Synergistic antihyperglycemic potential of plant drugs - a review

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ABSTRACT

In present scenario we are almost fully dependent on the allopathic medicines, though there is a very vast flora available and they are having various medicinal activity. Out of them so many plants are having antihyperglycemic and antihyperlipidemic activity. Till now so many researchers have evaluated many plants for their antihyperglycemic and antihyperlipedemic activities. But still we are lack of a effective ayurvedic dosage form which can complete the allopathic drugs. This difficulty can be overcome by using the synergism. Synergism can be defined as the interaction or cooperation of two or more substances to produce a combined effect greater than the sum of their separate effects. This effect of synergism can be applied on the plant drugs by taking into consideration two or more plant drugs so that a effective ayurvedic dosage form can be prepared.

Keywords:Antihyperglycemic,antihyperlopidemic,synergism,ayurvedic

Introduction

Evaluation of Antihyperglycemic Activity

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia and increased lipid profile due to defect in carbohydrate, protein and fat metabolism [1]. Long term hyperglycemic condition is associated with damage and failure of many organs such as eyes, kidney, nerves, heart, and blood vessels [2]. The defect in lipid, proteins and carbohydrate metabolism leads diabetic complications. Increased blood glucose levels modify the proteins such as elastin, collagen present in various tissues to glycoproteins responsible for the retinopathy, neuropathy, atherosclerosis and nephropathy [3]. Worldwide the occurrence of diabetes is estimated to progress, from 4 % in 1995 to 5.4 % by the year of 2025[4].Antidiabetic drugs treat diabetes mellitus lowering glucose levels in the blood. exenatide,liraglutide and pramlintide(insulin exception, all are administered orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents.
Diabetes mellitus type 1: The reason of type 1 is deficiency of Insulin. Insulin must be used in Type I, which must be injected.

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Diabetes mellitus type 2 : It is caused by insulin resistance by cells. Type 2 diabetes mellitus is the most common type of diabetes. Treatments include-

1. Agents that increase the amount of insulin secreted by the pancreas,
2. Agents that increase the sensitivity of target organs to insulin, and
3. Agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Antidiabetic drugs:

- Insulin

Examples of rapid acting insulins include

- Regular insulin (Humulin R, Novolin R)
- Insulin lispro (Humalog)
- Insulin aspart (Novolog)
- Insulin glulisine (Apidra)
- Prompt insulin zinc (Semilente, Slightly slower acting)

Examples of intermediate acting insulins include

- Isophane insulin, neutral protamineHagedorn (NPH) (Humulin N, Novolin N)
- Insulin zinc (Lente)

Examples of long acting insulins include

- Extended insulin zinc insulin (Ultralente)
- Insulin glargine (Lantus)
- Insulin detemir (Levemir)

Most anti-diabetic agents are contraindicated in pregnancy, in which insulin is preferred.

- Sulfonylureas - glimepiride, glipizide, glyburide
- Biguanides –metformin
- Thiazolidinediones (Tzd) - pioglitazone, Actos generic
- Alpha-glucosidase inhibitors –Acarbose
- Meglitinides –nateglinide
- Combination of sulfonylureas plus metformin - known by generic names of the two drugs
- Dipeptidyl Peptidase-4 Inhibitors- Examples are:
  - Vildagliptin (Galvus) EU Approved 2008
  - Sitagliptin (Januvia) FDA approved Oct 2006
  - Saxagliptin (Onglyza) FDA Approved July 2009
  - Linagliptin (Tradjenta) FDA Approved May 2, 2011
  - Alogliptin
  - Septagliptin

All above drugs are synthetic drugs which used to treat diabetes mellitus. Treatment for the diabetes mellitus is of very long duration and often life time. So there are vast complications and side effects in the patients using these drugs. So it is a very seriously need to switch over to herbal therapy to overcome the complications and side effects associated with the andtidiabetic therapy.

Synergistic Pharmacological activity of Herbal Drug Combinations

- **BL Fiebich *et al* study**

Fiebich BL *et al* used the extracts of *Hypericum*, *Passiflora* and Valeriana for the treatment of mild depression and anxiety. They used two well-established models for investigating antidepressant activity, namely the effects on synaptic uptake of serotonin and forced-swimming-test. In this study it was noticed that Passiflora having the synergistic effect on the pharmacological potency of Hypericium in both models [5].

