IJPSR (2018), Volume 9, Issue 3 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 June, 2017; received in revised form, 10 August, 2017; accepted, 17 September, 2017; published 01 March, 2018

PROTECTIVE EFFECT OF QUERCETIN ON BISPHENOL A - INDUCED ENZYMATIC CHANGES IN TESTIS OF MICE

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Keywords:

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ABSTRACT: Bisphenol A is well known endocrine disturbing chemical. Evidence has demonstrated that exposure to certain levels can cause toxic effect in humans and laboratory animal models. Quercetin is consistently the most active of the flavonoids in experimental studies. The present investigation was an attempt to evaluate the effect of Bisphenol A on testis and its amelioration by quercetin. Inbred Swiss strain male albino mice were orally administered with BPA (80, 120 and 240 mg/kg body weight/day) for 45 Days. On the completion of treatment, animals were sacrificed, testis was isolated and used for evaluation of energy metabolism (SDH and ATPase activity) and phosphatases activity (ACP, ALP). The results revealed that oral administration of BPA for 45 days caused significant dose-dependent reduction in activities of ATPase and SDH. However, ACP and ALP activities were significantly dose-dependent increased in BPA treated mice. Oral administration of Quercetin (30, 60 and 90 mg/kg body weight/day) along with high dose of BPA (240 mg/kg body weight/day) for 45 days caused significant amelioration in all biochemical parameters as compared to high dose of BPA treated group. Present study concludes that BPA causes reduction in energy metabolism and induces the activity of phosphatases. The effect was significant and dose-dependent. This amelioration in toxic effect of BPA might be due to antioxidant properties of quercetin.

INTRODUCTION: Interest in dietary phenolics has increased recently, due to their antioxidant properties (free radical scavenging and metal chelating) and their possible beneficial implications in human health. Quercetin (3, 3', 4', 5, 7-pentahydroxyflavone) is a natural polyphenolic flavonoid widely found in edible plants such as fruits, vegetables, herbs, grains and beverages (*i.e.* tea, red wine) [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(3).1256-62

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(3).1256-62

It is a versatile molecule, owing to its specific chemical structure, counteracts oxidative stress generated as a result of reactive oxygen species (ROS), have many pharmacological properties including antioxidant [2 - 4], neurological, antiviral [5, 6], anticancer [7, 8], cardiovascular [9, 10], antimicrobial [11], anti-inflammatory agent [12], Hepatoprotective [13, 14] and fertility [15, 16]. Bisphenol - A [2, 2-bis (4-hydroxyphenyl) propane] (BPA) is an important environmental contaminant [17].

Exposure to BPA is widespread and associated with a wide range of health outcomes in animal and human studies [18, 19]. BPA is an important component of polycarbonate and epoxy resins. It is mainly found in the composition of a wide variety of polycarbonate plastic, flame retardants, dental

sealant resins, and liners for food packaging [20, 21]. It is a known endocrine disruptor is a monomer of polycarbonate plastic and a constituent of epoxy and polystyrene resins [18, 22]. Food is considered as the main source of exposure to BPA as it leaches out from coatings [16, 23].

Various studies suggested that trace amounts of BPA also show estrogenic activity even at concentrations as low as 1 ng/l level [24 - 26]. Since a weak estrogen-like activity of BPA was reported by researchers, its effects on human health have become of emergent concern. BPA orally administered could easily cross the placental barrier and enter the fetus in animal experiment [27, 28].

Bisphenol A shows potential acute, short-term and sub-chronic toxicity [29 - 31]. Studies have shown that BPA can cause injury in the liver, kidney, brain and other organs in rodents [32 - 34]. Moreover, BPA easily crosses the blood-brain and placental barriers; it can affect the developing nervous system in fetuses, infants and young children [35]. Oral exposure to BPA has been reported to interfere with proliferation of the cell cycle in intermediate (neural) progenitor cells (IPCs) and neurogenesis in developing neocortex [36]. Therefore, the present study was designed to investigate the possible sub chronic toxic effect of BPA on testis of mice and mitigation of its toxicity by quercetin in testis of mice.

MATERIALS AND METHODS:

Chemicals: Quercetin and bisphenol A were acquired from Hi Media Laboratories Pvt. Ltd., Mumbai, India. Olive oil was obtained from Figaro, Madrid, Spain. All the other chemicals used in the study were of AR grade.

