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Protective effects of camellia oil in unpredictable stress induced behavioral and neurochemical changes in rats

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Abstract: Repeated episodes of stress results in the development of neuropsychiatric symptoms associated with severe depression. Synthetic antipsychotic medication helps people experiencing the stress induced behavioral problems . These medications have serious side effects. A variety of natural herbs and their extracts are frequently used to treat neurological disorders. *Camellia oleifera Abel.* oil is used for treatment of metabolic and endocrine problems. Moclobemide is monoamine oxidase inhibitor, widely prescribed for the treatment of depression and anxiety. This study evaluate the neuroprotective effects of *camellia* oil and moclobemide in animal model of learned helplessness. Stress produced behavioral deficits, increases plasma corticosterone levels , brain lipid peroxidation and decreases the levels of endogenous antioxidant enzymes. *Camellia* oil pre-treated rats improved behavioral activities, as well as significant reduction in plasma corticosterone and lipid peroxidation, along with rise in activity of antioxidant enzymes. Enhanced level of brain dopamine, dihydroxyphenlyacetic acid and decreased dopamine turnover was also observed in stressed rats. These stress induced changes can be prevented in rats pre-treatment with *camellia* oil. However, when compared with synthetic antidepressant moclobemide, the rats treated with *camellia* oil exhibited more promising result.

Keywords: Camellia oil, stress, anti-depressive, anxiolytic, antioxidant, dopamine.

INTRODUCTION

Neurological disorders have shown high prevalence and contributed to an increase in the burden on healthcare costs worldwide (Feigin *et al*., 2021). Neurological variations which includes anxious and depression-like behaviour with cognitive deficits are the most broadly defined effects of persistent exposure to stress (Matisz *et al*., 2021). Chronic stress reported to cause increase in oxidative stress which ultimately impairs neurogenesis and induce depressive symptoms in rodents (Sugama & Kakinuma, 2020 Blossom *et al*., 2020). It is also associated with impairment of the immune system which may induce susceptibility to infectious diseases (Monteiro *et al*., 2015). The widely used rodent model of unpredictable stress, mimic behavioral traits monitored in patients with anxiety, depression and related mood disorders, involves systematic and repeated exposure to intermittent series of unpredictable stressors lasting days or weeks (Sequeira-Cordero *et al*., 2019). The role of dopaminergic (DAergic) neurons has been the focus of attention in stress-induced maladaptation of critical brain circuits that produce major depressive disorders and anxiety problems (Yao *et al*., 2021). Moclobemide, a reversible inhibitor of type A monoamine oxidase (MAO) is common antidepressant and extensively recommended worldwide to counteract neurodegenerative diseases with fewer undesirable side effects (Nowakowska *et al*., 2001). *Camellia oleifera Abel. (C. oleifera)*, a medicinal plant, found in the East Asian region. Several flavonoids, lignans, tannins, and saponins were reported from different parts of *C. oleifera*. It is often entitled as ‘‘Eastern Olive Oil’’ and consists of monounsaturated, and polyunsaturated fatty acids (Yang *et al*., 2022). C*amellia oil* exhibits numerous biological activities (Ahmed *et al*., 2021). Studies show that *it* possesses antioxidative, anti-inflammatory and anti-tumor properties. Biflavonoids purified from the plant *C. oleifera* also revealed a protective ability against free radical damage to brain cells (Ye *et al*., 2012). The current study is intended to elucidate the beneficial effects of *camellia* oil and moclobemide against unpredictable stress-induced behavioral and neurochemical changes in rats.

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MATERIALS AND METHODS

Experimental protocol

Albino rats (male; Wistar strain; 150-200g) were purchased from Dow University of Health Sciences, Karachi, Pakistan. Animals caged separately in silent room of controlled temperature (22±2ºC) with connected water bottles and food supply for one week before beginning of the experimentation. Oil of *C. oleifera* seeds taken from Hsin-I Country Farmer's Association (Tu *et al*., 2017). Moclobemide and all other reagents used in study purchased from Sigma Aldrich, USA.

