Plant Biotechnology Persa 2021; 3(2); 39-47. **Review Article**

Plant Biotechnology Persa https://pbp.medilam.ac.ir

A Review on the Effectiveness of Red Belt Leaves (*Piper crocatum*) as Antihyperglysemic Activities

Khalis Arsy Al Khairy Siregar[1], Novia Misnawati Aisyiyah[1], Paula Mariana Kustiawan[1]*

[1]Faculty of Pharmacy, Muhammadiyah University Of East Borneo, Eas Borneo, Samarinda, Indonesia

Article Info

***Correspondence to:**
Paula Mariana Kustiawan
pmk195@umkt.ac.id

Article History:
Received: 30 April 2021
Accepted: 17 may 2021
ePublished: 13 march 2022

Keywords:
Antihyperglycemic, bioactivity, Piper crocatum, Potency

Abstract

In Indonesia, diabetes is third among the leading causes of death. Elevated blood sugar (hyperglycemia) is one of the clinical features of the disease. Indonesia has abundant potential herbal plants. The red betel leaf is one of the promising herbal plants (Piper crocatum). Alkaloids, saponins, tannins, and flavonoids are among the phytochemical components found in red betel leaf. This study was used as a medium of renewable information that was supported from several previous reference sources strengthening evidence of the benefits obtained from red betel leaf as an antihyperglycemic agent. The study uses a literature review method using journal database platforms such as Google Scholar, Pubmed, and ScienceDirect as search engines for journals related to this article. The potential activity of red betel leaf as an antihyperglycemic drug which can lower blood glucose was discovered from the findings of the numerous journal sources and related studies. Red betel leaf contains flavonoid compounds that are antioxidants. Antioxidants can bind to hydroxyl radicals that harm the pancreatic cells of the islets of Langerhans, allowing these substances to activate insulin activity and treat diseases like gout, cancer, hypertension, and diabetes. Red betel leaf has an effective candidate compound has the potential to be used as an antihyperglycemic agent to lower blood glucose.

How to cite this paper
Al Khairy Siregar KA, Aisyiyah NM, Kustiawan PM. A Review of Effectiveness of Red Belt Leaves (Piper crocatum) As Antihyperglysemic Activities. Plant Biotechnology Persa 2021; 3(2): 39-47.

Introduction

Diabetes is now a degenerative disease caused by an unhealthy lifestyle. It is characterized by increased blood sugar levels (hyperglycemia), impaired fat, carbohydrate, and protein metabolism, and an increased risk of cardiovascular complications [1];[2]. Hyperglycemia occurs because it is associated with the destruction of the insulin-producing cells of the pancreas. This damage is caused by an immune response in the form of genetic factors, viral infections such as the coxsackie virus and antibody attacks against β cells [3]. Treatment of diabetes mellitus such as the use of insulin and oral antihyperglycemic drugs is relatively more expensive, its use in the long term and can cause side effects that threaten health [1]. Currently, Indonesian people are starting to prioritize the use of herbal plants for treatment (back to nature) [4]. The biodiversity of Indonesia is unquestionable, with an abundance of herbal plants. This herbal plant, one of which being Red Betel Leaf, can be utilized as a therapeutic plant (Piper crocatum). Red betel leaves are common in Indonesian yards and may be found all across the country. The potential of red betel as an herbal plant is very much and also has various benefits [5]. Alkaloids, saponins, tannins, and flavonoids are among the phytochemical substances found in betel leaf, with alkaloids being the most prominent [6]. Antioxidants can bind to hydroxyl radicals, which can damage the cells of the pancreatic islets of Langerhans, where these compounds can stimulate the secretion of glucose to cure gout, cancer, hypertension, and diabetes mellitus [7]. It has been proven by several studies, one of which is red betel leaf extract (Piper crocatum) 2%. Capable of suppressing the increase in blood glucose levels after intraperitoneal administration of alloxan. Red betel leaf extract has been tested in the laboratory because it can lower blood glucose levels in male white rats (Rattus novergicus). As a result, research into red betel leaf (Piper crocatum) for lowering blood glucose levels is required [7]. The potential of red betel leaf as a candidate for medicinal plants is very large, so it needs development in its use as a modern medicinal ingredient [5].

Betel leaf is a plant that is very widely used but there is little literature that mentions the use of antihyperglycemic activity. From several journals reviewed and found many supporting elements because red betel leaf has antihyperglycemic activity.

