

Action of Multiherbal Formulation of Five Medicinal Plants on the Pancreas of Diabetic Albino Rats

Research Article

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Abstract

Herbal drugs have always remained an important source of medicine. As per the Indian traditional system of medicine, many medicinal plants have been used for the management of various health disorders, including *diabetes mellitus*. *Diabetes mellitus* is a non-communicable disease that is also referred to as a lifestyle disorder that requires modifications in diet, exercise, and behavior along with medication. *Allium sativum* (Garlic), *Azadirachta indica* (Neem), *Phyllanthus emblica* (Amla), *Tamarindus indica* (Imli), and *Zingiber officinale* (Ginger) are well-known and widely used medicinal plants in the world. Diabetic rats (FBS above 150 mg/dl) were treated orally with three different multiherbal formulations (F1, F2, and F3) at a dose of 300 mg/kg, once per day for 45 days. At the end of the study, their effects on the histology of the pancreas were evaluated. Pancreatic β cell regeneration of the multiherbal formulation (F2) was approximately equal to that of the standard drug. This study aimed to evaluate the possible effects of multiherbal formulations of these five plants on alloxan-induced diabetic rats.

Keywords: Diabetes Mellitus; Multiherbal Formulations; Histological Studies

Introduction

Diabetes mellitus is defined as a group of chronic metabolic disorders characterized by persistent hyperglycemia resulting from a complete or relative lack of insulin secretion or action. There have been increases in the search for new anti-diabetic agents that are cheaper, have greater effectiveness, and have fewer side effects because many of the available synthetic oral hypoglycemic agents are costly and produce predictable adverse drug reactions. In most developing countries and even some developed countries, over-the-counter use of polyherbals is on the high side, and the manufacturers claim a complete cure for diabetes mellitus. A polyherbal mixture is composed of different plant constituents and purified extracts with medicinal properties for maintaining good health and the treatment of different ailments. In this respect, a combination of herbs is believed to work synergistically and may have a more beneficial effect

than a single preparation [1, 2]. Different herbal formulations are preferred due to their maximum therapeutic efficacy, low cost, and lesser side effects. They are not addictive or habit-forming, and they are powerful nutritional agents that support the body naturally.

Garlic (*Allium sativum*), a member of the Alliaceae family, is one of the main essential vegetables all over the world. The importance of garlic is due to its use not only for therapeutic purposes but also for medicinal purposes in both traditional and modern medicine. All parts of the plant (inflorescence, leaves, and cloves) have been used since ancient times as a spice [3]. Garlic has a higher concentration of sulfur compounds (such as allicin, diallyl disulfide, S-allyl cysteine, and diallyl trisulfide), which are responsible for its many kinds of medicinal effects. It is eaten either as a raw vegetable (fresh leaves or dried cloves) or after processing in the form of garlic oil, garlic extracts, and garlic powder, which have many bioactive compounds that have

remedial properties for many diseases and physiological disorders like diabetes, hyperlipidemia, hypertension, platelet aggregation, and many more. Babylonians, Egyptians, Greeks, Phoenicians, and Romans used garlic as a cure for bacterial diseases, intestinal ailments, respiratory diseases, skin infections, tumors, worms, and wounds. Before the outcome of antibiotics, garlic was used against amoebic dysentery and epidemic diseases such as cholera, diphtheria, and tuberculosis. Garlic was largely used during World War II to treat wounds of soldiers and was used directly to wounds to prevent the spread of infection [4].

Neem belongs to the family Meliaceae, is recorded in ancient reports like '*Charak Samhita* and *Susruta Samhita*, and has been used in Ayurvedic medicine for more than 4000 years due to its curative activities. The people of India have long appreciated the neem tree for centuries; millions have cleaned their teeth with neem twigs, smeared skin diseases with neem leaf juice, and taken neem tea as a tonic [5]. Earlier studies on Neem exhibited that it has many naturally active compounds in almost every part of the plant (bark, branches, fruit, leaves, oil, roots, seeds, and trunk) with many curative activities. It is now considered a valuable source of unique natural products for the improvement of medicines against many disorders and also for the progression of industrial products. The biologically most active compound is azadirachtin, which is a mixture of seven isomeric compounds (azadirachtin A-G) and azadirachtin E, which is more effective. It is a tetran or triterpenoid, abundant in the seeds and present in a smaller concentration in the leaves. Neem is rich in phytocomponents such as alkaloids, carotenoids, flavonoids, glycosides, ketones, phenolic compounds, tannins, triterpenoids, steroids, etc. Other active substances are azadirachtol, azadirone, deacetylalanin, gedunin, meliacarpine, melianone, melianrol, nimbin, nimbolone, salanin, and vilosinin, with over 300 isolated and characterized constituents [6]. In Ayurveda, different parts of Neem are used for anorexia, biliousness, diabetes, epistaxis, eye problems, intestinal worms, leprosy, piles, skin ulcers, urinary disorders, and wounds. Its bark is used as an alternative, analgesic, and remedial treatment for fever. Intestinal worms and phlegm are eliminated by the use of flowers. Gum is effective against skin diseases like ringworms, scabies, wounds, and ulcers [7].