Rats were randomly categorized in two groups as an unstressed and stressed group (n=18). Each group is sub-divided into three groups as control, *camellia* oil, and moclobemide. Camellia oil and moclobemide were given daily with an oral dose of 2ml/kg/day (Cheng *et al*., 2014) and 10mg/kg/day (Nowakowska *et al*., 2001) respectively for three weeks. Control animals received water during the whole experiment. Rats were subjected to various unpredictable stress as described earlier (Perveen *et al*., 2018), whereas animals of unstressed group stayed in their cages during this period. 24 hours following the last stress session, behavioral assessment was conducted and animals were then decapitated. The brain and plasma samples then collected and kept at -70^{o}C to perform biochemical estimates. The experimentation was accomplished after formal approval of the institutional review board (IRB) with reference No. 03363/SC-2015. Instructional rules and guidelines of the Institute of Health Guide for Care and Use of Laboratory Animals (Publication No.85-23 revised 1995) were strictly monitored.

Behavioral analysis

Locomotion, anxiety and depression-like behaviours monitored through open field test (OFT), light/dark transition (LDT), and forced swim test (FST) respectively (Qadeer *et al*., 2018).

Biochemical estimation

Plasma corticosterone (CORT) level, lipid per oxidation (LPO) in terms of malondialdehyde (MDA) concentration and activities of antioxidant enzymes; super oxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in brain evaluated by previously reported method elsewhere (Qadeer *et al*., 2018).

Neurochemical studies

Neurochemical estimation was assessed to evaluate dopamine (DA) concentrations and its metabolite i.e., dihydroxyphenylacetic acid (DOPAC) using reversed-phase high performance liquid chromatography as reported earlier (Haider *et al*., 2020).

STATISTICAL ANALYSIS

All results are represented as mean ± SD. Data analysis performed through two-way ANOVA and Tukey's test via SPSS (version 20.0) software. p>0.05 considered non-significant.

RESULTS

OFT

Fig. 1a illustrates the effects of *C. oleifera* oil and moclobemide on locomotor action of animal. Results demonstrated a significant impact of stress (df=1,30; F= 8.109 p<0.01), drugs (df=2,30; F= 25.647 p<0.01), and non-significant (df=2,30; F= 1.840) interaction between the factors. Analysis through Tukey's test displayed significantly increased (p<0.05) squares crossings in stressed group compared to unstressed control. Oil of *C. oleifera* significantly reduced (p<0.05) square crossings compared to stressed control. Significantly enhanced (p<0.05) number of squares crossed was observed following the treatment of moclobemide compared with unstressed control.

LDT

Fig. 1b illustrates the effects of *camellia* oil and moclobemide on animal's anxiety states. Results demonstrated significant impact of stress (df=1,30; F=5.678 p<0.05), drugs (df=2,30; F=28.507 p<0.01), and interaction (df=2,30; F=9.904 p<0.01) between the factors. Analysis through Tukey's test displayed significantly decreased (p<0.05) time spent in lighted compartment by stressed animals as compared to unstressed control. Significantly enhanced time spent in lighted compartment observed following treatment of *camellia* oil (p<0.01) compared to stressed control while no significant result was observed following moclobemide treatment.

FST

Fig. 1c illustrates effects of *camellia* oil and moclobemide on the animal's depressant behavior. Results demonstrated the significant impact of stress (df=1,30; F=20.059 p<0.05), drugs (df=2,30; F=29.597 p<0.01), and non-significant interaction between factors (df=2,30; F=2.304). Analysis through Tukey's test revealed significantly (p<0.01) reduced struggling time of stressed rats compared to unstressed control. Following treatment of *camellia* oil and moclobemide revealed significant rise in struggling time (p<0.01) compared to stressed control rats.

LPO

Results of Two-way Anova is depicted in Table 1. Analysis through Tukey's test displayed significantly increased LPO (p<0.01) in stressed animals compared with unstressed control. Treatment of *camellia* oil significantly reduced LPO of both unstressed (p<0.05) and stressed animals (p<0.01) compared to their respective controls. Moreover, moclobemide treated animals showed significantly increased (p<0.01) LPO in unstressed and stressed group.