Taxonomic Classification of Red Betel Leaf

Betel leaf is a plant that is vines and depends on other plants for its life. And also this red betel leaf is one of the betel-betel tribe or Piperaceae, the position of the red betel plant in plant taxonomy is as follows:

Kingdom	**Plantae**
Sub Kingdom	Tracheobionta
Super Divisi	Spermatophyta
Divisi	Magnoliophyta
Kelas	Magnoliopsida
Sub Kelas	Magnolidae
Ordo	Piperales
Familia	Piperaceae
Genus	Piper
Species	Piper crocatum Ruiz & Pav

Figure 1. Red Betel Leaf Plant Illustration (Piper crocatum) [8]Plant Description

Red Betel Leaf Plant (Piper corcatum) The leaves are shiny and green with a pink tinge. The leaves form a heart and the tip is tapered, shiny, and uneven, the edges are flat, the surface is glossy, hairless and when the leaves are torn it will secrete

mucus, taste bitter and the aroma is more fragrant. The stem is slightly reddish-green and the surface of the skin is wrinkled, and the roots will grow in each node of the stem [9].

Empirical use of red betel leaf

This plant has been widely used by the people of Indonesia for various kinds of alternative medicine and is also used for ornamental plants and the completeness of traditional ceremonies [5]. One of them is at the Yogyakarta palace by using red betel as a traditional ceremony equipment "ngadi saliro" [10]. Menurut penelitian, daun sirih merah dapat mengobati diabetes, hepatitis, batu ginjal, menurunkan kolesterol, mencegah stroke, asam urat, hipertensi, prostatitis, radang mata, infeksi parasit plasmodium, keputihan, bisul, ketidaknyamanan sendi, dan bertindak sebagai antiseptik [10];[11];[12].

Betel Leaf Content

In general, betel leaf contains many active compounds, including flavonoids where flavonoid compounds have characteristics in the red betel leaf auron group [13]. Alkaloids, polyphenols, tannins, and essential oils, also found other compounds such as hydroxykavikol, kavikol, cavibetol, allypykatekol, carvakol, eugenol, eugenol methyl ether, p-terpenenna, esquiterpenes, phenyl propane, diastase, sugar, and starch [9];[14];[15]. Red betel leaf has been widely used as traditional medicine by the community. Betel leaf has many activities, one of which is a high antioxidant that can inhibit hyperglycemia. Several previous studies have been carried out to find out what compounds play an active role in providing many benefits, which will be described in Table 1.

Betel Leaf Phytochemical Screening

From the journals that have been studied, it was found that several compounds that play a dominant role in red betel leaf are flavonoids, alkaloids, tannins, saponins, and essential oils.

Table 1. Phytochemical Screening on Red Betel Leaf

Extract Solvent	Compound Content
Ethanol	steroids, alkaloids, flavonoids, and essential oils, and triterpenoids [16]
Ethanol	steroids, alkaloids, flavonoids, and essential oils, and triterpenoids [17].
Methanol	Alkaloids, saponin, triterpenoid, and steroids
Gelatin	Tannins
Aquadest	Polifenol, and tannins [18]
Ethanol	glycosides, steroids/triterpenoids, flavonoids, tannins, and anthraquinones [19]