Amla belongs to the family Euphorbiaceae. It is named *Phyllanthus emblica*, Indian gooseberry, or Amla. Amla is a major part of the ancient Ayurvedic preparation "Chyawanprash," which is believed to prolong the aging process and help keep young. The fruits of plants have been used in Ayurveda as a potent *rasayana*. Its fruits are widely used in Ayurveda and regularly used to increase immunity, diabetes, antioxidants, fight against cancer, chronic diseases like high cholesterol, hypertension, influenza, cold and cough, fatigue, infections, and inflammatory conditions. It is very effective in the treatment of acidity, anemia, graying of the hair, heart trouble, liver treatment, memory enhancement, ophthalmic disorders, peptic ulcers, analgesics, antipyretics, antitussives, cytoprotective, gastroprotective, and helpful in nullifying snake venom and increasing defense against many other diseases [8]. The ancient system of drugs used almost all of its parts, i.e., roots, leaves, and stems, and most of them were known for their remarkable fruit activities. The fruit is used either alone or in combination with other plants. The fruit is rich in alkaloids,

flavonoids, terpenoids, gallic acid, pectin, phyllaemblic compounds, quercetin, tannins, antioxidants, calcium, essential amino acids, iron, minerals, vitamin C, and many polyphenolic compounds that have been revealed to have useful biological properties. The leaves and bark of the tree are rich in tannin. It is one of the best herbs in Ayurveda for diabetes, bleeding complaints, stamina promoter, and strength. Amla is a natural, effective antioxidant with the richest natural source of vitamin C (200-900 mg per 100 g of edible portion) [9].

Tamarind belongs to the family Caesalpiniaceae, which is a sub-family in Leguminosae. It has been stated in *Ashtanga Sangraha*, *Caraka Samhita*, and *Susruta Samhita* with the name '*Amleeka*' under *Amla varga* (group of sour drugs). It is cultivated mainly for the pulp in the fruit, which is used to prepare a beverage and to flavor sweets, curries, and sauces. The flower and leaf are eaten as vegetables. Tamarind has phenolic compounds such as catechin, epicatechin, procyanidin B2, arabinose, glucose, galactose, mucilage, pectin, tartaric acid, triterpenes, uronic acid, and xylose [10]. The pulp has antipyretic, antiscorbutic, blood tonic, carminative, digestive, expectorant, laxative, and remedial properties for biliousness and bile disorders. The leaves have antihelmintic and vermifuge activities, destroying intestinal parasite activities, and other parts of the plant have antidiabetic, antihepatotoxic, anti-inflammatory, antimutagenic, and antioxidant activities [11]. Bioactive compounds of *Tamarindus indica* extract have a hypoglycemic effect, which may help suppress free radicals in diabetes. This will decrease blood glucose levels, have a protective effect on pancreatic β -cells, and re-establish plasma insulin levels [12].

Ginger, scientifically known as *Zingiber officinale* and belonging to the family Zingiberaceae, is one of the most important plants with many ethnomedical, medicinal, and nutritional values and is widely used worldwide as a spice, flavoring agent, and herbal remedy. Ginger is used in Ayurveda, Arabian, African, Caribbean, Chinese, Siddha, and many other remedial systems to cure a variety of diseases, viz., asthma, constipation, dyspepsia, indigestion, nausea, loss of appetite, pain, palpitation, vomiting, diarrhea, colic, flatulence, spasm, influenza, cold, and cough. The ginger extract contains tannins, flavonoids, saponins, alkaloids, simple phenols, glycosides, carbohydrates, reducing sugar, and steroids. The plant has characteristic flavor and odor because it contains a mixture of shogaols, gingerols, zingerone, and their derivatives, and many more bioactive compounds. Because of these phytochemical compounds, it has anti-cancer, antioxidant, anti-hyperglycemic, anti-inflammatory, anti-apoptotic, anti-hyperlipidemic, anti-emetic, and narcotic antagonist larvicidal activities [13, 14].