- **Chun-Tao Che *et al* Study**

Chun-Tao Che *et al* presented an overview of the traditional concept and practice of herb-herb combination in Chinese medicine, and highlighted the available scientific and clinical evidence to support the combined use of herbs. It was hoped that such information would provide a lead for developing new approaches for future therapeutic advancement and pharmaceutical product development. Very likely modern technologies combined with innovative research for the quality control of herbal products, identification of active components and understanding of the molecular mechanism, followed by well-designed animal and clinical studies would pave the way in advancing the wealth of empirical knowledge from herb-herb combination to new therapeutic modalities [6].

- **Gurdun Ulrich-Merzenich *et al* Study**

Gurdun Ulrich-Merzenich *et al* emphasized on the synergistic effects of the herbal drugs. Drug development in the phytomedicine is focused on the discovery and analysis of new structure from natural products. Generally it was assumed that a plant has one or few ingredients which determine its therapeutic efficacy. But in traditional systems of medicines like Ayurveda, Chinese or the European phytotherapy generally assumed that a synergistic effect of the all plant ingredients may bring out the maximum efficacy.In the present review article concepts of synergy was highlighted and various examples of the synergistic effect of plant constituents were given [7].

- **Swati Mani *et al* Study**

Swati *et al* evaluated the antidiabetic and antihyperlipidemic activities of Allopolyherbal formulation consisting of combinations of three well known medicinal plants used in traditional medicines (*Trigonellafoenum* graceum, *Momordica Charantia*, *Aegle Marmalos*) and synthetic oral hypoglycaemic drug (Glipizide). The optimized combination of lyophilized hydro-alcoholic extracts of drugs was 2:2:1 using OGTT model. The optimized polyherbal formulation was simultaneously administered with Glipizide and optimized using OGTT model in diabetic rats and further studied in Streptozotocin-induced diabetic rats for for 21 days. The results (Serum glucose level, lipid profile, hepatic enzymes & body weight) were compared with the standard drug Glipizide(10mg/kg body weight). The optimized Allopolyherbal formulation (500 + 5 mg/kg body wt.) has shown significant antihyperglycaemic and antihyperlipidemic activities. The results were comparable with the standard; even better than the Glipizide (10 mg/kg body wt.) alone. The proposed hypothesis has reduced the number of drug components from eight to three and dose almost 50% of both Polyherbal formulation and Glipizide. And alsominimized the cardiovascular risk factors associated with diabetes [8].

- **A E Nugroho AE*et al* Study**

Nugroho AE *et al* studied the combination of medicinal plants which were commonly used for lowering blood glucose in diabetic patients in order to provide additional benefits of the single drug. *Andrographis paniculata* and *Centellaasiatica* L are two traditional medicines form South Asian and Southeast Asian countries consumed by people for treating diabetes mellitus and its complications. Hyperglycemia in the rats was stimulated by high fructose-fat diet.for 70 days. The rats were orally administered with the combination of andrographolide-enriched extract of *A. paniculata* leaves and asiaticoside-enriched extract of *C. asiatica* herbs from day 70 for 7 days. Antidiabetic activity was evaluated by estimating mainly the blood glucose levels and other parameters such as HDL, LDL, cholesterol and triglyceride. The results showed that combination at the ratio of 70:30 exhibited a significant antidiabetic effect in high-fat-fructose-fed rat, and exhibited synergistic effects on blood cholesterol and HDL levels. It can be concluded that its antidiabetic effect was better than that of single treatment of andrographolide-enriched extract of *A. paniculata*or asiaticoside-enriched extract of *C. asiatica*. That combination was also potential to develop as a blood glucose-lowering agent for diabetic patients [9].

- **Aparajeya Panda *et al* Study**

Aparajeya Panda *et al* focused on polyherbal antidiabetic formulations of different plants used in the treatment of diabetes mixed in different concentrations. In the present study eleven medicinal plants with proven antidiabetic and related beneficial effects were selected for the preparation of five mixtures. The efficacy of prepared mixtures has been tested on streptozotocin (STZ) induced diabetic rats and compared with a commercially available drug glibenclamide. The mixtures at the dose levels of 400 mg/kg body wt. produced a significant decrease in blood glucose level by 69.6%, 70.97%, 64.45%, 71.82%, and 64.44% after 21 days of treatment. The elevated level of SGPT, SGOT, and ALP in the diabetic controlled group reflected the significant alteration of liver function by streptozotocin STZ induction and was found to be equipotent to glibenclamide in restoration of the elevated enzyme levels to normal. The elevated lipid levels (triglyceride and total cholesterol) were restored to near normal by these mixtures for all the estimated parameters. The results of the mixtures on treated group were found to restore the glycemic level to the near normal level thereby indicating antihyperglycemic activity of the formulated mixtures [10].

