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(54) **Title:** ANTI-DIABETIC HERBAL FORMULATION COMPRISING GLYCINE MAX

(57) **Abstract:** The invention provides a novel herbal preparation comprises of*Glycine max* active fraction containing 7S globulin protein extract, *Curcuma longa* and *Zingiber officinale* Linn. rhizome extract used in treatment of diabetes and diabetic related diseases.

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ANTI-DIABETIC HERBAL FORMULATION COMPRISING GLYCINE MAX

FIELD OF THE INVENTION

The invention provides a novel herbal preparation comprises of *Glycine max* active fraction containing 7S globulin protein extract, *Curcuma longa* and *Zingiber officinale* Linn. Rhizome extract used in treatment of diabetes.

BACKGROUND AND PRIOR ART

Diabetic mellitus is a chronic condition that is diagnosed by a blood test and requires life long management (American Diabetic association, 2002). The more patients understand about the disease the better they are enabled to make good decisions on its management. Dietary therapy and exercise are critical both in preventing and managing diabetic mellitus and the results of the diabetic prevention program research group indicate that changes in life style reduced the incidence of diabetic by 58% (Knowler et al., 2002). In type 1 diabetic mellitus, where there is an absolute deficiency of insulin replacement forms a major component of treatment. In type 2 diabetic mellitus, insulin release from the pancreas is altered and may also be absolutely deficient in amount, and therefore its replacement also plays a part in management, especially when diabetic mellitus has been present for a long time. As the number of people with diabetes multiply world wide, the disease takes an ever-increasing proportion of national and international health care budgets. It is projected to become one of the world's main disablers within the next 25 years. It is very popularly known in medical history as "silent killer". Regions with greatest potential are Asia and Africa, where diabetes mellitus rates could rise to two to three-folds than the present rates. Apart from currently available therapeutic options, many herbal medicines have been recommended for the treatment of diabetes and diabetic related diseases (Sabu and Kuttan, 2002; Zhang and Tan 2000; Chitra et.al., 1998; Padma et.al., 2000; Osadebe et.al., 2004; Obatomei et.al., 1994; Oojewole and Adewunni 2004). Plant medicines are used throughout the world for a range of diabetic presentations.

The development of scientifically validated models of alloxan induced- diabetic is vital to the analysis of the functional consequences of pancreatic damage and to testing the recovery efficacy of potentially therapeutic drugs. The role of medicinal

plants in increasing the secretion of insulin and acting as an anti-diabetic formulation in the form of tablet is still much underestimated. The retrieval hypothesis postulates the alloxan agents disrupt the pancreas function as the effect of alloxan agents diminish over time by the treatment of our present herbal formulation investigation resulted in the reappearance of normal functioning of pancreas. Drugs like glibenclamide, penformin-containing substances which has a stimulant activity on diabetic. Accordingly, studies shown that the herbal formulation having the property of improving the functioning of pancreas by alloxan induced diabetic and used in treatment of diabetic as a tablet and acting as a strong anti-diabetic formulation.

OBJECT OF THE INVENTION

The main object of the present invention is to provide a novel herbal combination in dosage form used as a anti-diabetic tablet, injection and formulation.

Another objective of the present invention is to prepare herbal dosage form that improves in the treatment of diabetic mellitus.

Yet another object of the present invention is to prepare herbal dosage from in the form of tablet for easy consumption.

SUMMARY OF THE INVENTION

Accordingly the present invention provides an herbal formulation useful in the treatment of herbal dosage form from the soya bean milk used as a anti-diabetic. The herbal formulation comprising of *Glycine max* active fraction containing 7 S globulin fraction extract, *Zingiber officinalis* (rhizome) and *curcumin* (a phenolic antioxidant). *Glycine max* (Soya bean) protein varies from light cream to white in colour. It is used as nourishing food. It was shown that it produce a significant improvement in general ability and behavioural pattern.

Glycine max Family: Leguminosae

Botanical description: An annual with erect or climbing stem reach a height of one half to six feet, densely clothed with leaves trifoliate, ovate-lanceolate, inconspicuous, borne on auxiliary racemes, white or purple to red purple, normally self pollinated; pods 3cm long in clusters of 3-5, densely hairy containing 3-4 seeds elliptical with hilum, compressed, yellow, choclate or black. Soyabean is a native of south-eastern Asia is considered, on the basis of genetical have

originated from slender, prostste plan. Soyabean is an important legume crop in Far East.

Medicinal uses: Soyabean ranks high among the leguminous crops of the world. It is grown mainly as a food crop of the world. It is grown mainly as a food crop in China, Japan and other country of East Asia. The seeds are consumed green, dry or sprouted, whole or split. The green seed are used as vegetable; roasted and salted seeds are used in cakes and candies. The seeds are ground in to flour and used for bakery products. The fatty oil extracted from the seed is used for the industrial purposes. The soya been used as a whole been, or processed as a soya milk, tofu, tempesh, soya sauce. The increasing popularly of soya food in mainly used in prevention of chronic diseases continues to be a top priority for scientist around the world. Even the FDA has conformed that the food containing the soya protein may reduce the risk of coronary heart diseases. There has been increasing interest of soya been as an antioxidant effect (Wealth of India, 1992).

