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Neuroprotective and antioxidant potential of *Ficus carica* leaves extract in scopolamine induced memory impairment

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Abstract: *Ficus* species has been reported to be used in prevention and therapy of various diseases but little information is available regarding the effects of its leaf extract on memory related disorders. This study was designed to monitor the effect of *Ficus carica* leaves (FCL) administration in healthy and rat model of memory impairment. Thirty male albino Wistar rats were divided into five groups: control, scopolamine (SCO), donepezil treated positive control, FCL extract treated and SCO+FCL extract treated rats. FCL extract was given at dose of 250 mg/kg daily for 3 weeks. Scopolamine (0.5 mg/kg) was injected to induce memory impairment before the evaluation of behavior. After three weeks of FCL extract treatment, behavioral, biochemical and neurochemical analysis were done. Results showed that FCL extract improved spatial working memory in scopolamine injected rats. FCL treatment reversed scopolamine-induced anxiety, depression and impairment in memory functions. Decreased acetylcholine level in scopolamine injected rats was reversed by FCL administration while antioxidant enzyme activity was also improved. It was therefore suggested that FCL extract exerts its effects by enhancing brain acetylcholine levels and by improving antioxidant enzyme activities. The findings may help to improve therapeutics in oxidative stress-induced memory impairment.

Keywords: Acetylcholine, antioxidant, anxiety, *Ficus carica*, memory.

INTRODUCTION

Free radicals are produced in the human bodies which cause different disorders such as liver injury, Alzheimer's diseases, atherosclerosis, cardiovascular diseases, diabetes and rheumatoid arthritis. Human body develops its own defense mechanism to remove or neutralize the free radicals with the help of antioxidant enzymes (Moldogazieva *et al*., 2019). However, due to heavy exposure to external environmental pollutants, such as smoke, ultraviolet radiation, and pesticides, the self-defense mechanism is sometimes insufficient to remove the excessive free radicals. Therefore, supplementation of phytochemicals with antioxidant properties has become a considerable attention in the present scenario. This could help to protect from various disorders. Polyphenols (Del Caro *et al.,* 2008), flavonoids (Veberic *et al.,* 2008*)* and other phytochemicals with antioxidant potential have the ability to inhibit the oxidative mechanisms that could cause various degenerative diseases (Sirisha *et al.,* 2010). These antioxidant compounds works as reducing agents, hydrogen donors, scavenge free radicals and quenches oxygen ions (Uttara *et al.,* 2009) and they decrease various free radicals and increase the antioxidants level in brain and plasma and prevent neuronal degeneration.

Medicinal plants are the main interest of researchers because of their safety profile and presence of antioxidant compounds that provide resistance against several diseases (Hajihosseini *et al*., 2017). Now a day's herbs have been widely used to cure many ailments because of their beneficial constituent. The Mediterranean region is diverse and is a source of variety of medicinal plants. Among them, *Ficus carica* Linn. (Family; Moraceae) commonly known as fig has been used traditionally to cure many diseases. Past researches have reported that different parts of *Ficus carica* contained numerous antioxidant constituents (Mohan *et al*., 2007; De Oliveira *et al*., 2009). It has been revealed previously that leaves of *Ficus carica* (FCL) comprises of powerful antioxidant activity as compared to other parts due to the presence of maximum amount of phenolic compounds (De Oliveira *et al*., 2009) that have the capability to remove free radicals and chelate prooxidant metal-ions. *Ficus carica* leaves are widely used in many regions of the world to treat metabolic, cardio and respiratory disorders as well as it is used to cure many types of cancers (Ayoub *et al.,* 2019). They are also used by diabetic patients and patients having coughs, asthma and constipation (Canal *et al.,* 2000; Belguith-Hadriche *et al.*, 2017). Other reported pharmacological effect of fig leaves extract includes anticancerous, hypoglycemic and anthelmintic activity in animal models (Sirisha *et al.,* 2010).