This study tends to evaluate the synergistic antidiabetic effect of a combination fraction of 5 plants [*Allium sativum* (Garlic), *Azadirachta indica* (Neem), *Phyllanthus emblica* (Amla), *Tamarindus indica* (Imli), and *Zingiber officinale* (Ginger)] (Table 1) in alloxan-induced diabetes mellitus in adult albino rats.

Materials and Methods

Collection of plant material

Garlic bulbs, Amla fruits, and Ginger rhizome were purchased from a local market, and Neem seeds and Imli leaves were collected

from adjacent areas and air-dried in shade at room temperature (25±5°C), which took about 1 week to 1 month to dry till total moisture was removed from the plant. These were ground into fine powder using an electric blender and stored at room temperature.

Preparation of plant extract

The medicinal principle is present in different parts of the plant, like the root, stem, leaf, flower, fruit, or plant exudates. Extraction is the separation of the required constituents from plant materials. These medicinal principles were separated by different processes (the Soxhlet apparatus and the triple maceration process). Extracts of garlic, neem, and amla (ethanolic extracts) and imli (hydroalcoholic extract-ethanol:water [80:20]) were extracted through the Soxhlet apparatus, and an aqueous extract of ginger was extracted through the triple maceration process.

Preparation of the dose

Formulations were prepared in gum acacia and physiological saline (0.9% NaCl) in a ratio of 1:1:1 of various herbs. Three different herbal formulations were used at a dose level of 300 mg/kg b.wt. Then it was given orally (1 ml/day) to diabetic rats for different durations, and their effects were studied after 45 days of chronic treatment.

Test Animal

The present study was carried out at the Department of Zoology, Institute of Basic Science, Bundelkhand University Campus, Jhansi (UP), India. For experimentation, sexually mature adult female Albino rats of the Wistar strain (200±10 gm) of about 3 months were purchased from the DRDE (Defense Research and Development Establishment) in Gwalior. Before the study, ethical clearance was obtained from the Institutional Animal Ethical Committee (CPCSEA) in the Government of India with approval No. BU/Pharm/IAEC/a/17/09, New Delhi. All the experiments and protocols were conducted in strict agreement with the guidelines and ethical principles provided by the Committee for Control and Supervision of Experiments on Animals (CPCSEA). The animals were acclimatized to the experimental room at a temperature of 25-30°C, controlled humidity conditions (50-55%), and a 12-hour light and 12-hour dark cycle. They were fed a rat-pelleted diet (Amrut Feeds, Pranav Agro Ltd., Sangli) and water ad-libitum.

Induction of diabetes

Diabetes was induced in rats by a single intraperitoneal injection of alloxan monohydrate (CDH, Bombay Ltd.). Alloxan monohydrate was dissolved in ice-cold physiological saline (0.9% NaCl) to constitute a 10% (w/v) solution, and a dose of 100 mg/kg b.wt. of rats was selected to induce diabetes. The fasting blood glucose level of rats was measured after 72 hours of alloxan injection. The rats with effective and permanent elevated blood glucose levels (above 150 mg/dl) were selected for the study.

Experimental Design

The research work was carried out for 15, 30, and 45 days, and 1 week before the experiment, diabetes was induced in rats, and rats were allowed to acclimatize to the laboratory environment. Thirty-six rats were grouped into six groups of six rats each, following the experimental design.

1. Group I: Normal Control
2. Group II: Diabetic Control
3. Group III: Diabetic; will receive the standard drug (Glibenclamide) at 5 mg/kg b.wt.
4. Group IV: Diabetic; will receive formulation-1 extract at 300 mg/kg b.wt.
5. Group V: Diabetic; will receive formulation-2 extract at 300 mg/kg b.wt.
6. Group VI: Diabetic; will receive formulation-3 extract at 300 mg/kg b.wt.

After daily administration of the dose for 45 days, autopsies of diabetic rats were also performed. This was done by giving anesthesia with chloroform, and pancreatic histopathological changes were studied in diabetic rats.

