

Interaction of *Momordica charantia* with Metformin in Diabetic Rats

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ABSTRACT

Now a day's people use herb or herbal remedies along with their medication in long term treatment of various disease. Concomitant use of herb and drug can interact with each other may cause herb drug interaction. The present study was designed to investigate the possible herb drug interaction between *Momordica Charantia* Fruit Juice (MCFJ) and metformin. Metformin was given orally in two different doses of 50 mg kg⁻¹ and 100 mg kg⁻¹. *Momordica charantia* fruit juice was administered at a dose of 20 mL kg⁻¹. The Blood glucose was estimated at 0, 7, 14, 21 and 28 days. Body weight of the rats of all the groups was recorded before and after the study period of 28 days. All the treatment shows significant (p<0.01) hypoglycemic effect. The hypoglycemic effect observed with combination of metformin and MCFJ was more than either drug alone. MCFJ alone or also in combination with metformin improve the body weight of diabetic rats. It is concluded that MCFJ along with metformin produce synergistic effect which may be beneficial or harmful so patients should take care when taking MCFJ along with metformin.

Keywords: Herb-Drug Interaction, *Momordica Charantia*, Metformin, Synergistic Effect

1. INTRODUCTION

Diabetes Mellitus (DM) is a major chronic life threatening disorder, in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by the pancreatic hormone, insulin; resulting in an increased blood glucose level. DM is a serious metabolic disease that has a significant impact on the health, quality of life and life expectancy of patients, as well as on the health care system Sancheti *et al.* (2009).

World Health Organization (WHO) estimates that more than 220 million people worldwide have diabetes and this number is likely to double by 2030 (Aragao *et al.*, 2010).

It is also one of the most prevalent (the estimated lifetime risk of developing diabetes for individuals born in 2000 is 32.8% for males and 38.5% for females) and costly chronic diseases, which significantly reduces life expectancy. In the year 2000, the total number of people with DM was 151 million and the number is projected to

increase by 46% to reach 221 million by the year 2010 and 300 million in 2025.

In spite of the fact that insulin has become one of the most important therapeutic drugs for diabetes, efforts are ongoing to find insulin substitutes from other sources. In fact, aside from classical chemically prepared antihyperglycemics, the use of traditional medicinal plants with hypoglycemic effect has recently gained popularity world-wide. More than 400 traditional plant have been claimed for the treatment of Diabetes Mellitus (DM) but only a few of them have scientifically evaluated Dallak *et al.* (2009).

Various plant extract have been found as hypoglycemic but, the mechanism by which they produce hypoglycemia have not been scientifically validated. (Atta-Ur-Rahman and Zaman, 1989; Platel and Srinivasan, 1997; Grover *et al.*, 2002). *Momordica charantia* is widely used antidiabetic herb. *Momordica charantia* also known as bitter melon, karela, balsum pear or bitter gourd is a popular plant used for the treating diabetes related

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condition among the indigenous population of Asia, South America, India and East Africa (Grover and Yadav, 2004; Abascal and Yarnell, 2005; Lans, 2006; Cefalu *et al.*, 2008).

M. charantia is one of the most important plant used in treatment of diabetes and investigation on traditional use of *M. charantia* in India proved it as hypoglycemic agent (Paul and Raychaudhuri, 2010). A recent study concluded that bitter melon fruit tablets can have marked beneficial effects in the treatment of diabetes mellitus. Bitter melon fruit tablets may be used as complementary medicine adjuvant with oral hypoglycaemic agents in the management of diabetes mellitus (Hasan and Khatoun, 2012).

The interaction of herbs with drug is well known. Herbal drug interaction may be Pharmacodynamic (PD) or Pharmacokinetic (PK) in nature. Pharmacodynamic interaction occurs when herbs produce either synergistic or antagonistic effect with conventional drug. When a herb alter the absorption, distribution, metabolism or elimination of a conventional drug, it is known as pharmacokinetic interaction.

