug modalities in the management of *prameha* and *madhumeha* (Type 2 diabetes)

The specific objectives of the study were:

1. To enlist commercially Marketed Ayurvedic Antidiabetic Formulations (MAAF) and study the labels and patient inserts.
2. Compare biological plausibility of medicinal plants from MAAF with respect to *Dravyaguna* (pharmacological) rationale from classical texts of Ayurveda
3. To study the utilization patterns of MAAF, OHA as mono system antidiabetic drugs as well as concurrent use of both among known diabetic patients.
4. To assess Knowledge, Attitude and Practices (KAP) of diabetic patients regarding Diabetes
5. To assess Knowledge, and Practices (KAP) of doctors prescribing these drugs.
6. To study the pharmacological activity and safety of selected Ayurvedic formulations using conventional laboratory -based techniques using Reverse Pharmacology

2.Review of literature

“Dynamic historiography is not to pick up the ashes of the past but to embers to light the new fires.”

Dr Ashok Vaidya, 2019

Aim of the this research programme is to document and study the usage of drug and non-drug modalities in the management of *prameha* and *madhumeha* (Type 2 diabetes mellitus) through Ayurvedic Pharmacoepidemiological approach. It is the novel research programme where for the first time pharmacoepidemiological study designs have applied to study the usage and effect of Ayurvedic antidiabetic medicines for the management of diabetes. This review covers Ayurvedic classics and other relevant recent literature about therapeutics of madhumeha, basics of pharmacoepidemiology and its application to drug discovery. Literature related to the current management of type 2 diabetes mellitus in modern medicine is also has been reviewed in brief.

2.1 *Madhumeha*: Historical approach

The word *Madhumeha* is union of two words i.e. *Madhu* and Meha. *Madhu* means honey/ nectar and *meha* means to urinate. The condition in which urine acquires appearance like honey and sweet taste is *Madhumeha*. The word *prameha* indicates increased frequency of urination; has been known to ancient time and described in *Vedas* around 2000 yrs. ago. The condition is labelled as *asrava vyadhi* in *Atharvaveda Samhita (I 21, II 3.2-4)*[36]. *Asrava* means excessive secretion or flow; specifically *mutratisara* i.e. polyuria (commentary of Sayanacharya). Mani- Mantra-Aushadhi also has been described as a part of therapy for

polyuria. In *Koushika sutra* of *Atharvaveda* it is documented that *Prameha* is one of the chronic and painful diseases (*Koushika sutra* 25:9-10 and 23-7)[57-58].

Ebers papyrus 1550 BC.is thought to be the earliest mention of polyuria. The description of polyuria (frequent urination) and its management written by Egyptian physician Hesy-Ra have been found in 3rd Dynasty of Egyptian papyrus[59]. Eknoyan GA reports that Aretaeus of Cappadocia Greek physician recorded clinical features regarding sweet urine, and its fatal consequence by the end of the first century A.D and coined the term *diabetes(siphon*-Greek word)[60]. Aretaeus described diabetes as "a melting down of the flesh and limbs into urine". Matthew Dobson in 18th century (1732-1784) reported that the sweetness of urine was due to sugar [61]. Avicenna described the symptoms of diabetes (960-1037 AD) and mentioned the complications such as gangrene and sexual dysfunction. Sweetness of urine was rediscovered by Thomos Willis (1675 AD). British Surgeon-General, John Rollo labelled the term *mellitus* (Latin, 'sweet like honey') in 1798 [62-65.]

Prameha (frequent urination) and *Madhumeha* have been described in classical Ayurveda Texts such as *Brihattrayi (Charak, Sushruta, and Vagbhata), Laghuttrayi (MadhavNidan, Sharangdhar, and Bhavprakas)* and other Ayurvedic texts and periodicals. . It is necessary to understand fully the precise description of aetiology, symptoms, pathophysiology, types, complications and complete management of the disease in these samhitas.

Agnivesh Samhita (revised by Charak; 600BC) is the oldest documentation available which mainly covers conservative and preventive management of diseases. Charaka has described *prameha* as acquired disease due to over nutrition (*Santarpana-nimittaja*) and has given the importance as *mahagada* (dreadful disease) as it is followed by many diseases. (*Prameho-anushanginanam shrestha*). It is known that diabetes is often associated by unavoidable complications such as dyslipidemia, hypertension and cardiovascular disease. The association of adipose tissue (*medodhatu*) with development of *prameha* is mentioned in the *samhita.*

क्लेदश्च मेदश्च कफश्च वृध्दः प्रमेहहेतुः प्रसमीक्ष्य तस्मात् ।।
च चि **6।51**

Indulgence of excessive sweet food during pregnancy has been linked to the development of gestational diabetes (*garbhini prameha*) as well as future risk of diabetes in offspring (charak

sharir 8\21) as described in *Garbhopghatkar bhavas* (factors responsible for ill health of foetus)[66].

मधुरनित्या प्रमेहिणं मूकमतिस्थूलं ....। च शा 8।21

Prameha affects mainly to those people who are – voracious eater, have aversion to bath and avoiding physical exercise. (Ch. Ni. 4/50). It is noteworthy that genetic predisposition and lifestyle changes are described as causative factors of *prameha* and *madhumeha*. Charaka has described *Sahaja* type of *prameha* that means it can occur due to defect in *Beeja* (ovum or sperm)*, Beejabhaga (*chromosomes) *or Beejabhagavayava* (genes) (Ch.Sha.4/30)[67].

Genetic predisposition in diabetes is well known. These details about *prameha* and *madhumeha* in ancient literature make one wonder that without technological aids how they must have perceived and described these clinical entities. Researchers have identified locus of predisposition on chromosome 2 and genetic variation as well as their linkage to Beta cell function[68-70].

Excessive sweet food during pregnancy can cause maternal obesity and gestational diabetes which forms unfavourable environment for foetus. It can lead to off-spring having high birth weight. Both the conditions i. e gestational diabetes (and maternal obesity) and high birth weight are linked to future risk of diabetes and cardiovascular diseases[71-73]. Yajnik *et al* have reported that low birth weight, was also associated with metabolic disorders and adult cardiovascular disease and diabetes in adulthood [74-76]. Pettitt DJ et al has reported U shaped relationship of birth weight and risk of diabetes[77]. Maternal diet during pregnancy has an important role in foetal development. Methylation of CpG sites in the placenta leptin gene of mothers and their healthy neonates (n =135) was studied. The results indicated that methylation was found to be lower in mothers who had high carbohydrate intake[78].

Renound surgeon S*ushruta (100 BC)* has given more comprehensive picture of the *Prameha* as well as *Madhumeha* and even *prameha pidaka* (carbuncles) for which separate chapters have been devoted (Su chi 11 to 13). Burning sensation of soles of hands and legs, fast growth of hair and nails has been mentioned in prodromal symptoms. Obesity leading to prameha and *prameha pidaka* has been described [79]. (Su su 15-32). Features indicative of bad

prognosis viz association of complications with polyuria and carbuncles (Su su 33: 4-8) have been detailed. Behaviour of at risk patients for *madhumeha* has also been outlined i.e. those who are walking would like to sit, those who are sitting would like to lie down and those who are lying down would like to sleep. The classification of the disease described as per the causative factors viz *Sahaja* (genetic predisposition) and apathyanimittaja (by indulgence of unhealthy life style) is similar to classification of diabetes from conventional medicine[80].The sutra is given as

> द्वौ प्रमेहौ भवतः सहजोऽअपथ्योनिमित्तश्च।
> तत्र सहजोमातृपितृबीजदोषकृत् अहिताहारजोऽपथ्यनिमित्तः।।सुचि 11।3

It is interesting to note the signs and symptoms of both the types.

> तयोः पूर्वेणोपद्रुतःकृशो रूक्षोऽल्पाशीपिपासुर्भृशंपरिसरणशीलश्चभवति ।
> उत्तरेणस्थूलोबह्वाशीस्निग्धः शय्यासनस्वप्नशीलः प्रायेणेति ।।सुचि 11। 3

The one who has got diabetes from birth are thin with dry skin, and more active. They are always thirsty; however with lesser appetite. The one who has developed the disease due to unhealthy lifestyle are overweight /obese with moist skin. They prefer physical inactivity or are lazy.

Vagbhat (600 AD) [81] , Maddhavkar[40] (700 AD), *Sharangdhar* (1300 AD) [82], *Bhavmishra* (16th century) [83], *Bhela*[84] , and *Harita*[85] also have described prodromal symptoms of *prameha* with its 20 types, pathogenesis, and the management. Vagbhat has advised Ayurvedic procedures (*panchkarma*) as per doshik dominance and the strength of the patient. *Sharangdhar* has described a couple of *arishtas* -biomedical fermented formulations (*Devdarvyarishta* and *babboolarishta*) for the disease. *Bhavprakash* has added some new vegetables and metallic preparations for the management of diabetes. Contemporary to *Agnivesha; Bhela* has classified prameha as *sahaja* (genetic) and *Janmottaraja* (due to diet and other epigenetic factors). Harita has used two medicinal plants *viz Dhava* (*Anogeissus latifolia* Wall) and *Arjuna (Terminalia Arjuna Linn)* very frequently in the management of diabetes. *Dhava* has been reported to have antidiabetic activity. Hypoglycemic activity of Hydro-alcoholic extract of *Anogeissus latifolia* from bark was comparable to Glibenclamide.

The gallic, chebullic & trigallic acid content from *Dhava* leaves, and bark have been reported to have antidiabetic activity [86-88].

Kashyap[89] (500 AD) has noted down the symptoms to recognise the disease in childhood. The sutra he quoted is as follows.

> गौरवंबध्दतः जाड्यमकस्मान्मूत्रनिर्गमः।
> प्रमेहेमाक्षिकाक्रांतंमूत्रंश्वेतघनंतथा ।।   काश्यप वेदनाध्याय 25।2

The child who develops prameha becomes obese, activity slows down, and urine becomes white, concentrated attracts flies.

Twenty types of prameha as per doshik dominance are described by Acharyas, four are due to Vata, six due to *Pitta* and ten are because of *Kapha*. The types are as per the colour, appearance and consistency of urine. The criteria behind the classification may be the colour and appearance; which might be the part of metabolic disorders manifested through urine. In conventional medicine diabetes is classified as Type 1 and type 2 diabetes mellitus depending upon the occurrence and causative factors. This classification is more comparable to classification by Sushruta.

Recommendation of various types of *vyayam* (physical activity) in the management of the disease shows the awareness regarding importance of physical activity. Heavy physical activity like digging a well or walking *shata yojana* (1 *yojana*=8 *miles*) has been described by Vagbhat. This approach of healthy lifestyle is now gaining a ground as a primary line of treatment for life style disorders in both the systems. Exercise was the part of daily regime in ancient time. With the technology advances, the physical activity woven in daily life continued to diminish. Rishis knew that regular exercise leads to reduction in fat and increased body strength in the form of musculature; however they have recommended exercising only till perspiration appears on forehead. Exercising 30 minutes a day and reduction of 5-7% in weight has been proved to reduce the risk of diabetes[90].

2.1.1 Ayurvedic *Nidan*

Sutra given in classics says that the condition in which patient excretes sweet urine like honey and sweetness is all over the body is known as *Madhumeha*.

मधुरंयच्चसर्वेषुप्रायोमध्विवमेहति ।
सर्वेपिमधुमेहाख्यामाधुर्याच्चतनोरतः ।।वा नि 12।21

Vagbhata has mentioned the sweetness of whole body may be pertaining to circulating hyperglycemia. Charaka has mentioned that flies are attracted to the patients even after applying sandal wood *lepa (local application)* may be because of increased sweetness of sweat. Sweat is known to its thermoregulatory functions. Besides this, sweat functions as medium of excretion of waste product and toxins has gained the interest in using sweat as a bio fluid for research in human physiology. One of the components of the sweat is sugar along with salt, ammonia, urea, and minerals[91]**.** Baker and Wolfe reported that sweat can be surrogate marker for blood glucose evaluation [92]. Moyar et al reported the correlation between sweat glucose and blood glucose in diabetic patients[93]. Even saliva has been reported as a biomarker for glucose estimation. Blood glucose and HbA1C have been correlated significantly with salivary glucose [94-95]. In ancient times sweetness of urine and clinical symptoms were the criteria for monitoring the disease; however diabetes is now diagnosed and monitored by fasting and post prandial blood glucose and glycated haemoglobin (HbA1c).˙ Since 1883 reagent papers with markings (developed by George Oliver) have started using for bedside urine testing. Up to 1960s -70s testing urine was the only way to know blood glucose. The strips named Dextrostix were developed by Ames Pharmaceuticals in 1960 to estimate blood sugar. Tom Clemens, from the same company converted optical reading mechanism of analysing colour of the strip to a numeric reading. A point of care (POC) device was discovered by Joachim Kohn, and glucose in blood was measured for the first time by Clinistix stips .Further the device was developed to current model by many scientists which is now in current practice [96].

Charaka has mentioned that all causative factors are pertaining to increase *Kapha* , *meda* (fat) and *mutra* (urine). Key aspect of causative factor is *Bahudravasleshma* (over hydration) which has a tendency to slacken off the *badhatwa* (compactness) of *meda* (adipose tissue), and *mamsa dhatu* (muscle tissue). Ayurvedic causes of Prameha have been given in a following *sutra* of charaka.

Causes of *prameha*

आस्यासुखंस्वप्नसुखंदधीनिग्राम्यौदकानुपरसाः पयांसि ।
नवान्नपानंगुडवैकृतंचप्रमेहहेतुकफकृच्चसर्वम् ।। चचि 6|4

Aasyasukha means physical inactivity/or stay always in comfort zone, *swapnasukha* means sleeping for more than standard period(more than 7-8 hours), curd, meat of domesticated, marshy and aquatic animals, milk and milk products, newly harvested grains, jaggery products, and all other causes which increase *kapha*. Association of beta casein from Bovine milk proteins with type 1 diabetes is reported [97]. Higher intake of red meat and poultry has been linked to risk of diabetes[98]. Meat of domestic animals is fattier with more omega 6 fatty acids than omega 3 fatty acid, compared to that of wild animals. The fatty acid profile is used to determine the Atherogenicity Index (AI), which is associated with cardiovascular disorders[99]. High fat diet especially trans fatty acid is known to increase insulin resistance[100-101].

Sushruta had mentioned day time sleep as a causative factor. Sleep deprivation (*Jagaranam*) leads to aggravation of *vata*. Sleep has been very important in health as it is one of the triad. Good sleep protects mental and physical health. Long duration of sleep has been linked to risk of diabetes[102]. Meta-analyses support a U-shaped association between sleep duration and incident type 2 diabetes[103].

Increased quantity and frequency of urine as well as its turbidity are the cardinal symptoms of prameha; however there are many other symptoms which occur before the urine turns turbid or sweet. Attraction of ants towards urine denotes sweetness of urine. *Kha-malavridhhi* (increase in discharge from eyes, ears, nose, and skin hair follicle pores), *nakha-kesh-ativruddhi* (faster growth of nail and hair), and *jatili-bhav-kesheshu* (increased hair knots) are the symptoms which denote involvement of deranged metabolism in skin and bones[104]. Influx of nutrients may speed up **nail** growth. A study of nail growth pattern in 153 cases showed that increased nail growth was found more in females than males. Indelible ink was used to record the growth[105]. Arunachalam Kumar has reported faster nail growth in diabetics[106]. Hasta-padtala daha (Burning sensation of soles) and *karapada supti* (decreased sensation) are well-known symptoms of neuropathy in diabetes.

Yog Ratnakar in has described a novel urine test "*tail BinduPariksa*" oil drop method for urine test. This test was used to perform for prognosis of the patient[107].

Charaka has mentioned *upadravas* (complications) of prameha in *Nidansthan* 6 as quoted in the sutra .

Complications of Prameha

तृष्णातिसारज्वरदाहदौर्बल्यारोचकाविपाकापूतिमांसपिडकालजीविद्रध्यादयश्च ||
चनि 4|48

Thirst, diarrhea, fever, burning sensation, weakness, distaste, digestion problems, and skin manifestations including carbuncles are the complications of the diseases. It is interesting to know that all these conditions stated 600 BC are equally evident /obvious even now. Additionally some complications as per the doshik dominance are also described. Respiratory infections urogenital infections, cardiac involvement and neurological conditions are also vividly mentioned by the seers.

One of the complications is *Prameha pidaka* (carbuncles) which has got attention of Sushruta[108]. A separate chapter has been devoted for its management. Ten types of carbuncles have been described by Sushruta and other Rishis. Aggravated doshas vitiate blood and muscle and cause inflammatory condition which is advised to be managed by *Raktamokshan* (bloodletting). If not attended, inflammation increases with pain and burning sensation. At this stage it has been advised to manage as per the wounds. If not attended well, pus formation takes place and big pockets of pus are formed by invading the tissues and then it becomes incurable. A carbuncle is a red, swollen, and painful cluster of boils that are connected to each other under the skin caused by bacterial infection. Diabetics generally with poor health and weakened immunity develop frequently. In the management of the carbuncles, Sushruta has contraindicated hot fomentation as it destroys body tissues. An iron preparation viz *Navayasloha* has been recommended for it as internal medicine.

2.1.2 Ayurvedic *chikitsa sutra* of *Prameha/Madhumeha*

Management of any disease in Ayurveda is carried out in 3 stages i.e. removal of causative factors (*Nidan Parivarjan*), appropriate medicines (*Aushadhi*) and preventive management (*Apunarudbhava Chikitsa*). Sushruta has explained the *shatkriyakala*[109] i.e. six stages of pathophysiology (*samprapti*) to be identified for the management of the diseases. These six

stages are *Sanchaya* (accumulation), *Prakopa* (aggravation), *Prasara* (migration), *SthanaSamshraya* (localization of *Doshas* in a particular tissue or organ), *Vyakti* (manifestationofa disease) and *Bheda* (differentiation or complication of a disease). It is sequential development of the disease and entire process from exposure to causative agents to manifestation of disease is known as *Samprapti* (pathogenesis). The study of *Samprapti* (pathogenesis) in each patient helps in planning specific management and assess prognosis. Stage wise reversal is possible if these stages are studied. The major factors in *shatkriyakala* of *prameha* & *madhumeha* are elaborated in the table 2.1

Table 2.1 Stages of *Shatkriyakala for prameha*

Stages	Dosha/dhatu dominance	Symptoms for Prameha
Sanchaya (accumulation)	*Kledak Kapha and Bahudrava sleshma*	*Agnimandya, Annagourav, Alaysa, medovrudhhi, (*GI disturbances-low appetite)
Prakopa (Aggravation)	*KledakKapha dushti*	*amanirmiti, Annadwesha, medodushti, medoshaithilya* (obesity)
Prasara (migration)	*Bahudravasheshma, kledvrudhhi, Bahuabaddhameda Rasa-rakta-mansadushti*	*Angasad* (flasidity), *Nakha-keshati vrruddhi* (skin changes), *galatalushosh* (thirst), *Rasayani* (lymphatics) *& sira shoth* (blood vessels inflammation
Sthansanshraya (localization)	*Kapha dominant tridosha in Medovaha Srotas*	*Stholya* (obesity), *hastapadtal daha* (burning soles), *Galatalushosh* (thirst-polydipsea) , *madhurasyata* (sweetness in mouth)
Vyakti (Manifestation)	*Mutravrudhhi Basti of Mutravahasrotus*	*Prabhoot-avila- mutrata* (Polyuria with turbidity of urine)
Bheda (differentiation/ Complication)	*Tridosha dominated by kapha and involvement of rasa, rakta, mansa, meda, majja,vasa, and lasika*	*Majja and medodhatu-avayava-dushti. Vata and pitta prakopa lakshane (*Neuropathy, vasculopathy)

Involvement of *meda* (adipose tissue), *rasa* (plasma/body fluids), *rakta* (blood), mamsa (muscle), *majja* (nervous tissue) dhatus and watery tissues like *ambu* (Body water),*vasa* (fat

from muscles), *lasika* (lymph) and *oja* (essence of body tissues) in the pathogenesis of Prameha, as mentioned in classics, has similarity with the ominous octet described in the pathogenesis of type 2 diabetes mellitus[110]. Involvement of tissues leading to damage of blood vessels, heart, kidney, eye, and nerve is also described as an *upadrava* (complications) of *prameha*. Commenalities in pathophysiology as per Ayurveda and conventional medicine is shown in Figure 2.1.

As per pathophysiology of diabetes high fat (*medokar*) and carbohydrate (*kaphakar*) diet along with physical inactivity (*Asyasukha*) increase the risk of obesity (*medovrudhhi/flasidity and bahuabadhha meda*) and ultered gutflora (formation of ama). Increased levels of circulating fatty acids (*kledavrudhhi*) and inflammation (*sirashoth*), lead to insulin resistance (*dhatvagnimandya*) and metabolic syndrome (medoroga*).* Circulating high levels of fatty acids and inflammatory cytokines induce a glucolipotoxic situation (*tridoshvrudhhi and sannipat* acomponying *ojakshaya*) Hyperglycemia (kaphavrudhhi) needs more water to flush glucose out of body resulting in polyuria (*Prabhutavil mutrata*).

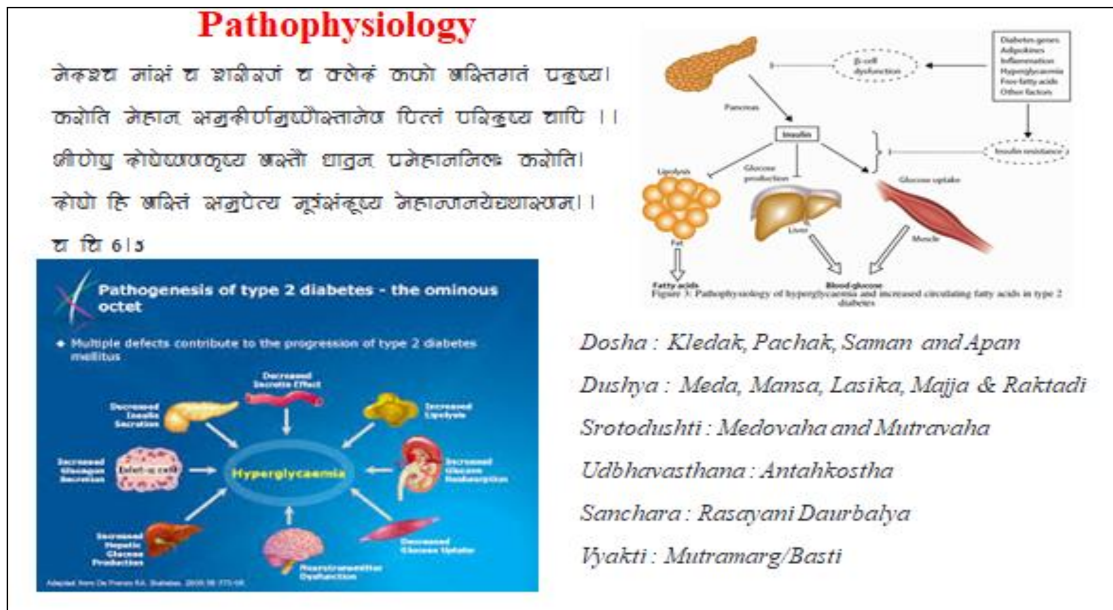

Figure 2.1 Pathophysiology as per Ayurveda and conventional medicine

Dr Ashok Vaidya (Research Director, Kasturba Health Society's Medical Research Centre), in one of his talk during CSIR –NMITLI diabetes monitoring meeting (2005) had proposed the pathophysiological correlates of *shatkriyakala* for diabetes mellitus as shown in table 2.2

Table 2.2 Correlates of *Shatkriyakal*

Stages of *Shatkriyakala*	Proposed correlates
Sanchaya (accumulation)	Cellular accumulation of lipids
Prakopa (Aggravation)	Cellular dysfunction / adipokines
Prasara(migration)	Circulatory distribution/ TG,FFA, cytokines
Sthansanshraya (localization)	Target site localization/ β cells
Vyakti (Manifestation)	Manifestation of disease/ AGTT
Bheda(differentiation/Complication)	Complication/Glycation, RAGE, Polyol pathway

TG: Triglycerides; FFA: Free Fatty Acids; AGTT: Abnormal Glucose Tolerance Test; RAGE: Receptor for Advance Glycation End Products

The therapeutic approaches to *prameha* in general and *madhumeha* in particular, in Ayurveda, have 2 basic principles (1) repletion of the body tissue (*brimhan*) and (2) depletion *(karshan*) of these as required in individual patients. Ayurvedic therapeutic approach suggests the use of spiritual intervention (*daivavyapashrya*), psychological measures (*satwavajaya)*, and drug and non-drug modalities (*yuktivyapashrraya*) also. Since Ayurvedic treatment is very much individualized, management guidelines (*Chikitsa sutra*) are proposed instead of algorithms. To decide the management line, patient is investigated for certain domains like body weight and strength. Patients when classified into *Sthool* (obese) and *Durbala* (weak) as per the state of dhatus, this basic approach is finalised for the therapeutic strategy.

Obese diabetic patients with good strength are subjected to *panchakarma*- a specific procedures to bring back the harmony of *dosha* and *dhatus*. *Doshik* dominance in the patient decides whether *vaman* (induced vomiting) or *virechan* (Induced purgation) is to be carried out. *Panchkarma* therapy is then followed by medicinal conservative therapy, which includes herbal or herbominaral formulations and specific diet and behaviour (*Pathyapathya*). Lean patients are not subjected to *panchkarma* treatment. They are managed by conservative treatment to protect their strength. Studies have shown that *panchakarma* like *vaman* (induced vomiting) and *virechan* (induced purgation) have added benefit for glycemic control[111-115]. Vagus nerve gets stimulated during *vamana* procedure. Afferent vagus nerve has been reported to inhibit inflammation through cholinergic-inflammatory pathway. As a result inflammation is reduced; this mechanism can be used to search new therapeutic for inflammatory diseases like diabetes [116-118].

Conventional medicine also has the algorithms of management of diabetes as per BMI of the patient and blood sugar[119]. Those who are obese are treated with lifestyle and Metformin first. As per the glycemic control achieved by the patient, addition of sulphonylurea or other class of OHA is decided. Weight reduction and glycemic control are the two goals of the management at this stage; whereas those who are thin and weak are not treated with metformin first as no weight reduction is to be achieved instead maintenance of strength is required.

The Greek physician Aretaeus recommended treatment of the thirst with a purgative to strengthen the stomach, followed by consuming water boiled with autumn fruit, milk, gruels of a variety of whole grains and astringent wines[120].

Therapy ends with *Rasayan chikista*, which reduces *sthanvaigunya (*specific target pathology) and maintains state of equilibrium. Use of appropriate Ayurvedic dietetic regimens will help maintain this equilibrium. Physical exercise (*vyayam*) as a part of daily routine (*Dinacharya*) has been emphasized.

Diet and physical activity play a central role in health and disease as per Ayurveda. A specific diet is recommended to get additional benefit with medicines. Patient can maintain his health as far as this pathyapathya (recommended life style) is followed. Importance of life style management in the treatment of diabetes has evolved only recently. Vigorous exercise is not recommended by *Harita* for a lean and week patient with severe diabetes. Many clinical trials have shown the effect of physical activity in daily life as inversely proportional with the risk of developing type 2 diabetes[121] .

Formulation of *Nisha* (*Curcuma longa*) and *Amalaki* (*Embalicmyrobolon*) is recommended as first line of treatment by all the texts. More than hundred medicinal plants and ten minerals in organic form *(Bhasma*) are recommended for the disease. At present medicinal plants have gained a lot of importance in the management of the disease and hence are investigated thoroughly. Besides hypoglycemic activity, antioxidant, hypolipidemic, anti-inflammatory activities of these plants also are being investigated as antidiabetic targets because diabetes is coming up as inflammatory disese associated with dyslipidemia, oxidative damage and endothelial dysfunction[122].

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2.1.3 *Pramehahara* classical formulations

Medicinal Plants recommended for *Prameha* and *madhumeha* in classics are seemed to have the properties targeting diverse aspects of pathopthysiology. These plants are selected on the basis of *Ayurvediya dravyaguna* (pharmacological properties) rationale such as *rasa* (taste), *veerya* (potency), *vipak* (post digestive effects), *prabhav* (unique action) and *gunas* (properties). Charaka and Vagbhata have described *dosha* specific decoctions of medicinal plants for *kaphaja* and *pittaja prameha* whereas Sushruta has described decoctions as per the subtypes of doshas. (Described in Results). It is of interest to note that medicated ghee and oils have been recommended for *vata* dominant *prameha* for internal and external use. Sugar formulations like *Drakshapak, Gokshurpak and Ashwagandha pak* have been discussed for strengthening of muscles and raising the immunity of the patients. These characteristics of formulations need to be discussed among the experts. The patients devoid of muscular strength (*bala-mansa-parikshaya*) are believed to be untreatable.

Individual herbs generally have not recommended in classics as therapies are based on ten determinant variables viz. age, Prakruti, season, agni besides dominant *dosha* and *dushya* (affected tissue) etc and hence one therapy may not be applicable to all patients even though they have same disease. Bhaishjya Ratnawali contains a compilation of formulations for *prameha*. Herbominaral formulations (*Rasoushadhis*) also have been described for *prameha* . Some of the formulations have been described in the following table with its ingredients.

Table 2.3 Herbominaral formulation from Rasendrasar Sangraha[123]

Formulation	Major Contents	Indications	Dose
Harishankar rasa	*Rasasindur, abhrak, haridra, amalaki*	All *prameha*	125 mg per day
Indra vati	*Rasasindur, vanga bhasma, arjun*	*Madhumeha*	250 mg per day
Prameha setu rasa	*Sasasindur, abharak bhasma, milk of vata*	*Pittaja Prameha*	250 mg per day
Anandabhairav rasa	*Rasasindur, vangabhasma, suvarnabhasma*	Chronicity of *prameha*	60-65 mg per day
Chandraprabha vati	*Rasasindur,loha, sisa,abhrak, vanga,*	All *prameha*	250-500 mg per day
Vangeshwar	*Rasasindur, vangabhasam*	All *prameha*	1 gm per day

Collection and storage of raw material, manufacturing details, Criteria of final products, Period of viability or expiry period have been described in *sharangadhar Samhita* [124]. It is interesting to know that guidelines regarding selection of place and details of formation of laboratories have been given[125]. Banani das *et al* have reviewed the *Rasoushadhis* used in *madhumeha* [126].

2.1.4 Review of studies of plants /formulations for diabetes:

Ayurvedic practitioners *(vaidyas)* used to examine individuals as a whole and not just the disease. The *vaidya* used to collect the required plant/s and other ingredients at auspicious times, with the recitation of *mantras*, and prepare his own drugs; however down the time line some *vaidyas* started companies of Ayurvedic medicines. Among those perhaps Vaidya Nanasaheb Puranik founded *Shree Dhootpapeshwar* Company in 1872 followed by *Bhaidyanath,* and *Dabur.* Vaidyas started receiving readymade Ayurvedic medicines for their practice. The nature of practice changed thereafter as various institutions, colleges and universities were established for the education which was based on tradition or a school of thoughts earlier.

Dr Ashok Vaidya and Dr DS Antarkar started screening of plants and formulations for antidiabetic potential in diabetic patients in 1970. Ten medicinal plants were studied in depth and few more in a preliminary manner. Safety and tolerability were established. Concurrently novel animal models of diabetes & insulin assessment at Ciba Research Centre and antidiabetic activity of the studied plants was documented. Quadruple competences of an Ayurvedic physician (Antarkar), a clinical pharmacologist (Vaidya), a basic endocrinologist (Talwalkar) and a phytochemist (Joshi) were integrated for the research[44]

That was a beginning of Reverse Pharmacology[24]. The findings from those studies (most unpublished) formed the basis of the nationwide project of CSIR-NMITLI (Council of Scientific and Industrial Research - New Millennium Indian Technology Leadership Initiative) on diabetes. The unique R&D network of industry, academia, CSIR laboratories were involved. The underlying approach for drug discovery was on the basis of Reverse Pharmacology.

The chosen path of Reverse Pharmacology required standardization of the plants and formulations with quality control prior to the experiential, exploratory and experimental studies. Para-clinical *in vitro* and *in vivo* experimental models were developed and used. Extensive documentation was carried out on the selected plants. Phytoactives such as swertiamarine, epigenin were studied in extended CSIR project for phytopharmaceuticles.

Current status of Indigenous drugs and Alternative medicines in the management of diabetes has been discussed in detail by Vaidya ADB et al in RSSDI textbook of diabetes[45]. Biological plausibility of medicinal plants has been described with Ayurvedic knowledge. Table 2.3 shows biological plausibility of antidiabetic potential of selected plants.

Table 2.4 Biological plausibility of antidiabetic potential

Plant	Activity	Model
Gymnema sylvestre (Madhunashini)	Hypoglycemia (secretion or release of insulin) Hypoglycemic	Invitro (STZ rats) Clinical
Momordica charantia (Karavellak)	Hypoglycemic (↓ IR) Hypoglycemic in GTT	STZ – DM rat, mice Clinical
Trigonella foenumgraecum (Methika)	Antidiabetic Hypoglycemic	Animal Clinical
Coccinia indica (Bimbi)	Hypoglycemic Improvement in GTT	Animal Clinical
Pterocarpus marsupium (Vijaysar)	Hypoglycemic Hypoglycemic	Animal Clinical

Several MD ,PhD students from Ayurveda faculty all over India have studied drug effect in diabetic patients which is compiled by Prof MS Baghel in his book 'Researches in Ayurveda' till 2007[14]. The work was started in 1965 at Gujrat Ayurveda University, Jamnagar. Dr Jyotishi GS. from –*Davyaguna* Dept–studied '*Madhumeha par mamajjakprayog'*.

Ayurvedic Research Database (Seventh Edition) (2001-2018) from IPGT&RA, GAU, Jamnagar is available in the form of DVD[127.] Efficacy of Ayurvedic medicines for diabetes

has been reported in literature [128,129]. Mishra et al[130] have cited a few clinical studies on medicinal plants and formulations in his chapter on diabetes. Ingredients and the effect of some of the formulations have been showed in the following table.

Table 2.5 Medicinal plants and formulations used in diabetic patients

Formulation	Main ingredient	N==	effect
Ayush 82	*Mangifera indica* *Syzigium cumini* *Momordica charantia* *Gymnema sylvestri*	100	Hypoglycemic
MA 471	*Enicostemma littorale* *Phyllanthus niruri* *Eugenia jambolana* *Melia Azadirachta* *Terminaliaarjuna* *Agel marmelos, shilajit*	69	Hypoglycemic and hypolipidemic
D 400	*Eugenia jambolana* *Pterocarpusmarsupium* *Ficusglomerulata* *Gymnema sylvestre* *Momordica charantia* *Ocimum sanctum* *Shilajit*	38	Hypoglycemic Cholesterol decreased
Abragachenduram	Black mica Dehydrated borax Root juice of *Trainthema decandra* *Ficus bengalensis* *Azatoda zylineca*	60 130	Hypoglycemic Hypoglycemic

Besides this a few other formulations have been studied clinically for antidiabetic activity [131-135].

2.1.5 Phyto-pharmaceutical approach of Antidiabetic plants

As a routine metabolism, plants produce many primary metabolites that are involved in normal growth, development, and reproduction. Some secondary metabolites which are not needed for growth are also produced. Primary metabolites such as carbohydrates, fats, amino acids, water, and minerals are present in all plants whereas secondary metabolites such as alkaloids, tannins, flavonoids, glycosides etc found in a smaller range, which have proven having health benefits to humans [136] .

Plants have been the important source for medicines since ancient time.Thousands of indigenous plants from all over the globe have been used for diverse ailments since prehistoric times. According to WHO, around 21,000 plants are used as a sources of drugs, among these nearly 2,500 species are found in India and about 800 plants are used as a antidiabetic plants[137,138]. Varma *et al* have reviewed thirty five medicinal plants having antidiabetic potential and concluded that antidiabetic research can be shifted towards traditionally available medicines[139]. These plants have wide range of biological plausibility to avoid unwanted side effects and cost of drug development [140-142].

Several drugs have been withdrawn couple of years after marketing because of severe adverse drug reactions (ADRs) and sometimes deaths. Currently there is a general trend towards using natural products and nutraceuticals due to fear of ADRs. Globally, as many as 50-60 % people are inclined to use traditional medicines[143]. Self-medication and Over the Counter (OTC) drugs are fairly common practice in India. As there is a pluralistic healthcare system in India, patients often use therapeutic modalities of several traditional systems simultaneously with conventional medicines. There has been a renewed interest in herbal drugs in developed countries due to increased demand of natural products. The yearly business of the Indian herbal medicinal industry is about Rs. 2,300 crores. *Isabgol, gudmar* herb, senna derivatives, *vinca* extract, cinchona alkaloids, ipecac root alkaloids etc. are some of the major pharmaceuticals exported from India lately. The drug market of herbal medicine in India is about $1 billionper year and over $60 billion globally per year [144-147].

