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EVALUATION OF NEUROPROTECTIVE EFFECT OF *CORIANDRUM SATIVUM* LINN. AGAINST ISCHEMIC-REPERFUSION INSULT IN BRAIN

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ABSTRACT

The present study was undertaken to evaluate neuroprotective effect of Coriandrum sativum against ischemic-reperfusion insult in brain. The global cerebral ischemia in Wistar albino rats was induced by blocking common carotid arteries for 30 mins followed by 45 mins of reperfusion. At the end of reperfusion period, histological changes, levels of lipid peroxidation, superoxide dismutase, catalase, glutathion, calcium and total protein was measured. Bilateral common carotid artery occlusion produces significant elevation in lipid peroxidation, calcium levels and infarct size, and decrease in endogeneous antioxidants such as reduced glutathion (GSH), superoxide dismutase (SOD) and catalase (CAT) levels. Pretreatment with methanolic extract of leaves of Coriandrum sativum (200 mgkg-1, p.o.) for 15 days increased endogeneous enzyme levels of superoxide dismutase, glutathion, catalase and total protein levels, and reduces cerebral infarct size, lipid peroxidation and calcium levels. It also attenuated reactive changes in brain histology like gliosis, lymphocytic infilteration and cellular edema. In conclusion results suggest protective role of Coriandrum sativum in ischemic-reperfusion injury and cerebrovascular insufficiency states. The results conclude the neuroprotective effect of Coriandrum sativum against cerebra; injury produced by bilateral common carotid artery ligation.

Keywords: Antioxidants, Bilateral common carotid artery occlusion, Coriandrum sativum, Free radicals, Ischemic-reperfusion injury.

INTRODUCTION

Studies indicate that reperfusion injury is involved directly in the potentiating of stroke damage. Components of the inflammatory response, including cytokine release and leukocyte adhesion, appear to play key roles in these deleterious effects (Hongolian Shi *et al*., 2007). Stroke is the third most common cause of death in the world after cardio-vascular diseases and cancer and one of the major health problems in India. A prevalence rate in the range of 40 to 270 per 100000 in rural population and 400 to 800 per 100000 in metropolitan cities had been reported when surveyed from many regions of India (Hongolian Shi *et al*., 2007).

In recent years a great deal of interest has been devoted to neuroprotective therapy, including antioxidant therapy, whose aims are to reduce the vulnerability of brain tissue to ischemia, to extend the therapeutic window for thrombolytic and to increase the efficacy of thrombolytic by reducing the reperfusion injury. The effect of antioxidants is to control damage that is caused by oxidative compounds, mainly free radicals (also called reactive oxidative species, ROS). Oxidative stress is initiated by reactive oxygen species (ROS) such as superoxide anion and hydrogen peroxide. Once generated, free radicals can react with all the cellular macromolecules leading to lipid peroxidation, DNA and

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protein oxidation (Fady Chamoun *et al*., 2000). Lipid peroxidation can lead to membrane damage. Malondialdehyde (MDA) and 4-hydroxynonenal (HNE), two breakdown products of lipid peroxidation, were increased in stroke patients (Vivek Kumar Gupta *et al*., 2011). Lipid peroxidation products have been particularly studied since the brain is very rich in polyunsaturated fatty acids, which are highly susceptible to free radical attack. An increase of conjugated dienes has been demonstrated after reperfusion following 30 minutes of severe ischemia. Lipid peroxidation products are also increased in this condition (Halliwell B; 1992). Brain levels of vitamin C have been found to be reduced both due to ischemia or ischemia followed by reperfusion. SOD activity and concentration in brain tissue after ischemia-reperfusion have been found to be decreased. Due to increased activity of excitatory amino acids like Glutamate, calcium level is found to be increased in ischemia and after reperfusion. Calcium activates proteolytic enzymes. Neuronal nitric oxide synthase is also calcium dependent and produces nitric oxide, which is able to react with superoxide generating the highly reactive radical peroxynitrite (Bruce-Keller *et al*., 1998, Watson BD *et al*., 1984).

