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Original Article

Protective Role of *Kaempferol* Against Acrylamide Intoxication

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ABSTRACT

Background: In present scenario Acrylamide (A) concentration in starchy food processed at high temperatures have become very serious health problems. It is also used in industries and research chemical and potent toxic to experimental animals as well as humans. The present study was carried out to investigate protective effects of *Kaempferol* (KPF) against A-induced toxicity in rats. KPF is a natural flavonol, found in tea, strawberries, broccoli, cabbage, beans, grapes, tomato and plant products used in traditional medicine such as ginkgo biloba, Moringa oleifera and propolis. **Methods:** A (38.27 mg/kg, p.o.) was administered to female Wistar rats for 10 consecutive days followed by therapy of KPF for 3 days at different doses (5, 10, 20, 40 mg/kg, p.o.). **Results:** Activities of transaminases (aspartate aminotransferase/alanine aminotransferase), urea, creatinine and lipid profile were significantly rise whereas decline in haemoglobin after A administration. A significant elevation of LPO were observed with concomitant depleted activities of SOD, CAT and GSH in toxicant treated group. Significant reduction was found in the activity of AChE in brain. Therapy of KPF showed its protective effect on biochemical and histopathological observation at all the doses in a dose dependent manner. **Conclusion:** The protective effect of KPF was observed against A-induced toxicity.

Key words: Carcinogenic, Flavonoid, Neurotoxic, Oxidative stress, Antioxidant.

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INTRODUCTION

Plants have been reported to have protective capability due to the presence of the polyphenols and flavonoid and have anti allergic-1, anti inflammatory and antioxidant properties both in animal and human models which prevent neurotoxicity.[1,2] *Kaempferol* (KPF, Figure1) is 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, a natural polyphenol, nontoxic, natural dietary compound that has been isolated from citrus fruits, grape fruit, tea, beans, brussels sprouts, cabbage, tomato, broccoli, apples, strawberries and other plant sources. It act as free radicals scavenger and superoxide radicals scavenger and preserve the activity of various antioxidant enzymes such as catalase, glutathione peroxidase and glutathione-s-transferase.[3] Some preclinical studies have shown that dietary *Kaempferol* has a wide range of pharmacological activities, including antioxidant, anti inflammatory, anti carcinogenic, antidepressant, antidiabetic, neuro protective, cardio protective and anti allergic activities.[3] KPF also reduces the risk of chronic diseases, especially cancer, controls intracellular signalling cascades and preserves normal cell viability. It modulates a number of key elements in cellular signal transduction pathways linked to apoptosis, angiogenesis, inflammation and metastasis.[4]

Now a days, the presence of a Acrylamide (A) in lots of fried and baked foods raises concerns due to its potential to cause toxicity and cancer in animals and human.[5] It is formed in carbohydrate-rich foods processed at high temperature during baking, grilling or frying.[6] A is a water soluble vinyl monomer which is used in water purification, cosmetic industries, glues and paper, aesthetic surgeries, as a soil stabilizer and for other industrial and laboratory purposes. Dietary exposure of A to humans through various food such as French fries, potato crisps, bread, cookies, and coffee.[7]

Children eat more A-rich foods than adults probably for their higher caloric intake. Its high level of exposure causes carcinogenesis, neurotoxicity and reproductive toxicity in mice and rats.[8]

Oxidative stress and mitochondrial dysfunctions have been demonstrated to be key mechanisms in chemical-induced cell injuries, which refers to enhanced generation of reactive oxygen species (ROS)/ reactive nitrogen species (RNS) and/ or depletion of antioxidant defense system so, imbalance between pro-oxidants and antioxidants.[9] The aim of present study to investigate the protective role of KPF against A toxicity in liver, kidney and brain in rats.