Phytochemistry: Soya been seeds contain protein 29.6-50.3, fat 13.5-24.2, fiber 2.84-2.67, carbohydrate 14.07-23.88. The decorticated bean contains about 12 % polysaccharides. It contains higher % of proteins than many other foodstuffs. Chief protein is a globulin, glycinine that accounts for 80-90% of the total protein of the seed. Besides the true proteins, it contains the following nitrogenous substances like adenine; arginine, glycine etc and total non-protein nitrogen varies from 2.8-6.8% of the total nitrogen. The average mineral composition of mature soya been is as Fe, K, Zn, I etc. it is a good source of beta amylase. It contains variety of pigments, isoflavones, glycosides etc.

Pharmacology: In human metabolism experiments soya been proteins comparable to other pulse protein, biological values digestibility coefficient. Soya been is valued in special diet and as an aid in reliving acidosis. The increasing popularly of soya food in mainly used in prevention of chronic diseases continues to be a top priority for scientist around the world. Even the FDA has conformed that the food containing the soya protein may reduce the risk of coronary heart diseases. Their has been increasing interest of soya been as an antioxidant effect and the particular the isoflavones. (Wealth of India, 1992)

CURCUMA LONGA Family: Zingiberaceae

Botanical description: The genus *Curcuma* comprising about fifty species, distributed in tropical and subtropical regions of Asia, belongs to the tribe Hedychieae and consists of a rather homogenous group of rhizomatous perennials. Govindarajan (1980 Food Science and Nutrition, 14: 119-301 and 1982 Food Science and Nutrition, 17:1-258) published critical reviews on turmeric *C. longa*. The taxonomic status of *Curcuma heyneana* was discussed by Firman *et al* (1988 *Phytochem.* 27: 3887-3891) based on essential oil analysis. Tomlinson's (1969) work based on the anatomical evidence, which has much relevance in the classification of the order Zingiberales.

Medicinal uses: Ethnobotanical details of some of the species of *Curcuma* has been reviewed and it was found that *Curcuma* is useful in the treatment of liver disorders and has a promising kind of broad spectrum hepatoprotective agent which is used in Indonesia (Lin *et al., American J. Chin. Med.,* 1995 23:243-254). *Curcuma longa* was used predominantly for endoparasites, internal and external injuries and pregnancy related conditions in ethnic community of Trinidad and Tobago. *Curcuma longa* is used as dietary intake in Nepal (Eigner and Scholz, *J Ethnopharmacol* 1999, 67(1): 1-6).

Phytochemistry: Essential oils are complex mixtures of odorous and steam-volatile compounds that are deposited in the subcuticular space of glandular hair, cell organells, idioblasts, excretory cavities and canals or exceptionally in heartwoods. In other words, they are very complex, aromatic, volatile mixture containing many different compounds. The constituents of essential oils belong to numerous classes of chemical substances, such as hydrocarbons, alcohols, aldehydes, ketones, acids, esters, oxides and ether (Thappa *et al, J. Essent. Oil Res.,* 1982, 11: 97-103). Essential oils largely comprises of terpenoid compounds, which constitute two or more isoprene units. Based on this, terpenoids are mainly classified into four groups *viz.* monoterpenes (with 2 isoprene units i.e. 10 carbon atoms) sesquiterpenes (with 15 carbon atoms), diterpenes (with 4 isoprine units i.e. 20 carbon atoms) and polyterpenes (with 5 or more isoprene units). These terpenoid compounds provide aroma and pungency to plants. The essential oil

forms the basic raw materials for perfume and flavour making industries. They are also used in the cosmetics and pharmaceutical industries. Many natural essential oils are used in aromatherapy to cure and prevent illness due to their therapeutic properties and also because of their fragrance which can influence human thoughts and emotions. Many of the essential oils are reported to have antimicrobial, insect repellent and insecticidal properties.

Pharmacological use: The genus *Curcuma* exhibits diverse pharmacological activities against cancer and tumorgensis. Anto *et al,* Mutation Res., 1996, 370:127-131, has reported the anticancer and antitumour properties of *Curcuma longa.* It was demonstrated that the inhibitory effect of curcumin on DNA and RNA synthesis in cultured HeLa cells. Dietary curcumin may inhibit azoxymethanol (40 M) induced colonic neoplasia in mice (Huang *et al., Cancer Lett* 1992, 64(2):117-21). The antimicrobial properties are well known and the result reported by many researchers pointed out the antibiotic activities of *Curcuma.* Banerjee and Nigam (J. Res. Ind. Med. Yoga Homoeo., 1978, 13: 63-70) reported the antibacterial and antifungal activity of various species of *Curcuma.* Molluscicidal property of *C. longa* was reported. The insecticidal property of different species of *Curcuma.* Curcumin showed anti-inflammatory effect in acute, subacute and chronic models of inflammation in mice and rat models. The oral ED_{50} in mice, against carrageenin-induced acute oedema was 100.2 mg/kg compared to 78 mg/kg of cortisone. Clinically curcumin did not produce any side effect up to 1600mg/kg/day for 4 weeks in phase-I trials in male volunteers. Phase-II clinical trials have been conducted in patients with rheumatoid arthritis and osteoarthritis. Curcumin inhibited rat liver microsomal delta 5 and delta 6 denaturizes (Shimizu *et al., Lipids* 1992, 27(7):509-12). *Curcuma* contains an active principle(s) other than curcuminoid, which can modify the metabolism of lipid and lipoproteins. Several reports suggest that curcumin as well as turmeric increase bile flow. Essential oils of turmeric have also been found to increase the bile flow. However, some investigators have found it to be ulcerogenic (Prasad *et al. J. Physiol. Pharmocol,* 1976, 20, 92). The gastric secretion was found to be reduced after 3 h in conscious rabbits by aqueous and methanolic extracts of turmeric (Sakai *et al. Chem. Pharm.*

