Effectiveness of Constitutional Homoeopathic treatment in cases of Upper Gastrointestinal disorders in Diabetic patients- A clinical trial

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Abstract-
Background: Prevalence of Diabetes has increased along with its gastrointestinal (GI) problems. Aberrant GI motility is a complication of GI tract-related diabetic autonomic neuropathy. Drugs employed to manage these complications takes long time and accompanied by significant side effects. The use of constitutional homoeopathic medications to reduce the burden of upper GI issues in DM patients has a scope. It is proposed to undertake this study to scientifically validate if the constitutional homoeopathic treatment is effective in treatment in cases of suffering from UGI disorder in diabetic patients.
Aims: To see the effectiveness of Constitutional Homoeopathic treatment in cases suffering from UGI disorders in Diabetic patients.
Objectives: To see improvement in Patient Assessment of Gastrointestinal Disorders–Symptom Severity Index (PAGI-SYM) scale in patients of UGI disorder in diabetic patients and to see changes in FBS and PPBS before and after the treatment of the patients.
Inference: the study concluded that in all the cases the calculated p- values of weight of the variables are less than 0.0001, so we can infer that there were significant changes between the baseline values and that after 2 months of treatment in PAGI-SYM scores, PPBS scores and FBS scores.

Keywords: **Constitutional Homoeopathic Treatment, Upper GI symptoms, Diabetic Patients, PAGI-SYM score.**

I. INTRODUCTION

According to the WHO, gastro-oesophageal reflux disease without oesophagitis is classified medically as diseases of the digestive system, with ICD-10 code K21.9. Diabetes frequently manifests as digestive problems, which can cause severe discomfort and incapacity. Diabetes produces a wide range of symptoms, such as heartburn, nausea, vomiting, abdominal discomfort, diarrhoea, and constipation, and it affects practically every portion of the digestive system, from the oesophagus to the rectum.

The enteric nerve system plays a more significant role in gastrointestinal disorders than autonomic neuropathy. A review revealed changes in the enteric nervous system, including enteric neurons, Cajal interstitial cells, and neurotransmission in diabetic individuals and animal models.[1]. Gastrointestinal symptoms like nausea, vomiting, diarrhea, abdominal discomfort, and constipation are frequently linked to diabetes mellitus (DM).[2,3.] Diabetes affects nearly every section of the gastrointestinal tract, yet some research indicates that it is uncertain how common diabetic gastroenteropathy is.[4,5] Diabetes mellitus is linked to a reduced baseline tone of the lower oesophageal sphincter (LES) of the esophagus, which may increase the symptoms of gastroesophageal reflux disease (GERD) [6]. Patients with DM who have decreased peristaltic motions have been shown to have delayed oesophageal motility in the esophagus[7]. According to reports, the prevalence of DM-related silent oesophageal dysmotility is higher than what patients describe based on their symptoms.[8,9] Numerous disruptions in the stomach's gastric motility have been documented as a consequence of diabetes mellitus. Diabetes mellitus (DM) has been associated with delayed stomach emptying and gastroparesis [9, 11] as well as with rapid gastric emptying, particularly in the early stages of the disease. Early satiety and dyspeptic symptoms have been linked to impaired relaxation of the gastric fundus.[12,13] Electrophysiological investigations have demonstrated slow wav contraction dysarhythmias, prolonged pyloric contractions, and poor duodenal-antrum coordination.[14,15,16] Due to the effects of neuropathy and hyperglycemias on GI motility, patients with diabetes experience a wide range of GI symptoms.[17,18]

It has been found that 76% of outpatients exhibit one or more gastrointestinal problems. Among diabetic patients,[19] and 50–55% experience upper GI discomfort [20, 21]. Heartburn and dysphagia are caused by oesophageal symptoms of

diabetic neuropathy, such as aberrant peristalsis, spontaneous contractions, and decreased lower esophageal sphincter tone [22,23]. There is conflicting evidence about the connection between dysmotility and hyperglycemia. Obesity, hyperglycemia, and reduced bicarbonate release from parotid glands are additional potential risk factors for reflux disease associated with diabetes [24].

