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Research Article

A RANDOMISED SINGLE BLIND ACTIVE CONTROLLED, PARALLEL GROUP STUDY COMPARING THE EFFICACY & SAFETY OF THE KARNIM PLUS® CAPSULES IN PATIENTS WITH MILD OR MODERATE DIABETES MELLITUS TYPE. II

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ABSTRACT

Diabetes is the most prevalent disease in the world affecting middle and old aged persons of the world directly impacting their life style and other metabolic hazards. Karnim plus is a remedy of Unijules Life Sciences ltd. And current multicentric, randomized, single blind, active controlled and parallel group with metformin capsule clinical study is conducted in two centres of Dr. D.Y. Patil College and Ashwin Ayurved college respectively. Total 121 patients were treated according to the previously approved protocol from institutional ethics committee for the treatment period of 24 weeks in a dose of 2 capsules BID before meal and primary efficacy parameters set to HbA1c, fasting and post meal blood sugar. From the study it was concluded that Karnim plus capsule and Metformin capsule are equally effective in controlling hyperglycemia with slightly more time to achieve significance result in Karnim plus. In case of HbA1c highly significant results were observed in Karnim plus capsule and also highly significance is observed in symptom score of clinical parameters. Cholesterol levels are significantly decreased in Karnim plus group than metformin group. This indicated that Karnim plus is effective remedy in controlling diabetes type II with no any adverse effects and controlling metabolism in a effective way than other OHA.

INTRODUCTION

The prevalence of NIDDM varies in different geographic regions and also in different ethnic groups [1]. The first authentic data on the prevalence of diabetes in India came from the multicentric study conducted by the Indian Council of Medical Research (ICMR) in the early seventies [2]. This study reported a prevalence of 2.3% in the urban and 1.5% in the rural areas. The criteria used in this study were different from those set by the WHO Expert Committee on Diabetes Mellitus. Many epidemiological studies carried out in different parts of the world reported an interesting finding that Indian migrants settled abroad had a high prevalence of NIDDM [3] which was believed to be due to greater affluence and a change to a more sedentary life style as compared to the native Indian population. However, the local host populations living in identical environment in these countries still had only a low prevalence rate of diabetes. Assuming that Indians as an ethnic group have a high degree of genetic predisposition to develop diabetes, one could expect higher prevalence of diabetes among the native urban populations with a comparable affluent life style.

There is a vast difference in the percentages of subjects with known to unknown or undetected diabetes in urban and rural populations. The new to known ratio was 1:2 in an urban population while

the corresponding data for the rural population was 3:1[4]. Similar findings have been reported for urban and rural populations of migrant Indians[5]. These differences are probably due to marked changes that have occurred in the quality of the food consumed. Urbanisation has probably led to a transition from consumption of natural form of food to a more refined food. This in combination with less physical activity could probably lead to unfavourable adiposity and hence increase the risk of developing diabetes. Factors influencing the prevalence of NIDDM Age and sex have been found to be the most positively associated parameters with NIDDM in both the urban and the rural populations surveyed in Madras [6]. The prevalence of diabetes was 41 % in the age group 55-64 years. It has been reported that in Southall, U.K., Asians aged 40-64 years had five times higher prevalence of diabetes as compared to the Europeans. Almost all the epidemiological studies have shown a male preponderance among the Indian diabetics inspite of increased rates of obesity in women.

Studies in India indicate that more than 50% of people with diabetes have poor glycaemic control (HbA1c > 8%), uncontrolled hypertension and dyslipidaemia, and a large percentage have diabetic vascular complications.[7]

Karnim plus capsule is a remedy of Unijules Life Sciences Ltd which has polyherbal combination of time tested herbs formulated in a standardized and advanced dosage form mainly acting on metabolic pathways. This is approved formulation by FDA. This study is randomized compared with active control group of Metformin capsule. This study is aimed to evaluate safety and efficacy w.r.t. glycemic control and metabolic control over patients of mild or moderate Diabetes mellitus type II

MATERIALS AND METHODS

This is a randomized, Single blind, Active controlled and parallel group controlled study about comparing efficacy and safety of Karnim plus capsules with active controlled group of Metformin capsules.