Bull. 1989, 37, 215). Curcumin and turmeric have been shown to protect liver against a variety of toxicants *in vitro* as well as *in vivo*. They include carbon tetrachloride, aflatoxin B-1, paracetamol iron, and cyclophosphamide in mouse, rat and duckling. Evidence for the hypocholesterolemic and hypolipidemic activities of curcumin has been provided when it was fed with diet to rats for 7 weeks at the concentration of 0.15% (Rao *et al.* 1970 *J. Nutri.* 100, 1307). Ethanolic extract of *C. longa* has been shown to have hypoglycemic activity in normal as well as alloxan - induced diabeties in rats. They have also isolated a lipopolysaccharide from the root of *Curcumin*, which is similar to bacterial lipopolysaccharides and is immunostimulant (Inagawa *et al. Chem Pharm Bull* 1992, 40, 1994). The wound healing property of turmeric was investigated long back and its local application was found to be effective (Gujral et al., *J. Ind. Med. Association* 22, 273 1958). A sum of approximately 26 compounds has been isolated from different Curcuma sp. having high antioxidant activity. Curcumin did not produce any toxicity either on single administration or on repeated oral administration over a period of 6 months in rat and monkey at doses up to 800 and 1800-mg/kg day, respectively. Curcumin administered orally to patients suffering from chronic antieri or ureitis (CAU) at a dose of 375 mg three times a day for 12 weeks and all the patients who received curcumin alone improved (Lal *et al., Phytother Res* 13(4): 318-22, 1999).

***Zingiber officinale* Linn.** Family: Zingiberaceae

Botanical description: An herbaceous rhizomatous perennial, reaching up to 90 cm in height under cultivation. Rhizomes are aromatic, thick lobed, pale yellowish, bearing simple alternate distiches narrow oblong lanceolate leaves. The herb develops several lateral shoots in clumps, which begin to dry when the plant matures. Leaves are long and 2-3 cm broad with sheathing bases, the blade gradually tapering to a point. Inflorescence solitary, lateral, radical, pendiculate oblong-cylindrical spikes. Flowers are rare, rather small, calyx superior, gamosepalous, three toothed; open splitting on one side, and corolla of three-sub equal oblong to lanceolate connate greenish segments. (The Wealth of India, NISCOM, D-23, C.S.I.R., New Delhi 1996).

Medicinal use: Ginger is carminative, pungent, stimulant, used widely for indigestion. It is chiefly used to cure diseases due to morbidity of kapha and vata. Ginger with limejuice and rock salt increases appetite and stimulates the secretion of gastric juices. It is said to be used for chronic bronchitis, cold, chest congestion, and cough, difficulty in breathing, dropsy, sore throat, throat ache, stomachache, vomiting and rheumatism. Zinger forms an important constituent of many pharmacopoeal ayurvedic formulations. (Misra B, Bhavaprakasha Nighantu, 5th ed., 1969, p. 14.; Sharma P, Dravyaguna vigyan, part 2, Chauukhamba Publications 1993, p. 331; Indian medicinal plant, a compendium of 500 sps., Part 5, orient Longman Publication, 1997, p. 431; Nadkarni, Indian Materia Medica, vol. 1, 1993, p. 1308; Yogaratnakra, Chauukhamba Publications 1993, p. 320-330; Bhavaprakasha with Vaidyotina commentary by Misra BS; Chikitsa Prakarana Madhyana Khadana- Chauukhamba Publications 1980, p. 683-701).

Phytochemistry: Ginger has been reported to contain usually 1-3 % of volatile oil, pungent principles, viz. gingerols and shogaols and about 6-8 lipids and others. Ginger oil contains zingiberene and bisaboline as major constituents along with other sesqui and mono terpines. Ginger oleoresin contains mainly the pungent principles gingerols and shogaols as well as zingeberine. Shogaols have recently been found twice as pungent as gingerols. (Kiuchi F, et. al., Chem. Pharm. Bull, 1982, 30, 754; waigner H, et al., Plant drug analysis, springer, 1996, 300; Akhila A and Tewari CROMAP, 1984, 6(3), 143-146).

Pharmacology: It is used for common cold, due to pathogenic wind cold, characterized by severe intolerance to cold, slight fever, headache, general ache, congestion and running nose. Antihistaminic activity has been studied in ginger. *Zingiber officinale* was indicated in allergic conditions in traditional text. However they were following crude methods. Toyoda J, Chem. Abst., 1969, 71, 33425; Yogaratnakra, Chauukhamba Publications 1993, p. 320-330; Bhavaprakasha with Vaidyotina commentary by Misra B. S; Chikitsa Prakarana Madhyana Khanda-Chauukhamba Publications 1980, p. 683-701).

BRIEF DESCRIPTION OF THE TABLES

Table I: Effect of formulation (F1) *Glycine max (soya bean)* active fraction containing 7S globulin fraction on alloxan induced diabetic rats.

Table II: Effect of formulation (F2) containing *Glycine max (soya bean)* active fraction containing 7S globulin fraction with *Curcuma longa* extract on alloxan induced diabetic rats.

