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Pharmacological Study

The Ayurvedic drug *Ksheerabala* (101) ameliorates alcohol-induced neurotoxicity by down-regulating the expression of transcription factor (NFkB) in rat brain

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Abstract

Introduction: Most of the pharmaceutical effects of alcohol are due to its accumulation in the brain. *Ksheerabala* (101) an Ayurvedic formulation mainly used against central nervous system disorders. **Aim:** To determine the antioxidant and neuroprotective effect of *Ksheerabala* (101) on alcohol-induced oxidative stress in rats. **Materials and Methods:** Male Albino rats of Sprague-Dawley strain were grouped into four; control, alcohol (4 g/kg), *Ksheerabala* (15 μL/1 ml milk/100 g) and *Ksheerabala* (15 μL/1 ml milk/100 g) + alcohol (4 g/kg). After the experimental period (90 days), the animals were sacrificed and the effect of *Ksheerabala* (101) was studied on oxidative stress, inflammatory markers, and induction of transcription factor in brain. Results were statistically analyzed by one-way ANOVA. **Results:** The activities of antioxidant enzymes and reduced glutathione which were decreased in alcohol-treated rats, increased significantly in co-administered groups. The lipid peroxidation products and protein carbonyls which were increased significantly in alcohol-treated rats decreased significantly in co-administered groups. The expression of gamma-glutamyl cysteine synthase decreased significantly in alcohol-treated rats and increased significantly in co-administered groups. The transcription factor nuclear factor-κB (NFκB) which was up-regulated in alcohol-treated rats was down-regulated in co-administered rats. The histopathology reinforced these results. **Conclusion:** *Ksheerabala* (101) attenuates alcohol-induced oxidative stress and down-regulates the expression of NFκB in rat brain.

Key words: Alcohol, histopathology, *Ksheerabala* (101), neurotoxicity, oxidative stress

Introduction

Alcohol is the world's most widely used psychoactive drug, but chronic alcohol consumption leads to permanent organ damage or death. Alcohol abuse can result in brain damage and neurodegeneration.[1] Alcohol may also injure the brain by increasing oxidative stress.[2] Although the mechanisms behind oxidative stress is not well-understood, numerous studies have demonstrated that chronic ethanol consumption is accompanied by both oxidative damage to cellular proteins, lipids, and DNA[3,4] and reduced levels of the endogenous antioxidants.[5] Excessive production of reactive oxygen species has been proposed as a potential mechanism for ethanol-induced neuronal damage.[6] There is evidence suggesting the involvement of oxidative stress in neurodegenerative diseases.[7]

Growing evidence indicates the role that inflammation plays as a potential pathogenic factor in many central nervous system (CNS) diseases, including neurodegenerative diseases.[8,9] The hallmark of the neuroinflammation is the activation of glial cells and the production of cytokines and inflammatory mediators that trigger neural damage.[9] Alcohol not only stimulates glial cells, but may also induce a proinflammatory response in the brain.[10] Chronic alcohol intake upregulates inflammatory mediators in both brain and astroglial cells, activating signaling events associated with inflammation.[11]

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Many drugs in Ayurveda possess neuroprotective effect. *Ksheerabala* (101) is an Ayurvedic drug, which is also used as a nerve tonic. The textual reference of *Ksheerabala* (101) is found in *Ashtangahridaya*.[12] It is used in Ayurveda to treat arthritis, CNS disorders and insomnia. It also enhances the functioning of sense organs. The main contents of *Ksheerabala* (101) are *Bala* (*Sida Cordifolia* Linn., belongs to Malvaceae family), *Ksheera* (cow's milk) and *Tila Taila* (Sesamum oil). Previous study showed that *Ksheerabala* reduces the oxidative stress induced by quinolinic acid.[13] Hence, the main focus of the present study was to evaluate the antioxidant and neuroprotective properties of *Ksheerabala* (101) against alcohol-induced neurotoxicity.

Materials and Methods

Animals

Male albino rats (Sprague-Dawley strain) weighing between 100 and 140 g bred and reared in our animal house were used for the experiment.