Not all the protection comes from antioxidants produced in the body as its free radical "surveillance" system. A significant amount comes from dietary components that also serve as antioxidants. Thus antioxidants have been the focus of studies for developing neuroprotective agents to be used in the therapy for cerebral damage by ischemic reperfusion, which is an acute and progressive neuro-degenerative disorder.

Flavanoids have shown to be neuroprotective in I/R injury induced brain damage in animal studies. Polyphenolic compounds have also shown neuroprotective effect in ischemic reperfusion injury. Coriandrum sativum is rich in flavanoids and phenols (Axel Diederchisen).

Coriandrum sativum (Linn.) of family Umbelliferae, a glabrous, aromatic, herbaceous annual plant, is well known for its use as antioxidant. Essential oil, flavanoids, fatty acids, and sterols have been isolated from different parts of C. sativum (Axel Diederchisen). Above this it also contains antioxidant nutrients like vitamin C and vitamin A (Axel Diederchisen). It has been reported to possess antibacterial (Isao Kubo et. Al; 2004), antioxidant activities (Helle Wangensteen *et al*., 2004), anxiolytic (Emamghoreishi M *et al*., 2005) and anti-diabetic (Alison M et.al 1999).

Coriandrum sativum is reported to have a very effective antioxidant activity profile showing 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, lipoxygenase inhibition, and phospholipid peroxidation inhibition, iron chelating activity, hydroxyl radical scavenging activity, superoxide dismutation, glutathione reduction and antilipid peroxidation (Helle Wangensteen *et al*., 2004). It is reported that ethanolic extract of C. sativum possesses hepatoprotective activity which may be due to antioxidant potential of phenolic compounds (Chithra V and Leelamma S, 1997). The articles also suggest protective role of C. sativum against lead nitrate induced oxidative stress and tissue damage in the liver and kidney in male mice (Leena Kansal, 2011). So, this study was planned to investigate neuroprotective effect of Methanolic extract of C. sativum in cerebral ischemic reperfusion injury correlating with its antioxidant property.

However, no work has ever been carried out to evaluate the neuroprotective effect of leaves of C. sativum on cerebral ischemic reperfusion injury. Thus, it was considered worthwhile to investigate the effect of C. sativum on global cerebral I/R-induced cerebral injury in rat.

MATERIALS AND METHODS

Chemicals and drugs

Thiobarbituric acid, Ketamine, Sodium chloride, Potassium chloride, Sodium Pyrophoshate, 10% Formalin, Methanol, Acetone, Follin Ciocalteu reagent, Sodium potassium tartarate, Sodium dodecyl sulphate, Carbonate buffer, Xanthine solution, Phosphate buffer, Hydrogen peroxide, Trichloro acetic acid, 5, 5’ – dithios (2- nitro benzoic acid)(DTNB),TTC (2, 3, 5 triphenyltetrazolium chloride) stain.

Animals

The Wistar Albino rats of either sex 200-250 gm were used for the study. The animals were housed under well-controlled conditions of temperature (22 ± 2°C), humidity (55 ± 5%) and 12h/12h light-dark cycle. They were allowed free access to standard rodent pellet diet and drinking water. The food was withdrawn 12 h prior to surgical procedure; however, water was allowed ad libitum. The experimental protocol was approved by Institutional Animal Ethics Committee as per the guidance of committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India (Protocol NO. RKCP/COL/RP/12/29), New Delhi.

Plant material

The leaves of Coriandrum sativum were collected from local market of Rajkot. The collected samples were

authentified morphologically by the Head of Botany department, Christ College, Rajkot, Gujarat, India.

Plant material extraction

500 gm shade dried powder of Coriandrum sativum was defatted with petroleum ether. It was extracted with methanol (60-80°C) for 28 hours using soxhlet apparatus. Extract was filtered and evaporated at 40°C up to one-third of the initial volume. Remaining solvent was completely evaporated (Helle Wangensteen *et al*., 2004).