Table III: Effect of formulation (F3) containing *Glycine max (soya bean)* active fraction containing 7S globulin fraction, *Curcuma longa* with *Zingiber officinalis* on alloxan induced diabetic rats.

Table IV: Effect of formulation (F4) with out *Glycine max (soya bean)* active fraction containing 7S globulin fraction on alloxan induced diabetic rats.

Table V: Effect of formulation (F3) containing *Glycine max* (soya bean) active fraction containing 7S globulin fraction, *Curcuma longa, Zingiber officinale* on relative mean ± SEM organ weights of rats (n=6).

Table VI: Effect of formulation (F3) containing *Glycine max* (soya bean) active fraction containing 7S globulin fraction, *Curcuma longa* and *Zingiber officinale* on Glucose tolerance test in rats.

Detailed description of the present invention

Accordingly, the present invention provides a novel of the invention of an herbal formulation(s) obtained from decoction of two most potent plants having the property of anti-diabetic and used in treatment of diabetes mellitus as a tablet, injection and as a liquid formulation(s).

In another embodiment of the present invention the novelty of the invention is a said herbal formulation having the property of anti-diabetic and used in treatment of diabetic mellitus as a tablet and as a formulation.

Further, in another embodiment of the invention, an herbal anti-diabetic synergistic formulation(s) containing extracts of plant in pharmacologically effective form.

In another embodiment of the invention, herbal formulation(s) the plants selected from the genus *Glycine max* (2-5 wt %).

In another embodiment of the invention, the 7S globulin fraction of *Glycine max* seed.

In another embodiment of the invention, the plants selected from the genus *Curcuma longa* (1-3 wt %).

In another embodiment of the invention, the plants selected from the genus *Zingiber officinale* (1-3.5 wt %).

In another embodiment of the invention, the composition as a soft/ hard gelatin capsule of oral dosage forms.

In another embodiment of the invention, the extract of *Glycine max is of* active fraction containing 7 S globulin fraction extracts, *Zingiber officinalis* and *Curcuma longa* is of rhizome extracts.

In another embodiment of the invention, the formulation having the property of improving the anti-diabetic property and used in treatment of type II diabetes and type I diabetes.

In another embodiment of the invention, the formulation is used as anti- oxidant, cooling, oleaginous, astringent, nerves relaxant properties and anti-diabetic property.

In another embodiment of the invention, the formulation is use to treat diabetic related diseases, blood purifier, anti-periodic and externally applied sprain and wound.

In another embodiment of the invention, the said formulation is used as a tonic.

In another embodiment of the invention, the said formulation is use as an anti-parasitic for many skin affections.

In another embodiment of the invention, the said formulation is use as antacid, carminative.

In another embodiment of the invention, the said formulation is use as cholerectic action.

In another embodiment of the invention, the said formulation is use as anti-arthritis.

In another embodiment of the invention, the said formulation further comprises the specific gravity 0.992 - 1.505.

In another embodiment of the invention, the formulation further comprises the refractive index of 1.5463 -1. 6914.

In another embodiment of the invention, the formulation used in cakes and candies.

In another embodiment of the invention, the said formulation further comprises proteins, 80.6 - 90.7%.

In another embodiment of the invention, the formulation further comprises Amino acids 1.0 - 19.0%

In another embodiment of the invention, the said formulation further comprises the fibre 2.845 – 6.27%.

In another embodiment of the invention, the formulation further comprises the phosphorus, 0.69%

In another embodiment of the invention, the formulation further comprises fat, 13.5 – 24.2%.

In another embodiment of the invention, the formulation further comprises carbohydrates, 14.3 -23.5%.

In another embodiment of the invention, the suspension at a dose of 50 to 200 mg/kg did not show any abnormality of general condition in treatment as anti-diabetic activity.

In another embodiment of the invention, the suspension at a dose of 50 to 200 mg/kg on anti-diabetic showed significant and dose dependent activity.

In another embodiment of the invention, the suspension at a dose of 50 to 200 mg/kg showed significant and dose dependent antioxidant activity.

In another embodiment of the invention, the liquid dosage form of *Glycine max* at a dose of 50- 200 mg/kg showed an 11.91- 26.65% protection in diabetes.

In another embodiment of the invention, the liquid dosage form of *Glycine max* at a dose of 50- 200 mg/kg shown a 28.77% glucose tolerance.

In another embodiment of the invention, the suspension form of *Glycine max* at a dose of 50- 200 mg/kg shown a 19.5- 45.53% protection in diabetes dose dependently with the combination of *Glycine max* with *Curcuma longa.*

In another embodiment of the invention, the suspension form of *Glycine max* at a dose of 50- 200 mg/kg shown a 29.8- 55.0% protection in diabetes dose dependently with the combination of *Glycine max*, *Curcuma longa* with *Zingiber officinalis*.

The invention thus meets the need for a new process in which the optimal proportions of vitamins, amino acids, long chain fatty acids and active therapeutic marker compounds are retained in the product and underlies the efficacy of the compound as anti diabetic.

Further in another embodiment of present invention the *Glycine max* (soya bean) seed fraction containing 7S globulin -like protein (Komatsu and Hiranc, 1991) according to the invention can be incorporated into a variety of food products, including, without limitation, butter, cakes, candies, ice cream and mayonnaise-chocolate products, preparation of jaggery, water based brinks such as wines and mineral waters. The inventive oil is also suitable for encapsulation in gelatine shells to form soft gels/capsules. Regardless of the particular form in which the inventive oil is prepared, the daily dosage of the fraction to experimental animals fall within the ranges set forth above. Depending on the concentration of the inventive protein fraction in the above form, the total amount of the food product per serving or encapsulated will also vary the desired therapeutic activity.