A total of 24 rats were divided into 4 groups of 6 rats each.

- Group I: Control
- Group II: Alcohol (4 g/kg b.wt)
- Group III: *Ksheerabala* (15 µl/100 g b.wt/day)
- Group IV: Alcohol (4 g/kg body weight + *Ksheerabala* (15 µl/100 g b.wt/day).

Animals were housed in polypropylene cages. Cages were kept in a room that was maintained between 28°C and 32°C. The light cycle was 12 h light and dark. Animals were handled using the laboratory animal welfare guidelines.[14] Rats were fed with rat feed (Ashirvad Private Ltd., India). Food and water were given *ad libitum*. The study protocol was approved by the institutional animal ethics committee [IAEC–KU-14/2009-2010-BC-MI (22)].

The dose of alcohol[15] and *Ksheerabala* (101)[13] were selected from the previous studies. Alcohol (4 g/kg body weight, 1:1 dilution) and *Ksheerabala* (101) (15 µl dissolved in 1 ml milk/100 g b.wt) were given orally by gastric intubation. Alcohol was purchased from Merck India and *Ksheerabala* (101) was procured from Kottakkal Arya Vaidyasala, Kottakkal, Kerala, India (Batch No. 126165).

Alcohol and *Ksheerabala* (101) were given separately every morning for 90 days to the co-administered group. At the end of the experimental period, the animals were sacrificed. The brain was dissected out and cleaned with ice-cold phosphate buffer saline, blotted dry and immediately transferred to ice-cold containers for various biochemical evaluations. Blood was collected in clean, dry test tubes and allowed to clot for 30 min at room temperature. The clear serum was separated after centrifugation at 2000 g for 10 min and used immediately for the assay of various parameters.

Biochemical analysis

The tissue was extracted[16] and superoxide dismutase (SOD),[17] catalase,[18] glutathione reductase (GR) activity,[19] glutathione peroxidase (GPx) activity,[20,21] malondialdehyde (MDA) estimation,[22] hydroperoxides (HP) estimation,[23] conjugated dienes, (CD)[24] protein carbonyls estimation,[25] tissue protein estimation,[26] glutathione (GSH),[27] isolation of monocytes,[28] cyclooxygenase (COX) activity,[29] and lipooxygenase (LOX)[30] were assayed.

Total RNA isolation

Total RNA was isolated from the brain using TRI Reagent (Sigma-Aldrich).[31]

Reverse transcription polymerase chain reaction

The isolated RNA was used for reverse transcription- polymerase chain reaction (RT-PCR) to study the expression of nuclear factor-κB (NFκB), gamma- glutamyl cysteine synthase (γGCS) and glyceraldehyde-3-phosphate dehydrogenase. Primer sequences are given in Table 1. Total tissue RNA (2 mg) was primed with 0.05 mg oligo dT and reverse-transcribed by omniscript RT using a cDNA synthesis kit (Qiagen). PCR was carried out using an Eppendorf thermocycler (model 5332). The PCR mixture contained 10 mM-Tris (pH 8.3), 50 mM-KCl, 1.5 mM-$MgCl_2$, deoxynucleoside triphosphate (20 mM each), gene-specific primers (0.5 mM each) and Taq polymerase (0.025 units/ml). After an initial denaturation step at 94°C, 35 amplification cycles were performed. A final extension step of 5 min at 72°C was performed in order to complete the PCR. The amplified product was analyzed by electrophoresis on 2% agarose gel containing ethidium bromide. Then, the gels were subjected to densitometric scanning (Bio-Rad Gel Doc) to determine the optical density of each, and then normalized.

Statistical analysis

The results were analyzed using a statistical program SPSS/PC+, Version 17.0 (SPSS Inc., Chicago, IL, USA). A one-way ANOVA was employed for comparison among the six groups. Duncan's *post-hoc* multiple comparison tests of significant differences among groups were determined, $P < 0.05$ was considered to be significant.