The inability of the stomach to empty and move normally is the hallmark of gastroparesis. Prolonged gastric emptying postpones significant morbidity from anorexia, vomiting, nausea, and fullness in the stomach [25]. Type 1 and type 2 diabetes mellitus are known to produce gastroparesis and are usually linked to impaired stomach motility [26, 27]. There is variability in the association between symptoms and delayed stomach emptying, and some people with delayed gastric emptying may not have any symptoms at all. According to cross-sectional research, delayed stomach emptying is present in between 30% and 50% of people with type 1 and type 2 diabetes [28,29]. Diabetic gastroesophageal reflux disease is a cause of substantial morbidity in patients, resulting in frequent nausea and vomiting, whereas in other individuals it may just show up as erratic hypo- and hyperglycemia with a generally abnormal glycemic control [30]. For this reason, "gastric hypoglycemia" is a well-researched phenomena [31, 32], and it could play a significant role in explaining hypoglycemia that remains unexplained in people with brittle diabetes [32, 33].

Up to 41% of diabetics may experience symptoms of gastroesophageal reflux disease[33]. About 30% of patients with type 2 diabetes and 27%–65% of patients with type 1 diabetes exhibit delayed stomach emptying [34]. Patients with diabetes mellitus may also be more prone to suffering GI symptoms depending on their ethnicity. According to a study's findings, people with diabetes mellitus may have reduced wellbeing and quality of life as a result of gastrointestinal issues. GI symptoms have been shown in the literature to have a negative effect on diabetes mellitus patients' health-related quality of life [35, 36]. Furthermore, a number of studies have demonstrated that individuals with type II diabetes have a higher prevalence of GI symptoms and a lower quality of life [36,37,38, 39]. The occurrence in patients with Type II Diabetes had higher rates of GI symptoms and worse quality of life since they make up a larger proportion of the patient population [40].

According to a study, the use of metformin is strongly and independently associated with diarrhoea and faecal incontinence, which are the only gastrointestinal symptoms that seem to be induced by oral hypoglycaemias [41].

A study found that patients who got the intervention diet had a considerably larger reduction in the intensity of the main gastroparetic symptoms, including regurgitation/heartburn [42], postprandial fullness, and bloating. Patients who received the control diet did not exhibit these symptoms as much. Therefore, a wide range of upper and lower gastrointestinal diseases that are inextricably linked to patients' quality of life have been linked to diabetes mellitus. Modern medicine has a plethora of options for managing these episodes, ranging from PPI to cutting-edge compounds. The goal is to identify a gentle homoeopathic option because homoeopathy has demonstrated efficacy in treating various problems of diabetes mellitus on multiple occasions.

In an article of Associations Physicians India, One of the most common illnesses of the gastrointestinal system is gastroesophageal reflux disease, or GERD. It is well documented to frequently coexist with other chronic conditions like obesity, diabetes mellitus (DM), hypertension, asthma, and chronic obstructive pulmonary disease (COPD). Questionnaires, such the frequency scale for the symptoms of GERD (FSSG), are a quick, easy, noninvasive, and affordable way to examine symptoms. These surveys are frequently used to help with diagnosis and finding the right course of treatment. Clinical results for people with GERD may be enhanced by prompt identification and treatment. Nonetheless, data suggests that prolonged and high PPI use is associated with unfavourable incidents. This study presents an evidence-based summary of the association between GERD and obesity, COPD, asthma, diabetes mellitus, and hypertension in addition to an overview of the diagnosis and treatment of GERD[43]. In a study highlights the importance of questioning patients about QOL impairment due to abdominal symptoms, especially in the early and the late periods of diabetes[44].

II. AIMS

To see the effectiveness of Constitutional Homoeopathic treatment in cases suffering from upper gastrointestinal disorders in Diabetic patients.

III. OBJECTIVES

Primary objective- To see the improvement in Patient Assessment of Gastrointestinal Disorders– Symptom Severity Index (PAGI-SYM) scale[46] in UGI disorder of diabetic patients.

Secondary objective- To see changes in FBS and PPBS before and after the treatment of the patients.

IV. MATERIALS AND METHODS

Study setting and Study duration-
The study is carried out in OPD, IPD, of RVHMC and Hospital Dabok, Udaipur. Sample collected from OPD, IPD and Diabetic OPD, Diabetic camp organized by RVHMC. It is a 36 months study of diabetic patients, with follow up every 15 days interval.

Selection of samples-
50 diabetic patients with upper gastrointestinal disorders were screened for evaluation, and selected on basis of judgmental sampling on the basis of inclusion and exclusion criteria.

