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Hypoglycemic Effect of Mixed Herbal Extract and Vitamin E in Biphenol A Induced Albino Rats

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Abstract: ***BPA has been found in many common food containers and packaging, and in the epoxy lining of metal food cans, from which, especially after heating, it can leach into food products. BPA can also be stored in adipose tissue. The purpose of this study is to review the available knowledge of epidemiologic evidence on BPA exposure and diabetes, and to know the value of alternative medicine to cure diabetes.***

Keywords: BPA, Diabetes, Herbal extract, Vitamin E, antioxidant.

1. Introduction

Diabetes this dreadful disease is found in all parts of the world and is becoming a serious threat to mankind health. It is caused by the deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. There are lots of chemical agents available to control and to treat diabetic patients, but total recovery from diabetes has not been reported up to this date. Alternative to these synthetic agents, many herbal plants with hypoglycaemic properties are known from across the world. The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. A list of medicinal plants with proven antidiabetic and related beneficial effects and of herbal drugs used in treatment of diabetes is compiled.

BisphenolA (BPA) is an organic synthetic compound employed to produce plastics and epoxy resins. It is used as a structural component in polycarbonate beverage bottles and as coating for metal surface in food containers and packaging. The adverse effects of BPA on human health are widely disputed. BPA has been recently associated with a wide variety of medical disorders and, in particular, it was identified as potential endocrine-disrupting compound with diabetogenic action. Most of the clinical observational studies in humans reveal a positive link between BPA exposure, evaluated by the measurement of urinary BPA levels, and the risk of developing type 2 diabetes mellitus. Clinical studies on humans and preclinical studies on in vivo, ex vivo, and in vitro models indicate that BPA, mostly at low doses, may have a role in increasing type 2 diabetes mellitus developmental risk, directly acting on pancreatic cells, in which BPA induces the impairment of insulin and glucagon secretion, triggers inhibition of cell growth and apoptosis, and acts on muscle, hepatic, and adipose cell function, triggering an insulin-resistant state.

Bisphenol A (BPA) is the main component of the clear hard resin polycarbonate; the widespread diffusion of BPA makes the exposure persistent for human beings. Indeed, BPA has been found in many common food containers and packaging, and in the epoxy lining of metal food cans, from which, especially after heating, it can leach into food products.[1,2] The primary source of exposure to BPA for the general population is diet. The exposure different from the dietary intake is lower than dietary exposure by at least one order of magnitude.[2] BPA is a lipophilic synthetic organic compound that, when metabolized, acquires characteristics of hydrophylicity. In humans, after dietary intake, BPA is absorbed through the gastrointestinal tract and transported to the liver.[2]

In the 1950s, polymer chemists discovered that BPA molecules could be polymerized to make polycarbonate plastic, and it soon became a basic compound in the manufacture of the resin lining food and beverage cans and of the polycarbonate used in food and beverage storage containers. The leaching of BPA out of such products is increased by heating, contact with alkaline/acid substances, and repeated use and exposure to microwaves. Bisphenol A is highly glucuronidated in the liver and is primarily excreted into the bile. However, unconjugated (bioactive) BPA can be found in the blood and, in its glucuronidated form, in urine. Unconjugated BPA circulating in blood indicates an internal exposure to the compound, as does its presence in urine, but in this latter case it also suggests a failure of first-pass conjugation and removal or deconjugation. Furthermore, age, sex, liver function, and physiological status (eg, pregnancy) could influence BPA metabolism. Being lipophilic, BPA can also be stored in adipose tissue. The purpose of this study is to review the available knowledge of epidemiologic evidence on BPA exposure and diabetes, and to know the value of alternative medicine to cure diabetes.

Momordicacharantia: (bitter gourd)
Local Name: Kaattupagar-kai. The plant is commonly known as Bitter guard and has many varieties Momordicacharantia is commonly used as an antidiabetic and antihyperglycemic agent in India as well as other Asian countries. Extracts of fruit pulp, seed, leaves and whole plant was shown to have hypoglycemic effect in various animal models.

Trigonellafoenumgraecum: (fenugreek)
It is found all over India and the fenugreek seeds are usually used as one of the major constituents of Indian spices. 4-hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose stimulated insulin release by isolated islet cells. Administration of fenugreek seeds also improved

glucose metabolism and normalized creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduced hepatic and renal glucose-6-phosphatase and fructose –1, 6-biphosphatase activity. This plant also shows antioxidant activity.