2.2 Type 2 Diabetes mellitus (T2DM)

Earlier diabetes was known as a condition of polyuria, polydipsia and emaciation. It is now known as the metabolic disorder characterised by increased blood sugar levels due to either reduced secretion or use of insulin. It is preceded by insulin resistance for about 10-15 years compensating normal blood sugar. Obesity, Metabolic syndrome and diabetes share a

common soil of insulin resistance. Obesity causes inflammation as increased adipocyte starts secreting proinflammatory cytokines such as tumor necrosis factor (TNF alpha). Elevated levels of TNF-α , interleukin-6 (IL-6), interleukin (IL-8)and C-reactive protein (CRP), have been reported in various diabetic and insulin-resistant states [148-150]

2.2.1 Epidemiology of diabetes

As per International Diabetes Federation (IDF) report, nearly 425 million adults were diabetic worldwide in 2017, and projected to be 629 million by 2045[151]. It is predicted that by 2030 diabetes mellitus may affect up to 79.4 million persons in India. In another study the overall prevalence of diabetes in 15 states of India was 7·3%; and varied from 4·3% in Bihar to 10·0% in Punjab. It was lower in rural areas than urban areas[152]. Diabetes Prevalence & GDP Per Capita, By State is shown in Fig2.2

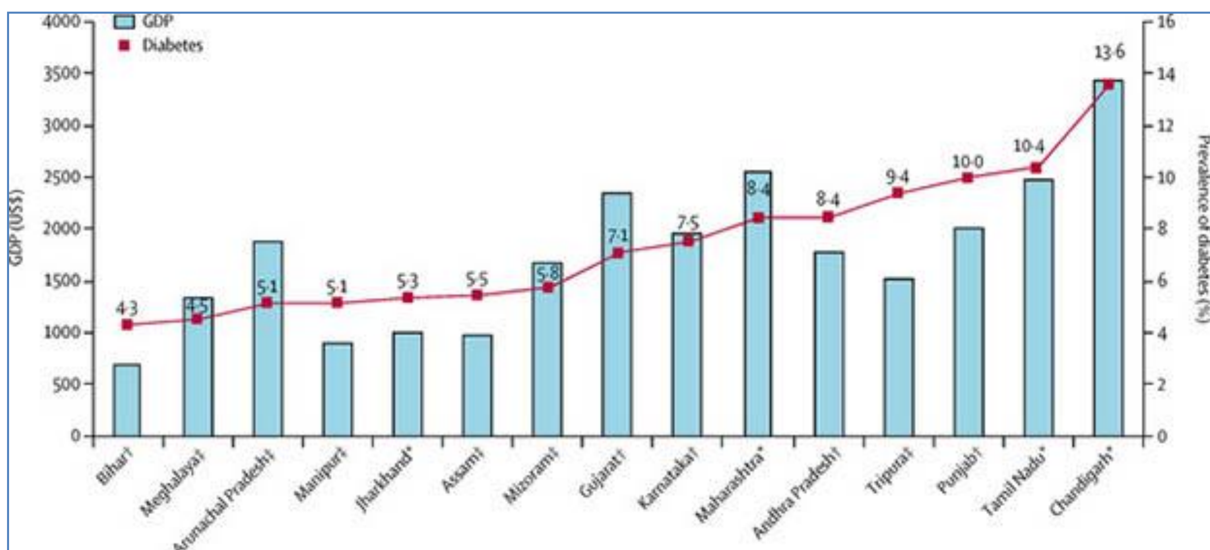


Fig2.2 shows diabetes prevalence per state in India

A study conducted in North India, demonstrated that prevalence of type 2 diabetes in the rural population was found to be 8.03%. Prevalence was high in females than males as well as from the age group of 50-59 years [153].

Agarwal RP (2014) et al reported the prevalence of complications of diabetes among 11,157 diabetic patients in Northwest India. Diabetic retinopathy was more prevalent among the complications (32.5%) followed by nephropathy (30.2%) peripheral neuropathy (26.8%), and coronary heart disease (25.8%). Duration of diabetes and HbA1C had significant association with retinopathy, neuropathy and nephropathy[154].

Mallik and Bruce MSP (2019) reported that prevalent complication noted was neuropathy (69.2%) followed by retinopathy (57.33%), macroangiopathy (56.09%), presence of foot ulcer (30.84%) and nephropathy in 20.39%. Eectile dysfunction was major complication in men (83.90%)[155].

2.2.2 Diabetes: Health and economic burden to nation

Diabetes is one of the diseases that has influenced health-care expenses greatly. Diabetes caused at least 548 billion dollars in health expenditure in 2013 – 11% of total spending on adults. Diabetes costs around median of Rs. 22,456.97/- per patient per annum with no complications; while complications add on to Rs. 30,634.45/-[156].

In high risk population, early detection of diabetes and change in life style will reduce economic and health burden on person, family, society and the nation; however for overt diabetics with compilations, awareness program of lifestyle changes, availability of medication and medical advice, are beneficial in adopting the long term strategic policy of antidiabetic care[157].

2.2.3 Clinical Features of type 2 diabetes mellitus[158]

Polyuria and turbid urine are the cardinal symptoms of a patients with diabetes additionally dehydration and dry mouth, thirst (polydipsia), Increased appetite (polyphagia) and unusual weight loss; tingling or numbness in the hands or feet, dry and itchy skin are some of the symptoms; however occasionally some patients are asymptomatic. They accidently become diagnosed during blood investigations for any surgery. Non healing wounds or urogenital infections are the commonly presenting symptoms.

2.2.4 Diagnostic criteria [159]

Diagnosis of diabetes mellitus involves fasting and 2-h after glucose load (75 g) criteria as per recommendations of WHO since 1999,

Table 2.6 Diagnosis of Type 2 Diabetes mellitus

Category	FASTING	2 hrs PG
Normal	<100 mg /dl (5.6 mmol/L)	<140 mg/dl (7.8 mmol/L)
IFG	100-125 mg/dl (5.6-6.9 mmol/L)	--
IGT	--	140-199 mg/dl(7.8-11.1mmol/L)
Diabetes	≥126 mg/dl	≥200mg/dl (≥11.1 mmol/L)

IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, Glucose load: 75 g glucose load orally

2.2.5 Complications[160-161]

Degree and duration of hyperglycemia favours various long-term complications affecting, micro and macro vessels, and thereby affecting the organs like eye, kidney, foot, heart and nerves. The most common complications of diabetes are as follows

Table 2.7 Diverse complications of Diabetes

Acute complications	Chronic complications	others
1. Diabetic ketoacidosis 2. Lactic acidosis	1. Macrovascular • Retinopathy • Nephopathy • Neuropathy 2. Macrovascular • Hypertension • Coronary Heart disease • Cerebrovascular disease • Peripheral vascular disease	1. Infections • Urogenital • Ocular • Oral 2. Cataract 3. Wounds&sores 4. Connective tissue disorders

2.2.6 Management of Type 2 diabetes mellitus

Correct diagnosis of diabetes is important in good management practices. Type 2 diabetes is known as one of the lifestyle disorders. As diabetes is often associated with obesity, hypertension, dyslipidemia and sometimes cardiac involvement, the paradigm of diabetes management has been shifted from only control of blood sugar to correction of other risk factors of associated morbid conditions. Patient education and involvement of his family play a major role in control of diabetes. Appropriate medicines, corrected/ balanced diet and substantial physical activity carry major proportion in the management; however stress management and patient education have also gained importance now.

- Medicines:

Medicinal management of diabetes started from 1922 when insulin was successfully administered to the first patient of diabetes. Insulin was the only treatment till 1950 when metformin was developed from the French lilac plant, *Galega officinalis*. Traditionally in Europe and Japan, aerial parts of this plant were in use for diabetes[162]. Metformin is the commonest oral hypoglycemic agent till date. In 1956, Germany introduced the first-

generation sulfonylureas (tolbutamide, chlorpropamide, acetohexamide, and tolazamide). In 1984, second-generation sulfonylureas (glyburide and glipizide), and after 10-11 years third-generation sulfonylurea (Glimepiride) was introduced and approved in the United States. In the early 1980s, first thiazolidinedione was discovered in Japan; however in 1997, troglitazone was available for clinical use. Repaglinide (non-sulfonylurea insulin secretagogues), was the first agent from Meglitinides approved for use in 1997 [163,164].

α - Glucosidase inhibitor (Acarbose) was approved by the US FDA in 1995. Glucagon like peptide-1 receptor agonist stimulates insulin secretion which is then facilitated by Dipeptidyl Peptidase –IV inhibitors to control hyperglycemia . They are also approved for clinical use[165].

- Oral Hypoglycemic agents

Table 2.8 Modes of action of oral antidiabetic agents[166-168]

Class	medicine	Mode of action
Biguanides	Metformin	Increases AMPK , decrease gluconeogenesis, increase glucose uptake in muscle
Sulfonylureas	glipizide, glyburide, gliclazide, glimepiride	bind to K-ATP channel in the beta cells; influx of calcium and the stimulation of insulin secretion.
Thiazolidinedione	rosiglitazone, pioglitazone	bind to PPAR γ increase peripheral uptake of glucose and decrease hepatic glucose production
Meglitinides	Repaglinide nateglinide	bind to K-ATP channel in the beta cells; influx of calcium and the stimulation of insulin secretion.
α-Glucosidase inhibitors	acarbose, miglitol, voglibose	inhibit alpha-glucosidase enzymes in the intestine inhibiting the polysaccharide reabsorption as well as the metabolism of sucrose to glucose and fructose.
DPP-4 inhibitors	sitagliptin, saxagliptin, vildagliptin,	inhibit the enzyme (DPP- 4) and prolong the action of GLP . This inhibits glucagon release, increases insulin secretion, and

	linagliptin,	decreases gastric emptying
SGLT2 inhibitors	Dapagliflozin canagliflozin	inhibit (SGLT-2) in proximal tubules of renal glomeruli, inhibition of 90% glucose reabsorption

Over the last several years significant advancement have been made in diabetes management but the role of lifestyle modification in terms of weight loss, healthy eating patterns , regular exercise and increased physical activity are still the cornerstone of treatment and are the most efficacious ways of controlling glycaemia.

- Balanced diet:

Balanced diet contains correct proportion of carbohydrate, protein, fats, minerals and water. Since carbohydrate break down to glucose which is not beneficial for the diabetic person, quality and quantity of carbohydrate in meal is to be planned. Food with low glycemic index (GI) is recommended. Part of carbohydrate in meals has to be replaced by protein and fiber rich vegetables. The calory value of the meal is to be calculated. It is well known that dietary habits and physical inactivity are two important factors in developing obesity and diabetes. This has been reviewed by Sami et al [169]. Different patterns and practices of diet were reviewed for the relationship with diabetes.

- Physical activity

Physical activity is the modality of energy expenditure which is required for carbohydrate metabolism. Contraction of skeletal muscles during exercise increases blood flow in the muscle and improve glucose uptake into the cells, increases sensitivity to insulin. Regular exercise helps reduce intra-abdominal fat and hence reduces insulin resistance.

In a prospective study of 16 years conducted in 68,907 female nurses, an association of obesity and physical activity with the development of type 2diabetes was studied. At the end 4,030 incident cases of type 2 diabetes were documented. Obesity was more associated than physical inactivity with incidence of diabetes; however physical inactivity is coming up as an independent contributor to type 2 diabetes[170,171].

- Stress management:

Stress is the factor that affects physical and mental tension and health. Stress induces cortisol, adrenalin, noradrenaline, glucagon and growth hormone levels in the body that affect blood sugar. Persistent increase in stress is a risk factor for diabetes [172,173]. Hence stress management becomes important. Yoga, music, hobbies are some of the general modalities to relieve the stress; however individual attention may give better results.

- Patient education:

The purpose of patient education is to make the patient aware of his medical condition and help him to take care of his health. To improve the knowledge, awareness programs are conducted. Diabetes care and education specialists are certified professionals related to diabetes education. Patient's Knowledge of diabetes has shown to improve blood sugar control and health [174,175]

2.3 Pharmacoepidemiology

2.3.1 Definition, Evolution, Methods, Advantages and Disadvantages

The word Pharmacoepidemiology (PE) is comprised of two words i.e. Pharmacology and Epidemiology. Effects of drugs are studied in Pharmacology. Clinical pharmacology involves investigating effects of drugs in humans. Epidemiology is the study of distribution & determinants of disease in population. Pharmacoepidemiology[17,18] is the branch of science bridging the two disciplines; studies the use and effects of the drug in a large number of people. (Brian Strom and Stephen Kimmel 2006).

The term Pharmacoepidemiology first appeared in British Medical Journal by Lawson in 1984. He stated that "drug surveillance needs fostering of a new discipline for which a skill is needed to understand the inherent limitations of information available". Professional attention is needed for the proper use of the data. He suggested prospective and retrospective cohorts case control studies to collect the data[176].

Evolution of the discipline:

The discipline of Pharmacoepidemiology has evolved as the response to alarming adverse drug reactions. Simultaneously regulatory bodies also noticed these reactions and created more stringent drug regulatory laws. Adverse drug reactions continue to happen even now in spite of stricter drug regulations. The harm that drugs can cause has led to the development of

the field of Pharmacoepidemiology[177]. Since 2000, the stress was also laid on beneficial drug effect, quality of life studies and health economics.

Table 2.9 Evolution of Pharmacoepidemiology discipline

Event	Response	Responding agency
Unacceptable adulteration and misbranding of food & Drugs 1906	Power Removal of the food/drug from market if found adulterated	US – The Pure Food & Drug Act
Deaths of 100 people Elixir of sulfanilimide dissolved in diethylene glycol 1937	Pre clinical toxicity and clinical safety data prior to marketing	US FDA Food , drug & cosmetic Act 1938
Aplastic Anemia due to Chloramphenicol 1950	• first textbook of adverse drug reaction 1952 • registry of adverse drug effects Iatrogenic Blood Dycrasia;1952 • collection of adverse drug reaction;1960 • Drug monitoring	AMA council on pharmacy and chemistry FDA 1960
Phocomelia (Thalidomide Disaster) 1961	• Committee on Safety of medicine • National Drug monitoring programme • Regulatory changes in Previous FDA I law • Proof of drug safety • Preclinical pharmacological and toxicological testing before human. Pharmacoepidemiology	UK 1968 WHO USA 1962 IND SUBMISSION
	• Drug utilization studies • Beginning of pharmacoepidemiology	1962

In spite of all the care taken before approving the drugs, major adverse drug reactions kept occurring in 1970's, 1980s'and 1990's. Many drugs withdrawal took place even after couple of years of marketing. One of the aims of pharmacoepidemiology was study of beneficial drug effects. The international society for Pharmacoepidemiology was formed in 1996. FDA started collecting spontaneous reports of adverse reaction under MED-Watch program. PE covers the field-studies of drug-usage, safety (ADRs), efficacy, acceptability and interactions of drugs. PE, besides providing the numerical data on adverse events can also be a source of novel beneficial effects of a drug, which may open up a path to new drug discovery or repositioning of a drug.

,

In Ayurveda, *Janapada* is a word for large population. *Janapadadhwansa* means demolition of whole community. Charaka has mentioned four determinants of demolition in large community such as polluted air, water, place (land) and time [19]. These factors are important in progressive order because of the degree of their indispensability. The root cause of derangement of these four factors is *adharma* (unjust/unrighteousness/misdeeds) (314/315). Samal J has tried to analyse various concepts of Ayurveda applicable to epidemiology and interpret their current implication[178].

The stake holders in fields of pharmacoepidemiology are shown in Fig 2.3

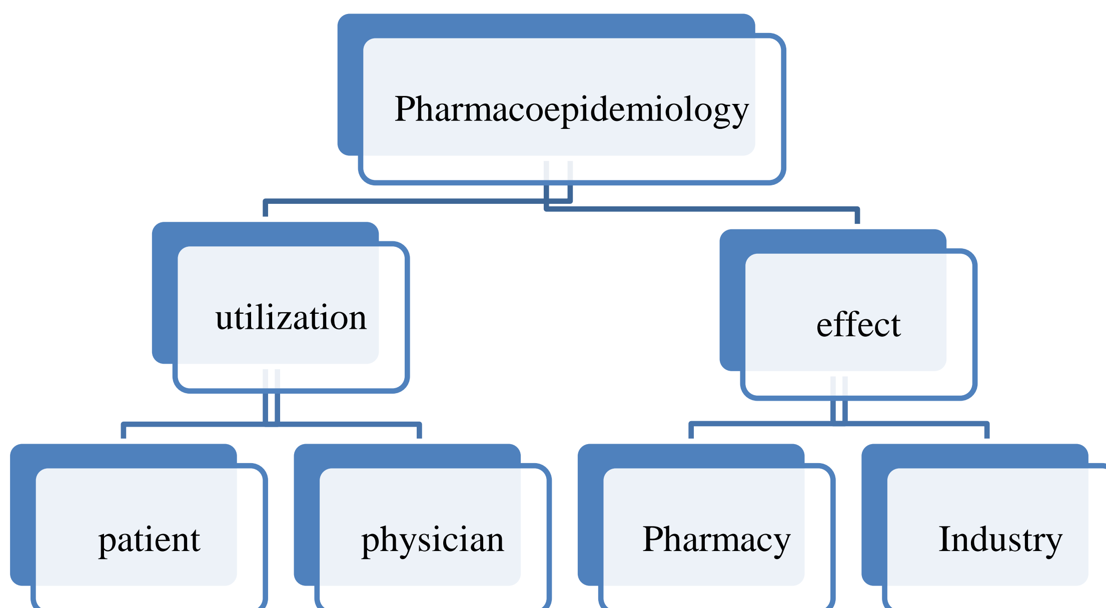


Fig 2.3 shows the stake holders in fields of pharmacoepidemiology

Currently PE borrows methods of epidemiology to get information on on drug effect and adverse drug reactions. These are study designs by which determinants of diseases are looked in population.

Table 2.10 Various methods of epidemiology burrowed by PE[179].

Study Name	Description
Case Report	Reports of a single patients who was exposed to drug and experience as a particular usually adverse reaction.
Case Series	Reports of patients all of whom have a single exposure having common disease.
Analysis of secular trends	To examine the trends after an exposure (presumed cause) and in a disease (effects) and test whether these trends coinside)
Case control study	Comparison between patients with disease & controls without disease
Cohort studies	Studies that identify subset of a defined population & observe them over time
RCT	For disperses in outcome (development of disease)

It has been said that these methods have their own advantages and disadvantages. RCT is the most convincing study design, which controls the unknown confounders, but is most expensive and difficult. Cohort study reveals multiple outcome information. Incidence data of disease, drug usage etc. becomes available. However case reports and case series are relatively less expensive (cheap) and easy quantitation of incidence is done but cannot be used for by hypothesis testing. Case control study is also less expensive, logistically easier and faster; can study uncommon diseases; whereas cohort study is little expensive, may take more time; however can study multiple outcomes. One may apply one or two of these methods of PE or evolve new ones for evaluating Ayurvedic medicines.

The strength of PE studies over RCT is to detect rare adverse events that may occur over a long period. Perkins S et al (2000) has suggested using propensity score to reduce the bias by confounding variables[180]. In 1993 D Smet introduced the word Herbal Pharmacoepidemiology, the methodology by which uses and effects of herbal drug can be studied in large numbers of people. This would add substantial knowledge about herbals and

herbal market. Smet believed that herbal medicines often have a long history of traditional use by people[18].

Recently MHRA (Medicines and Healthcare products Regulatory Agency (MHRA/UK and EU) have accepted that a long term (>30 years) use of any herbal preparation, in the country of origin or more than 15 years' use in the country of import would indicate its usage safety[11,12]. Despite such a clause, it is desirable that there are studies to garner scientific evidence for safety and efficacy of Ayurvedic drugs [181,182]. There is a prevalent perception by community at large and by practicing Ayurvedic Physicians about safety of medicines; however this needs to be meticulously recorded and diligently documented.

Guidelines for good pharmacoepidemiology practice (GPP) have been published. It helps the investigator to plan and conduct the study as well as to solve the issues pertaining to evaluation of PE research. It also has provided the guidance on regulatory requirements[183].

2.3.2 Pharmacoepidemiology in India

In India, people often use over the counter medicines besides prescription. Moreover they have facility to choose medicine from any traditional health care systems available in India. Hence use of drug for any given condition and its outcome becomes complicated to evaluate activity or efficacy. In such a scenario, PE becomes more important to maintain close observation on drug use and its effect.

Dr. Nilima Kshirsagar has prepared the proposal for ICMR/DHR Government of India, for creating a network (of registries, institutions, investigators) for drug utilization & pharmacoepidemiology and expressed the need of experts, trained researchers, investigators, good practices, methodologies for such studies [184].

There are very few pharmacoepidemiological studies that have been conducted in India. A pharmacoepidemiological study for extent and pattern of self-medication was conducted in 130 pharmacists in Indore city. It was found that rate of self-medication was higher for fever, cough and cold, sex problems, than infection, headache, eye problem, nutritional loss etc. majority of drugs that were dispensed were from antipyretic, analgesic, inflammatory, antihistaminic and anti-allergic categories of sources dispensed without the proper prescription[185]. In an another PE study in Warangal district in Andhra Pradesh, medical files of 1753 admitted patients of cancer were reviewed. It was noted that incidence of cancer is

high in females. Most common type of cancer was cervical cancer in females and oral cancer in males[186].

- Health care data base:

Awareness about drug usage patterns (quantitative/or qualitative) is a crucial component of information to decide the rationale use of medicines, and to asses risk-benefit ratio of a medicine and decision on minimising the risk. Computerization and central governance in healthcare have been a help to keep databases of clinical case records and drug consumption at pharmacy levels. Such databases are often used to address the research questions for pharmacoepidemiological studies and thereby to improve the health care services. Healthcare practitioners and government agencies/ ministry of health will be benefitted most by the analysis of such data[187].

A project PROTECT[188], on drug consumption databases in Europe summarizes on collection of information on national drug consumption databases in Europe. That project developed a drug directory for 14 European countries and established the European Network of PROTECT Drug consumption databases for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The Dutch drug database (G-Standard) is used by all parties in healthcare, with the government. That includes health insurers, wholesalers, manufacturers also [189]. Computerised system at medical stores and/or *Aushadhi bhandar* for medicines has not yet been developed. No centralised system for any Traditional health care system is available to grass root level, hence data on consumption of Ayurvedic medicines cannot be recorded. It is also difficult to study expenditure on drugs.

2.4 Ayurvedic Pharmacoepidemiology: applied methods

Pharmacoepidemiology is established to document adverse effect of the drugs from conventional system medicines. No such discipline is available to document adverse effect, novel beneficial effects and clinical conditions for Ayurvedic medicinal therapy. Ayurvedic Pharmacoepidemiology (AyPE) is a new inter-discipline proposed by Vaidya RA et al (2003) for the study of the usage, acceptability, efficacy, compatibility, interactions and cost-effectiveness of Ayurvedic drugs in a large number of people [20]. Alarming headlines about the toxicity of Ayurvedic medicines in newspapers, journals and media, without appropriate scientific studies can have an adverse impact on a system of health used for centuries[21,22].

Publications regarding usage of complementary and alternative medicines in US and UK, and in India are on rise. Turnover of herbal market in India and globally has been increased. In response to these aspects, Ayurvedic Pharmacoepidemiology is evolving as a discipline to document usage of Ayurvedic medicines, formulations (either generic or proprietary), safety, and novel beneficial as well as adverse events/effects.

AyPE needs triple competence in clinical pharmacology, medicine, and epidemiology or a team with such diverse expertise. Such a discipline is the demand of the time. This is because as per WHO estimates, almost 80% of population of many Asian and African countries relies on traditional medicine for primary health care[23].

Scope of AyPE:

As medicinal plants have diverse utility for multiple health conditions AyPE will also help to capture new indications for a given plant. This will be a challenge because Ayurvedic disease management measures comprise not only the medicines but *pathapathya* also. Hence to evaluate severity of adverse effect association of *bala, prakriti, kala, matra, agni, vaya, satva, satmya, ahara* should be kept in mind.

Some of Ayurvedic formulations are given as medicines for the treatment of identified diseases as well as for preventive or promotive health measures. Hence it is a challenge to identify purpose of its use as well as periodicity (seasonal) or duration of the regimen. Other aspects of enquiry which are specific are related to Ayurvedic Pharmacodynamic properties. Hence a careful elicitation of the history of its usage would demand technical person and expertise of Ayurvedic physician and epidemiologist.

As mentioned earlier there exist a prevalent impression and claims about wide spread use and safety of Ayurvedic medicines, however their usage frequency, effectiveness associated with concurrent use of these conventional medicine are not documented and studied. The AyPE – endeavours will also offer opportunities to identify novel beneficial effects (e.g. *Rauwolfia surpentina* and *Mucuna pruriens)*[190], pathophysiology of diseases, and mechanisms of pharmacological actions. The other challenge is of drug interaction where Ayurvedic and medicines from other systems are used concurrently for e.g. diabetic patients. The starting point of such an endeavour rests in the experiential and exploratory phase of Reverse Pharmacology. These aspects can be studied through case reports, case series, traditional vast

experience of senior vaidyas and their notes. The organised endeavour in this respect can be undertaken by multidisciplinary and multisystem teams.

2.5 Survey Methodology[191]:

A survey means a general view, or description of someone or something. A survey is defined as a research method used for collecting data from identified group of participants. The most important work is to generate an appropriate questionnaire. Depending on the questions three types of questionnaire are made. Survey research is often used to evaluate thoughts, opinions, and feelings. They are conducted by either direct interview by means of instruments and phone calls or indirect by means of internet and survey instruments. The questions are either close ended, open ended or partially categorised. Close ended questionnaire are easy to analyse but sometimes biased whereas open ended questions are time consuming and difficult to analyse as they are in participants' own words but gets participants own response. Partially categorized questions are similar to open ended questions; however some are pre-categorized to simplify the analysis. Usually "others" choice of answer is kept to explain the views.

- Phone call survey :

A telephone survey is used to gather the data from the general population. It is also used to collect the data from a specific target population. Trained interviewers used telephone numbers for communication. Using a telephone to reach participants is a cheaper option to have personal conversation without the hassle.

- Online survey

An online survey is also a questionnaire which is uploaded on internet by a web link. They are generally developed as Web forms with a database to store the answers. Statistical software is used for the analysis. This survey allows you to reach thousands of participants in lesser time; however we may not get honest answers as we don't have control on the participant. It is not possible to motivate participants to answer each question.

- Drug utilization survey (DUS)

Drug utilization is one of the several methods of Pharmacoepidemiology. Drug utilization is defined as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences [192]. It explains the

magnitude, nature and factors of drug exposure. It facilitates the rational use of drugs in population. It also conveys the effectiveness of the drug which can be used to decide the appropriate provision of the budget for health care. The hints and hits surfaced during the drug utilization study becomes the reservoir for Drug discovery through Reverse Pharmacology for natural products.

- Knowledge Attitude and Practice (KAP) survey:

KAP Survey is one of the epidemiological methods that collect the knowledge regarding any proposed thing [193,194]. It has 3 domains like Knowledge, Attitude, and Practice. Knowledge plays a pivotal role in any disease management or in developing any medication for the same. Awareness of the disease, positive attitude and prompt practices especially of diabetic patients may reduce this burden and increase quality of life.

Survey collects the fact or field reality of the social, cultural and economic factors which may influence health, confirm or negate a proposition or assumptions and offer new approaches of a situation's reality. KAP surveys have achieved their place among the methods to be used to explore health behaviour, and stayed back to be used widely to gain information on health-seeking practices [195].

KAP Survey being one of the borrowed methods of Pharmacoepidemiology, we proposed this method for Ayurvedic Pharmacoepidemiology also. It is the need of the hour to study the extent of knowledge of diabetes and the practices of those diabetic patients who visit Integrative diabetes clinics to manage the disease. Hence the aim of this cross sectional study is to document the knowledge, attitude and practices regarding diabetes among the diabetic patients visiting in Integrative diabetes clinics[196].There are few studies where drug utilization and study of Ayurvedic medicines have been conducted[197],[198].

Dr Girish Tillu in his Ph D thesis (2015) titled ' Pharmacoepidemiology of Ayurvedic Medicines; has analyzed marketed Ayurvedic medicines for arthritis, KAP survey for patients of arthritis was carried out . Drug utilization survey for arthritis was also done. Dr Tillu explored two more new methods viz. developing treatment algorithm for arthritis and focused group discussion of patients with arthritis for treatment of arthritis.

Clinical algorithm is nothing but a flow chart of clinical decisions in sequence. By its use students can be trained well, clinical practice is then better understood and supervised

correctly[199,200]. Judicious use of algorithm would add more value in the research performed using Ayurvedic Pharmacoepidemiology.

Developing algorithm for Ayurvedic management of any disease is different than the conventional management of disease as it is highly individualized as there are many deciding variables such as age, body constitution, *agni*, strength, stage of the disease, diet, season etc beside *doshas* and *dushyas*. Hence management guidelines are given.

Focus group discussion is the frequently used method of data collection having qualitative approach to gain knowledge. A known group of individuals from similar backgrounds or understandings are selected to discuss the issue. Participants are asked questions related to identified subject and discussion among the participants is recorded or minutes are taken. . It is assumed that the group processes triggered by a moderator facilitates sharing of knowledge among groups and communities, which is otherwise difficult to obtain with a series of individual interviews[201].

The drawback of this method is that the knowledge collected is not shared equally among a studied group, or community. Rather, it collects common information as well as difference of opinion.in terms of understandings, and views.

3. Materials and Methods:

“Nothing happens quite by chance. It's a question of accretion of information and experience.”

Jonas Salk

The proposed research question for this research programme was; what is the usage of Marketed Antidiabetic Ayurvedic Formulations and Plants by the diabetic patients in the management of their diabetes.

This study sort to answer the following research questions ;

1. Do Marketed Antidiabetic Ayurvedic Formulations provide the information about the medicine that shoud be provided to the patient as its provided for allopathic medicines?
2. What is the extent of usage of drug and non-drug modalities in the management of *prameha* and *madhumeha* (Type 2 diabetes)
3. What is the knowledge and what are the practices adopted by Ayurvedic physicians for treatment of diabetic patients
4. What is the pharmacological activity, and safety of two selected Ayurvedic formulations (*Nisha -Amalaki and Mamejava Ghanavati*) using conventional laboratory-based techniques as per Reverse Pharmacology path.

Reverse Pharmacology (RP) is a science which collects documented experiential hits, integrates with transdisciplinary exploratory studies to give leads. Experimental research on

these leads further develops into drug candidates, adding value to drug discovery process. Figure 3.1 shows the benefits of Reverse Pharmacology.

. Fig 3.1 Drug Discovery Process as per Reverse Pharmacology

Reference: Vaidya ADB. Reverse pharmacology-a paradigm shift for drug discovery and development. Curr Res Drug Discover. 2014;1:39–44

For current Research work, literature search, study of marketed formulations, drug utilization and KAP survey have been taken as methods. These methods collects the information which in turn gives the hints and hits / leads to perform exploratory and experimental studies concurrently with relevant science to give drug candidate.

Sources of material

A. Data collected from literature

1. Literature: Ancient classical Ayurvedic Texts , Ayurvedic Classical Texts Nighantus and current literature of Journal and books

B. Data collected from patients by survey and clinical studies

1. Knowledge attitude and practices by diabetic patients visiting diabetes clinic.
2. Knowledge and practices of Ayurvedic Physicians regarding management of diabetes of their patients
3. Drug utilization study of diabetic patients from Mumbai
4. Clinical case records of diabetic patients at Out Patient Department (OPD) of I-AIM Hospital at Bangalore.
5. CSIR NMITLI clinical trials at Mumbai

C. Marketed Antidiabetic Ayurvedic Formulations

D. Data from Experimental study : *in-vitro* study of α-glucosidase inhibition.

Methods:

1. Literature search on Ayurvedic procedures, *pathyas* and *dravyas* for the management of *madhumeha*.
2. Analysis of Marketed Antidiabetic Ayurvedic Formulations: Analysis of labels of the formulations as per the Drug and Cosmetic Act 1945 as well as for patient information and packaging of the formulation as per WHO guidelines.
3. Drug utilization study in diabetic patients:
    1. Survey at *Swadeshi Arogya Mela in Mumbai* (Pilot study under the project has been conducted earlier), Mumbai.):
    2. Survey at Tertiary Health Care center in Mumbai (Endocrine Department
    3. Survey at Ayurvedic Hospital of FRLHT, Bengaluru:

       Survey questionnaire were prepared which included usage of Ayurvedic as well as conventional medicines for the management of diabetes.
4. Knowledge Attitude and Practice survey :
    1. In diabetic patient: Survey instruments to collect data regarding patients' knowledge about their disease, their attitude towards management and the practice of managing their diabetes.
    2. In Ayurvedic Physicians. The other survey documented Knowledge and practices of Ayurvedic Physicians towards management of diabetes of their diabetic patients were recorded by another instrument.
5. Clinical studies of selected medicinal plants/formulation under the project CSIR NMITLI Diabetes: Two formulations *Nisha Amalaki* and *Mamejava Ghana vati* were studied in diabetic patients under the nationwide project of CSIR NMITLI Diabetes project (MRC-KHS). These two formulations were also studied for drug interaction in healthy volunteers.
6. In vitro study of α glucosidase inhibition activity:

   Market samples of *NishaAmalaki* (Combination of *Curcuma longa* Linn and *Phyllanthus emblica* Linn) and *Mamejava Ghana (Enicostemma littorale* Blume) were screened for α glucosidase inhibition activity at Life Sciences laboratory; Trans-Disciplinary University – Bengaluru, and their active principles were screened at KHS –MRC, Mumbai.

Data Collection methods:

- Interview of diabetic patients, Ayurvedic Physician

- Clinical trials in diabetic patients

Data Analysis/ Statistical Methods

- **Data collected from literature**

  Data was recorded and review was prepared.
- **Data collected from patients by survey and clinical studies**

  Data collected were recorded in excel sheets. Statistical analysis was performed by SPSS software (version 18) and graph pad prism 5. Data is presented in tabular and graphical form. The information regarding KAP was collected by administering survey. The responses were converted in the form of scores and evaluated as per the domains of KAP. Data were analysed using conventional and advanced statistical techniques viz., Mean, standard deviation (SD), Standard Error (SE), Chi^2 test, and ANOVA.
- **Marketed Antidiabetic Ayurvedic Formulations**

  Data was recorded in excel sheets. Data is presented in tabular and graphical form.
- **Data from Experimental study :**

  Data was recorded in excel sheets. Data is presented in tabular and graphical form.

Ethical Consideration

All aspects of the thesis were approved by Intersystem Biomedica Ethics Committee. The letter is given as an appendices no five and six in the thesis. Written informed consents was taken from the participants of all surveys and clinical studies.

3.1 Ancient and current Literature survey:

Literature survey was done on Ayurvedic procedures, *pathyas* and *dravyas* performed for the management of diabetes.

3.1.1 Ancient literature:

The classical ancient but still relevant literature was accessed at several libraries for - all the *sutras* and *tikas* on diverse aspects of *Madhumeha*. In addition detailed interviews and discussion were carried out with seven senior vaidyas practicing in Mumbai for clarification on certain aspects of interpretation of *sutras*. Ancient classical Ayurvedic Texts such as

Atharva veda samhita, Ayurvedic Classical Texts such as Charak samhita, Sushrut samhita, Vagbhat samhita, Madhav Nidan samhita, Yogratnakar samhita, Sharangshar samhita, Bhel samhita, Harit samhita, Kashayap samhita, Rasaratna Samuchhaya, Nighantus such as Dhanvantari Nighantu, Raj Nighantu, Kaiyadev Nighantu, Madanpal Nighantu, and Priya Nighantu and current literature of journals such as AYU(Gujrat), JAIM (Bangalore), Ayurved Patrika (Nashik), AAM (Lucknow) and books on *Kaya chikitsa* (Internal Medicine), *Dravyaguna Vidnyan* (Ayurvedic Pharmacology).

3.1.2 Current Literature

Textbooks of medicines, endocrinology, national and international journals, sites of various diabetic association viz IDF, ADA, etc. WHO, and various online sources were searched to get most recent description of diabetes, management guidelines, new oral hypoglycemic agents, paradigm shift in antidiabetic targets.

3.2 Marketed Antidiabetic Ayurvedic Formulations (MAAF):Study of labels, patient information and packaging of the formulations

For the study of Marketed Ayurvedic Antidiabetic Formulations the investigator made personal visits to the outlets selling Ayurvedic medicines. At the time of conducting the survey it was not possible to obtain the complete list of *Aushdhi Bhandars*. Therefore snowball sampling was resorted to. Also many owners were not willing to impart the necessary information. Aushadhi Bhandars were not using the computerised system for sale of the formulations like Netherland and other countries. It was observed that many small scale industries have marketed their products which are available as OTC without registration due to lack of stringent Government regulations that are applied to Allopathic drugs.Hence we were unable to obtain information on total numbers of formulations to decide on the sample size of 180.

Ayurvedic drug outlets (Aushadhi Bhandar) were approached to purchase the Marketed Antidiabetic Ayurvedic formulations.

Stage one : MAAFs (n=180) were purchased from *Aushadhi Bhandars* and Ayurvedic drug outlets. Information provided on the labels was recorded and analyzed. The Analysis of all the 180 MAAFs was done according to dosage form of the formulation, dosages and dosing schedules, vehicle, timing of administration, parts of the plant used, and number of ingredients per formulation. Defined Daily Doses (DDD) of maximally used medicinal plants

were calculated as weight of the respected plant per UNIT dose and multiplied by number of doses per day.

Labels of first consecutive 100 formulations were evaluated for regulatory compliance as per the standard format of the rules (1945) of the Drug and Cosmetics Act 1940 (XVII, 161) [202]. Evaluation of formulation was carried out for the following aspects: Name and the address of the manufacturer, Manufacturing license number, Date of manufacture, Batch number, Net weight of the formulation, References of the formulation in case of Classical Formulations, List of ingredients, and their quality status (like API etc), Drug quantity in metric units, Warning; indication/contraindication, and Language of information used for labels and package inserts (Hindi and English).

Stage 2: In stage 2 of the study package inserts of additionally obtained 53 MAAF were analysed as per WHO guidelines for evaluating package inserts of traditional medicine[203]. The guideline provides a format for the following necessary components namely: product label and package inserts where information about name of the product, quantitative list of active ingredients, dosage forms and indications, expiry date, lot number, and holder of marketing authorization is necessary. Dosages as per the age (if applicable), mode of administration, duration of use, major adverse effects (if any), over dosage information, contraindications, warnings etc. are important clues for specific indications. The package inserts were also reviewed for these additional criteria.

3.3 Drug utilization Study :

3.3.1 *Swadeshi Arogya Mela* in Mumbai:

It was a cross sectional observational study. The plan of survey was discussed in advance with the representatives of the organizing committee of *Swadeshi Arogya Mela*. Pamphlets that carried Type 2 diabetes related health educational material as well as invitation for health checkup and random blood sugar examination were distributed through the good offices of the organizers.

The space given to the institution (MRC-KHS) was adequate for partitioning into cubicles for registration, demographic profile, anthropometry and BMI, and blood pressure examination. A separate cubical was allotted for random blood sugar (by glucometer) and handing over the reports. Counseling and advice regarding management of their diabetes and prevention of its complication including life style management were also offered by the specialists. A special

cubical was allotted for the survey of drug usage. The multidisciplinary team consisting of Ayurvedic physicians, medical practitioner, diabetologists, endocrinologist, nutritionist and technical staff made it possible for an efficient conduct of the predesigned survey and reporting with counseling of the visitor patients.