SOD

Results of Two-way Anova is depicted in table 1. Analysis through Tukey's test displayed significantly decreased (p<0.01) SOD activity in stressed group compared to unstressed controls. Treatment of *camellia* oil significantly enhanced SOD activity in both unstressed (p<0.05) and stressed animals (p<0.01) compared to their

Table 1: Effect of camellia oil (CO) and moclobemide (MOC) on biochemical and neurochemical parameters in unstressed and stressed rats.

	Unstressed			Stressed			Two-way ANOVA
	Control	CO	MOC	Control	CO	MOC	
LPO (MDA; µmol/g)	70.33 ±9.3	*50.6 ±4.92	**114.8 ±12.82	++105.8± 12.25	**64.66± 5.53	**++153.3 ± 14.45	$F_{Stress\ (1,30)} = 54.860$; p<0.01 $F_{Drug\ (2,30)} = 180.325$;p<0.01 $F_{Interaction\ (2,30)} = 9.881$; p<0.01
SOD (U/g)	1.38 ±0.12	*1.63 ±0.18	**0.75± 0.12	++1.02± 0.13	**1.47± 0.10	**0.58± 0.08	$F_{Stress\ (1,30)} = 28.693$; p<0.01 $F_{Drug\ (2,30)} = 140.277$; p<0.01 $F_{Interaction\ (2,30)} = 2.228$
CAT (µmol/min/g)	155.5 ±7.08	143.2 ±5.3	*136.06 ±8.82	++123.81± 13.65	**150.31 ± 15.01	++108.6± 6.35	$F_{Stress\ (1,30)} = 13.264$; p<0.01 $F_{Drug\ (2,30)} = 26.070$; p<0.01 $F_{Interaction\ (2,30)} =5.288$; p<0.05
GPx (µmol/min/g)	262.8 ±28.16	*312.1 ±36.4	225.3± 38.59	++201.66± 15.10	**302± 16.82	**++138± 17.74	$F_{Stress\ (1,30)} = 34.026$; p<0.01 $F_{Drug\ (2,30)} = 64.573$; p<0.01 $F_{Interaction\ (2,30)} = 6.245$; p<0.05
CORT (µg/dl)	223.9 ±30.96	188.4 ±19.54	**279.55 ± 11.54	++424.6± 37.39	**206.18 ± 14.69	**316.23 ±31.39	$F_{Stress\ (1,30)} = 114.677$; p<0.01 $F_{Drug\ (2,30)} = 94.941$; p<0.01 $F_{Interaction\ (2,30)} = 53.480$; p<0.01
DA (ng/g)	61.098 ±4.707	52.6 ±5.68	**313.49 ± 29.82	++136.47± 12.23	**70.6± 4.501	**++255.4 ± 25.81	$F_{Stress\ (1,30)} = 4.208$; p<0.05 $F_{Drug\ (2,30)} = 576.359$; p<0.01 $F_{Interaction\ (2,30)} = 45.294$; p<0.01
DOPAC (ng/g)	277.96 ±29.80	*227.6 ±16.80	**194.2± 15.94	++370.52± 36.40	*++317.8 ± 22.218	**++278.4 4 ±25.27	$F_{Stress\ (1,30)} = 110.063$; p<0.01 $F_{Drug\ (2,30)} = 36.160$; p<0.01 $F_{Interaction\ (2,30)} = 0.087$
DA turnover (DOPAC/DA)	4.55 ±0.44	4.36 ±0.59	**0.627± 0.10	++2.72± 0.27	**4.52± 0.57	**1.096 ±0.12	$F_{Stress\ (1,20)} = 8.862$; p<0.01 $F_{Drug\ (1,20)} = 260.335$; p<0.01 $F_{Interaction\ (1,20)} = 28.729$; p<0.01

All the values are expressed as mean ± S.D (n=6). Significant differences by Tukey's test: *p<0.05, **p<0.01 from their respective untreated controls. +p<0.05, ++p<0.01 from their respective unstressed treated control.

respective controls. Pre-treatment of moclobemide significantly (p<0.01) decreased SOD activity in both unstressed and stressed animals compared with their respective controls.

