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NEUROPROTECTIVE EFFECTS OF PIMPINELLA ANISUM ON NEUROTOXICITY INDUCED BY BISPHINOL A ON NORMAL AND DIABEITC RATS

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ABSTRACT

Objective: Bisphenol A (BPA) was a polycarbonate plastic used in plastic containers, baby's bottle, water bottles, laptops, mobiles, and food canes, etc. It is associated with obesity and insulin resistance. The food and Drug Administration (FAD), The Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA) recommended more study on this material. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia. Diabetes can cause many complications like cardiovascular risk, chronic renal failure, nephropathy etc. The present study was done to know how to decrease the toxic effect of BPA by *Pimpinella anisum* (Anise) on the physiological and neurological parameter on normal and diabetic rats induced by Streptozetocin (STZ).

Methods: Rats involved in this study were divided into eight groups: 1st control group and received citrate buffer, 2nd diabetic group treated with STZ (50mg/kg. b. wt), 3rd BPA group treated with BPA (30mg/kgbwt), 4th Anise group treated with anise oil. (3g/kgb. wt),5th STZ + BPA group combination between STZ and BPA with the same dose, 6th group treated with (STZ+Anise), 7th group treated with (STZ + Anise + BPA) and 8th group received Anise and BPA. All control and treatment were subsisted one month ago. Norepinephrine (NE), Dopamine DA and Serotonin (5HT) were determined in homogenate brain tissue by HPLC.

Results: The results showed the significant increase in NE, DA and 5HT in diabetic rats treated with (STZ), and in diabetic rats with BPA (STZ + BPA) in comparison with vehicle and diabetic (STZ) group. The results also showed a significant increase in glucose, triglyceride, cholesterol, ALT and AST. After treatment with (Anis), a significant decrease in NE, DOP and 5HT in diabetic rats treated with Anise (STZ + Anise) and diabetic rats treated with (Anise + BPA) in comparison with vehicle and diabetic (STZ) group. Thus, from this study,

Conclusion: It is concluded that, (BPA) has neurotoxic and this neurotoxicity was increased with diabetes and decreased by the treatment with anise.

Keywords: Bisphinol A, Streptozetocin, *Pimpinella anisum*, Neurotoxicity.

INTRODUCTION

Bisphenol A (BPA) is an industrial chemical that has been present in many hard plastic bottles and metal-based food and beverage cans, both the National Toxicology Program and the National Institutes of Health and FDA (2011) have some concerns about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children. Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia, which results from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long- term damage, dysfunction and failure of various organs, especially the eyes kidney nerves, hearts and blood vessels (American Diabetes Association, 2011). Hyperglycemia and hyperlipidemia are two important characters of diabetes mellitus in which diabetic patients experience various vascular complications such as atherosclerosis, coronary heart disease, diabetic nephropathy and neuropathy [1].

There was increasing evidence indicating that enhanced production of free radicals may be an important contributing factor in the complications seen in diabetes. Many herbs and plant products have shown hypoglycemic action. *Pimpinella anisum* (anise) essential oil has reportedly antibacterial, antidiabetic, antiviral, insecticidal, expectorant, antispasmodic, and has estrogenic effects [2]. Commercially, anise oil is used to flavor cough syrups, chewing gum, ice cream, toothpaste, mouse bait and licorice-flavored candy, beverages and liqueurs, including anisette ouzo and muscatel wine. Oil is also added to perfumes, tobacco, soaps and skin creams. Many of these properties are due to the presence of anethole in the essential oil. Anise also has a long-standing folk reputation as an aphrodisiac. It is approved by the German Commission E to treat dyspeptic complaints and catarrh of the respiratory tract. Although anise has traditionally been used to encourage lactation. Oxidative stress of BPA plays an important role in the development of toxicity of neurotransmitters in the brain of diabetic rats treated with STZ. *Pimpinella anisum* plays an important role as an antioxidant effect in decreasing the toxicity induced by BPA on neurotransimitter of brain in diabetic rats and decrease hyperglycemia.