This is a multicentric study conducted in two centres which is D.Y. Patil college of Ayurved, Hospital and research centre, Nerul, Mumbai, Maharashtra and Ashwin Ayurved college and hospital Manchi hill Sangamner Dist. Ahmadnagar Maharashtra.

Proper Protocol and CRF (Case report form) was developed and presented to the Institutional ethics committee of both the study centres, necessary amendment were done as per the suggestions of EC and proper protocol of GCP (good clinical practices) is followed during the course of the study.

All investigational medicinal products (IMP) i.e. Karnim plus capsules and Metformin capsules were provided to the study sites with proper packing and labelling by the company and audited by quality assurance department of Unijules life sciences ltd and from external clinical research auditor for compliance of protocol, patients recruited and source data verification.

Patients were recruited from the OPD of both the study sites with following inclusive and exclusive criteria.

Inclusion criteria

Patients of either sex between the age group 18-75 yrs both inclusive with a diagnosis of type II diabetes mellitus were selected for the study. Patients already taking Metformin. Patients must complete a study diary as instructed by doctor and staff and return the study diary as instructed by the study doctor. Patients must be willing and able to adhere to the protocol and No change in DM II treatment and no DM II-related hospital visits have been done during the past 3 weeks, were selected for the study.

Exclusion criteria

Patients of Type 1 diabetes. Patients having FBS>276 mg/dl at the time of screening. Patients having multiorgan involvement either Cardiac hepatic or renal. Diabetes that is a result of pancreatic injury, or secondary forms of diabetes. Evidence of serious diabetic complications. Laboratory value abnormalities as defined by the protocol. Has a history of hypersensitivity or allergy to Metformin, other DPP-4 inhibitors, or related compounds. Pregnancy induced DM type II. Serious secondary disorder like HIV, HBS Ag, Has history of cancer and those has any major illness or debility that in the investigator's opinion prohibits the subject from completing the study were excluded from the study.

Objective and Efficacy parameters

Primary objective of the study is to compare efficacy of Karnim plus capsule with control drug Metformin capsule and secondary objective is to assess comparative safety of karnim plus capsules with metformin capsules. For this following primary and secondary efficacy parameters were decided.

Primary efficacy parameters were change in baseline values of HbA1c, fasting blood glucose (FBS) levels and post prandial (PP) blood glucose levels. Secondary efficacy parameters were change

in metabolic parameters like lipid profiles, and total and sub-domain scores of symptoms of diabetes i.e. polyuria, plyphasia, polydepsia etc. Symptoms scores assessed as a grade scale of 0 to 3 i.e. normal to sevior.

Study procedure

Patients complying to above mention inclusion criteria were included in the study and explained about the study drug, its effect, dosing schedule and they were provided with patient information shit and asked for signing a written informed consent form.

After that patient went for screening period of 2 days and treatment period of 24 weeks by the method of randomization to either treatment of Study drug (Karnim plus capsule) and control drug (Metformin capsule). The patients were advised to take medicines at a dose of 2 capsules with water 15 min. Before meal.

At screening visit detailed physical examination, vital signs and symptom scores were performed and documented by the investigator and blood collection were done for tests like blood sugar, HbA1c, CBC, LFT, KFT, Lipid profiles etc. After 2 days all reports were analyzed and reviewed for eligibility of the patients for the study. Those who found eligible were selected for 24 weeks treatment period of either treatment of Karnim plus capsules (Group I) or Metformin capsules (Group II).

Than follow-up visits were scheduled after every two weeks upto 24th week. During each visit physical examinations, vital signs and symptoms score were examined and documented in case report form as mentioned in protocol. HbA1c is checked before and after the treatment and fasting blood glucose (FBS) and post prandial (PP) blood glucose levels were assessed during each visit. A window period of +/- 2 days is allowed for the patient. During each visit checking of daily diary, use of rescue medication and compliance of medication was checked.