Experimental Animals: In this study, inbred healthy adult Swiss strain male albino mice weighing 35 - 40 gm were obtained from Cadila pharmaceutical Research Center, Ahmedabad, India. Animals were kept in the Animal House of Zoology Department of Gujarat University, Ahmedabad, India. They were housed in an air - conditioned room at a temperature of 25 ± 2 ºC and 50 - 55% relative humidity with a 12 h light / dark cycle throughout the experiment. Animals were fed with certified pelleted rodent feed supplied by Amrut Feeds, Pranav Agro Industries Ltd., Pune, India and potable water *ad libitum*. All the experimental protocols were approved by the Committee for the Purpose of Control and Supervision of Experiment on Animals (Reg. – 167/1999/CPCSEA), New Delhi, India. Animals were handled according to the guidelines published by Indian National Science Academy, New Delhi, India (1991).

Dose Selection: Different doses of BPA used for treatment were bases on its LD_{50} value [37] (240, 120 and 80 mg/kg bw/day respectively). Animals were treated orally for 45 days. For the amelioration of BPA induced toxicity, different doses of quercetin (30, 60 and 90 mg/kg bw/day) were selected based on the study of Sangai and Verma (2014) [38].

Experimental Design: Experimental Protocol is shown in **Table 1**. Mice were randomly divided into nine groups, each containing 10 animals. Treatment schedule of the animals was as follows. Animals from group I (untreated control) were kept untreated and given free access to feed and water. Group II (vehicle control) animals were administered with olive oil (0.2 ml/animal/day), which has been used as vehicle to dissolve bisphenol A. Group III (antidote control) animals were treated with quercetin (90 mg/kg bodyweight/day), which has been used for amelioration of BPA - induced toxicity.

Animals of group IV, V and VI received three different doses of bisphenol A (80, 120 and 240 mg/kg bw/day) for 45 days. Animals of group VII, VIII and IX received three different doses of quercetin (30, 60 and 90 mg/kg bw/day) along with high dose of BPA (240 mg/kg bw/day). All treatments were given orally using a feeding tube attached to hypodermic syringe for 45 days. Animals were sacrificed on 46th day by using mild anaesthesia and the testis was dissected out, blotted free from blood and used for biochemical analysis.

Biochemical Analysis:

Analysis of Energy Metabolism: The ATPase (E.C.3.6.1.3) activity in testis of control and all treated groups of animals were assayed by the method of Quinn and White (1968) [39]; while inorganic phosphate liberated was estimated using the method of Fiske and Subbarow (1925) [40]. The enzyme activity was expressed as µ moles

inorganic phosphate released/mg protein/30 min. The activity of SDH (E.C.1.3.99.1) was estimated in the testis of control and all treated groups of animals according to the method of Beatty *et al.,* (1966) [41]. The enzyme activity was expressed as µg formazon formed/mg protein/15 min.

TABLE 1: EXPERIMENTAL PROTOCOL

	Experimental groups	Numbers of animal	Duration (days)	Necropsy
	Control groups			
1	Untreated control	10	45	46th
2	Vehicle control (0.2 ml olive oil/animal/day)	10	45	46th
3	Antidote control (90 mg quercetin/kg body weight/day)	10	45	46th
	BPA- treated groups			
4	BPA-low dose (80 mg/kg body weight/day)	10	45	46th
5	BPA-medium dose (120mg /kg body weight/day)	10	45	46th
6	BPA-high dose (240 mg/kg body weight/day)	10	45	46th
	BPA-HD + quercetin- treated groups			
7	BPA HD + quercetin (30 mg/kg body weight/day)	10	45	46th
8	BPA HD + quercetin (60 mg/kg body weight/day)	10	45	46th
9	BPA HD + quercetin (90 mg/kg body weight/day)	10	45	46th

Phosphatases Activity: Acid phosphatise (E.C.3.1. 3.2) and alkaline phosphatise (E.C. 3.1.3.1) activity was estimated in testis by the method of Bessey *et al.,* (1946) [42]. The phosphatases activity in testis was expressed as µmoles p-nitrophenol released/mg protein / 30 min.

Statistical Analysis: The results were expressed as the mean ± SEM. The data were statistically analyzed using one way analysis of variance (ANOVA) followed by Tukey's post hoc test in Graph pad prism 6 (graph pad, software, USA). Statistically significance was accepted with $p < 0.05$. Correlation Coefficient was measured to estimate the strength of linear association between two Variables.