MATERIAL AND METHODS

Chemicals

Epinephrine, DA and 5HT Standard for High Performance Liquid Chromatography HPLC and STZ were purchased from SIGMA Company; Anise oil was purchased from MOBACO Company.

The present study was carried out using adult male albino rats obtained from the animal house of National Organization of Drug Control and Research (NODCAR) their average body weights ranged from 180-200g. The animals were housed in standard conditions, where the animals were allowed to access the standard diet and water *ad libtum.*

Animals and experimental design

Animals were divided into two main groups namely

- Non-diabetic groups.
- Diabetic groups.

Each group was divided into 4 sub groups

Non-diabetic group (normal group)

1-control group animal were received 1 ml citrate buffer orally daily for 4weeks.

2-BPA-treated group animals were received BPA in a dose 30 mg/kgb. wt orally for 4weeks.

3-Anise oil treated group animals were received Anise oil orally in a dose 3g/kgb. wt orally for 4 weeks.

4-Anise oil treated group +BPA treated group.

Diabetic group

After the induction of diabetes in rats in a dose (50 mg/kg) according to [3]. Animals were subdivided into 4 groups according to medication. Drug medications were started at the 3rdday of diabetes induction.

1- STZ-group animals were served as diabetic control group (50mg/kgb. wt).

2- STZ+BPA group diabetic animals were received a daily dose of BPA (25mg/kg).

3- STZ + Anise group diabetic animals were received Anise oil 3 gm/kg daily dose of BPA (25mg/kg).

4- STZ + BPA + Anise group diabetic animals were received a daily dose of BPA + Anise (25mg/kg+3g/kg).

In this study induction of diabetes was done by the injection of a single dose of STZ (50 mg / kg b-wt) intrapersonal (i. p) in citrate buffer pH 4.5 [3].

The consistent level al hyperglycemia were reached on the third day of injection and were indicated by glucose level monitoring experiment. The treatments started 3 days after the induction of diabetes and drugs was given daily for a month. Blood samples and brain were taken after 4 weeks. Blood was collected from the retro plexus orbital puncture, which is a simple, convenient and successful procedure that allows bleeding of the same animal more than one time with minimal stress [4]. Brain will homogenate in 70% methanol: water then centrifuge at 5000 r. p. m. Supernatant was taken for determination of neurotransmitter Norepinpherne, DA and 5HT by HPLC.

RESULTS

Effect of treatment with Pimpinella Anisum and Bisphenol A (Anise, BPA) and their combined (Anise + BPA) of Serum Glucose concentration (mg/dl) In Non-diabetic and Diabetic Male Albino Rats

The effect of BPA (30 mg/Kg b. wt), Anise (3 gm/kg b. wt) and their combined treatment (BPA + Anise) on serum glucose concentration is represented in Tab. (1) and Fig. (1) After treatment with anti-diabetic medicinal plant Anise and BPA (Anise and BPA) for 4 weeks, there were no different changes. On the other hand diabetic groups showed a significant increase (P<0.05) in blood glucose level (347.42 mg/dl) as compared with control (83.71 mg/dl). Meanwhile, treatment of diabetic animals with Anise and Anise + BPA showed significant decrease in glucose concentration (136.28 and 140.42mg/dl) respectively as compared with diabetic non-treated one (347.42 mg/dl) (while diabetic rats treated with BPA were (330.5mg/dl).

Effect of treatment with Pimienella Anisum (Anise,BPA)and their combined (Anis+BPA)on Serum TG Concentration (mg/dl)In Non-diabetic and Diabetic Male Albino Rat

The effect of BPA (30 mg/Kg b. wt), Anise (3 gm/kg b. wt) and their combined treatment (BPA + Anise) on serum TG concentration is represented in Tab. (1) and Fig. (1) After treatment with anti-diabetic medicinal plant Anise and BPA (Anise and BPA) for 4 weeks, there were no different changes. On the other hand diabetic groups showed a significant increase (P<0.05) in blood TG level (136.50 mg/dl) as compared with control (77.50 mg/dl). Meanwhile, treatment of diabetic animals with Anise and Anise + BPA showed significant decrease in TG concentration (130.90 and 130.15mg/dl) respectively as compared with diabetic non-treated one (136.50).