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Little information is available regarding the effects of FCL extracts on central nervous system and its neuroprotective effects. Considering the rich content of antioxidant in FCL we examined the outcomes of FCL extract at dosage of 250 mg/kg on various behaviors such as memory, anxiety and depression in relation with biochemical and neurochemical parameters in healthy and scopolamine-induced memory impaired male rats.

MATERIALS AND METHODS

Extract preparation

Fresh FCL were collected from garden located in KPK during the month of March. Leaves were identified by the Department of Botany, Federal Urdu University of Arts, Science and Technology, Karachi. FCL leaves were washed and shade dried for three days and powdered in an electric blender. Powdered leaves (500g) were soaked in two liter ethanol for 7 days at room temperature. It was then filtered through Whatman's no.1 filter paper then filtrate was dried to form extract with the help of rotary evaporator.

Animals

Male albino Wistar rats of weight (150-180g) were kept in isolated cages at room temperature (24 ± 2ºC) for 3-4 days before the beginning of experiment. All experimentations were conducted according to a procedure approved by IRB of Federal Urdu University, Karachi.

Experimental protocol

Experimental rodents were randomly assigned into five groups: control, scopolamine (SCO) treated memory impaired rats, donepezil treated positive control, FCL extract treated and SCO+FCL extract treated rats. FCL extract (250 mg/kg) and donepezil (3 mg/kg) were given to their respective group daily for 3 weeks (Rajdev *et al.,* 2020). Scopolamine (0.5 mg/kg) was given 30 min before performing behavioral activity (Boiangiu *et al.,* 2020) to scopolamine treated rats, donepezil treated positive control and SCO+FCL rats. After 3 weeks memory functions, depression and anxiety like symptoms were monitored. After evaluation of behavioral effects rats were decapitated to get brain samples for the analysis of biochemical and neurochemical parameters. Performance of biochemical assays included anti-oxidant enzymes (catalase and glutathione peroxidase). Acetylcholine levels were also determined in rat's brain.

Behavioral procedures

Morris water maze test

Effects on memory functions of rats were examined by Morris water maze (MWM). This test was done to evaluate spatial working memory functions and was determined 24 h after training (Haider *et al*., 2015).

Forced swimming test (FST)

To observe the effects of drugs on depressive symptoms in animals FST was performed (Porsolt *et al*., 1977; Siddiqui *et al*., 2017). The immobility time during which rats remain suspended in water without movement was recorded for 6 min.

Light/dark transition test

Anxiolytic effects were determined by light/dark transition box. Procedure was same as described previously (Haleem and Mahmood, 2019).

Biochemical and neurochemical estimations

Antioxidant enzymes such as glutathione peroxidase, catalase and levels of acetylcholine were estimated by manual methods. Catalase levels were estimated as described before (Sinha, 1972). Glutathione peroxidase level was evaluated with the procedure given by Flohe and Gunzler (1984). Acetylcholine values were determined in whole brain with the help of Hestrin's method (1949).

STATISTICAL ANALYSIS

Behavioral, biochemical and neurochemical results were represented as means ± SD. Data was analyzed by one way ANOVA using SPSS 16.0. Tukey's HSD test was carried out for *post-hoc* evaluation, $p<0.05$ was considered significant.

RESULTS

Spatial working memory was impaired ($p<0.01$) in scopolamine group as compared to control rats. Memory functions of donepezil treated positive control ($p<0.01$) and SCO+FCL treated rats ($p<0.01$) were enhanced as compared to scopolamine treated rats (fig.1). Memory functions in FCL extract group were unaffected as compared to control.

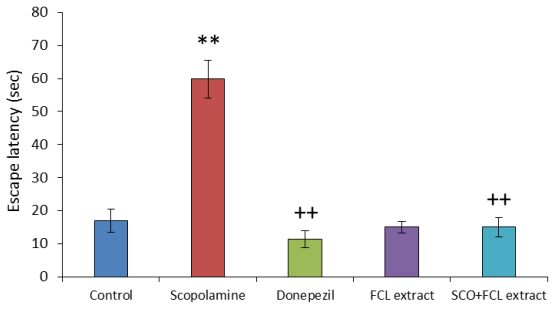

Fig. 1: Effects of FCL extract on spatial working memory in healthy and memory impaired rats.
Statistically significant difference: **p<0.01 vs control, ++p<0.01vs scopolamine injected rats.

