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ANTIDIABETIC POTENTIAL OF *GANODERMA LUCIDUM*

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ABSTRACT

Diabetes and its different types are an age-old disease for clinicians since centuries. Many aspects of diabetes need to be explored with respect to physiological actions of insulin and the various clinical features of this disease such as tissue complications, since this is life style disease, so proper treatment in relation to diet and anti-diabetic agents is emphasized. In the present review attempts have been made to understand various aspects of diabetes in relation with its cause, epidemiology, path physiology, site and mechanism of action for anti-diabetic potential of *Ganoderma lucidum* as drug of choice for the future research.

INTRODUCTION

Diabetes mellitus is a group of syndromes. These syndromes are characterized by hyperglycemia; changed metabolism of lipids, carbohydrates and proteins, further an increased risk of complications from vascular disease is seen. Hyperglycemia (Increase in blood glucose in the body) is a condition in which blood glucose level is high and there is diminished action of insulin either because of decrease in the circulatory concentration of insulin (Insulin deficiency) or due to a decrease in the response of peripheral tissues to insulin (insulin resistance). These abnormalities give use to altered metabolism of lipids, carbohydrates and amino acids. All these effects produce hyperglycemia. Diabetes mellitus may arise occasionally from any disease which results in extensive destruction pancreatic islets, e.g. pancreatitis, certain drug, iron overload (hemochromatosis), Tumors, certain acquired or genetic endrocrinopathies and surgical excision. Diabetes gives rise to long term complications in blood vessels, kidneys, eyes and nerves. These result in major causes of morbidity and death from diabetes. This discovery is attributed to bunting and best during the early decades of 20th century (Banting *et al*., 1992). They obtained a pancreatic extract that was effective in decreasing the concentration of blood glucose in diabetic dogs. Then stable extracts were prepared during that era and patients in many parts of North America were treated with insulin form porcine and bovine sources. In present time, recombinant DNA Technology has made use of human insulin for therapy (American Diabetes Association, 2004).

Several studies have described the antidiabetic and antioxidant properties of the phytochemicals isolated from plant and marine seaweeds. Now a days, more attention on the use of secondary metabolites of fungal products for the control of diabetics (He et al. 2006; Seto et al. 2009). Among the fungal species, *Ganoderma lucidum* is a potential one to control diabetics because of its hypoglycemic and antioxidant properties (Zheng et al. 2012; Pan et al. 2013; Bach et al. 2018). Hence this review has been designed to discuss the various aspects of diabetes in relation with its cause, epidemiology, path physiology, site and the anti-diabetic properties of *Ganoderma lucidum.*

Causes of Diabetes

Diabetes mellitus is actually a chronic disorder related to abnormality of carbohydrate, fat and protein metabolism. This is due to defective or deficient insulin secretary response. This results into impaired glucose use, which is a characteristic feature of diabetes mellitus i.e. resultant hyperglycemia. Diabetes mellitus arise form primary disorders of the islet cell – insulin signaling system. In general, this disease occurs due to the diminished secretion of insulin by the beta cells of the islets of lagerphones (Bonner – weir and Ohci 1982). Heredity is also a cause of diabetes. Heredity causes (Leahy, 1990) susceptibility of the β cells. In some cases, it has been observed that it is the hereditary tendency for β cell degeneration.

Obesity is also a factor which causes development of clinical diabetes. Obesity results in decrease in the number of insulin receptors in the insulin target cell throughout the body. This results in decrease in the amount of insulin for its normal metabolic effects (Atkinson *et al*., 2001).

EPIDEMIOLOGY

The incidence of diabetes occurs in all age groups. In USA 10 per cent of all diabetes mellitus have IDDM, or

type I diabetes, the incidence of 18 persons per 1, 00,000 inhabitants per year is observed. In U.K., 17 persons per 1, 00,000 of population have got diabetes. In Europe, the disease of IDDM varies with latitude in Europe, statistical survey state that in Finland this disease is 43 people per 1, 00,000 of population. The case is lowest in France, Italy and Israel i.e., 8 persons per 1, 00,000 of population statistical survey state that the majority of diabetic patients have NIDDM. In the US, about 90 per cent of all diabetic patients have NIDDM. In certain tropical countries, it has been observed that the cause of diabetes is chronic pancreatitis which is due to nutritional or toxic agents (Chan *et al*., 1987).

