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Research Article

CHOLINERGIC INHIBITORY EFFECTS OF *BACOPA MONNIERI* AND ACEPHATE IN THE KIDNEY OF RAT

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A B S T R A C T

The leaves of *Bacopa monnieri* are very effective in a wide range of health problems. The present study was performed to investigate the effect of Bacopa extract and acephate on Acetylcholinesterase activity, its kinetics and histological parameters in the kidney of male albino Wistar rats. Rats were divided into four groups of five animals each. Group, I served as control and given orally groundnut oil. Group II, III and IV have given acephate and leaf extract of *Bacopa monnieri* each alone and in their combinations respectively. Acetylcholinesterase (AChE) activity was measured by Ellman's method and AChE kinetics was analyzed by Line Weaver Burk plots. The Kidney showed significant differences ($P < 0.05$) of 65-71% AChE inhibition in the test groups intoxicated with *Bacopa monnieri* and acephate when compared with the control. The kinetic study reveals the competitive nature of AChE inhibition of both *Bacopa monnieri* and acephate. On the other hand, acephate showed histopathological alterations in kidney like necrosis in renal tubules and space in Bowman's capsule layer. However, *Bacopa monnieri* causes mild changes in the kidney structure.

INTRODUCTION

Over the past few decades, several studies have shown detrimental effects on animals and humans due to man-made chemicals and other toxicants (Delfino, 2009). They cause acute toxicity due to their ability of the phosphorylation of acetylcholinesterase (AChE, EC: 3.1.1.7), the enzyme which hydrolyses neurotransmitter acetylcholine in muscular and neural synaptic clefts, leading to the irreversible inhibition of its active site and resulting overstimulation of postsynaptic cholinergic receptors due to the accumulation of the neurotransmitter acetylcholine in synapses and used as marker of OP exposure and effects (Fulton and Key, 2001). Most of the OP pesticides are lipophilic hence interact with the tissues and rapidly absorbed and accumulated in fat, liver, kidneys and salivary glands (Vale, 1988). AChE is a widely known biomarker of exposure to organophosphate pesticides due to its sensibility to such compounds (Rodriguez and Gold, 2000).

Anticholinesterases play important role in the treatment of Alzheimer's disease (AD), a progressive neurodegenerative disorder associated with memory impairment and cognitive deficit.

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It is characterized by low levels of acetylcholine in the brain of AD patients. The inhibition of acetylcholinesterase (AChE), an enzyme that catalyzes acetylcholine hydrolysis, increases the levels of acetylcholine in the brain, thus improving cholinergic functions in AD patients. Inhibition of AChE serves as a new approach for the treatment of Alzheimer's disease (AD). Many AChE inhibitors are presently used for the suggestive treatment of AD. Currently, available drugs donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne, Reminyl), and tacrine (Cognex) for the treatment of AD have limited efficacy and some kind of side effect. Galantamine, a recognized drug for AD, and huperzine A, another promising compound, have derived from plants (Tonduli *et al.,* 2000*). Bacopa Monnieri* acts as the inhibitor of AChE in rat cortex and hippocampus (Tembhre *et al.,* 2015). Therefore, in search of natural sources of AChEI, several studies on the AChE inhibiting plants have been reported over the last years (Houghton, *et al.,* 2006; Williams, *et al*., 2011; Mukherjee, *et al.,* 2007). There are abundant plants in nature having potential AChE inhibitory power and have therapeutic potential against AD (Shekarchi, *et al*., 2013; Kaur *et al.,* 2017).

The toxicity of organophosphates in animals has received attention since past decades. Kidney, the major detoxification organ for many xenobiotics is frequently susceptible to nephrotoxic effects. The kidney approximately receives about 20-25% of the resting cardiac output. Therefore, it receives the

relatively higher load of drug or chemical. The process involved in forming concentrated urine also serves to concentrate potential toxicants into tubular cells (Rekha *et al.,* 2013). Nephrotoxicity is one of the toxic manifestations of many pesticides after its chronic and acute exposure as well.