Known type 2 diabetic patients visited to the assigned booth. Predesigned survey form was used to record the demographic data, history of duration of diabetes, information regarding pharmacological and nonpharmacological modalities (diet and physical activity, Yoga and others).The form also included record of their random blood sugar as estimated at the booth site on the same day.

It was deemed worthwhile to study attendees of *Swadeshi Arogya Mela* , because it would be easier to obtain information about usage of Ayurvedic medicines . However it is acknowledge that there is selection bias and It may not necessarily reflect field reality of the community at large.

3.3.2 Drug Utilization Survey at a Tertiary Health Care center in Mumbai:

It was a cross sectional Epidemiological Survey. A survey was conducted at Endocrine out-patient department of a tertiary health care centre- NAIR Hospital in Mumbai. Ethical approval of the study protocol was obtained from the ISBEC for the Institution before the study is undertaken.

The survey questionnaire was prepared and Information as per the questionnaire was recorded. The doctors from the team were trained for the questionnaire to reduce inter observer variations. Ambulatory patients of Type 2 DM of all ages and both sex were selected ad hoc for the study. Type 1 Diabetic Patients and admitted patients were excluded. After consultation by the physician (Dr Ameya Joshi), anthropometric measurements such as height, weight, waist circumference and the vitals such as blood pressure and pulse were taken. Prescriptions and the patient’s health records were reviewed simultaneously during the interview of the patient. The demographic data, disease data and utilization of Ayurvedic medicines for diabetes, oral hypoglycemic agents and insulin as well as life style measures that were followed by patients were also recorded and analyzed. Data are presented in tables and graphs.

For the study at Nair Hospital, the investigator was at the hospital over a period of 6 months. All patients attending the OPD during this period were included.

3.3.3 Retrospective survey of clinical case records at Ayurvedic Hospital of FRLHT (Bengaluru)

Following approval from institutional ethical committee, clinical case records of all diabetic patients, who have completed follow ups of 6 months for the period 3 years till December 2016 (January 2014 to December 2016- 3 years) were reviewed. The criteria for inclusion was that the patient should have completed 6 months of the treatment. Therefore from the computerised records for the previous 3 years , all those patients who met the criteria were included in the study.

All available data for each patient were recorded in EXCEL sheets and analyzed to evaluate usage, safety and efficacy of the Ayurvedic Antidiabetic Therapy that they have received at *Swasthavrutta* Department I-AIM Health Care of Foundation of Revitalization of Local Health Traditions (FRLHT), Bangalore. Clinical safety was assessed by change in clinical signs and symptoms and adverse event reporting, as well as records of organ function tests in clinical case records. The effects of the treatment was assessed by changes in fasting blood-glucose (FBG), postprandial blood sugar (PBG), glycosylated hemoglobin (HbA1c), blood lipid profiles and body mass index (BMI) at 3 months and 6 months. Frequency distribution curves of the Ayurvedic and modern drugs made in groups of controlled and uncontrolled diabetes patients.

3.4 Knowledge, Attitude and Practices (KAP) Survey :

KAP Survey is a standard method of Pharmacoepidemiology (PE), adopted for Ayurvedic Pharmacoepidemiology. KAP surveys in diabetes have contributed significantly both to the methods as well as to reality of health-seeking practices. However such surveys in Integrative diabetic clinics are sparse.

3.4.1 KAP survey of Diabetic patients for the management of their disease:

All aspects of the thesis were approved by Intersystem Biomedica Ethics Committee. Written informed consent was taken from all the participants.

Snowball sampling method was used for cross sectional survey. Type 2 diabetic patients visiting Integrative Diabetes clinic at KHS- MRC were interviewed with a prior permission of the Ethics committee. Information based on structured interview was recorded in predesigned survey instrument. All the data were entered in Excel sheets.

Knowledge component had four questions to describe the level of knowledge, having score of maximum twenty and minimum of zero was assigned to level of knowledge. To determine the attitude towards management of their diabetes, assessment was carried out by administering five questions to the diabetic subjects. These questions had maximum score of twelve and minimum of zero and to decide the factual practice, three questions with the maximum score of seventeen and minimum of zero were incorporated.

Quantitative data was analyzed with the aid of the Statistical Package for Social Sciences (SPSS) version 20. Tests of statistical significance were carried out using Chi-square tests for proportions. The results were presented in the form of tables for easy appreciation. For each test, a p-value of less than 0.05 was taken statistically significant.

3.4.2 Knowledge and practices of Ayurvedic Physicians towards diabetic management:

This was also a cross sectional survey with snowball sampling method. Ayurvedic physicians were surveyed with a pre designed questionnaire after EC approval. Written informed consent was taken from all the participants.

Knowledge component had four questions to describe the level of knowledge, having score of maximum twelve and minimum of zero. To decide the factual practice, four questions with the maximum score of nineteen and minimum of zero were incorporated. All the information recorded in questionnaire was analyzed by SPSS software. Student's t test for significant difference between two means and Chi square test was used for whether there was any association of knowledge and practices. $P<0.05$ was considered as statistically significant.

3.5. Clinical studies of two selected Ayurvedic Antidiabetic formulations under the project CSIR NMITLI Diabetes:

The clinical Research work conducted by Dr Ashok Vaidya and Vaidya Antarkar resulted in establishing safety and antidiabetic activity of some Ayurvedic Medicinal Plants in Diabetic Patients. Further under the CSIR-NMITLI project at KHS-MRC , after consensus of Clinical Pharmacologists, *Dravyagunadnya* (Ayurvedic pharmacology), Endocrinologists.

Diabetologists, Phytochemists and Ayurvedic Experts two formulations were selected for Phase I, II and III studies. These clinical trials were conducted under Reverse Pharmacology path. Ethical approval of ISBEC has been taken for both the studies and excluded severe hyperglycaemic patients. As a research Associate I was involved as Ayurvedic expert in all these studies.

Two formulations *NishaAmalaki* (combination of *Curcuma longa* Linn and *Phylanthus emblica* Linn in 2:3 proportion) and *Mamejava Ghana vati* (formulation made by evaporation of decoction of Plant *Enicostemma littorale* Blume as per Ayurvedic Methodology*)* were studied in diabetic patients as well as for drug interaction in healthy volunteers.

Exploratory studies for complementary effect of *NishaAmalaki and* Mamejava Ghana vati were conducted in treated uncontrolled type 2 diabetes mellitus patients. These 2 formulations are marketed formulations and are in current use as OTC by patients and in prescription of Ayurvedic Physician also. The trials were conducted under the close supervision of an Ayurvedic MD Physician and an experienced diabetologist from Modern medicine.

3.5.1 *Nisha amalaki* trial:

With prior EC permission, treated uncontrolled T2DM patients (n=30) were enrolled in an exploratory study as per the selection criteria. Nisha Amalaki powder (in ration of 2:3 combinations) was given in a dose of 5 Gms thrice a day for 12 weeks as add on with current antidiabetic management. Patients were called on 15th day, after one month, after 2 months and after 3 months for follow up. Clinical as well as investigational Safety and antidiabetic activity were explored. Fasting and PP blood sugar, lipids, HbA1c, serum insulin every month ,and C peptide and CRP tests were carried out before and after the therapy.

3.5.2 Mamejava Ghana vati trial:

With prior EC permission, treated uncontrolled T2DM patients (n=30) were enrolled in an exploratory study as per the selection criteria. Mamejava ghanavati prepared as per Ayurvedic Methodology was given in a fix flexible dose of 250 mg thrice a day for 2 weeks and then 500 mg thrice a day for next 6 weeks at two centers with identical protocol. Safety and activity was explored. Fasting and PP blood sugar, lipids, HbA1c, serum insulin, C peptide and CRP tests were carried out before and after the therapy.

3.5.3 Drug interaction studies of these 2 formulations with metformin[33]:

The study was planned in 2 parts. With prior EC permission, the identified volunteers were screened to get six healthy volunteers. In the beginning six volunteers (n=6) were randomized to metformin alone or with *Nishaamalaki* powder and later with *Mamejava ghana* tablets in a cross over design with a 7 days wash out period. A single dose of metformin (500 mg) alone or with *Nishaamalaki* (10 gm powder)in part one study was administered simultaneously per os (PO).In the part two study a single dose of metformin (500 mg) alone or with *Mamejava ghana* (750 mg),as oral antidiabetic Ayurvedic tablets, was administered simultaneously orally. Venous blood samples were taken at 0, ½, 1,1½, 2, 2½, 3, 4, 5, 7, 9 and 24 hour time cuts. One volunteer was common to both the studies was subjected to another formulation *Nishaamalaki* tablets (tablets of DMFN 01 powder-single dose 750 mg) with the same protocol.

Metformin concentration in plasma was estimated by reverse phase HPLC method with C18 column and UV /visible detector at 235 nm for the measurement of peak areas. The mobile phase consisting of 5% acetonitrile and 95% 0.05 M $(NH_4)_2HPO_4$ with 0.10 gm/100ml heptane sulphonic acid, was pumped at a flow rate of 1 ml/min. The method was validated by MS. Ethic's committee permission and Informed consent from volunteers was taken prior to the study.

3.6 Alpha Glucosidase inhibition activity [204] :

Rationale for this activity: Alpha amylase (α-A) and Alpha glucosidase (α-G) are the digestive enzymes involved in carbohydrate digestion in mouth and small intestine. Alpha amylase hydrolyzes glycosidic bonds in starch to form glucose, maltose, maltriose and dextrin. Alpha-glucosidase breaks down oligo saccharides (disaccharides and polysaccharides) and other complex carbohydrates into mono saccharides (glucose) for absorption in the intestine. Inhibition of these digestive enzymes has been studied as a target to develop antidiabetic agent to control postprandial hyperglycemia. Many medicinal plants have been investigated for the same; however Ayurveda inspired formulations having antidiabetic potential and studied as per Reverse Pharmacology Path with their active phytoconstituents are needed to explore for this target. Market samples of *mamejava* plant and *Mamejava ghanavati* of various manufacturing companies with active principles viz Swartiamarine, catechine, Apigenin, were subjected to standard α-A and α-G inhibition assay.

3.6.1 Alpha Glucosidase inhibition activity of two Marketed Antidiabetic Ayurvedic Formulations:

Market samples of *NishaAmalaki* (Combination of *Curcuma longa* Linn and *Phyllanthus emblica* Linn) and *Mamejava Ghana (Enicostemma littorale* Blume) were screened for α glucosidase inhibition activity at Life Sciences laboratory; Trans-Disciplinary University – Banguluru, and their active principles were screened at KHS –MRC, Mumbai.

- Preparation of samples of marketed formulations:

One gm of formulation powder was added to 5 ml of sodium phosphate buffer (pH 6.9). Vortexed and kept for 4 hours. Supernatant was used as samples. Tannin content of each sample was estimated using Gallic acid as a standard. For the assay, quantity of sample to be taken was calculated as per the tannin content.

- Alpha glucosidase (α-G) inhibition:

Assay was carried out with following standard protocol [205] with modifications to suit to 96-well plate format. Different concentrations of the samples were taken and the volume was made up to 50 µL with 0.02 M sodium phosphate buffer (pH 6.9). To this, 50 µL of a-G (0.5 U/mL) was added and incubated for 10 min at room temperature, followed by the addition of 50 µL of 3.0 mM p-nitrophenylglucopyranoside (pNPG) as substrate and incubated for 20 minutes at 37^0 C. The reaction was stopped by adding 50 µL of 0.1 M Na_2CO_3.

Absorbance was read at 405 nm, using plate reader. For enzyme activity, 50 mL of buffer was used as control for a-G and a set of test samples without enzyme was used to measure the basal level of reducing sugars present in the test samples. The absorbance was subtracted from the corresponding test readings. The percentage inhibition of enzyme activity for α-G was calculated as follows.

$$\% \text{ Inhibition} = \frac{(\text{Abs Control} - \text{Abs Test})}{\text{Abs Control}} \times 100$$

3.6.2 Inhibition of α-glucosidase by phytoactives of *E. Littorale*

Additionally alpha glucosidase inhibition assay was carried out at KHS-MRC with a little modified method. Phytoactives of Mamejava viz, Swartiamarine and Apigenin were selected for the study. Alpha-glucosidase (α-G) enzyme inhibitory activity of standards swertiamarin, sweroside, stigmasterol and extracts and fractions of *Enicostemma littorale* Blume was carried out using standard protocol given by Kazeem *et al* [206]. Standard curve of substrate was carried out. Acarbose (SIGMA) was used as positive control. All reagents and the test

compounds were prepared in 0.02M sodium phosphate buffer (pH 6.9). For the assay, 50µl of different concentrations of the samples (0 to 0.2mg/ml) were taken in a 96 well plate. To this 50µl of 0.5µ/ml of the enzyme α-G (Saccharomyces Cerevisiae, Sigma Aldrich) was added and incubated for 10 mins at room temperature. This was followed by the addition of 50µl of 0.6mM p-nitrophenyl- α-D-glucopyranoside (EMD Millipore Corp, USA) as a substrate and incubated for 20 minutes at 37°C. The reaction was stopped by adding 0.1M sodium carbonate and the absorbance of the color developed was read at 405nm. Appropriate negative controls (containing only buffer and enzyme/substrate) and compound controls (containing only test compound and enzyme) were set up in parallel and the experiment was performed in triplicates. The results are expressed as OD v/s concentration.

Reverse Pharmacology integrates documented clinical and therapeutic experiences and experiential observations in to leads that can through various steps result in developing candidate phytomolecules for drugs. For this detailed study of existing literature of Ayurveda which is applicable to the present research work is required along with obtaining the information through transdisciplinary approaches for safety, efficacy and mechanistic understanding. Thus in the present study Ayurvedic Pharmacoepidemiology (AyPE) is a part of Reverse Pharmacology.

The present study was largely devoted to AyPE that included study of marketed formulations, drug utilization and KAP survey. Further, based on an extensive literature search and a consultative process with experts from multiple disciplines, candidate plant materials were identified. Among these two formulations were selected for performing exploratory and experimental studies concurrently with relevant science to give potential drug candidate(s).

4.Results

Your talents and abilities will improve over time, but for that you have to start

--Martin Luther King

4.1 Therapeutics of *Madhumeha.* (Ayurvedic procedures, *dravyas* and *pathyas*)

Ayurvedic management of any disease aims at reversal of the pathogenesis of the disease and reestablishment of health of the patient. It comprises pharmacological and non-pharmacological modalities. Pharmacological management contains Panchkarma procedures as per the severity of *doshik* dominance and the strength of a patient followed by conservative treatment. Conservative treatment includes diverse herbal, herbo- mineral and mineral formulations as per doshik dominance with relevant *anupan. Anupan* is the element which is used to enhance the activity of the medicine. *Non pharmacological modality comprises* exercise and specific diets (*vyayam and pathyapathya*) and psychospiritual approach (*Satvavajay*) [207,208] .

Various combinations of medicinal plants are recommended in the classics for *prameha/madhumeha* and for the complications thereof as per the *doshik* dominance; however, an Ayurvedic Physician has the liberty to use new combination of plant/s based on the patient's condition and needs. These plants are selected based on their properties such as *rasa* (taste), *guna* (properties), *veerya* (potency), *vipaka* (post digestive effects) and *prabhav* (unique action) in order to restore the equilibrium in *doshas* and *dushyas* as per the *Prakruti* of patients. Charaka was the first to give the guidelines of the management of *Prameha* and *Madhumeha*[19]. The sutra describing these guidelines is given below. It is noteworthy that he has classified patients with *Prameha* for the management of *prameha,* patients are to be classified as per their body weight and frame as obese and lean as well as on the basis of

strength as strong and weak (or emaciated). This classification based on body weight and frame is largely similar or equivalent to the use of body mass index (BMI)

स्थूलः प्रमेही बलवानिहैका कृशास्तथैका परिदुर्बलश्च ।
संबृहणं तत्र कृशस्य कार्यं संशोधनं दोषबलाधिकस्य ।।
च चि 6।15

Figure 4.1.1 Guidelines for management of Prameha

Obese and strong patients with abundance of *doshik* imbalance are treated by Ayurvedic panchkarma procedures like *vaman* (induced vomiting) and *virechan* (induced purgation) to bring back the harmony of *doshas* and *dushya*s. *Doshik* dominance decides whether vomiting or purgation is to be induced. Panchkarma therapy is then followed by conservative medicinal therapy, which includes herbal or herbomineral formulations and specific prescriptions for diet and behaviour i.e. lifestyle (Pathyapathya).

As part of conservative management, Charak has recommended the decoctions of medicinal plants as per *doshik* dominance. Ten aqueous decoctions for *Kapha prameha,* ten decoctions for *Pittaja prameha* and oil preparations for *Vata* dominance have been advised by him. Tables 4.1.1 and 4.1.2 list the decoctions for *kapha* and *pitta* dominant *prameha.*

Table 4.1.1 Decoction to treat *kaphaja* prameha[209]

Medicinal plant	Botanical Name	Medicinal Plant	Botanical Name
Decoction 1		**Decoction 6**	
Katphal	*Myrica esculenta*	*Devdaru*	*Cedrus deodara*
Musta	*Cyperus rotundus*	*Kushta*	*Saussurea costus*
Lodhra	*Symplocos recemosa*	*Aguru*	*Aquilaria malaccensis roxb*
Haritaki	*Terminalia chebula*	*Chandana*	*Santalum album Linn*
Decoction 2		**Decoction7**	
Patha	*Cissampelos pareira*	*Daruharidra*	*Berberis aristata*
Vidanga	*Emblia ribes*	*Agnimantha*	*Premna integrifolia*
Arjun	*Terminalia arjuna*	*Trifala*	*Terminalia chebula,*

			Terminalia belerica, and Phyllanthus emblica
Decoction 3		Patha	*Cissampelos pareira*
Haridra	*Curcuma longa*	**Decoction 8**	
Daruharidra	*Berberis aristata*	*Patha*	*Cissampelos pareira*
Tagar	*Cassia tora Linn*	*Murva*	*Marsdenia tenacissima*
Vidanga	*Emblia ribes*	*Gokshur*	*Tribulus terestris*
Decoction 4		**Decoction 9**	
Kadamba	*Anthocephalus chinesis*	*Yavani*	*Carium copticum Benth Hook*
Sala	*Shorea robusta Geartn*	*Ushira*	Vetiveria Zizanioides
Arjun	*Terminalia arjuna*	*Haritaki*	*Terminalia chebula*
Yavani	*Carium copticum Benth Hook*	*Guduchi*	*Tinospora cordipholia*
Decoction 5		**Decoction 10**	
Daruharidra	*Berberis aristata*	*Chavya*	*Piper chaba Hunter*
Vidanga	*Emblia ribes*	*Haritaki*	*Terminalia chebula*
Khadira	*Acasia catechu wild*	*Chitrak*	*Plumbago zeylanica*
Dhava	*Anogeissus latifolia*	*Saptaparna*	*Alstonia scholaris*
Chandan	*Santalum album Linn*		

Table 4.1.2 Decoction to treat *pittaja* prameha [201]

Medicinal plant	Botanical Name	Medicinal Plant	Botanical Name
Decoction 1		**Decoction 6**	
Ushir	*Vetiveria Zizanioides*	*Nimba*	*Azadirachta indica*
Lodra	*Symplocos recemosa*	*Arjun*	*Terminalia arjuna*
Arjun	*Terminalia arjuna*	*Guduchi*	*Tinospora cordifolia*
Chandan	*Terminalia arjuna Linn*	*Haridra*	*Curcuma longa*
		Utpala	*Nymphaea stellata*
Decoction 2		**Decoction7**	
Ushir	*Vetiveria Zizanioides*	*Shirish*	*Albizia lebbek*
Musta	*Cyperus rotundus*	*Sarja*	*Premna Integrifolia*

Amaltas	*Charantia trifolia*	*Arjun*	*Terminalia arjuna*
Abhaya	*Terminalia chebula*	*Nagakeshar*	*Mesua ferrea*
Decoction 3		**Decoction 8**	
Patala	*Cydonea oblonga*	*Priyangu*	*Aglaia elaeagnoidea*
Nimba	*Azadirachta indica*	*Kamal*	*Nelumbo nucifera*
Amalaki	*Phyllanthus emblica*	*utpala*	*Nymphaea stellata*
Guduchi	*Tinospora cordifolia*	*Palash*	*Tribulus terestris*
Decoction 4		**Decoction 9**	
Musta	*Cyprus rotundus*	*Ashvatha*	*Ficus religiosa*
Haritaki	*Terminalia chebula*	*Patha*	*Cissampelos pareira*
Padmaka	*Prunus cerasoides*	*Asan*	*Pterocarpus marsupium*
Kutaja	*Holarrhena antidysentrica*	*Vetasa*	*Salix tetrasperma*
Decoction 5		**Decoction 10**	
Lodhra	*Symplocos recemosa*	*Daruharidra*	*Berberis aristata*
Hriber	*Coleus vettiveroides*	*Utpala*	*Nymphaea stellata*
Kaliyak	*Coscinium feneststum*	*Musta*	*Cyprus rotundus*
Dhataki	*Woodfordia floribunda*		

Sushruta has described the decoction of combination of medicinal plants as per the twenty types of prameha as follows:

Table 4.1.3 Decoctions for twenty types of *prameh*a as per Sushruta [200]

Formulations	Botanical Names	Formulations	Botanical Names
Kaphaja Prameha		***Pittaja Prameha***	
1.Udaka Meha		*1.Kshar Meha*	
Parijat	*Nycthanthus arbor-tristis*	*Trifala*	*Terminalia chebula, Terminalia belerica, and Phyllanthus emblica*
2.Ikshuwalika Meha		*2.Kala Meha*	
Vaijayanti	*Premna serratifolia*	*Nyagrodhadi*	*Ficus bengalensis and other Ficus species*
3.Sandra Meha		*3.Neela Meha*	
Sapta parna	*Alstonia scholaris*	*Salasaradi/*	*Shorea robusta*

		ashwatha	Ficus religiosa
4. Sura Meha		4. Haridra Meha	
Nimba	Azadirachta indica	Rajavruksha	Cassia fistula
5.Pishta Meha		5.Manjitha Meha	
Haridra Daruharidra	Curcuma longa Berberis aristata	Manjishtha, Chandan	Rubia cordifolia Santallum album
6.Shukra Meha		6. Rakta Meha	
Durva, shaival, plava, hatha, Karanja, Kaseruk, Kakubha, chandan	Cynodon dactylon Alge, Eichhornia, Cyperus scariosus, Millettia pinnata, Trapa natans, Terminalia arjuna Santallum album,	Guduchi, Tinduka Kashmarya, khajur	Tinospora cordifolia, Strychnos nux-vomica Gmelina arborea Phoenix dactylifera
		Vataja Prameha	
7.SikataMeha		1.Vasa Meha	
Chitrak	Plumbago zeylanica	Agnimantha/ Shishapa	Gmelina arborea Dalbergia sissoo
8.Shanairmeha		2.Sarpi Meha	
khadira	Acacia catechu	Kushtha, kutaja patha, hingu, katurohini, guduchi, chitrak	Saussurea lappa, Holarrhena antidysenterica, Cissampelos parietal, Ferula assa-foetida, Picrorhiza kurroa, Tinospora cordifolia, Plumbago zeylanica
9. Lavana meha		3.Hasti Meha	
Patha Aguru Haridra	Cissampelos pareira Aquilaria Malaccensis Curcuma longa	Tinduka, kapitha, shirish, palash, patha,	Strychnos nux-vomica, Feronia linonia, Albizia lebbek, Butea frundosa Cissampelos parietal,

		Murva, dusparsha	*Marsdenia tenacissima, Fagonia cretica*
10. Fenameha		*4.kshoudra Meha*	
Trifala *Aragwadh* *Mrudwika*	*Terminalia chebula, Terminalia belerica, &Phyllanthus emblica,* *Cassia fistula,* *vitis vinifera*	*Khadir,* *kramuka*	*Acasia catechu,* *Areca catechu*

Sushruta has described therapy with *Shilajit* (Black bitumen) for *madhumeha* patients in a separate chapter (Su chi 13)[201]. Good quality of *shilajit* is procured and triturated with decoction of *salsaradi* group of plants and given to the patient in the morning with the decoction of same group of plants. Additionally use of *suvarna makshik* (chalcopyrite; $CuFeS_2$) and *roupya makshik* (Marcasite; FeS_2) also has been mentioned[202-206].
Vagbhata has advised as per the doshik dominance

Table 4.1.4 Decoction from *Ashtang Hridaya samhita* [81]

Kapha Prameha	**Botanical Name**	***Pittaja prameha***	**Botanical Name**
Rodhra *Abhaya* *Toyada* *Katphal*	*Symplocos racemosa* *Terminalia chebula* *Cyprus rotundus* *Myrica esculenta*	*Ushir* *Rodhra* *Arjun* *Chandan*	*Vetiveria zizanioides* *Symplocos racemosa* *Terminalia arjuna* *Terminalia arjuna*
Patha *Vidang* *Arjun* *Dhanva*	*Cissampelos parietal* *Emblia ribes* *Terminalia arjuna* *Neolamarckia cadamba*	*Patol* *Nimba* *Amalaka* *Amruta*	*Trichosanthes Dioica* *Azadirachta indica* *Phyllanthus emblica* *Tinospora cordifolia*
Gayatri *Darvi* *Krumihrut* *Dhav*	*Acacia catechu* *Berberis aristata* *Emblia ribes* *Anogeissus latifolia*	*Rodhra* *Kaliyak* *Dhataki*	*Symplocos racemosa* *Coscinium feneststum* *Woodfordia floribunda.*

Bhela[84] *and Harita*[85] were contemporaries of Charaka; however they have not recommended decoctions as per **doshik** dominance but as per twenty types of *prameha.* Harita has recommended *Dhava* (*Anogeissus latifolia)* and *Arjuna* (*Terminalia arjuna)* more frequently whereas Bhela has recommended *yavanna* (use of barley) frequently in diet and use of sugar in *pittaja prameha* subtypes. *Bhavprakash*[83] *and Yogaratnakar*[41] have compiled decoctions both as per *doshik* dominance and according to twenty types. Additionally *Yogratnakar* has advised *Ashwagandhapak, drakshapak, poogapak and Lodhrasava.* Furthermore, he has acclaimed fourteen *rasoushadhi* (herbominaral medicines) including *parad* (Mercury), *gandhak* (Sulphur), *suvarnamakshik* (Chalcopyrite), *loha* (Iron), *abharak* (Mica), *suvarna* (Gold), *rajat* (silver), *nag* (Lead), *vanga* (Tin), *shilajit* (Black bitumen), and *kharper* (Zinc).

Bhaishajya Ratnawali [42] (Compendium of formulations) has described various combinations of herbal and herbominaral medicines and dosage forms for the disease. The frequently used medicinal plants for diabetes are viz. *harda (Terminalia chebula), behada (Terminalia belerica), amalaki (Phyllanthus emblica), haridra (Curcuma longa), musta (Cyperus rotundus), vidanga (Emblia ribes), daruharidra (Berberis aristata), Arjun (Terminalia arjuna), devdaru (Cedrus deodara),* and *guduchi (Tinospora cordifolia). Pramehaghna* (antidiabetic) properties of these plants are believed to reverse the pathogenesis of the disease. Ayurvedic Dravyaguna rationale is given in following tables:

Table 4.1.5 Ayurvedic Dravyaguna rationale 1

	Amalaki [217]	*Haritaki* [218]	*Bibhitak* [219]	*Haridra* [220]	*Mausta*[221]
Botanical Name	*Phyllanthus emblica*	*Terminalia chebula*	*Terminalia belerica*	*Curcuma longa*	*Cyerus rotundus*
गुण	लघु रूक्ष	लघु रूक्ष	लघु रूक्ष	लघु रूक्ष	लघु रूक्ष
रस	अम्ल पंचरस लवणावर्जित	कषाय पंचरस लवणावर्जित	कषाय	तिक्त मधूर	तिक्त कटु कषाय
वीर्य	शीत	उष्ण	उष्ण	उष्ण	शीत
विपाक	मधुर	मधुर	मधुर	कटु	कटु
प्रभाव	रसायन	मेध्य रसायन	....	रसायन	....
दोषघ्नता	त्रिदोषघ्न	त्रिदोषघ्न	कफवात	कफपित्त	पित्तकफ
धातुकार्य	सप्तधातु	सप्तधातु	सप्तधातु	सप्तधातु	रस मज्जा
व्याधिकार्य	रक्तपित्त प्रमेह दाह शोफ	श्वास कास प्रमेह अर्श मुत्रकृच्छ व्रण	श्वास कास नेत्र्य केश्य स्वर्य तृट्	वर्ण्य त्वच्य मेह शोथ व्रण विष अस्र	दीपन पाचन ग्राही ज्वर अरूचि

		यकृत व्याधि विषमज्वर चक्षु		रोग	जन्तुजित्

Table 4.1.6 Ayurvedic Dravyaguna rationale 2

	Daruharidra [222]	*Arjuna* [223]	*Devdaru* [224]	*Guduchi* [225]	*Vidanga* [226]
Botanical name	*Berberis aristata*	*Terminalia arjuna*	*Cedrus deodara*	*Tinospora cordifolia*	*Emblia ribes*
गुण	लघु रूक्ष तीक्ष्ण	लघु रूक्ष	लघ स्निग्ध	लघु स्निग्ध	लघु रूक्ष
रस	कटू	कषाय	तिक्त	तिक्त मधूर	कटु
वीर्य	उष्ण	शीत	उष्ण	उष्ण	उष्ण
विपाक	कटू	कटूविष	कटू	कटु	कटु
प्रभाव	………	हृद्य रसायन	………..	रसायन	कृमिघ्न
दोषघ्नता	कफवात	कफपित्त	कफवात	कफपित्त	कफवात
धातुकार्य	मेद मांस रक्त	मांस रक्त मेद	मेद	सप्तधातु	
व्याधिकार्य	प्रमेह दाह शोफ कण्डू व्रण कर्ण नेत्र मुखोद्भूत रूजा	प्रमेह व्रण क्षतक्षय विष अस्र मेद	आम ज्वर शोथ प्रमेह श्वास कास कण्डू विबंध	वर्ण्य त्वच्य मेह शोथ व्रण विष अस्र रोग	वह्निकर शूल आध्मान उदर कृमि वातविबंध

Kashay rasa (Astringent taste), katuvipak (Pungent after effects) and ruksha guna (dryness) ameliorate aggravated and vitiated *kapha dosha* and at the same time reduce *dravatwa* of *kapha* (over hydration*)* and increased *abaddhatwa* of *meda* (looseness of adipose tissue) thereby correcting the metabolism of *medovahasrotas*. *Kashay rasa, sheeta veerya* reduce vitiated pitta thereby burning sensation and inflammatory changes. *Kashay rasa;* made up of Earth and Air elements; with *ruksha guna* absorbs secretions (*upashoshan*) such as wound secretion, increased urination *(Bahumutrata)* and bloody discharge (*raktastanbhan*)[227]. *Kashay rasa* and *ruksha guna* have capacity to hold the peristalsis thereby reducing intestinal motility disorders (e.g. *Atisar/pravahika*) and gastric emptying-time, additionally contributing to good digestion. The association of astringency of flavonoids and phenolic acids with gut health has been reported [228].

In case of *madhumeha, vata dosha* dominates over *kapha dosha;* as a result, *madhura-vipaki and bruhaniya (muscle strengthening) dravyas* are required to be introduced in the management to pacify *vata dosha* [229].

Diverse models of rats and mice like Streptozotocine-induced diabetes mellitus (STZ-DM), alloxan-induced diabetes mellitus (AX-DM), special diabetic strains, *in-vivo* models for liver and kidney changes as well as endothelial function etc. have been used for investigations by researchers. Varying experimental conditions, methods, various extracts of plants have been studied to examine the antidiabetic potential of the plants. Table 4.1.7 summarizes the various plants, the antidiabetic activity and possible mechanism in different experimental models.

Table 4.1.7 Antidiabetic potential of various plants

Plants	Activity	Models
Harda (Terminalia chebula)	Antidiabetic[230] Antioxidant[231] Hepatoprotective[232]	STZ DM rats invitro C57/BL6 Mice
Behada (Terminalia belerica)	Antidiabetic[233] Antioxidant [234] Antiobesity and metabolic disorder [235]	AXN DM Rat Rat mice
Amalaki(Phyllanthus emblica)	Antidiabetic [236] Antidyslipidemic[237] Hepatoprotective[238] Immunomodulatory[239] Endothelial dysfunction & Antioxidant[240]	*In-vivo* and *in-silico* STZ DM rats Rats REVIEW/mice Clinical, patients with metabolic syndrome
Haridra (Curcuma longa)	Anti-inflammatory[241] Antioxidant[242] Antidiabetic[243] Antidyslipidemic[244]	Review In-vitro KK-Ay mice Rats
Musta (Cyperus rotundus)	Antidiabetic[245] Antioxidant[246] Free radical scavenging[247]	Alloxan DM Rats In-vitro *in-vitro*

	Decrease AGE[248] Neuroprotective[249]	In-vitro Neuroblastoma (SH-SY5Y cells)
Vidanga (Emblia ribes)	Antidiabetic[250] Antioxidant[251]	Alloxan DM rats *In-vitro*
Daruharidra (Berberis aristata)	Antihyperglycemic[252] Hypolipidemic[253] Antiosteoporotic[254] Antioxidant[255] Antiinflammatory[256] Antidepressant effect[257]	Alloxan DM rats Rats Rat (ovary ectamised) Rats Rabbits Mice
Arjuna (Terminalia arjuna	Improvement in Cardiac muscle strength[258] Anti-inflammatory,[259] Antiplatelet & hypolipidemic [260] Antioxidant[261] Endothelial dysfuction and CHD[262,263]	Clinical/ patients Mice and rats Alloxan diabetic rats Clinical Rats Clinical Clinical/Review
Devdaru (Cedrus deodara)	Antihyperlipidemic [264] Antidiabetic and antioxidant [265] Antiinflammatory[266] Wound healing [267]	Rat Rat Rat Review
Guduchi (Tinospora cordifolia)	Hypoglycemic[268] α glucosidase inhibition[269] Antioxidant [270] Cardioprotective [271]	Rabbits/rats In-vitro Rats Rats

Pathyapathya

Prameha is said to be the disease of *apathyanimittaja* i.e. unhealthy lifestyle (diet and behaviour). Hence, besides removal of cause (which is *apathya ahara and asyasukha)*;

replacement by positive diet (*Pathya ahara)* as well as physical activity (*patha vihar*) hold central importance.

Pathyapathya is the finding of healthy way to get rid of the diseases. *Pathyapathya vibodhak* [272] is the one of the classics devoted to this area. Ayurveda believes deviation from healthy lifestyle will lead to diseases and withdrawing from unhealthy diet and behaviour will regain the health. *Vaidya Lolimbraja* in his *Vaidya Jeevan Samhita*[273]*,* expressed the importance of *Pathya Ahara* (wholesome food) by stating that if a patient consumes wholesome food then there is no need of medicine and if a patient continuously consumes unwholesome food, then also there is no need of medicine as it will not be effective .Fig 4.1.2 gives the importance of recommended diet and behaviour.

पथ्येसति गदार्तस्य किमौषध निषेवणैः।
पथ्येऽसति गदार्तस्य किमौषध निषेवणैः।। वैद्यजीवन

Fig 4.1.2 Importance of pathyapathya

Brihattrayi and Laghuttrayi have described healthy diet and behaviour for *prameha* and *madhumeha.*Charaka (600 BC) has identified diverse variety of rice as a causative factor of *Prameha* and recommended various diet items prepared from *yava* (Barley). *Bhrushta (Bharjit) yava* (roasted barley), *shulya mansa* (Tandur) etc . Use of *mudga* (green gram) and *Amalaki* (gooseberry) are also advised to consume in daily diet. *Udvartana* i.e. body massage with herbal powder has also been recommended for reducing excess water, fat accumulated under the skin which helps in tightening of the tissues[274].

Sushruta recommended use of *kapitha* (wood apple) and *marich* (black pepper) in diet [80]. Wood apple or elephant apple is rich in beta carotene, vitamin B, vitamin C, thiamine and riboflavin. *Marich* is well known to be a bio enhancer [275]. Sushruta also had advised to stay with *mriga* (deer) or *gou* (cow). Use of *gomutra* in diet and wandering with cows whole day was recommended; which was possible then. However currently, this particular modality is difficult; however projects on use of *panchgavya* and diabetes can be taken for research. Also, the ‘wandering’ would have ensured considerable amount of walking /physical exercise which is also regarded as one of the pillars of management of diabetes in modern medicine. Fig 4.3 shows that use of roasted meat and *kapitha* and black pepper improves digestion and gut health

अंगारशुल्योपदंशं वा माध्वीकमभीक्ष्णं क्षौद्र कपीत्थ
मरिचानुविध्दानि चास्मै पानभोजनान्युपहरेत्। सु चि 11।6

Fig 4.1.3 Pathya (diet) recommended by Sushruta

Pathyapathya for Prameha has been compiled in Bhavprakash [83] as follows

श्यामाककोद्रवोद्दालगोधूमाश्चणकास्तथा।
आढक्यश्च कुलत्थाश्चपुराणा मेहिनां हिताः।
मेहिनां तिक्तशाकानि जाङ्गला हरिणाण्डजाः।
यवान्नविकृतिर्मुद्गाः शस्यन्ते लिषष्टिकाः॥ {भा.प्र.म.ख.३८/४१-४२}

Fig 4.1.4 Diet as per Bhavmishra

Table 4.1.8 Wholesome foods advised to be consumed

Anna varga	Food items
Shuka Dhanya (Cereals)	Yava (Barley), Godhuma (wheat), Shashtika Shali, jeernashali, kodrava, uddalaka, Shyamaka (variety of rice)
Shimbi Dhanya (Pulses)	Mudga (green gram), Chanaka (Bengal gram), Adhaki(red gram), Kulatha (horse gram).
Shaka varga (Vegetables)	tikthashakas- karavellaka (karela), methika (fenugrek), nimba(neem), patola(parwal), shigru(drum stick)
Phala varga (Fruits)	Jambu(jamun), amalaka (amala), kapitha (wood apple), shrungataka (water chestnut), tinduka (gab, indian persimmon), dadima (pomegranate)
Beeja varga (Seeds)	Kamalbeej (lotus seeds) , utpala, methika (methidana. fenugreek)
Mamsavarga (Meets)	Vishkira mamsa, pratuda, jangalamamsa, harinamamsa, shashaka, kapota, titira, lavakamamsa (types of meat of animals who wander for their food)
Krutanna varga (Man maid)	yavamantha, yavaudana, vatya, saktu, apupa, yusha (various preparation of barley)
Taila varga (Oils)	danti, ingudi, atasi(flax), sarshapa (mustard) Taila

Madya varga (Alcohols)	Purana sura (old)
Udakavarga (Water)	sarodaka, kushodaka, madhudaka (medicated water)
Others:	Madhu(honey), lasuna (garlic), hingu (asafoetida), saindhava (salt)

Ayurvedic properties of some of the dravyas with modern correlates are given in Table 4.1.9.