All adverse events were noted and recorded about nature and severity of the symptom, onset action, time to resolution of symptom. Patients were allowed to withdraw from the study at any time and any stage of the study.

All data were complied and analyzed by using appropriate analytical test i.e. paired t test for grouped data and unpaired t test for comparing ungrouped data of group I and group II.

RESULTS

Total 256 patients were screened in both the study sites out of which 134 patients were enrolled for the 24 weeks treatment period. Out of these total 122 patients have completed the total treatment period of 24 weeks. Total 61 patients in each group have completed the treatment period.

In case of fasting blood sugar (FBS) which was primary efficacy parameter of the study, it was found that in treatment group I i.e. of Karnim plus capsule significant changes are observed after 4 week of treatment. (Graph 1.1) After 2 week the values are decreased but these was not statistically significant. Where as in treatment group II i.e. of Metformin capsules it was observed that there was significant changes in FBS after 2 week of treatment and afterward in 4 week and further treatment course. This indicate that Karnim plus capsule is little slower in influencing blood glucose level as compared to metformin capsule but equally effective after 4 week of treatment. That may be because of herbal nature of the product, Karnim acts slowly and not as faster as metformin capule which is of synthetic nature. But this significancy is carried upto 24 weeks of treatment.

In case of post meal blood sugar (PP) same kind of observations as like FBS was noted, (Graph 1.2) which confirms that Karnim plus capsules will require at least 4 week time to normalize blood sugar levels to be within the normal range.

Interesting observations were noted in case of HbA1c. (Graph 1.3) Which was done before treatment and after 24 weeks of treatment. In case of Group I of Karnim plus capsules it shows highly significant decrease in before treatment and after treatment values whereas in trial group II significant decrease is noted. It proves that Karnim plus is slightly more effective than Metformin in controlling HbA1c i.e. glycocylated haemoglobin. This proves that in long therapy Karnim plus capsules has more impact over micro pathological levels than conventional OHA. Changes or correction at enzymatic level are more effective by the Karnim plus capsules.

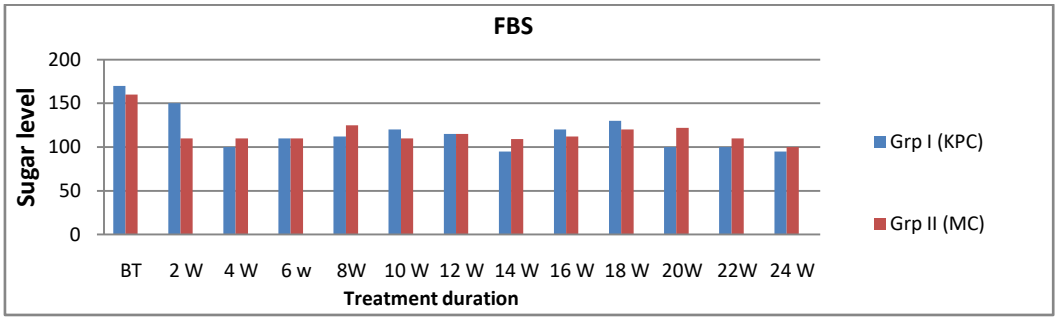
It was also observed that Cholesterol levels are significantly decreased after 24 weeks of treatment with Karnim plus capsules (Graph 1.4) whereas nonsignificant changes were observed in treatment with Metformin capsules. It again proves that Karnim plus is more effective in controlling metabolism and enzymatic changes within the digestive pathway. That may be because of polyherbal nature which has several herbs having proved action on the overall metabolic pathway.