Diagnostic criteria-
GERD is characterized by acid reflux disease (GERD), which is described as heartburn that occurs more than twice a week and leaves the mouth tasting bitter, sour, or acidic, or by regurgitating food or liquid. Based on self-reported symptoms, GERD participants were removed if their predominant medical complaint was any another GI condition, such as oesophagitis, peptic ulcer, or irritable bowel syndrome.

Three criteria were used to define dyspepsia: (1) early satiety plus postprandial fullness, two times per week, without constipation or vomiting (a subject had to meet both criteria, but only one frequency requirement); (2) frequent nausea, one day per week, with or without vomiting; or (3) Rome II criteria of upper abdominal pain or discomfort [45.]

Inclusion criteria –
- Patients of age group 30-60 yrs.
- Patients suffering from upper gastrointestinal disorder of at least 1 month duration.
- Patients regularly taking medicines at least 4 days a week for upper gastrointestinal disorders.
- Patients suffering from diabetes mellitus at least 5 years duration.

[Note: Patients on life-saving conventional drug therapies, e.g. anti-diabetics, anti hypertensive's, thyroid drugs etc. for co-morbidities under control, will be continued]

Exclusion criteria –
- Patients diagnosed with any severe micro vascular complications of DM.
- Patients with Psychiatric illness.
- Patients diagnosed with surgical upper gastrointestinal diseases.
- Evidence that dyspepsia was exclusively relieved by defecation or associated with change of stool frequency or form or heartburn as primary complaints.
- Patients with known liver diseases like hepatitis, cholelithiasis, etc.
- Non-ambulant patients.
- Uncontrolled, unevaluated and/or complicated diabetes mellitus, hypertension, and other co-morbidities.
- Patients with any vital organ failure.
- History of homeopathic treatment for any chronic disease within last 6 months.
- Self-reported immune-compromised states.
- Alcohol/drug addiction or dependence.
- Inability to comply with the study protocol.

Withdrawal criteria-
- Acute emergency condition if developed during the study.
- Patient not complying with regular follow up schedules.
- Occurrence of serious adverse event(s) or serious intercurrent illness.

Study design
The study was an open, interventional, prospective, single arm, non-controlled study. It was a 36 months study of diabetic patients, with follow up every 15 days interval till 2 months in a standard case taking format.

Patient Assessment of Gastrointestinal Disorders–Symptom Severity Index (PAGI-SYM) scale is fulfilled at baseline and at 8 weeks interval. So each patient was be evaluated for 8 weeks to see the consequent improvement present or not.

The PAGI-SYM is a brief symptom severity instrument that measures common GI symptoms. Results suggest that the PAGI-SYM is responsive and sensitive to change in clinical status in subjects with GERD or dyspepsia. Diabetic diet and management as per norms was strictly followed and patients were advised to follow managements.

Intervention-
Patients were given homoeopathic medicine in appropriate potencies based on the presenting totality of symptoms. Homeopathic medicine in 6cH, 12cH, and 30cH potencies used in the study was dispensed from the already available storage of medicine in the pharmacy of the institution. Patients were given homeopathic medicine, selected on the basis of totality of symptoms. Repetition was done depending on the case where needed.

Data Recording and Analysis-
Data was recorded in authenticated and approved case taking along and follow-up sheet with recordings of Fasting Blood sugar and Post prandial Blood sugar along with the PAGI-SYM index for these patients.

Data analysis was done under the guidance of a statistician.

V. ANALYSIS AND INTERPRETATION OF DATA COLLECTED

Data analysis- detailed analysis, presentations and interpretation of the research data concerning the improvement of PAGI-SYM score and FBS, PPBS of Diabetic patients were collected and maintained in proper excel sheets of follow up. The study was guided by the objectives of the study. **The data was analyzed using R software latest version 4.3.2 available** at https://www.r-project.org. and the results were presented in the following tables and figures.

At first, we have calculated some descriptive summary measures of the data sets and performed the A-D goodness of fit tests. In Figure 1, the histograms (based on relative frequencies) corresponding to all the instances are presented.

Inference: If the A-D test p- value is more than 0.05, the data set is believed to be normally distributed. One can then proceed for a paired t- test for further statistical analysis regarding the test of significance. In case the A-D test p-value is less than 0.05 then the data set is not believed to be normally distributed. Under such a scenario, one should preferably go for the statistical test known as the Wilcoxon Signed Rank test.