RESULTS: The effect of BPA on activities of enzymes in testis and its possible amelioration by pre-treatment with quercetin is shown in **Table 2**. No significant difference was observed in activities of enzymes in testis of different control groups of animals (Groups I - III). BPA treatment caused significant ($p < 0.05$) dose-dependent decrease in ATPase ($r = 0.926$) and SDH ($r = 0.962$) activities as compared to untreated control. Maximum alteration observed was up to 48.70% and 55.44% for ATPase and SDH respectively in high dose BPA-treated animals (Group VI) compared to vehicle control (**Graph 1**). On the other hand, BPA treatment (Group IV - VI) caused significant ($p < 0.05$) increase in ACP (BPA-LD: 40.68%, BPA-MD: 102.98%, BPA-HD: 179.77%) and ALP (BPA-LD: 72.54%, BPA-MD: 173.87%, BPA - HD: 327.83%) activities in testis of BPA - treated mice which was dose-dependent ($r = 0.899$, 0.938 respectively) (**Graph 2**). Oral administration of quercetin treatment along with BPA-HD caused significant ($p < 0.05$), dose-dependent increase in ATPase ($r = 0.972$) and SDH ($r = 0.926$) activities. In all these enzyme activities, maximum amelioration was observed in 90 mg/kg bw/day dose of quercetin along with BPA - HD as per calculated by organoprotective index (**Table 2**). Similarly, Oral administration of quercetin along with BPA-HD (Group VII - IX) caused significant ($p < 0.05$) decrease in ACP and ALP activities as compared to BPA - HD (Group VI) which was dose-dependent ($r = 0.886$, 0.885 respectively).

TABLE 2: AMELIORATIVE EFFECT OF BPA-INDUCED CHANGES ON LIPID PEROXIDATION AND ENZYMATIC ANTIOXIDANTS IN TESTIS OF MICE

S. no.	Experimental group	Energy metabolism		Phosphatase	
		ATPase	SDH	ACP	ALP
	Control groups				
1	Untreated control	2.505±0.032	23.143±0.195	1.247±0.085	0.634±0.034
2	Vehicle control (0.2 ml olive oil / animal / day)	2.500±0.071	23.066±0.504	1.253±0.149	0.622±0.036
3	Antidote control (90 mg quercetin / animal / day)	2.480±0.044	22.979±0.113	1.257±0.055	0.637±0.012
	BPA-treated groups				
4	BPA-Low dose (80mg/kg bodyweight/day)	2.124±0.041[a] (15.03)	17.874±0.297[a] (22.51)	1.763±0.071[a] (40.68)	1.073±0.034[a] (72.54)
5	BPA-Medium dose (120 mg/kg bodyweight/day)	1.586±0.063[a] (36.54)	13.848±0.481[a] (39.96)	2.543±0.097[a] (102.98)	1.703±0.052[a] (173.87)
6	BPA-High dose (240 mg/kg bodyweight/day)	1.282±0.040[a] (48.70)	10.278±0.257[a] (55.44)	3.505±0.138[a] (179.77)	2.661±0.120[a] (327.83)
	HD BPA (240 mg/kg body weight) + quercetin treated groups				
7	BPA-HD + quercetin (30 mg/kg body weight/day)	1.543±0.022[b] (21.39)	14.815±0.515[b] (35.48)	3.062±0.039[b] (19.66)	2.107±0.111[b] (27.16)
8	BPA-HD + quercetin (60 mg/kg body weight/day)	2.066±0.026[b] (64.35)	17.358±0.468[b] (55.37)	2.371±0.078[b] (50.36)	1.491±0.039[b] (57.36)
9	BPA-HD + quercetin (90 mg/kg body weight/day)	2.388±0.017[b] (90.84)	21.196±0.546[b] (85.38)	1.513±0.096[b] (88.45)	0.780±0.022[b] (92.24)

Values are mean ± SEM; n = 10.

Level of significance: [a]$p < 0.05$, as compared to vehicle control; [b]$p < 0.05$, as compared to BPA-HD-treated.

No significant difference was noted between different control groups (Groups I - III).

Units: ACP- µ moles p-nitrophenol released/mg protein / 30 min; ALP- µ moles p-nitrophenol released / mg protein / 30 min; ATPase - µ moles inorganic phosphate released/mg protein / 30 min; SDH- µg formazon formed/mg protein / 15 min.

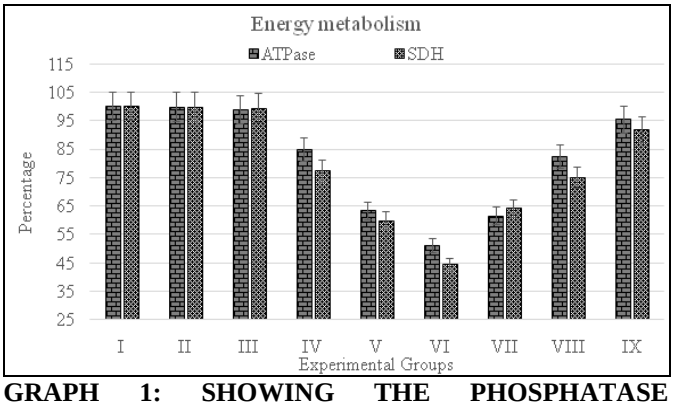
DISCUSSION: Bisphenol A is well-known xenoestrogenic chemical released in environment. Earlier studies have revealed that BPA treatment caused significant decrease bodyweights as well as testis weight [43]. Histopathological alteration was found in testis of BPA treated mice testis [44]. The reproductive toxicity of BPA is caused by interaction with androgen and estrogen receptors [45, 46]. Testicular toxicity of BPA has been reported by Takahashi and Oishi (2003) [47].