Depression-like symptoms were produced ($p<0.01$) in scopolamine treated rats as immobility time was

significantly increased (fig. 2). Positive control exhibited decrease in depression-like symptoms as compared to scopolamine group. FCL extract treated rats significantly decreased depression-like symptoms as compared to control ($p<0.01$). FCL extract administration in scopolamine treated rats significantly reduced depression like symptoms as compared to scopolamine group ($p<0.01$).

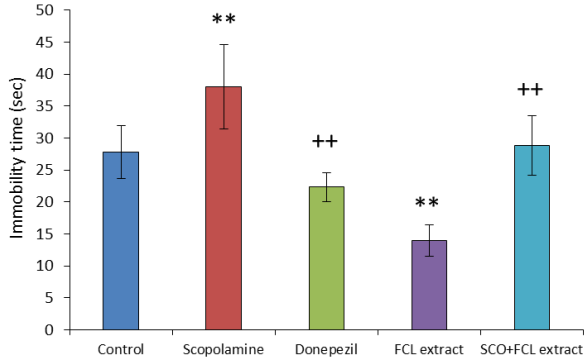

Fig. 2: Effects of FCL extract on depression like symptoms in healthy and memory impaired rats.
Statistically significant difference: **p<0.01 vs control, ++p<0.01vs scopolamine injected rats.

Scopolamine significantly ($p<0.01$) produced anxiety symptoms as compared to control. Donepezil and FCL treatment in scopolamine administered rats significantly decreased ($p<0.01$) anxiety-like symptoms as compared to scopolamine treated rats. FCL extract administration significantly decreased anxiety like symptoms in FCL extract group as compared to control (fig. 3).

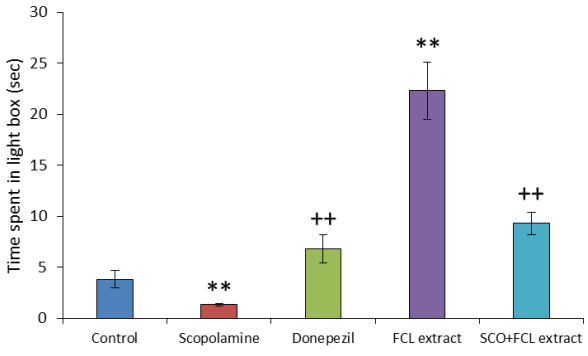

Fig. 3: Effects of FCL extract on anxiety in healthy and memory impaired rats.
Statistically significant difference: **p<0.01 vs control, ++p<0.01vs scopolamine injected rats.

***Ficus carica* leaves extract outcome on acetylcholine level**

Brain acetylcholine levels in scopolamine treated rats were significantly ($p<0.05$) decreased as compared to control (fig. 4). Acetylcholine level was significantly increased in scopolamine rats treated with FCL extract ($p<0.01$) and donepezil treated rats ($p<0.05$) as compared to scopolamine treated rats.

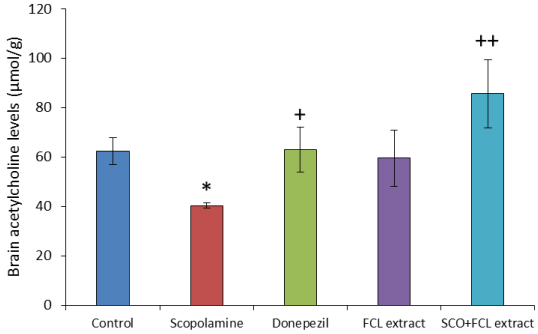

Fig. 4: Effects of FCL extract on acetylcholine level in healthy and memory impaired rats.
Statistically significant difference: *p<0.05vs control, +p<0.05, ++p<0.01vs scopolamine injected rats.