CAT

Results of Two-way Anova is depicted in table 1. Analysis through Tukey's test displayed significantly decreased (p<0.01) CAT activity in stressed group compared to unstressed control. Treatment with *camellia* oil showed significant rise in (p<0.01) activity of CAT compared to stressed group. Furthermore, moclobemide pretreatment significantly decreased (p<0.05) CAT activity in unstressed animals compared with its respective control.

GPx

Results of Two-way Anova is depicted in table 1. Analysis through Tukey's test displayed significantly decreased (p<0.01) GPx activity in stressed group compared with unstressed rats. Treatment of *camellia* oil showed significant increase in GPx activity of unstressed (p<0.05) and stressed (p<0.01) animals compared to their respective controls. Significantly reduced (p<0.01) GPx activity was revealed following moclobemide pretreatment in stressed animals compared to its respective control.

Corticosterone CORT

Results of Two-way Anova is depicted in table 1. Analysis through Tukey's test displayed significantly increased (p<0.01) plasma CORT concentration in stressed animals compared to unstressed control. Pretreatment of *C. oleifera* oil and moclobemide caused significant (p<0.01) reduction in plasma concentration of CORT compared with its respective stressed control.

DA, DOPAC and DA turnover

Results of Two-way Anova is depicted in table 1. Analysis through Tukey's test displayed significant enhanced levels of DA (p<0.01), DOPAC (p<0.01) and decreased turnover (p<0.01) in stressed animals compared with unstressed group. Pretreatment of *camellia* oil to stressed rats revealed declined levels of DA (p<0.01), DOPAC (p<0.05) and raised DA turnover (p<0.01) compared with stressed control. Administration of moclobemide significantly (p<0.01) increased DA levels, reduced DOPAC as well as turnover in both unstressed and stressed animals compared to their respective controls.

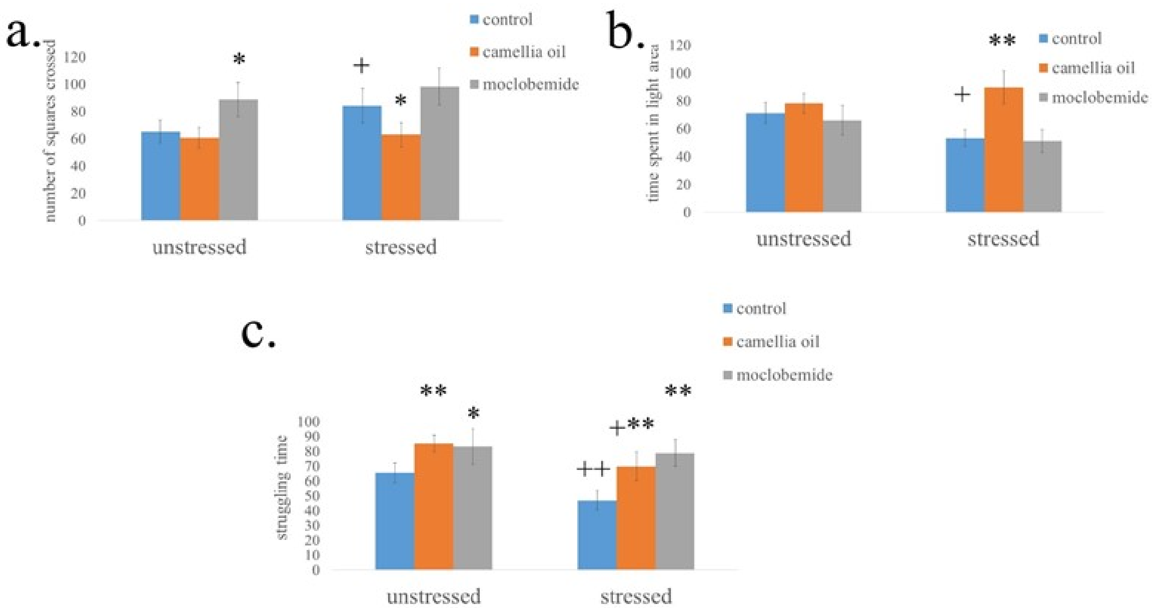

Fig. 1: Effects of camellia oil and moclobemide on behaviours (a. OFT, b. LDT, c. FST) in unstressed and stressed rats. All the values are expressed as mean ± S.D (n=6). Significant differences by Tukey's test: *p<0.05, **p<0.01 from their respective untreated controls. +p<0.05, ++p<0.01 from their respective unstressed treated control.