Results

The activities of catalase, SOD, GPx, GR [Table 2] were significantly decreased in the brain of the alcohol-treated group

Table 1: Primer sequences used for RT-PCR analysis

Genes	Primer sequences	Gene accession number
GAPDH	Forward 5' TGA CAA CTC CCT CAA GAT TGT CA 3' Reverse 5' GGC ATG GAC TGT GGT CAT GA 3'	NM 017008.4
NFκB	Forward 5'CAC CAA AGA CCC ACC TCA CC 3' Reverse 5' GGA CCG CAT TCA AGT CAT AGT 3'	NF 001105720.2
γGCS	Forward 5'CCT TCT GGC ACA GCA CGT TG 3' Reverse 5' TAA GAC GGC ATC TCG CTC CT3'	J 05181.1

GAPDH: Glyceraldehyde-3 phosphate dehydrogenase, NFκB: Nuclear transcription factor kB, γGCS: Gamma-glutamyl cysteine synthase, RT-PCR: Reverse transcription-polymerase chain reaction

Table 2: Activities of antioxidant enzymes in the brain

Groups	Catalase (units*/ mg protein)	SOD (units#/ oxidized/min)	Glutathione peroxidase (µmole NADPH oxidized/min)	Glutathione reductase (µmole NADPH oxidized/min)
Control	7.90±0.76[a]	9.95±0.96[a]	3.88±0.37[a]	51.97±4.99[a]
Alcohol	3.40±0.33[b]	4.10±0.39[b]	1.08±0.10[b]	35.28±3.38[b]
Ksheerabala	8.08±0.78[a]	10.74±1.03[a]	4.17±0.40[a]	53.54±5.14[a]
Alcohol + *Ksheerabala*	7.76±0.74[a]	9.73±0.94[a]	2.89±0.47[c]	47.14±4.53[c]

Values are given as mean±SD.Values not sharing a common superscript differ significantly at $P<0.05$. b is significantly different from a and c is significantly different from a and b. *Units:Velocity constant/s, #Units: Enzyme concentration required to inhibit the chromogen production by 50% in 1-min. *F* values: Catalase - 73.82, SOD - 82.33, glutathione peroxidase - 130.56, glutathione reductase - 21.34. Df between groups - 3. Df within groups – 20. SD: standard deviation , SOD: Superoxide dismutase, NADPH: Nicotinamide adenine dinucleotide phosphate

compared to the control. There was also a significant increase in the activities of these enzymes and the concentration of GSH in group administered *Ksheerabala* (101) along with alcohol compared with alcohol group.

The level of lipid peroxidation products MDA, HP, and CD in brain [Table 3] was increased significantly in alcohol-treated groups compared to control group and the concentration of these reduced significantly in co-administered group when compared with alcohol-treated group. The level of GSH was significantly decreased in the brain of the alcohol-treated group compared to the control. The concentration of protein carbonyls increased significantly in alcohol-treated group compared to the control group and the concentration of these reduced significantly in co-administered group when compared with alcohol-treated group [Table 4].

The activities of inflammatory markers COX and LOX in monocytes [Table 5] were increased significantly in alcohol-treated rats compared to control group and their activities were decreased significantly in co-administered group compared to alcohol-treated rats.

The mRNA expressions of NFκB and γGCS were evaluated by RT-PCR. In alcohol-treated rat brain, PCR products of NFκB had a marked increase compared to control rats. Treatment with *Ksheerabala* reduced the levels of expression of NFκB [Figure 1] gene. There was no significant change in the expression of these genes in *Ksheerabala* treated rats. The mRNA expression of γGCS [Figure 2] was markedly decreased in alcoholic rats, and the changes were reversed by treatment with *Ksheerabala*.