Observed that diabetes sometimes results from point mutations in the Insulin gene. Mutations result in amino acid substitution. This sort of substitution produces insulin with low potency. This may also alter the processing of pro-insulin to insulin, (Bennett *et al*., 1997).

Physiology of insulin

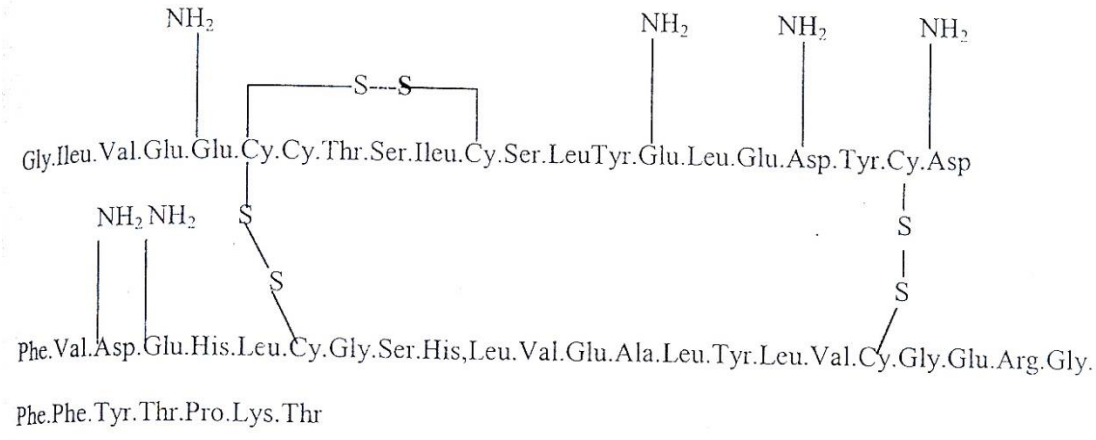
Insulin is a hormone related to energy abundance that is, secretion of insulin is associated with energy abundance. Where excess quantity of carbohydrate is in diet, Insulin is secreted in large quantity. Insulin helps in storing the excess energy substances. If excess carbohydrate is in diet, insulin causes it to get stored as glycogen in liver and muscles. Insulin helps in storage of fat in adipose tissues. Excess carbohydrates which cannot get stored as glycogen get converted into fat under the stimulus of insulin. This fat is stored in the adipose tissue. Insulin helps in uptake of amino acids by cells. Then the amino acids get converted into protein further, Insulin prevents the breakdown of proteins present in the cells.

Liver has a role of blood glucose buffer system. This means when the blood glucose level reaches a high concentration generally after a meal then the rate of insulin secretion too rises. Maximum amount of Glucose absorbed form the gut gets stored in the liver in the form of glycogen. After successive hours when the blood glucose concentration and the rate of insulin secretion fall then liver releases glucose back into the blood. A fall in glucose level stimulates glucagons secretion. Glycogen then functions in the opposite direction i.e., to increase the glucose level to normal. In normal persons, the blood glucose concentration is 180-90 mg/dl of blood each morning before breakfast.

Chemistry of insulin

Insulin is a protein. Its molecular weight is 5808. Insulin has two amino acid chains, connected to each other by disulfide linkages. If the two amino acid chains are split apart then insulin molecule loses its functional activity. Beta cells of pancreas synthesize insulin firstly; translation of the insulin RNA by (Raffel *et al*., 1987) ribosomes attached to the endoplasmic reticulum forms an insulin pre-pro-hormone. Its molecular weight is 11,500. This insulin preprohormone is cleaved in the endoplasmic reticulum to form a pro-insulin. The molecular weight of pro-insulin is 9000. Most of the pro-insulin cleaved in the Golgi apparatus to form insulin before getting into secretary granules. The pro-insulin is inactive in nature. Insulin circulates in an unbound form in blood. A portion of insulin combines with receptors in the target cells, while the remainder gets degraded by the enzymes insulinase mainly in liver, to some extent in kidneys, muscles and slightly in other tissues (Duckworth, 1988).