DISCUSSION

Neuropsychological ailments such as anxiety, depression, and dementia are triggered in response to stressful events in life. Stress is generally characterized by behavioral deficits followed by morphological damages in central nervous system (CNS) which ultimately down regulate neurogenesis, impaired neurotransmissions and stimulation of HPA system (Qiao *et al*., 2020; Sakthivel *et al*., 2018). Present findings demonstrated the potential antidepressant and anxiolytic activity of *camellia* oil in repeated unpredictable stressed rats. Stress increased the locomotor activity in OFT and produced anxiogenic and depressogenic effects evident by reduced time spent in enlighten box (LDT) and struggling time in FST. Stressful conditions induce hyperactivity in response to open field novelty and mild threats has been previously reported (Sequeira-Cordero *et al*., 2019; Matisz *et al*., 2021). Anxiogenic and depressive symptoms following chronic unpredictable stress are also reported previously (Qiao *et al*., 2020). In current study, pre-treatment of *C. Oleifera* seed oil improved the locomotor activity in stressed rats. Alternatively, repeated administration of moclobemide showed no difference in anxiogenic behaviour of rats monitored in OFT and LDT. Pre-treatment of *camellia* oil produced anxiolytic effects in stressed rats by increasing the time spent in the enlighten area of LDT. Moreover, Pre-treatment with *camellia* oil and moclobemide produced anti-depressogenic effects in stressed rats by enhancing struggling time in FST, respectively.

Corticotropin-releasing factor (CRF) has an effective role in stress as it modulates HPA axis and ultimately increases the glucocorticoids secretion from adrenal cortex (Sugama & Kakinuma, 2020). Present study demonstrates a remarkable increase in plasma concentration of corticosterone in rats subjected to unpredictable stress. However, rats treated with *camellia* oil showed decrease level of plasma corticosterone. Increased plasma CORT following stress has also been reported previously (Gokul *et al*., 2019). An increase in stress hormones initiates inflammatory response followed by augmented secretion of inflammatory mediators from brain tissues (Blossom *et al*., 2020). Neurogenesis dysfunction is highly associated with abnormal secretion of cortisol (Blossom *et al*., 2020). *Camellia* oil decreases the stressed induced increase in plasma CORT levels. Similarly, rats pre-treated with moclobemide, in the present findings, also counteracted stress-related increased CORT levels, however, these effects are more in *camellia* oil pre-treated rats as compared to moclobemide pre-treated rats. Stress induced increased CORT levels are associated with the respective reduction of struggling time during FST, indicating HPA axis involvement (Ara & Bano, 2012; Garabadu *et al*., 2015). This is in consistent with the earlier report, which stated that moclobemide can restore the normal functioning of HPA hormonal axis and inhibit the rise in ACTH by preventing the decrease in the density of type I glucocorticoid receptors (Nowakowska *et al*., 2001).

Stress conditions are highly associated with excessive production of reactive oxygen species and reactive nitrogen species (ROS/RNS) resulting in neuronal inflammation and causing the destruction of neuronal cells (Thakare *et al*., 2018; Qiao *et al*., 2020).