***Ficus carica* leaves extract outcome on antioxidant enzymes (catalase and glutathione peroxidase)**

Fig. 5 shows that SCO+FCL extract treated rats exhibited increased catalase level as compared to control and scopolamine treated rats ($p<0.01$). Glutathione peroxidase levels were significantly decreased in scopolamine treated rats as compared to control ($p<0.01$) whereas the enzyme activity was significantly increased in positive control and SCO+FCL treated rats as compared to scopolamine group (fig. 6).

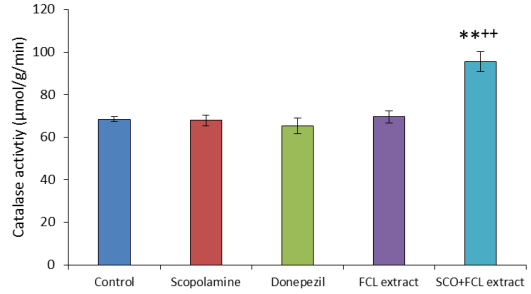

Fig. 5: Effects of FCL extract on catalase level in healthy and memory impaired rats. Statistically significant difference:**p<0.01 vs control, ++p<0.01vs scopolamine injected rats.

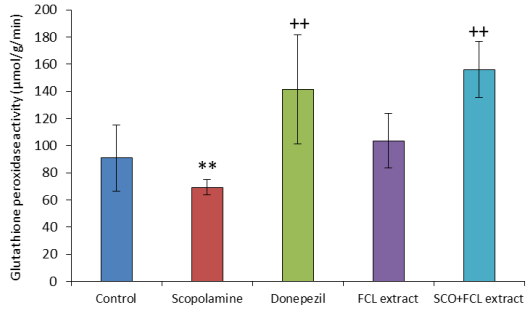

Fig. 6: Effects of FCL extract on glutathione peroxidase level in healthy and memory impaired rats. Statistically

significant difference: **p<0.01 vs control, ++p<0.01vs scopolamine injected rats.

DISCUSSION

In this study scopolamine administration significantly impaired spatial working memory in rats as compared to control. Administration of donepezil in positive control group enhanced spatial working memory as compared to scopolamine injected rats. Moreover, FCL administration had positive effects in reversing scopolamine induced memory impairment in rats. Scopolamine administration in addition to memory impairment increased depression-like symptoms and produced anxiety-like symptoms in rats. Administration of conventional drug donepezil in positive control significantly reversed depression- and anxiety-like symptoms exhibited by scopolamine injected rats. FCL administration reversed scopolamine-induced depressive, anxiety symptoms and impairment in spatial working memory in SCO+FCL treated rats. FCL administration also significantly decreased depression and anxiety-like symptoms in FCL extract group as compared to control. FCL treatment significantly increased brain acetylcholine levels and improved antioxidant enzyme levels.

Anxiety has been previously reported to be related with biochemical, behavioral and neurobiological alterations (Kessler *et al*., 2005). However, psychological abnormalities could also trigger anxiety. Medicinal plants are very effective alternative approach to discover novel medicines for the treatment of anxiety (Emamghoreishi *et al*., 2005). Numerous herbal medicines which cause mood enhancing effect also exhibit anxiolytic effects. It was reported previously that anxiolytic and antidepressant activity is due to the alteration of psychological pathways (Sarris *et al*., 2005). Previous study revealed that FCL extract showed the presence of flavonoids which have been recently implicated for various pharmacological activities and they have been identified to possess anxiolytic properties (Srinivasan *et al.,* 2018). Present study revealed that FCL administration significantly produced anxiolytic effects in FCL extract group and FCL+SCO group.

