

Assessment of Therapeutic Outcome and Medication Adherence in Diabetics Consumed Insulin, Oral Hypoglycemics and Poly Herbal Drugs

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ABSTRACT

Introduction: The overwhelming of consumption of antidiabetes poly herbal products (PHP) would influence the outcomes of hyperglycemia management. The underlying reasons were yet to be revealed; thought to be the herb-drug interactions and delayed adherence towards the conventional anti-diabetes drugs. We hypothesized that consumption of poly herbal antidiabetes products would influence the therapeutic outcome while on treatment with Insulin, oral hypoglycemic (OHG) drugs and/or both. We also hypothesized that trends towards poly herbal antidiabetes products would change the adherence towards conventional drug treatments and life style modifications. **Methods:** A total of 1251 patients with both type 1 and 2 diabetes mellitus of age 20-60 year, their fasting blood sugar (FBS) >110 mg/dl and /or random blood sugar (RBS) >150 mg/dl and urine sugar level >50 mg/dl were enrolled. The patients used herbal products, steroids, pregnant and lactating women and diabetic micro vascular disorders were excluded. The physical and vital parameters, symptoms of hyper/hypoglycemia were monitored. Diabetes Self-Assessment Questionnaire 16 (DSMQ-16); the scale used to assess their glucose management, physical activity, dietary control and physician contact was administered to each patient as a measure of adherence to the treatment. **Results:** The adherence level towards Insulin was found to be decreased while oral hypoglycemic drugs

showed well. The consumption of PHP was most prevalent as well as adherence level. The markers of hyperglycemia were found to be altered in patient consumed PHP along with OHG drugs ($p < 0.05$). The random blood sugar (RBS) levels were not found to be normalized ($p < 0.05$) while fasting blood sugar (FBS) were found to be responded ($p < 0.05$). **Conclusion:** The PHP had a significant influence on OHG drugs. Since the adherence towards Insulin was decreased and assumed OHG-herb interactions the hyperglycemia management was not carried out. We recommend non-compartment Pharmacokinetic as well as Pharmacodynamics studies along with therapeutic drug monitoring.

Key words: Poly herbal, Oral hypoglycemic drugs, Insulin, Adherence.

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INTRODUCTION

There is increasing consumptions of medicinal herbs and herbal products globally, cutting across social and racial classes, as it is observed both in developing and developed countries.¹⁻² Medicinal plants were the major agents for primary health care for many centuries before the advent of modern medicine.³ Regulations in most countries do not require the demonstration of therapeutic efficacy, safety, or quality on the part of herbal remedies as most of them are promoted as natural and harmless.⁴⁻⁵ It is since time, the poly herbal products (PHP) gaining attractions towards diabetes management, as complementary and alternative over the conventional treatment methods. The increased trends towards PHP thought to decrease the adherence on oral hypoglycemic (OHG) and Insulin and/or with life style modifications. Even though herbal products are of natural origin, because of its complex mixtures of bioactive entities, it was hypothesized to interact with allopathic drugs.⁶ The components of herbal products consumed must also be eliminated from the body by the same mechanism that removes drugs, there is a potential for interaction between herbal components and drugs.⁷

The DSMQ-16 was developed by the Research Institute of the Diabetes Academy Mergentheim to assess various behavior changes associated

with metabolic control within common treatment regimens for both type 1 and type 2 diabetes adults.⁸ The behavior changes and emotional distress like depression and anxiety can interfere with self-care⁹ and therefore negatively impact glycemic control.¹⁰ This could make the patients away from the conventional treatment and cause medication non adherence. This was the thought behind selection of DSMQ-16 as a tool to measure medication adherence.

We also hypothesized that trends towards poly herbal products would change the adherence towards conventional drug treatments and life style modifications. This could be able to alter the treatment outcomes¹⁰ through alteration of pharmacokinetic changes and sometimes result in life threatening consequences. The present study aimed to study the outcomes of diabetes hyperglycemia management in patients consumed PHP along with or without Insulin and OHG.