Results

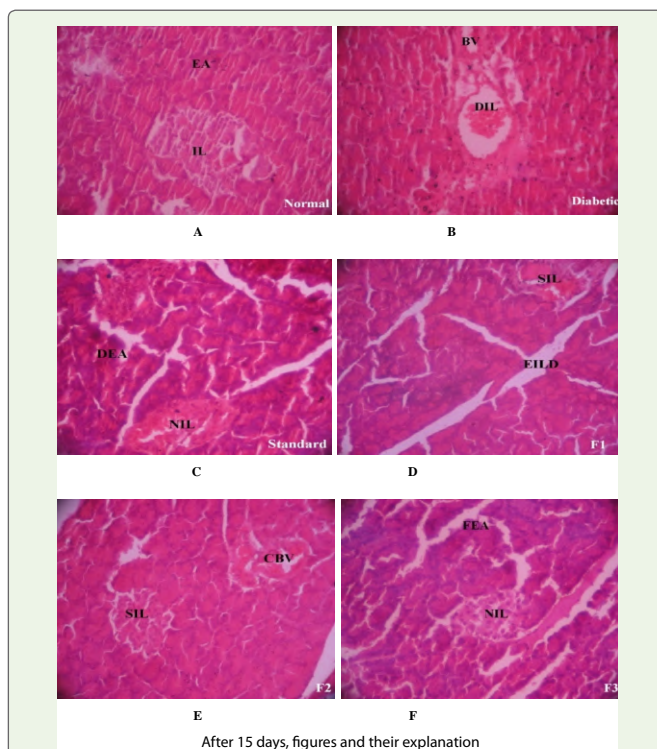
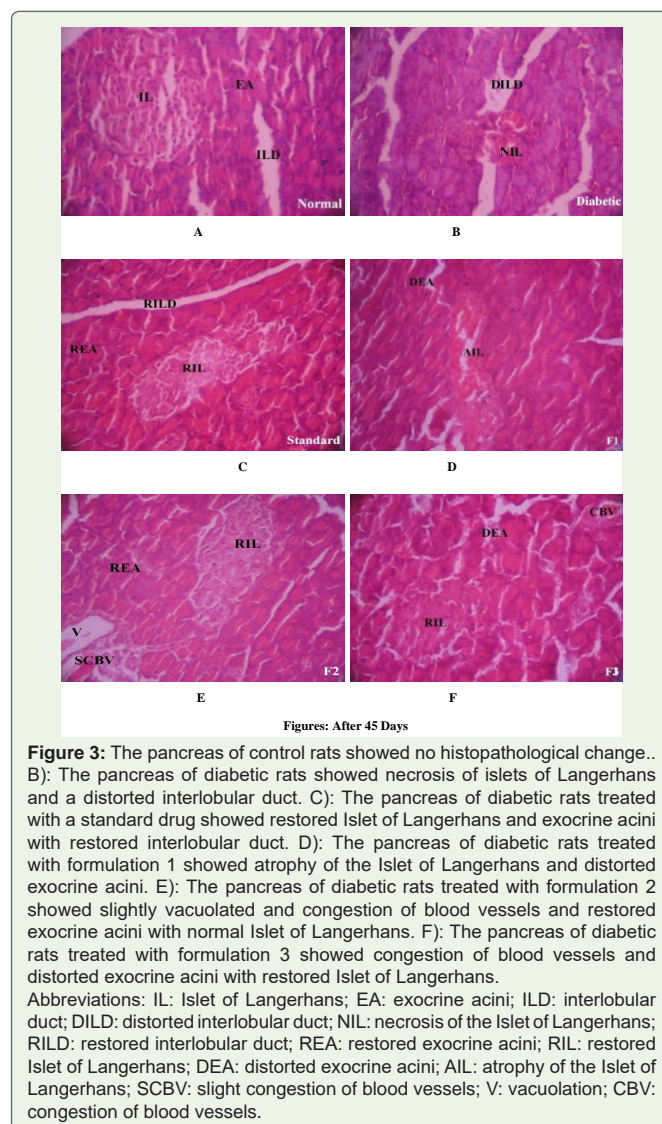
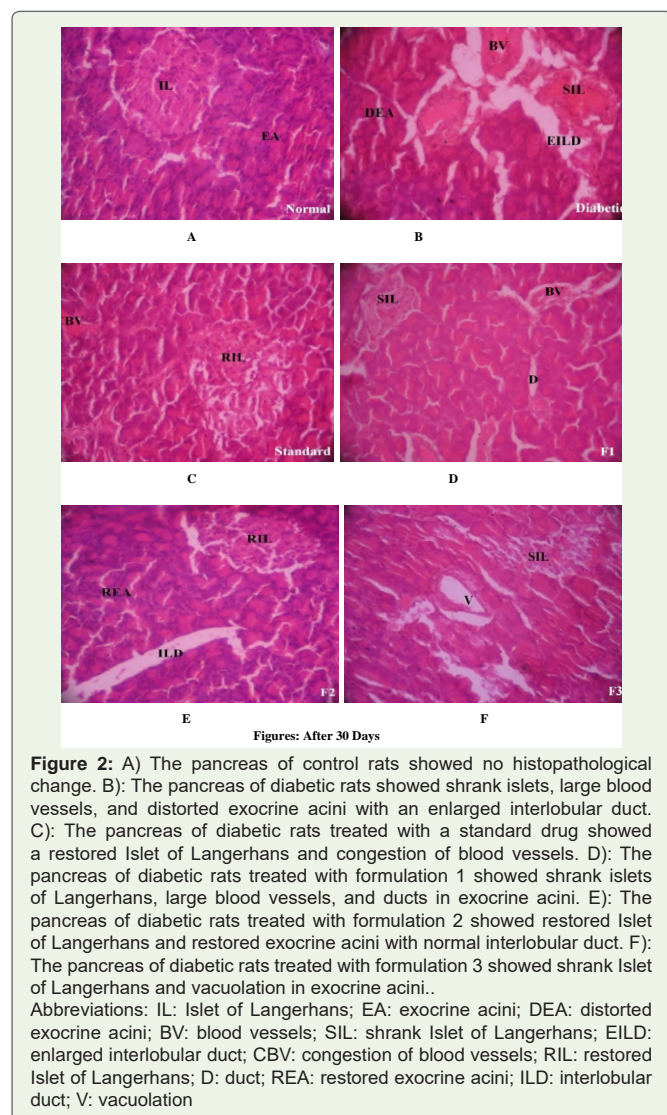