Table 3: Concentration of lipid peroxidation products in the brain

Groups	MDA (mM/100 g wet tissue)	HP (mM/100 g wet tissue)	CD (mM/100 g wet tissue)
Control	2.05±0.20[a]	33.28±3.19[a]	40.62±3. 68[a]
Alcohol	6.74±0.65[b]	72.73±6.98[b]	66.82±6.41[b]
Ksheerabala	1.81±0.17[a]	35.12±3.37[a]	40.14±3.03[a]
Alcohol + *Ksheerabala*	2.33±0.22[c]	38.19±3.66[c]	48.17±4.22[c]

Values are given as mean±SD.Values not sharing a common superscript differ significantly at $P<0.05$. b is significantly different from a and c is significantly different from a and b. *F* values: MDA - 266.08, HP - 117.17, CD - 124.98. Df between groups - 3. Df within groups - 20.SD: Standard deviation, MDA: Malondialdehyde, HP: Hydroperoxides, CD: Conjugated dienes

Table 4: Concentration of protein carbonyls and reduced glutathione in brain

Groups	Protein carbonyls (nM/mg protein)	Reduced glutathione (mM/100 g tissue)
Control	0.88±0.08[a]	30.84±2.82[a]
Alcohol	3.80±0.36[b]	13.88±1.31[b]
Ksheerabala	0.94±0.09[a,c]	35.02±3.19[c]
Alcohol + *Ksheerabala*	1.1±0.10[c]	28.89±2.63[a]

Values are given as mean±SD.Values not sharing a common superscript differ significantly at $P<0.05$. b is significantly different from a and c is significantly different from a and b. *F* values protein carbonyls - 329.62, reduced glutathione - 76.43. Df between groups - 3. Df within groups -20. SD: Standard deviation

Table 5: Activities of inflammatory markers in monocytes

Groups	COX-2 (µmoles of MDA liberated/min/mg protein)	5-LOX (OD shift/ min)/mg protein
Control	0.39±0.05[a]	1.27±0.12[a]
Alcohol	2.32±0.22[b]	4.44±0.44[b]
Ksheerabala	0.39±0.04[a]	1.17±0.12[a]
Alcohol + *Ksheerabala*	1.39±0.14[c]	2.05±0.20[c]

Values are given as mean±SD.Values not sharing a common superscript differ significantly at $P<0.05$. b is significantly different from a and c is significantly different from a and b. *F* values: COX-2-321.47, 5-LOX - 248.61. Df between groups - 3. Df within groups - 20. SD: Standard deviation, COX: Cyclooxygenase, MDA: Malondialdehyde, LOX: Lipoxygenase

Discussion

The brain is one of the major target organs for the actions of alcohol, and heavy alcohol consumption has long been associated with brain damage. The brain processes large amounts of oxygen in a relatively small mass, and has a high content of substrates available for oxidation (that is, polyunsaturated fatty acids and catecholamines) in conjunction with low antioxidant activities; making it extremely susceptible to oxidative damage.[32] Experiments with cells of rat brains have shown that a single dose of alcohol results in increases in lipid HP levels.[33] Our results are in line with the findings that alcohol causes oxidative damage in the brain. This was evidenced by higher levels of lipid peroxidation products and lower activities of scavenging enzymes. In addition to the attenuation of antioxidant enzyme activity, the antioxidant GSH was also shown to be decreased by ethanol exposure. This is in line with the observations of previous study.[34] The reduced level of GSH can be correlated with decreased expression of γGCS, the rate-limiting enzyme of GSH biosynthesis.[35] In the present study, it was observed an increase in activities of these enzymes, decreased lipid peroxidation products and increased GSH content in the brain of rats administered *Ksheerabala* (101) along with alcohol