- **Anuja Patil *et al* Study**

AnujaPatil *et al* revealed the antidiabetic effects of different polyherbal combinations of six medicinal plants used in traditional medicine. Aim of this study was to evaluate antidiabetic action of polyherbal combination of six medicinal plants. Aqueous extracts of *Stevia rebaudiana, Momordica charantia, Tamarindus indica, Gymnema sylvestre, Alliumsativum* and *Murraya koenigii* were used for polyherbal combinations. All these combinations were studied for their acute toxicity and 250 mg/kg dose was selected. OGTT, antidiabetic and anti-α amylase and α-glucosidase activity and liver function tests were performed for all the combinations. Reduction in blood glucose level was determined in antidiabetic activity for 0 to 20 days and histopathology of the pancreas was performed after 20th day. IC50 value is determined in anti-α amylase activity. Results revealed that all combinations were safe and dose was selected at 250 mg/kg. One Polyherbal combination among all selected Polyherbal combination showed significant antidiabetic activity in OGTT and STZ-diabetic rats. This combination showed significant anti-α amylase and α-glucosidase activity which is better than other combinations and also produced beneficial improvement in lipid profile [11].

- **Sheela K *et al* study**

Sheela K *et al* studied the antidiabetic and antioxidant activity of two herbal tea extracts of *Benincasa hispida* and *Andrographis paniculata* Nees in Streptozotocin induced diabetic rats. The histopathological studies showed the significant data to confirm the control of diabetes by the herbal tea extracts. The result indicated that *Andrographis paniculata* Nees (Kalmegh) is endowed with significant antidiabetic activity than *Bennicasa hispida* (ash gourd). On the basis of this study it was concluded that *Andrographis paniculata* (Kalmegh) has very good efficacy and safety in lowering blood glucose level [12].

- **Bugga Paramesha *et al* Study**

Bugga Paramesha *et al* evaluated the antidiabetic and hypolipidaemic activity of ethanolic extracts of *Amaranthusviridis* and *Ceibapentadra* and their combination on Dexamethasone induced Type-II diabetic Swiss albino rats. This study showed a significant increase in serum Tri-glycerides, Total cholesterol, LDL, VLDL and blood glucose levels and significant decrease in body weight, HDL, liver and tissue glycogen levels in diabetes control group when compared with normal group of animals. The treatment group showed significant improvement in all biochemical parameters. This study concluded that Ethanolic extract of *Amaranthus viridis* and *Ceiba pentandra* and their combination showed a significant decrease in serum glucose, TG, TC, LDL, VLDL and

significant increase in body weight, HDL, liver glycogen and tissue glycogen levels [13].

- **T.Satyanarayan *et al* Study**

The objectives of this study is to induce diabetes mellitus using Streptozotocin in normal adult Wistar rats and study the anti-diabetic activity of polyherbal formulation by comparison of changes in body weight, consumption of food and water, volume of urine and levels of glucose between normal and diabetic rats. So many Indian plants have been found to be useful to successfully manage the diabetes. The effect of ethanolic extract of poly herbal formulation containing leaves and seeds of Trigonella foenum- graecum, fruits of *Momordica charantia* and fruits of *Emblica officinalis* was investigated in normal, glucose load conditions and streptozotocin induced diabetic rats. Significant hypoglycemic activity was exhibited by the poly herbal formulation [14].