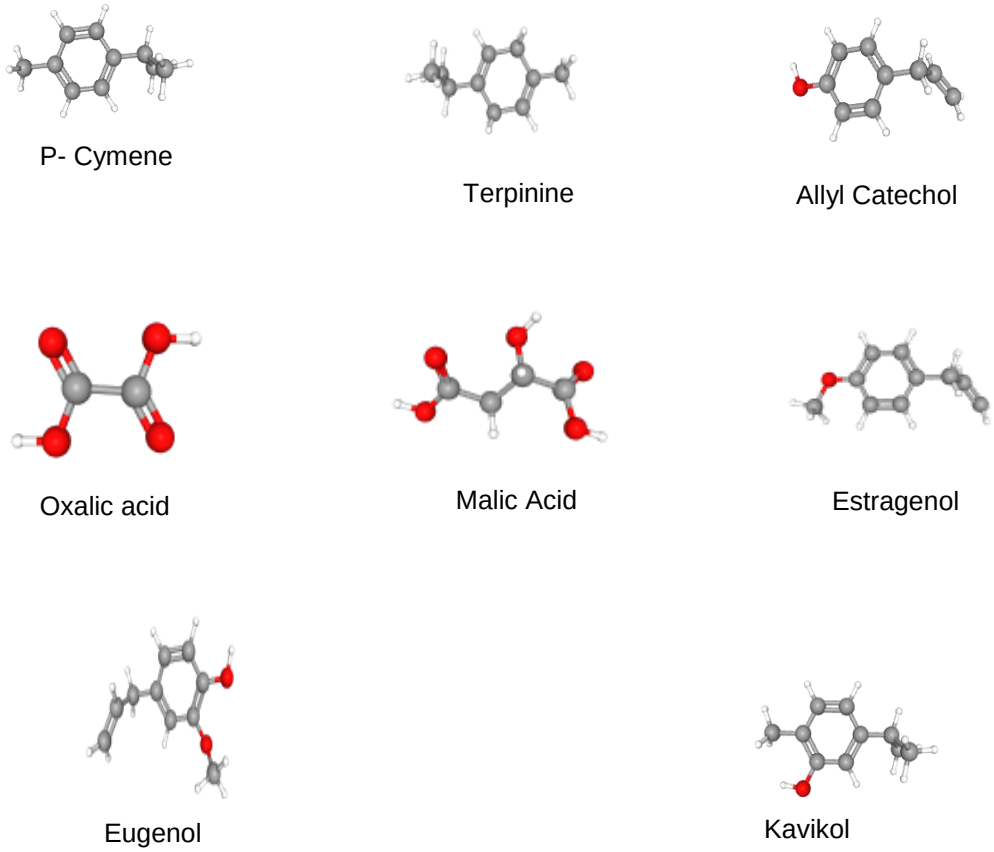

Figure 2. Red Betel Leaf Compound [20];[21]

The other secondary metabolites contained in red betel leaf are carvacrol, eugenol, p-cymene, terpenene, P-cymene, carvacrol, allyl catechol, oxalic acid, malic acid Of the several compounds found, there were two compounds whose use was detected, namely Eugenol and Kavikol where these compounds were able to lower blood glucose levels by activating pancreatic cells to protect cells from oxidative damage then increase granulation, improve cell function for insulin production, and also have an effect insulin mimetics. In the liver increases glycogenesis and glycolysis, and reduces gluconeogenesis thereby increasing liver glucose [22]. In addition, eugenol also reduces blood glucose and glycosylated hemoglobin (HbA1c), and increases plasma insulin levels [23]. And also found from the results of red betel leaf isolated the presence of a neolignan compound, 1-allyl-3,5-dimethoxy-7-methyl-oxo-6-(3,4,5-trimethoxyphenyl) bicyclo [3,2,1] oct-2-en-8-yl acetate [23].

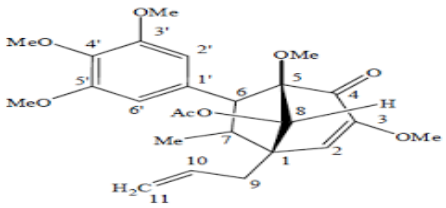

Figure 3. 1-allyl-3,5-dimethoxy-7-methyl- oxo-6-(3,4,5-trimethoxyphenyl) bicyclo [3,2,1] oct-2-en-8-yl acetate

Flavonoids have antioxidant activity that can be used to bind free radicals and form complexes with metals because flavonoid compounds have at least two hydroxyl groups [24]. In type 2 diabetes

Flavonoids provide pancreatic cell activity and insulin release from pancreatic cells:

Protection against pancreatic cell damage

Increased proliferation of pancreatic cells

Preservation of insulin signaling by increasing insulin secretion.

Increased utilization of sugar in organs and tissues, flavonoids can affect transduction through increased glucose utilization and insulin receptor signaling, increasing glucose utilization.

Decreased Glycogenolysis: Flavonoids increase glycogenolysis by increasing glucokinase levels, thereby reducing the expression of the G-6-Pase carboxylate gene and phosphoenolpyruvate carboxykinase, resulting in either gluconeogenesis or glycogenolysis, or both, which have been shown to inhibit.

patients, flavonoids can prevent lipid peroxidation, reduce tissue damage caused by free radicals, and inhibit the action of glucokinase enzymes that can make glucose molecules oxidative stress. [25].