Examples

The invention is further illustrated by the following non-limiting examples.

Formulation 1 (F1)

Glycine max (Soya bean)	3wt. %
Lactose	66.7g
Starch	10g
Water	q.s. to make 100 ml

Dry mature seed of *Glycine max* (Soya bean) are washed in purified distilled water of pyrogen free, and were immersed in hot water (30-60^0 c) for 2-3 hr. the seeds released 7 S globulin were used along with the extract that obtained after squeezed in a silicon cloth to get a white exudates.

Mix the plant constituents and filter the solution and add specified quantity of starch and heat until the starch dissolves and then cool and make up the volume with required amount of water to make 100 ml.

The formulation is useful to a anti-diabetic. Accordingly, the investigation deals with the oral dosage form have been described in detail giving the formula of the ingredients along with the method and mode of usage of the standardized formulation.

Formulation 2 (F2)

Glycine max (Soya bean)	3wt. %
Curcuma longa	1.5wt. %
Lactose	2.5%
Starch	0.5%
Water	q.s. to make 100 ml

Dry mature seed of *Glycine max* (Soya bean) are washed in purified distilled water of pyrogen free, and were immersed in hot water (30-60^0 c) for 2-3 hr. the seeds released 7 S globulin were used along with the extract that obtained after squeezed in a silicon cloth to get a white exudates. The *Curcuma longa* were collected and dried in shade. The dried material (1Kg) is then powdered and extracted with water for 5 days. At the end of this, the solvent is decanted and filtered if necessary to remove the plant debris. The extract is then concentrated under vacuum at less than 50 ^{o}C. Then the extract is lyophilized to obtain the extract in powder form.

Mix the plant extracts and dissolve them water, filter the solution and add specified quantity of starch and heat the until the starch dissolves and then cool and make up the volume with required amount of water to make 100 ml. The formulation is useful to a anti-diabetic. Accordingly, the investigation deals with the oral dosage form have been described in detail giving the formula of the ingredients along with the method and mode of usage of the standardized formulation.

Formulation 3 (F3)

Glycine max (Soya bean)	3wt. %
Curcuma longa	1.5 %
Zingiber officinale	1.5%
Lactose	45.7g
Starch	10g
Water	q.s. to make 100 ml

Dry mature seed of *Glycine max* (Soya bean) are washed in purified distilled water of pyrogen free, and were immersed in hot water (30-60^0 c) for 2-3 hr. the seeds released 7 S globulin were used along with the extract that obtained after squeezed in a silicon cloth to get a white exudates. The *Curcuma longa and Zingiber officinale* were collected and dried in shade. The dried material (1Kg) is then powdered and extracted with water for 5 days. At the end of this, the solvent is decanted and filtered if necessary to remove the plant debris. The extract is then concentrated under vacuum at less than 50^{0}C. Then the extract is lyophilized to obtain the extract in powder form.

Mix the plant extracts and dissolve them water, filter the solution and add specified quantity of starch and heat the until the starch dissolves and then cool and make up the volume with required amount of water to make 100 ml.

The formulation is useful to a anti-diabetic. Accordingly, the investigation deals with the oral dosage form have been described in detail giving the formula of the ingredients along with the method and mode of usage of the standardized formulation.

Formulation 4 (F4)

Curcuma longa	1.5 %
Zingiber officinale	2.5%
Lactose	20g
Starch	10g
Water	q.s. to make 100 ml

The *Curcuma longa and Zingiber officinale* were collected and dried in shade. The dried material (1Kg) is then powdered and extracted with water for 5 days. At the

end of this, the solvent is decanted and filtered if necessary to remove the plant debris. The extract is then concentrated under vacuum at less than 50°C. Then the extract is lyophilized to obtain the extract in powder form. Mix the plant extracts and dissolve them water, filter the solution and add specified quantity of starch and heat the until the starch dissolves and then cool and make up the volume with required amount of water to make 100 ml.

The formulation is useful to a anti-diabetic. Accordingly, the investigation deals with the oral dosage form have been described in detail giving the formula of the ingredients along with the method and mode of usage of the standardized formulation.

Alloxan-induced hyperglycemia

Hyperglycemia was induced by a single intraperitoneal injection of 120 mg/kg of alloxan monohydrate in sterile saline. After five days of alloxan injection, the diabetic rats (glucose level >350mg/dl) were separated and divided into different groups of six animals each. Blood samples were collected from the tail vein just prior to and 1 and 3h after *Glycine max* (soya bean) administration. And same procedure repeated for effect of formulation with and with out *Glycine max* (soya bean) protein on alloxan- induced rats. (Venkatesh et al, 2003)

Effect formulation on glucose tolerance in rats

Fasted rats were divided into four groups of six rats each. Groups of rats were treated with the formulation and after 30 min of the rats of all groups were orally treated 2g/kg of glucose. Blood samples were collected from the tail vein just prior to glucose administration and at 30 and 90 min after glucose loading. Serum was separated and blood glucose levels were measured immediately by glucose oxidase method. (Venkatesh et al, 2003)

Table I:

Group	Experiment	Blood glucose (mg/100ml)		
		Basal value	1h	3h
I	Diabetic control (distilled water)	355.08 ± 18.66	348.42 ± 20.91	342.02 ± 21.16
II	F1 (50mg/kg)	346.08 ± 17.11	325.75 ± 18.33	309.24 ± 19.22
III	F1 (100mg/kg)	389.54 ± 16.33	340.61 ± 17.01	305.99 ± 18.22[a]
IV	F1 (200mg/kg)	392.77 ± 13.17	348.61 ± 16.58	288.11 ± 17.44[b]

Values are mean ± S.D. for six rats;

P [a] < 0.01 and [b]< 0.001 compared to respective basal value group.