- **Halim Eshrat M *et al* Study**

HalimEshrat M *et al* were screened dietary spice components of *Curcuma longa* and *Abroma augusta*for their protective effect against reactive oxygen species induced lipid peroxidation. They have been found to be efficient antioxidant when administered in combination. The purpose of the study was to investigate the effect of oral administration (300 mg / Kg) of the aqueous extract of turmeric whose active ingredient is Curcumin and Abromine powder as a hypoglycemic agent mixed with diet. The administration of an aqueous extract of turmeric and abromine powder resulted in a significant reduction in blood glucose and an increase in total haemoglobin. The aqueous extract also resulted in decreased free radical formation in the tissues studied. The decrease in thiobarbituricacid reactive substances and increase in reduced glutathione , superoxide dismutase and catalase clearly showed the antioxidant property of the mixture. It is suggested that these changes initially counteract the oxidative stress in diabetes however, a gradual decrease in the antioxidative process may be one of the factors which results in chronic diabetes. These results indicated that the mixture of the two plants have shown antidiabetic activity and also reduced oxidative stress in Diabetes. A combination of *Abromaaugusta* and *Curcuma longa* also restored the other general parameters in diabetic animals. The results were statistically analyzed and indicated that combination of herbal extracts showed better efficacy as compared to individual herbal plant extracts used [15].

- **Idha Kusumawati *et al* Study**

Idha Kusumawati *et al* evaluated the hypoglycemic activity of the herbal tea combination of *Momordica charantia* L. and the leaves of *Lagerstroemia speciosa* in alloxan-induced diabetic mice. Hypoglycemic activity of the herbal tea (0.4 ml/20 g body weight) was tested in five groups of Balb/C mice with at least five animals each and the results were statistically compared with the results of CMC-Na 0.5% (negative control) and a known antidiabetic drug glibenclamide 0.013 mg/20 g body weight. Oral administration the herbal tea of *M.charantia* and its combination with *L.speciosa* leaves in ratio (2:1), (1:1), and (1:2) for 7 days exhibited significant reduction of blood glucose level in alloxan-induced diabetic mice [16].

- **M.C. Sabu *et al* Study**

M.C. Sabu *et al* evaluated Methanolic extract (75%) of *Terminalia chebula*, *Terminalia belerica*, *Emblica officinalis* and their combination named 'Triphala' (equal proportion of above three plant extracts) are being used extensively in Indian system of medicine. They were found to inhibit lipid peroxide formation and to scavenge hydroxyl and superoxide radicals *in vitro*. The concentration of plant extracts that inhibited 50% of lipid peroxidation induced with Fe^{2+}/ascorbate were found to be 85.5, 27, 74 and 69 mg/ml, respectively. The concentration needed for the inhibition of hydoxyl radical scavenging were 165, 71, 155.5 and 151 mg/ml, and that for superoxide scavenging activity were found to be 20.5, 40.5, 6.5 and 12.5 mg/ml, respectively. Oral administration of the extracts (100 mg/kg body weight) reduced the blood sugar level in normal and in alloxan (120 mg/kg) diabetic rats significantly within 4 h. Continued, daily administration of the drug produced a sustained effect [17].

- **Ratendra Kumar *et al* Study**

Ratendra Kumar *et al* examined and compared the effect of Polyherbal (PH), Allopolyherbal-A (APH-A), Allopolyherbal-B (APH-B), and Allopolyherbal-C (APH-C) formulations on hyperglycemia, lipid profile, renal, and hepatic function in streptozotocin (STZ) induced diabetes mellitus in rats. Blood glucose levels were measured on 0, 7, 14, and 21 days of the study; total cholesterol, triglycerides, LDL, VLDL, HDL, serum creatinine, SGOT, and SGPT were estimated on 21^{st} day. It was found that Gliclazide, Polyherbal (PH), Allopolyherbal-A (APH-A), Allopolyherbal-B (APH-B), and Allopolyherbal-C (APH-C) formulations treated rats showed significant decrease in blood glucose, total cholesterol, triglycerides, LDL, VLDL, serum creatinine, SGOT, and SGPT level, along with significant increase in HDL. It was concluded that the combination of allopathic hypoglycemic drugs with hypoglycemic Polyherbal formulations provides effective and rapid glycemic control and can also minimize the cardiovascular risk factors of type II diabetes mellitus [18].