Table 4.1.9 Some of the dravyas which are commonly recommended are:

Anna dravya	Ayurvedic Properties	Current research /Biological Plausibility	Reference
Yava (Barley)	*guru, ruksha, swadu, shita sara, vrushya, sthairyakara*	beta- glucan soluble fibres. Hypoglycemic	276
Shashtishali (Rice) Njavara	*laghu, snigdha, tridoshaghna, grahi*	High protein and thiamine, riboflavin. Rich in high fibre, Anti-inflammatory, antioxidant	277-279
Goghuma (Wheat)	*guru snigdha, madhura, shita, jivana, vatapittahara, vrushya sandanakara, sthairyakrut*	insoluble fibres, whole wheat flour has a fairly low glycemic index prebiotic effect on the human gut microbiota composition	280
Mudga (Green gram)	*Laghu, snigdha kasaya, svadu, grahi, shita, , medasleshma pitta hara*	Low glycemic index. Rich source of protein and contains tannin and phytic acid which have hypoglycemic effect .	281 -283
Chanak (Bengal gram)	*Laghu,riksha,sheet, vishtambhi, kaphapitta shamak, vatvardhak, mehjit*	Low Glycemic Index, good source of proteins and fiber, isoflavones.	284-287
Kulathha (Dholicos)	*laghu, ushna,tikshna , amla paki, kapha medohara*	ability to reduce hyperglycaemia by slowing down carbohydrate digestion and reduces insulin resistance	288

Madhu (Honey)	*Laghu,ruksha, madhura kasaya anurasa, lekhaniya, medohara*	Scavenges reactive oxygen species, ameliorates oxidative stress & reduces hyperglycaemia. Reduces atherosclerosis	289-291
Haridra (Turmeric)	*laghu ,ruksha, katutikta, ushna, kaphapittahara, mehaghna, rasayan vranaghana,shothaghna*	Antioxidant Anti-inflammatory Antidiabetic Anti-depressant	292
Amalaki (Amala)	*ruksha ,ruksha, pancha rasa yukta (except lavana), shita, tridoshahara, rasayan*	Immunomodulatory Antioxidant,Hypolipidemic Anti-depressant Anti-inflammatory, antidiabetic	293
Jambu (Blackberry)	*guru, ruksha kashay, madhur rasa , sheetaveerya kapha-pittahar, .*	Anti-atherosclerotic activity modulating the gut microbiome in mice. Anti-dyslipidemic Cardioprotective, nephroprotective, Antiobesity and useful in liver steatosis	15
Tikta shak (Veg with pungent taste)	Bitter	Increases appetite, good source of fibers, vitamins, minerals. Have Low glycemic index.	294

Different classics have recommended more or less similar diet items; however down the time line new items have been added. Few articles have been published with current evidence regarding Pathyapathya[295-297]

Bhaishajya Ratnavali [298] additionally have mentioned vegetables like *parwal* (pointed gourd), *karle* (bitter gourd), *shevga* (drum sticks), and *kakdi* (cucumber), and other food items like *umber*(cluster figs), *lasuna* (garlic), *jambhul* (Jamun), *shingada* (water chestnut), *khajur*, (dates), *amalak* (amala), *kapitha* (wood apple), *atasi* (flax seed) also as recommended diet for a diabetic person. All these vegetables are beneficial for diabetic patients by helping digestion, boosting the immunity and controlling the glucose homeostasis.

Following food items are not recommended by the rishis. They are *Gud* (Jaggery), *Dadhi* (curd/yogurt), *Paya* (milk & milk products), *Sura* (Alcohol), *Ghruta* (ghee), *Ikshurasa* (sugarcane juice), *Aanoop manms* (Meat of marshy animals) and *Navanna* (newly harvested grains).

Physical activity: recommendations in the classics:

Ancient seers have given great importance to physical activity in the individual's daily regime (*Dinacharchya*). As diabetes is said to be a life style disorder different types of physical activities have been recommended in the classics. Exercise like *Bahuyudhha* (*kushti*) *Krida* (sports), *Gaja Arohan* (Elephant riding), *Ashwa Arohan* (horse riding), *Padaticharya* (walking), *Shatayojana* (100 miles), *Ruksha udvartan* (application of dry powder on body), *Snan parishek* (bath), *Ratri Jagaran* (reduce the time of sleeping if it is more), *Mrugai saha jeeven* (live with deer or cow), *Salilashaya khanan* (digging a well).

Although diverse types of exercises with different intensity have been advised for diabetic patients; excessive exercise has not been advised by Harita [299] . *Balardha or ardhashakti vyayam* (moderate exercise) i.e exercise up to half of the strength of the person has been advised[300]. Sushruta has advised journeying one hundred *yojanas* (one yojana/ 6 miles approx. per day) on foot as part of the management of frank diabetes (S.Ci.11/12). Studies on exercise have shown positive effect in diabetic patients such as regulation of glucose uptake and on inflammatory processes[301-304].

Charaka has given importance to *Udvartana* (powder massage) and bath. *Ruksha udwartana*, *abhyangam* (oil massage) and baths are recommended as means to tackle *vata* dominance of the disease through skin which is the one of the sites of *vata dosha*. These procedures additionally decrease the over hydration as well as help *mansa medadi dhatu* to be compressed. *Abhyangam* is recommended in daily regime after *vyayam* (exercise) to keep the skin with muscles and fat healthy. Oil massage increases blood flow and eventually, fastens removal of metabolic waste and heals the mind and body from the stresses of daily life. This has been a traditional practice used for neonates till date. Studies have shown that oil massage increases weight and length of preterm neonates[305.306]. A case report by Nabar *et al* has discussed the effect of oil application by a diabetic Ayurvedic physician for the

anagement of his diabetes [307]. Classics have described the benefits of powder massage herein.

उद्वर्तनं कफहरं मेदसः प्रविलायनम्।
स्थिरिकरणां अंगानां त्वक्प्रसादक परम्।।
वा सू 2।15

Fig 4.1.5 Benefits of Dry powder body massage

Massage is done in opposite direction of vellus hair for at least 45 minutes. By massaging dry powder on skin, the skin becomes healthy with glow. Subcutaneous fat reduces leading to the body more compact. Studies on *udvartan* have shown beneficial effect on body weight, BMI, serum lipids, and stress, sleep and quality of life [308-311].

Day time sleep and/or over indulgence in sleep and physical inactivity have not been recommended as they increase *kapha dosha* and *medodhatu*. Many studies using modern scientific methods and procedures provide evidence that sleep deprivation is associated with increased risk of insulin resistance, obesity and diabetes. Sleep deprivation may raise nocturnal catecholamine levels and contribute to cardiovascular disease, and association of sleep deprivation with increased catecholamine and decrease in IL-6 has been reported [312-316].

4.2 Marketed Ayurvedic Antidiabetic Formulations (MAAF): Labeling, Drug Information and Branding[318]

India did not have a computerised system for sale of the Ayurvedic formulations like in the Netherlands and some other countries when the investigator was conducting her study. Many small scale industries are marketing their products without registration. These products are sold across the counter/ OTCs at pharmacies/chemists shops as India did not have stringent regulations. Hence total numbers of formulations was not available to decide the sample size. Ayurvedic drug outlets (*Aushadhi Bhandars*) were approached to purchase the Marketed Antidiabetic Ayurvedic formulations. One hundred and eighty formulations purchased were analysed for Packaging, brand names, dosage forms and ingredients.

- Packaging:

MAAF were packaged using varied packaging materials and forms. .

Plastic bottles, commonly used form of packaging, were in different sizes with inclusions of protecting devices. Out of 96 plastic bottles,93 bottles were sealed with aluminium foil whereas 3 bottles contained plastic discs. The other form of packaging were glass bottles for liquids (n=8), plastic sachets (n=3), paper cartons with plastic bags (n=19) and silver foil bags

(n=5) for powders, and blister strips (n=48) for capsules and tablets. Glass bottles contained plastic cork with metal caps. Silica gel bags to absorb humidity were not included in most of the formulations. MAAFs were in the form of capsules (n=66), tablets (n=65), powders (n=37), liquids (n=8), granules (n=3) and one herbal wooden cup of *Pterocarpus marsupium*. Packaging and dosage forms are shown in figures 4.2.1 to 4.2.3

Figure 4.2.1   Packaging of MAAF: Packaging material and dosage forms

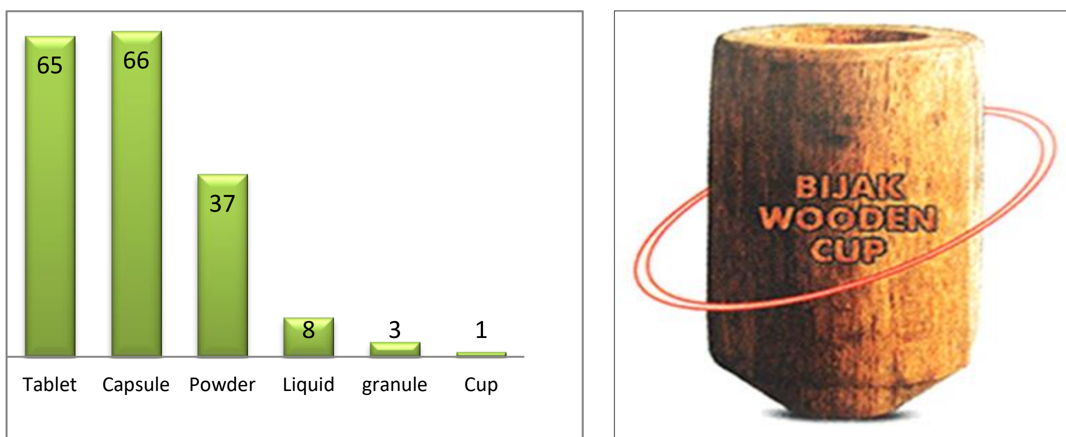


Figure 4.2.2 Dosage forms of the formulation   Figure 4.3.3 Wooden glass of *Pterocarpus*

- Labels:

Detailed study of labels was limited to the first consecutive 100 MAAFs. They were investigated for the compliance to standard format of Drug and Cosmetics Act 1940 and rules 1945 of Ayurvedic Formulations (Table 4.3.1). It was reassuring to find that basic 3 components i.e. manufacturing license number, manufacturing date, and batch number were

printed on the label in all 100 formulations. Information about the identity of manufacturer was available for 88 formulations. However, information regarding indications was displayed on only 30 labels and contraindications were printed on only 5 labels.

Table 4.2.1 Analysis of MAAF labels (n=100) for regulatory compliance.

Sr No	Format component	Was present in : N=
1	Name of and the address of the manufacturer	88
2	Manufacturing license no	100
3	Date of Manufacture	100
4	Batch Number	100
5	Net weight of the formulation	94
6	Classical Formulation : Reference of the formulation	Yes
7	List of ingredients	95
8	Drug quantity in metric units	83
9	Warning (Indication/Contraindication)	5
10	Language of information: Labels and package inserts	Either Hindi or English but not both

The list of ingredients along with the quantity was detailed on the labels of these multi-herbal MAAFs as most of these formulations contained more than one plant. Two to five plants were listed as ingredients in 26 formulations, 6-10 plants in 78 formulations, 11-20 plants in 43 and > 20 plants in 21 formulations.

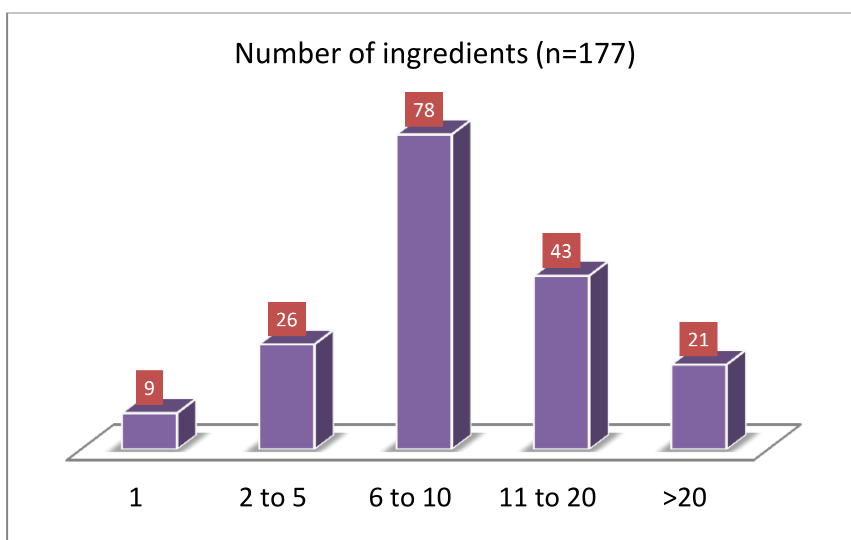


Fig 4.2.4 Classification as per number of ingredients

It was noted that there was a wide variation in the way composition was displayed on these labels. Some of them mentioned the quantity of raw herb per unit dose whereas the formulation was in powder form. While some of them mentioned the quantity of extract used for unit formulation, but it did not relate to the quantity of raw herb from which it was obtained. The daily dose (DD) of *Jambu* ranged from 30 mg to 4.9 gm per day. On detailed scrutiny of the labels, it was observed that the Daily dose of Jambu was 30 mg to 500 mg when extract was used in tablets and capsules. In its powder form, dosage varied from 2gms to 5 gm.

Study of the frequency of various plants and minerals incorporated in MAAFs has demonstrated that *Jambu* (*Eugenia jambolana* Lam) was the most frequently used plant (62.8 % formulations). The next in order of frequency were *Gudmar- Gymnema sylvestre* Linn (55.6%), *Neem –Azadirachta indica* Linn (51.1%), *Karela- Momordica charanta* (47.2%), and *Haridra –Curcuma longa* Linn (47.2%).
Shilajit- Asphaltum (37.2%), *Trivanga bhasma* (12.8%) – (combination of *bhasmas* prepared from *Shuddha Naga* (purified galena), *Shuddha Vanga* (purified tinstone), and *Shuddha Yashada* (purified caramine)), *Yashada* (Zinc) *bhasma* (8.9%), *Vanga* (Tin) *bhasma* (7.8%), and *Abhrak* (mica) *bhasma*- (7.2%) were frequently used minerals in the formulations.

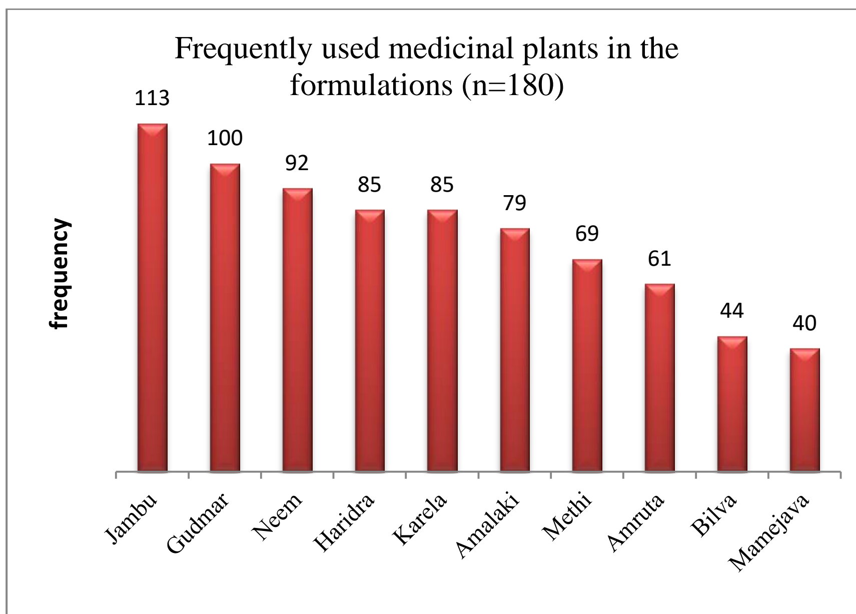


Figure 4.2.5 Number of Formulations containing different plant materials

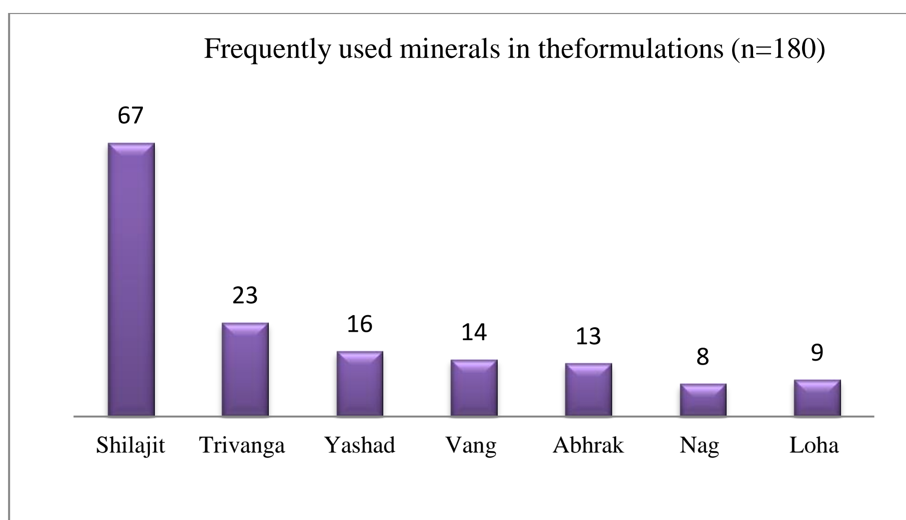


Figure 4.2.6 Number of Formulations containing different minerals/bhasmas

Other information, vital for Ayurvedic medication is *anupan. Anupan* is a substance which is given after the main medication. *Anupan* is supposed to carry the medicine to the minute parts of the body and enhance the function of the medicine given. This information was available for 72 of the 100 formulations examined. Water was recommended as anupan in 50 formulations. Other anupan recommended were *Vijaysar (Pterocarpus marsupium) kwath, Belpatra (Aegel marmelos) swaras,* milk, honey etc. Dosages and dosing schedule (*matra and kala*) were mentioned on all the labels except on 9 formulations. However, in 11 formulations the instruction printed was "as directed by physician". Varied range of dosing schedule was noticed for each category. The maximum and minimum amount for tablets was from 2 to 6 tablets and amount for capsules 2 to 9 capsules per day. For powders it was from 10 gms to 30 gms and for liquids, from 5ml to 120 ml (4 ounce) per day. Timing of administration i.e *Aushadhi Kala* was specified in 32.8% of formulations. The most common recommended timing was before meals. Caution regarding storage-conditions and shelf-life of the formulations was largely missing.

- Package inserts:

A study of the regulation for packaging and labelling of Ayurvedic medicine reveal non mandatory status for providing a package insert along with each of the proprietary Ayurvedic medicinal pack. It was noteworthy that only fifteen of 53 formulations had package inserts. The paper used for package inserts was in different sizes, colors and of different quality. Introductions that explained symptoms and other clinical features of diabetes, product dosage, indication and customer help line were present in 13 out of 15 inserts. Five package inserts provided information about type 2 diabetes,its prevalence, etiology, state- of -the art allopathic

as well as Ayurvedic therapeutic approaches. Precautions regarding hypoglycemic symptoms and titration of dosages were given in 11 inserts. Inserts of four formulations were in both English and Hindi languages. Four inserts had information about contraindication for use for management of Juvenile diabetes. Information about safe use of the formulation during pregnancy and /or lactation was strikingly absent in all the package inserts. Similarly, information about their use in geriatric population was also lacking. Only one package insert complied with WHO guidelines for pharmaceutical product including its contraindication for type 1 diabetes. The information included in that particular insert was available in six Indian languages in addition to one in English.

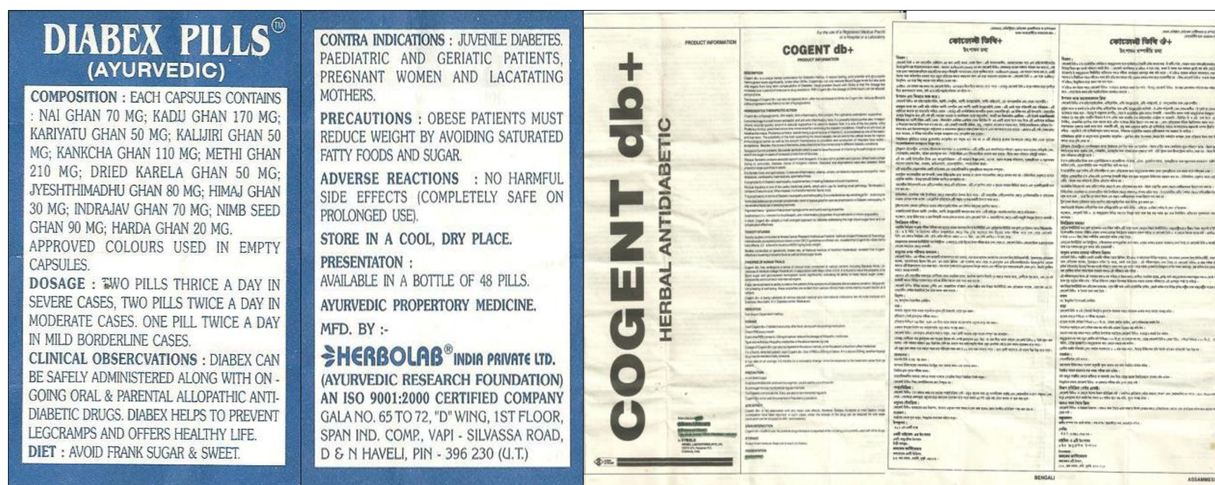


Figure 4.2.7 Example of package inserts

- Brand names:

Brand names of these MAAFs were found to have the following characteristics and were the names were likely to catch the attention of customers:

- Proclaiming antidiabetic activity e.g. Madhumehari, Madhuna, Madhuparasta,
- Mimicking the brand names of conventional antidiabetics e.g. Diabenol, Debnil,
- Enticing by inclusion of the word ‘Sugar’ word e.g. Sugar balance, Sugar knocker,
- Explaining the target site of action e.g Pancreone, Pancare,
- There were some formulations with brand names like Zypter, Ilogen, Mercina, that did not seem to be associated with any function or activity.

None of the labels indicated whether the product name had trade mark registration – a protection provided in India. Some of the brand names appear to reflect that the products are meant to “completely cure diabetes”. This would be an exaggerated claim. There is a need for

the licensing authorities to exercise caution while approving licenses with such brand names. Ayurvedic industry also needs to consider registering their brand names under trademark registration so that different states do not issue licenses for MAAF products with the same brand names. This is not an exhaustive list, and the meanings given for the TM names of the products are the best descriptors as understood by the authors.

Table 4.2.2 - Brand names and Meaning of MAAFs

Name of the formulation	**Meaning**	**Name of the formulation**	**Meaning**
Madhumehari	Adversary of Diabetes	D-Kwit	Diabetes quits
Mehantak	Terminator of diabetes.	Sugar knocker	Knocks out diabetes
Madhuhar	Eliminator of diabetes	Arogyavardhini	Enhancing health
Madhunashini	Destroyer of diabetes	Vasantakusumakar	spring blossoming flowers
Diacare	Taking care of diabetes	Chandraprabha	Aura increases
Gluconil	Eliminating glucose	Prameha gajakeshari	Lion –Elephant analogy

4.3 <u>Drug utilization Studies</u>

4.3.1 *Swadeshi Arogya Mela*: Pilot study in Mumbai [319]

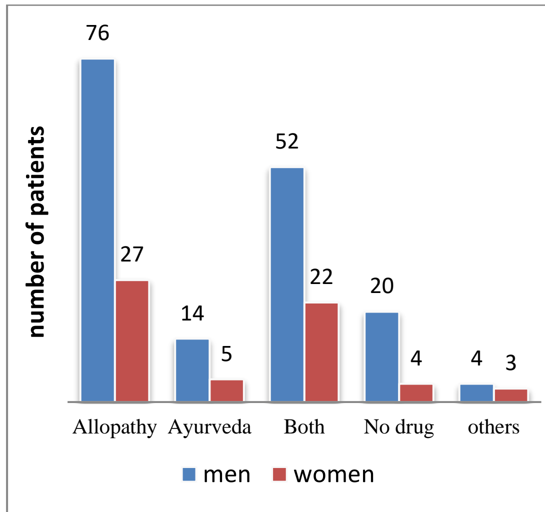
Two hundred and twenty seven diabetic patients (166 men + 61 women), ages ranging from 35 to 75 yrs visited the counter during the four days when the *Swadeshi Arogya mela* was held. Duration of diabetes participants since they had been diagnosed with diabetes varied from 1year to more than 20 years.

The pharmacological antidiabetic management included only allopathic medicines (45.4%), only Ayurvedic (8.4%), concomitant use of both Ayurvedic and Allopathic systems of medicine (32.6%) and others (3 %). A small percentage (10.6%) of the participants reported that they were not taking any drug (figs 4.3.1 and 4.3.2).

Among the oral hypoglycemic agents (OHA) from Allopathic system of medicine, glibenclamide (28.2%) was the most frequently consumed followed by Metformin (23.6%), Insulin (8%) and glimepiride (7.5%).

Forty one percent (41%) of diabetic patients were consuming traditional Ayurvedic medicine. The most common MAAF were *Lokmanya Churna, Madhumehari Dane, Tablet Diabecon,* Capsule *Karnim and* Capsule *Karela*. Besides MAAF, diverse combinations of Ayurvedic medicinal plants viz *Karela, Methi, Jamun, Neem, Awala* also were taken by the patients.

With reference to nonpharmacological management, dietary modifications were followed by 72.7% patients in terms of reduced consumption of sugar and oil. However, diet modified by a dietician or physician was followed by only 16% of cases. Walking was the most commonly practiced physical activity, followed by 72.7% diabetics.



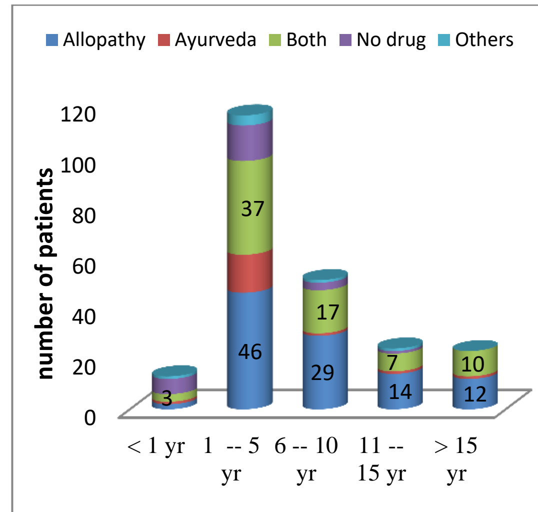


Fig 4.3.1 Type of antidiabetic management As per gender

Fig 4.3.2 Type of Antidiabetic Treatmentas as per duration of diabetes

Fig 4.3.3 shows most common traditional and conventional antidiabetic medicines consumed by visitors

Swadeshi Arogya Mela Memories

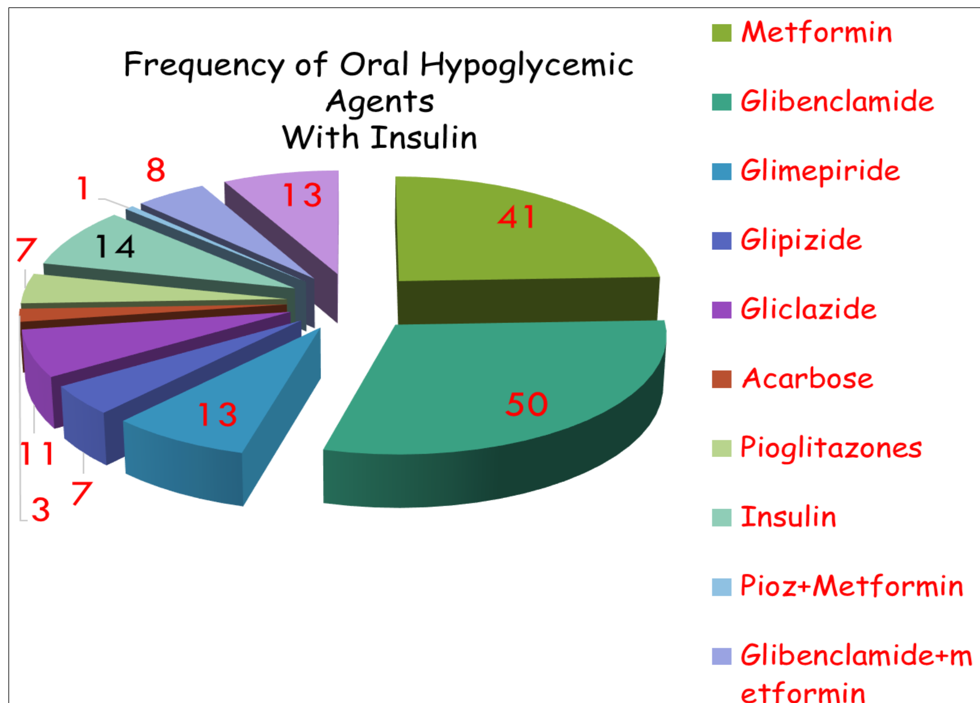
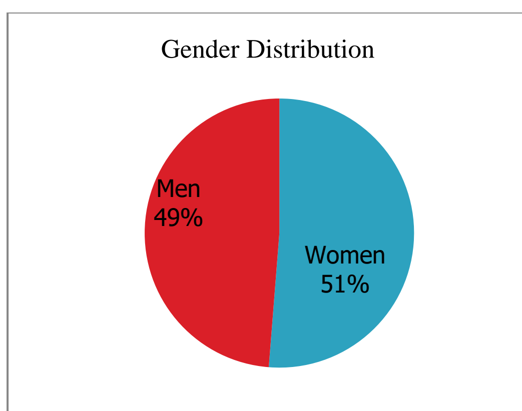


Fig 4.3.4 number of visitors using different Allopathic Oral Anti diabetics, Insulin

4.3.2 Hospital - Based Drug Utilization study

The study on utilization of Ayurvedic Medicines in persons with Type 2 diabetics was conducted in patients attending the Endocrine Department of a tertiary health care hospital, namely Nair Hospital located in central Mumbai.

A total of 279 type 2 diabetic patients (136 men and 143 women) who came for treatment to the outpatients' department over a period of 8 months were interviewed. Their health records were also examined. The percentage of subjects were slightly more (51%) than the percentage of men in this study sample.



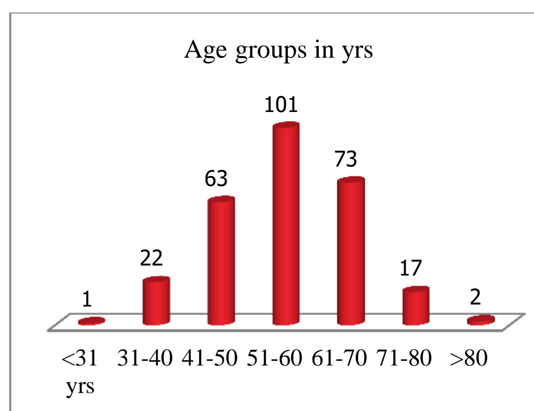
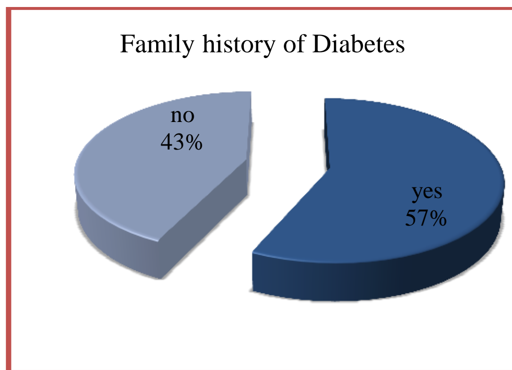


Fig 4.3.5 .Gender distribution of participants   Fig 4.3.6 Participants as per age groups

The age of the participants was in the range of 32 yrs to 88 years of age. Eighty five patients were in the age range of 41 to 70 yrs of age. With reference to education level, 56.3 % patients had completed secondary school but 20.4% of participants were illiterate. Among the participants, 42.7% were t housewives and 22.9% were retired persons. Duration of diabetes was less than 10 years for more than half of the subjects (64.5%). Positive family history of diabetes was present in 57% patients.



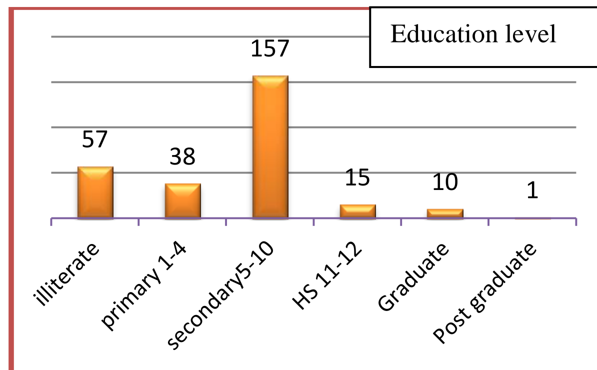
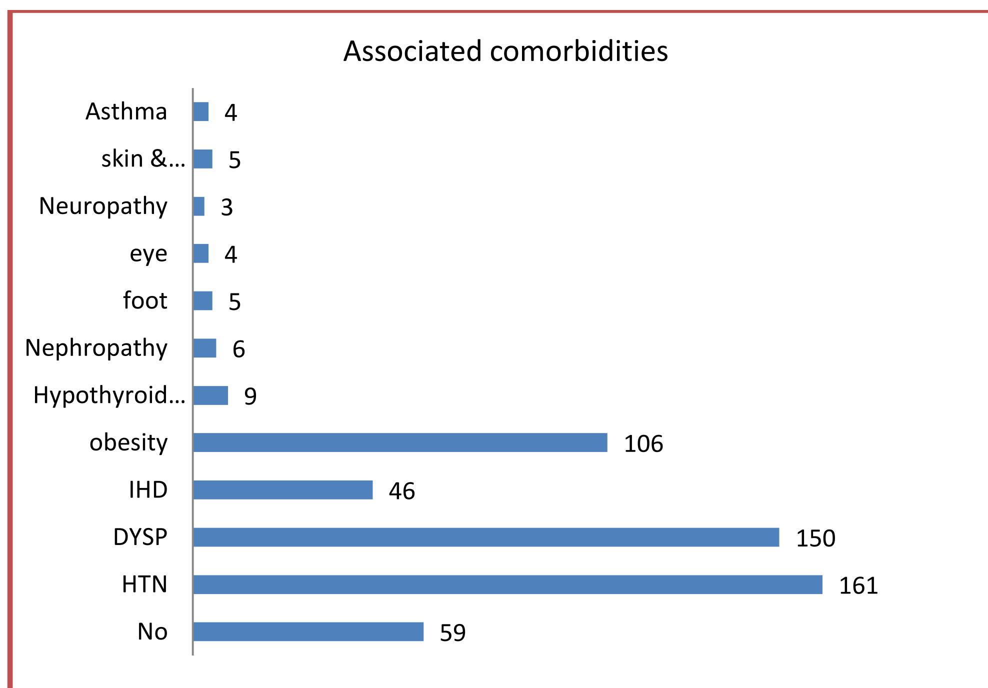


Fig 4.3.7 Family history for diabetes Fig 4.3.8 Classification as per education level

Co-morbid conditions were present in 79% patients, with hypertension being prevalent in 57.7% of the patients followed by dyslipidemia (53.8%). Overall prevalence of overweight +obesity based on the criteria for Asian Indians [320] was very high (77.7 % of participants) . with 61.6% being obese whereas only 16.1% of the participants were overweight.



Eye: Retinopathy; Foot: Diabeteic foot; IHD: Ischemic Heart Disease; DYSP: Dyslipidemia ; HTN: Hypertension; No: No comorbidity

Fig 4.3.9 associated morbidities of participants

Mean values of fasting (FPG) and post prandial glucose (PPG) were 138.3± 52.4 mg% and 184.2 ± 84.7mg% respectively. Blood glucose values were controlled for fifty-one diabetic patients as judged by normal glucose values (fasting <110 mg% and PP < 140 mg %.). However, 190 patients (68.1) had elevated FPG (>110 mg%) and 175 patients (62.7%) had high post prandial glucose values (>140 mg%), indicating that a large proportion of patients had uncontrolled blood glucose. Blood glucose values were not available for ten subjects. Status of glucose control is given in figure 4.3.10.