MATERIALS AND METHODS

Study design

This observational study was conducted in diabetes mellitus patients of age 20-60 yr. The male and female patients diagnosed with both type 1

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and type 2 diabetes mellitus, their fasting blood sugar (FBS) >110 mg/dl and /or Random Blood Sugar (RBS) >150 mg/dl and urine sugar level >50 mg/dl. The patients used PHP<15 days, Herbal products other than antidiabetes, steroid therapy, pregnant and lactating women, diabetic nephropathy, diabetic neuropathy, diabetic micro angioplasty, surgical procedures <90 days, hypertensive crisis, hypertensive nephropathy, did not obtain ICF and did not completed study conditions were excluded.

All the patients were asked to follow diabetic diet advised by clinical co-investigator for 6 months study period. The parameters like Body Mass Index (BMI), Waist Hip Ratio (WHR), Fasting blood sugar (FBS), Random blood sugar (RBS), HbA1C, heart rate, systolic and diastolic blood pressure, body temperature, WBCs Serum urea were measured for 6 months at an interval of 30±3 days. The Tamil translated version of DSMQ-16 was also administered to each patient by interview method.

Analysis and interpretation

The parameters were collected on 29th, 60th, 92th, 126th, 156th and 185th day for duration of 6 months exclude first day of patient enroll. The patients with incomplete data and did not come for review on 30±3 day were excluded from study. The different reading obtained from total 6 reviews were analyzed and interpreted by compared the average values of each parameters among the study groups. The statistical analysis was done by paired sample 't' test with the use of SPSS 20 version and significance was set at p<0.05.

RESULTS

This prospective observational study had conducted in a total of 1251 diabetes patient, of which, 679 (52.47%) were used Insulin, OHG and PHP and 452 (36.31%) were used only Poly herbal products Figure 1. The consumption of PHP was increased proportionally with increase in age whereas the combination of Insulin, OHG and PHP was found to be prevalent in young and middle age groups; in fact, age induced Insulin resistance and drug intolerance would shift the patients away from Insulin and OHG. The physiological markers of diabetes were showed significant variations over the review period of 6 months as shown in Table 1. The threshold of hyperglycemia was seemed to be deviated even treatment with Insulin, OHG, but presumably OHG and Insulin were able to control FBS and RBS (p<0.05) than PHP alone. The chronic diabetes associated inflammatory reactions would expected in the study

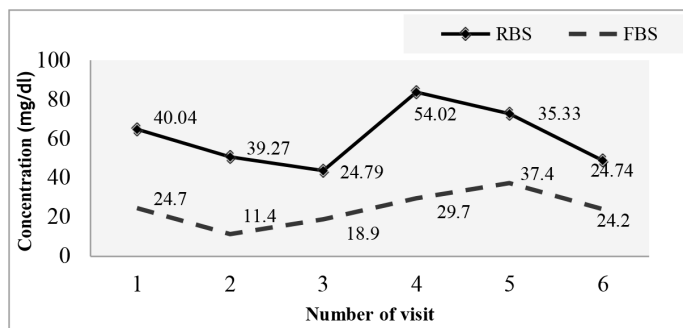


Figure 1: The SD values of FBS and RBS levels in patients consumed Insulin, OHG and PHP.

population; WBCs had shown significant increase (p<0.05) even though body temperature was normal (p>0.05).

As most of the patients preferred combination of allopathic and herbal medicines, taking herbs with conventional therapeutic drugs might cause varying effect; in fact, due to risk of potential herb drug interaction. Table 1 showed the biochemical and physiological markers were responded to the conventional antidiabetes treatment and PHP were differed in several aspects. The direct markers like FBS and RBS were improved in PHP group better than other. The insulin resistance was persisted in Insulin, OHG and PHP, indicated by the values of WHR and BMI. The non-adherence, the real world limiting factor for effectiveness of diabetes therapy 10 was found to be prevalent in the study population; but adherence to PHP was increased which represented more than one third as shown in Table 3. The interesting fact was RBS, the biomarkers of extended effects of OHG, was not showed constant control; seemed fluctuation (Figure 1 and 2) The HbA1C were decreased over 6 months of treatment period in patients used only PHP as shown in Figure 4. The drug-herb interactions might have influenced HbA1C levels in patients used Insulin, OHG (Figure 3) wherein patients used only PHP, seemed HbA1C levels were improved over review period (Figure 4).