MATERIALS AND METHODS

Experimental animals

Wistar female albino rats weighing 160 ± 10 g from departmental animal facility were selected where they received standard pellet diet (Pranav Agro Industries, New Delhi, India having metal contents in ppm dry weight Cu, 10; Mn, 33; Zn, 45; and Co, 5) and drinking water ad libitum. They were maintained in an air-conditioned animal room; temperature of 25^{0}C; relative humidity 55.5%; ventilation frequency of18 times per hour; and a 12-h light/dark cycle. Animals used in this study were treated and cared for in accordance with the guidelines recommended by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Chemicals

Acrylamide, *Kaempferol* (Sigma Aldrich) and other analytical grade laboratory reagents were procured from Merck (Germany), HiMedia and SRL chemical (India).

Experimental design

Group 1: Control

Group 2: KPF, 40 mg/kg, *p.o.* for 03 days

Group 3: A at 38.27 mg/kg, *p.o.*(1/3 rd of LD50) for 10 days, 11–13days Rest

Group 4: A (As Group3) + KPF, 5 mg/kg, *p.o.* for 03 days

Group 5: A (As Group3) + KPF, 10 mg/kg, *p.o.* for 03 days

Group 6: A (As Group3) + KPF, 20 mg/kg, *p.o.* for 03 days

Group 7: A (As Group3) + KPF, 40 mg/kg, *p.o.*for 03 days

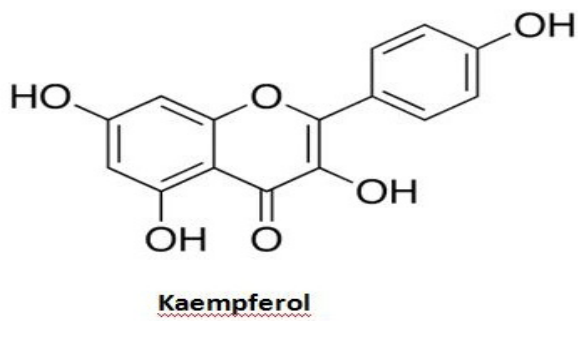

Figure 1: Structure of *Kaempferol*.