Experimental protocol

The Wistar Albino rats of either sex (200-250 gm) were divided into 5 groups of six rats each. Vehicle or drugs were fed once daily for 15 consecutive days prior to the experiment and treated as follows:

Group 1: Sham operated (n=6). Received vehicle i.e. distilled water.

Group 2: BCCAO control (n=6). Received vehicle i.e. distilled water, BCCAO for 30 min, followed by reperfusion for 45 min.

Group 3: Quercetin (10mg/Kg/p.o./day) treated group (n=6), BCCAO for 30 min followed by reperfusion for 45 min.

Group 4: Drug-extract treated (n=6). Methanolic extract of Coriandrum sativum (200 mg/kg/p.o./day) (MeCs), BCCAO for 30 min followed by reperfusion for 45 min.

Induction of Global cerebral ischemia

Surgical procedure was performed according to method of Iwasaki *et al*. The rats were anaesthetized by ketamine (100 mg/kg, i.p.) and supplemented as needed. Common carotid arteries were approached by midline incision of neck and were carefully separated from accompanying vago-sympathetic trunk. Rat brain ischemia was induced by blocking bilateral common carotid arteries (BCCAO) for 30 min and then reperfusion was allowed for 45 min by releasing the block. Temperature was maintained 37 ± 0.5 ◦C throughout the surgical procedure. Sham operated rats received the same surgical procedure except the common carotid arteries were not occluded.

Preparation of post mitochondrial solution

Following decapitation, the brain was removed and washed in cooled 0.9% saline, kept on ice and subsequently blotted on filter paper, then weighed and homogenized as 10% w/v in cold phosphate buffer (0.05 M, pH 7.4). The homogenate was centrifuged at 10,000 × g for 10 min at 4 ◦C and post-mitochondrial supernant (PMS) was kept on ice until assayed (MPW-350R, Korea).

Estimation of biochemical parameters

Lipid Peroxidation level

To 0.2 ml of brain homogenate, 0.2 ml of 4% sodium dodecyl sulphate, 1.5 ml of 20 % acetic acid and 1.5 ml of 0.5% Thiobarbituric acid was added. The mixture was heated for 60 min at 95°C in a temperature controlled water bath to give a pink colour. The mixture was centrifuged at 3500 rpm for 10 minute. The absorbance of the supernatant was read spectrophotometrically at 532 nm (Ohkawa et.al 1997).

Superoxide Dismutase (SOD) level

Supernatant (0.1ml) of sample was mixed with 0.1 ml EDTA (1x10-4 M), 0.5 ml of carbonate buffer (pH 9.7) and 1 ml of Epinephrine (3x 10-3M). The optical density of formed adrenochrome was read at 480 nm for 3 min at an interval of 30 sec. the enzyme activity has been expressed in terms of U/min/mg protein. One unit of enzyme activity is defined as the concentration required for the inhibition of the chromogen production by 50% in one minute under the defined assay conditions. The SOD activity (U/mg of protein) was calculated by using the standard plot (Mishra *et al*., 1979).

Catalase (Cat) level

A 50µl supernant was added to buffered substrate (50 mM phosphate buffer, pH 7 containing 10 mM H2O2) to make total volume 3 ml. The decrease in the absorbance was read at 240 nm for 2.5 min at an interval of 15 sec. The activity was calculated using extinction co-efficient of H2O2 0.041/µmoles/cm2. Results were expressed as µmoles of H2O2 utilized/min/mg protein (Aeibi *et al*., 1974).

Glutathion (GSH) level

To 1 ml of sample (brain homogenate), 1 ml of 10%TCA was added. The precipitated fraction was centrifuged and to 0.5 ml supernatant, 2 ml of DTNB reagent was added. The final volume was made up to 3ml with phosphate buffer. The colour developed was read at 412 nm. Standard curve for GSH was prepared using glutathione. Results were expressed as µmole of GSH/mg tissue (Beutler *et al*., 1963).