Effect of treatment with Pimpinella Anisum (Anise, BPA) and their combined (Anise+ BPA) on Serum cholesterol Concentration (mg/dl) In Non-diabetic and Diabetic Male Albino Rats)

The effect of BPA (30 mg/Kg b. wt), Anise (3 gm/kg b. wt) and their combined treatment (BPA + Anise) on serum Chol(concentration is represented in Tab. (1) and Fig. (1) After treatment with anti-diabetic medicinal plant Anise and BPA (Anise and BPA) for 4 weeks, there were no different changes. On the other hand diabetic groups showed a significant increase (P<0.05) in blood cholesterol level (123.71 mg/dl) as compared with control (51.14 mg/dl). Meanwhile, treatment of diabetic animals with Anise and (Anise + BPA) showed significant decrease in cholesterol concentration (90.11 and 90.23 mg/dl) respectively as compared with diabetic non-treated one (123.71 mg/dl) (while diabetic rats treated with BPA was (121.11mg/dl).

Effect of treatment with Pimpinella Anisum (Anise, BPA) and their combined (Anise +BPA) on Serum AST Concentration (mg/dl)In Non-diabetic and Diabetic Male Albino Rat

While serum AST activity of non-diabetic rats decreased significantly (P<0.05) after 4 weeks treatment with Anise, BPA and Anise+BPA (43.93, 42.99and 43.99 U/ml), as compared to control group (45.02 U/ml). At the end of the experiment, diabetic non-treated group showed the significant increase (P<0.05) in their AST activity (84.71 U/ml), as compared to control group (45.02 U/ml). Treatment of diabetic animals with (Anise, BPA and Anise+BPA) for 4 weeks, induced significant decrease (P<0.05) in their AST activity (70.90, 83.71 and 71.38 U/ml), respectively as compared to diabetic control group (84.71 U/ml).

Effect of treatment with Pimpinella Anisum (Anise, BPA)and their combined (Anise+ BPA) on Serum ALT Concentration (mg/dl)In Non-diabetic and Diabetic Male Albino Rat

Serum ALT activity of non-diabetic rats decreased significantly (P<0.05) after their treatment with Anise, BPA and Anise+BPA for 4 weeks (27.42 and 39.42 and 29.42 U/ml), respectively as compared to control group (47.71 U/ml). In contrast, serum ALT activity of diabetic control group exhibited significant increase (P<0.05) after 4 weeks (100.28 U/ml), as compared to control group (47.71U/ml). Treatment of diabetic animals with (Anise, BPA, Anise+BPA) for 4 weeks, induced the significant decrease in their serum ALT activity (75.85, 95.85 and 85.42 U/ml), respectively as compared to diabetic control group (100.28 U/ml).

DISCUSSION

Diabetes Mellitus is a metabolic disorder associated with insulin deficiency which not only affects the carbohydrate metabolism but also is associated with various central and peripheral complications. [5]. Chronic hyperglycemia during diabetes mellitus is a major initiator of diabetic microvascular complications like retinopathy, neuropathy, nephropathy Glucose processing uses a variety of diverse metabolic pathways. [6] decided that chronic hyperglycemia can induce multiple cellular changes leading to metabolic disorders. The central nervous system (CNS) neurotransmitters play an important role in the regulation of glucose homeostasis. These neurotransmitters mediate rapid intracellular communications not only within the central nervous system but also in the peripheral tissues.[7] They exert their function through receptors present in both neuronal and non neuronal cell surface that trigger second messenger signaling pathways.