F1- Formulation containing only *Glycine max*

The results of the present study of table-I shows that there is a significant decrease in blood glucose level at 100mg/kg and 200 mg/kg of containing only *Glycine max* (Soya bean) active fraction containing 7S globulin fraction in alloxan induced diabetes at 3h and percentage protection ranged 11.91-26.65 percentage in controlling the diabetes.

Table II:

Group	Experiment	Blood glucose (mg/100ml)		
		Basal value	1h	3h
I	Diabetic control (distilled water)	345.08 ± 15.66	350.42 ± 22.91	354.02 ± 18.16
II	F2 (50mg/kg)	366.08 ± 15.11	334.75 ± 17.33	306.24 ± 18.22[a]
III	F2 (100mg/kg)	384.08 ± 19.11	337.58 ± 17.01	275.24 ± 16.89[b]
IV	F2 (200mg/kg)	372.54 ± 19.08	315.61 ± 16.54	255.99 ± 14.65[c]

Values are mean ± S.D. for six rats;

P [a]< 0.05, [b]< 0.01 and [c]< 0.001 compared to respective basal value group.

F2- Formulation containing *Glycine max (soya bean)* active fraction containing 7S globulin fraction with *Curcuma longa* extract.

The results of the present study of table-II shows that there is a significant decrease in blood glucose level at a dose range 50-100 mg/kg showed significant results and the percentage protection ranged 19.5-45.53 percent in lowering the increased level of blood glucose level.

Table III:

Group	Experiment	Blood glucose (mg/100ml)		
		Basal value	1h	3h
I	Diabetic control (distilled water)	352.20 ± 21.01	355.60 ± 23.10	353.80 ± 23.80
II	F3 (50mg/kg)	358.30 ± 18.95	342.20± 17.33	251.60 ± 18.22[a]
III	F3 (100mg/kg)	360.10 ± 19.21	330.60 ± 18.91	210.51 ± 15.55[b]
IV	F3 (200mg/kg)	365.20 ± 17.99	215.61 ± 15.64[b]	166.99 ± 13.65[c]

Values are mean ± S.D. for six rats;

P [a]< 0.05, [b]< 0.01 and [c]< 0.001 compared to respective basal value group.

F3- Formulation containing *Glycine max (soya bean)* active fraction containing 7S globulin fraction, *Curcuma longa* with *Zingiber officinale*

The results of the present study of table-III shows a significant decrease in blood glucose level at 1h at a dose 200mg/kg and the percentage protection in controlling the increased level of blood glucose were significant at dose range 50-200mg/kg at 3h and percentage protection ranged 29.8-55.0 percent.

Table IV:

Group	Experiment	Blood glucose (mg/100ml)		
		Basal value	1h	3h
I	Diabetic control (distilled water)	365.08 ± 19.01	358.42 ± 18.35	368.12 ± 20.37
II	F4 (50mg/kg)	372.77 ± 15.68	368.61 ± 16.58	348.11 ± 19.54
III	F4 (100mg/kg)	358.08 ± 14.35	325.75 ± 16.24	316.24 ± 17.64
IV	F4 (200mg/kg)	365.24 ± 18.02	348.15 ± 16.29	304.29 ± 14.61[a]

Values are mean ± S.D. for six rats;

P [a] < 0.01 compared to respective basal value group.

F4- Formulation contains Curcuma longa and Zingiber officinale without Soya bean active fraction containing 7S globulin fraction.

The results of the present study of table-IV showed the probable significant effect ($P<0.05$) at 3h at a dose range of 200mg/kg. But the results of table III of formulation F3 is highly significant even when we compared with the percentage protection of that shown 29.8-55.0 percent.

Table V:

Type of treatment	Treatment group	Body weight (g)	Kidney (g)	Liver (g)	Spleen (g)
6 days oral treatment	Control	172.0 ± 10.3	0.8 3 ± 0.03	5.73 ± 0.45	0.59 ± 0.06
	F3 (50)	164.3 ± 9.6	0.91 ± 0.03	5.56 ± 0.59	0.71 ± 0.04
	F3 (100)	162.9 ± 13.3	0.87 ± 0.07	5.76 ± 0.55	0.75 ± 0.01
	F3 (200)	167.5 ± 10.0	0.85 ± 0.09	5.71 ± 0.61	0.59 ± 0.05

F3- Formulation containing *Glycine max* (soya bean) active fraction containing 7S globulin fraction, *Curcuma longa, Zingiber officinale.*

Note: No mortality/ gross abnormality were observed in the animals during the treatment of formulation F3.