Azadirachtaindica: (Neem)
Hydroalcoholic extracts of this plant showed anti-hyperglycemic activity in streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition in isolated rat hemidiaphragm. Apart from having anti-diabetic activity, this plant also has anti-bacterial, antimalarial, antifertility, hepatoprotective and antioxidant effects.

A. paniculata is an important medicinal plant of *Andrographis* genus. A total number of species of this genus varied in different reports, which comprises either [3,4,5,6,7,8,9]; species. The exact numbers of species of *Andrographis* genus are not validated yet. Total number of chromosomes of AP is 25 and 50 in gametophytic[10] and sporophytic [11]count, respectively. In addition, genotypic differences are important considerations to find out high yielding germplasms.

A. paniculata is an annual, branched, erect, and herbaceous plant which grows in hedgerows throughout the plane lands, hill slopes, waste ground, farms, moist habitat, seashores, and roadsides. It also can be cultivated in garden. Moist shady places, forests, and wastelands are preferable for their well development [12]; [13]This plant grows abundantly in Southern and Southeastern Asia including India, Java, Sri Lanka, Pakistan, and Indonesia, while it is cultivated in India, China, Thailand, Brunei, Indonesia, the West Indies such as Jamaica, Barbados, and Bahamas, Hong Kong, and the tropical areas in America and also in southwestern Nigeria (Jarukamjorn . N and Nemoto.N;[14]

Vitamin E (α-tocopherol) is considered one of the most important dietary antioxidant in biological systems due to its association with cell membrane and its ability to act directly on reactive oxygen species (ROS) preventing peroxidation. Besides the well characterized function of vitamin E as antioxidant alternative roles such as that of a membrane stabilizer, and a regulation of membrane fluidity have been proposed. The protective role of vitamin E on the oxidative stress develops due to antileprosy chemotherapy in leprosy patients was recorded. In the present study is carried out to evaluate the impact of vitamin E supplementation on the blood glucose during BPA administration

2. Materials and Methods

Experimental animals
As the female albino rats involves in the reproductive cycle and disturbs the research so male albino rats 180 - 200 g. 100 days old which were maintained at 24+ 1^0C with alternate twelve hours light /dark periods and animals were fed on a standard laboratory pellet diet and water.

Experimental Protocol
The rats were divided into 4 groups comprising of 2 animals in each group.
Group I Control-sham operated animals (C)
Group II BPA induced for 07 days animals-Control [BPA (EC)]
Group III BPA induced animals after 7 days given vitamin E [T (VIT E)]
Group IV BPA induced animals after 7 days given herb extract T (ME)]
The study was carried out to assess the diabetes in the blood of BPA induced rats and to find the efficacy of vitamin-E and herbal extract supplementation.

Hypoglycemic activity:
Hypoglycemic study was conducted to test the efficacy of the leaf extract, as per the method described earlier in four different experimental models groups and the blood sugar lowering efficacy of the the leaves extract was studied.

Oral Supplementation of BPA
Bisphenol A (BPA) (40mg/kg body wt) was mixed with water and given orally through drinking water bottle.

Vitamin E supplementation
Rats were fed with vitamin E (α-tocopherol) of 200mg/Kg body weight, as reported earlier [15] for 30 days[16]

Estimation of blood glucose:
In each case 200ul of blood sample was collected from the tail vein and estimated with the help of glucometer. The blood samples were collected from the tail vein of rats of four groups and estimated the glucose level with the help of glucometer.

3. Result and Discussion

For blood glucose level, there was a significant difference between normal and BPA induced group (Table I). In the other hand, there was a significant reduction of blood glucose in mixed extract treated in BPA induced rats compared to BPA induced rats without treatment with herbal extract. Interestingly, the reduction of blood glucose showed a better trend. (Table II). The results of effect of mixed extracts of which are expressed as change in blood glucose level are shown in table No.II. More significant anti-diabetic activity was observed. Blood sugar level was increased as in BPA supplemented animals, since it causes a massive destruction of β- cells of islets of Langerhans and inducing. There were similar trend was observed in plasma glucose level as shown in Table. The result show that mixed extract gave a similar regimen as hypoglycemic agent.
In light of the result, present study strongly indicates that mixed extract have good antidiabetic activities, in which this case lowering the effect of BPA induced mild hyperglycemic rats.

Table 1: Effect of BPA

Control rats (C)	Experimental control BPA (EC)
66 mg/dl	107 mg/dl

Table 2: Effect of Mixed Herbal Extract in BPA Induced Animals.