Neurotransmitters have been reported to show significant alterations during hyperglycemia resulting in altered functions causing neuronal degeneration [8]. Neurochemical and neuro-imaging evidences have been reported to show regionally selective sympathetic denervation in diabetic neuropathy. The changes in the brain monoamines during experimental diabetes have been reported that the 5HT content is doubled in the hypothalamus with no apparent alteration of its metabolite 5-hydroxy indole acetic acid (5-HIAA) levels, suggesting a reduced release [9]. In this study the neurotransmitters NE, DA and Sero showed significant increase in groups treated with STZ and STZ+BPA (P<0.05) and this result was agree with [10]. who decided that in the brain stem, 5HT and DA with the relative metabolites 5-HIAA and dihydroxyphenylacetic acid (DOPAC) and noradrenaline are significantly increased. Insulin deficiency is the major factor involved as a trigger of the monoaminergic changes in the diabetic brain STZ induces diabetes produced marked alterations of monoamine concentrations in the

brain regions of rats [11]. And agree with [7] who decided that the effects of streptozotocin (STZ)-induced diabetes on DA and 5HT release in revealed that striatal DA release increased in acute diabetic state and this release depleted during the chronic state.

Table 1: Effect of treatment with *Pimpinella anisum* (Anise + BPA) on biochemical parameter in serum concentration (mg/dl) in non-diabetic and diabetic male albino rat

Groups	Glucose	TG	Chol	AST	ALT
Control	83.71±1.83	78.79±0.12	51.14±0.44	45.02±1.32	47.71±1.06
Anise	73.81±0.96	77.50±0.30	43.18±1.43	34.93±0.17	27.42±0.48
BPA	85.82±0.11	76.5±0.12	50.90±0.16	42.99±0.20	49.71±5.71
BPA + Anise	74.70±0.66	77.9±0.73	40±0.43	43.99±0.32	29.42±0.23
STZ	347.42±8.55	136.5±0.56	123.71±2.31	84.71±2.37	100.28±4.99
STZ+BPA	330.5±1.83	135.6±0.9	121.11±3.1	83.71±1.59	95.85±0.63
STZ + BPA + Anise	149.42±2.85	130.15±0.25	91.23±0.15	71.38±2.15	85.42±0.71

Data represent the mean ± S. E. M. of observations from 8 rats, Significantly different from control group at P<0.05. ,Significantly different for (BPA + Anise) from BPA group at P<0.05, Significantly different for (STZ + Anise, STZ + PBA and STZ + Anise + PBA) from STZ group at P<0.05.

Table 2: Effect of treatment with Pimpinella Anisum (Anise+BPA) on Neurotransmitter of Brain Tissues Concentration (mg/dl) In Non-diabetic and Diabetic Male Albino Rat

	NE	Dopamine	Serotonin
Control	0.67 ± 0.035	1.25 ± 0.057	1.24 ± 0.056
Anise	0.69 ± 0.034	1.1 ± 0.05	1.33 ± 0.061
BPA	1.13 ± 0.057a	1.79 ± 0.082a	1.42 ± 0.065
BPA + Anise	0.91 ± 0.046ab	1.69 ± 0.077a	1.33 ± 0.06
STZ	1.41 ± 0.073a	2.46 ± 0.15a	1.98 ± 0.088a
STZ + Anise	1.21 ± 0.062ac	2.15 ± 0.13ac	1.46 ± 0.064c
STZ+PBA	1.89 ± 0.096ac	2.51 ± 0.09a	2.24 ± 0.098ac
STZ + Anise + PBA	1.13 ± 0.057ac	2.02 ± 0.073ac	1.93 ± 0.085a

Data represent the mean ± S. E. M. of observations from 8 rats, Significantly different from control group at P<0.05, Significantly different for (BPA + Anise) from BPA group at P<0.05, Significantly different for (STZ + Anise, STZ + PBA and STZ + Anise + PBA) from STZ group at P<0.05.