Calcium level

Labeled three test-tubes as blank, standard and test; and proceeded in table 1. Prepared samples were mixed well and incubated at room temperature (25oC) for 5 minutes. Absorbance of the standard and test samples was measured at 630nm against the blank, within 60 min (Batasakis *et al*., 1964).

Total protein level

To 0.2 ml of brain homogenate, 0.2 ml of 4% sodium dodecyl sulphate, 1.5 ml of 20 % acetic acid and 1.5 ml of 0.5% Thiobarbituric acid was added. The

mixture was heated for 60 min at 95°C in a temperature controlled water bath to give a pink colour. The mixture was centrifuged at 3500 rpm for 10 minute. The absorbance of the supernatant was read spectrophotometrically at 532 nm (Lowry *et al*., 1955).

Measurement of cerebral infarct area

Evaluation of infarct area by 2, 3, 5-triphenyltetrazolium chloride (TTC) staining method was used. Following ischemia or reperfusion, animals were decapitated, and the brains were removed. After that the brains were placed briefly in cold saline. Four coronal brain slices (2-mm thick) were made. Then the slices were incubated in phosphate buffered saline (pH 7.4) containing 2% 2, 3, 5- triphenyltetrazolium chloride (TTC) at 37°C for 10min and then kept in neutral-buffered formalin overnight. The images of the TTC-stained sections were captured by a digital camera and Adobe Photoshop 7.0. Then the cerebral infarction area was observed and compared between various treatment groups and negative control group (Bederson *et al*., 1986).

Histopathology

The brains from control and experimental groups were fixed with 10% formalin and embedded in paraffin wax and cut into longitudinal section of 5 µm thickness. The sections were stained with haematoxylin and eosin dye for histopathological observation the change in inflammation structure was observed and compared.

Statistical analysis

All the data are presented as means ±SEM. The significance of difference in means between control and treated animals for different parameters was determined by using One-way Analysis of Variance (ANOVA) followed by multiple comparison Tukey's test. Data were considered statistically significant at $P < 0.05$ and highly significant at $P < 0.001$. Statistical analysis was performed using INSTAT statistical software.

RESULTS

Biochemical estimation

The results showed in Table 2 demonstrate neuroprotective activity of MeCs. The BCCAO control group showed significant increase in lipid peroxidation and calcium levels and significant decrease in endogenous antioxidant enzyme levels (SOD, Catalase, and Glutathion) and total protein level as compared to sham operated group. The MeCs 200 mg/kg and Quercetin 10 mg/kg pretreated animals attenuated the oxidative stress by significantly reducing the levels of lipid peroxidation ($p < 0.001$) and calcium ($p < 0.001$) and significantly increased the levels of SOD ($p < 0.001$), Cat ($p < 0.001$), GSH ($p < 0.001$) and total proteins ($p < 0.001$).

Measurement of infarction area

The infarction in representative sections stained with 2, 3, 5-triphenyltetrazolium chloride (TTC) from different groups is shown in Figure 1. There was marked reduction in cerebral infarction area in hippocampus region in MeCs treated group as compared to BCCAO control group.

Histopathology

From the Histopathological studies (Figure 2), it was observed that 30 min BCCAO followed by 45 min of reperfusion produced shrinkage, atrophy and necrosis of neurons along with vacuolization and inflammatory infilteration in forebrains of BCCAO control group rats as compared to sham operated rats (B). The reactive changes were significantly attenuated better in methanolic extract C. sativum (200 mg/kg) (D) pretreated groups for 15 days as compared to BCCAO control groups. These changes were not evident in Sham operated group (A) and Quercetin treated groups (C).