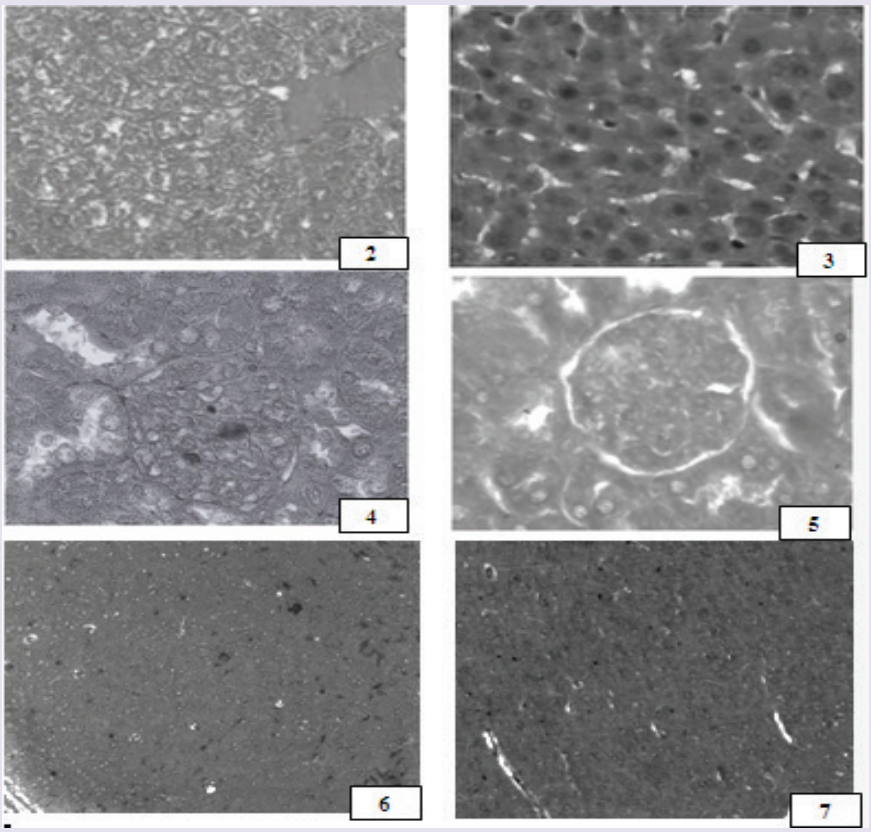

Figure 2: A caused disruption in hepatic cords, heterochromatic nuclei, hypertrophy and vacuolation in cytoplasm of hepatocyte (X 400). Figure 3: KPF group showed well-maintained hepatic cord, clear central vein with hexagonal hepatocytes (X 400). Figure 4: Administration of A showed swallowed glomeruli and swelling and vacuolation in epithelial cells of renal tubule (X 400). Figure 5: Treatment with KPF revealed well-formed Bowman's capsule with intact endothelial lining and reduced vacuolation in renal tubules (X 400). Figure 6: A induced vacuolization, degenerated pyramidal cells and reduced nerve fibres in cerebrum (X 100). Figure 7: Brain of KPF therapy showed loss of vacuolization, well formed purkinje and pyramidal cells (X 100).

Animals of all the groups were sacrificed after 24 h of last treatment for biochemical analyses.

Biochemical assays

Blood was collected by puncturing the retro-orbital venosus sinus and serum was isolated for the estimation of AST and ALT.[10,11] Serum cholesterol, triglyceride, albumin, creatinine and urea (kit method) were estimated by auto analyser. The activity of acetyl cholinesterase (AChE)[12] was determined in different parts of brain. Hepatic, renal and cerebral LPO[13]and GSH[14] were estimated. The activities of Catalase (CAT)[15] and Superoxide dismutase (SOD)[16] were determined in liver, kidney and brain.

Histopathological assays

Histopathological examination was performed on the organs and tissues of all animals. Liver, kidney and brain were dissected out washed in saline and fixed in Bouin's fluid. Paraffin-embedded tissue sections at 6 μm of all organs were routinely prepared, stained with hematoxylin and eosin (H&E) and examined by light microscopy.

Statistical analysis

P values were evaluated at the level of ≤0.05 by student's t test. Significance of the difference among various groups was evaluated by one way analysis of variance (ANOVA)@ F=p≤0.05.

RESULTS

Biochemical results

Tables 1 and 2 represent the blood biochemistry in serum. Increased the activities of AST and ALT significantly in the A exposed group as compared to the other groups (p≤0.05), while therapy with KPF at 5,10,20,40 mg/Kg doses restored the levels of serum transaminases (Table 1). A administration significantly (p≤0.05) decreased the haemoglobin percentage and increased albumin level (Table 1). There was significant elevation in lipid profile such as triglycerides, cholesterol along with urea and creatinine in A exposed group which clearly showed altered brain and kidney functions (Table 2). Therapy with KPF at 5,10,20,40 mg/Kg doses prevented all the parameters statistically significant. A administration in rats significantly reduced the AChE activity in all parts of brain as compared to control rats. However, KPF treatment at 20,40 mg/Kg significantly (p≤0.05) ameliorated the activity of AChE (Table 3).

Table 4 represents the tissue levels of TBARS and GSH. It was found that acrylamide administration significantly increased TBARS levels in liver, kidney and brain tissues as compared to the other groups (p≤0.05), while KPF administration decreased the TBARS levels significantly in A and KPF group when compared to A group (Table 4). The GSH levels decreased significantly (p≤0.05) in liver, kidney and brain tissues after A exposure as compared to other groups, but when KPF given orally at 5,10,20,40 mg/Kg along with A, GSH levels improved significantly when compared to A group (p≤0.05).

Acrylamide administration decreased the level of SOD and CAT activities significantly in liver, kidney and brain tissues as compared to other groups (p≤0.05). However, when Acrylamide and KPF at 5,10,20,40 mg/Kg were administered together, SOD and CAT activities were increased significantly when compared to A group (p≤0.05) (Table 5).