In case of clinical parameters, mean symptom score was analysed within the treatment weeks and within the two treatment groups also, which shows significant changes in polyurea (Graph 1.5),

polyphasia (Graph 1.6) and general weakness (Graph 1.7), after 4 weeks of treatment in group I (KPC) and after 8 weeks in treatment group II (MC). Which indicated that Karnim plus capsules is more effective in controlling associated secondary parameters of DM II than other OHA, which could be again due to polyherbal nature of the drug.

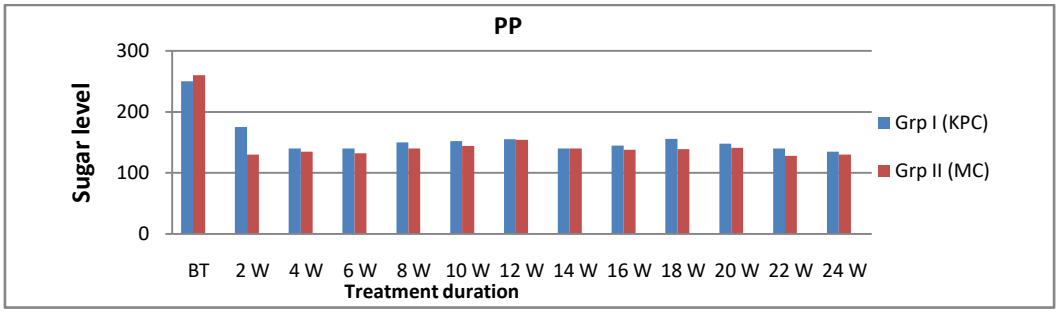
In case of no. of patients in which urine sugar is present, (Table 1.1) significant results were noted in both the groups between before and after treatment and no significant difference are observed between group I and group II.

Graph 1.1



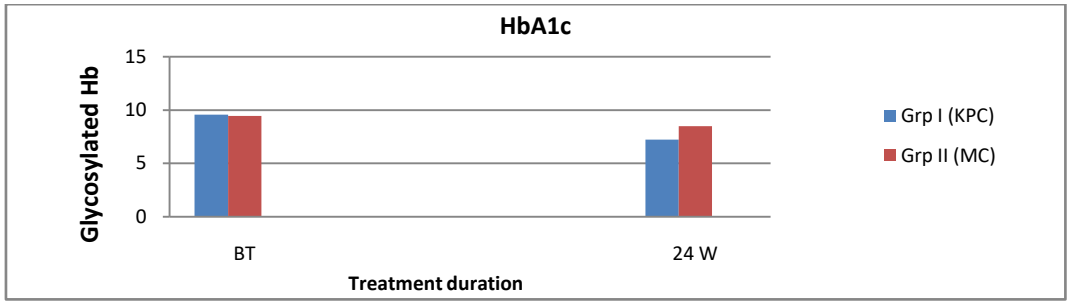
** Significant results observed in BT and AT in both the groups and non significant results within the two groups

Graph 1.2



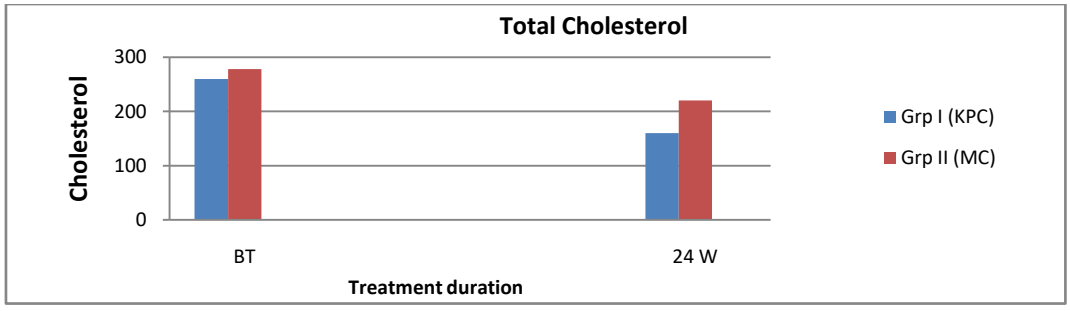
** Significant results observed in BT and AT in both the groups and non significant results within the two groups