In order to show effects on target cells, Insulin binds with and activates membrane receptor proteins. This membrane receptor protein has mol. wt. of 3,00,000. This activated receptor causes subsequent effects. The insulin receptor is made up of four submits which are held together by disulfide linkages. Two alpha subunits lie outside the cell membrane and two beta subunits that penetrate through the membrane, and it protrudes into the cytoplasm of the cell. Firstly, the insulin binds with the alpha subunits on the outside of cell and then due to the linkages with the beta subunits the latter protruding into the cell becomes auto Phosphorylated. This Auto-phosphorylation makes them an activated enzyme, a local protein Kinase, (Denton, 1986). This local protein Kinase causes Phosphorylation of multiple other intra cellular enzymes. The consequence is to activate some of these enzymes and to inactivate the other. Thus, insulin directs the intracellular metabolic machinery to yield the desired response.



HUMAN INSULIN MOLECULE

Different types of Diabetes Mellitus and its path physiology

Type 1 Diabetes Mellitus

This is due to absolute deficiency of insulin which is the result of an immune – mediated destruction of pancreatic β cells. The auto immune process is due macrophages and T-lymphocytes with circulating auto anti bodies. These auto antibodies attack various β cells antigens. The islet cell antibody is the commonly detected antibody.

Type 2 Diabetes Mellitus

The symptoms of this type include (i) Defects in insulin secretion (ii) resistance to insulin involving muscle, liver and the adipocyte.

Gestational Diabetes Mellitus (GDM)

This is glucose intolerance being recognized during pregnancy. It can complicate pregnancy leading to prenatal morbidity and mortality, so clinical detection is important.

Other specific types of diabetes

Maturity onset diabetes of youth (MODY) is due to impaired insulin secretion with minimal or no insulin resistance, so hyperglycemia is noticed at an early stage.

Genetic inability to convert pro-insulin to insulin causes mild hyperglycemia pathological features of Diabetes Mellitus are due to the following factors.

1) Decrease in utilization of glucose by the body cells. This results in increase in blood glucose concentration to 300 to 1200 mg / dl.
2) Increase in mobilization of fats from the fat storage areas. This results abnormal fat metabolism and deposition of cholesterol in arterial walls causing atherosclerosis.
3) Tissues get depleted form protein i.e., protein depletion in tissues.

Pathological Physiology of Diabetes mellitus

1. Loss of Glucose in the urine in Diabetes

If Glucose entry inside the kidney tubules in the glomerular filtrate rise above a certain limit, then a significant proportion of the excess glucose cannot get reabsorbed. This gets into the urine and this type of condition occurs when blood glucose concentration rises above 180 mg /dl.

2. Acidosis and coma in diabetes

There is a shift from carbohydrate to fat metabolism in diabetes. Then the level of keto acids aceto-acetic acid and β-hydroxybutyric acid in the body fluids rise to 10m Eq / lit. This extra acid results in acidosis. The direct increase in blood keto acids cause a decrease in sodium concentration so sodium concentration in ECF decreases. This diabetic part of sodium is replaced by increase quantity of hydrogen ions. It leads to acidosis. This diabetic acidosis result into rapid and deep breathing known as 'Kussmaul respiration'. It results in excessive expiration of carbon dioxide. This excessive expiration leads to a marked decrease in HCO_3 content of the ECF. This condition leads to acidosis coma as blood pH falls below 7.0.

3. Dehydrating effect of elevated blood glucose levels in diabetes

Elevated blood glucose level causes dehydration of the tissue cells. As glucose doesn't diffuse easily through the pores of cell membrane and increased osmotic pressure of ECF caused osmotic transfer of water out of the cells.

4. Other diabetic symptoms or the pathological physiology of insulin lack

a. Polyuria - This occurs due to the osmotic diuretic effect of glucose in the kidney tubules.
b. Polydipsia - This occurs due to dehydration resulting from polyuria.
c. Polyphagia and loss of weight - This occurs due to failure of glucose and protein metabolism by the body (American Diabetes Association 2004).

Diet

A well-balanced diet is must for diabetic patients. Type I diabetics must take food at properly spaced intervals. Type II diabetic patients are obese, so they need to follow a weight reduction diet.

Regulation of carbohydrate, protein and fat is must here, carbohydrates account for 45 per cent to 50 per cent of total caloric intake, protein account for 15 per cent – 20 per cent while fats account for 35 per cent – 40 per cent (Kolata, 1987). Type I insulin dependent diabetes needs lifelong diet modification. The diet should be in position to provide enough energy for growth and main penance. But it must not cause weight gain. Smaller and more frequent meals are good for such patients. A bed time snack prevents by poglycemia from occurring during night. Type II or non-insulin dependent diabetes occurs in obese adults 90 per cent of all diabetes in United States is Type II or non-insulin dependent diabetes. The best way to avoid this is to lose weight, exercise regularly and to avoid fat rich diet regularly and to avoid fat rich diets (Crapo and Vinik 1987).