Histopathological results

Light microscopy examination of liver of control rats revealed well maintained hepatic lobules and sinusoidal spaces. A caused congestion in central vein, disruption in hepatic cords and hypertrophy and vacuolation in eosinophilic cytoplasm of hepatocyte along with heterochromatic nuclei (Figure 2). The histological appearance of the KPF group showed improvement in the liver with well-maintained hepatic cord arrangement, clear central vein with almost hexagonal hepatocytes (Figure 3).

Kidney tissues of the control rats showed normal histological structure of the glomeruli and tubules in the cortex and medulla. Administration of A showed swallowed glomeruli, distortion in endothelial lining, swelling and vacuolation in epithelial cells of proximal convoluted tubule (Figure 4). Treatment with KPF revealed well-formed Bowman's capsule with intact endothelial lining, loss of vacuolation in proximal tubules with well-formed lumen (Figure 5).

Brain sections of control rats showed normal histological structure of the cerebral cortex. Histopathological examination of the brain tissues of A-treated rats showed vacuolization, degenerated pyramidal cells and reduced nerve fibres in cerebrum. (Figure 6). Brain of KPF treated rats showed signs of recovery such as loss of vacuolization, well formed purkinje and pyramidal cells (Figure 7). Both the higher doses showed almost equal protection in biochemical as well as Histopathological observation.

DISCUSSION

A monomer is a potent neurotoxin and capable of inducing CNS and PNS damages in humans and animals which also induces ataxia, skeletal muscle weakness and weight loss. A used in industrial products for water treatment and grouting, cigarette smoking, and poly Acrylamide gel electrophoresis, which primarily measured as A-Hb adducts present in blood.[17]

Once absorbed, Acrylamide may be conjugated by glutathione-S-transferase (GST) to N-acetyl-S-(3-amino-3-oxopropyl) cysteine or it reacts with cytochrome P450 (CYP450) to produce major metabolite glycidamide.[18] Glycidamide may be further metabolized by epoxide hydrolase to glyceramide or by conjugation to glutathione, or it may react with proteins, including haemoglobin, or with deoxyribonucleic acid (DNA). A formed A-Hb, GA-Hb and GA-DNA adduct.[19] A is dissolved in water very well and distributed to all the tissues in a rapidly after being taken orally and induced hematological and neurotoxic changes in animals.[20] The hemoglobin (Hb) is linked to the total population of red blood cells, the present study revealed that Hb decreased significantly after A administration in rats which might be either due to the retarded synthesis or destruction hemoglobin. Similar results were found by author.[21]

A induced oxidative stress in cells by unbalancing oxidant/antioxidant ratio.[22] In the present study, elevated level of TBARS observed in A-treated rats indicate excessive formation of free radicals and activation of LPO system resulting in tissue damage. TBARS produced by products of LPO that occurs in hydrophobic core of bio membranes. Our study found that the level of thiobarbituric acid reactive products had increased significantly in liver, kidney and brain after. A administrated may be due to the failure of detoxification.GSH is synthesized in all organs, especially in the liver, and is present in all mammalian cells. A administration increases the generation of free oxygen radicals and significant decreases the GSH in the experimental animals. Similar results noted by indicates many researchers.[23-25]

A induced toxicity may be due to depletion in antioxidant enzymes as observed in present study which indicates loss of free radical scavenging activity. A exposure significantly inhibited the antioxidant enzymatic activities CAT and SOD levels in liver, kidney and brain. This may suggests an increased utilization of these antioxidant enzymes to counter the increased level of free radicals induced by A in these tissues. Similar findings were observed by many authors.[24,25]

A significant increase in AST and ALT activity was found in serum of rats exposed to A. These marker enzymes AST and ALT are cytoplasmic

Table 1: Protective effect of *Kaempferol* against Acrylamide on liver function tests and Hb% in rats