Acephate was chosen as test compound because it is the toxic one of organophosphate (OP) pesticides for vertebrates and it is used extensively in agricultural crop production and in public health programs (Luiz Roberto, *et al.,* 2005) and consequently contaminate food and water. Several studies have shown that OP pesticides caused biochemical and histological alterations in various tissues (Barnett and David, 1984; Chamber *et al.,* 1990; Abdeen *et al*., 1994). Dermal exposure of cypermethrin to rats caused congestion of vessels, diffuse and focal lymphocytic infiltration, edema and necrosis of proximal tubules of the kidney (Inayat *et al.,* 2007).

Bacopa monnieri is known to improve memory and cognitive abilities by improving synaptic communication (Singh and Dhawan, 1997). It enhances the growth and proliferation of dendrites, the "branched" nerve cell extensions along which neural impulses travel, enhancing neural signaling. *Bacopa Monnieri* has shown anticholinergic effects on rat (Ahirwar *et al.,* 2012; Le XT *et al.,* 2013; Sireeratawong *et al.*, 2016). Because of the potential ethnobotanical and pharmacological applications of the plant, this study was designed to investigate the possible efficacy of the *B. monnieri* extract and acephate on acetylcholinesterase inhibitory activity, kinetics and histopathology in the kidney of male albino Wistar rats.

MATERIALS AND METHODS

Preparation of Plant extracts: Authenticated plants of *Bacopa monnieri* were collected from Jawaharlal Nehru Agriculture University, Jabalpur (M.P.), India. The fresh leaves and twigs were dried in the shade and ground to powder. The dried powder was extracted twice with 90 % ethanol at the ratio of 1 g: 7 ml in a Soxhlet apparatus. The extract was subjected to evaporation of solvent at room temperature till the semisolid mass remained. The yield was 10 % of the fresh weight. The extract was kept in deep freeze until used for the experiments.

Chemicals: 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) and acetylthiocholine iodide (ATCI) were obtained from Hi-media, Bovine Serum Albumin (BSA), ethanol and all other chemicals were purchased from Merck. Acephate (O, S-Dimethyl acetylphosphoramidothioate) 75% purity was used.

Experimental Animals: Healthy adult male albino Wistar rats of 225±25 gms were acclimatized for 7 days in polypropylene cages under controlled environmental conditions (room temp. 30 ± 2°C with 12:12 h. light/dark cycle). They were allowed to free access to commercial rat feed and tap water ad libitum. All experiments were performed as per the guidelines of the committee for the purpose of control and supervision on experiments on animals (CPCSEA Reg. No.-1283/c/09/CPCSEA) with the permission from Institutional Animal Ethics Committee (IAEC) of PBRI, Bhopal India (Approval No. PBRI/13/IAEC/PN-296a).

Estimation of Acetylcholinesterase Activity: AChE activity was assayed in kidney homogenates in 0.1 M phosphate buffer (pH 7.4) using acetylthiocholine iodide as the substrate by the spectrophotometric method of (Ellman *et al.,* 1961) at 412 nm in SL 164 UV-VIS spectrophotometer. The AChE specific activity was expressed in µmoles of ATChI hydrolyzed/min./mg protein. All measurements were done in duplicate. AChE Percentage inhibition was calculated using the equation:

$$\text{Percentage inhibition} = \frac{(\text{Control} - \text{Treated}) \times 100}{\text{Control}}$$

Calculation of AChE Kinetics: Lineweaver-Burk plots were drawn from assays using acephate (37.8 mg/kg) and *Bacopa monnieri* extract (100 mg/kg) at four different substrate concentrations (0.66 mM, 0.44 mM, 0.33 mM, 0.26 mM ATCI). From these, kinetic parameters (Km & Vmax) were determined for each assay by plotting the reciprocals of velocity and substrate concentrations.