Most of the diabetic patients use the various antidiabetic herb along with antidiabetic drug for controlling their blood glucose level these days and hence there may be a chance of interaction between herbs and drug. This interaction may be synergistic or antagonistic. Thus the present study was undertaken to investigate any possible pharmacodynamic interaction of *Momordica Charantia* Fruit Juice (MCFJ) with oral hypoglycemic agent named metformin.

2. MATERIALS AND METHODS

2.1. Plant Material

Momordica charantia fruit were purchased from the local market and identified by the National Botanical Research Institute, Lucknow, India. A voucher specimen no is 97768.

2.2. Preparation of Fruit juice

Momordica charantia fruit is cut and seed was separated then grinded into electronic grinder. The mixture was mixed with 5 mL distilled water and filtered with muslin cloth. The prepared juice was collected and kept in refrigerator.

2.3. Experimental Animal

Healthy adult rats of wistar strain were used in the present study. The animals were housed in clean polypropylene cages and maintained in a well ventilated temperature controlled animal house with constant 12 h light/dark schedule. The animals were fed with standard

rat pellet diet and clean drinking water was made available ad libitum. All animal procedures have been approved and a prior permission from the Institutional Animal Ethical Committee was obtained as per prescribed guidelines.

2.4. Experimental Design

2.4.1. Induction of Diabetes

Rats were fasted overnight before inducing diabetes with streptozotocin. The rats were given an intraperitoneal injection of streptozotocin (50 mg kg⁻¹) freshly prepared in 0.1M sodium citrate buffer. The diabetic state was confirmed 48 h after streptozotocin injection. Threshold value of fasting blood glucose was taken as >200 mg dL⁻¹.

Diabetic rats were weighed matched for body weight and divided into following group consisting five animals each:

- Group I-Diabetic Control
- Group II-Diabetic rats administered with MCFJ at a dose of 20 mL kg⁻¹ body weight
- Group III-Diabetic rats administered with Metformin at low dose of (50 mg kg⁻¹)
- Group IV-Diabetic rats administered with Metformin at high dose of (100 mg kg⁻¹)
- Group V-Diabetic rats administered with MCFJ and low dose of Metformin
- Group VI-Diabetic rats administered with MCFJ and high dose of Metformin

2.5. Blood Glucose Estimation

Blood sample was obtained through puncture tail vein and glucose was estimated on 0, 7, 14, 21 and 28th day by Accu-Check Glucometer.

2.6. Body Weight Determination

Weight of rats was recorded at before and after the study period of 28 days. % change in body weight is calculated and graph is plotted.

2.7. Statistical Analysis

Result were expressed as mean ± SEM. Statistical analysis was carried out by using one way analysis of variance followed by Dunnett test. A value of p<0.05, p<0.01 and p<0.001 were considered significant.

3. RESULTS

The effect of oral administration of metformin, MCFJ and their combinations on blood glucose level showed in **Fig. 1**.