Graph 1.3



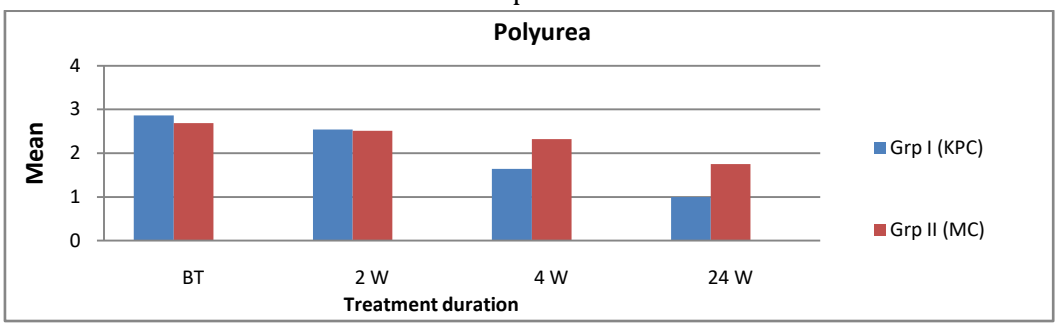
** Highly Significant results observed in BT and AT in Group I and significant in group II

Graph 1.4



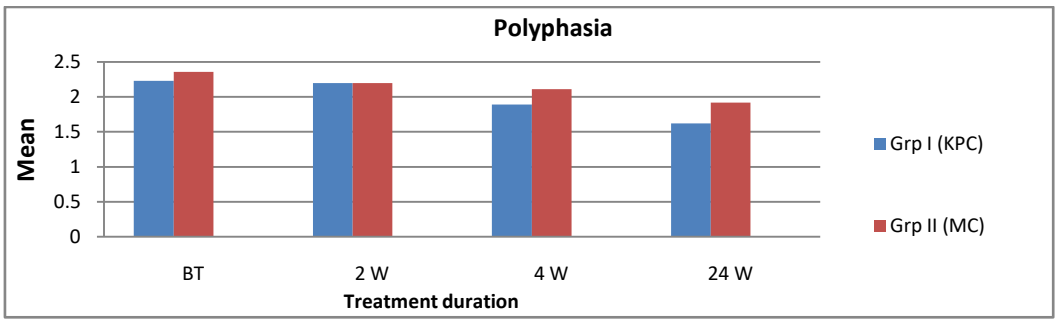
** Highly Significant results observed in BT and AT in Group I and non significant in group II

Graph 1.5



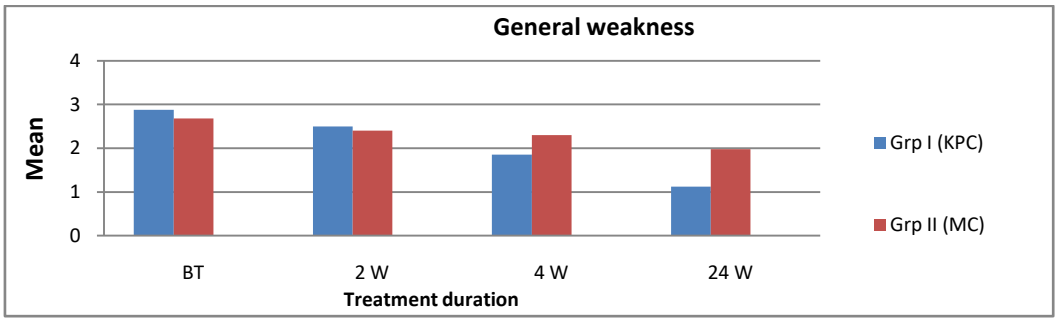
** Significant results were noted in group I after 4 week of treatment and non significant in group II after 4 week but significant after 24 week