Treatments	AST	ALT	Albumin	Haemoglobin
	(IU /L)	(IU /L)	(mg/dl)	(%)
Control	61.44 ± 3.39	42.00 ± 2.32	3.10 ± 0.17	16.50 ± 0.91
KPF40Per se	61.00 ± 3.37	40.00 ± 2.21	2.80 ± 0.15	15.80 ± 0.87
A	137.4 ± 7.59#	170.0± 9.39#	4.48 ± 0.24#	9.400 ± 0.51#
A + KPF5	128.3 ± 7.09	80.47± 4.44*	3.30 ± 0.18*	12.93 ± 0.65*
A + KPF10	124.2 ± 6.86	72.03± 3.98*	3.25 ± 0.17*	13.40 ± 0.67*
A + KPF20	82.60 ± 4.56*	49.11± 2.71*	3.16 ± 0.17*	13.70 ± 0.69*
A + KPF 40	88.59 ± 4.89*	52.50± 2.90*	3.17 ± 0.17*	14.00 ± 0.70*
F Value	38.90@	112.1@	9.973@	10.79@

Values are mean + S.E., N = 6. # P≤0.05 vs control group, * P≤0.05 vs A administered group. ANOVA (F values) @ = Significant, ns= Non significant at 5 % level.

Table 2: Effect of *Kaempferol* on Lipid profile and kidney function tests against Acrylamide induced toxicity in rats

Treatments	Triglycerides	Cholesterol	Urea	Creatinine
	(mg/dl)	(mg/dl)	(mg/dl)	(mg /dl)
Control	66.00 ± 3.64	46.00 ± 2.54	33.00 ± 1.82	0.13 ± 0.007
KPF 40 Per se	68.00 ± 3.75	42.00 ± 2.32	32.00 ± 1.76	0.20 ± 0.011
A	123 .0± 6.79#	160.0 ± 8.84#	82.00 ± 4.53#	0.80 ± 0.044#
A + KPF 5	87.35 ± 4.82*	54.90 ± 3.03*	81.85 ± 4.52*	0.20 ± 0.011*
A + KPF 10	69.00 ± 3.81*	52.50 ± 2.90*	78.90 ± 4.36	0.17 ± 0.009*
A + KPF 20	68.00± 3.75*	48.50± 2.68*	50.10 ± 2.76*	0.15 ± 0.008*
A + KPF 40	68.80± 3.80*	48.00 ± 2.65*	49.50 ± 2.73*	0.14 ± 0.007*
F Value	26.10@	101.7@	38.99@	199.1@

Values are mean + S.E., N = 6. # P≤0.05 vs control group, * P≤0.05 vs A administered group. ANOVA (F values) @ = Significant, ns= Non significant at 5 % level.

Table 3: Influence of *Kaempferol* against Acrylamide on acetylcholinesterase (µ mole / min / mg protein)

Treatments	Fore Brain	Mid Brain	Hind Brain
Control	42.00 ± 2.32	22.50 ± 1.24	39.72 ± 2.19
KPF 40*Per se*	41.60 ± 2.29	21.60 ± 1.19	40.00 ± 2.21
A	11.59± 0.64#	7.920 ± 0.43#	11.85 ± 0.65#
A + KPF5	14.55 ± 0.80*	13.28 ± 0.73	17.18 ± 0.94*
A + KPF10	17.65 ± 0.97*	16.11 ± 0.89*	20.92 ± 1.15*
A + KPF20	27.89± 1.54*	17.54 ± 0.96*	21.72 ± 1.20*
A + KPF40	27.24± 1.50*	17.28 ± 0.95*	19.05 ± 1.05*
F Value	73.73@	32.61@	69.04@

Values are mean + S.E., N = 6. # P≤0.05 vs control group, * P≤0.05 vs A administered group. ANOVA (F values) @ = Significant, ns= Non significant at 5 % level.