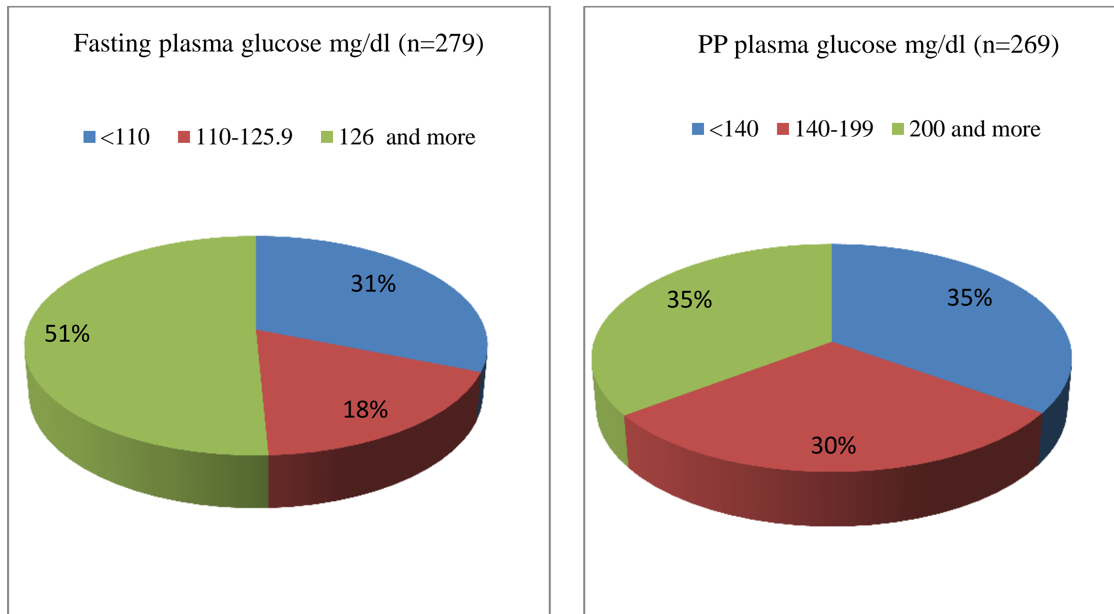


Figure 4.3.10 Status of fasting and post prandial glucose control

Use of Conventional Antidiabetic medicines

Metformin was the most frequently prescribed drug (19.4 %) among the single drug therapies followed by Insulin Injection. Metformin+ Glibenclamide combination was most common (21.2%) combination followed by metformin + glimepiride combination (10%). Only 4% patients were on only insulin injections. Frequency of the most common conventional medicines in 246 patients is described in figure 2. Rest 33 patients have different combinations with 3 to 4 antidiabetic medicines. Voglibose, vildagliptin and pioglitazones were also consumed by one or 2 diabetic patients.

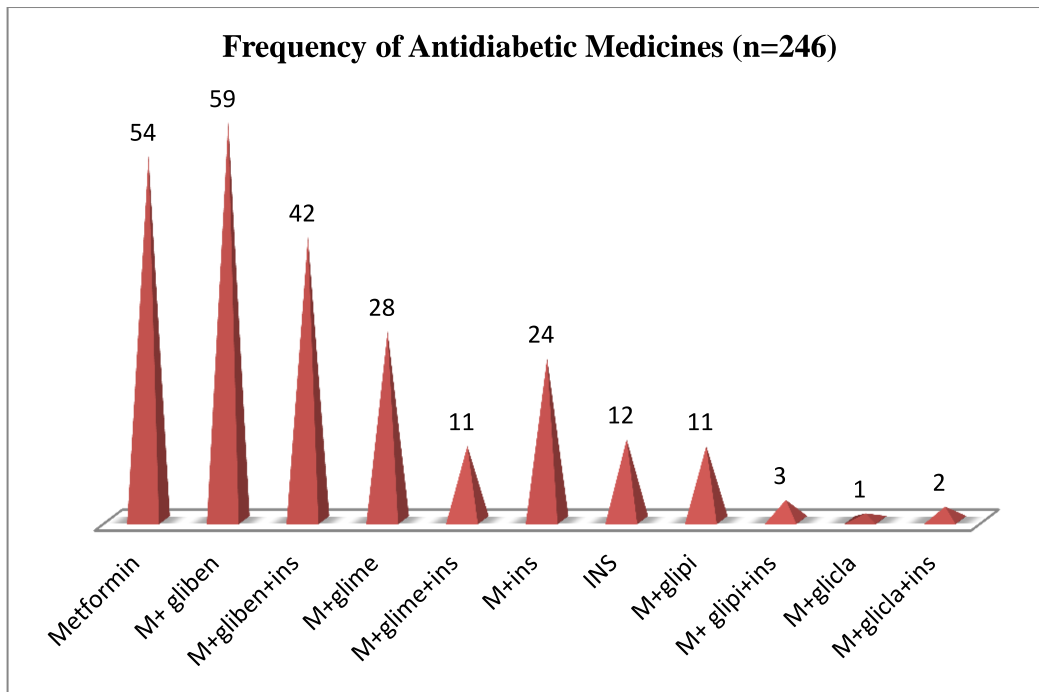


Figure 4.3.11 Frequency of antidiabetic medicines (n=243)

Combination of 2 drugs for the management was more prevalent than single or any other combinations of 3 or 4 drugs. Figure4.3.12 shows frequency of single and multidrug combination

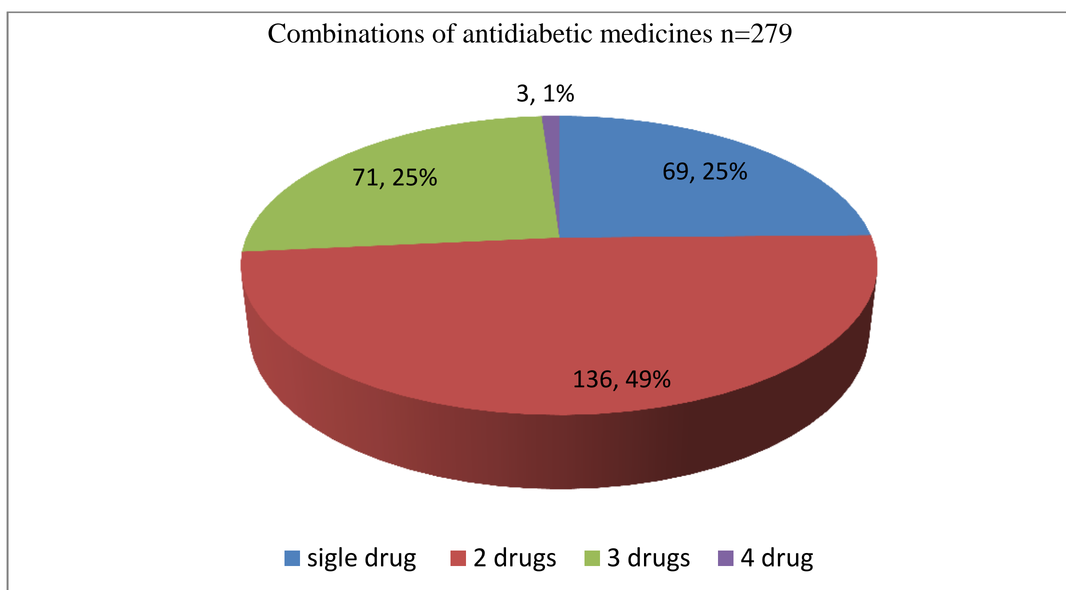


Fig 4.3.12 Percentage of multidrug (antidiabetic) combination

Screening for complications of diabetes:

Hypertension and dyslipidemia were the most frequently associated morbidities. As a part of management protocol of diabetes at the department, patients are instructed to check fasting

and postprandial sugar, total cholesterol, triglycerides, BUN, and S. Creatinine. They are also advised to carry out fundoscopy, foot evaluation and take diet advice. Total cholesterol and triglycerides were done by 65.5 % patients, Serum Creatinine and BUN were done by 75.6 % patients and fundoscopy was carried out by 48.8 % patient (of which 45.5% had no diabetic retinopathy and 8 had undergone cataract operation). Six patients gave history of diabetic foot. Three patients had peripheral neuropathy, 28 had no neuropathy and 248 patients did not even investigate for neuropathy.

Life style measures

In our study 272 (97.5%) patients were following the life style measures. Modification in diet as per the advice of dieticien was carried out by 44 (15.8%) diabetic patients, 227 (81.4%) patients preferred the restriction in sugar and oil content in diet only and 8 (2.8%) did not make any change. Walking was preferred physical activity by the patients; however 73 (26%) are not following any specific physical activity for the management of diabetes. Data on physical activity of patients is shown in figure 4.4.13..

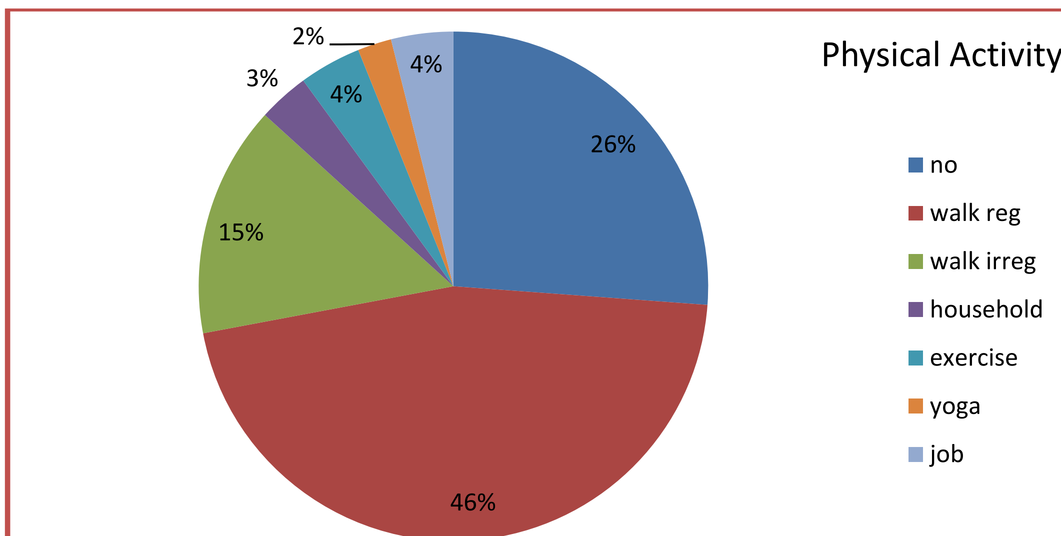
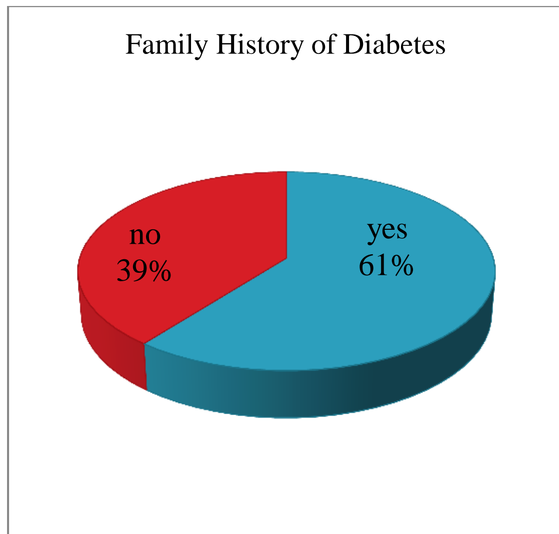


Fig 4.3.13 Various forms of Physical activity and the absence of it

Ayurvedic Medicines users

Only 33 (21 men and 12 women) of 279 diabetic patients were consuming Ayurvedic Medicine concurrently with conventional Antidiabetic medicine for the management of the disease. They were in the age range of 31-80 yrs having duration of diabetes between < 1 and >20 yrs. Positive family history was present in 20 of 33 subjects. More than half were

(22/33) in the age range of 51-70 yrs and one third subjects were having duration of diabetes <5 yrs. Twenty seven patients were obese. More than half had dyslipidemia (19/33) and hypertension (17/33) as co morbidities.



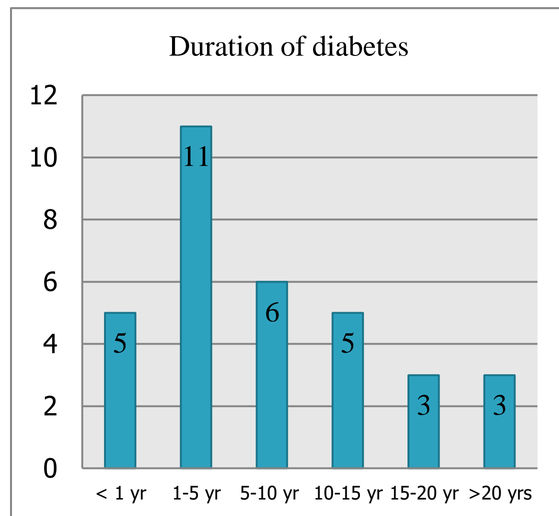


Fig 4.3.14 Family history of diabetes Fig 4.3.15 Classification as per duration of DM

These patients obtained their Ayurvedic medicines mainly from Ayurvedic Aushadhi Bhandars at their convenience; however friends, relatives, kirana (grocery shops), and chemists were also the source of medicine for the patients.

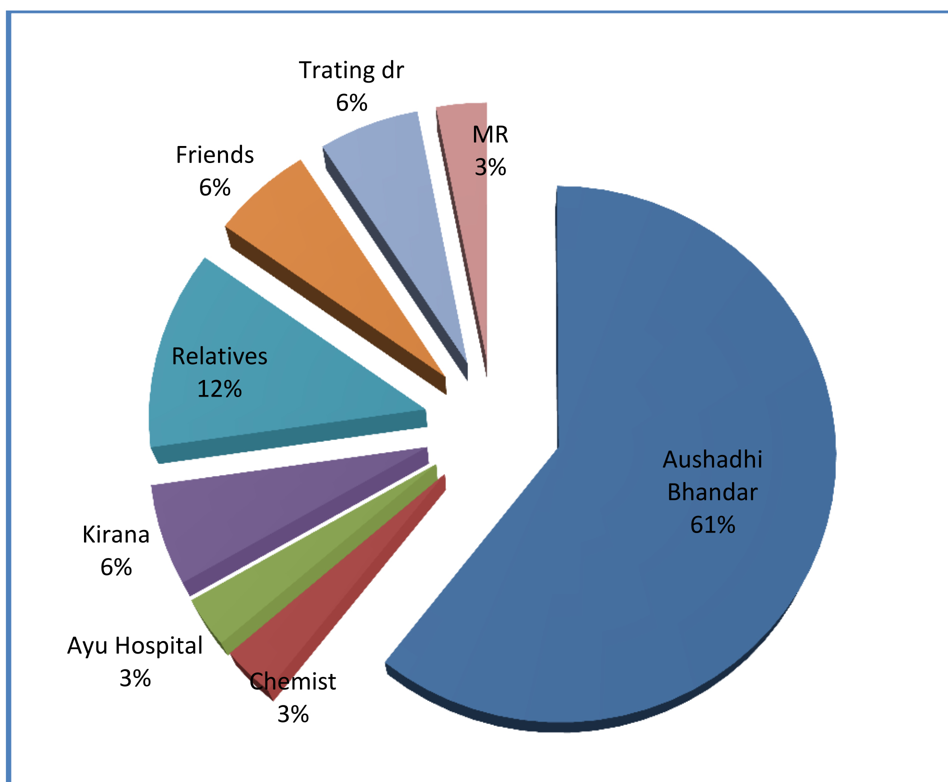


Fig 4.3.16 Places from where medicines are procured

Most of them consumed (21/33) on empty stomach with water. Other schedule of consuming Ayurvedic medicines were as follows: randomly twice a day, before meals, after meals, once in the morning, and only at night.

Reduced blood sugar (13/33) was the commonest benefit of taking Ayurvedic medicines reported. Other benefits viz., reduced the symptoms (8/33), Feeling fresh (10/33) and improved digestion (5/33), Feeling light (3/33), appetite increased (1/33) and health maintenance (3/33) were also reported. Only 3 of 33 reported side effects of the medicines viz, constipation (1), loose motion (1), and foul smell to stool (1). All the patients were affirmative to continue the Ayurvedic Medicines in future; however all the patients tend to consume Allopathic medicines for intercurrent illnesses except 3 of 33 patients who opted for Ayurvedic medicines. The status of glucose control is shown in fig 4.3.17 and 4.3.18 .

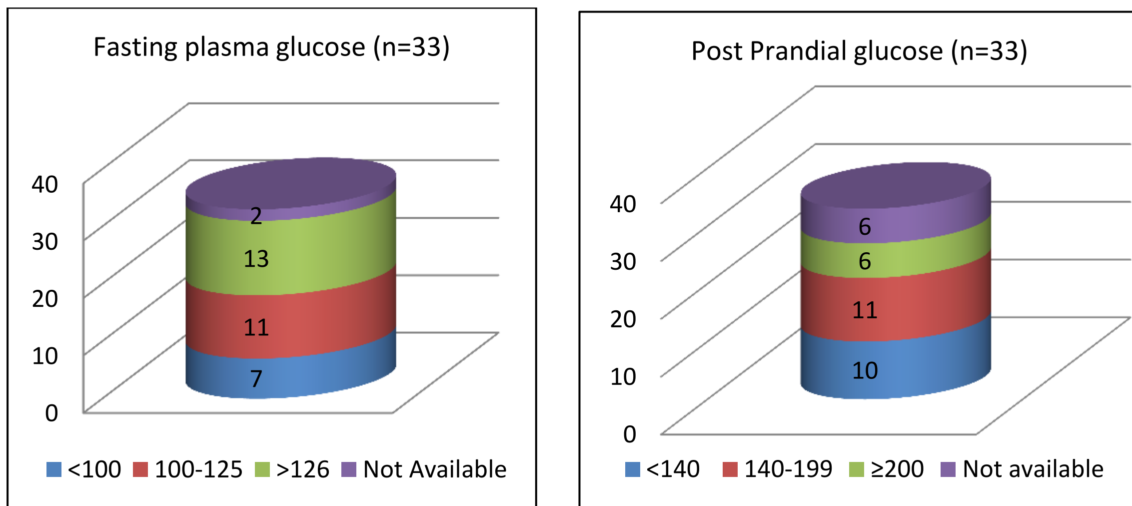


Figure 4.3.17 and 4.3.18 Status of fasting and post prandial glucose control of 33 patients

Thirty one of 33 were following lifestyle measures advised by physician and dietician at the department; even though restricted diet was followed by most of the patients than modified diet suggested by dietician. Walking was the most favoured physical activity by the patients.

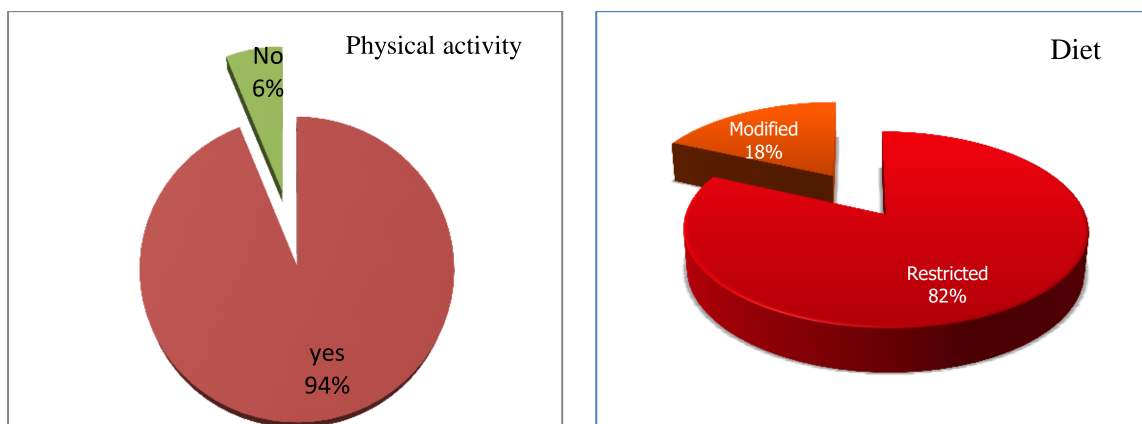


Fig 4.3.19 Status of life style measures (Physical activity and diet)

List of the of Ayurvedic classical medicines, proprietary medicines with their frequency is given in table 4. 3.2 and medicinal plants in table 4.3.3

Table 4.3.1 and Table 4.3.2 List of Ayurvedic medicines and medicinal Plants

List of Ayurvedic medicines	N	List of Ayurvedic medicinal Plants	N
Divya Madhunashini Vati	2	Jamun (Eugenia Jambolana)	7
Yasaka Liquid	3	Methi (*Trigonella foenum-graecum)*	6
Chandraprabha vati	2	Kadu kirait	2
Arogya vardhini vati	1	Karela (Momordica charantia)	5
Nimbadi churna	1	Ajvayan	3
Shilajitwadi Vati	1	Jirak	4
Methi- ajwayan- kadujire- jire	3	Paneer fool	1
Diabetes powder	1		

Benefits:

Reduced blood sugar (13/33) was the commonest benefit of taking Ayurvedic medicines reported. Only 3 of 33 reported side effects of the medicines viz, constipation (1), loose motion (1), and foul smell to stool (1). All the patients were agreed upon to continue the Ayurvedic Medicines in future.

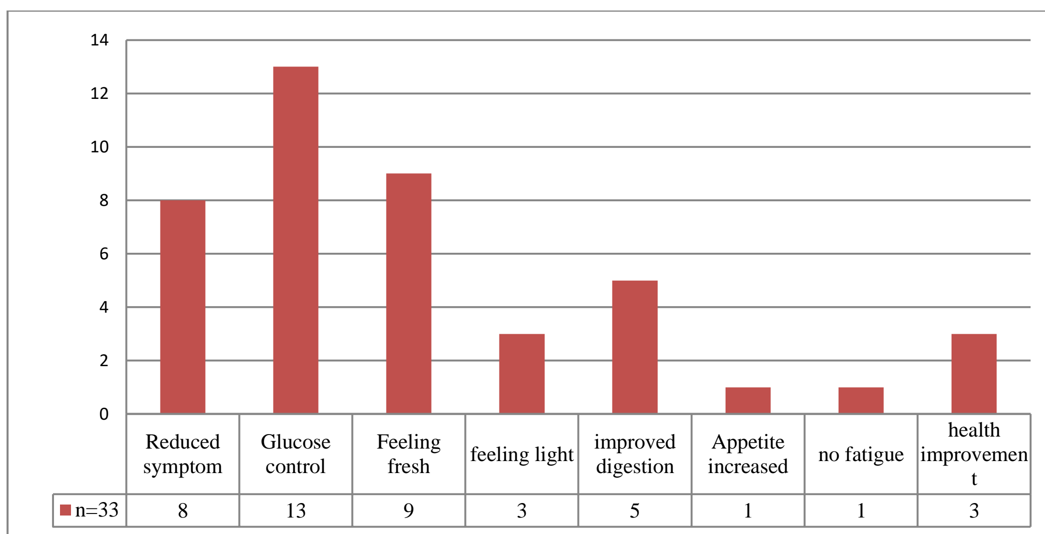


Fig 4.3.20 Patient reported benefits of taking Ayurvedic medicines

4.3.3 Retrospective study of case record forms at FRLHT, Bengaluru

Case record of diabetic patients visiting *Swasthavritta* department were reviewed. During the 3 year – period (December 2016-January 2014), among the 900 diabetics, 461 patients did not come back after baseline. For the remaining 449 patients, follow up was upto 30 months; 65 cases given the followup till 6 months; out of which 8 cases were diagnosed prameha with sthoulya (obesity). Fifty seven patients (23women, 34 men) were as per the protocol selected for the study.

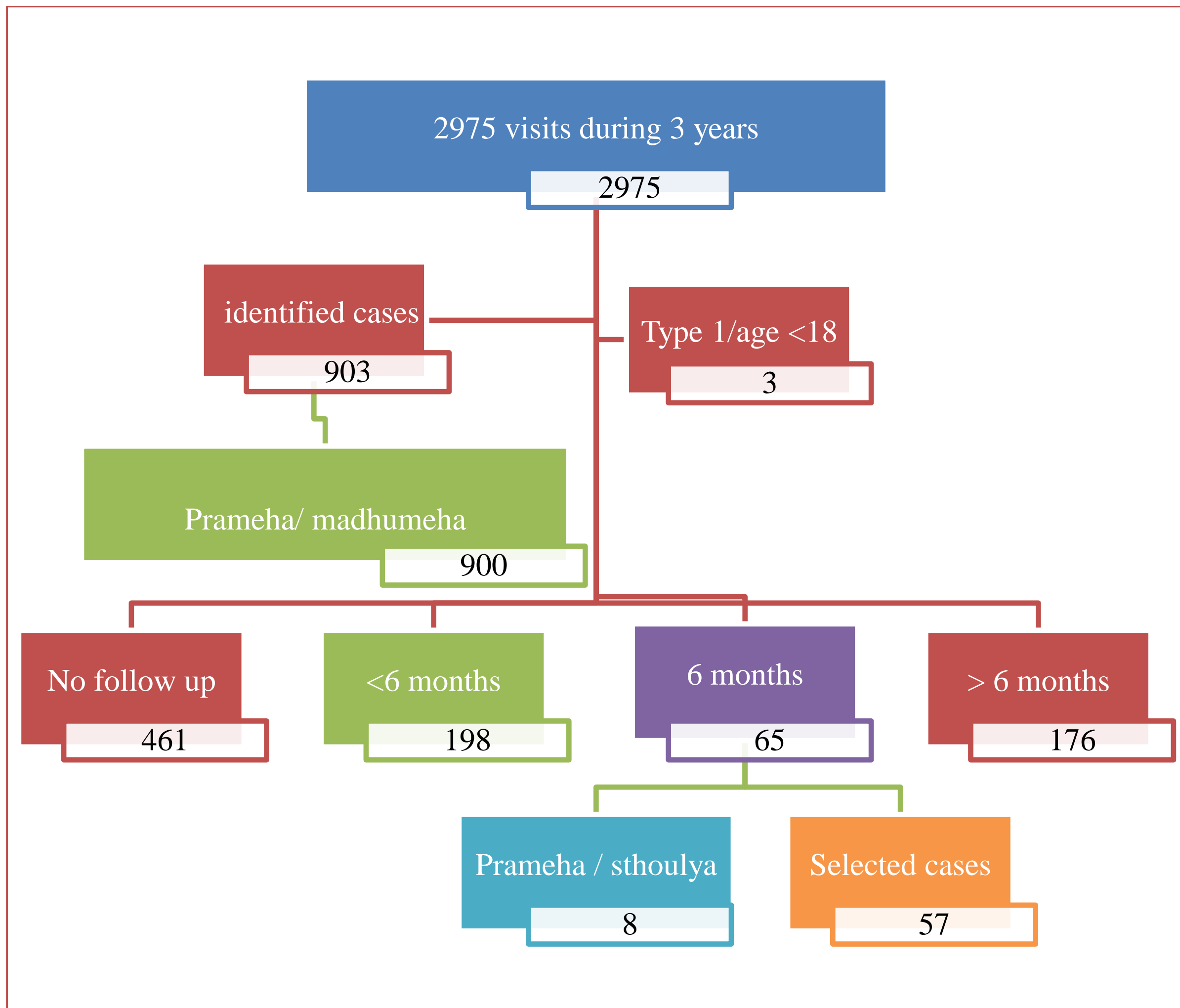


Fig 4.3.21 Flow chart of selecting cases

Positive Family history for diabetes was recorded in 23 patients. Record of written comorbidity was not found in 31 of 57 case records; hypertension being the most prevalent (16/31;52%) followed by dyslipidemia (4/31), neuropathy (4/31), retinopathy (3/31). Presence of diabetic foot and carbuncle were also recorded.

Vasant kusumakar ras was most frequently prescribed (39.3% visits) medicine followed by *Nishaamalaki vati* (37% visits), D-nil capsules (28 %) and Diabecon DS (28%) tablets. Seventy two (72%) patients were already receiving various concurrent conventional antidiabetic medications. Most common two drug combination consumed was Glimepiride-Metformin combination (25%). Among single drugs; Metformin alone (19.5%) glimepiride (17 %), insulin injections (17%), Gliptins (17 %) and Voglibose (12.2 %),were common.

Table 4.3.3 Common Ayurvedic medicines as per visit prescribed .

Number of patients	N=57	N=53	N=57	N=169 visits	
Medicines	**Baseline**	**3 months**	**6 months**	**Total visits**	%
Nisha amalaki tablet	23	19	22	64	37.5
D Nil tablet	18	15	15	48	28
Vasant kusumakar	17	23	28	68	39.8
Diabecon DS tablet	13	16	19	48	28
Hyponidd tablet	7	3	7	17	9.9
Mehnil tablet	6	12	14	32	18.7
Insulan D tablet	6	6	11	27	15.8
Glysicot granules	6	6	4	16	9.4

The use of patented medicines is more than classical formulations-this is an important observation.

The range of baseline fasting and post lunch sugar values was from 77 to 336 mg/dl and 86 to 436 mg/dl respectively. The mean values with SD and SE has been given in the following table.

Table 4.3.4 Mean ± SD and SE of glucose values before and after the treatment (n=57).

	Base		3 Months		6 months	
	FPG	PPPG	FPG	PPPG	FPG	PPPG

Mean	161.7	247.3	134.7	199.0	140.9	203.5
SD	49.32	76.64	39.24	67.84	50.56	64.85
SE	6.84	10.63	5.55	9.59	6.81	8.74
P value					<0.05	<0.005

SD: Standerd Deviation, SE: Standerd Error

No adverse events were found during 6 months of therapy, except for one patient reporting loose motion after *Nisha Kathakadi Kashay* which was then discontinued. In view of 41 of 57 diabetic patients receiving combination of modern antidiabetics with Ayurvedic therapy it is reasonable to suggest that no severe adverse reactions were noted.

Table 4.3.5 Mean ± SD and SE of HbA1c values before and after the treatment (n=57).

	Base	3 months	6 months
Mean	8.735	7.621	7.069
Std. Deviation	1.862	1.861	1.087
Std. Error	0.3062	0.4973	0.3016

There was significant reductions in mean of FBG ($p < 0.05$), PPBG ($p < 0.005$) and HbA1C ($p < 0.005$) after 6 months compared to baseline.

Life style management was not described on case record; however a mention of '*Advised dietary and lifestyle modification*s' was noted.

Though nearly half of the patients did not come back for follow up, Half came back. By reviewing 57 case records directionality of the utilization of Ayurvedic Medicines and the drug effects can be documented. Based on the results new project can be proposed on large population. Fifty seven records showed significant reduction in HbA1C directing possibility of conducting Phase 2 studies for drug discovery.

In this study of case records, Ayurvedic therapy for diabetes was found to be clinically safe as patients did not report nor they discontinued the treatment because of any adverse event. The study shows limited retrievable information and insufficient records**.** Review of records requires adequate planning and use of appropriate data sources.

4.4 Knowledge Attitude and Practice survey

4.4.1 KAP survey of Diabetic patients at integrative clinic of diabetes at MRC KHS

A total of 293 (168 men and 125 women) diabetic patients were interviewed. More than half (57 %) of all patients were men, 66% were in the age range of 47 to 67 yrs of age, 23.5% were illiterate and 8.9 % were post graduate. Around 33% were having business as their occupation. Around half of the subjects (49.1%) were having duration of diabetes less than 5 years. Demographic Data is shown in following figures

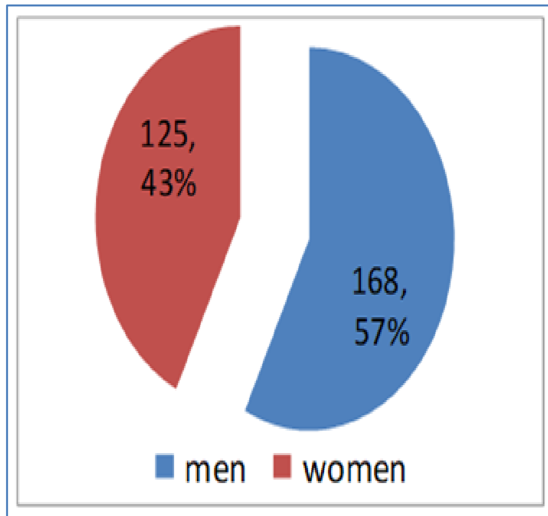


Fig 4.4.1. Gender distribution

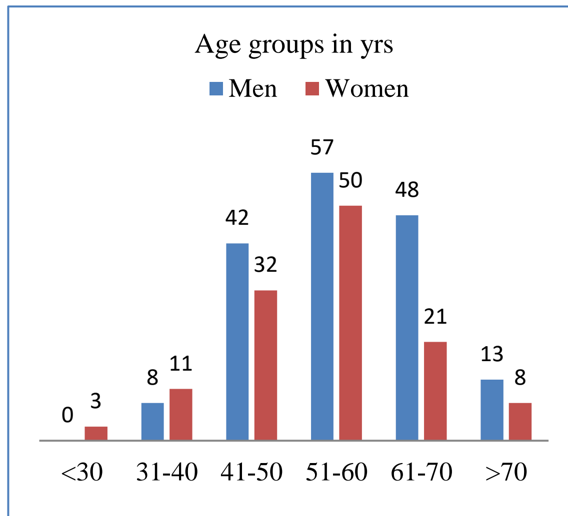


Fig 4.4.2 Age distribution

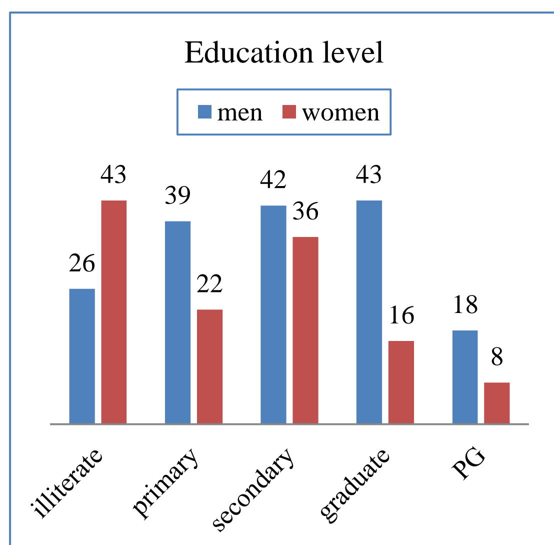


Fig 4.4.3 Classification as per education level

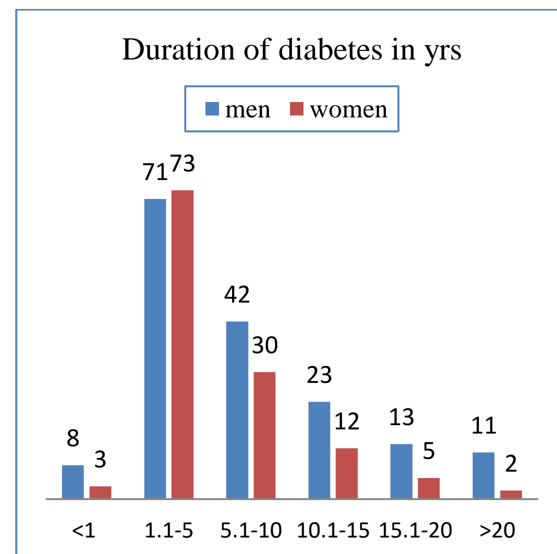


Fig 4.4.4 classification as per duration of DM

Table 4.4.1 Demographic characteristics of diabetic patients as per gender (n = 293)

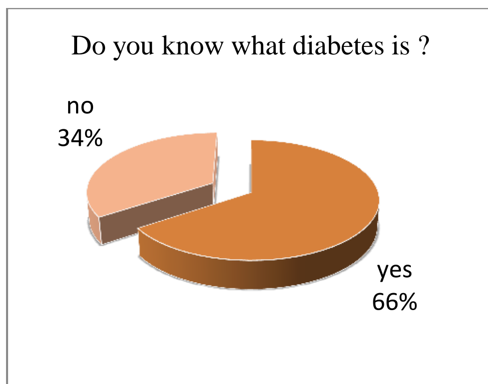
Characteristics	Men N (%)	Women N (%)	Total N (%)	P value
N =	168(57)	125(43)	293(100)	
Age				
mean± SD	56.5±9.9	53.8±10.2	55.4±10.1	0.02
27-37	4(2.4)	6(4.8)	10(3.4)	
38-47	28(16.7)	25(20)	53(18)	
48-57	57(33.9)	49(39.2)	106(36.1)	
58-67	54(32.1)	33(26.4)	87(29.7)	
68-77	25(14.9)	12(9.6)	37(12.6)	
Education				
illiterate	26(15.5)	43(34.4)	69(55.2)	0.3195
primary	39(23.2)	22(17.6)	61(20.8)	
secondary	42(25)	36(28.8)	78(624)	
graduate	43(25.6)	16(12.8)	59(20.1)	
PG	18(10.7)	8(6.4)	26(8.9)	
occupation				
Home maker	0(0)	90(72)	90(30.7)	0.700
service	40(23.8)	3(2.4)	43(14.7)	
business	70(41.7)	27(21.6)	97(33.1)	
retired	52(31)	3(2.4)	55(18.8)	
others	6(3.6)	2(1.6)	8(2.7)	
Duration of DM				
<1	8(4.8)	3(2.4)	11(3.8)	0.644
1.1-5	71(42.2)	73(58.4)	144(49.2)	
5.1-10	42(25)	30(24)	72(24.6)	
10.1-15	23(13.7)	12(9.6)	35(12)	
15.1-20	13(7.7)	5(4)	18(6.1)	
>20	11(6.5)	2(1.6)	13(4.4)	

Knowledge

Thirty four (34%) diabetic patients did not know what the nature of the diseases is. However 74% knew polyurea is the symptom of the diabetes followed by delayed wound healing.

Significant association of knowledge with education (p=0.005), occupation (p=0.001 and) and gender (0.003) was observed.

Regarding the causes of diabetes hereditary as a cause of diabetes was significantly associated with education (p=0.01) and occupation (p=0.02). Interestingly there was no significant association of education with knowledge of complications; however retinopathy was the most frequently opted complication (74%) followed by cardiovascular diseases (CVD-69%).



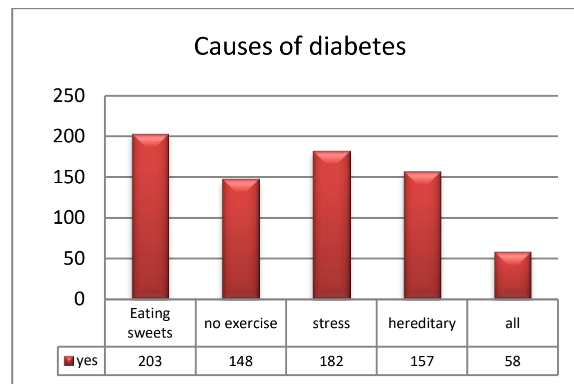


Fig 4.4.5 Do you know what diabetes is? Fig 4.4.6 What are the causes of diabetes?