Can be used as glucosidase inhibitors that suppress glucose absorption in the intestine, flavonoids can be used as glucosidase inhibitors, preventing carbohydrate digestion and slowing down glucose absorption. In addition, sucrose, maltase, and amylase inhibitors have demonstrated potential for hypoglycemia in the treatment of diabetes [26].

Antihyperglycemic Potential

The findings of a journal review on red betel revealed that it has strong antihyperglycemic action, with red betel leaves being cooked and the boiling water being processed into components to reduce blood glucose levels, which will be described in table 2.

Compound Content	Activity	Findings / Mechanisms	Information
Flavonoids, alkaloids, polyphenolic compounds, tannins, and essential oils	**Antihyperglycemia**	Boiled water of red betel leaf (Piper crocatum Ruiz and Pav) has an antihyperglycemic effect in male rats. It is expressed as a significance value < 0.05. Boiled water of red betel leaf (Piper crocatum Ruiz and Pav) had no effect on reducing blood cholesterol levels in male rats. This is indicated by a significance value greater than 0.05. From the data above, it can be concluded that boiled water of red betel leaf (Piper crocatum Ruiz and Pav) can be used as an herbal alternative to lower blood sugar [27].	
alkaloids, saponins, tannins, and flavonoids	**Antihyperglycemia**	There is a significant effect between the treatment of red betel leaf decoction on the reduction of blood sugar levels in white rats	In white rats, the most effective dose of red betel leaf decoction for

		induced by alloxan and there is a very significant correlation between the treatment and the decrease in blood glucose, where the correlation is directly proportional [14].	lowering blood sugar levels is 3 ml/150 grams weight/day.
alkaloids, saponins, tannins and flavonoids	**Antidiabetic**	The average value of GDS before giving red betel leaf boiled water was more than 200 mg/dl. The average value of GDS after giving red betel leaf boiled water is less than 200 mg/dl. So, there is a difference in GDS levels in Diabetes Mellitus patients before and after giving red betel leaf boiled water [6].	
tannins, alkaloids, polyphenols, alkaloids, and polyphenols	**Antidiabetic**	There is an effect of giving boiled red betel leaf (piper crocatum) on changes in blood sugar levels in Type II DM patients [28]	Giving red betel leaf decoction in the form of a decoction three times a day lowers blood pressure levels.
tannins, flavonoids, and polyphenols	**Antihyperglycemia**	Based on the results of the analysis, the p value of 0.001 < 0.05 red betel leaf extract (*Piper crocatum*) can reduce blood glucose levels in mice (*Mus musculus*). Furthermore, there was no significant difference in the decrease in blood glucose levels of mice (Mus musculus) at each dose level of red betel leaf extract (*Piper crocatum*).[3].	The dose of 0.078 gram/20gr BW is the effective dose range for reducing blood glucose levels in mice
alkaloids, saponins, tannins and flavonoids	**Antihyperglycemia**	Giving red betel leaf extract (*Piper crocatum*) 2% was able to reduce blood glucose levels in experimental animals, namely male white rats (*Rattus novergicus*)[7].	
alkaloids, flavonoids, tannins and saponins and peptides	**Antihyperglycemia**	Red betel leaf extract (*Piper crocatum Ruiz & Pav.*) can reduce the blood glucose of male mice (*Mus musculus L.*) induced by sucrose [29].	The most appropriate dose of red betel leaf extract (*Piper crocatum Ruiz &*

	Pav.) in lowering blood glucose of male mice (*Mus musculus L.*) induced by sucrose was 2.8 g/kg bb mice.

Antihyperglycemic Activity

Blood sugar levels in white rats were reduced when they were given boiling red betel leaf. This may be interpreted in two ways: Processes that occur both inside and outside the pancreas [30]. The intra-pancreatic mechanism functions by mending and protecting injured pancreatic cells while also increasing insulin secretion. Alkaloids and flavonoids have this capacity [31];[32]. Alkaloids proved to have the ability to regenerate damaged pancreatic β cells [31];[32]. The increase in insulin secretion is caused by the sympathetic nervous stimulation effect of the alkaloids which affects increasing insulin secretion. Flavonoids have an antioxidant effect so that they can protect pancreatic cell damage from free radicals [33]. Extra-pancreatic mechanisms can occur through various mechanisms. Alkaloids lower blood glucose by inhibiting the absorption of glucose in the intestine, increasing glucose transport in the blood, stimulating glycogen synthesis, and inhibiting glucose synthesis by inhibiting the enzymes glucose 6-phosphatase, fructose 1,8-bisphosphatase, and increasing glucose oxidation through glucose 6-phosphate dehydrogenase. Glucose 6-phosphatase and fructose 1,6-bisphosphatase are enzymes that play a role in gluconeogenesis. Inhibition of these two enzymes will reduce the formation of glucose from other substrates besides carbohydrates. Saponins work by decreasing glucose absorption in the intestine, inhibiting the glucose transporter GLUT 1, increasing glucose utilization in peripheral tissues and glycogen deviation, and increasing insulin receptor sensitivity in tissues [30];[33].