Fig. 1. Neuroprotective effect of methanolic extract of *Coriandrum sativum* against global cerebral ischemia/reperfusion damage in rats evaluated by2, 3, 5-triphenyltetrazolium chloride (TTC) staining. Brain coronal sections were prepared (2mmthickness) and then each section was stained with TTC. A: Sham operated; B: BCCAO control group: Quercetin 10 mg/kg treated group and BCCAO; D: MeCs 200mg/kg treated group and BCCAO. A large infarction area observed mainly in the caudal side of hippocampus in the damaged brain of BCCAO control rats (B) whereas the infarction was markedly reduced in the rat brains treated with 200mg/kg MeCs (D) and also in Quercetin-treated animals(C)

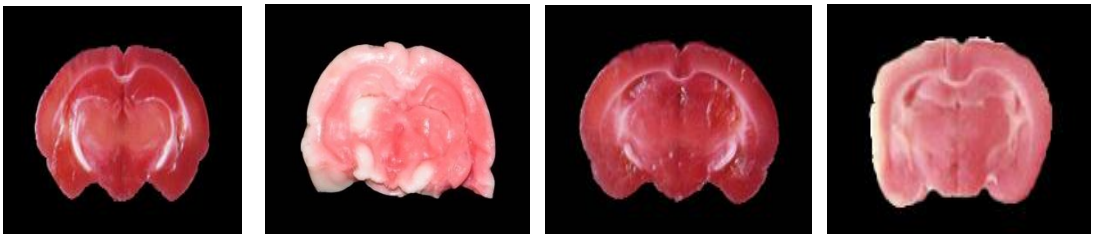

Fig. 2. Neuroprotective effect of methanolic extract of *Coriandrum sativum* against global cerebral ischemia/reperfusion damage in rats. Photographs of brain sections from different treatment groups stained with Heamotoxyllin & Eosin 10. Plates; A: Sham operated; B: BCCAO control group; C: Quercetin 10 mg/kg treated and BCCAO; D: MeCs 200 mg/kg treated and BCCAO. Ischemia (B) caused marked congestion of blood vessels and neutrophil infiltration and increased intracellular spaces. These effects were further augmented by reperfusion i.e. lymphocytic proliferation and neuronal necrosis. There is significant reversal of damage observed in MeCs-treated groups (D) and also in Quercetin-treated group (C). The sham operated group (A) maintained the normal architecture. The reversal was marked as the values were mostly comparable with BCCAO control group (B)

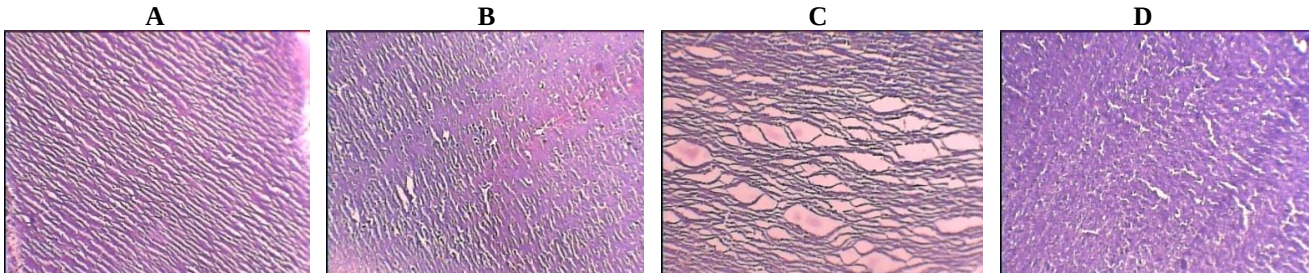

Table 1 Procedure for calcium estimation

Addition sequence	Blank (ml)	Standard (ml)	Test (ml)
Buffer Reagent (L1)	0.5	0.5	0.5
Colour Reagent (L2)	0.5	0.5	0.5
Distilled Water	0.02	-	0.05
Calcium standard (S)	5	5	5
Sample	-	-	0.02

Table 2 Neuroprotective effect of *Rauwolfia serpentina* against bilateral common carotid artery ligation in rats