Table VI:

Group	Experiment	Blood glucose (mg/100ml)		
		Fasting	30min	90min
I	Glucose (2g)	87.08 ± 1.72	165.43 ± 4.98	134.65± 4.33
II	F3 (50mg/kg)	82.06 ± 1.45	145.13 ± 3.75	138.09 ± 2.54
III	F3 (100mg/kg)	86.71 ± 1.63	152.54 ± 3.56	125.75±2.76[a]
IV	F3 (200mg/kg)	79.82 ± 2.12	143.51 ± 3.58	102.22 ± 3.65[b]

Values are mean ± S.D. for six rats;

P [a]< 0.01 and [b]< 0.001 compared to respective basal value group.

The results showed a significant effect with the formulation F3 containing *Glycine max* (Soya bean active fraction containing 7S globulin fraction), *Curcuma longa* and *Zingiber officinale* at 90 min and the levels were revealed near to the normal values in the scientifically validated model of glucose tolerance test in rats.

References

Agarwal et al., Indian Journal of Experimental Biology, 38, pp994-998, 2000.

Asres K, Indian Drugs, 30,pp 189-190,1993.

Barik et al, Indian Journal of Chemistry, 20B, pp 938-939, 1981.

Bean et al, Journal of Natural Product, 48, pp 500, 1985.

Chitra P, Sajithlal GB, Chandrakasan G. Influence of Aloevera on the healing of dermal wounds in diabetic rats. J. Ethanopharmacol. 1998; 59: 195- 201.

Chopra RN et al, Glossary of Indian Medicinal Plants, 1956.

Chopra RN et al, Indian journal of medical research, 29, pp769, 1941.

Chottopadhyay RR, Indian Journal Of Experimental Biology, 31,pp893, 1993.

Holmann et al, Textbook of Diabetics, pp467-469, 1991,

Joy KL, Kuttan R, Journal of Ethnopharmacology, 67(2), pp 143, 1999.

Kameshwara Rao et al, manphar vaidhya partika, 1,pp 33, 1997.

Kamiya et al, Phytochemistry, 57, pp 297-301, 2001.

Kirthikar KR and Basu BD, Indian Medicinal plants, 1, 1981.

Obatomi DK, Bikomo EO, Temple VJ. Anti diabetic properties of the African mistletoe in STZ induced diabetic rats. .J. Ethanopharmacol. 1994; 43(1): 13- 17.

Osadebe PO, Okide GB, Akabogu IC. Study on anti diabetic activities of crude methanolic extracts of *Lorathus micranthus* (Linn) sourced from five different host trees. .J. of Ethanopharmacol. 2004; 95(2-3): 133- 138.

Padma P, Khosa RL, Chansouria JPN. Lipid peroxidation during healing of cutaneous wounds in albino rats. Ind. J. of Natural Products. 2000; 18(2): 16-19.

Pari L, Journal of Ethnopharmacology, 68(1), pp 321, 1999.

Romesh P, Yuvarajan CR, Journal of Natural Product, 58, pp1242-1243, 1995.

Sabu MC, Kuttan R. Anti diabetic activity of medicinal plants and its relationship with their anti oxidant property. J. Ethanopharmacol. 2002; 81(2): 155- 160.

Saraswati Bai N, Bull. Cent. Res. Inst, 3, pp89-107, 1954.

Satake et al, Chem. Pharma Bull, 47, pp1444-1447, 1999.

Setsuko Komatsu and Hisashi Hiranc, Federation of European Biochemical sciences 294(3) 210- 212, 1991.

Singh et al, Indian Journal of Pharmaceutical Sciences, 46, pp148-149, 1984.

Subramanyan, Current Science,14, pp204, 1945.

Thorpe, Chemurg Dig, 10 (2), pp11, 1951.

Trease and Evan, Textbook of Pharmacognosy, 1983.

35. Trinder P Ann Clinical Biochem 6 pp24-27 1969

Valiathan MS, current science, 75,pp1120-1122, 1988.

Venkatesh et al, Fitoterapia, 74, pp.274-279, 2003.

Venkatesh et, al, Pharmaceutical Biology, 41, 2003.

Zhang XF, Tan B.K.Anti hyperglycaemic and anti oxidant properties of Andrographis paniculata

in normal and diabetic rats. Clin. Exp. Pharmacol. Physiol.2000;27 (5-6):358-

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We Claim

1. A formulation comprising an extract of *Glycine max* in the range of 2-5 wt% along with extract(s) of *Curcuma longa* in the range of 1-3 wt% and/ or *Zingiber officinale* in the range of 1-3.5 wt% optionally along with pharmaceutically acceptable carrier(s), said formulation is used in treatment of diabetes and diabetes related diseases.
2. A formulation as claimed in claim 1, wherein the Glycine max extract is seed extract.
3. A formulation as claimed in claim 1, wherein the Glycine extract contains 7S globulin.
4. A formulation as claimed in claim 1, wherein the *Zingiber officinalis* extract is rhizome extracts.
5. A formulation as claimed in claim 1, wherein said formulation is administered to a subject as soft/ hard gelatin capsule, injection or oral dosage forms.
6. A formulation as claimed in claim 1, wherein the formulation is used in cakes and candies.
7. A formulation as claimed in claim 5, wherein the subject is mammal and preferably human.
8. A formulation as claimed in claim 1, wherein the said formulation having the property of improving the anti-diabetic property and used in treatment of type II diabetes and type I diabetes.
9. A formulation as claimed in claim 1, wherein the formulation is used as a free radical scavenger, anti-oxidant and anti-diabetic.
10. A formulation as claimed in claim 1, wherein the formulation is used to treat diabetic related diseases, as inflammation and wound.
11. A formulation as claimed in claim 1, wherein the formulation is used as anti-parasitic for many skin infections.