- **Sari, K. R *et al* Study**

Sari, K. R *et al* studied that exploration of herbs combination could be an alternative way for developing traditional medicine in order to provide better result or benefits in the therapy of diseases.*Andrographis paniculata* (Burm.f.)Ness and *Gynura procumbens*(Lour.)Merr are two medicinal plants that are already well known for traditional treatment of diabetes mellitus (DM). Combination of potent hypoglycaemic effect of *A. paniculata* and poten antioxidant effect of *G. procumbens* is expected to produce an optimun antidiabetic effect. The aim of this study was to evaluate the antidiabetic effect of their combination in alloxan-induced hyperglycemic rats. In the study, the combination of *A. paniculata* and *G. procumbens* significantly decreased the blood glucose level up to 76%. Fifteen days administration of this combination could improve the condition of pancreatic islet due to alloxan. The combination also increased the pancreatic insulin expression. The highest antidiabetic effect of the combination was achieved at the dose of 100:112.5 mg/kg body wt. In conclusion, the combination of *A. paniculata* and *G. procumbens* is potential to develop as an antidiabetic agent [19].

- **Savula Jyothsna1 *et al* Study**

Momordica charantia is commonly known as bitter melon and *Momordicadioica* commonly known as bitter melon both are very commonly available plants of Andra Pradesh both fruits are proved to have antidiabetic activity. The main objective of the present research work was to compare the anti-diabetic activity of the *Momordica charantia* and *Momordicadioica* fruit crude extracts obtained by various extraction methods. Ethanolic and Aqueous extracts of both *Momordica charantia* and *Momordicadioica* fruits were prepared by Maceration, Percolation and Soxhlation, and subjected to phytochemical screening and tested for anti-diabetic activity in alloxan induced diabetic rats. Phytochemical screening showed positive tests for alkaloids, terpenoids, Saponins (aqueous), Glycosides & Carbohydrates in both fruit extracts. The macerated ethanolic extracts of *Momordica charantia* fruit and the Combination of Macerated extracts of both *Momordica charantia* and *Momordicadiocia* showed significant anti-diabetic activity at a dose of 250mg/kg orally [20].

- **S. Umamaheswari *et al* Study**

Diabet, a polyherbal formulation marketed for diabetes, was investigated for its glucose tolerance, hypoglycemic and antidiabetic activity in rats. The glucose tolerance test and hypoglycemic studies were carried out in normal rats at a dose of 500 mg/kg. Antidiabetic effect was analyzed in alloxan- induced diabetic rats at 500mg/kg of the polyherbal formulation. Glibenclamide (4mg/kg) was used as the standard drug. The biochemical parameters (glucose, urea, creatinine, serum cholesterol, serum triglyceride, high density lipoprotein, low density lipoprotein, hemoglobin and glycosylated hemoglobin) of the polyherbal formulation were assessed in diabetic rats at 500mg/kg. The product showed its effectiveness in oral glucose tolerance test and Antidiabetic activity, but it does not produce hypoglycemic effect. Treatment of diabetic rats with the product restored the elevated biochemical parameters significantly. The present study supports the use of this product as an antidiabetic [21].

- **T O Fakeye *et al* Study**

T O Fakeye *et al* investigated the interacting effects of co-administration of *Carica papaya* leaf extract on the hypoglycemic activity of metformin and glimepiride in an animal model. Leaf extract of *Carica papaya* significantly delays the onset of hypoglycaemic activity of glimepiride, and increases the hypoglycaemic effect of metformin with the variables interacting differently for each drug-extract combinations [22].

- **Nishi Saxena *et al* Study**

Nishi Saxena *et al* were prepared a herbal suspension containing alcoholic extract of *Annona squamosa* leaves, *Aegele marmelos* leaves and *Azadirachta indica* leaves and evaluated for its organoleptic characteristics, physicochemical parameters and antidiabetic activity. The suspension was free flowing and easily dispersible. The organoleptic and physicochemical properties were satisfactory. Antidiabetic activity was studied in streptozotocin induced diabetic rats using Glibenclamide 600µg/kg as a standard drug. Herbal suspension at both the doses of 25 and 50µg/ml was having significant activity. The weight gain and decrease in blood glucose level was less than that of standard drug. Thus it was concluded that prepared oral herbal suspension is safe for use with promising antidiabetic activity [23].