From the results in Table 1, it is evident that PPBS scores at baseline and PAGI-SYM scores at baseline can be believed to be originating from normal distribution since their p-values are greater than 0.05. On the other hand, the other scores cannot be thought of as generating from normal population since the associated p-values are less than 0.05. Similar behaviour is reflected in the histogram plots. Hence, we go for the appropriate tests of significance of the PAGI-SYM scores, PPBS scores and the FBS scores before and after 2 months of treatment. The results are available in the following Table 2.

Inference: As we can see that in all the cases the calculated p- values of weight of the variables are less than 0.0001, we can infer that there was a significant change between the baseline values and that after 2 months of treatment in PAGI-SYM scores, PPBS scores and FBS scores.

Table 1: Descriptive measures of the different variables and results for A-D test:

VARIABLES	TIMELINE	MEAN (SD)	MEDIAN	A-D TEST p-VALUE	SKEWNESS	KURTOSIS
PAGI-SYM Score	At Baseline	71.14 (9.83)	71.5	0.6204	0.0524	2.2446
	After treatment	40.22 (12.77)	37.5	0.0386	0.5030	2.2577
PPBS	At Baseline	312.54 (70.76)	301.5	0.0836	0.2266	2.0233
	After treatment	233.08 (33.90)	221	0.0002	0.5781	2.6133
FBS	At Baseline	177.06 (55.46)	171.5	0.0019	0.3769	1.9003
	After treatment	150.32 (39.90)	138	0.0007	0.3397	2.1562

Abbreviations: SD**:** Standard Deviation, A-D test: Anderson-Darling test.

VI. OBSERVATION

Patients had a steady improvement in the outcome parameters as seen statistically in all cases of PAGI-SYM score, FBS and PPBS. The heartburn as a primary subjective symptoms of sensation and pain had marked improvement as seen in the Microsoft excel format. The patients were meticulously followed up and the diet was strictly regulated one.

VII. DISCUSSION

The project intended to find out if constitutional homoeopathic medicines could help in cases of upper GI complications in known diabetic patients. There are several factors to influence the upper gastro intestinal symptoms in diabetic patients. The study design was kept open non randomized so all participants had the same access to medication and management to clearly identify the scope of Homoeopathic treatment in relieving the symptoms of this case.

Investigations primarily were done in RVHMC lab focused on glycaemic control of patients. A positive association with Diabetes and upper GI symptoms was identified at the beginning of the study along with other common complications of Diabetes mellitus.

At the commencement of the study few facts were highlighted like food habit irregularity, food quality with uses of excessive spices and absence of proper dietary fibers in diet were present in most of the cases. Injudicious use of over

the counter medicines to alleviate day to day problems was noticed in most of the cases. These events triggered the episodes of gastritis of and on and patients were mostly dependent on common PPIs for relieving of these annoying symptoms. Habit of medication in enormous quantity was also a major hurdle to commence a proper Homoeopathic treatment. Patients were regularly monitored to stop the injudicious use of the over the counter medication to obtain relief from the specific symptoms of the disease. To make the patients use to small doses of Homoeopathic medicines was a major task in the study.

The study revealed the effectiveness of Homoeopathic medicines in both higher and lower potency in fractional doses for repetitions as most effective in controlling the symptoms of upper GI system.

The most commonly used Homoeopathic medicines were Nux-vom, Antium-crud, China, Lycopodium, Arsenicum album, Pulsatilla, Sulphur, Mur-acid, Carbo-veg, Mag-carb, Colchicum, Natrum-mur and Merc-sol.

Proper statistical analysis revealed that Homoeopathic treatment has a positive role in the management of upper GI symptoms in DM patients. Detailed study of history and initiation of complaints primarily pointed out the unmasked symptoms of the case. Patients were mainly encouraged to elaborate their problems and focussed on their first very annoying symptom with a very distinct modality of the symptom. Most of the symptoms that patient experienced had marked modality that helped in selection of the drug. The nature of complaints was identical but they had marked different modalities. The PAGI-SYM scoring was evaluated before and after treatment and few components showed marked improvement in gradations than others. On evaluation these symptoms were primarily of sensations of the patients and pain experienced by the patients. Analysis also evaluated that the Blood sugar control was also better in consecutive blood sugar monitoring.