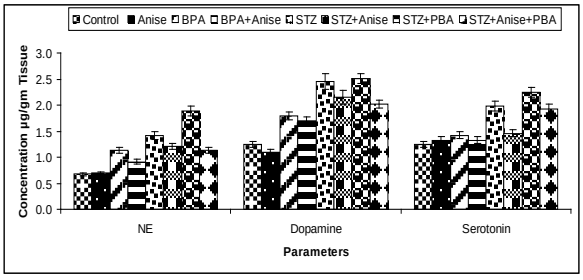

Fig. 1: Effect of treatment with Pimpinella Anisum (Anise+BPA) on Neurotransmitter of Brain Tissues Concentration (mg/dl) In Non-diabetic and Diabetic Male Albino Rat

The progression of diabetes is associated with an impaired ability of the neurons in the CNS to release neurotransmitters resulting 10 behavioral changes [11] and diabetes provide a revealant example of endogenous choronic oxidative stress and hyperglycemia thus we evaluated the brain oxidative stress and this oxidative stress increased by BPA this results was agree with [12] who suggested the oxidative stress causes oxygen radicals formation with resultant neurodegenerative and possibly plaque formation in the central nervous system. Also BPA was reported to bind with G-protein coupled receptor (GPER) and play a role in pancreatic islet cell function and glycemic control,bone growth, cardiovascular complication [13-14]. BPAs, activities for receptors involved in neural activities were apparent at higher concentrations like serotonin receptors 6 (HTR6), dopamine receptors 2(DRD2) [15] serotonin 5-HT6 receptors are located primarily the straiatum, olfactory tubercles, nucleus accumbens and hippocampus function of 5-HT6 receptors include modulation of cholinergic and dopaminergic neurotransmission and they have a role in spatial learning and memory [16-17]. Also diabetic groups showed a significant increase in glucose, triglyceride, cholesterol, total protein, AST and ALT (p>0.01) as compared with control non diabetic rats. This result was agreed with [18].

In the present results revealed that the Pimpinella Anisum (Anise) caused hypoglycemia and decreased the glucose level in control (non-diabetic animals, this agree with (11, 19) whom decided that Anise increase insulin secretion from pancreatic β-cells. In diabetic rats treated with STZ the glucose level was elevated this agree with [18], but the effect of anti diabetic medicinal plant (Anise) appeared significantly by decreasing the glucose levels. this decreasing expanded all the time of experiment,(4weeks) comparing with diabetic animals. this results agree with (1, 8, 20). also treatment with Anise, Anise + BPA decrease the AST, ALT, TG, and Chol in diabetic rats compared with diabetic rats treated with STZ. this results agree with [21] and. Also anise oil acts as antioxidants play an important role to protect the body against the oxidative stress and free radical damages which are the cause of various elements such as diabetes. heart disease, cancer, brain dysfunction [22].

In a study done on the antioxidant effect of anise oil (anthole) [9]. Amongst many herbal oils anise has a beneficial effects on memory disorder, depression, cerebral ischemia and Alzheimer disease [23-24]. In Alzheimer s disease, the enzymes acetylcholine esterase (AchE) is responsible for degrading and inactivating acetylcholine which is a neurotransmitters substance, involved in the signal transferring between the synapses [23-24]. Because the antimicrobial, anti-inflammatory antispasmodic and complicated disease like diabetes and Alzheimer s disease Acetylcholine esterase inhibitors drugs act by counteracting the acetylcholine in the brain [25-26]. The antioxidant effect of the pimpinella anisum decrease the neurotoxic effects of BPA and decrease diabetes by lowering effects of glucose cholesterol, TG and lipid profile [9, 2].

CONCLUSION

It is concluded that, the *Pimpinella anisum* oil has neuroprotective and antioxidant effect on BPA neurotoxicity and oxidative stress induced by STZ on male albino rats.

CONFLICT OF INTERESTS

Declared None

REFRANCES

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