- **Divya Pingili *et al* Study**

Divya Pingili *et al* were evaluated methanolic and hydro alcoholic polyherbal extracts having *Terminalia arjuna* (Roxb.) Wight &Arn, *Piper nigrum* Linn.and *Cuminum cyminum* Linn. for their *in vitro* antioxidant activity by 1,1-diphenyl- 2-picryl hydrazyl (DPPH) and superoxide radical scavenging method; *in vitro* antidiabetic activity by α-glucosidase and α-amylase inhibitory method; and anticancer activity by 3-(4,5-dimethylthiazole-2yl)-2,5-diphenyl tetrazolium bromide (MTT) assay against A549 human lung cell carcinoma. Antioxidant activity of methanolic extract of *Terminalia arjuna* (S1) was found to be more potent compared to other polyherbal extractions. S1 also

inhibited α-glucosidase enzyme and hydroalcoholic extract inhibited α-amylase enzyme. Few polyherbal combinations are found to possess significant anticancer activity against A549 human lung cell carcinoma [24].

- **Kumeshini Sukalingam *et al* Study**

Kumeshini Sukalingam *et al* studied the polyherbal formulations which enhance the therapeutic action and reduce the concentrations of single herbs, thereby reducing adverse events. The study focused on polyherbal formulations of five different medicinal plants(Mango, Guava, Amla, Garlic and Onion) used for the treatment of Type II diabetic patients. In the present study five medicinal plants (Mango, Guava, Amla, Garlic and Onion) with proven antidiabetic and related beneficial effects were selected for the preparation. The efficacy of prepared formulations were tested on Type II diabetic patients and compared with placebo diabetic control patients. The results of the formulations on Type II diabetic group were strong evidence that not only it restored the glycemic level but also reduced the lipid profile to the near normal. Based on the findings, the polyherbal formulations have significant antidiabetic potential for Type II diabetic patients [25].

- **Agung Endro Nugroho *et al* Study**

Agung Endro Nugroho *et al* explored the antihyperglycemic effect of herbal extract combination of *Andrographis paniculata* (Burm. f.) Ness and *Azadirachta indica* A. Juss in alloxan-induced rats compared to single extract treatment. Diabetic condition was induced by alloxan monohydrate in the rats. After stable diabetic condition, the rats were administered either with single or extract combination for 15 consecutive days. Blood glucose profiles monitored as per schedule. Preprandial and postprandial blood glucose levels of alloxan induced rats could be decreased after administration of the combined herbal extract of *A. paniculata* (Burm. f.) Ness and *A. indica* A. Juss.In this study it was concluded that combined extracts exhibited higher hypoglycemic effects than this of the single extract treatment [26].

- **Ghiware Nitin B. *et al* Study**

Ghiware Nitin B. *et al* investigated the most suitable dosage forms among three orally administrable dosage forms of fruits of *Piper nigrum* (Maricha) and leaves of *Nyctanthes arbortristis* (Parijataka), in combination, were developed. Tablet form of drugs from solid dosage form and two formulations from liquid class were designed and developed. To overcome the solubility problem of herbal drug in one of the liquid class, decoction form of drugs in specific vehicle was used. This form of drugs hereafter considered as Liquid Oral Dosage Form of drugs. To prepare a liquid form with suspended particles of drugs, Suspension form was also designed. Formulated dosage forms then evaluated for various parameters. Oral herbal dosage forms in combination like Tablets, Liquid Oral & Suspension showed good elegance & palatability. Tablet dosage forms showed good quality with regards to characteristics like hardness, friability, and weight variation and disintegration time. Liquid dosage forms like Liquid Oral & Suspension having good stability on storage. Thus it can be concluded that these combined oral herbal dosage forms could be suitable dosage form for *Piper nigrum* (Maricha) fruits and *Nyctanthesarbortristis* (Parijataka) leaves [27].

- **Harshad Shete *et al* Study**

Trigonella foenum, trachy spermum Capticum &*Nigella sativa* have been reported for the potential anti-oxidant and anti-hyperlipidemic activity. The combinations of the extracts of these drugs were having been potentially developed for the treatment of diabetes mellitus. The combination of methanolic extracts of *T.foenum, T.capticum* &*N.sativa* in 1:1:1 proportion was used for the evaluation of antidiabetic activity in Streptozotocin induced Sprague Dawley rats. Two dose levels (100mg & 200 mg) of methanolic extracts of three herbs were administered orally to both male and female rats. Normal blood glucose level (normoglycemic model), oral glucose tolerance test (OGTT), fasting blood glucose level, serum insulin, serum lipid profile, atherogenic index and extrapancreatic effects like glucose uptake, liver glycogenolysis& liver glycogen were studied. After 15 days treatment with above mentioned two dose levels there was a significant improvement in all the above mentioned parameters [28].