Protein Assay*:* Protein concentration in the kidney homogenates was determined according to the Lowry Method (Lowry *et al.,* 1951) using bovine serum albumin as the standard. Samples of homogenate were diluted with reagents then 0.5 ml Folin's reagent was added and after 20 min. read at 620 nm against a reagent blank.

Experimental Treatment Protocol: The Rats were randomly divided into four groups of 8 animals each and treated with oral doses of acephate and extract of *Bacopa monnieri* using a cannula. Group-I, served as control (vehicle) received orally groundnut oil (1ml/kg b. wt.). Group-II, received the oral dose of 37mg/kg b. wt. of acephate (1/25th LD50) daily for 96h. Group-III, received 100 mg/kg b. wt. ethanolic leaf extract of *Bacopa monnieri* for 7 days orally in double distilled water. Group-IV, received 100 mg/1kg b. wt. ethanolic leaf extract of *Bacopa monnieri* (100 mg/1kg) b. wt. in double distilled water for 7 days daily prior to 37.8 mg/kg b. wt. of acephate for 4 days. The feeding was stopped before 12 hours of intoxication.

Preparation of Kidney Homogenates*:* At the end of the experiment after 96 h. rats were euthanized and kidney tissues were dissected out immediately on an ice-cold plate, washed with the physiological saline solution (0.59% NaCl). 10 % (wt. /vol.) tissues homogenate was prepared in 0.1 M phosphate buffer (pH 7.4) followed by centrifugation at 5000 rpm at 4˚C for 10 min. All homogenates were kept at -4˚C and analyzed for the AChE activity, inhibition and enzyme kinetics.

Histological Assessment: Kidney tissues from each group of rats were fixed in aqueous Bouin's fluid, dehydrated and embedded in paraffin wax. Serial sections were cut at 5 µ and stained with Haematoxylin and Eosin. The sections were studied under the microscope and microphotographed with the computer-aided microscope (Leica).

Statistical Analysis*:* For the data of statistical comparison between different treatments and control, data were analyzed by Student's t-test to determine the effect of the treatment. The level for the accepted statistical significance was $P<0.05$.

RESULTS

Effect of Acephate and Bacopa monnieri on Acetylcholinesterase activity

The specific activity of acetylcholinesterase was investigated spectrophotometrically for the kidney of control and treated rats, which is described in table 1. It was clear from (Fig. 1 and Table 1) that the administration of either acephate or ethanolic extract of *Bacopa monnieri* each alone to normal rats offered a marked decrease ($P<0.05$) in the kidney acetylcholinesterase

activity. A significant 65.84% AChE inhibition in kidney was induced in the rat treated with oral gavages of 37.8 mg/kg b.wt. of acephate for 96 hours. There was marked 28.6% AChE inhibition in rat treated with 100 mg/kg body weight oral dose of ethanolic extract of *Bacopa monnieri* for 7 days. A synergistic inhibitory effect was shown by 71.8% AChE in the kidney when they were treated with ethanolic extract of *Bacopa monnieri* (100mg/kg b. wt.) for 7 days prior to the treatment of acephate (37.8 mg/kg b. wt.) for 96 hours.

Table 1 Acetylcholinesterase activity, inhibition, Km and Vmax of the kidney of Rat intoxicated with Acephate (37.8 mg/kg b. wt.), *Bacopa monnieri* (100 mg/kg b. wt.) The AChE specific activity is expressed in µ moles of ATCI hydrolyzed / mg protein /min.

Parameters	Control	Acephate	*Bacopa monnieri*	*Bacopa monnieri* and Acephate
AChE specific activity	2.84 ± 1.41	0.97 ± 0.49**	2.0 ± 1.51***	0.80 ± 0.33*
AChE % inhibition	-	- 65.84%	-28.6%	-71.8%
Km x 10^{-3} M	0.90± 0.35	2.5 ± 0.84* +177.7 %	1.42 ± 0.78** +57.7 %	1.8± 1.32*** +100 %
Vmax (A / mg protein / min)	0.33	0.33	0.33	0.33

Each value is mean ± S.D. of 5 individual observations. P < 0.01*; P < 0.02**; P < 0.05***.