Uncontrollable stress results in impairment of structural plasticity which enhanced the activities of pro-inflammatory cytokines in the brain. Neurons are rich in polyunsaturated fatty acids and highly prone to oxidative stress (Lippi, 2021; Patel *et al*., 2019, Virmani *et al*., 2021). Continuous unpredictable stress elevated the lipid per oxidation as indicated by increased concentration of MDA in stressed group. However, pre-treatment of *camellia* oil results in a substantial decline in MDA concentration which reveals that *camellia* oil may have a neuroprotective effect. *Camellia* oil enriched with saturated and unsaturated fatty acids and may protect the cellular damage (Ma *et al*., 2011). Down regulation of inflammatory cytokines and improve neurogenesis by *C. Oleifera* as reported earlier (Ye *et al*., 2014). Depression induces oxidative stress and suppresses antioxidant enzymes activity (Gokul *et al*., 2019). Decline in SOD, CAT, and GPX was observed in current study. On contrary, pre-treatment of *camellia* oil in stressed model group markedly enhanced the activity of antioxidant enzymes and decreased depression-like symptoms by neutralizing the destructive free radicals and neuronal cell death by decreasing lipid per oxidation. Instead, repeated pre-treatment with moclobemide, in our findings, revealed ineffective in diminution of lipid per oxidation due to stress, evident by remarkably increased MDA levels. Oxidative stress is a signature marker for pathophysiology of depression. Previous data revealed that antidepressant agents may also cause an imbalance between redox mechanisms and accelerates oxidative stress (Ahmadian *et al*., 2017). Moclobemide facilitated ROS formation mediates the diminished activity of SOD, CAT and GPx, but shows ineffectiveness to restore antioxidant pool of brain tissues.

Role of DAergic neurotransmission in anxiogenic and depressive behaviours is well established (Dong *et al*., 2020; Baik, 2020). Whereas, stress effects on DAergic neuronal activity is complicated which possibly depends on following features; type, duration, intensity, and controllability of stressors (Yao *et al*., 2021). The current study revealed subsequent unpredictable stress increased DA and its metabolite DOPAC in rat brain. Stress triggers the neurodegeneration of DAergic neurons in substantia nigra pars compacta as a result of increased oxidative stress (Sugama *et al*., 2016) which causes the need for more synthesis and release of DA in the synapse. Highly activated MAOs during stressed conditions favors the catabolism of DA (Lee *et al*., 2013). Decreased DOPAC/DA ratios were also observed in this study following the exposure to unpredictable stress in rats suggesting higher DA system response. Increments in these parameters are reversed by the pre-treatment of *camellia* oil. Tyrosine hydroxylase (TH), a rate-limiting enzyme in DA synthesis reported to be associated with depressive symptomatology in mood disorders (Fu *et al*., 2006). It is reported that *C. oleifera* components alter the expression of TH (Ye *et al*., 2014; Yang *et al*., 2017). Furthermore, components of *camellia* oil; polyphenols, fatty acids and flavonoids have previously been reported to improve the DAergic system and attenuate stress-like symptoms (Sandoval-Avila *et al*., 2019). It is therefore suggested that the amelioration of behavioral deficits following *camellia* oil pre-treatment is due to its effect on TH activity and preventive role against the deterioration of DAergic neurons from ROS damage. Moclobemide induced rise in rat brain level of DA, concomitant decline of its metabolite DOPAC and turnover which explains the inhibitory effect of drug on deamination of DA in CNS.

Augmenting evidence suggests that motor impairments are induced due to dysfunctioning of DAergic system (Olsen *et al*., 2021; Fujita *et al*., 2020). Stress was found to increase TH and DA neuron activity and this active excitation of DA system is associated with locomotor behaviour of animals (Valenti *et al*., 2012; Baik, 2020). Previous studies further confirmed the relation concerning high DA neuron firing rate and high locomotor response to novelty in rats (Mejias *et al*., 2021). *Camellia* oil contains fatty acid which is earlier reported to inhibit DAergic neuronal firing as long chain fatty acids taken up by neurons, blocks cellular transport hence counters behavioral effects (Hryhorczuk *et al*., 2018). It is therefore suggested that *camellia* oil attenuates stress induced hyperlocomotion through its preventive effect against DAergic system. Regardless of substantial rise in DA levels, moclobemide treatment fails to affect locomotion possibly because of its compensatory mechanisms counteracting the gradual rise of synaptic DA (Iurlo *et al*., 2001).

CONCLUSION

Current work reveals that *camellia* oil has the potential to attenuate repeated unpredictable stress induced hyperlocomotion, anxiogenic and depressive behaviour. Alteration in neurochemical changes such as induction of oxidative stress, modulation in corticosterone level and dampened DAergic system following stress also improved by *camellia* oil. *Camellia* oil has found more effective in suppression of neurophysiological changes induced response to stress in comparison with moclobemide. Conclusively, compounds isolated from natural sources are highly recommended and can be considered for the management of stress induced depression.

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