Figure 1: A) The pancreas of control rats showed no histopathological change. B) The pancreas of diabetic rats showed distorted islets of Langerhans and vacuolated blood vessels. C) The pancreas of diabetic rats treated with a standard drug showed distorted exocrine acini and necrosis of the Islet of Langerhans. D) The pancreas of diabetic rats treated with formulation 1 showed an enlarged interlobular duct and shrank Islets of Langerhans. E) The pancreas of diabetic rats treated with formulation 2 showed congestion of blood vessels and shrank Islets of Langerhans. F) The pancreas of diabetic rats treated with formulation 3 showed fragmented exocrine acini and necrosis of Islets of Langerhans. Abbreviations: H and E stain: hematoxylin and eosin stain; IL: Islet of Langerhans; EA: exocrine acini; ILD: interlobular duct; BV: blood vessels; DIL: distorted Islet of Langerhans; DEA: distorted exocrine acini; NIL: necrosis of the Islet of Langerhans; SIL: shrank Islet of Langerhans; EILD: enlarged interlobular duct; CBV: congestion of blood vessels; FEA: fragmented exocrine acini.



Discussion

In the present study, alloxan-induced diabetic rats were treated orally with three different formulations (Table 1) of *Allium sativum* (Garlic), *Azadirachta indica* (Neem), *Phyllanthus emblica* (Amla), *Tamarindus indica* (Imli), and *Zingiber officinale* (Ginger) at a dose of 300 mg/kg for 45 consecutive days. Among the three formulations, formulation 2, which contains *Allium sativum*, *Azadirachta indica*, and *Zingiber officinale*, was more effective as compared to the other two formulations. It may be due to the protective effect of the plant and the presence of certain phytochemical constituents like saponins, which may be helpful in maintaining the function of certain enzymes. At the end of the study, their effects on pancreatic histology were evaluated, and pancreatic β cell regeneration by formulations was approximately equal to that of the standard drug. Several previous studies show that various herbs and medicinal plants possess medicinal properties and can overcome toxicity due to certain external agents.