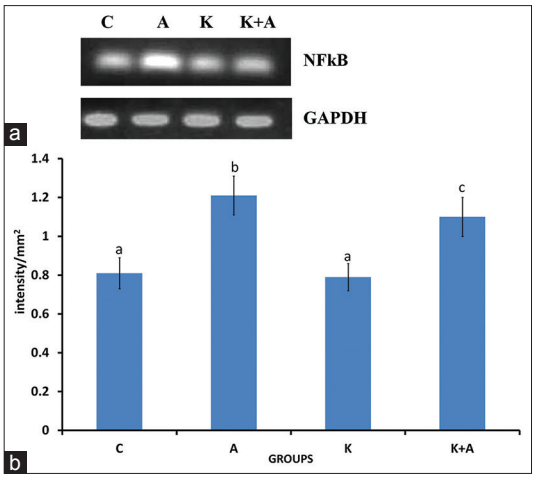

Figure 1: (a) Expression of nuclear factor kB (NFkB) at mRNA level, (b) Intensity of NFkB mRNA using gel doc. C: Control; A: Alcohol; K: Ksheerabala; K+A: Ksheerabala + Alcohol. The mean intensity was measured and expressed as INT/mm². Results are expressed as the average of quadruplicate experiments ± standard deviation. Different letter indicates values statistically significant at *P* < 0.05

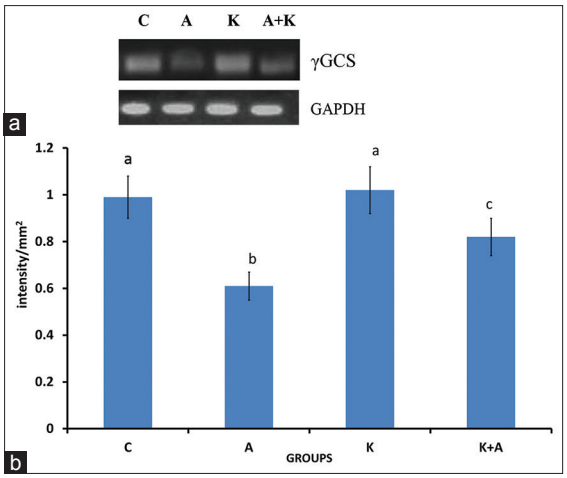

Figure 2: (a) Expression of gamma-glutamyl cysteine synthetase (gamma-glutamylcysteine synthetase) at mRNA level; (b) Intensity of γGCS mRNA using gel doc. C: Control; A: Alcohol; K: Ksheerabala; K+A: Ksheerabala + Alcohol. The mean intensity was measured and expressed as INT/mm². Results are expressed as the average of quadruplicate experiments ± standard deviation. Different letter indicates values statistically significant at *P* < 0.05

indicating that *Ksheerabala* (101) possess significant protective effect against alcohol-induced oxidative damage. This is in agreement with earlier studies in which *Ksheerabala* reduced quinolinic acid-induced neurotoxicities.[13]

Oxidative damage to proteins generates increased carbonyl groups due to oxidation of sensitive amino acids, such as histidine, proline, arginine, and lysine. These oxidatively modified proteins are functionally inactive and are degraded by the enzyme alkaline protease.[36] In consistent with this fact, there was an increase in the level of protein carbonyls in alcohol-treated rats. The co-administration of *Ksheerabala* (101) along with alcohol reduced the peroxidation of proteins in the brain.

Oxidative stress and inflammation are likely linked and may be difficult to tease apart. Several animal studies suggest that chronic alcohol intake alters CNS immune and inflammatory responses through interference with NFκB and expression of NFκB controlled genes.[37] NFκB is classically activated through dissociation from IkB in the cytoplasm.[38] DNA-binding and transactivation functions are also regulated through posttranslational modifications of NFκB proteins in the cell nucleus. Thus, chronic alcohol administration up-regulates inflammatory mediators in the animal brain, and isolated astrocytes followed by activation of NFκB and the upregulation of inducible NO synthase[39] and COX-2 expression. In inflammation, the prostaglandins are synthesized as a result of various cytokines signaling COX-2 transcription. It was found that 5-LOX pathway is crucially involved in brain disorders, and 5-LOX inhibition could act as a neuroprotective.[40] Prostaglandin E2, the main prostaglandin synthesized during inflammation, is formed via COX-mediated catalysis. The down-regulation in the expression of NFκB in the co-administered rats indicates that *Ksheerabala* (101) can down-regulate the alcohol induced upregulation of these genes, and thus COX and LOX mediated inflammation. The reduced activities of COX and LOX in co-administered group in comparison with alcohol also support this.