DISCUSSION

The use of herbal products in diabetes has a pandemic existence in today's world. The PHP products need to be considered for quality standards

Table 1: Shows the comparison of vital physiological and biochemical parameters in patients consumed Insulin, OHG and PHP. Values expressed as average ± SD.

Parameters	Frequency of review					
	1	2	3	4	5	6
FBS	194.24±24.7	129.12±11.4	149.49±18.9	145.71±29.7	194.54±37.4	129.29±24.2*
RBS	290.55±40.04	250.24±39.27	310.67±24.79	230.99±54.02	290.02±35.33	250.44±24.74*
HbA1C	6.8±0.59	5.9±1.02	6.5±0.67	7.2±1.11	6.8±0.48	7.2±0.57*
SBP	150.09±30.04	170.22±10.54	150.97±24.01	140.35±19.59	130.94±12.24	120.24±24.65*
DBP	104.21±12.34	102.34±12.87	90.84±12.97	112.87±07.47	90.04±08.55	85.99±12.77*
HR	110.79±12.33	90.71±05.79	94.74±13.49	64.04±4.99	84.62±9.44	79.55±10.02*
RR	18.01±2.33	21.74±2.91	24.02±5.32	15.74±3.67	20.12±3.62	16.83±2.19*
Body Temp.	98.6±0.97	98.9±0.27	98.9±0.1	98.6±0.01	98.9±0.03	98.6±0.7
BMI	27.09±1.55	33.09±1.22	34.2±2.01	31.77±1.09	24.74±1.89	29.33±3.02*
WHR	0.92±0.11	0.94±0.3	0.71±0.15	0.74±0.89	0.75±0.12	0.71±0.09*
Serum Urea	65.01±09.24	72.01±2.15	94.09±9.04	30.33±3.99	110.1±9.37	97.99±12.78*
WBCs	5734.04±307.01	7237.04±230.1	7404.22±230.11	8468.01±240.88	10504.11±410.21	9747.09±340.11*

*p<0.05, One-way ANOVA, 1-29th day, 2-60th day, 3-92th day, 4-126th day, 5-156th day, 6-185th day, duration-06 months, n-679, duration-06 months

Table 2: Shows the variations in vital physiological and biochemical parameters in patients consumed only PHP. Values expressed as average +SD.

Parameters	Frequency of review					
	1	2	3	4	5	6
FBS	149.22±14.7	152.52±27.9	210.31±19.9	194.99±28.3	179.54±24.7	187.87±29.4*
RBS	310.57±24.04	240.33±54.11	204.55±35.42	209.27±24.84	242.09±45.04	109.47±25.15*
HbA1C	7.1±0.59	5.9±0.75	6.5±0.84	5.9±0.82	5.7±0.62	6.2±0.54*
SBP	140.21±34.54	110.24±3.02	145.21±19.47	150.97±19.04	180.21±09.44	130.89±34.78*
DBP	95.97±13.47	80.87±15.01	90.87±17.44	90.88±18.97	100.04±11.44	90.74±29.41*
HR	64.84±4.79	76.54±8.01	110.22±5.21	90.79±9.55	94.27±13.04	79.09±7.99*
RR	22.04±4.11	14.89±3.74	19.84±4.28	20.81±4.09	18.37±5.99	22.84±2.11*
Body Temp.	98.6±0.71	98.6±0.11	98.6±0.9	98.9±0.14	98.9±0.24	98.6±0.01
BMI	33.09±2.97	31.77±3.11	22.76±2.89	24.74±1.89	33.09±3.97	27.89±5.04*
WHR	0.9±0.19	0.92±0.01	0.94.04±1.21	0.97±0.08	0.85±0.19	0.99±0.54*
Serum Urea	124.54±24.02	72.56±3.97	89.97±5.44	124.67±14.02	72.34±2.19	87.97±04.34*
WBCs	12362.47±110.34	60478.34±201.21	7400.99±190.47	9774.04±120.09	6435.23±179.54	7945.02±84.24*

*p<0.05, One-way ANOVA, 1-29th day, 2-60th day, 3-92th day, 4-126th day, 5-156th day, 6-185th day, duration-06 months, duration-06 months, n-679, duration-06 months

Table 3: Shows the adherence to diabetes management in subjects consumed Insulin, OHG and PHP. Values expressed as average ± SD.