Conclusion

The efficacy of red betel leaf or Piper crocatum as an antihyperglycemic, which can reduce blood glucose, is demonstrated by the results of the literature that has been processed and compared. And also has other activities to prevent premature ejaculation, anticonvulsant, antiseptic, analgesic, anti-dandruff, antidiabetic, liver protector, antidiarrhea, maintain immunity, and reduce swelling. This high activity is supported by abundant secondary compounds consisting of terpenoids, tannins, essential oils, and also flavonoids which are the most dominant compounds that produce high antioxidant activity.

Authors' contribution

All authors contributed equally to the manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues have been fully observed by the author

Funding/Support

None.

References

1. Amani ZA, Mustarichie R. Article Review: Antihyperglycemic Activity of Several Plants in Indonesia. Farmaka 2018; 116(1): 127–132.
2. Arokiyaraj S, Balamurugan R, Augustian, P. Antihyperglycemic effect of Hypericum perforatum ethyl acetate extract on streptozotocin-induced diabetic rats. Asian Pac. J. Trop. Biomed 2011; 1(5): 386–390.
3. Afsari R, Kusmiyati IW, Merta M.The Effect of Giving Red Betel Leaf Extract (*Piper Crocatum*) Against Reducing Blood Sugar Levels in Mice (Mus musculus). J. Biol. Trop 2016; 16(1): 49–55.
4. Juliantina F, Citra DA, Nirwani B, Nurmasitoh T, Bowo ET. Benefits Of Red Betel (*Piper Crocatum*) As Anti-Bacterial Agent Against Gram Positive And Gram Negative Bacteria, J. Kedokt. dan Kesehat. Indones 2009; 1(1): 1.