Similar results were reported where two different doses (50 and 100 mg/kg) of zingerone (zingerone is an active constituent of ginger) exhibited a significant reduction in blood glucose. When zingerone was used at a dose of 100 mg/kg, it offered better protection, which was not seen at 50 mg/kg. 50 mg/kg of zingerone showed a lesser degree of improvement in β -cell degeneration, whereas 100 mg/kg of zingerone displayed almost normal pancreatic acini along with a significant increase in the size as well as number of β -cells in the islets of Langerhans. The protective potential of zingerone may be possible because of its antioxidant nature and scavenging potential for free radicals [15]. It was observed that a daily dose of garlic and resveratrol (trans-3,5,4-trihydroxystilbene, a naturally occurring polyphenol phytoalexin compound found in grapes, peanuts, blueberries, and red wine) showed a significant decrease in blood glucose levels, and a decreased serum insulin level was significantly improved. Pancreas-treated garlic and resveratrol showed an increase in islet cell number, islet size, and islet diameter. The acinar cells and the islet cells were observed in a near-normal proportion

[16]. Similarly, in a study, serum glucose significantly decreased in turmeric, ginger, and cinnamon combination-treated diabetic rats. Turmeric, ginger, and cinnamon combination-treated diabetic rats showed a significant increase in the number and size of Langerhans islets. These spices may increase pancreatic β -cell viability and protect them by reactivating the antioxidant defense system [17]. In a study of glutathione-enriched formulations that contain essential nutrients and antioxidants in supplemented rats, the size of the pancreas as well as the number of β -cells in the cord were similar to those of a normal control. β -cells appear healthy with eosinophilic granular cytoplasm. No fibrosis, inflammation, or necrosis occurred in glutathione-treated rats because it could block the damage caused by the oxidative stress generated in the tissues by its radical scavenging mechanism [18].

Antidiabetic effects of different polyherbal combinations of six medicinal plants (*Momordica charantia*, *Murraya koenigii*, *Allium sativum*, *Tamarindus indica*, *Gymnema sylvestre*, and *Stevia rebaudiana*) used in traditional medicine. A reduction in blood glucose level was determined in all the polyherbal combinations at a dose of 250 mg/kg. Abnormal histological signs of diabetic rats' disease, viz., a decrease in pancreatic islet numbers and their size, atrophy, vacuolation, and invasion of connective tissues in the parenchyma of pancreatic islets, were decreased in all polyherbal combinations. Flavonoids, tannins, and sterols present in this combination might be responsible for the effect [19]. In a research study, polyherbal formulation (*Glycosmis pentaphylla*, *Tridax procumbens*, and *Mangifera indica* in the ratio of 2:2:1) increased plasma insulin levels and had promising antidiabetic activity. The reduction in glucose levels may be due to an increase in plasma insulin levels or enhanced transport of blood glucose in the peripheral tissue. The pancreas of polyherbal formulation-treated diabetic rats at doses of 250 mg/kg and 500 mg/kg showed mild congestion and a mild decrease in the number of islets of Langerhans with a normal β -cell population, indicating a significant amount of recovery. The active compounds like alkaloids, flavonoids, glycosides, saponins, sterols, phenolic compounds, and tannins present in the polyherbal formulation might be responsible for the effect [20]. Polyherbal antidiabetic tablets (*Gymnema sylvestre*, *Momordica charantia*, *Phyllanthus amarus*, *Ocimum sanctum*, *Trigonella foenum-graecum*, and *Allium sativum*) have shown a significant reduction in blood sugar. Minimal islet cell regeneration and a few collagen fibers around the islets were seen in polyherbal antidiabetic tablet-treated diabetic rats. Regeneration or proliferation of the pancreatic β -cells is possibly due to the prevention of free radical formation [21].

In research, when diabetic rats were treated with a herbal remedy called Katakakhadiradi Kashyam (KKK) orally at doses of 100, 200, and 300 mg/kg/bw. for 28 days, it restored pancreatic injury by controlling the blood glucose level in diabetic rats. Katakakhadiradi Kashayam contains 10 grams of twelve different plants. The following herbs are employed in the preparation of the Katakakhadiradi Kashayam: *Strychnos potatorum*, *Acacia catechu*, *Embelica officinalis*, *Berberis aristata*, *Biophytum sensitivum*, *Barringtonia acutangula*, *Cyperus rotundus*, *Salacia reticulata*, *Curcuma longa*, *Terminalia chebula*, *Mangifera indica*, and *Cyclea peltata*. The antihyperglycemic activity of Katakakhadiradi Kashayam is mainly attributed to the synergistic efficacy of the various phytochemicals present in

the prepared polyherbal formulation. These phytochemicals of Katakakhadiradi Kashayam potentially inhibited further damage to the remaining β -cells in the islets of Langerhans by wiping up the circulating reactive oxygen species induced by the STZ induction. Katakakhadiradi Kashayam ingredients have been shown to have antioxidant properties. By its antioxidant characteristics, katakakhadiradi kashaym has an antidiabetic effect [22].