Parameters	Frequency of review					
	1	2	3	4	5	6
Dietary Control*	4.9±1.2	4.3±1.2	6.7±2.1	5.2±1.9	4.4±2.1	5.7±1.3
Glucose management*	6.4±1.2	7.1±2.5	4.2±2.1	4.5±2.2	3.6±1.2	5.4±1.1
Physical Activity*	8.4±2.1	6.7±1.3	3.9±2.1	5.5±2.3	7.6±1.5	6.7±1.3
Physician contact	5.9±1.9	4.9±2.3	6.4±2.1	8.7±1.9	7.8±2.9	5.4±3.1

*p<0.05, One-way ANOVA, I-29th day, II-60th day, III-92th day, IV-126th day, V-156th day, VI-185th day, duration-06 months, n-679, duration-06 months, scale-DSMQ-16

Table 4: Shows the adherence to diabetes management in subjects consumed only PHP. Values expressed as average ± SD.

Parameters	Frequency of review					
	1	2	3	4	5	6
Dietary Control*	5.9±1.9	5.3±1.32	6.7±2.2	6.2±1.9	5.4±2.3	7.7±2.3
Glucose management*	5.4±1.9	7.1±2.5	6.2±2.3	5.5±1.2	5.6±2.9	6.5±2.1
Physical Activity*	6.4±2.25	7.7±2.2	5.9±2.5	7.5±1.3	7.4±2.9	7.7±2.3
Physician contact	7.9±1.9	4.9±2.3	5.4±1.1	7.7±2.9	7.4±1.9	4.4±2.1

*p<0.05, One-way ANOVA, I-29th day, II-60th day, III-92th day, IV-126th day, V-156th day, VI-185th day, duration-06 months, n-452, duration-06 months, scale-DSMQ-16

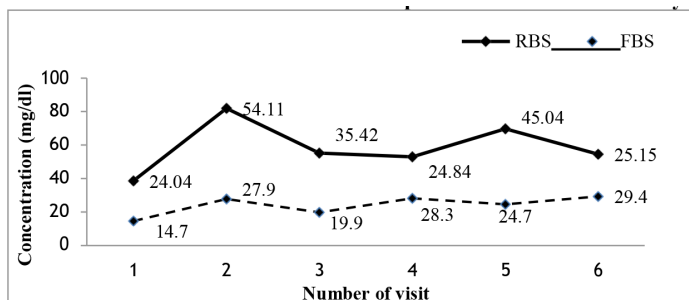


Figure 2: The SD values of FBS and RBS levels in patients consumed PHP only.

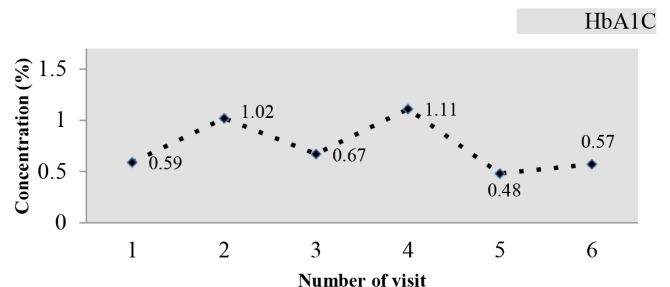


Figure 3: The SD values of HbA1C levels in patients consumed Insulin, OHG and PHP.

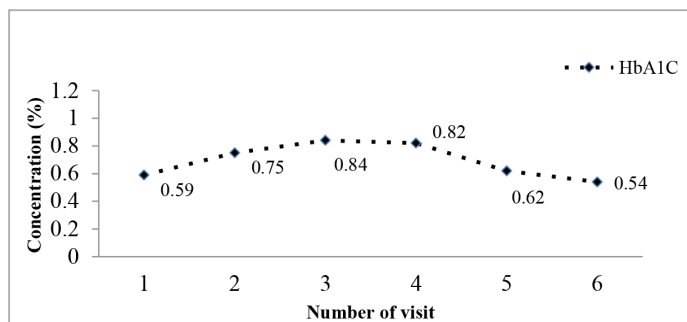


Figure 4: The SD values of HbA1C levels in patients consumed PHP only.