12. A formulation as claimed in claim 1, wherein the said formulation is used as antacid, carminative.
13. A formulation as claimed in claim 1, wherein the said formulation is used as cholerectic action.
14. A formulation as claimed in claim 1, wherein the said formulation is used as anti-arthritis.
15. A formulation as claimed in claim 1, wherein the said formulation having the specific gravity of 0.992 – 1.505.
16. A formulation as claimed in claim 1, wherein the formulation has a refractive index of 1.5463 -1. 6914.
17. A formulation as claimed in claim 1, wherein the pharmaceutically acceptable carrier is selected from a group comprising protein, carbohydrate, amino acids, phosphorous, fat and fiber.
18. A formulation as claimed in claim 1, wherein the said formulation further comprises proteins in the range of 80.6 - 90.7 wt %.
19. A formulation as claimed in claim 1, wherein the formulation further comprises amino acids in the range of 1.0 - 19.0 wt %
20. A formulation as claimed in claim 1, wherein the said formulation further comprises the fibre in the range of 2.845 – 6.27 wt %.
21. A formulation as claimed in claim 1, wherein the formulation further comprises phosphorus in the range of 0.55 - 0.75 wt %.
22. A formulation as claimed in claim 1, wherein the formulation further comprises fat in the range of 13.5 – 24.2 wt %.
23. A formulation as claimed in claim 1, wherein the formulation further comprises carbohydrates in the range of 14.3 –23.5 wt %.
24. A use of formulation of claim 1 in the treatment of diabetes and diabetes related diseases.
25. A use as claimed in claim 24, wherein the suspension form of *Glycine max* with *Curcuma longa* and *Zingiber officinalis* at a dose of 50- 200 mg/kg reduces the blood glucose level by at least 55.0%.

26. **A use as claimed in claim 24, wherein the said formulation at a dose of 50 to 200mg/kg does not show any abnormality of general condition in mammal preferably human.**

27. A use as claimed in claim 24, wherein the said extract of *Glycine max* at a dose of 50- 200 mg/kg reduces blood glucose level by at least 26.65% in mammal preferably human.

28. A use as claimed in claim 24, wherein the extract of *Glycine max* at a dose of 50-200 mg/kg show a 28.77% glucose tolerance in mammal preferably human.

29. A use as claimed in claim 24, wherein the extract of *Glycine max* with *Curcuma longa* at a dose of 50- 200 mg/kg reduce blood glucose level by at least 45.53% in mammal preferably human.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/003585

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/185913 A1 (PUSHPANGADAN PALPU ET AL) 2 October 2003 (2003-10-02) page 2, column 2, paragraph 7 - page 5, column 2, paragraph 1; claims 1-3,16-20; examples 2,5,7; table 1	1-29
X	US 2003/035851 A1 (CHEN SOPHIE) 20 February 2003 (2003-02-20) page 4; claims 39-41	1-23
Y	US 2003/147979 A1 (MAE TATSUMASA ET AL) 7 August 2003 (2003-08-07) page 1 - page 2; claims 4-7	1-29

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 July 2005	29/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Markopoulos, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/003585

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EIGNER D ET AL: "Ferula asa-foetida and Curcuma longa in traditional medical treatment and diet in Nepal" JOURNAL OF ETHNOPHARMACOLOGY, vol. 67, no. 1, October 1999 (1999-10), pages 1-6, XP002335002 ISSN: 0378-8741 cited in the application page 2 page 4 - page 5	1-29
Y	VEDAVANAM K ET AL: "Antioxidant action and potential antidiabetic properties of an isoflevonoid-containing soyabean phytochemical extract spe" PHYTOTHERAPY RESEARCH, JOHN WILEY & SONS LTD. CHICHESTER, GB, vol. 13, no. 7, 1999, pages 601-608, XP002973175 ISSN: 0951-418X page 605, column 2 - page 606, column 2	1-29
Y	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; February 2004 (2004-02), MORIYAMA TATSUYA ET AL: "Soybean beta-conglycinin diet suppresses serum triglyceride levels in normal and genetically obese mice by induction of beta-oxidation, downregulation of fatty acid synthase, and inhibition of triglyceride absorption." XP002335003 Database accession no. NLM14981298 abstract & BIOSCIENCE, BIOTECHNOLOGY, AND BIOCHEMISTRY. FEB 2004, vol. 68, no. 2, February 2004 (2004-02), pages 352-359, ISSN: 0916-8451	1-29
Y	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; November 2001 (2001-11), STREETER JOHN G: "Simple partial purification of D-pinitol from soybean leaves" XP002335004 Database accession no. PREV200200433075 abstract & CROP SCIENCE, vol. 41, no. 6, November 2001 (2001-11), pages 1985-1987, ISSN: 0011-183X	1-29

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/003585

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Section Ch, Week 200366 Derwent Publications Ltd., London, GB; Class B04, AN 2003-690274 XP002335035 & CN 1 397 293 A (LI C) 19 February 2003 (2003-02-19) abstract -----	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/003585

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 24-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2004/003585

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003185913 A1	02-10-2003	NONE	
US 2003035851 A1	20-02-2003	NONE	
US 2003147979 A1	07-08-2003	JP 2003128539 A US 2004253329 A1	08-05-2003 16-12-2004
CN 1397293 A	19-02-2003	NONE	