5. F. Manoi Sirih merah sebagai tanaman obat multifungsi. 2007.
6. D. Effendi L, Indriati B. The Effectiveness of Red Betel Leaf Boiled Water on Reducing Blood Sugar Levels in Diabetes Mellitus Patients in the Work Area of the 2018 Saling Health Center. J. Keperawatan Muhammadiyah Bengkulu 2018; 7: 62–70, 2019.
7. Dewi YF, Anthara MS, and Dharmanyudha AAGO. The Effectiveness of Red Betel Leaf Extract (*Piper Crocatum*) Against Weight Gaining in Male White Rats (Rattus Novergicus) Diabetic Conditions Induced by Alloxan, Bul. Vet. Udayana 2014; 6(1): 73–79, 2014.
8. "Stock Images." https://www.istockphoto.com/ (accessed May 19, 2021).
9. Fadlilah M. Benefit of Red Betel (Piper Crocatum Ruiz & Pav .) As Antibiotics. J. Major. 2015; 4(3): 5.
10. Ma'rifah A. Effect of Red Betel Leaf Extract (Piper crocatum) On the grownth of the Bacteria of Staphylococcus aureus. Universitas Islam Negeri Syarif Hidayatullah, 2012.
11. Gani N, Momuat LI, Pitoi MM. Plasma Lipid Profile of Hypercholesterolemic Wistar Mice on Giving Red Gedi (Abelmoschus manihot L.). J. MIPA UNSRAT 2013; 2(1): 44–49.
12. Sudewo, Get Rid of Diseases with Red Betel. Jakarta: Argomedia Pustaka, 2005.
13. Parfati N, Windono T. Red betel (Piper crocatum Ruiz & Pav) literature review. Media Pharm. Indones 2016; 1(2): 106–115.
14. Hati K, Setiawan M, Yuliarta D. The Effect of Red Betel Leaf (Piper Crocatum) Decoction On Reducing Blood Sugar Level in White Rats (Alloxan-induced Rattus norvegicus)," Saintika Med. 2017; , 9(1): 59.
15. Putri AK. Study of Morphology of Piper betle L. and Its Use in Daily Life 2019, doi: 10.31219/osf.io/94yvq.
16. Rukmini A, Utomo DH, Laily AN. Family Piperaceae Phytochemical Screening," J. Biol. dan Pembelajarannya 2020; 7(1): 28–32.
17. Safithri M, Fahma F. Potency of Piper crocatum Decoction as an Antihiperglycemia in Rat Strain Sprague dawley," HAYATI J. Biosci 2008;15(1): 45–48.
18. Fitriyani A, Winarti L, Muslichah S, Nuri N. Anti-Inflammatory Test of Red Betel Leaf (Piper crocatum Ruiz & Pav) Methanol Extract on White Rats. Majalah Obat Tradisional 2011; 16(1): 34–42.
19. Reveny J. Antimicrobial Power of Red Betel Leaf Extract and Fraction (Piper betle Linn.). J. ILMU DASAR 2011; 12: 6–12.
20. Sengupta R, Banik JK. A Review On Betel Leaf (PAN)," Int. J. Pharm. Sci. Res 2013; 4(12): 4519–4524.
21. "PubChem," 2021. https://pubchem.ncbi.nlm.nih.gov/#draw=true (accessed Mar. 28, 2021).
22. Chaudhry ZR, Naseer A, Chaudhry SR, Chaudhry ER, Chaudhry FR. Comparison of Extracts of Syzygium Aromaticum on the Weight of STZ induced Diabetic Rats, J. Islam. Int. Med 2016; 11(1): 24–28.
23. Iswandha I, Liyanovitasari R. The Effectiveness Of Building Clove (*Syzygium Aromaticum*) On Blood Glucose In Diabetes Mellitus Patients In The Work Area Of Kaliwungu Puskesmas, Semarang Regency. Universitas Ngudi Waluyo, 2019; 3.
24. Sandhar Bimlesh HK, Kumar B, Prasher S, Tiwari P, Salhan M, Sharma P. A Review of Phytochemistry and Pharmacology of Flavonoids. Int. Pharm. Sci 2011; 1(1): 25–41.
25. Anggi VM. The effect hypoglycemic of ethanol extract combination red betel leaf (Piper crocatum) and Dayak onion (Eleutherine palmifolia Merr) in streptozotocin-induced. Pharmacogn. J 2019; 11(6): 1401–1405.
26. Abdullah FF.Relationship between Diabetes and Flavonoid Structure as a Potential Source of Compounds," Universitas Garut, 2020. https://fmipa.uniga.ac.id/read/2020/06/hubungan-penyakit-diabetes-dan-struktur-flavonoid-sebagai-sumber-senyawa-yang-potensial.html (accessed May 29, 2021).
27. Shinta DY, Sudyanto S. Administration Of Red Belt Leaves (Piper Crocatum Ruiz & Pav) Water On Glucose And Blood Cholesterol Levels Of Male White Miice," Sainstek J. Sains dan Teknol 2017; 8(2): 180.
28. Etriyanti VI. The Influence Of Red Belt Leaves (Piper crocatum) Booking On Blood Sugar Levels In Type II Diabetes Melitus Patients. J. Kesehat. Saintika Meditory J. Kesehat. Saintika Meditory 2018; 1(2): 79–88.

29. Saputra MR, Yuniarti E, Sumarmin R. The Effect of Red Betel Leaf (Piper crocatum Ruiz & Pav.) Extract On Blood Glucose Induced Male Mouse (Mus musculus L.)," EKSAKTA Berk. Ilm. Bid. MIPA 2018; 19(1): 43–55.
30. Shane-McWhorter L. Biological Complementary Therapies: A Focus on Botanical Products in Diabetes. Diabetes Spectr 2001; 14(4): 199–208.
31. Xiu L. Pancreatic islet regeneration by ephedrine in mice with streptozotocin-induced diabetes," Am. J. Chin. Med., vol. 29, no. 3–4, pp. 493–500, 2001.
32. Ogata T. Promotion of β-cell differentiation by conophylline in fetal and neonatal rat pancreas," Diabetes 2004; 53(10): 2596–2602.
33. Agrawal D. Diabetes and Traditional Medicine : New Reseach. 2000, [Online]. Available: http:/ www.infinity foundation. com/ mandala/t_es/t_es_ agraw_ diabetes.html.