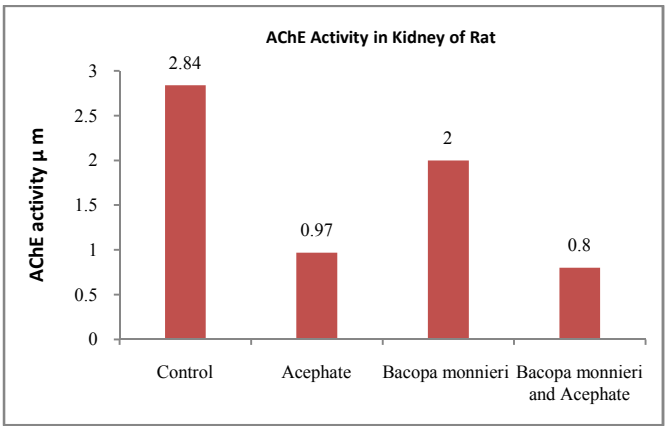

Fig 1 Acetylcholinesterase activity in the kidney of rat intoxicated with acephate (37.8 mg/kg b. wt.), *Bacopa monnieri* (100 mg/kg b. wt.). The AChE specific activity is expressed in µ moles of ATCI hydrolyzed/mg protein/min.

Effect of Acephate and Bacopa monnieri on Acetylcholinesterase kinetics

Km values for AChE in kidney were observed for control and treated groups of rats by Line Weaver-Burk plots (fig. 2 & table 1).

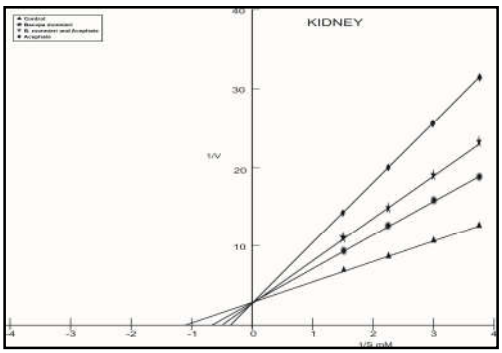

Fig 2 Lineweaver-Burk plot of in vivo inhibition of acetylcholinesterase in Kidney of Rat ▲Control and exposed to ♦Acephate (37.8 mg/kg b. wt.), ●*Bacopa monnieri* (100 mg/kg b. wt.) and *pretreatment of *Bacopa monnieri* followed by treatment of Acephate. Each point represents the mean of five assays.

The Km of kidney AChE of the control group was 0.90 X 10^{-3}M. The Km was increased 3 times in acephate treated rat in comparison to control group. Similarly, 57% (1.42 X 10^{-3} M) increase in Km was noted with the treatment of *Bacopa monnieri*. However, in the mixed group of rats, a marked increase in Km was found, which was increased to 1.8 X 10^{-3}M from 0.90 X 10^{-3}M (control). Ethanolic extract of *Bacopa monnieri* and acephate both produced competitive inhibition as denoted by increasing Km values and constant values of Vmax in control and treated groups of rats (Table – 1).

Effect of Acephate and Bacopa monnieri on histology of rat kidney

Rats of group I, showed the normal structure of the kidney having numerous renal tubules with complete epithelial layers and interstitial tissues (Fig. 3). In group II, Acephate (37mg/kg b.wt.) induced damage in the epithelium of renal tubules, slight degeneration in the glomeruli, necrosis, and dilation in some of the renal tubules (fig. 4). Rat kidneys of group III, treated with *Bacopa monnieri* extract slightly affected the renal architecture as shown by vacuolation at some places and narrow spaces among the tubules (fig. 5). However, in the rats of group IV, combination of *Bacopa monnieri* and acephate elicited necrosis, pyknosis, rupture of proximal and distal convoluted tubules, lobulated appearance of renal corpuscles and small spaces were seen among renal and Bowmen's capsule (fig. 6).