as elaborately by World Health Organization (WHO). The forecast of WHO had already said that by 2050 the PHP would bring global market to five trillion dollars¹⁰ our study showed the society's trends towards PHP were increased. Over a period, patients may become progressively less responsive to therapy with oral hypoglycemic agents. The drug-herb interactions have impact on treatment outcome and thus cause deterioration of their diabetic state. The factors behind could be OHG-PHP or Insulin-PHP interactions or the pharmacokinetic failure of OHG and Insulin.

The complex nature of PHP might delay the absorption of antidiabetes drugs. The use of multiple pharmacologically active compounds increases the chances of interactions taking place. Hence, the chance of herb-drug interactions is theoretically higher than drug-drug interactions, if solely because synthetic drugs usually contain single chemical entities.¹¹ The potential risk of certain adverse effects, the severity of adverse drug reactions regarding drug induced problems in the elderly patients¹² and their association with poly pharmacy results in more relevant appearance of adverse reactions. Thus, the risk of adverse effects is related to the number of medicines taken by the elderly patients that receive more medicines, sometimes inappropriately.^{12,11} Our study population had not used any medicines; since patients used OTC drugs and medicines were excluded, the possible herb interaction might take place with OHG and Insulin. The previous scientific studies conducted on herb-drug interactions had made important findings in the monographs of OHG like Glibenclamide; where the details on extensive interaction with herbs were not established.¹³ As pointed out, herb-drug interactions are under reported even though few case reports or case series addressed. This indicates that the scientific data collection regarding herb-drug interactions continues to be an antique part and remains as unmet need in rationalizing the use of herbal drugs as related medications. Since, the major goal of every treatment of diabetes mellitus is to reduce the elevated blood glucose levels, the concern of herb-drug interactions has given least importance. Another side, this herb-drug interaction has not been well documented nor any guidelines¹⁴ to use in diabetes patients.

Therefore, the symptoms of hypoglycemia or interrupted effects of conventional anti-diabetes drugs might not seem serious for these patients because the consequences will not happen immediately¹⁵ if once the drugs were skipped. This non-adherence might be challenge for the patients¹⁶ where body might not have responded back to OHG and/or Insulin as the FBS and RBS values were fluctuated. The RBS levels fluctuated at each frequency of review in fact not because of diet. The serum urea was found increased in both set of population; could be the early symptoms of diabetes nephropathy^{17,15} or reduced water consumption. The leukocyte counts reflect the presence of hyperglycemic crisis and acute infection which had a linear correlation¹⁸ in earlier studies. In this study, the possibilities of systemic inflammation have been indicated by

increased WBCs but values of body temperature ($p < 0.05$) rejected the symptoms of underlying infections.

The other factors behind the non-adherence and over trending to PHP were not evaluated in our study but we assumed that lack of time; travel and public embarrassment¹⁹ might affected. Since, OHG offers post prandial glucose control these alterations were assumed due to pharmacokinetic failure²⁰ as well as delayed absorption²¹ caused by herbal ingredients. Hence, the blood glucose levels were altered significantly, based on that polyherbal products indicating potential antidiabetes activity. In reduction of plasma blood glucose levels by poly herbal products might produce their claimed effects²² on glucose control, but the patient's use of PHP with OHG and Insulin significantly reduced their glycemic control.

CONCLUSION

The use of PHP with conventional anti-diabetes drugs either OHG or Insulin will cause treatment failure in glycemic control. The proposed mechanisms could be herb-drug interaction, drug displacement from receptor site, delayed or inhibited absorption from stomach. The impact of PHP over OHG and Insulin treatment outcomes were not studied earlier, this result could be a lamp. We recommend further pharmacokinetic studies on the same population for more authenticated results. The diabetes patients should be aware of devastating effects of use OHG and Insulin with PHP. Similarly, the quality control of OHG should be more strengthened to ensure prescribed glycemic control in a face in India runs many generic versions of OHG. The steps to increase the adherence levels of the community towards conventional anti diabetes drugs also to be enhanced.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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