Graph 1.6



** Significant results were noted in group I after 24 week of treatment in group I and II

Graph 1.7



** Significant results were noted in group I after 4 week of treatment and non significant in group II after 4 week but significant after 24 week

Table 1.1

	Urine sugar				
Parameters		b.t.	4 W	12W	24W
KPC treated (Group I)	Present	50	15	8	4**
	Absent	11	46	53	57
MC treated (Group II)	Present	55	20	7	3**
	Absent	6	41	54	58

** Highly Significant changes after 24 W of treatment in group I and group II

DISCUSSION

The prevalence of diabetes is rising all over the world due to population growth, aging, urbanisation and an increase of obesity and physical inactivity. Unlike in the West, where older persons are most affected, diabetes in Asian countries is disproportionately high in young to middle-aged adults. This could have long-lasting adverse effects on a nation's health and economy, especially for developing countries. The International Diabetes Federation (IDF) estimates the total number of people in India with diabetes to be around 50.8 million in 2010, rising to 87.0 million by 2030. The primary goal in the management of diabetes mellitus is the attainment of near-normal glycaemia. In India, more than half of patients have poor glycaemic control and have vascular complications. Therefore, there is an

urgent need to develop novel therapeutic agents of diabetes without the development and progression of complications or compromising on safety.

'KARNIM PLUS®' is a formulation (Table 1.1) composed of medicinal herbs with proven pharmacological actions, which take care of all major complication of diabetes. The pharmacological action of individual herbs indicates that the major ingredients of 'KARNIM PLUS' are as follows ***Karela* (*Momordica charantia*)** has been found effective in lowering the blood glucose in man. The anti-diabetic activity of *M. charantia* is due to two active ingredients, Polypeptide -P and Charantin. Polypeptide -P is a 17 amino acid polypeptide, 16 of which are similar to crystalline insulin of bovine origin. This polypeptide has been shown to be ' insulinomimetic.' A number of other polypeptides from *M. charantia* seeds have been studied in vivo for the insulin like activities of stimulation of lipogenesis and inhibition of corticotropin-induced lipolysis. The mechanism was suggested to involve interaction of peptides with α-adrenergic or corticotropin receptors. The other active constituent, charantin is a mixture of two steroid glycosides: β-sitosterol-D-glucoside and 5,25-stigmastadien-3-β-ol-D-glucoside. Studies performed in vitro with *M. charantia* fruit extracts indicated a significant enhancement of glucose uptake in muscle tissue and of glycogen accumulation in muscles and hepatic tissue but no effect on glucose uptake or triglyceride synthesis in adipose tissue. Inhibition of glucose uptake by intestinal fragments was also observed and attributed to glycosidic constituent of the fruit extract. *M. charantia* has been demonstrated to possess a dose dependent increase in the scavenging activity against superoxide radical and hydroxyl radicals. *M. charantia* is a potent scavenger of superoxide and Hydroxy radicals. The antidiabetic effect of the plant is mediated through oxygen radical scavenging mechanism. Indeed the body itself possess enzymes such as Superoxide dismutase which routinely protects the β-cells in pancreas through their scavenging action. The free radical scavenging antidiabetic role of *M. charantia* supports an additional prophylactic role as many diabetogenic chemicals such as Alloxan, Streptozotocin, Pyrinuron, Food nitrosoamines, cynogenic glycosides such as Linamarin and other sources of Dietary cyanide induce diabetes through damage to pancreatic β-cells via free radical generation. Thus it appears that therapeutic activity of *M. charantia* against diabetes is due to pancreatic, extra-pancreatic and pancreas-protective properties. ***Neem* (*Azadirachta indica*)** has been demonstrated to exert hypoglycemic effect in streptozotocin induced diabetes. It shows its anti-diabetic action by stimulating the insulin secretion by the β cells of Islets of Langerhans of the pancreas in a manner similar to the sulfonyl ureas like chlorpropamide. Recurrent infections due to high blood glucose levels and slowed down immune responses due to gradual deterioration of immune system because of loss of body proteins is a common feature in diabetes. *A. indica* has been demonstrated to induce production of interleukin by stimulating specific types of T-cells of the immune system, the lack of which is a common feature of diabetes. So it can be said that *A. indica* enhances cell-mediated immune responses and thus can normalize the deteriorating immune system in diabetes. ***Ocimum sanctum* (*Tulsi*)** promotes uptake of glucose by peripheral tissue most likely by decreasing peripheral resistance to insulin. *O. sanctum* has been demonstrated to reduce blood glucose level in diabetic rats and also to promote action of other diabetic medications including oral hypoglycemics and exogenous insulin. *O. sanctum* is also effective in aggravated hyperglycemia precipitated by stress by virtue of its capacity to normalise stress induced neurological changes. *O. sanctum* has been demonstrated to have a normalizing effect on the levels of adrenaline, noradrenaline and monoamine oxidase which are generally decreased in stressed condition and thereby help the body to cope better with stress induced hyperglycemia.