Table 4: Antioxidative effect of *Kaempferol* against Acrylamide on Lipid Peroxidation and Reduced Glutathione of rats

	Lipid Peroxidation (n mole MDA / mg protein)			Glutathione (µ mole / g)		
Treatments	Liver	Kidney	Brain	Liver	Kidney	Brain
Control	0.23 ± 0.01	0.35 ± 0.01	0.36 ± 0.01	8.50 ± 0.46	8.20 ± 0.44	8.00 ± 0.44
KPF40Per se	0.26 ± 0.01	0.37 ± 0.02	0.40 ± 0.02	8.30 ± 0.45	7.91 ± 0.43	8.20 ± 0.45
A	1.30 ± 0.07#	2.20 ± 0.12#	2.37 ± 0.13#	5.60 ± 0.30#	6.10 ± 0.33#	5.60 ± 0.30#
A + KPF5	0.96 ± 0.05*	1.62 ± 0.08*	1.38 ± 0.07	6.30 ± 0.34	7.21 ± 0.35	6.93 ± 0.38*
A + KPF10	0.74 ± 0.04*	1.58 ± 0.08*	1.25 ± 0.06*	7.18 ± 0.39*	7.81 ± 0.38*	7.46 ± 0.41*
A + KPF20	0.66 ± 0.03*	0.73 ± 0.04*	0.95 ± 0.05*	8.21 ± 0.45*	7.94 ± 0.41*	7.50 ± 0.41*
A + KPF40	0.57 ± 0.03*	0.60 ± 0.03*	0.99 ± 0.05*	8.29 ± 0.45*	8.11 ± 0.41*	7.62 ± 0.42*
F Value	93.07@	132.6@	113.8@	9.057@	3.669@	5.413@

Values are mean + S.E., N = 6. # P≤0.05 vs control group, * P≤0.05 vs A administered group. ANOVA (F values) @ = Significant at 5 % level.

Table 5: Protective effect of *Kaempferol* against Acrylamide on oxidative stress markers in rats

	Superoxide dismutase (μ/min/mg protein)			Catalase (μmol H_2O_2/min/mg protein)		
Treatments	Liver	Kidney	Brain	Liver	Kidney	Brain
Control	63.00 ± 3.48	61.00 ± 3.37	64.00 ± 3.53	68.00 ± 3.75	75.00 ± 4.14	76.00 ± 4.20
KPF40Per se	65.00 ± 3.59	63.00 ± 3.48	67.00 ± 3.70	70.00 ± 3.86	77.00 ± 4.25	78.00 ± 4.31
A	34.00 ± 1.87#	30.00 ± 1.65#	39.00 ± 2.15#	32.00 ± 1.76#	45.00 ± 2.48#	44.80 ± 2.47#
A + KPF5	51.12 ± 2.82*	40.22 ± 2.22*	49.00± 2.70*	47.94 ± 2.65*	59.65 ± 3.29*	50.00 ± 2.76
A + KPF10	54.89 ± 3.03*	44.07 ± 2.43*	60.00± 3.31*	52.46 ± 2.90*	62.00 ± 3.42*	52.00 ± 2.87
A + KPF 20	62.88 ± 3.47*	58.85 ± 3.25*	63.00 ± 3.48*	63.37 ± 3.50*	70.00 ± 3.86*	56.70 ± 3.13*
A + KPF 40	59.30 ± 3.27*	60.55 ± 3.34*	61.00 ± 3.37*	63.50 ± 3.51*	71.00 ± 3.92*	60.25 ± 3.33*
F Value	14.22@	23.81@	11.46@	21.31@	10.95@	17.42.1@

Values are mean + S.E., N = 6. # P≤0.05 vs control group, * P≤0.05 vs A administered group. ANOVA (F values) @ = Significant at 5 % level.

in origin and release into the circulation depends on the abnormal dynamic properties of the cell membrane following exposure to A or suffering from liver malfunctioning. These finding supported by many workers.[25,30] In the present investigation the elevated level of albumin is indicative of cellular leakages and loss of functional integrity of hepatocytes or hepatocellular dysfunction by A.[22] There was significant elevation in lipid profile such as triglycerides and cholesterol. Hypercholesterolemia is evidence of liver damage characterized by the development of cytoplasm fatty vacuolation and necrosis of the centrilobular hepatocytes with lymphocytic infiltration. A molecule has two reactive sites, viz, the conjugated double bond and the amide group which can conjugate with the -SH group of a sulfur containing amino acids and α-NH2 group of a free amino acid. The present study showed that, administration of A altered in the serum creatinine and urea compared to untreated groups might be due to impairment in renal function. This agrees with the results of Shelly.[26-28,30]