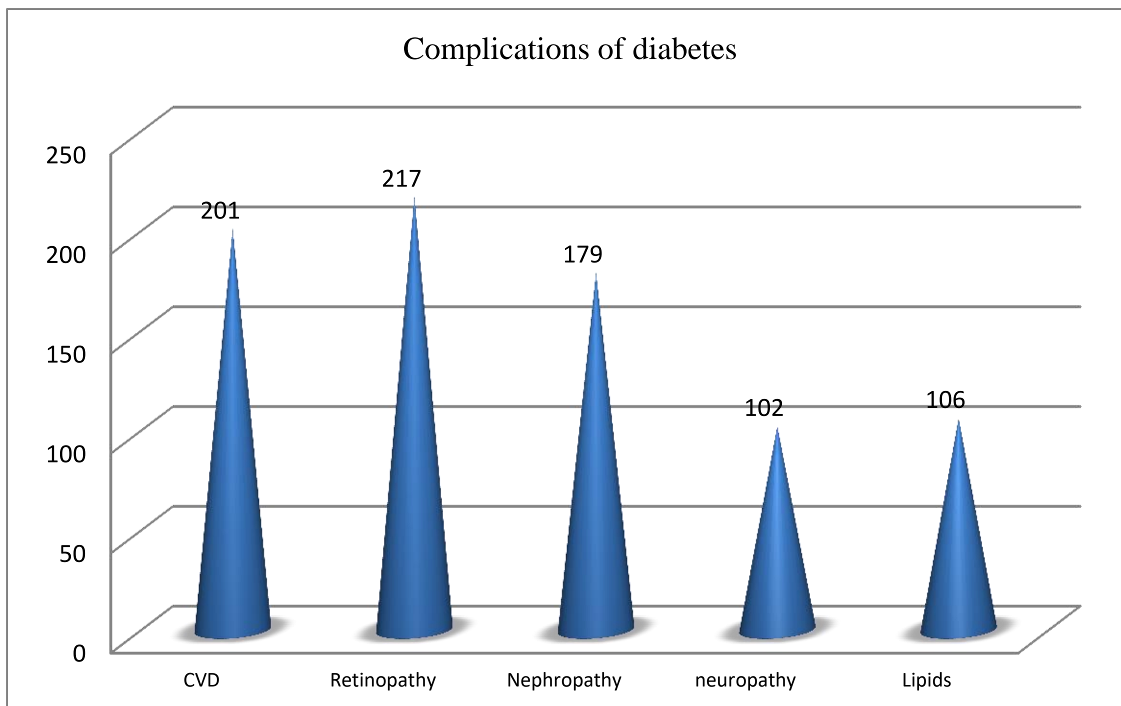


Fig 4.4.7 What are the complications a diabetic patient may suffer in future?

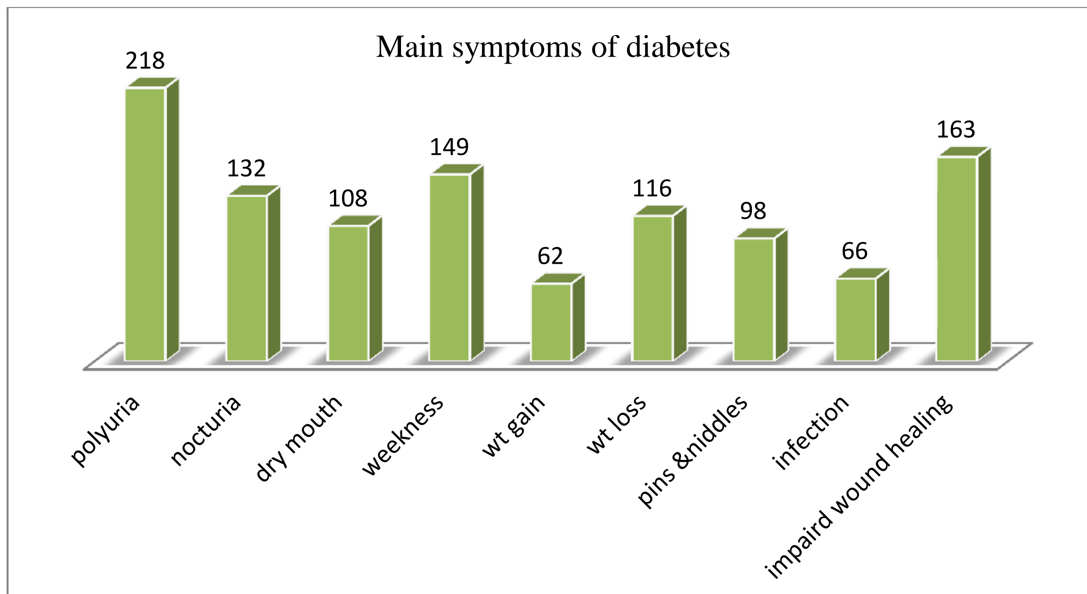


Fig 4.4.8 What are the main symptoms of Diabetes?

Attitude:

Fourteen percent subjects (14 %) felt that diabetes can be cured and 71% diabetics have positive attitude towards Ayurvedic Medicines. Diet modification (p= 0.00) and yoga (p= 0.02) were significantly associated with education. Exercise and the diet modification were the most opted modalities as the best treatment of diabetes. All most all the patients (95.6%) think that blood sugar control is important for the health and education regarding the disease will help for better control. Seventy one % diabetics perceived that Ayurveda can be used to control the diabetes.

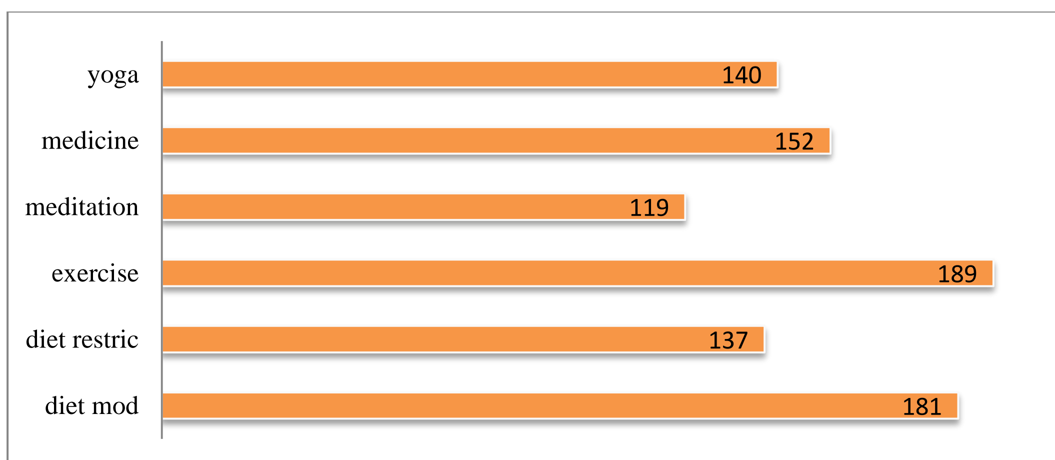


Fig 4.4.9 What do you think is the best treatment of Diabetes?

Practices:

More than 96% diabetic patients are consuming medicine either Allopathic or Ayurvedic or medicine from both the systems of medicine. Distribution of types medicines from Health care systems is shown in fig 4.4.10

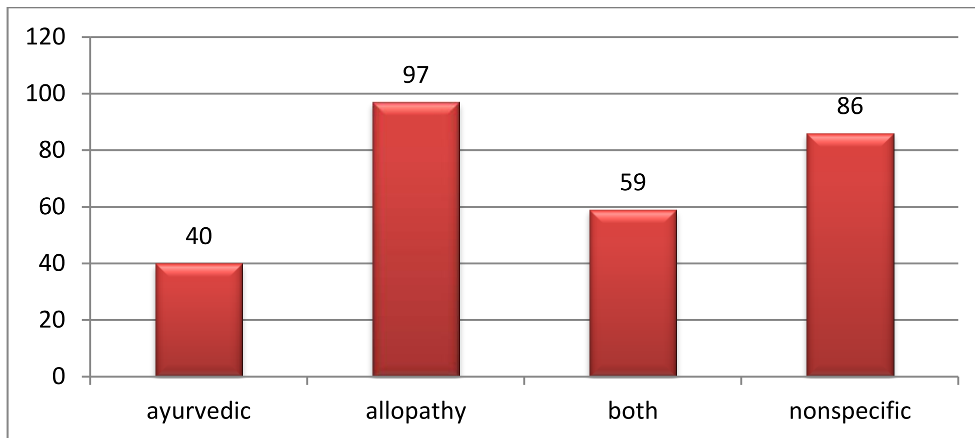


Fig 4.4.10 What Pharmacological management are you following to control blood sugar?

Physical activity (47 %) and diet modifications (44%) were the most important modalities were followed by the subjects to manage the diabetes. Practice of yoga (22.5%) and meditation (13.6%) were also indicated as nonpharmacological modality followed by the subjects.

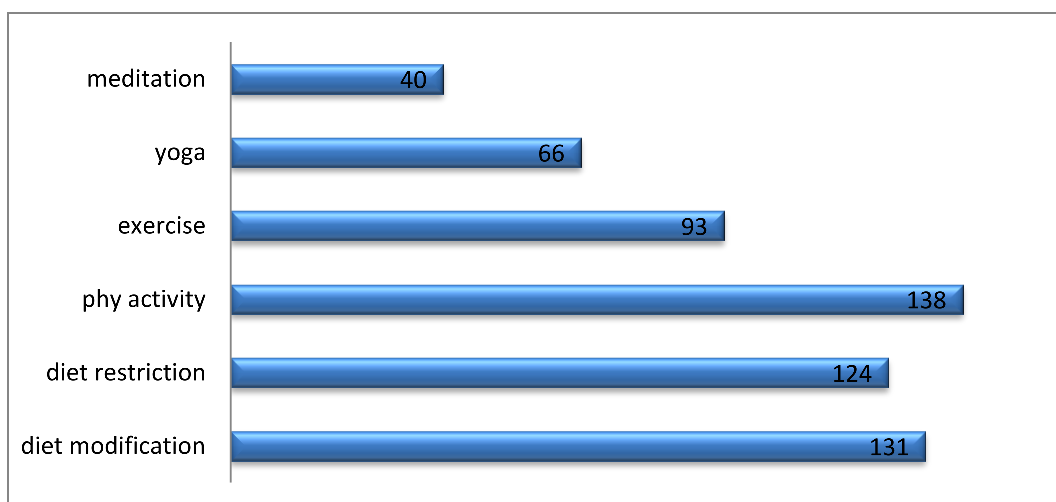


Fig 4.4.11 What non pharmacological management are you following to control blood sugar?

Majority of diabetic patients were consulting diabetologists (73%) for their management of diabetes followed by Family Physician (52.6%); whereas 8% diabetic patients were consulting Ayurvedic Physician also. Sixty one percent (61%) patients were regular in consulting medical advice which are significantly associated (p= 0.02) with their education.

That means almost 40 % patients were not regular in their management of diabetes. More than 60 % of diabetic patients checked their blood pressure (63.5%), and blood sugar (64.2%) regularly; however lesser percentage (40%) of patients were regular for lipid profile.

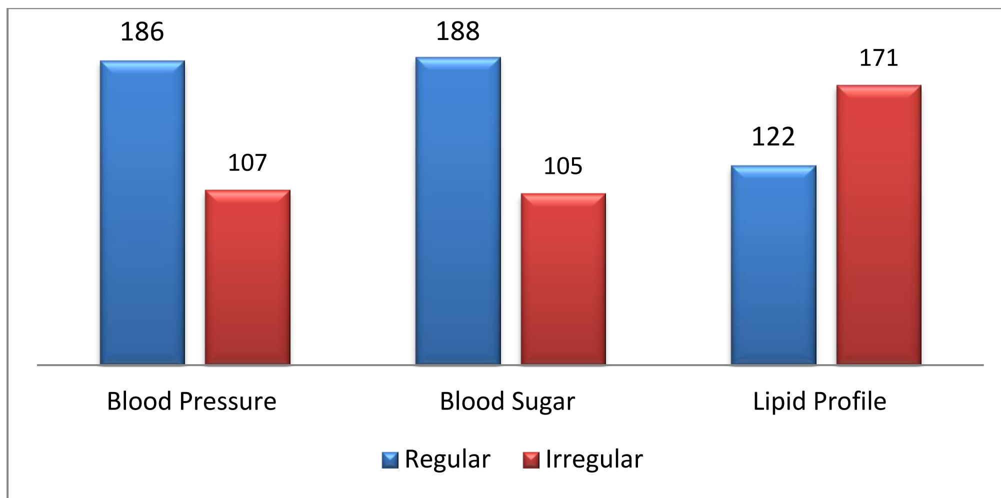


Fig 4.4.12 How frequently do you check your Blood pressure, glucose and cholesterol?

More than 60 % of diabetic persons were regular in checking blood sugar and blood pressure however they found irregular in periodic checking of lipid profile.

Table 4.4.2 Category of practice of checking for Blood pressure, glucose and cholesterol

Category	Regular N (%)	Irregular N (%)
Blood Pressure	186 (63.5)	107 (36.5)
Blood Sugar	188 (64.2)	105 (35.8)
Lipid Profile	122 (41.6)	171 (58.4)

Fifty two percent (52 %) patients were educated by their relatives or friends about diabetes and only 34% patients attend education programme of diabetes which was significantly associated with education (P= 0.000), age (P= 0.039), occupation (P= 0.003), and even with duration of diabetes (P= 0.02) . KAP scores were calculated as per the numbers of answers to questions. Association of knowledge, attitude and practices were noted with demography. Median values are given in the table

Table 4.4.3 Median values with range of KAP scores as per demographic data

Variables	Category	Knowledge score	Attitude score	Practice score	P value
Gender	Men (n=164)	10 (4-19)	7 (2-12)	8 (2-13)	NS
	Women (n=125)	9 (3-18)	7 (1-10)	7 (2-14)	
Age in yrs	27-37 (n=10)	9 (3-12)	7 (2-11)	7 (2-9)	NS
	38-47 (n=53)	10 (5-17)	6 (3-10)	7 (2-14)	
	48-57 (n=106)	10 (4-19)	7(2-12)	7 (3-13)	
	58-67 (n=87)	9 (3-17)	7(1-11)	7 (2-12)	
	68-77 (n=37)	9(4-19)	7 (4-10)	9 (2-12)	
Education	Illiterate (n=69)	8(4-15)	6 (1-11)	7(3-12)	<0.0001
	Primary (n=61)	9 (3-19)	7 (4-10)	8 (2-13)	
	Secondary(n=78)	9(3-18)	7 (2-10)	7 (2-12)	
	Graduate (n=59)	10 (4-18)	7 (3-10)	8(2-12)	
	PG (n=26)	11(6-19)	8 (5-12)	10(5-14)	
Occupation	Home maker (n=92)	9(3-18)	6 (1=10)	7 (2-13)	NS
	service(n=43)	10 (4-19)	7 (4-12)	8(2-12)	
	business(n=97)	11(4-19)	7 (2-11)	9 (3-14)	
	retired(n=53)	9 (4-16)	7 (4-10)	7 (2-12)	
	others(n=8)	8 (6-15)	7 (5-11)	9(5-11)	
Duration of DM in yrs	<1 (n=11)	10(4-15)	6(1-10)	8(4-12)	NS
	1.1-5 (n=144)	10 (3 -19)	7 (2-12)	7 (2-14)	
	5.1-10 (n=72)	10(4-19)	7 (3-10)	8 (2-13)	
	10.1-15 (n=35)	9 (3-16)	8 (5-11)	7 (2-12)	
	15.1-20 (n=18)	8(4-18)	7(4-10)	8(2-10)	
	>20 (n=13)	10 (6-15)	6 (5-10)	8 (5-13)	

NS: Not significant

Among all patients, mean ± SD of knowledge, attitude and practice was 9.69±3.4, 6.95±1.8, and 7.53±2.5 respectively. Median score for knowledge, attitude, and practice were 10, 7 and 7 correspondingly. The percentages of patients who had ≥ 75 percentile of knowledge, attitude and practice are 27.6 %, 37.9 % and 39.9 % respectively.

Knowledge (p=0.0007) Attitude (p=0.0001) and practice (p=0.0001) regarding diabetes was significantly different when compared to level of education. It was interesting to note that those who had knowledge ≤ 25 percentile were following good practice (p= 0.0001).

Knowledge and Practice scores of the participants as per the age groups are shownfound to be significantly different. (P=0.0001).

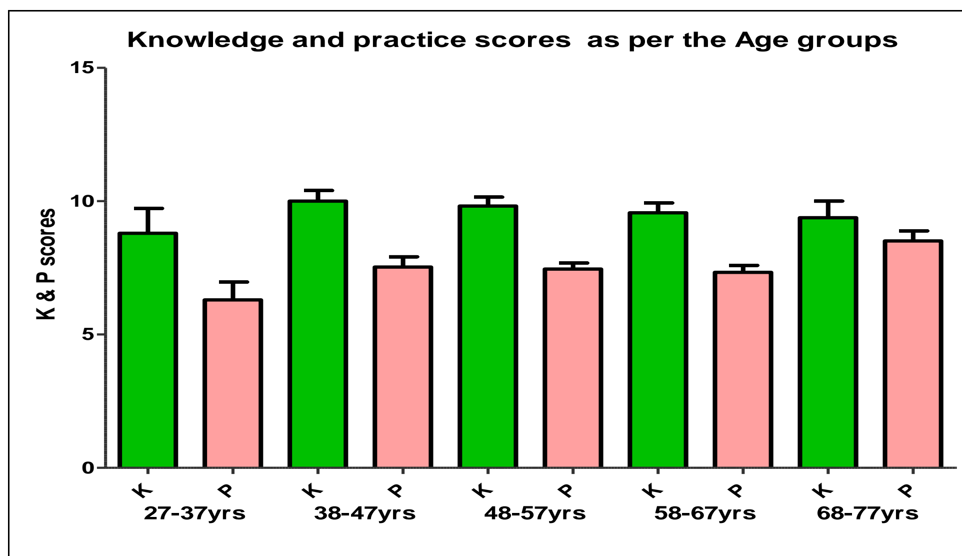
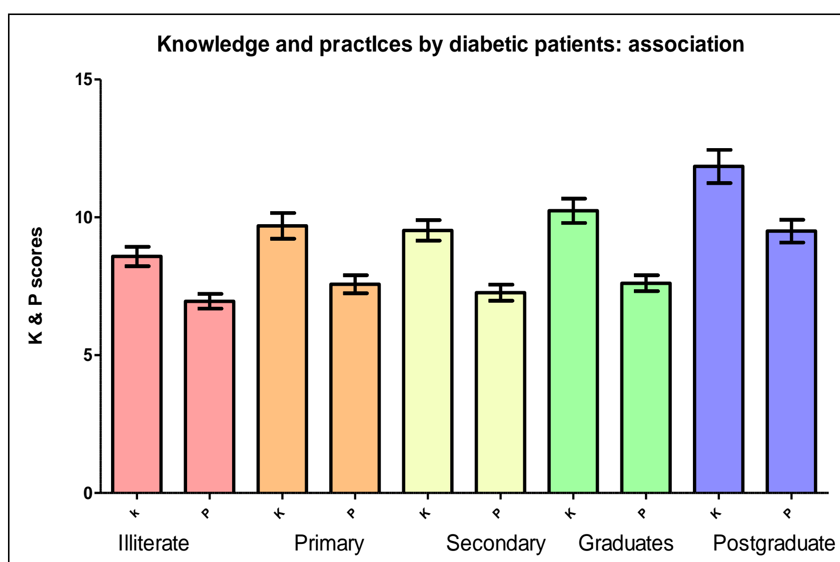


Figure 4.4.13 Association of scores of Knowledge and practices of diabetic patients for the management of diabetes with age groups

These scores were also found to be different as per the education (p) <0.0001).



K: Knowledge; A:Attitude; P: Practice

Figure 4.4.14 Association of KAP scores with level of education

4.4.2 Knowledge and Practices of Ayurvedic Physicians for the management of diabetes

Data of 143 (99 men and 44 women) Ayurvedic physicians were analyzed. Gender classification shows preponderance of men than women. Majority Ayurvedic physicians were practicing Ayurveda.

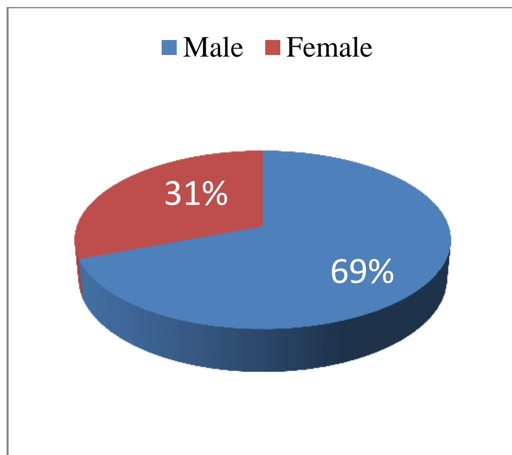


Fig 4.4.15 Gender distribution

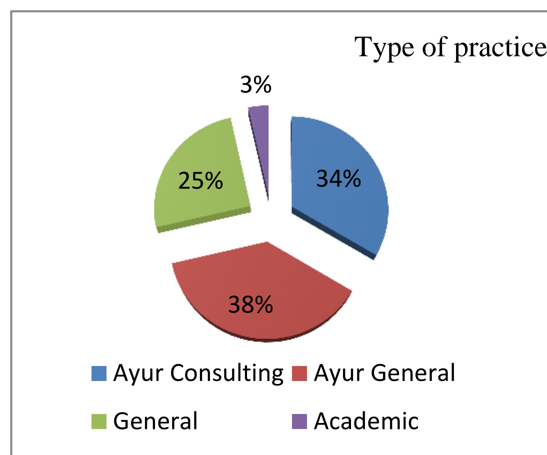


Fig 4.4.16 Classification as per type of practice

Table 4.4.4 Classification of Ayurvedic Physicians as per degree and age groups

Degree	n	%
BAMS	84	58.7
MD	45	31.5
MS	2	1.4
Others	12	8.4

Age groups in years	n	%
23-30	54	37.7
31-40	40	27.9
41-50	33	23
51-60	9	6.3
>60	7	4.9

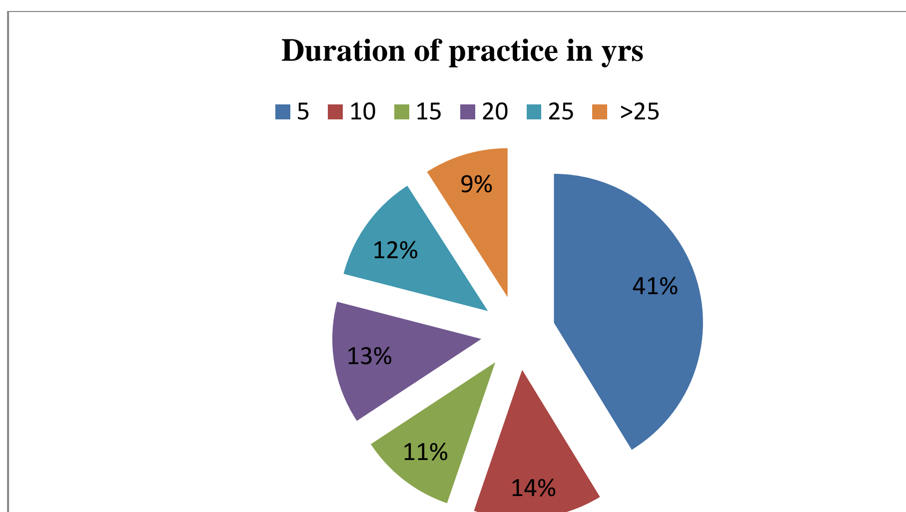


Fig 4.4.17 Duration of practice of Ayurvedic Physicians

Among the participants, 33.6% were Ayurvedic Consultants, 37.8 % were practicing Ayurveda in general practice, 25 % were general practitioners and 5 of them (3.5%) were from Academics. Range of duration of practice was 1to 50 years.

Scope of Ayurvedic treatment for diabetes is felt 'very good' by 46% participants. More than half (57.3%) participants felt that Fasting and PP glucose test is the best test to diagnose diabetes and 44% felt that HbA1C is the best test to monitor the glucose control.

Almost 80% physicians use F&PP sugar test to diagnose diabetes followed by Ayurvedic Nidan (53%). The two investigations that were additionally carried out along with sugar test were serum lipid test by (83.2%) of physicians and eye check-up by (51%) of physicians respectively.

Amongst the drug modality, Ayurvedic medicines (74.1%) and Oral Hypoglycemic Agents (61.5%) were prescribed frequently by the physicians. Among the non-drug modality of managing diabetes; walking was advised by 71% physicians followed equally by exercise (67.8%), yoga (66.4%) and diet (63.6%).

Among all physicians, 50.4% physicians had ≥ 75 percentile of knowledge, and 29.4 % physicians had ≥ 75 percentile of practice points.

BAMS physicians believed that scope of Ayurvedic treatment for diabetes is very good.

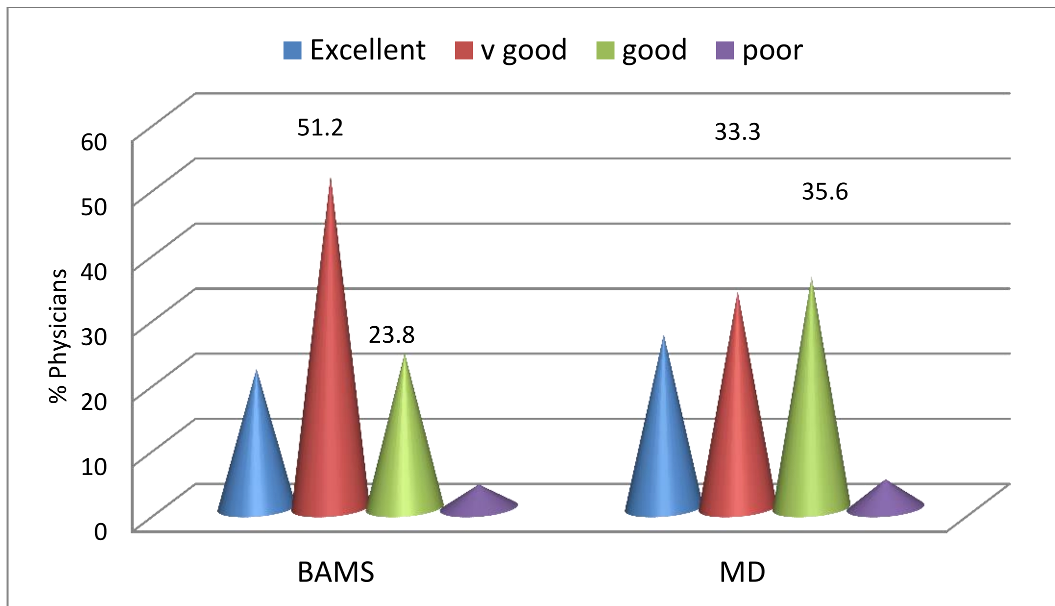


Fig 4.4 .18 What is the scope of Ayurvedic treatment?

Table 4.4.5 Association of knowledge about Ayurvedic management of diabetes in Ayurvedic Physicians.

	BAMS %	MD%	χ^2	P value
Scope of Ayu Treatment				
Excellent	21.4	26.7		
Very good	51.2	33.3		
Good	23.8	35.6		
poor	3.6	4.4	3.930	0.269
Best test to diagnose DM				
FPG	16.7	17.8	0.026	0.873
F and PP sugar	59.5	46.7	1.957	0.162
GTT	27.4	40	2.152	0.142
HbA1c	36.9	40	0.119	0.730
Best test to monitor DM				
FPG	38.1	46.7	0.889	0.346
PPPG	39.3	35.6	0.173	0.677
HbA1C	40.5	46.7	0.459	0.498
Symptoms	29.8	35.6	0.454	0.501
Investigations to diagnosis DM				

F and PP	72.6	84.4	2.296	0.130
HbA1c	27.4	37.8	1.481	0.224
Symptoms	46.4	37.8	2.589	0.274
Ayu Nidan	54.8	56.8	0.049	0.824

Table 4.4.6 Association of Practice of Ayurvedic management of diabetes in Ayurvedic Physicians

	BAMS %	MD%	χ^2	P value
Other investigations asked				
Lipids	83.3	86.7	0.249	0.618
Foot examination	32.1	42.2	1.298	0.255
Eye examination	50	55.6	0.362	0.547
Micral urine test	53.6	62.2	0.893	0.345
ECG	47.6	51.1	0.143	0.705
Line of treatment				
Drug				
Only OHA	58	62.2	0.184	0.668
Only Ayu	72.6	82.2	1.48.	0.224
Both	40.5	55.6	2.685	0.101
Insulin	16.7	24.4	1.135	0.287
Panchkarma	23.8	33.3	1.344	0.246
Nondrug				
diet	59.5	73.3	2.436	0.119
Exercise	67.9	71.1	0.145	0.703
Yoga	64.3	71.1	0.614	0.433
Meditation	42.9	48.9	0.431	0.512
Walking	76.2	64.4	2.009	0.156

Percentages of knowledge scores and practice scores were calculated to compare knowledge and practices; however the number of MD doctors in the study is almost 50% of that of BAMS doctors which was one of the limitations.

Table 4.4.7 mean of percentage scores of knowledge and practice of Ayurvedic Physicians as per degree

	Mean of % score of knowledge	Mean of % score of Practice	P value
BAMS	46.67± 12.74	49.64±14.24	0.1314
MD	48.00 ±11.4	55.22±13.77	0.0038*

4.5 Clinical studies of selected medicinal plants under the project CSIR NMITLI Diabetes:

Reverse Pharmacology path was chosen for the clinical studies. While paraclinical targets and models were being setup, documentation of history of use of selected plants was done Two formulations i.e. DM-FN-01 (*Nisha-amalaki* in 2:3 combinations) and DM FN –02 (*Mamejava ghanavati*) were finalized and studied for safety, tolerability and activity. These formulations are available in market for diabetesan in regular use of Ayurvedic Physicians.

For the project, Zandu Pharmaceutical Works Ltd supplied the formulation DM-FN-01. It is the combination of the 2 plants viz DM 001(Rhizome of Curcuma longa) and DM 002 (Fruit of Phyllanthus emblica) in powder form in 2:3 combinations packed in aluminium sachets (5 gm/sachet) .

DM FN –02 is the *ghanavati* of a single whole plant DM 004 (*Enicostemma littorale*) in a tablet form (250 mg). The formulation was supplied by Shree Dhootpapeshwar Ltd .Table 4.5.1 shows the clinical studies of the selected formulations at 5 centres in healthy volunteers and patients with type2 diabetes mellitus under the project.

Table 4.5.1 The clinical studies of the selected plants

Formulation	Study	Target
DM-FN-01 (Nisha Amalaki)	Phase II	Treated uncontrolled diabetes mellitus for Safety & activity/Tolerability
	Phase II	Newly detected diabetes mellitus for Safety & activity/Tolerability
	Drug-Interaction study	Volunteer Study / Interaction with Metformin

DM-FN-02 (Mamejava Ghanavati)	Phase II	Treated uncontrolled diabetes mellitus for Safety & activity/Tolerability
	Drug-Interaction study	Volunteer Study / Interaction with Metformin

4.5.1 Exploratory study for complementary effect of Nisha amalaki (DM FN-01) in treated uncontrolled type 2 diabetes mellitus

Effect of DMFN 01 in patients with treated uncontrolled type 2 diabetes was evaluated when patients consumed the formulation in the dosages of 5 gms thrice a day for 3 months along with concurrent antidiabetic treatment.

Thirteen of twenty patients completed the study. The formulation was found to be safe with reasonable tolerability despite the bulk. Symptoms related Gastro Intestinal system viz Nausea, anorexia, loose motions and flatulence were noted more frequently than any other system. Beneficial symptoms like improved bowel movements, fresh and energetic feeling and glowing skin with reduced acanthosis were also noted.

Insulin sensitization was observed in 2 out of 4 hyperinsulinemic and insulin resistant individuals. Reduction in glycosylated hemoglobin (HbA1c) was observed in 4 out of 13 patients. Maintenance of the HbA1c was noticed in the other 6 patients. Remaining 3 patients showed the worsening of the HbA1c. Neither hypoglycemic nor antihyperglycemic activity were observed.

Table 4.5.2 HbA1c of diabetic patients who completed 3 months therapy

	RP	KA	KN	RS	PT	LM	BT	MJ	GA	SS	PM	NA	SB
Baseline	7.4	10.4	7.2	10.5	7.1	7	7	6.6	7.5	9.8	8.8	9.2	8.3
1 month	8.1	9.1	8.1	10.9	7.3	6.6	7	6.4	7.3	9	7.9	9.6	8
2 months	8.5	9.1	7.5	10.4	7.4	7.5	6.5	7.7	6.6	8.4	7.7	11.3	8.8
3 months	8	9.1	7.2	11.3	7.4	7.3	7	7	6.8	9.7	7.3	12.3	8.5

There was no significant effect of the formulation observed on lipids also; however reduction in HbA1C, micro albuminuria and CRP suggest the need to focus on anti-inflammatory and anti-oxidant activity. Hence the study with experimental design was planned to find out activity in newly detected patients with type-2 diabetes.

4.5.2 Study in newly detected diabetic patients

There was a definite lowering of blood sugar level (OGTT values) in the patients with Medical Nutritional Therapy (MNT) with *Nisha amalaki* – DM-FN 01 (NA) as compared to only MNT at the end of 30 days of therapy shown in figures fig 4.6.1 & 4.6.2

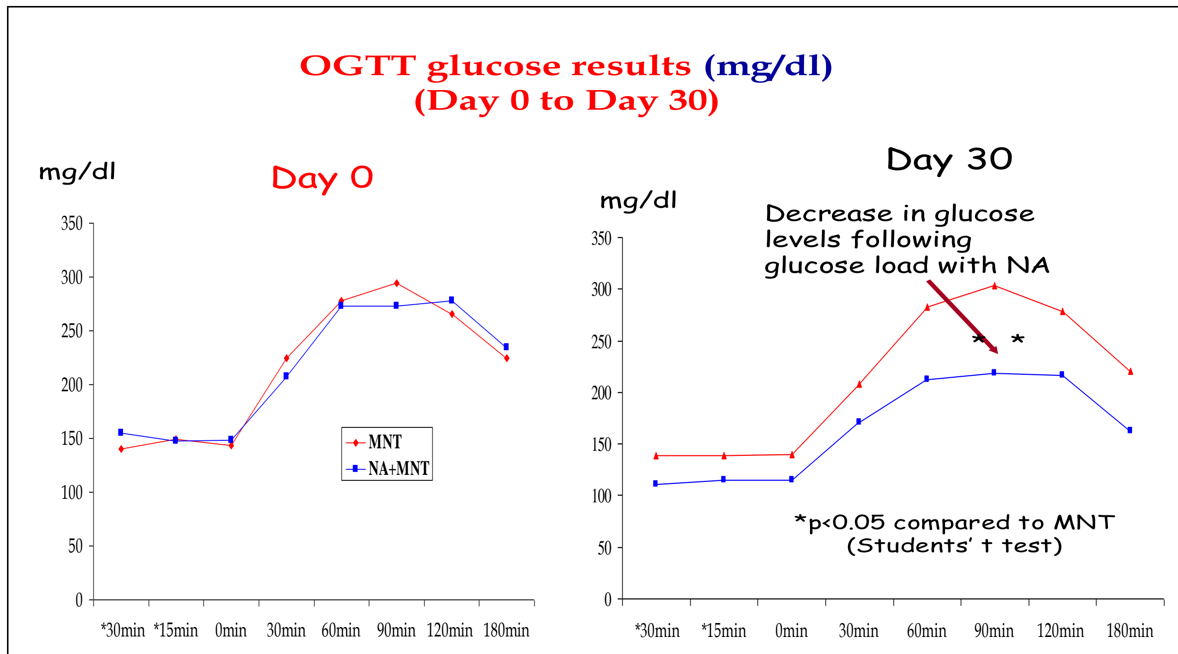


Fig.4.5.1 Decrease in glucose levels

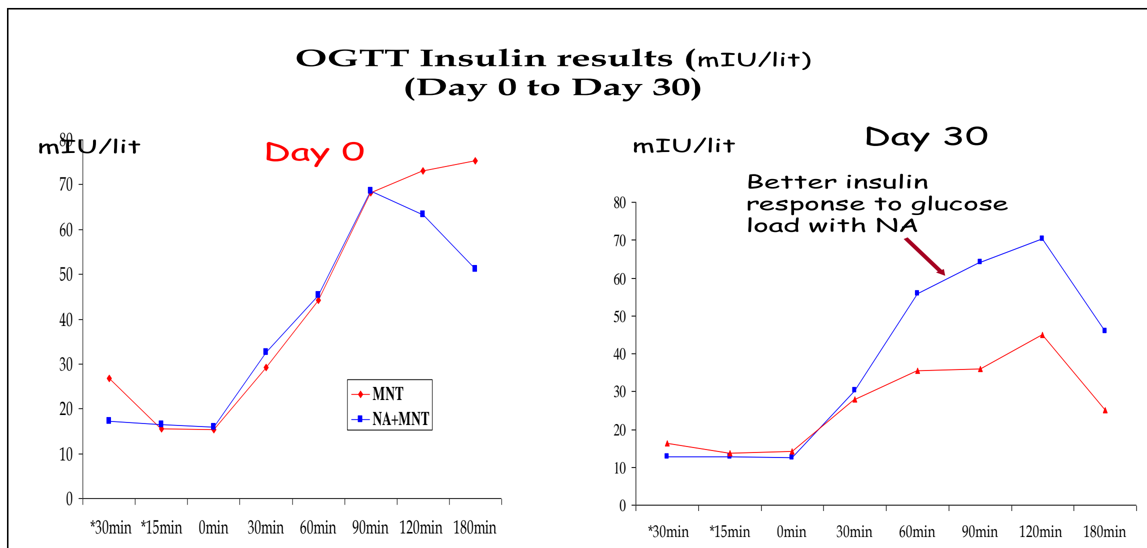


Fig 4.5.2 Better Insulin response to glucose load

HbA$_1$c values decreased at the end of 30 days of therapy in the MNT + NA group as compared to MNT only. It was of interest to observe that HbA$_1$c values of MNT group also

decreased at the end of 60 days when NA was added for last 30 days. Fig. 4.6.3 shows the decrease in HbA1c in the group taking *NA* powder. Improvement in energy level was observed clinically.