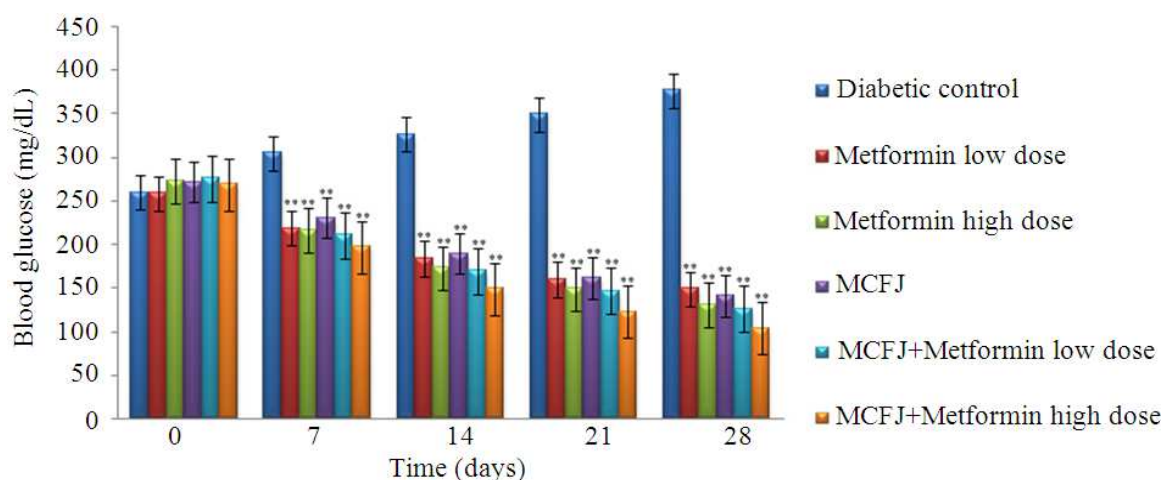


Fig. 1. Effect of MCFJ, Metformin, combinations of Metformin and MCFJ on blood glucose in diabetic rats all values are expressed as mean \pm S.E.M (n = 5). **p<0.01, as compared to diabetic control. One-way ANOVA followed by Dunnet test

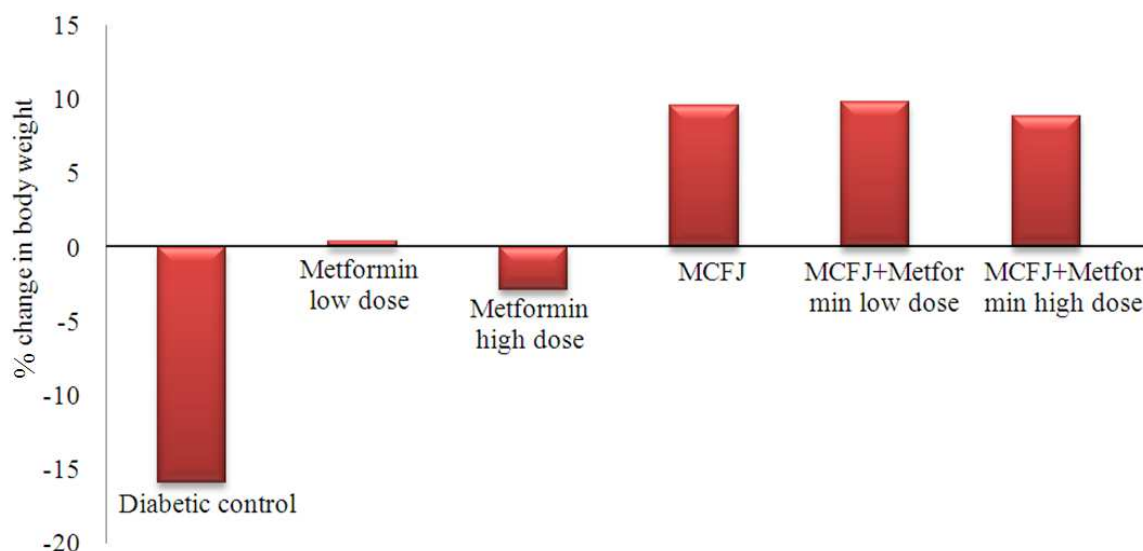


Fig. 2. Effect of MCFJ, Metformin, Combinations of Metformin and MCFJ on body Weight in diabetic rats

All the treatment groups showed significant ($p < 0.01$) hypoglycemic effect compared to diabetic control group on 7, 14, 21 and 28 day of treatment. After the 28 days of treatment the % reduction in blood glucose level of low, high dose of metformin and MCFJ were 42.7, 52 and 48.1% respectively. While the combination of low and high dose of metformin with MCFJ showed 54.3 and 61.3% blood glucose reduction respectively. Data shows that % reduction of combination of low dose of metformin with MCFJ was more than high dose metformin alone.