Treatment of diabetes

Treatment requires good achievement for glycemia, B.P. and lipid levels. Regular monitoring for complications in this disease is needed. Medications, dietary and exercise modifications are needed.

The principle behind the treatment of diabetes mellitus is to administer enough insulin. This is done so that the patient will have nearly normal state of carbohydrate, fat and protein.

Metabolism (Koffler *et al*., 1989)

Previously insulin used for treatment was derived for

animal pancreas. Recently, human insulin produced by recombinant DNA process is used as many patients develop immunity and sensitization against animal insulin. Insulin is available in the market in various forms. "Regular" insulin has duration of action from 3-8 hours. Other forms of insulin, which are precipitated with zinc or with various protein derivatives, are slowly absorbed from the site of injection. Their effects last up to 10 to 48 hours Anti-diabetics can be classified as:

1. Oral hypoglycemic (Sulfonylureas)
Chlorpropamide, Tolbutamide, Glibenclamide, Glilpizide, Gliclazide, Glimepiride.

2. Oralhypoglycaemics (Bi-guanides)
Phenformin, metformin, Combination preparations of phenformin and metformin.

3. Others
Acarbose, Repaginate, Guargum and herbal preparation.

4. Different types of insulin's
a. Short-acting insulins: Neutral insulin (soluble).
b. Intermediate – acting insulin: Isophane insulin, Insulin zinc suspension (Lente insulin).
c. Long-acting insulin: Extended insulin zinc suspension (Ultralente).

Premixed Biphasic insulin's: Sulphonyl Urea's (Ferner and Neil 1988)
These drugs stimulate insulin secretion from beta cell of pancreas. They induce increased activity of peripheral insulin, intracellular receptors, also reduce glucagons, secretion chlorpropamide, Tolbutamide, Glibenclamide Gliclazide, Glipizide are the drugs which act by the Mechanism of Sulphonyl area.

Biguanides
Biguanides such as phenformic and metformin act by increasing peripheral anaerobic glycolysis. They interface with absorption of carbohydrate in gut and suppress hepatid glyconeogenesis.

Other agents
1. Acarbose
Acarbose is a pseudo-tetrasaccharide. It is obtained from the fermentation process of the fungus actinoplanesutahensis.

MOA
It acts by competitively inhibiting pancreatic alpha-amylase and intestinal alphaglycosidase hydrolase enzymes. Thus it slows down carbohydrate digestion. It prolongs digestion time and reduces the rate of glucose absorption. Thus it lowers post prandial hyperglycemia without producing hyper insulinaemia.

2. Repaglinide
Repaglinide is novel insulin synagogue. It is used for the management of Type 2 diabetes mellitus Repag linide acts on the β cells of the pancreas. It lowers post parandial blood glucose and fasting blood glucose in patients with type 2 Diabetes Mellitus.

3. Nateglinide
It is a novel D-phenyl-alanine derivative used in the treatment of Type 2 diabetes mellitus. It specially forgets post parandial hyper-glycaemia. Nateglinide inhibits ATP sensitive K+ channels in β cells of pancreas in the presence of glucose and therapy simulation of parandial release of insulin takes place.

4. Rosiglitazone
It is a thiazolidinedione class of drugs which improve insulin resistance patients with type 2 Diabetes Mellitus. Rosiglitazone is a potent and highly selective agonist for the nuclear receptor peroxisome proliferators activator receptor gamma (PPAR – gamma). The main function of PPAR – gamma is to increase the transcription of certain insulin – sensitive genes, thus improves the insulin sensitivity.

5. Pioglitazone
Pioglitazone activates the nuclear peroxisome proliferators activated receptor gamma (PPAR) gamma that result in increased transcription of a number of insulin responsive genes, which are involved in the control of glucose and lipid metabolism. This drug decrease insulin resistance in the periphery and in the liver which results in increased insulin dependents glucose disposal and decrease in hepatic gluconeogenesis.

6. Guargum
Guargum is high molecular weight gydro colloidal polysaccharide. It is available in granular form. Guargum on oral administration leads to viscous gel formation in intestine. This result in decreased carbohydrate absorption. Thus, blood glucose level is decreased (Bolli, *et al*., 1999).