Sr. No.	Treatment Groups	Lipid Peroxidation (nmoles/mg of protein)	SOD (U/mg of protein)	Catalase (U/mg of protein)	GSH (nmoles/mg of protein)	Calcium (mg/dl)	Total proteins
1.	**Sham operated**	4.82 ± 0.11	16.69 ±0.06	0.30 ± 0.04	3.30 ±0.09	2.07 ±0.14	620.00 ±8.01
2.	**BCCAO control**	8.11 ± 0.081*	10.82 ±0.07*	0.08 ±0.01*	1.20 ±0.07*	9.20 ±0.09*	111.68 ± 2.09*
3.	**Quercetin treated**	1.73 ±0.15**	20.34 ± 0.06**	0.65 ± 0.06**	4.22 ±0.21**	6.34 ± 0.13**	395.00 ± 4.87**
4.	**200 mg/kg MeCs + BCCAO**	1.83 ± 0.07**	13.39 ±0.22**	0.85 ±0.05**	3,13 ± 0.19**	3.30 ± 0.08**	340.03 ± 2.66**

*Values are expressed in mean ± SEM n=6, One-way analysis of Variance (ANOVA) followed by multiple comparision Tukey's test, * indicates significance of data when compared to sham group and level of significance is p<0.001. ** indicates significance of data when compared to BCCAO control group and level of significance is p<0.001.*

***Sham**- Sham Operated, **BCCAO**- Bilateral common carotid artery occlusion, **Std**- Standard drug Quercetin treated group(10mg/kg), **MeCs**- Methanolic extract of Coriandrum sativum (200mg/kg).*

DISCUSSIONS

The present study revealed neuroprotective potential of MeCs at 200mg/kg. We estimated LPO, SOD, CAT, GSH, calcium and total protein levels in the brain tissue as an index to assess the severity of oxidative damage.

In the present study, the antioxidant and

neuroprotective potential of MeCs was studied against BCAO-induced oxidative stress in rats. Experimental models of stroke have been developed in animals in an attempt to mimic the events of human cerebral ischemia. It is well documented that transient global cerebral ischemia results in neurological abnormality. Therefore, global cerebral ischemia of short duration followed by reperfusion has been employed in the present study (Raghvendra *et al*., 2009).

It was shown that Coriandrum sativum have phenolic compounds and flavonoides, suggesting that these compounds contribute to the antioxidative activity. Phenolic substances such as flavonoids, cumarins, cinnamic acid and caffeic acids are believed to have antioxidant properties, which may play an important role in protecting cells and any organ from oxidative degeneration (Helle Wangensteen *et al*., 2004).

Bilateral common carotid artery occlusion for 30 min followed by 45 min of reperfusion was associated with increase generation of ROS and free radicals (Raghvendra *et al*., 2009).

The large number of polyunsaturated fatty acids (PUFA's) makes cell membranes particularly vulnerable to lipid peroxidation. The oxidation of PUFA causes them to be more hydrophilic, thereby altering the structure of membrane with resultant changes in fluidity and permeability. Lipid peroxidation can inhibit the function of membrane bound receptors and enzymes. The thiobarbituric acid reacting substance (TBARS) assay is used as an indicator of lipid peroxidation and levels of free radicals. The assay is based on the reactions of thiobarbituric acid with malondialdehyde produced during lipid peroxidation (Sun AY *et al*., 1998). As observed in our study, the BCCAO controlled group showed increase in malondialdehyde in brain affected by ischemic-reperfusion injury which suggested enhanced lipid peroxidation. Methanolic drug extract pretreated animals showed significantly ($p<0.001$) less lipid peroxides due to ischemic-reperfusion injury as compared to than untreated animals. Quercetin (a standard antioxidant agents) - treated animals also showed lesser degree of lipid peroxidation than control group. Hence, it is possible that mechanism of protection of brain by C. sativum extract might be due to its antioxidant effect.