- **Pranav Kumar Prabhakar *et al* Study**

Pranav Kumar Prabhakar *et al* were analyzed the effect of two compound namely chlogenic acid and ferulic acid, and a plant alkaloid, berberine, alone and also in combination with two commercial oral hypoglycemic drugs, namely Metformin and 2,4-thiazolodinedione (THZ), on the uptake of 2-deoxyglucose by L6 myotubes. 2-deoxyglucose uptake is determined using an enzymatic assay. All the three natural products enhance the uptake of 2-deoxyglucose in time and dose dependent manner. A combination of different concentrations of chlorogenic acid and metformin or 2,4-thiazolodinedione, has a synergistic effect in the uptake of 2-deoxyglucose with a minimum of 5 and 5.3 times respectively with reference to the base value (without the drugs or the natural products). Ferulic acid in combination with metformin or THZ has also shown a synergistic effect and the 2-deoxyglucose uptake increased by 4.98 & 5, 11 times, when compared to the

control. Whereas, berberine, in combination with the metformin of THZ, has shown an additive effect with maximum 2-deoxyglucose uptake of 4.1 and 4.7 times from the base value, respectively. This study suggested that the phytochemicals can replace the commercial drugs in part, which could lead to a reduction in toxicity and side effects [29].

- **Patel Snehal S *et al* Study**

Patel Snehal S *et al* evaluated antihyperglycemic, antihyperlipidemic and antioxidant activities of Dihar, a polyherbal formulation containing drugs from eight different herbs viz., *Syzygium cumini, Momordica charantia, Emblical officinalis, Gymnema sylvestra, Enicostemma littorale, Azadirachta indica, Tinospora cordifolia* and *cucuma longa* in Streptozotocin induced type 1 diabetic rats. Treatment with Dihar (100 mg/kg) for 6 weeks produced decrease in STZ induced serum glucose and lipids levels as compared to control. Dihar produced significant decrease in serum creatinine and urea levels in diabetic rats. There was a significant decrease in reduced glutathione, superoxide dismutase, catalase levels. The results suggest Dihar to be beneficial for the treatment of type-1 diabetes [30].

- **Mukesh Yadav *et al* Study**

MukeshYadav *et al* investigated hypoglycemic and antihyperglycemic potential of five extracts (water, ethanol, methanol, hexane, and chloroform) of four plants (i.e., seeds of **Eugenia jambolana**, fruits of **Momordica charantia**, leaves of **Gymnema sylvestre**, and seeds of **Trigonella foenum graecum**) alone and/or in combination with glimepiride in rats. Ethanol extract of **E. jambolana**, water extract of **M. charantia**, ethanol extract of **G. sylvestre**, and water extract of **T. graecum** exhibited highest hypoglycemic and antihyperglycemic activity (most active) in rats among all the extracts, while hexane extracts exhibited least activities. Most active extracts were further studied to dose-dependent (200, 100, and 50 mg/kg body weight (bw)) hypoglycemic and antihyperglycemic effects alone and in combination with glimepiride (20, 10, and 5 mg/kg bw). The combination of most active extracts (200 mg/kg bw) and lower dose of glimepiride (5 mg/kg bw) showed safer and potent hypoglycemic as well as antihyperglycemic activities without creating severe hypoglycemia in normal rats, while higher doses (200 mg/kg bw of most active extracts, and 10 and 20 mg/kg bw of glimepiride) were generated lethal hypoglycemia in normal rats. From this study, it may be concluded that the ethanol extract of **E. jambolana** seeds, water extract of **M. charantia** fruits, ethanol extract of **G. sylvestre** leaves, and water extract of T. graecum seeds have higher hypoglycemic and antihyperglycemic potential and may use as complementary medicine to treat the diabetic population by significantly reducing dose of standard drugs [31].

Conclusion

In the above studies all the researchers have evaluated the synergistic action of herbal drug combinations. Few researchers have evaluated synergism by taking the allopathic and ayurvedic drugs simultaneously and shows that herbal drug potentiate the action of allopathic drug and thus decrease the dose. By synergistic effect dose of the drugs can be reduced and the action can be increased by many folds. But still further study is needed to evaluate more about synergistic effects of the herbal drug combinations and to convert them in suitable formulation which can replace or minimize the dose of the existing allopathic antidiabetic drugs.

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