Medicinal plants contain several secondary metabolic bioactive compounds that have been reported to reduce oxidative stress by eliminating free radicals (Rasmann and Agrawal, 2011). Evidence showed that herbal medicines for the depression treatment have become first choice of patient due to accessibility and fewer lethal effects (Zheng *et al.,* 2010). *Ficus carica* plant comprises several bioactive compounds such as coumarins, flavonoids, sterols, triterpenoids, anthocyanins (Sirisha *et al.,* 2010). Previously, phytochemical analysis of *Ficus carica* showed that its leaves contained flavonoids (quercetin) that is claimed to be responsible for its positive effects on CNS (Aroonsri *et al.,* 2008). Polyhydroxyphenols which is also known as polyphenols (phenolic acids, flavonoids) have been reported to reduce oxidative stress which is the main causative factor of depression and other CNS associated disorders (Bouayed and Bohn, 2010). Present study revealed decrease in immobility time exhibiting antidepressant effect by FCL extract administration in FCL extract group and FCL+SCO group.

Present study revealed that scopolamine impaired memory functions in rats as evaluated by means of MWM test which was also reported in previous studies (Rabiei *et al.,* 2015). Several earlier studies have shown that flavonoids and other phytochemicals have improved learning and memory functions and also have a role in preventing dementia in humans (Nassiri-Asl *et al*., 2010). Antioxidant properties of FCL were previously attributed to flavonoids and also to non-enzymatic phenolic compounds like gallic acid and ellagic acid (Sirisha *et al.*, 2010). Previously it was reported that MWM performance remained unaffected following treatment with FCL extract (Ashfaq *et al*., 2018) that is consistent with the present findings, however, FCL extract significantly enhanced memory performance in scopolamine injected rats.

Catalase is an antioxidant enzyme that is able to decrease oxidative stress by converting hydrogen peroxide into water and oxygen. Decrease in catalase levels has been related to the onset of many age-associated degenerative diseases. FCL extract increased catalase activity in SCO+FCL rats when compared with scopolamine group. Glutathione peroxidase levels were decreased in scopolamine injected rats that was reversed by donepezil and FCL extract. Neurochemical estimations revealed that FCL extract administration increased brain acetylcholine in SCO+FCL group as compared to scopolamine treated rats that was not seen in FCL extract group. *Ficus carica* plant comprises several bioactive compounds such as coumarins, flavonoids, sterols, triterpenoids, anthocyanins (Sirisha *et al.,* 2010). Flavonoids are naturally occurring polyphenolic compounds that could enhance cholinergic neurotransmission (Liaquat *et al*., 2018). Decreased acetylcholine levels have been linked with cognitive dysfunctions (Ebadi *et al*., 2020) whereas increased acetylcholine neurotransmission has been reported to enhance memory functions (Fernandez de Sevilla *et al*., 2020). Therefore, enhancement in memory performance in SCO+FCL rats may be attributed to flavonoid contents of FCL which may have increased brain acetylcholine levels observed in this group.

As compared to other organ, brain tissue is more susceptible to damage by the influence of free radicals due to its increased demand of oxygen, and increased lipid content. The common effective approach to reduce

the lethal effects of free radicals is to consume medicinal plants which possess increased amount of antioxidants (Sulakhiya *et al.,* 2016). Previous results revealed that learning and memory impairments and other CNS disorders occur as a result of oxidative stress (Hosseini *et al.,* 2015). In this study neurochemical and biochemical analysis showed that FCL extract altered antioxidant enzymes and acetylcholine levels. It is therefore suggested that memory enhancing effect of FCL in scopolamine injected rats could be due to increased brain acetylcholine levels and improved antioxidant enzymes activity as observed in the present study.

CONCLUSION

FCL improved spatial working memory which may be associated with increased levels of acetylcholine and improved oxidative status. FCL also exhibited anxiolytic and anti-depressant effects in healthy rats. FCL extract administration significantly reversed scopolamine induced-memory impairment, anxiety and depressive symptoms in rats. These results may help to improve therapeutics in oxidative stress-induced memory related disorders.

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