New technologies for insulin delivery
1. Insulin inhalers
It is used in the treatment of both type I and type II diabetes. Inhaled insulin enhances patient satisfaction, quality of life and acceptance of intensive insulin therapy in a diabetic patient.

2. Insulin spray
This involves the buccal route. Buccal area has abundant blood supply. This route eliminates the destruction of insulin by first pass metabolism.

3. Insulin pill
Azopolymer coated pellets deliver insulin to the colon. The Azopolymer protects the entrapped therapeutic agent until the pellets enter the colon. Bacteria present in colon secrete enzymes that can breakdown the azopolymer. So insulin release gets initiated once the pellets reach the large intestine.

Micro encapsulation of insulin in polymeric microspheres coated with pH responsive polymers like alginate is also available. Alginate coating protects the spheres from getting broken down in the acidic pH of the stomach. But dissolution is seen in the intestine where the pH increases to more than 7 and liberates the entrapped insulin (Shashkin *et al*., 2006).

Medicinal Mushroom

Mushrooms are an extremely rich species in the world. More than 140,000 mushroom species were identified in the earth. It has been analyzed for their nutritional value and other medicinal properties. The mushrooms have been extensively used as part of the food dish for several decades. It is also having the medicinal properties and reported from last three decades. The various research is also being reported that the mushrooms with the pharmacologically important compounds isolated from the fruiting bodies of the mushrooms. The polysaccharide and polysaccharide-protein complexes were isolated from the mushroom fruiting bodies and it shows effective anticancer and immunostimulant activities. Now a days, the mushroom polysaccharides data is available around 660 species from 182 genera of Basidiomycetes (Wasser, 2010). The medicinal property of mushrooms include cardiovascular, antioxidant, antitumor, immunomodulating, radical scavenging, anti-hypercholesterolemia, antiviral, antibacterial, antiparasitic, hepatoprotective, and antidiabetic effects (Dai et al. 2010). In China, mushrooms have been incorporated into food dishes, teas, soups, health tonics, tinctures and herbal formulas. Mushrooms are also used as dietary supplements (DSs) in foods forms and as nutraceuticals.

Bioactive Components

Mushrooms contains several bioactive metabolites have been isolated from various mushrooms in the form of polysaccharides (hetero-beta glucans), protein complexes (e.g., xyloglucans and acidic beta-glucan–containing uronic acid), and dietary fiber (Mizuno et al. 1999). Other secondary metabolites are identified in mushrooms as pharma-active compounds such as lectins, lactones, terpenoids, alkaloids, antibiotics, and metal chelating agents. Medicinal mushrooms also contain a number of enzymes such as laccase, superoxide dismutase, glucose oxidase, and peroxidase. These enzymes play important roles in preventing oxidative stress (Asatiani et al. 2010).

Ganoderma lucidum

A commercially valuable medicinal mushroom *Ganoderma lucidum* species commonly called as 'Ling-Zhi' in Chinese, 'Reishi' in Japanese, and 'Yeongji' in Korean. *Ganoderma lucidum* is belongs to the basidiomycete, white rot fungus that has been reported as a one the major variety of the medicinal mushroom. In China, *G. lucidum* is commonly used as a food ingredient and foodstuffs to rise human strength and longevity (Sliva, 2006). *G. lucidum* have been reported that contains several pharmacological compounds to treat diabetic, hepatotoxic, cancer, and immunomodulatory properties (Boh, 2013). The animal model and in *in vitro* study reveals that the *G. lucidum* has proved its constituents used for therapeutic application (Olaku and White, 2011) and health benefits (Cheuk et al., 2007). G. lucidum contains various bioactive molecules, such as triterpenoids, polysaccharides, nucleotides, fatty acids, glycoproteins, sterols, steroids, proteins and peptides (Batra et al., 2013; Wachtel-Galor et al., 2011).

Furthermore, the bioactive molecules such as triterpenoids, polysaccharides, nucleotides, fatty acids, glycoproteins, sterols, steroids, proteins and peptides are isolated from *G. lucidum* contains various (Batra et al., 2013; Wachtel-Galor et al., 2011). Among the isolates, polysaccharides, triterpenoids, and glycoproteins have hypoglycemic effects Teng et al., 2012).