***Picrorrhiza kurroa* (*Kutki*):** is useful in treating hyperglycemia. The anti-hyperglycemic activity attributed to the bitter principle 'kutkin'. This principle is known to stimulate secretion of gastrin, secretin and cholecystokinin pancreazymin which then stimulate secretion of insulin by β-cells of pancreas. Beside anti-hyperglycemic activity, *P. kurroa* also possess immunomodulator and hepato-protective activity. The iroid glycoside fraction of the herb is responsible for the immunostimulation and is capable of inducing both antigen-specific and non-specific responses. Thus *P. kurroa* helps to potentiate the body's immune responses which are usually diminished in diabetes. Increased glycogenolysis and decreased gluconeogenesis in liver due to dysfunctioning of insulin dependent metabolic pathways is a characteristic feature of diabetes. This affects normal functioning of liver ultimately disrupting the metabolic balance of body and may lead to life threatening conditions like ketosis and acidosis. *P. kurroa* has been

demonstrated to posses hepato-protective action and normalizes the functioning of liver due to presence of active ingredients Picrosides I and II which are glycosidic in nature. So besides lowering blood glucose hepatoprotection in diabetes is an added advantage of *P. kurroa.* ***Zingiber officinale*** **(Sounth)** exerts its anti-hyperglycemic effect by stimulating the β cells to secrete insulin. This action is attributed to its active constituents 6,8 and 10 gingerols which cause inhibition of Na+/ K+ pump. Reduced potassium conductance causes membrane depolarisation and influx of Ca++ ions through voltage sensitive Ca++ channels which ultimately stimulates insulin secretion by β cells of pancreas. Elevated fatty acid level and onset of athero-sclerosis is a common feature in diabetes due to increased lipolysis. *Z. officinale* is effective in lowering blood lipid levels and thus circumvents the danger of development of atherosclerosis in diabetic patients.

CONCLUSION

From the above mentioned results following conclusion can be drawn Karnim plus capsule and Metformin capsule is equally effective in controlling blood sugar levels, i.e. they have equal anti-hyperglycemic effect on the patients of Diabetis Mellitus type II. Significant antihyperglycemic effect of Karnim plus capsule will be observed after at least 4 weeks of treatment which will be sustained in due course of treatment. Considering better effect over HbA1c and cholesterol it can be concluded that Karnim plus capsule has more potent metabolic effect than Metformin capsule.

From the above study it is concluded that herbal treatment of Karnim is equally beneficial to patients of DM II for controlling blood sugar level and rather more effective in controlling other associated clinical parameters and overall digestion and metabolism of an individual. Treatment of Karnim plus capsule for patients of DM II is completely safe and non hazardous. It has good adaptability, convenience dosing, and good assimilation through the gut flora.

It doesn't produce any untoward significant changes in LFT and KFT profiles. Patients with newly diagnosed type II DM can be safely given treatment with Karnim capsules alone. However, a larger clinical trial is proposed to evaluate its efficacy in a wider perspective.

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