Superoxide dismutase is an important endogenous antioxidant and prevents production of free radicals (Chaudhary G *et al*., 2003). Superoxide dismutase levels were significantly higher in C. sativum extract-treated animals when compared to BCCAO control animals. The BCCAO controlled group showed a decreased level of SOD as compared to sham operated group. As an antioxidant, both extracts scavenges free radicals and reactive oxygen molecules, which are produced during metabolic pathways of detoxification.

Catalase decomposes hydrogen peroxidase and converts it to water and diatomic oxygen, whereas superoxide dismutase generates H2O2 from free radicals. An increase in production of superoxide dismutase without a subsequent elevation of catalase leads to the accumulation of hydrogen peroxidase, which is converted to hydroxyl radicals that produced deleterious effect on brain (Pigeolet E *et al*., 1998). In the present study, catalase levels were found to be less in animals subjected to ischemic-reperfusion injury. The reactive-oxygen-species-induced lipid peroxidation causes more production of hydroxyl radicals, which then inactivates catalase. In C. sativum extract-treated animals, increase in the catalase activity was observed which suggest generation of hydroxyl radicals. Thus, catalase activity can be more in alcoholic drug extract-treated animals. These findings are in agreement with another experiment. Quercetin-treated animals also showed a similar effect.

Reduced Glutathion (GSH) is one of the primary endogeneous antioxidant defense systems in brain, which removes hydrogen peroxides and lipid peroxidase. Decline in GSH levels could either increase or reflect oxidative state. In present study decreased GSH levels were observed hippocampus of ischemic rats. Depletion of GSH level in BCCAO control group as compared to sham operated group signified the same thing. It has been shown that depletion in GSH levels in ischemic reperfusion injury can be attributed to several factors such as cleavage GSH levels to cysteine, decrease in synthesis of GSH and formation of mixed disulfides, causing their cellular stores to be depleted (Nagini *et al*., 2003; Kosower NS *et al*., 1978). Interestingly, the rats fed with extracts of C. sativum showed increase in GSH levels as compared to BCCAO control group.

A number of events predispose the brain to generation of ROS like rapid decrease in ATP levels, calcium release from intracellular stores and loss of calcium haemostasis (Kosower NS *et al*., 1978). Thus calcium levels were estimated which were found to be reduced significantly in brains of ischemic-reperfused rats. BCCAO control group exhibited increased level of calcium as compared to sham operated group. The brains of rats fed with extracts of C. sativum showed markedly reduced levels due to reduction in excitotoxicity and regulation of depolarised states. Quercetin treated group exhibited same.

Calcium activates proteolytic enzymes. Thus proteins levels are estimated (Simonian NA, 1996). The total protein levels were found to be decreased in

reperfused rats. Drug treated group showed increased brain protein levels as compared to control group.

2, 3, 5-triphenyltetrazolium chloride (TTC) is converted to red formazone pigment by nicotinamide adenine dinucleotide (NAD) and dehydrogenase present in living cells. Hence viable cells were stained deep red. The infarcted cells loose these enzymes and, thus, remained unstained dull yellow (Simonian NA; 1996). The BCCAO control group thus showed higher cerebral infarction due to increased cell death, which was found to be reduced in C. sativum and Quercetin treated groups.

Ischemic-reperfusion injury is known to produce necrosis of brain, which can be directly visualized by histological study; biopsy of the rat brain subjected to ischemic-reperfusion injury showed significant necrosis (Facchinetti F *et al*., 1998). The severe neuronal loss, observed as shrinkage of neurons and atrophy, was observed in Histopathological sections of ischemic reperfused brains. Interestingly the effect was attenuated by administrating 200 mg/kg and 40 0 mg/kg of C. sativum and extract.

CONCLUSION

From the above discussion it can be concluded that Coriandrum sativum has antioxidant property, which is responsible for beneficial effects in cerebral ischemia-reperfusion injury. It also reduced calcium mediated neuronal damage. Stroke being one of the most important cause of mortality and morbidity, it could be propitious to go on with further studies with C. sativum in these patients as this herbal drug showed improvement in cerebral infarction and reductions in oxidative stress in ischemia-reperfusion model.

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