In present study we have administered Bisphenol A for 45 days to study sub-chronic exposure. We studied that Bisphenol A reduces the energy metabolism by reducing the activities of enzymes involved in energy metabolism. In present study we studied that BPA treatment for 45 days caused significant, dose-dependent decrease in ATPase and SDH activities in testis of mice. Mitochondria are the targets of several environmental toxicants including environmental estrogens [48]. SDH is a key enzyme of mitochondrial Krebs cycle and it is mainly concerned with aerobic oxidation of acetyl coA and generation of ATP. Among Krebs cycle dehydrogenases, SDH is very active than any other enzyme [49]. ATPase is required for enzymatic hydrolysis of ATP which is important for intracellular transfer of energy. Reduction in ATPase and SDH activity could be due to alteration in mitochondria. A study by Nakagawa and Tayama [50], revealed that the incubation of hepatocytes with BPA elicited a concentration and time-dependent cell death, accompanied by loss of intracellular ATP and total adenine nucleotide pools. Co-administration of quercetin along with BPA significantly increased ATPase and SDH activities in tissues might be preventing mitochondrial dysfunction from ROS due to its antioxidative property. It has been previously reported that quercetin potentially reduce BPA-induced oxidative stress and mitochondrial dysfunction in mice [51, 52].

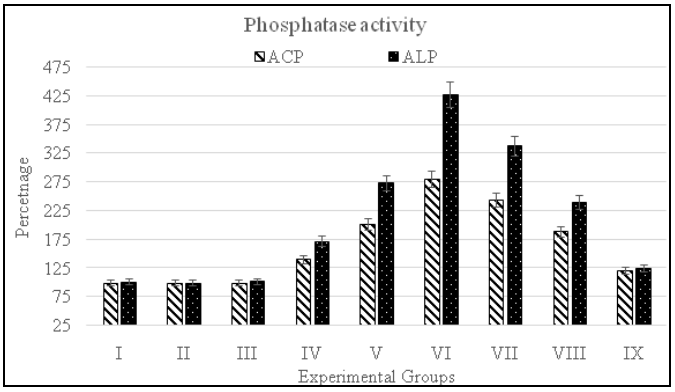
Acid phosphatase is a marker enzyme for the lysosomal integrity and important for the tissue reorganization and tissue repair [53]. Oral administration of BPA for 45 days caused significant dose - dependent increase in ACP activity in testis of mice. This might be due to increased release of lysosomal enzyme by

damaging lysosomal integrity causing lysis of cell. Activity of ALP was also significantly increased by BPA treatment in testis of mice. Alkaline phosphatase is a marker enzyme for plasma and endoplasmic reticulum. Bisphenol A treatment causes alteration in endoplasmic reticulum [45 - 56]. This could be the reason for increasing ALP activity. However, quercetin treatment significantly decreased ACP and ALP activities by preventing damage to the tissue [57].

Different concentrations of quercetin caused significant reduction in ACP and ALP activities as well as increase the activities of ATPase and SOD and restored these levels close to corresponding control values. Quercetin increases the body's endogenous antioxidants to reduce oxidative damage. The anti-oxidant properties are largely a function of the chemical structure of quercetin, particularly the presence and location of the hydroxyl (-OH) substitutions and the catechol-type B-ring [58 - 62]. Similar investigations have also been reported antioxidant properties of quercetin [63 - 65].



GRAPH 1: SHOWING THE PHOSPHATASE ACTIVITY (%) ATPase - Adenosine triphosphatase; SDH - Succinate dehydrogenase



GRAPH 2: SHOWING THE PHOSPHATASE ACTIVITY (%) ACP - Acid phosphatase; ALP - Alkaline phosphatase

CONCLUSION: Present study revealed that treatment of BPA for 45 days causes lysosomal and mitochondrial enzymatic changes in experimental animals by disturbing the balance between ROS and antioxidant defenses system in testis. However co-administration of quercetin for 45 days caused significant amelioration in enzymatic activities. This study concludes that bisphenol A causes toxicity in testis of mice by disturbing mitochondrial and lysosomal integrity; it can be mitigated by the quercetin.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: The authors do not have any conflict of interest.

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How to cite this article:
Samova S, Doctor H and Verma R: Protective effect of quercetin on Bisphenol A - induced enzymatic changes in testis of mice. Int J Pharm Sci & Res 2018; 9(3): 1256-62. doi: 10.13040/IJPSR.0975-8232.9(3).1256-62.