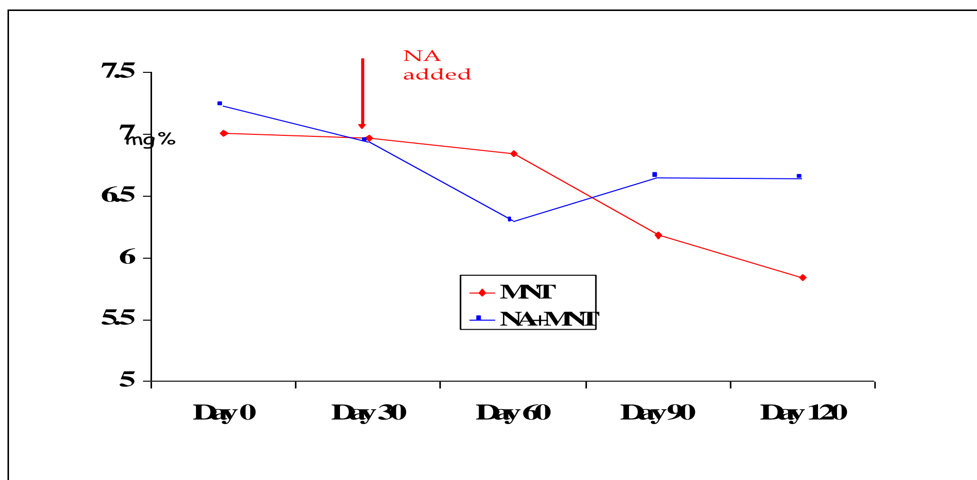


Fig 4.5.3 HbA1c values in MNT+NA treated group

4.5.3 Exploratory study for complementary effect of Mamejava Ghana vati (DMFN 02)in treated uncontrolled type 2 diabetes mellitus

Mamejava Ghanavati was found to be safe with good tolerability and acceptability. Clinically beneficial effects were seen as sense of wellbeing, increase in energy and decrease in false hunger, body ache, leg pain, and back pain. Average weight loss of 1.5 kg at the end of 2 months of therapy was observed.

Glycemic control:

No significant change was observed in fasting plasma glucose (FPG) but reduction in postprandial plasma glucose (PPG) and HbA_1c was noted. Glucose and HbA_1c values are shown in table 4.6.3

Table 4.5.3: Fasting and postprandial plasma glucose –before and after the treatment

FPG			**PPPG**			**HbA_1c**		
Pre	**Post**	**Δ**	**Pre**	**Post**	**Δ**	**Pre**	**Post**	**Δ**
144	128	-16	200	132	-68	8.1	6.5	-1.6
120	124	+4	150	160	+10	6.8	6.2	-0.6
192	180	-12	296	280	-16	9.1	7.1	-2.0
120	102	-18	202	154	-48	7	6.2	-0.8

116	100	-16	211	176	-35	6.8	6.5	-0.3
110	108	-2	168	157	-11	7.7	6.8	-0.9
200	174	-26	303	210	-93	8	6.2	-1.8
160	131	-29	200	215	+15	8.8	7.1	-1.7
118	106	-12	152	138	-14	7.2	6	-1.2
110	109	-1	184	170	-14	7.6	6.1	-1.5
174	174	0	220	190	-30	9.4	7.5	-1.9
115	106	-9	168	160	-8	7	6.6	-0.4
174	142	-32	298	208	-90	9	8.6	-0.4
142	127	-15	280	220	-60	6.9	6.6	-0.3
112	100	-12	227	180	-47	7.1	6	-1.1
110	92	-18	155	130	-25	7	6.1	-0.9
132	118	-14	235	211	-24	6.8	6.5	-0.3
198	180	-18	232	218	-14	8	7.1	-0.9
155	172	+17	300	182	-118	7.2	7.4	+0.2
130	131	+1	175	141	-34	6.8	6.4	-0.4
143	125	-18	274	153	-21	8.2	7.4	-0.8
107	138	+31	174	148	-26	7.3	7.2	-0.1
113	163	+50	162	232	+70	7.1	7.1	0
193	162	-31	231	220	-11	9	7.8	-1.2
100	111	+11	155	197	+44	7.6	7.4	-0.2
125	125	0	174	185	+11	8.4	8.3	-0.1
Mean 139	**131.8**		**212.5**	**183.3**		**7.7**	**6.9**	
SD 31.7	**38**		**51.6**	**36.5**		**0.8**	**0.7**	
P value		**0.065**			**p<0.003**			**p<0.0001**

No significant change was observed in fasting plasma glucose. Significant reduction in postprandial plasma glucose ($p<0.003$) was observed. There was a significant decrease in HbA_1c values ($p <0.0001$).

No significant change was observed in fasting insulin value but directionality was seen in decline of Post Prandial insulin (PP) indicating a possibility of insulin sensitization. All fasting values above 20 uIU/ml (n=7) were reduced as well as 7 out of 12 fasting values which were below 10 uIU/ml. were increased. Postprandial insulin values were available in 7

patients out of 26 diabetic patients. Decision to measure post prandial insulin arouse only after as it was realized that there was directionality in PP glucose as well as in glycosylated Hemoglobin. However in that time only seven patients were remaining to be enrolled and hence even when PP insulin assessment was not required as per the protocol, the assays were done. Significant decrease was observed in pp insulin. Figure 4.6.4 shows temporal relationship between PP insulin and glycated haemoglobin in each of the seven individuals

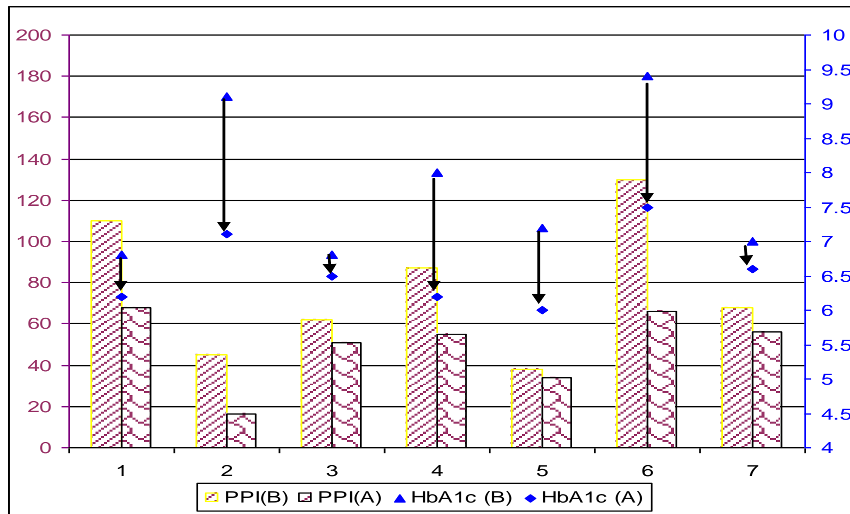


Fig 4.5.4 temporal relationship between PP insulin and HbA1c

Lipemic control: No significant change was seen in S. Cholesterol after the treatment but positive directionality was observed in S. Triglyceride values which had decreased.

Table 4.5.4 Hyper triglyceride Group (n=8/26)

S .Triglycerides	
Pre	**Post**
205	170
208	170
246	218
203	182
238	180
248	128
231	189
191	137
Mean 221.25	171.75
Sd 22	28.6

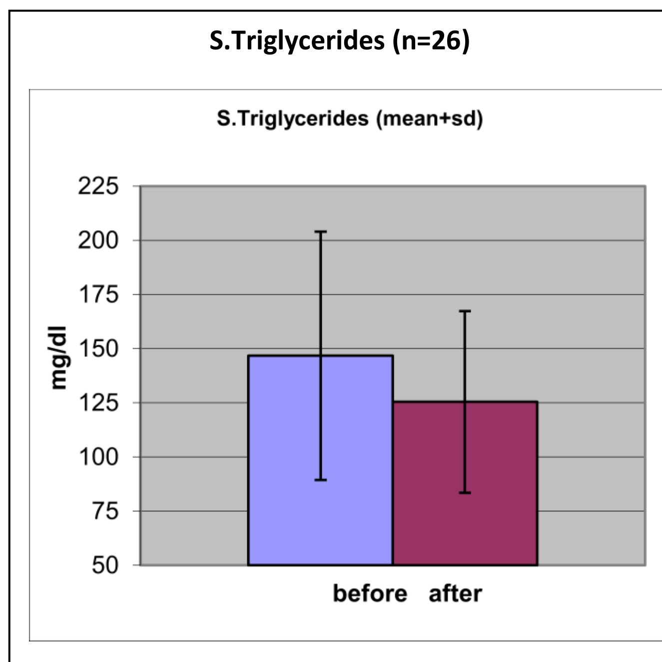


Fig.4.5.5: Triglyceride before & after Treatment

Out of 26 S. Triglyceride values, 8 values were above 160 mg/dl , indicative of baseline hypertriglyceridemia. Mean S. Triglycerides above 160 mg% has decreased from 221.25 ± 22 to 171.75 ± 28.6($p<0.0027$).

Anti-inflammatory markers: .

1.PAI-1 was evaluated as an anti-inflammatory marker at VKAN . Five out of 8 demonstrated reduction after the treatment. The values are given in table 4.5.5 and shown in figure 4.5.6.

Table 4.5.5 PAI-1 values

ID No.	PAI-1 (Fasting)(ng/ml)	
	Pre	**Post**
1	86	56
2	120	108
3	92	78
5	96	56
7	45	88
9	73	78
11	42	61
12	99	72
Mean	**81.63**	**74.63**
SE	**9.537**	**6.271**

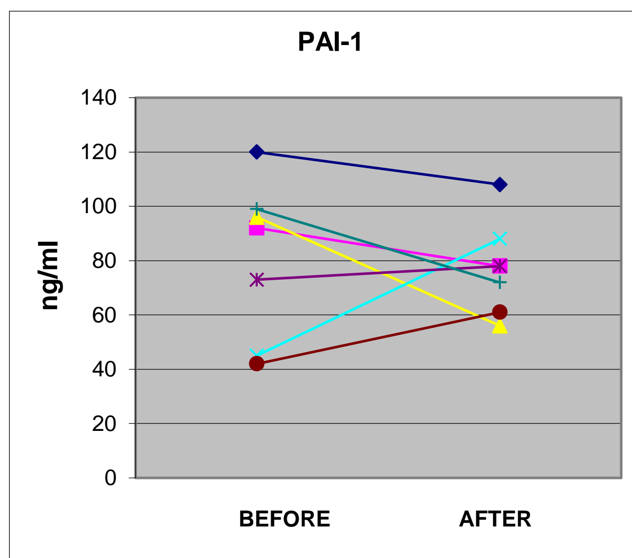


Figure 4.5.6: PAI-1 before & after Rx

All values are above the normal range (1-25 ng/ml) . Five values are reduced . Directionality suggests the decrease in inflammation

4. CRP values: CRP was evaluated in all patients. The values are given in table 3.6 and shown in figure 4.6.7

Table 4.5.6: CRP values (mg/L

CRP (Fasting)	
Pre	Post
4.8	1.9
16	7
0.58	0.21
0.9	4
0.9	0.5
5.8	4.2
0.8	0.6
11	7
0.3	0.2
0.5	0.54
0.9	0.32
5.6	4.2
4	0.9
2.5	1.7
0.1	0.1
5	2.7
7.4	5
6	4
6.4	2.2
1	0.6
10.4	7.7
1.5	0.7
4.3	3.2
15.3	6.7
0.9	0.4
1.2	2.3
Mean 4.39	2.65
SD 4.5	2.4
SE	0.47

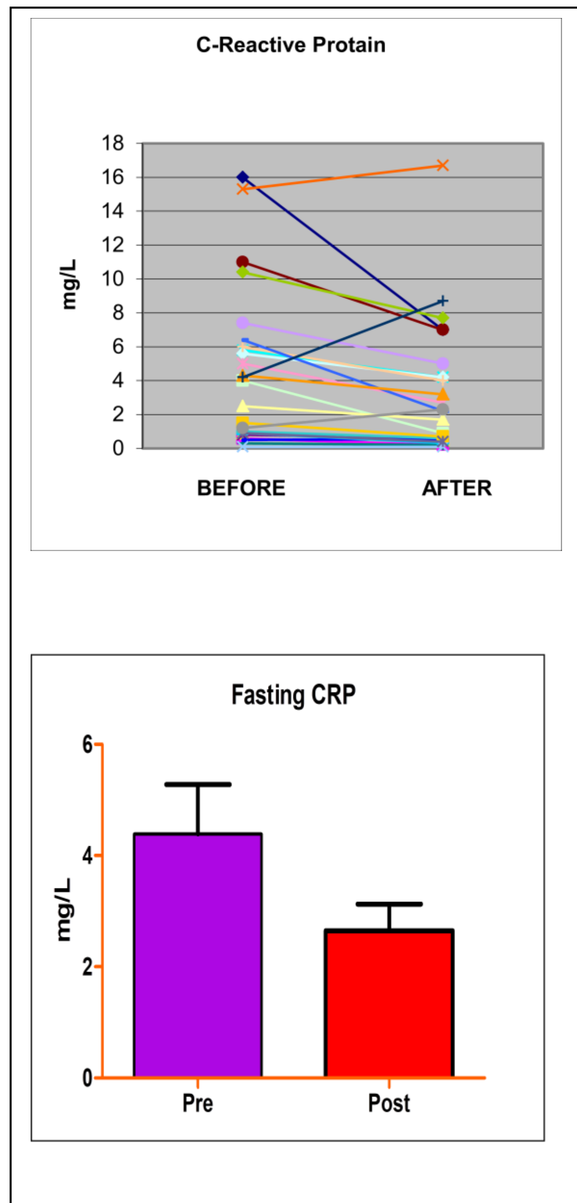


Figure 4.5.7 : CRP before & after Rx

There are 13 values above 2.5 mg/l and 12 values are decreased. Mean has decreased from 4.39 ± 4.5 to3.03 ± 3.6 (P=0.002). Four values are above normal range (0-6 mg/L) . All are reduced.

The above results are indicative of antiglycation, anti-inflammatory hypotriglyceridemic and possibly insulin sensitizing and insulin secretogaugic activities of DMFN O2.
DM-FN-02 at the prescribed dose (i.e. 250 mg TID x 2 weeks, then 500 mg TID x 6 weeks) was found to be safe with good tolerability and acceptability. It has not shown any anti-hyper or hypoglycemic activity in the FPG as well as fasting insulin values; however significant reduction in HbA1c values ($p<0.0001$) and in postprandial plasma glucose ($p<0.003$) was observed. No significant change was observed in S. Cholesterol after the treatment. However, positive directionality was observed in fasting S. triglycerides values. There is significant change in S. Triglycerides above the normal values ($p<0.002$). Directionality in PAI-1 and CRP markers suggests the decrease in inflammation.

4.5.4 A study of plasma levels of Metformin with or without oral Antidiabetic formulations[33.]
DM-FN-01 (Powder form/10gm) in group 1 and DMFN O2 (Tablets/ 500 mg) in group 2 were administered with or without metformin (500 mg) PO on empty stomach in 12 healthy male volunteers. The order of administration was randomized with 7 days of washout period. Plasma levels of Metformin were done by the HPLC assay which was validated by MS.
Only Metformin arm:

The absorption of metformin was fast in the majority of cases with mean maximum concentration (C_{max}) of 0.94-2.44 µg/ml between 1.5 and 5 h. The mean area under the curve (AUC) was 9.22 ± 2.48 (mean ± standard deviation [SD]) µg/ml × h for all 12 volunteers, with no significant (NS) difference between Group A and Group B when metformin alone is considered. T_{max} for metformin plasma levels in all 12 volunteers was between1.5 and 4 h.
Group A : Metformin with DMFN 01

simultaneous administration of DMFN01, showed a reduction in the mean C_{max} from 1.58 ± 0.52 (mean ± SD) µg/ml to 0.71 ± 0.2 µg/ml (a mean decrease of 55%), and in the mean of AUC (0-24 h) from 10.07 ± 3.41 (mean ± SD) µg/ml × h to 4.94 ± 1.39 µg/ml × h (mean decrease of 51%) of metformin (Student's paired *t*-test; $P < 0.\ 002$). There was NS difference in Tmax of metformin with or without DMFN01. All volunteers showed a reduction from 25% to 71% in C_{max} and from 37% to 65% of AUC of metformin

Group B: Metformin with DMFN 02

The results were variable. There was no significant reduction in the mean C_{max} of Metformin alone or metformin with DMFN02 from 1.42 ± 0.19 versus 1.35 ± 0.4 (mean ± SD) µg/ml, and also in the mean AUC (0-24 h) of 8.38 ± 2.1 µg/ml × h versus 7.77 ± 1.78 (mean ± SD) ng/ml × h (paired *t*-test; $P = 0.645$) respectively.

Figure 4.5.8 Plasma concentrations (mean ± standard deviation) of metformin alone after a single dose (500 mg) and concurrent with DMFN 01 and Figure 4.5.9 Plasma concentrations (mean ± standard deviation) of metformin alone after a single dose (500 mg) and concurrent with DMFN02 tablet (750 mg) is shown below

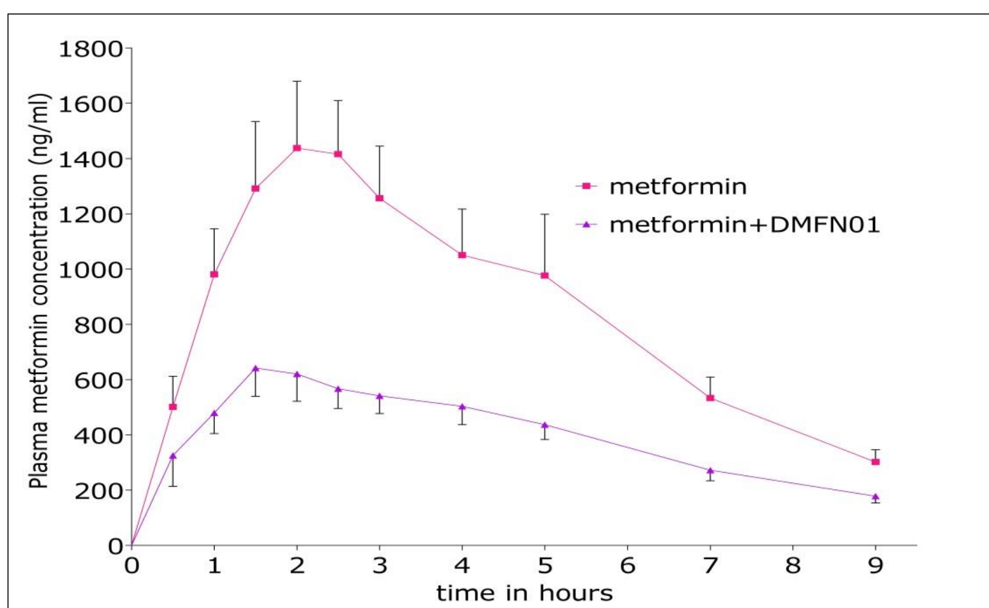


Figure 4.5.8 Plasma concentrations (mean ± standard deviation) of metformin alone after a single dose (500 mg) and concurrent with DMFN 01

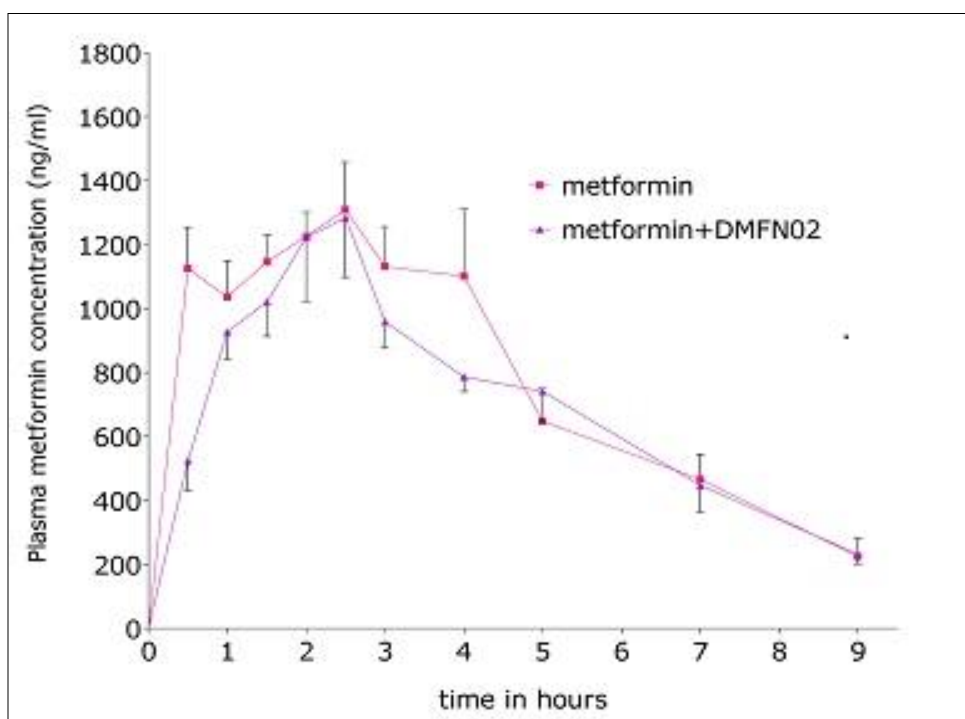


Figure 4.5.9 Plasma concentrations (mean ± standard deviation) of metformin alone after a single dose (500 mg) and concurrent with DMFN02 tablet (750 mg).

Volunteer no. 1 showed an increase of 26.5% and volunteer no. 5 showed a decrease of 44% in C_{max} of metformin and reduced AUC by 41% (individual data not shown). Rest of the volunteers (n = 4) showed a decrease of <20% in C_{max} of metformin. The C_{max} ranged from 0.74 to 1.86 µg/ml in this group, when metformin was co-administered with DMFN02 tablets. There was no significant difference in the mean AUC of metformin with or without DMFN02. However, in volunteer no. 3, AUC was increased by 44.3%. In volunteers 5 and 6 there was a reduction in AUC of 41.2% and 22.8% respectively. There was NS difference in T_{max} of metformin with or without DMFN02.

Metformin plasma levels in volunteer no. 1, who was common to both groups and participated in DMFN01A study are shown in Figure 4.6.10 This volunteer showed a reduction in peak concentration of metformin by 60% and AUC by 65% when metformin was co-administered with DMFN01 powder. However, when co-administered with DMFN01-A tablets there was NS difference in Cmax or AUC of metformin as compared to metformin alone (Cmax 1336 µg/ml vs. 1409 µg/ml; AUC-6179 µg/ml × h vs. 6816 µg/ml × h; paired *t*-test NS). There were no adverse clinical reactions to metformin or DMFN01, DMFN02 and DMFN01A (during the study).

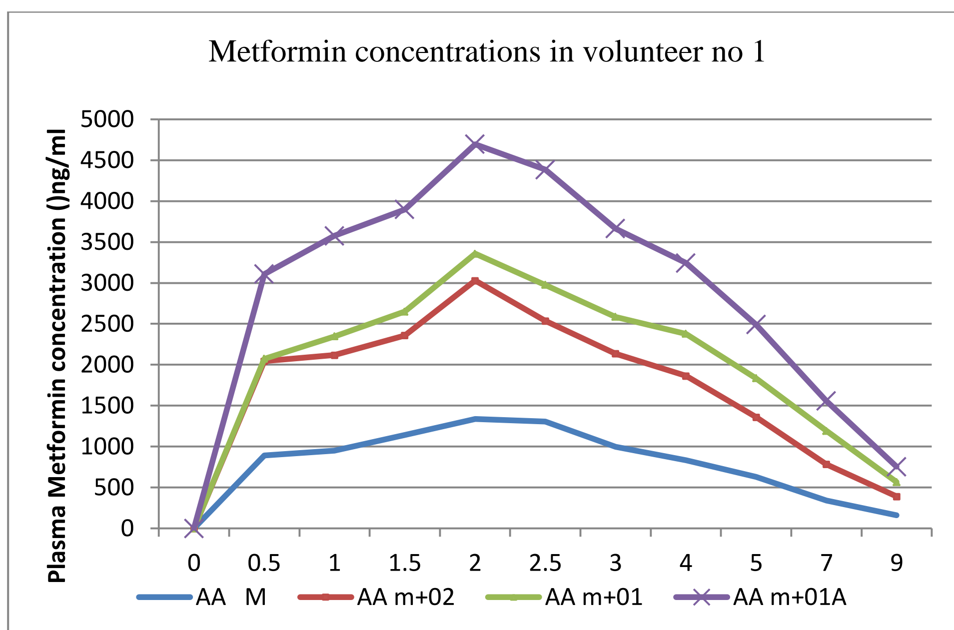


Fig 4.6.10 Plasma concentrations of metformin during metformin alone and with DMFN 01 powder and DMFN 01A tablets

None had any side effect due to administration of either drug except one volunteer reported stomatitis after 2 days of cross over after Metformin, which was not drug related.

4.6 Alpha Glucosidase(α G) inhibition

4.6.1 Alpha Glucosidase inhibition activity of MAAF of *Mamejava* (*Enicostemma littorale* Blume)

Tannin content of four market samples viz. Mamejava Powder, and three mamejava ghanavati (of different companies) was estimated by an assay. Concentration (ug/mL) of these 4 samples in 200µl reaction volume was decided. All the four samples of marketed formulations inhibited α-G activity in a concentration dependent manner.

Figure 4.6.1 shows the inhibition of alpha glucosidase enzyme with IC_{50} values.

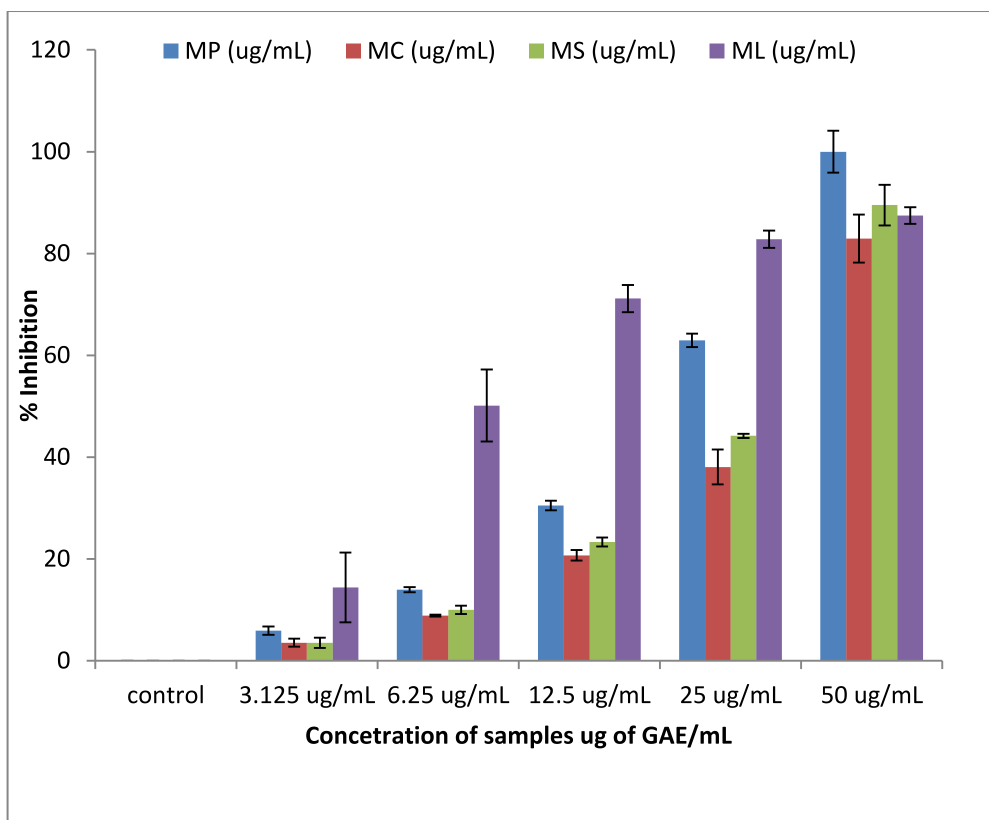


Figure 4.6.1 shows the inhibition of alpha glucosidase enzyme with IC $_{50}$ values.

All the four marketed samples of mamejawa inhibited α-G activity in a concentration dependent manner. Table 4.6.1 shows the EC 50 values of different mamejawa samples on alpha G inhibition. The observations indicate that Mamejawa Lion has higher potency in inhibiting the alpha glucosidase followed by Mamejawa Powder, SDM and Chaithanya.

Table 4.6.1 EC 50 values of different *Mamejwa* samples

	Mamejwa P	Chaitanya	SDM	Lion
EC 50	17.73	22.72	21.69	16.37

4.6.2 Similar study of inhibition of digestion enzyme α glucosidase by selected phytoactives of Mamejava at MRC-KHS has not shown any significant activity.

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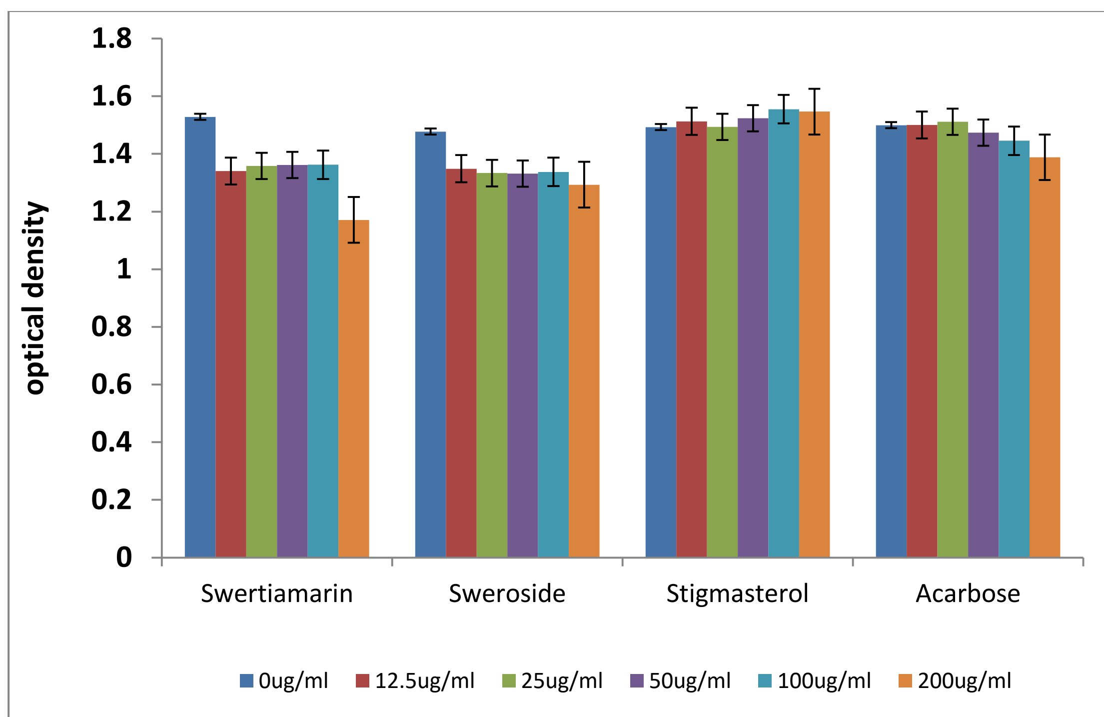

Figure 4.6.2 shows inhibition of α-glucosid enzyme by Phytoactives of *Mamejava*

Fig. Shows inhibitory activity of active compounds of *Mamejwa* . The y axis gives actual reading of the respective data in terms of optical density. It can be seen from the graph, these compounds showed marginal activity. Percent activity for these data has not been calculated due to insignificant activity

5.Discussion

“When one door closes, another opens; but we often look so long and so regretfully upon the closed door that we do not see the one which has opened for us.”

– Alexander Graham Bell

Discussion

Pharmacoepidemiology is the branch of science that involves study of drug usage and its effect on large population[17]. This field has arisen as a response to evaluate adverse drug reactions. It started with the event of unacceptable adulteration and misbranding of food & Drugs in 1906. The nodal agency in US created ‘The Pure Food & Drug Act’ in order to ensure the safety of people. However, it was in 1962 that the formal discipline of pharmacoepidemiology was established.

The term Pharmacoepidemiology was first used in 1984 in British Medical Journal by Lawson. Lawson suggested that prospective and retrospective cohorts, case control studies be used to collect data on drug safety [321]. Data has to be seen by skilled persons who can understand the inherent limitations of information available. In 1993, Smet introduced Herbal Pharmacoepidemiology, to study the use and effects of herbal drugs based on the premise that herbal medicines often have a long history of traditional use by people[18]. Regulatory agencies in the UK and European Union (Medicines and Healthcare products Regulatory Agency (MHRA/UK and EU) have accepted that a long term (>30 years) use of any herbal preparation, in the country of origin or more than 15 years’ use in the country of import would indicate its usage safety[11,12].

India has a long, glorious history of usage of herbal and herbominaral drugs through Ayurveda. Classical Ayurveda drug management concomitantly incorporates dietary and behavioural modifications (*Ahar and Vihar*). More than 80 % people from India still rely on traditional medicines for health elements[137]. Safety of patients has been inbuilt in the thought process of Ayurvedic health care system. Ayurveda's primary objective is '*swasthasya Swasthya rakshanam'* i.e. maintenance of health. To maintain the health, daily regime (*Dinacharya*), seasonal regime (ritucharya) and good conduct (*sadvrutta*) have been vividly described. Concept of *Pradnyaparadh (*going against norms, intuition and common sense*)* has been stated as one of the three main causes of illness[322] viz. *Asatmendriyarth-sanyog* (incompatibility driven of objects and sensory/motor organs), *Pradnaparadh* (driven by deficient mindful application), *Parinam* (time driven). Avoidance of these three main causes largely helps to maintain the health.

Ayurveda stresses upon the medical management which does not precipitates other illnesses while treating main medical condition. (*'Chikitsa Nasti Shuddhastu Yo Anyam Anyam Udirayet').* The medicine should be appropriate; care should have been taken in its preparation and has the capacity of targeting many mechanisms at a time. Ayurveda always recommended various dosage forms that could be appropriately used for all ages and all conditions. (*Bahukalpam bahugunam sampannam yogyam oushadam*) [323]. Jaiswal and William have reviewed the age old history and the basic philosophies of Ayurveda to help the researchers to gain more clarity of traditional systems of medicine, and overcome the challenges towards their global acceptance and harmonization of such medicinal systems[324]. While describing pharmacological properties, cautions about some medicines have been mentioned e.g: *Kutki (Picrorrhiza kurua), Bhallatak (Semicarpus anacardium)*. Guidelines about collection, storage, preparation methods and shelf life (*saveeryatavadhi*) have been stated.

Around 8000 Ayurvedic medicine industries are manufacturing and marketing, classical and proprietary formulations these are available for patients as Over-The-Counter (OTC) products Self-medication and OTC products are fairly common practice in India particularly so for AYUSH medicines. As there is a pluralistic healthcare system in India, patients often use therapeutic modalities of several traditional systems including simultaneously with conventional medicines. However, there is a relative paucity of data regarding usage of Ayurvedic medicines in the community. The potential of drug-drug or herb-drug interactions

is of concern for safety and reduced/enhanced therapeutic activity [35]. Currently, no studies are available as to the usage frequency of OTC medicines of different systems of healthcare. This has been clearly highlighted by Chandra S. She proposed that retrospective studies using interdisciplinary approaches are needed for public benefit[325]. Gayakar *et al.* had conducted the survey of community with pharmacy background and non-pharmacy community regarding knowledge about knowledge, attitude, practices regarding over the counter medications and found that their knowledge was poor hence felt the need of create awareness and educate people regarding advantages and disadvantages of self-medication[326].

It is important and relevant to investigate the extent and the nature of the field usage of Ayurvedic medicines. Ayurvedic pharmacoepidemiology approach can provide early evidence of the safety, efficacy and acceptability of Ayurvedic drugs. These studies are need of the hour. Such an endeavor may precede Observational Therapeutics and Reverse Pharmacology[24,25].

Pharmacoepidemiology has borrowed methods from epidemiology to achieve the objectives. They are case reports, case series, analysis of secular trends, case control studies, cohort study and randomised control studies. Case reports and case series are relatively less expensive and it is relatively easy quantify of incidence is done but cannot be used for hypothesis testing. Case control study is also less expensive, logistically easier and faster; can study uncommon diseases; whereas cohort study is little expensive, may take more time; however can study multiple outcomes. One may apply one or two of these methods of PE or evolve new ones for evaluating Ayurvedic medicines usage in the community.

Several approaches to unearth effective and safe drugs from Ayurvedic Management are currently available including Reverse Pharmacology, observational therapeutics, and Pharmacoepidemiology. These are important approaches to identify the hints for further drug discovery and development. In view of the multisystem use of medications in large population, it is important and relevant to study the extent of usage of traditional Ayurvedic medicines through Ayurvedic Pharmacoepidemiology (AyPE)[20]. Additional studies are also required to document the beneficial and adverse effects of the medicines through surveys, clinical, biochemical and other investigational studies in patients consuming these medicines. It will encompass fields such as Ayurvedic prescription audits, Ayurvedic drug outlets

/utilization, population pharmacokinetics / dynamics, and documentation of unexpected beneficial effects of Ayurvedic Drugs.