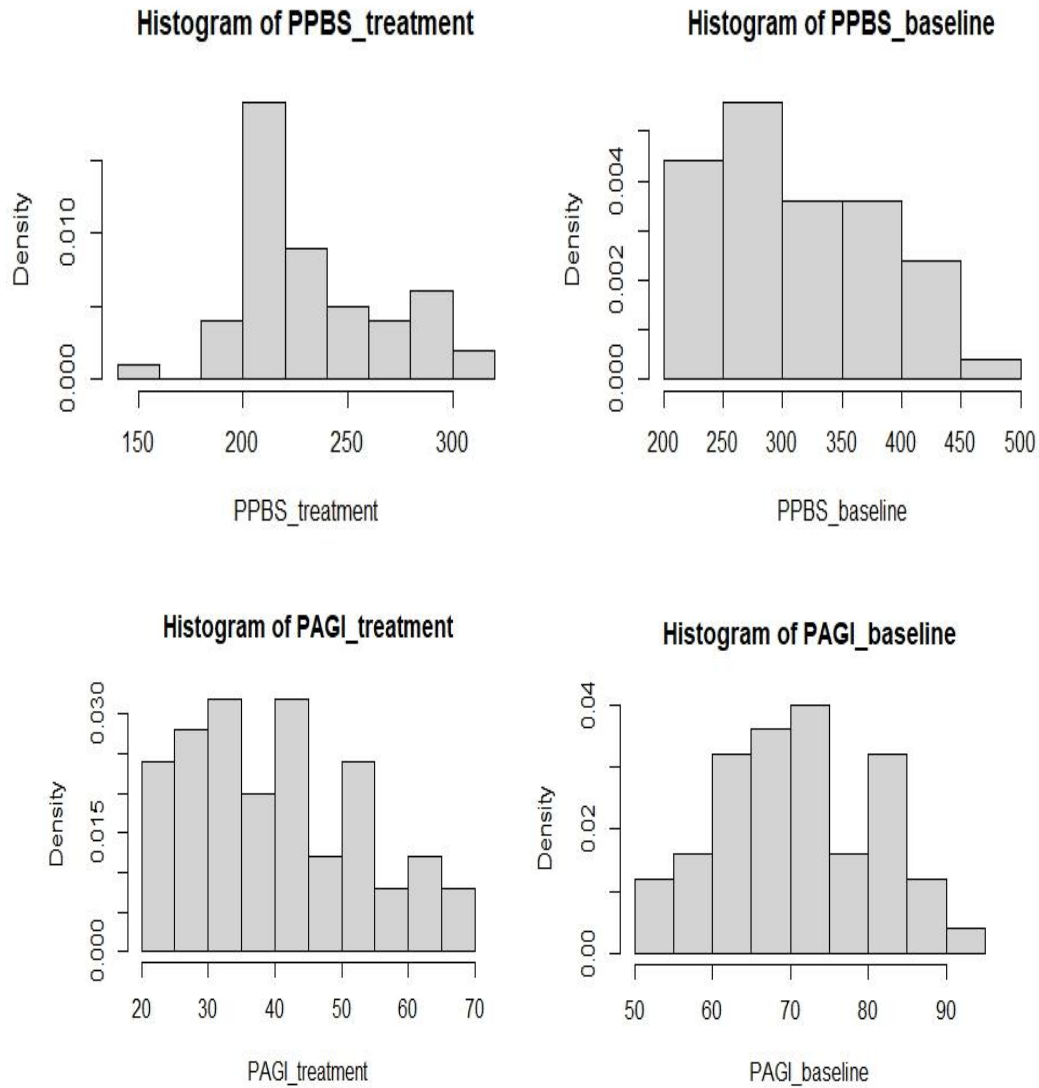**Figure 1 : Histograms based on the relative frequencies**
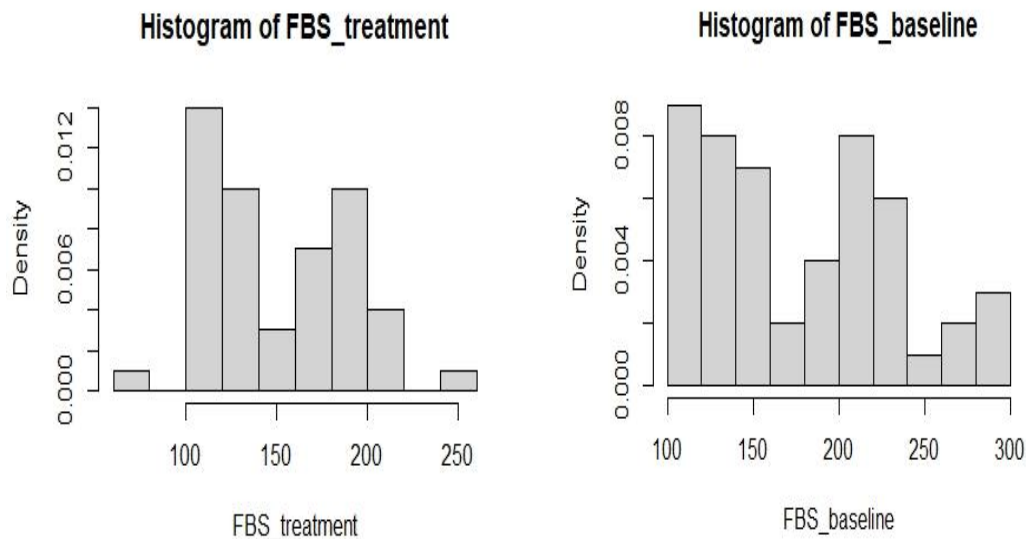
Table 2: Showing the test statistic values and the corresponding p-values