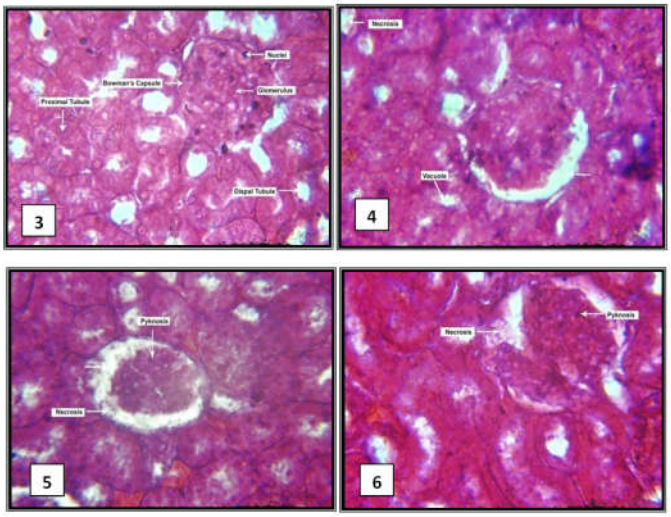

Fig 3-6 Photomicrograph of T. S. of Kidney of Rat, stained with H.E. X 400 [3] Control showing the normal structure, [4] Intoxicated with acephate (37.8 mg/kg b.wt.) showing necrosis in renal tubules and space in Bowman's capsule layer (Arrow), [5] Exposed to *Bacopa monnieri* (100 mg/kg b. wt.) showing spaces in Bowman's capsule layer, [6] Intoxication with *Bacopa monnieri* (100 mg/kg b. wt.) +Acephate (37.8 mg/kg b. wt.) showing necrosis in Bowman's capsule.

DISCUSSION

Medicinal plants have been largely used in traditional medicine as remedies for many kinds of human diseases. The present study was performed on the acute toxicity of acephate and Bacopa monnieri alone and in their combination on AChE, its kinetics and histology in the kidney of male rats. Acephate and Bacopa monnieri administration were found to cause depression of acetylcholinesterase activity in the kidney of the rat. Our results indicated that there was significant (P < 0.01) potentiation of AChE depression with combined treatment of acephate and *Bacopa monnieri*. The results of the present study showed that extract of *Bacopa monnieri* had reasonable AChEI properties (29 %) in the concentration of 100 mg /kg

b.w. It is worth mentioning that, in a previous study, we have shown that acephate and the ethanolic extract of *Bacopa monnieri* exhibited a significant AChE inhibitory effect in the hippocampus and cortex of adult rats and heart of chick (Tembhre *et al.,* 2015; Ahirwar and Tembhre, 2016; Gour *et al.*, 2016). The brain homogenate obtained from rats fed with *B. monnieri* extract showed anti-AChE activity (Le XT *et al.,* 2013). In a clinical trial in healthy elderly, the ability of the plant to enhance memory, cognition, and attention was implicated to its ability to suppress AChE (Peth-Nui *et al.,* 2012). Extract of Bacopa monnieri enhanced cognitive function and the number of cholinergic neuron in male Wistar rats AD model induced by ethyl choline aziridinium ion (AF64A) (Uabundit *et al.,* 2010).