Polyherbal plant extract (PHPE) prevents hyperglycemia and hyperlipidemia in STZ-induced diabetic rats by its blood glucose-lowering effect. In a study, diabetic rats were treated with chloroform leaf extract of *Azadirachta indica*, aqueous leaf extract of *Bougainvillea spectabilis*, and ethanolic seed extract of *Trigonella foenum graecum* in a ratio of 1:2:3, respectively, at a dose of 600 mg/kg body weight by oral gavages for 28 days. The pancreas of PHPE-treated diabetic rats revealed partial restoration in size and number of Langerhans islets. A reduction in widening between acinar and islet cells was also noted [23]. Antidiabetic effects of the Ayurvedic formulations (Avipattikara Churna and Triphala Churna) both *in-vitro* and *in-vivo* at dose levels of 200 and 400 mg/kg are significant. Ayurvedic formulations (Avipattikara Churna and Triphala Churna) increase plasma insulin levels and have promising antidiabetic activity. Ingredients of Avipattikara Churna were *Zingiber officinale*, *Piper nigrum*, *Piper longum*, *Terminalia chebula*, *Terminalia bellirica*, *Phyllanthus emblica*, *Cyperus rotundus*, salt (*vida lavana*), *Embelia ribes*, *Elettaria cardamomum*, *Cinnamomum tamala*, *Syzgium aromaticum*, *Operculina turpethum*, and *Saccharum officinarum*, and the ingredients of Triphala Churna were *Terminalia chebula*, *Terminalia bellirica*, and *Phyllanthus emblica*. The antidiabetic potential of both formulations decreased levels of blood glucose. The reduction in glucose levels may be due to an increase in plasma insulin levels or enhanced transport of blood glucose in the peripheral tissue. The polyherbal formulation showed mild obstruction and a moderate decrease in the number of islets of Langerhans with a normal β -cell population, indicating a significant amount of recovery [24].

Conclusion

Our results are in agreement with all of the above earlier findings of a single plant, formulations, or extracted phytochemical constituents. These earlier studies showed protective effects on pancreatic β -cells, insulin-producing properties, inhibition and intervention of cyto-degeneration of pancreatic β -cells, helped in scavenging the free radicals, and stimulated the β -cells to secrete insulin in alloxan-induced diabetic rats, resulting in the improvement

Table 1: Ratio of three multi-herbal formulations

S.No.	Multiherbal formulation	Plant Extract	Ratio
1.	Formulation 1 (F1)	<i>Azadirachta indica</i> (Neem seed), <i>Phyllanthus emblica</i> (Amla fruit), and <i>Tamarindus indica</i> (Imli leaf).	1:1:1
2.	Formulation 2 (F2)	<i>Allium sativum</i> (Garlic bulb), <i>Zingiber officinale</i> (Ginger rhizome), and <i>Azadirachta indica</i> (Neem seed).	1:1:1
3.	Formulation 3 (F3)	<i>Allium sativum</i> (Garlic bulb), <i>Azadirachta indica</i> (Neem seed), <i>Phyllanthus emblica</i> (Amla fruit), <i>Tamarindus indica</i> (Imli leaf), and <i>Zingiber officinale</i> (Ginger rhizome).	1:1:1

of carbohydrate metabolism towards the re-establishment of normal blood glucose levels. It could be clearly understood that changes occur in the histoarchitecture of the pancreas due to the induction of diabetes and the various formulations (**Table 1**) and standard drugs available in the market. The need of this study is to develop a potent herbal preparation that could be easily afforded by people and has the fewest side effects.

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Author's contributions

The present research work was designed by Dr. Radha Singh. The experiment was performed by Dr. Radha Singh under the supervision of Dr. Kusum Singh.

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