In this context and in view of diabetes mellitus (Type II) being a major public health challenge in India, and the cardiovascular, renal, retinal and neural complications of this metabolic disorder, the present study with AyPE was deemed worthwhile India has become the diabetic capital of the world. Diabetic patients in India have easy access to the pluralistic health care. They often consume Ayurvedic medicines for controlling diabetes, reducing side-effects, complementary use and prevention of complications[327-,328]. However, data on exact nature of usage of Ayurvedic and other traditional medicine for diabetes are scarce. Hence there is a dier need to conduct Pharmacoepidemiological studies in India[329].

Disease-centric approach is adopted for present research work through the methods of pharmacoepidemiology.

Table 5.1 Potentials and limitations of these methods are given in the table

Method	Potentials	limitations
Literature search	Baseline information is available regarding use by community and probable benefits and side effects	--
Analysis of MAAF*	Data Can be used for awareness programme	More number and various location could have done
drug utilization study	Snowball sampling method	No epidemiological design
KAP** study	Snowball sampling method	No epidemiological design
Case report	Novel benefit of integrative effect was seen	Single isolated case reports have inherent limitations
Clinical studies	Safety and activity established	---

*Marketed Ayurvedic Antidiabetic Formulations; ** Knowledge Attitude Practice

The detailed literature search that was conducted served to identify the knowledge about the Ayurvedic aspect of pathophysiology and therapeutics of diabetes (pharmacological and non-pharmacological modalities). Ancient references from Atharva Veda make the mention of polyuria and the medicinal formulations that can be prescribed. Ayurvedic classical treaties have described the condition *Prameha* (prediabetes / metabolic disorders) and *madhumeha*

with pathogenesis that needs to be understood well in the context of modern terminologies used in the literature related to diabetes mellitus. In the pathogenesis of *prameha*, involvement of ten body tissues has been mentioned, indicating that the diabetes was recognized as a systemic problem; however the manifestation mentioned was polyuria that involves the urinary system. It must be remembered that urine examination was the only examination used for diagnosis and prognosis with other symptoms till blood examination and the methods for this were discovered much later by Harvey in the 17th century [330].

Genetic predisposition, association of consumption of sweet and oily food with obesity, diabetes and cardiac disease have been described. Similarly association of increased appetite and thirst with increased adipose tissue is described. Respiratory infections urogenital infections, cardiac involvement and neurological conditions in complications with *prameha pidika* (carbuncles) are also described in detail by the sages. This information has to be studied in the light of current research to study the mechanistic understanding.

Various herbal and herbominaral formulations have been recommended as a therapy with unique Ayurvedic dravyaguna rationale for various conditions of *Prameha* and *madhumeha*. Biological plausibility of some medicinal plants having antidiabetic potential that have been written about in the texts has been published by Vaidya ADB et al [42]. Rational thinking underlying the therapeutic guidelines as a whole advocates specifically the reversal of pathophysiology (*shatkriyakalas*). Reversibility of *Prameha* and *medoroga* (prediabetes condition/ metabolic disorder) with diet, exercise and medicines has been written about in the Classics whereas Ayurveda clearly mentions that madhumeha cannot be reversed.

Studying *pathyapathya* i.e (recommended diet and physical activity) for this disease was fruitful. All the classical texts have described that over indulgence in sweet, oily and dense foods and physical inactivity are two major causes of Prameha and that it is one of the lifestyle diseases which is proven now. *Yava* (barley), *Godhuma* (wheat), *Chanaka* (Bengal gram), *mudga* (green gram), and *Kulathha* (red gram) have been recommended to be included in the diet. These foods have low glycemic indices and are now shown to have antidiabetic potential. Compositional analysis shows that they contain less amount of fat, have a relatively higher fiber content, are sources of B- vitamins, some minerals and are good sources of some phytochemicals[331-333]. Several nutraceutical combinations have entered the international market through ethnopharmacological exploration made by different traditional

practices. Pandey *et al* has discussed herbal medicines in dietary supplements of the Ayurvedic system of medicine and its role in translational medicine in order to overcome malnutrition and related disorders[334].

Exercise which was recognized as one of the *Upasthambas* is known to induce GLUT4 expression in skeletal muscles, besides helping to reduce weight and body fat. This may partly reduce insulin resistance and increase glucose uptake and storage of glycogen [335,336].

Study of labels and patient inserts of Marketed Ayurvedic Antidiabetic Formulations (MAAF) showed that the industry follows mandatory instructions for labelling the medicines such as name of the manufacturer, manufacturing date, expiry date etc; however the specific information viz. *bheshaj kala* (time of administration), *anupan* (vehicle), and indication - contraindication as per Ayurvedic concept therapy was lacking. Incorporation of the vital information about the drug's use during pregnancy and lactation and contraindication of Type 1 diabetes would make the use of MAAF safer. Plants used in these Ayurvedic antidiabetic medicinal plants are mostly of *tikta katu kashay rasa* and their combination makes the formulation bitterer. Long term use of such formulations may cause *vata-prakop* resulting in any mild to moderate side effects. Hence the dosage schedule with appropriate *anupan* should be mentioned on labels. A similar study of study of hundred labels of Ayurvedic medicines collected from Himachal Pradesh reported that guidelines as per the Drugs and Cosmetics Act, 1940 (D& C Act) were not followed appropriately[337]. Another study of fifty labels of Ayurvedic medicines also reported noncompliance with Act[338].

Brand names of the formulations were catchy may be to attract the attention of diabetic patients for self-medication; claiming antidiabetic activity. In most of the formulations, reference of the classical text in use of ingredients in prameha is mentioned. However final formulation is not tested in humans or even in animals. The names claiming complete cure from diabetes (e.g. *Pramehantak rasa* or sugar knocker, D-qwit) misguide diabetic patients. Hence concurrent use of MAAF with other antidiabetic modern drugs/oral hypoglycemic agents (OHA) may cause reducing or enhancing antidiabetic efficacy of the current antidiabetic medication from either system. Reduction of bioavailability of metformin in healthy volunteers has been reported when they were consuming orally an Ayurvedic formulation in powder form simultaneously along with metformin [35]. Geriatric population is often under poly- pill therapies increasing chances of such drug interactions. Precaution

should be printed to keep an interval of at least two hours between OHA & MAAF drugs in absence of the data from such interaction studies.

Package inserts for modern medicines are excessively detailed containing technical information also for medico-legal and for defensive purposes which cannot be understood by patients. Package inserts of MAAF did not contain such extensive information. There is a need to review the regulations for package inserts making it compulsory for industry to write vital information about the use in pediatric, geriatric population and pregnant ladies. Additionally package inserts for Ayurvedic drugs should also contain information about the ingredients, dosages, method of administration, timings with *anupan,* and *pathyapathya* (do's and don'ts) etc. along with its user friendly design /approach.

The assessment of rational combination of plants, the nature of active extracts and their impact on therapeutic outcomes can then generate globally relevant evidence. Further critical analysis of selected plants for their biological plausibility of targeting important pathophysiological mechanisms for type 2 diabetes along with understanding of its *dravyaguna* rationale are need of the time. The concept of Ayurvedic Dravyaguna rational with biological plausibility for most frequently used plant in MAAF i.e., *Eugenia jambolana* has been explored[15]. Comprehending Ayurvedic rationale of these formulations with mechanistic understanding would facilitate integrative management of diabetes. Patwardhan K *et al* has proposed crucial policy interventions to be introduced at different levels such as amendments to Drug and Cosmetic Act, providing guidelines regarding prescription, clinical monitoring and consumer guidelines. The "take home message" for the diabetic patients is not use OTC medicines for the management of diabetes. There will not be concorn of safety essues vis a vis side effects and drug interaction.

Many drug utilization studies in India and abroad have been reported for consumption of Complementary and Alternative medicines (CAM) which are often with use of some supplementary food and nonpharmacological modality with regional origin[339-342].

The survey in *Swadeshi Arogya mela* was our first pilot study to document the use of Ayurvedic and /or traditional herbal medicines for diabetes. It covered the diabetic visitors at Swadeshi Arogya mela which may not necessarily reflect field reality at large. It was deemed worthwhile to study attendees of *Swadeshi Arogya Mela* , because it would be easier to obtain

information about usage of Ayurvedic medicines. However it is acknowledge that there is selection bias and it may not necessarily reflect field reality of the community at large.

However important information gathered from the survey indicated that almost 41 % of the diabetic visitors were taking Ayurvedic medicine; more than 30 % were concurrently receiving Allopathic antidiabetic drugs. However important information gathered from the survey indicated that almost 41 % of the diabetic visitors were taking Ayurvedic medicine; more than 30 % were concurrently receiving Allopathic antidiabetic drugs.

In this survey *Methi (Trigonella foenum greacum*), *Awala (Phyllanthus emblica), Jamum (Eugenia jambolana), Neem (Azadirachta indica), and Karela (Momordica charantia)* were found to be used the frequently. All these plants have been studied for antidiabetic, antioxidant, antidyslipidemic and anti-inflammatory activities in animals and even in human. Ethnobotanical surveys of medicinal plants in India have also reported the use of *Neem (Azadirachta indica), gudmar (Gymnema sylvestree), jambu (Eugenia jambolana),* and *Bilva (Aegle marmalos)* in diabetes [343-345]. Walking was the preferred physical activity than exercise and yoga. Walking, though low impact exercise, is a good form of exercise and can be done for longer periods of time to gain metabolic health. Partly restricted diet was preferred more than a modified one. Randomized controlled trials have clearly demonstrated that lifestyle management is highly capable of preventing and managing the early stage of type 2 diabetes[346]. Concurrent use of Ayurvedic medicines with conventional antidiabetic medicines further raises question about drug interaction. It may minimize drug efficacy of one or the other[35]. AyPE will have to address to this field realities of multisystem-drug usage. The data gained by drug utilization eventually be used to review rationality of drug therapy for which more structured and detailed interviews regarding the extent of use and nature of Ayurvedic medicine are needed.

Another study of drug utilization for Ayurvedic Medicines, conducted in Type 2 diabetic Patients attending endocrine department of a tertiary health care hospital in Mumbai is one of the first of its kind as we study the Ayurvedic drug utilization in endocrine dept. of hospital in diabetic patients. In this study we found that very less number of patients of T2 DM patients (12%) were consuming Ayurvedic medicines for diabetes. The results cannot be generalised to the community may be because the recruitment of diabetic patients in this study was from only one hospital. We also noted that patients wanted to consume Ayurvedic medicines

concurrently with OHA often with the faith that Ayurvedic medicines are safe and after some time OHA can be discontinued. People often use complementary therapies to help them feel better and cope with their disease and treatment. Many complementary therapies concentrate on relaxation and reducing stress. They might help to calm your emotions, relieve anxiety, and increase your general sense of health and well-being [347.]

The medicinal plants which are consumed by the patients in powder form are *jamun (Eugenia jambolana), methi (Trigonella foenum-graecum), karela (Momordica charantia), jirak (Cuminum cyminum) and ajwayan (Trachyspermum ammi).* All these plants have beendescribed in Ayurvedic Pharmacology (Dravyaguna Vidnyan) books that are used in prameha.[208,348-350]. Clinical Studies of medicinal plants with antidiabetic potential have been reported in literature[44,129,351]. *Jamun, methi, karela* have shown anti hyperglycemic effect *in-vivo*[352-354]. *Jira, Kali Jeeri* and *Ajwain* also have exhibited their antidiabetic potential[355-357]. *Chandraprabha* and *Arogyavardhini* formulations are classical formulations, meant for fat metabolism and clinical studies have shown the antidiabetic activity also [47,50].

Study of clinical case records was another method explored to document utilization and safety of Ayurvedic medicines consumed by diabetic patients visiting at *Swasthavrutta* Department I-AIM Health Care of Foundation of Revitalization of Local Health Traditions (FRLHT), Bangalore. Retrospective study of clinical records is relatively easy and less expensive; however it may be constrained by the limited retrievable information and insufficient records**.** It is a type of research design in which pre-recorded, patient-centered data are used to answer one or more research questions bears, **Level of Evidence = III[358].** Researchers cannot control outcome assessment, and instead have to rely on others for accurate record keeping. Some key statistics cannot be measured, and significant biases may affect the outcomeof the study.

In this study of case records, Ayurvedic therapy for diabetes was found to be clinically safe as patients did not report nor they discontinued the treatment because of any adverse event. Use of the Ayurvedic formulations resulted in significant reduction in glucose and HbA1c. Prospective study of case records along with use of biomarkers would give better insights into Ayurvedic antidiabetics.

Various data sources like case charts, computerized registries are available for organising such reviews. However each has its own specific strengths and weaknesses. It is a useful method of analysis of recorded data [359-360]. Although pharmacoepidemiology uses all epidemiologic study designs and data sources, in recent years there has been enormous growth in the updating the databases for pharmacoepidemiological studies[361]. One of the retrospective studies of case records of hospitalised children with type 1 diabetes assessed the predictors of adverse outcome in patients with T1DM[362]. In an another retrospective study of clinical records of diabetic patients in an academic naturopathic outpatient clinic, patterns of patient status, details of treatment recommendations, and levels of evidence have been studied and reported by Bradley et al[363]. Panda AK reported safety and efficacy of IME-9 tablets in newly diagnosed diabetic patients by studying individual data retrospectively [364].

KAP Surveys give us the field reality and illustrate the knowledge of people about certain things, how they feel, and how they behave. The design is easy, can get qualitative and quantitative data, and can easily generalise the results. Our KAP survey of diabetic patients presented that 66 % patients have knowledge about diabetes. This shows more than 40 % patients need awareness program regarding diabetes. Overall attitude and practice components were still lower than knowledge component (mean± SD of knowledge, attitude and practice was 9.69±3.4, 6.95±1.8, and 7.53±2.5 respectively). Although the practice levels among our study participants are lower than anticipated; there is a need for structured programmes to improve knowledge of patients. Patient education and training are the needs of the hour now to maintain the health of diabetic patients as India has become the diabetes capital of the world with more than 62 million diabetic Indians, which is more than 7.1% of the adult population[365,366] Diabetes self-management education has been reported to statistically significant decrease in A1C levels. [367]

In India, N. Murugesan et al reported the low median score of awareness in general population (n=3681) in southern India especially in women and subjects with low education. He also recommended the urgent need for strategies to spread awareness about diabetes in the diabetic patients as well as in general population[368]. Viral N. Shah from Saurashtra region, Gujrat surveyed 230 diabetic patients attending tertiary education hospitals in Gujrat-and found that half of patients agreed that exercise supported their diabetes control, 75% knew that diet was important in diabetes control . Most of them believed in self-care[369]. The

difference in finding among diverse studies done in various regions may be due to patient's educational status, environment, and healthcare facilities.

In another KAP survey of Ayurvedic physicians we noted 50.4 % of Ayurvedic physicians had ≥ 75 percentile of knowledge score and 29.4 % had ≥ 75 percentile practice scores . Our study reveals good knowledge compare to practice. Medical practitioners in India have been surveyed for Knowledge, attitude, and practices towards diabetes management. Shera *et al* reported overall 62% family Physicians from Pakistan have good knowledge about diabetes management [370].Gawde *et al* surveyed allopathic resident doctors and reported that allopathic resident doctors had little knowledge about Ayurveda and Ayurvedic medicine use but are engaged in prescription of Ayurvedic medicines[371] . Ayurvedic physicians are surveyed for use of Masanumasik Kashaya during pregnancy[372]. The potential drawback of our study is a report from a single study hence cannot be generalized to the diabetic population of Mumbai.

In order to study the pharmacological activity and safety of selected Ayurvedic formulations using conventional laboratory -based techniques, path of Reverse Pharmacology was chosen. Vaidya et al coined this term for the drug discovery and development from natural product. The process is less expensive, less time consuming and having less bottle necks. Reverse Pharmacology is defined as the science of integrating documented clinical/experiential hits, into leads by transdisciplinary exploratory studies and further developing these into drug candidates by experimental and clinical research[373]. Reverse pharmacological approaches depend mainly on available data on actual human use (drug utilization), clinical experiences and observations of physicians with literature trends. This experiential knowledge is then tested experimentally to draw action of mechanisms. Concurrent paraclinical targets and models are setup and /or tested with relevant science for the drug candidate. Thus, natural products may be studied on fast track using innovative approaches and technologies for drug discovery and development[374,375].Hence study of drug utilization under Ayurvedic Pharmacoepidemiology would be vast reservoir to choose the hints for reverse Pharmacological studies. However Survey tools have to be designed and validated for Ayurvedic Pharmacoepidemiology.

Nisha Amalaki is the formulation recommended by all the Ayurvedic samhitas for the management of *Prameha* and *Mamejava Ghana vati* is the formulation which is prevalently used by diabetic population especially in Gujarat and Saurashtra region. Both the

formulations were studied for antidiabetic effect in diabetic patients and for drug interaction in healthy volunteers also. *Nisha amalaki* was found beneficial to reduce insulin resistance and *Mamejava ghanavati* was beneficial to reduce postprandial glucose excursion and glycation as well as to reduce hypertryglycerides.

Drug-drug interactions have clinical relevance when oral hypoglycemic agents (OHA) are co-prescribed with statins, and anti-hypertensive agents. Herbs and drugs may have pharmacodynamic or pharmacokinetic interactions. Metformin is known to have interactions with several drugs, diet and even with *Guargum.* In order to have the benefits of complementary therapy, it is important to carry out specific drug interaction studies before advising integrative therapy. Keeping interval betweenthe administrations of these medicines with respect to metformin can help in avoiding drug interaction[35].

In Reverse Pharmacology (RP) discipline exploratory study having knowledge of human use are regarded as being equivalent to Phase II studies of clinical pharmacology. As this was an exploratory study other antidiabetic drug/placebo were not used. Based on this further clinical study was conducted by the Institution wherein Mamejava ghanavati was compared with metformin. But that was not part of my thesis.

Market samples of *NishaAmalaki* (Combination of *Curcuma longa* Linn and *Phyllanthus emblica* Linn) and *Mamejava Ghana (Enicostemma littorale* Blume) were screened for α glucosidase inhibition activity at Life Sciences laboratory; Trans-Disciplinary University – Bangaluru , and their active principles were screened at KHS –MRC, Mumbai

Alpha Glucosidase enzyme from the brush border of intestine hydrolyses the starch to glucose which is then absorbed in intestine. The concept of inhibition of alpha glucosidase enzyme was thought by Schmidt lower blood glucose in 1977[376]. The first agent in the class Alpha Glucosidase inhibitors (AGI) was Acarbose, isolated from cultures of Actinoplanes. The placement of AGI is thought to be in the management of diabetic patients with rice dominant carbohydrate rich meals. It needs to be taken just before the meals as it affects conversion of complex carbohydrates. Selected MAAF and phytoactives showed dose dependent inhibition of the enzyme suggesting a new target for antidiabetic drug discovery from natural product. From the same laboratory *Lodhrasava* (medicated fermented

formulation) and combination of *Nishaamalaki* with honey also have showed significant effect on enzyme inhibition [377,378].

Limitations of the study and Challenges faced:

- Drug Out lets: No computerized data is available. No central body is known to get information. Therefore snowball sampling was resorted to in the present study.
- Manufacturers & pharmacy shopkeepers are reluctant to give information. Hence very little information could be obtained from these sources.
- Drug usage: India has a geographical variation in usage of traditional medicines. E.g. Siddha Medicines are prevalent in Tamilnadu region and Ayurveda is prevalent in Kerala region. The present study was restricted to use of Ayurvedic system.
- Training of staff: To study the effect of Ayurvedic drugs in community competence is required which is difficult. Consensus of Ayurvedic physician, clinical Pharmacologist, Epidemiologist is important. Hence training of staff is needed.
- Methods, Analytical tools and statistics are lacking.
    - Insufficient Documentation.

5. Conclusions

“All our dreams can come true if we have the courage to pursue them.”

– Walt Disney

Conclusions-

The present study has made a modest beginning in Ayurvedic Pharmacoepidemiology and Therapeutics of Madhumeha, by conducting studies using designs of epidemiology and pharmacoepidemiology. As a matter of fact, it is in line with the latest policy of US FDA for research grants for Real-World Data (RWD) and Real-World Evidence (RWE) [379]. Immense efforts and years of research and huge amounts of money have been spent on preclinical, and clinical Phase 1,2,3 and 4 trials. In spite of discovery of new drugs, for many, the costs of managing hospitalization are high, mortality due to Adverse Drug Reactions (ADRs) and Drug Interactions (DIs) due to some of the new molecules has been reported. Consequently, this has drawn the attention of regulatory authorities to the possibility of studying traditional medical systems such as Ayurveda for new mode(s) of safe drug use and also new drug discovery.

It is now proposed that ‘large or mega- data available from pharmaco-epidemiological studies from real world use can be collected and will be very useful for identifying ADRs, Drug Interactions which may not have manifested in limited number of patients registered for post-marketing surveillance for five years. Ways of avoiding ADRs by new combinations or therapeutic management can be identified. Additionally this could contribute to new drug development through repurposing of drugs, with proven safety, for new indications.

Reverse Pharmacology, initiated by Dr Ashok B Vaidya, our Research Director, as the tool for identifying safe and effective Ayurvedic formulations and also as contributing to new

drug development is the key for research in Ayurvedic medicine. Fig 5.1 deals with the diverse paths of drug development from medicinal plants .These paths are not mutually exclusive. However Reverse Pharmacology path is likely to provide globally acceptable drugs by assuring quality, safety, and experimental and clinical evidence of activity and efficacy. NMITLI projects adopted this path with fruitful results for several indications viz arthritis, hepatitis, diabetes

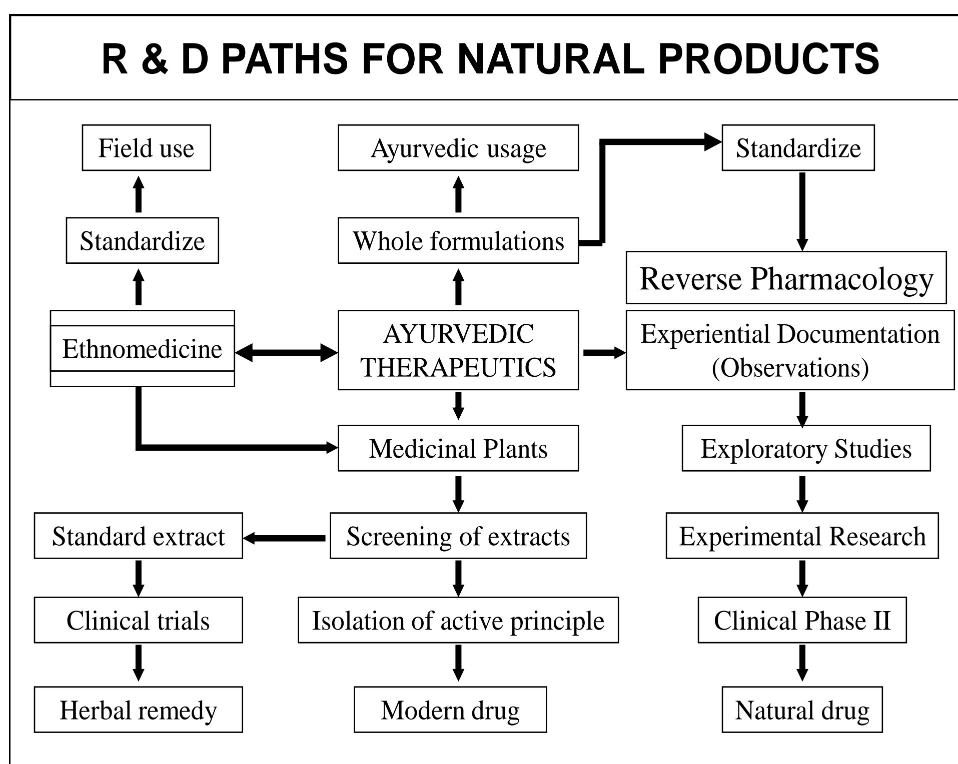

Fig 6.1 The diverse paths of drug development from medicinal plants.

It can be seen from the figure that this path can lead to new drug discovery. This has led to many leads and hits in drug development as can exemplified by *Mucuna pruriens, Kutaki, Nisha-Amalaki, Panchavalkal, Ashwagandha, Mamejawa,* Phytoestrogens etc [373]. This has contributed to the acceptance of a new category of 'Phytopharmaceutical' by the Drug Regulatory authorities in India and also to the concept of 'Ayurceuticals'[380]

Another approach, unique to our Centre is the discipline of Ayurvedic - pharmacoepidemiology which was initiated in 2003 by Vaidya RA *et al*[20]. One student has already received a doctoral degree from Pune University on 'Pharmacoepidemiology of Ayurveda Medicines for Arthritis' by Dr Girish Tillu (Pune University 2016). This thesis

represents the second of such efforts. The focus of the present thesis is antidiabetic formulations because India is now unfortunately the Diabetes capital of the world. This as stated earlier is similar to the RWD and RWE of the new initiatives by the FDA.

Reverse Pharmacology allows us to identify through literature search, experiential and exploratory studies hits and leads of clinical significance in diseases of interest. It allows us to conduct paraclinical '*in vitro*' or *'in vivo'* studies and strengthens the case for marketed formulations or new extracts or molecules. Ayurvedic Pharmacoepidemiology (AyPE) allows us to weed out undesired and poor quality formulations. Studies based on RP & AyPE can help us in new drug discovery also.

As medicinal plants have diverse utility for multiple health conditions, AyPE will help to capture new indications for a given plant. This will be a challenge as Ayurvedic measures comprise not only the medicines but *pathapathya* also. Hence to evaluate both efficacy or adverse effect, association of *bala, prakriti, kala, matra, agni, vaya, satva, satmya, ahara* should be kept in mind. Many formulations are also used as preventive or promotive health measures for long term and often as self-medication. Additionally, some of Ayurvedic formulations are given as therapeutic modality for the treatment of identified diseases with different doses or as combinations. Hence it is a challenge to identify purpose of its use as well as periodicity (seasonal) or duration of the regimen. In order to elicit therapeutic rationale of Ayurvedic medicine as per Ayurvedic Pharmacodynamic properties AyPE will have to pool expertise of Ayurvedic Physicians, clinical pharmacologists and epidemiologists.

The notable outcomes of the study, as per the objectives as below:

1. MAAF survey-

A large number of oral antidiabetic Ayurvedic formulations are available without prescription in Indian market today with brand names claiming the antidiabetic therapeutic activity. Appropriate guidelines for standard labeling, instructions for patient and physician detailing timing and frequency of dosing, indications and contraindications for Ayurvedic medicines need to be evolved. Ayurvedic manufacturers need to consider and register their trade names under Trade Mark Registration act to avoid duplicity and misuse of same names, across the state of India. Drug regulators should continue to license MAAF with brand names but exercise caution to avoid brand names that convey exaggerated claims. The results of this

study highlight the need for regulatory authorities to develop guidelines and regulations in this regard.

2. Correlation of Ayurvedic text information and & marketed formulations:

Eujenia jambolana Linn (*Jambu*/ Black plum; *E jambolana*) was found to be frequently (62.8%) used ingredient in Marketed Ayurvedic Antidiabetic Formulations. Hence it was selected for the review on correlations of dravyaguna with biological antidiabetic plausibility. In view of the need to address multiple targets besides hyperglycemia, the diversity of Ayurvedic properties of the plant can be reviewed for integrating the available phytopharmacological data. Ayurvedic dravyaguna rationale and Biological Plausibility (BP) of Eugenia for anti-diabetic activity are currently reviewed in view of developing a new drug candidate for type 2 diabetes mellitus using Reverse Pharmacology. Classical and emerging Ayurvedic literature as well as modern pharmacological literature of the plant were reviewed here for Ayurvedic properties and biological plausibility for anti-diabetic potentials.

3. To study the utilization patterns of MAAF, OHA as mono system antidiabetic drugs as well as concurrent use of both among known diabetic patients.

3.1 *Swadeshi Arogya Mela* in Mumbai:

Forty one percent (41%) of diabetic patients were consuming traditional Ayurvedic medicines. The most common MAAF were *Lokmanya Churna, Madhumehari Dane, Tablet Diabecon,* Capsule *Karnim and* Capsule *Karela*. Besides MAAF, diverse combinations of Ayurvedic medicinal plants viz *Karela, Methi, Jamun, Neem, Awala* also were taken by the patients.

3.2 Drug Utilization Survey at a Tertiary Health Care center in Mumbai

Only 33 (21 men and 12 women) of 279 diabetic patients were consuming Ayurvedic Medicine concurrently with conventional Antidiabetic medicine for the management of the disease. Positive family history was present in 20 of 33 subjects. These patients obtained their Ayurvedic medicines mainly from Ayurvedic Aushadhi Bhandars at their convenience; however friends, relatives, kirana (grocery shops), and chemists were also the source of medicine for the patients. Reduced blood sugar (13/33) was the commonest benefit of taking Ayurvedic medicines reported.

3.3 Retrospective survey of clinical case records at Ayurvedic Hospital of FRLHT (Bengaluru)

The use of patented medicines is more than classical formulations-this is an important observation. There was significant reductions in mean of FBG ($p < 0.05$), PPBG ($p < 0.005$) and HbA1C ($p < 0.005$) after 6 months compared to baseline. The study shows limited retrievable information and insufficient records. Review of records requires adequate planning and use of appropriate data sources.

Data generated by drug utilization study on usage on Ayurvedic formulation and/or therapy will help to register new drugs. Data on adverse drug events/reaction will help to prepare registry which will contribute to develop data on indications, contraindications, and rational prescription of the drug. Data regarding novel beneficial effect will help to increase the usage of the drugs by the patients and quality of life. Either beneficial or adverse effect or no effect will throw light on drug interactions and provide an area of research.

The study of labels and drug utilization surfaces the issue of medication error. Medication error may occur because of illiteracy, unawareness, miscommunication and irrational use of medication. Medical audit is the process of quality improvement that seeks betterment of patient care and outcomes. A prospective, observational study of medication errors was conducted in prescriptions of 1109 patients. It reported that potential significant Drug- Drug Interaction (DDI) were observed in 191 (17%) and serious DDIs in 48 (4%) prescriptions only 170 (17%) prescriptions were rational. Majority of prescriptions were semi rational (53%) followed by irrational (30%)[381] .Medication error can be prevented by promoting educational actions on prescribing guidelines, availability of computarised alert system, executing the tools of guidelines, involving encouraging multidisciplinary team in patient care with a pharmacist[382]. World Health Organization (WHO)-has recommended core drug use indicators to prevent irrational use of medicines[383]. Such a concept is lacking in traditional medicines.

4. To assess Knowledge, Attitude and Practices (KAP) of diabetic patients regarding diabetes

Knowledge ($p=0.0007$) Attitude ($p=0.0001$) and practice ($p=0.0001$) regarding diabetes was significantly different when compared to level of education. It was interesting to note that those who had knowledge ≤ 25 percentile were following good practice ($p= 0.0001$).

Knowledge and Practice scores of the participants as per the age groups are shown found to be significantly different. ($P=0.0001$).

Awareness of diabetic patients regarding management of their diabetes is very important. Proper management can help to decrease economic burden as well as prevent complications in patients. The results of the present study highlight the need for education of community at large about diabetes, its causes, its effects and appropriate management through variety of communication channels. There is a need to tackle the myths and wrong beliefs that may prevail in the community.

5. To assess Knowledge, and Practices (KAP) of doctors prescribing these drugs. Knowledge and practices of Ayurvedic Physicians towards diabetic management:

   Among all physicians, 50.4% physicians had ≥ 75 percentile of knowledge, and 29.4 % physicians had ≥ 75 percentile of practice points. Percentages of knowledge scores and practice scores were calculated to compare knowledge and practices; however the number of MD doctors in the study is almost 50% of that of BAMS doctors which was one of the limitations.

   Ayurvedic physicians must be encouraged for Integrative management. Diabetes management has been shifted from only anti- hyperglycemic activity to antidiabetic activity. Use of physical activity, appropriate diet and sufficient sleep has proven antidiabetic activity. Awareness about the safety of conventional medicine has compelled the community to incline towards traditional or Ayurvedic Medicines; however there is no computerised data available regarding use of medicines from Ayurvedic drug stores as in Netherlands. Hence Drug outlet studies for drug usage were not possible in India.

6. To study the pharmacological activity and safety of selected Ayurvedic formulations using conventional laboratory -based techniques using Reverse Pharmacology

   Clinical studies of selected Ayurvedic Antidiabetic formulations under the project CSIR NMITLI Diabetes:

   6.1 *Nisha amalaki* trial: There was no significant effect of the formulation observed on glucose or lipids; however reduction in HbA1C, micro albuminuria and CRP suggest the need to focus on anti-inflammatory and anti-oxidant activity. Hence the study with experimental design was planned to find out activity in newly detected patients with type-2 diabetes. The study exhibited a definite lowering of blood sugar level (OGTT values) in the newly detected diabetic patients with Medical Nutritional Therapy (MNT) and *Nisha amalaki* – DM-FN 01

(NA) as compared to only MNT at the end of 30 days of therapy. The study showed reduction in $HbA_{l}c$ values at the end of 30 days of therapy in the MNT + NA group as compared to MNT only. It was of interest to observe that $HbA_{l}c$ values of MNT group also decreased at the end of 60 days when NA was added for last 30 days

6.2 Mamejava Ghana vati trial: DM-FN-02 at the prescribed dose (i.e. 250 mg TID x 2 weeks, then 500 mg TID x 6 weeks) was found to be safe with good tolerability and acceptability. It has not shown any anti-hyper or hypoglycemic activity in the fasting glucose as well as fasting insulin values; however significant reduction in HbA1c values ($p<0.0001$) and in postprandial plasma glucose ($p<0.003$) was observed. No significant change was observed in S. Cholesterol after the treatment. However, positive directionality was observed in fasting S. triglycerides values. There is significant change in S. Triglycerides above the normal values ($p<0.002$). Directionality in PAI-1 and CRP markers suggests the decrease in inflammation.

6.3 Drug interaction studies of these 2 formulations with metformin :

Simultaneous administration of DMFN01, showed a reduction in the mean C_{max} (a mean decrease of 55%), and in the mean of AUC (0-24 h) (mean decrease of 51%) of metformin (Student's paired *t*-test; $P < 0.002$).There was no significant difference in the mean AUC of metformin with or without DMFN02. The study showed herb drug interaction and propose time interval between conventional and Ayurvedic Medicine.

CSIR NMITLI Diabetes study showed the evidence of anti hyperglycemic, antidyslipidemic, antioxidant, anti-inflammatory activity of Ayurveda inspired formulation Mamejava ghana vati for diabetes. Concurrent *in-vivo* and *in-vitro* experiments using this plant have shown its anti-oxidant, anti-inflammatory activity along with DNA repair activity using various targets and mechanisms. The plant has reached to the drug candidate stage by these Reverse pharmacology approach. Many studies report the antidiabetic activity of medicinal plants which need to be studies under Reverse Pharmacology Path so as to get drug candidates.

6.4 Alpha Glucosidase inhibition activity

All the four marketed samples of *mamejawa* inhibited α-G activity in a concentration dependent manner however phytoactives of *E. Littorale* showed marginal activity.

Alpha Glucosidase inhibition study by MAAF and phytoactives showed dose dependent inhibition of the enzyme suggesting a new target for antidiabetic drug discovery. These methods showed the scope for new molecules – identification of beta glucosidase inhibitors in Ayurvedic formulations.

Although Ayurvedic medicine is being practiced for centuries there have been no published data on marketed drugs, particularly with respect to minimal essential information that should be available for the physicians or consumers and most of the practice has been largely based on trust. Data on several hundred years on usage of Ayurvedic Traditional Medicines in general and diabetes in particular has not been collated and published. Nevertheless it is obvious from the market survey conducted and reported in the thesis, the first of its kind, that information on many marketed formulations is far from satisfactory and this leaves the consumers very vulnerable because of false assumption about formulation, standardization and proper indications, dosage, or drug interactions. Indeed it can be dangerous because most of these formulations are available as OTC preparations.

Summary

The present study has made a modest beginning in Ayurvedic Pharmacoepidemiology and Therapeutics of Madhumeha, by conducting studies using designs of epidemiology and pharmacoepidemiology. As a matter of fact, it is in line with the latest policy of US FDA for research grants for Real-World Data (RWD) and Real-World Evidence (RWE)

Although Ayurvedic medicine is being practiced for centuries there have been no published data on marketed drugs, particularly with respect to minimal essential information that should be available for the physicians or consumers and most of the practice has been largely based on trust. Data on several hundred years on usage of Ayurvedic Traditional Medicines in general and diabetes in particular has not been collated and published. Nevertheless it is obvious from the market survey conducted and reported in the thesis, the first of its kind, that information on many marketed formulations is far from satisfactory and this leaves the consumers very vulnerable because of false assumption about formulation, standardization and proper indications, dosage, or drug interactions. Indeed it can be dangerous because most of these formulations are available as OTC preparations.

Classical and emerging Ayurvedic literature as well as modern pharmacological literature of the plant was reviewed here for Ayurvedic properties and biological plausibility for anti-diabetic potentials. The study of labels and drug utilization surfaces the issue of medication error. Data generated by drug utilization study on usage on Ayurvedic formulation and/or therapy will help to register new drugs. Data on adverse drug events/reaction will help to prepare registry which will contribute to develop data on indications, contraindications, and rational prescription of the drug.

KAP survey of of diabetic patients regarding diabetes highlights the need for education of community at large about diabetes, its causes, its effects and appropriate management through variety of communication channels.

CSIR NMITLI Diabetes study showed the evidence of anti hyperglycemic, antidyslipidemic, antioxidant, anti-inflammatory activity of Ayurveda inspired formulation Mamejava ghana vati for diabetes. Concurrent *in-vivo* and *in-vitro* experiments using this plant have shown its anti-oxidant, anti-inflammatory activity along with DNA repair activity using various targets and mechanisms. The plant has reached to the drug candidate stage by these Reverse

pharmacology approach. Many studies report the antidiabetic activity of medicinal plants which need to be studies under Reverse Pharmacology Path so as to get drug candidates.

Alpha Glucosidase inhibition study by MAAF and phytoactives showed dose dependent inhibition of the enzyme suggesting a new target for antidiabetic drug discovery

Reverse Pharmacology, initiated by Dr Ashok B Vaidya, our Research Director, as the tool for identifying safe and effective Ayurvedic formulations and also as contributing to new drug development is the key for research in Ayurvedic medicine.

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