The antioxidant and anti-inflammatory effect of *Ksheerabala* (101) may due to the additive effect of its individual components. The main contents of *Ksheerabala* (101) are *Bala* (*S. cordifolia*), *Ksheera* (cow's milk) and *Tila Taila* (Sesamum oil). There are reports that milk caseins possess significant antioxidant activity.[41] The studies have shown that sesame oil protects against lipopolysaccharide-stimulated oxidative stress in rats.[42] The consumption of this oil influences beneficially the blood glucose, glycosylated hemoglobin, lipid peroxidation, and antioxidant levels in diabetic rats.[43] The plant *S. cordifolia* belongs to the family Malvaceae is a widely used herb for a number of neurodegenerative disorders. The previous studies showed that it had a protective effect on quinolinic acid-induced neurotoxicity,[44] and it had a potent action against alcohol-induced hepatotoxicity.[15]

Conclusion

The results confirmed that alcohol-induced toxic effects may be due to free radical mechanisms and provide evidence that *Ksheerabala* (101) significantly protects brain cells and reduces the severity of damage caused by alcohol intoxication. The mechanism of action may be by suppression of the activation of a transcription factor, that is, NFκB and concomitant reduction in the neuroinflammation. However, further clinical trials are needed to determine whether *Ksheerabala* (101) that inhibit the activation of NFκB will be effective in preventing and possibly treating alcohol-induced brain injury in humans.

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Conflicts of interest
There are no conflicts of interest.

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हिन्दी सारांश

मद्यसेवित चूहों के मस्तिष्क से ट्रांसक्रिप्सन न्यूक्लियर फैक्टर के.बी. को कम करने में क्षीरबला (१०१) का प्रभाव

एस. रेजिथा, पी. प्रतिभा, इंदिरा मदमबट

मस्तिष्क पर मद्य का अधिकांश प्रभाव उसके संचय के कारण होता है। मद्य प्रेरित ऑक्सिडेटीव तनाव वाले चूहों पर आयुर्वेदिक दवा क्षीरबला (१०१) के एंटीऑक्सिडेंट और न्यूरोप्रोटेक्टिव प्रभाव को जानने के उद्देश्य से स्प्रॉग डाउले नर अब्लिनो चूहों को तीन समूह में बांटा गया। नियंत्रक समूह में मद्य (४ ग्रा./कि.ग्रा.), दूसरे समूह में क्षीरबला (१५ माइक्रो लि./ १ मि.ली. दूध/१०० ग्रा.) और तीसरे समूह में क्षीरबला (१५ माइक्रो लि./मिली.दूध/१०० ग्रा.) + मद्य (४ ग्रा./कि.ग्रा.) दिया गया । प्रयोगात्मक अवधि (९० दिन) के बाद चूहों का मारा गया और उनके मस्तिष्क पर क्षीरबला का ओक्सिडेटीव तनाव, सूजन निशान और मस्तिष्क में प्रतिलेखन कारक प्रभाव देखा गया। मद्य देने पर एंटीऑक्सीडेंट एन्जाइमों की गतिविधियां और ग्लुटाथिओन की कमी होती है। क्षीरबला और मद्य एक साथ देने पर ये दोनों चीजें बढ़ती हैं। लिपिड पेरोक्सिडेशन उत्पादक और प्रोटीन कार्बोनिल्स मद्य देने पर बढ़ता हैं और दोनों एक साथ देने पर घटते हैं। गामा ग्लुटामिल सिस्टीन सिंथेस मद्य देने पर कम हो जाता है और क्षीरबला और मद्य एक साथ देने पर बढ़ता है। प्रतिलेखन कारक (न्यूक्लियर फैक्टर के.बी.) मद्य देने पर बढ़ता है और क्षीरबला देने पर कम होता है। ऊतक विकृति विज्ञान इसको प्रमाणित करता है कि क्षीरबला मद्य देने पर चूहों के मस्तिष्क का ऑक्सिडेटीव तनाव के साथ न्यूक्लियर फैक्टर के.बी. को भी कम कर देता है।