Control rats (C)	Experimental control BPA (EC)	Treated with Mixed Extract at 8th day (end of 1st hour) [T (ME)]	Treated with Mixed Extract at 8th day (end of 3rd hour) [T (ME)]	Treated with Mixed Extract at 8th day (end of 5th hour) [T (ME)]
66 mg/dl	107 mg/dl	103mg/dl	72mg/dl	56mg/dl

Table 3: Effect of Vitamin E on BPA Induced Rats

Control rats (C)	Experimental control BPA (EC)	Treated with Vitamin E at 8th day (end of 1st hour) [T (VitE)]	Treated with Vitamin E at 8th day (end of 3rd hour) [T (VitE)]	Treated with Vitamin E at 8th day (end of 5th hour) [T (VitE)]
66 mg/dl	107 mg/dl	107mg/dl	80mg/dl	69mg/dl

4. Discussion

There is substantial evidence indicating that BPA contributes to the risk of cancer, developmental problems, diabetes, obesity, metabolic syndrome, and possibly also contributes to infertility. The mechanisms at the root of these multiple effects are numerous and involve BPA binding to membrane and nuclear estrogen receptors, interference with other nuclear and non nuclear receptors, alterations in the synthesis or in the metabolism of hormone, and epigenetic deregulation.

A team of researchers from West Virginia University analyzed urine samples collected between 2003 and 2008 as part of the National Health and Nutrition Examination Survey. The results, which were published in the *Journal of Clinical Endocrinology and Metabolism*, showed that higher levels of BPA were associated with an increased risk of developing type 2 diabetes.

BPA acts by mimicking the action of estradiol. The exposure to BPA in inappropriate concentrations, and during an improper time window, can affect multiple organ system development and function, including control of energy balance and glucose homeostasis.

Diabetic nephropathy is the most serious complication in diabetes mellitus, and one of the most important micro vascular complications of diabetic patients. It has been suggested to result from interactions between metabolic and hemodynamic factors involved with hyperglycemia. Currently available drugs for diabetes have a number of limitations, such as adverse effects and high rates of secondary failure[17];[18]This situation has led to the search for alternative therapies from natural products that have low or no side effects and multi-target actions[19]In the present study, the main compound of mixed extract significantly relieved hyperglycemia, in BPA induced diabetic rats. Mixed extract suggesting that it can improve the sensitivity or stimulate secretion of insulin in the BPA-induced diabetic rats. Nevertheless, further research is needed.

Several studies have documented that oxidative stress is accelerated in diabetes mellitus owing to an increase in the production of oxygen free radicals, lipid peroxidation and low-density lipoprotei [20];[21] Here BPA act as a stress creator and produce Free radicals can diffuse intracelluarly and result in mitochondrial enzyme damage and DNA breaks, all of which impair cellular function and contribute to the pathophysiology of diabetes. [22] [23]In the present study, diabetic condition was significantly improved in rats receiving mixed extract. Furthermore, we observed in the present study, diabetic condition was significantly improved in rats receiving vitamin E. An improved condition was seen in mixed extract and vitamin E given groups. Mixed extract given and treated diabetic groups compared with the untreated diabetic control group, the blood sugar levels were reduced when compared to the control group

Extract fed animal has the better potential in the treatment of hyperglycemia observed in diabetic condition. The inference is leaf mixed extract has the best activity profile. The probable mode of action observed that it is necessary to begin the discussion by analyzing the mechanism of action of existing hypoglycemic agents and make an attempt to extrapolate them to the test drug's effect.

These herbal extract promote insulin secretion from the β-cells of Islet of Langerhans. Drugs with this mechanism of action have the tendency to produce hypoglycemia if the dose is increased and in normal glycemic animals also. If the herbal extract have this type of activity they produce good hypoglycemic activity even in normoglycemic rats.

BPA induction in rats induced a blood sugar level increase which was effectively reversed by the administration of vitamin E. A similar protective effect of vitamin E. Vitamin E also restored the BPA-induced increase of blood sugar level of rats in group III. Administration of vitamin E decrease the BPA effect and so thus reduce the blood sugar level of rats in group III. In conclusion, BPA alters the bood sugar level by creating oxidative stress, which could be reversed by vitamin E and mixed extract.

5. Conclusion

The present investigation clearly showed that mixed herb extract crude extract had a very great potential as drug alternative in diabetic patients and related disorder demonstrated significant hypoglycemic activity. In conclusion, our present study reveals that mixed extract has beneficial effects in improving blood glucose in diabetic rats. This study provides experimental evidence that *mixed extract* may be a potential therapeutic agent for hyperglycemia that is associated with diabetic complications including diabetic nephropathy. *Bitter gourd, fenugreek, Neem, Andrographis paniculata, Gymnemasylvestre*

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