Combination of high dose metformin with MCFJ showed highest hypoglycemic activity.

Percent change in body weight after 28 days treatment by all the groups show in **Fig. 2**. The body weight of diabetic control rats decreases 15.9% during the study period. Low dose of metformin showed only 0.4% increase while high dose of metformin showed 2.9% decrease in body weight. MCFJ alone showed 9.6% increase in body weight. Combination of low dose and high dose of metformin with MCFJ showed 9.8 and 8.9% increase in body weight. It is clear from the data

that MCFJ improved body weight when combined with low and high dose of metformin.

4. DISCUSSION

Millions of people today use herbal therapies along with prescription and nonprescription medications. Although considered natural, many of these herbal therapies can interact with other medications, causing either potentially dangerous side effects and/or reduced benefits from the medications. Currently, there is very little information published on herb-drug interactions whilst the use of herbs is progressively growing across the world (Gohil and Patel, 2007).

Drug-interaction studies are usually conducted in animal models to assess the safety of the combination, before they are conducted in humans. The normal rat model served to quickly identify the interaction and the diabetic rat model served to validate the interaction in an actual-use condition of the drugs. The rat model was used for the pharmacodynamic-interaction study, since it is the most widely used species in drug metabolism and drug interaction studies (Satyanarayana and Kilari, 2006). The present study was undertaken to investigate the effect of *Momordica charantia* fruit juice on hypoglycemic action of well known oral hypoglycemic agent Metformin.

STZ-induced hyperglycemia has been described as a useful experimental model to study the activity of hypoglycemic agents. The mechanism by which STZ brings about a diabetic state includes selective destruction of pancreatic beta cells, leading to hypoinsulinemia which as a result decreased glucose uptake and hyperglycemia which is the characteristic feature of diabetes mellitus. STZ-induced diabetes is characterized by a severe loss in body weight and increased food intake. Body weight loss might be the result of protein wasting due to unavailability of carbohydrate as an energy source (Balamurugan *et al.*, 2011).

Metformin is recognized as a first-line antidiabetic agent for the management of type 2 diabetes (Esposito *et al.*, 2011). It is suitable irrespective of age, body weight, severity of hyperglycemia and provides a convenient pharmacological base for combined therapy with other antidiabetic agents (Scarpello and Howlett, 2008). Metformin has a lower mortality and cardiovascular risk as compared with most insulin secreting agents such as glimepiride, glibenclamide, glipizide and tolbutamide in patients with type 2 diabetes mellitus (Schramm *et al.*, 2011). Another benefit of metformin is that it does not produce hypoglycemia because it does not stimulate insulin secretion when it is given alone in patients with type

diabetes mellitus (Wright *et al.*, 2006). Metformin is also renowned to facilitate modest weight loss in type 2 diabetic patients (Golay, 2008).

All the treatment showed significant ($p < 0.01$) hypoglycemic effect compared to diabetic control group on 7, 14, 21 and 28 day of treatment. Body weight was decreased in diabetic rats after 28 days treatment. Administration of MCFJ increased body weight of diabetic rats and same results were obtained in combinations of metformin with MCFJ which may be due to improvement of blood glucose levels of rats.

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications e.g., herbs traditionally used to decrease glucose concentrations in diabetes could theoretically precipitate hypoglycemia if taken in combination with conventional drugs (Adriane, 2000).

Result of the study showed that MCFJ potentiate the hypoglycemic effect of metformin in diabetic rats i.e., MCFJ along with metformin showed synergistic effect. This synergistic effect may be helpful in reducing the dose of metformin in treatment of diabetes, which will be helpful in minimizing the adverse effect related to metformin.

5. CONCLUSION

The study concluded that administration of MCFJ with metformin for the treatment of diabetes showed synergistic effect which may be beneficial and harmful also. Combination of oral hypoglycemic drug and herb may lead to severe hypoglycemic condition which may be life threatening so patient should be careful in taking oral hypoglycemic drug along with herbs.

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