AChE is the presynaptic (cholinergic) and postsynaptic (cholinoceptive) components of cholinergic pathways where it terminates the synaptic action of acetylcholine through catalytic hydrolysis. A significant depletion in AChE activity in different region of rats brain suggest impairment of neurotransmission at central and peripheral synapses or synaptic dysfunction.[27] These findings are also supported by various investigators.[25,29]

Our biochemical findings substantiate by our histological observations. Liver tissues taken from A group showed degeneration and necrosis of hepatic parenchyma, vacuolation, congestion of the blood vessels, diffusion of Kupffer cells, and mononuclear inflammatory cells in rats. These observations agreed with the findings of other author.[30] The kidneys of A treated rats showed infiltration of few mononuclear cells, degeneration of lining cells of renal tubules may be due to excretion of A and its metabolites through kidneys. Similar results were reported in rats and rabbits by many workers.[30,31] Evidences suggested that the neurotoxicity produced by A exposure is linked to nerve terminal damage in the central and peripheral nervous system which is mediated by injury to nerve terminals and cerebellar purkinje cells.[29,32]

KPF is a natural poly phenol and have been established antioxidant effects in several studies.[2,33] KPF reduce diseases due to its potential antioxidant and anti-inflammatory activities.[2,34]

Preclinical studies have shown that this dietary compound has antioxidant, anti inflammatory, and anti allergic activities.[35] In recent decades, several studies have shown neuro protective effects of KPF may prevent generation of ROS. Results showed that TBARS levels significantly reduced and GSH was increased in KPF therapy groups which may be due to inhibition of ROS production in cells in rat. KPF protected apoptosis in neurons and significantly reduce the proliferation of neural progenitor cells.[36] The results of the present study suggested that *Kaempferol*, as a nontoxic, inexpensive dietary component, is a promising agent for ameliorating A toxicity through inhibition of oxidative stress and enhanced the antioxidant enzymes. The present study suggest that KPF therapy is beneficial against A induced toxicity. Further works are needed to fully characterize and elucidate its possible mode of action and that is in progress.

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CONFLICT OF INTEREST

The authors state that there are no conflicts of interest to disclose.

ABBREVIATION USED

AChE: Acetyl cholinesterase; **ALT:** Alanine aminotransferase; **ANOVA:** Analysis of variance; **AST:** Aspartate aminotransferase; **GSH:** Reduced glutathione; **Hb**: Hemoglobin; **LPO:** Lipid peroxidation; **SOD:** Super oxide dismutase; **CAT:** Catalase; **A:** Acrylamide; **KPF:** *Kaempferol*; **DST:** Department of Science and Technology; **TBARS:** Thiobarbituric acid reactive substances.

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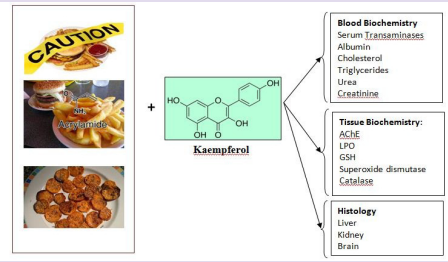
PICTORIAL ABSTRACT



SUMMARY

- *Kaempferol* (KPF) is a polyphenol which is present in citrus fruits, tea, cabbage, strawberries and other plant sources.
- KPF act as free radicals scavenger.
- Pharmacological activities of KPF includes antiinflammatory, anticarcinogenic, antidiabetic and antiallergic.
- These findings encourage studying KPF further as a potential agents against acrylamide intoxication.

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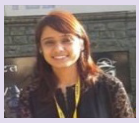

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