Test	Outcome Measures	Value of the test statistic	p-Value
Wilcoxon Signed Rank test	PAGI-SYM	1271	9.882×10^{-10}
Wilcoxon Signed Rank test	PPBS	1245	4.636×10^{-9}
Paired-t test	FBS	4.596	3.043×10^{-5}

Figure 2 : Chart for homoeopathic medicines allocation to enrolled patients in the study.
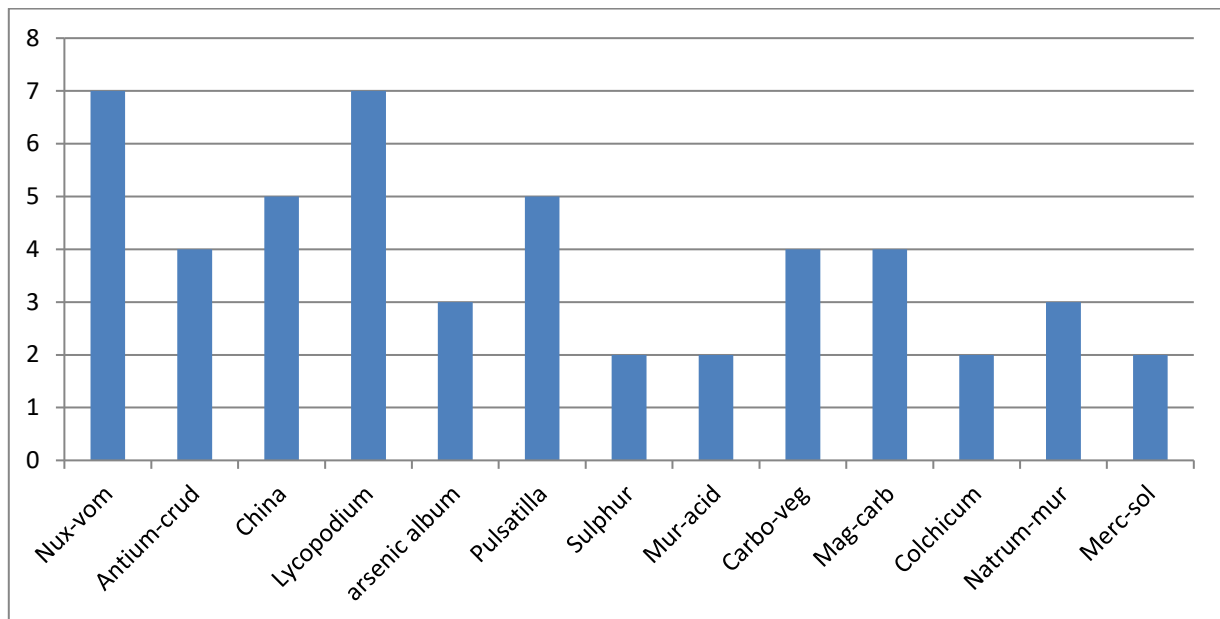
VIII. LIMITATION AND RECOMENDATION

The constraint of being a single researcher of the study was an important factor for its final analysis, as it was done on a relative small sample size as compared to the magnitude of the problem. The primary parameter for evaluation was questionnaire based and it has the limitations of biasness in the understanding and interpretation but secondary outcome were better monitored and justified. A large sample size will definitely bring more significant results with Homoeopathic treatment of these cases and in evaluation if a significant laboratory parameter if taken will bear more importance but that needs a significant funding to these projects.

IX. ACKNOWLEDGMENT

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