It has been established that the bioactive compound Bacoside A (a mix of saponins) is responsible for cognitive effects of *B. monnieri* (Ramasamy *et al.,* 2015). The hypothesized nootropic mechanisms are acetylcholinesterase inhibition, choline acetyltransferase activation, Aβ reduction, increased cerebral blood flow, and monoamine (dopamine and serotonin) potentiation (Aguiar and Borowski, 2013; Ramasamy *et al.,* 2015). Mukherjee *et al.* (2007) highlight the plants and/or their active constituents reported to have AChE inhibitory activity (% inhibition; concentration), with the most significant inhibitors thought to be alkaloids and a few glycosides. Plant extract of *Bacopa monnieri* is known to contain saponins, a mixture of bacoside A3, bacopaside I, bacopaside II, bacopaside X, and of bacopasaponin C. (Rauf *et al.,* 2013). Our results of *Bacopa monnieri* on AChE inhibitory activity may partly explain the traditional use of the plant for improving dementia. This is in concurrence with the findings of Saini *et al.* (2012) who found that *Bacopa monnieri* (50 mg/kg per day oral) supplementation reversed memory impairment in colchicine-treated rat model of Alzheimer disease. Our findings are in consistency with Sireeratawong *et al.* (2016) who demonstrated acute and chronic toxicities of *Bacopa monnieri* extract in the kidney Sprague-Dawley rats. It has been reported earlier that acephate inhibit acetylcholinesterase enzyme (AChE) in nervous system tissues (Mahajna *et al.,* 1997; Spassova *et al.,* 2000). Acephate and its metabolite methamidophos inhibit acetylcholinesterase enzyme (AChE) in nervous system tissues, which varies with dose (Wang *et al.,* 2013). We also observed a significant depression of AChE in the kidney AChE. Similarly, other pesticides like permethrin at 0.25% dose reported to produce 53.12% AChE inhibition however, equivalent dose of monocrotophos induces 68% inhibition in AChE activity in Kidney (Tabsum *et al.,* 2003).

A kinetic study gives good insight of type of enzyme inhibition. In the present study, we have determined toxicity of acephate and *Bacopa monnieri* on AChE kinetics in rat kidney. Our results indicate a significant increase in Km values and unchanged Vmax due to their exposures indicating competitive inhibition. The kinetic inhibition activity of *Bacopa monnieri* extract on AChE in the kidney has not been reported; therefore this work is first to report its competitive inhibitory nature to AChE. In our previous study acephate and *Bacopa monnieri* were reported to produce competitive inhibition in AChE of rat hippocampus (Tembhre *et al.,* 2015) and in heart of chick (Gour *et al.,* 2016).

The biochemical findings obtained in the current work were substantiated with histopathological observations. Neither gross nor histopathological abnormalities were observed in the kidney of *B. monnieri*-treated rats. The renal tubules as well as the glomeruli were affected after acephate treatment. The renal tubules lost their characteristic appearance and their lumens were filled with amorphous cellular derbies. The glomeruli have degenerated and the renal blood vessels were congested. Shrinkage of glomeruli with wide urinary spaces derives its support from the findings of Srivastava *et al.* (1990), Issa *et al.* (2011) and was probably due to renal vasoconstriction in response to nephrotoxicant (Schellman, 1995). In the present study, there was dilatation of both proximal and distal convoluted tubules. These changes may be in response to the nephrotoxic drug as proximal convoluted tubules are the most common site of toxicant-induced renal injury (Schellmann, 1995). Earlier studies have shown that acute and subchronic exposure to pesticides produces Glomerular degeneration, tubular degeneration, tubular widened lumen and compressed blood vessel (Khogali *et al.,* 2005; Kerem *et al.,* 2007 and Afshar *et al.,* 2008).

CONCLUSION

It clearly demonstrates that *B. monnieri* suppresses AChE activity resulting in enhanced cholinergic function. Studies have shown that AChE inhibition, in turn, enhances attention and memory processing in the brain and gives rise to the increased working memory. Since early-phase Alzheimer's disease is reported to occur due to cholinergic degeneration and oxidative stress, *B. monnieri* leaf extract may provide a benefit in terms of decreasing memory impairment in early-phase Alzheimer's disease and even in attention deficit disorder. Considering the complexity of herbal medicines, it is necessary to evaluate their safety before the use and this research requires further investigation.

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