Anti-diabetic activity of *G. lucidum*

The cell wall of *G. lucidum* contains polysaccharides which possess hypoglycemic effects by the mechanism of increasing plasma insulin levels and significantly decreasing the blood plasma sugar levels in the mice experimental study (Hikino et al., 1985). Polysaccharides are extracted from *G. lucidum* enhance the enzymatic action of hepatic glucokinase, phosphofructokinase, and glucose-6-phosphate dehydrogenase activities and also inhibits glycogen synthetase activity, which decreasing hepatic glucose production and the action of preventing hyperglycemia (Agius, 2007; McCormack et al., 2001). The triterpenoids are isolated from *G. lucidum*, which is the major inhibitors of the enzyme aldose reductase and a-glucosidase (Fatmawati et al., 2013). The aldose reductase is the one of the major enzymes in the glucose to sorbitol metabolic (polyol) pathway. The sorbitol is a major marker substance in the neuropathy, nephropathy, cataracts, and retinopathy conditions and it leads to diabetic complications (Bhatnagar and Srivastava, 1992). The research carried out on 17 commercially available mushrooms, among these *G. lucidum* showing the highest aldose reductase inhibitory activity. The blood galactitol level experiment was conducted on galactose-fed rats, the ethanol extracts from *G. lucidum* reduced 50% by compared to the control group in blood glucose level.

The extract of *G. lucidum* Ling Zhi-8 (LZ-8) contains an important therapeutic proteins, which have immunomodulatory and controlling I diabetes activities. The enzyme protein tyrosine phosphatase 1B (PTP1B) is also isolated from *G. lucidum* and its action on therapeutic target in diabetes receptors. It is a major role on the insulin receptor signaling and decreases the expression of insulin receptor b subunit by negative regulations (Combs, 2010; Feldhammer et al., 2013). The protein was extracted from *G. lucidum*, which has mitogen activity and reduce the plasma glucose concentration. It was proved in NOD mice, the protein LZ-8 significantly decreased the blood lymphocyte infiltration and increased serum antibody detection of

insulin in beta cells (Kino et al., 1990).

Anoderma Lucidum

Ganoderma lucidum (G. lucidum) and related species have the longest historical usage for medicinal properties dating back at least four thousand years.[19] In Japan it is called Reishi and in China and Korea it is variously called Ling Chu and Ling Zhi (Mushroom of immortality). Traditionally it has been used widely in the treatment of hepatopathy, chronic hepatitis, nephritis, hypertension, arthritis, insomnia, bronchitis, asthma and gastric ulcer. Scientific studies have confirmed that the substances extracted from the mushrooms can reduce blood pressure, blood cholesterol and blood sugar level as well as inhibition of platelet aggregation.

Ganoderma species are famous tonic in Chinese medicines. They are widely distributed in India on tree trunks. *Ganoderma* belongs to the polyporaceae family of Basidiomycota. Generally *Ganoderma* species are described as beneficial to all viscera and non-toxic.[20] For 4000 years *G. lucidum* has been used as a part of Chinese and Japanese medicine especially for the treatment of most of the human ailments including chronic hepatitis, nephritis, hepatopathy, neurasthenia, arthritis, bronchitis, asthma, gastric ulcer etc.

Extracts from fruiting bodies and mycelia of *G. lucidum* occurring in South India were found to possess *in vitro* antioxidant activity[21, 22] and antimutagenic activities[22] The results of the antioxidant assays showed that ethyl acetate, methanol and aqueous extract of *G. lucidum* effectively scavenged the $O2^{-\cdot}$ and $^{\cdot}OH$ radicals (Table 1). However the aqueous extract was not effective to inhibit the ferrous ion induced lipid peroxidation.[21] The extract showed significant reducing power and radical scavenging property as evident from FRAP assay (Fig. 3) and DPPH radical scavenging assay (Fig. 4).[23] The extract of *G. lucidum* also effectively to inhibited EAC cell line induced solid tumor in mice when administered orally (Fig. 2).[21] The prophylactic treatment by the extract could inhibit the tumor growth significantly or increased the life span.

CONCLUSION

In conclusion, this review articles highlights onset of diabetes with its effects, epidemiology, patho-physiology and mechanism of action for anti-diabetic compounds. Furthermore, the mushroom containing the pharma-active compounds of polysaccharides, triterpenoids, and glycoproteins hypoglycemic effects of *Ganoderma lucidum* has been explained.

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