https://doi.org/10.33451/florafauna.v28i2pp295-302
FLORA AND FAUNA
ISSN 2456 - 9364 (Online)
2022 Vol. 28 No. 2 PP 295-302
ISSN 0971 - 6920 (Print)

Toxic impacts of Acrylamide : A Review

Jayanti Jatav and *Habiba Bano

Department of Zoology,
University of Rajasthan,
JAIPUR-302004 (RAJ) INDIA
*Corresponding Author
E-mail : banohabiba@gmail.com

Received **:** 20.09.2022; ***Revised*** **:** 26.09.2022; ***Accepted*** : 18.10.2022

ABSTRACT

Acrylamide, a harmful chemical produced during the cooking methods, particularly when certain carbohydrate-rich foods are fried, toasted, roasted or baked at high temperatures, has become a major health concern in recent years. It is most prevalent in roasted almonds, French fries and potato crisps, especially when the amino acid asparagine is free and reacts with fructose and glucose sugars. It has been reported to cause alarming health problems due to its widespread consumption, predominantly among the younger generation, which prefers processed and baked foods these days. The current review focuses on various toxic effects of acrylamide such as neurotoxicity, carcinogenicity, genotoxicity, reproductive toxicity, immunotoxicity, hepatotoxicity, cardiotoxicity, hematotoxicity, nephrotoxicity, developmental toxicity including many others.

Figures : 03 References : 63 Table : 00
KEY WORDS : Acrylamide, Food, Human, Toxicity

Introduction

People have been using heat to prepare their foodstuff for thousands of years. Thermal processing is necessary for nutritional quality, microbiological safety, and desired sensory characteristics; nevertheless, undesired substances have emerged as a result of food processing methods[52]. Acrylamide is one such water-soluble molecule that is liberated as a monomer, in carbohydrates-rich foods during the cooking process at high temperatures[7]. Asparagine reacts with glucose to produce a product that gives food its color and flavor. This is called the Maillard reaction, and it occurs at higher rates when the temperature[8] exceeds 120°C. Acrylamide is found in a variety of foods, including bakery products, breakfast cereals, cappuccino powder, roasted coffee, biscuits, wafers cookies, potato chips, fried potatoes, French fries *etc*[28,40]. Besides this, it also has a wide range of applications in a variety of industries[10]. Acrylamide has been known as an industrial chemical compound that was primarily utilized in various industrial systems, such as plastics manufacturing, paper and glue production, processing of waste water and drinking water, as well as in the treatment of sewage[52].

Several studies employing human cells have revealed that prolonged low-level exposure to acrylamide can cause central and peripheral nervous system deterioration with motor and cognitive impairments[41]. According to animal studies, acrylamide causes nephrotoxicity, developmental toxicity, hepatotoxicity, carcinogenicity, neurotoxicity, genotoxicity, reproductive toxicty[1,12,19,26,35,37,62] with neurotoxicity being the most common.

Neurotoxicity

Acrylamide has been considered to be a potential neurotoxin to human beings according to the reports of the World Health Organization[58]. An effect of acrylamide neurotoxicity has been demonstrated in both occupationally exposed humans and animals. The lowest observed effect limit (LOEL) for neurotoxicity in laboratory animals is 2g/kg/day, and no observed effect limit (*NOEL*) is 0.2 to 0.5 g/kg/day, respectively[27]. Repeated daily exposure to acrylamide causes skeletal muscle weakness, hind-limb foot splay, and ataxia in a variety of laboratory animals, including mice, rats, cats, monkeys, rabbits, and guinea pigs[6,18,25,30,39]. Under *in vitro* conditions, Apoptosis and mitochondrial dysfunction have been observed in BV-2 microglial cells, as well as in rat primary astrocytes exposed to acrylamide[34].

Acrylamide is found in breast milk and a significant amount of it is passed through the placenta to the developing foetus[4]. Its exposure causes dopaminergic neurodegeneration and alpha-synuclein accumulation, which eventually leads to Parkinson's disease pathology[33]. Several studies have examined the neurotoxic effects of acrylamide as it is used in the workplace[35].

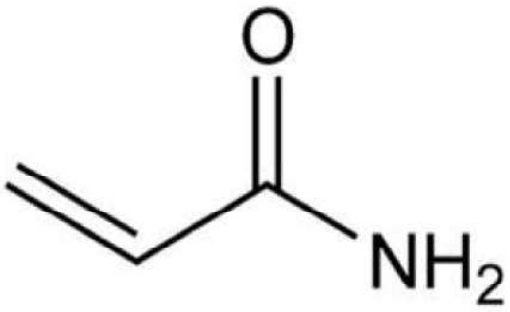

Fig. 1 : Molecular structure of Acrylamide

Carcinogenicity and Genotoxicity

The International Agency for Research on Cancer (IARC) has classified acrylamide as potentially carcinogenic to humans[44]. Long-term acrylamide exposure or intake has been associated with a variety of cancers in mice and rats, including pancreatic, breast, prostate, endometrial, and ovarian cancers[42,45,46]. Acrylamide is metabolized to an epoxide metabolite called Glycinamide (GA) in humans and animals by an enzyme called CYP2E1, which causes mutations and DNA disruption[21]. Even though there is ample evidence to support the carcinogenic effects of acrylamide in laboratory animals, there is no relevant evidence that its effects are also carcinogenic in humans according to the few empirical studies conducted so far on dietary and occupational exposure to acrylamide[61].

The findings indicate that acrylamide can increase the risk of some malignancies. Postmenopausal women exposed to acrylamide are more likely to develop breast and kidney cancers. Several studies have been conducted on acrylamide and its main metabolite, glycidamide, to determine their genotoxicity[40].

The researchers found that repeated doses of 10 mg/kg of acrylamide for 2 weeks, or single doses of 10, 20, or 30 mg/kg of acrylamide, significantly increased DNA impairment in mice bone marrow cells, as indicated by micronuclei and chromatic aberration[3]. In another study, *in vitro* tests, and *in vivo* animal models revealed that acrylamide has a genotoxic effect in cell culture[14].

Reproductive toxicity

In human beings, no evidence of reproductive toxicity has been reported; however, when rats were given 0.5 to 10 mg/kg of acrylamide, their development was slowed and their sperm count was reduced when compared to the control group. Furthermore, histopathological lesions have also been observed in the testis of treated rats[56].

When acrylamide (20 mg/kg) was repeatedly injected into male rats for 20 days, their testosterone and prolactin concentrations decreased in a dose-dependent response [2]. A study conducted on female mice treated with acrylamide found reproductive toxicity, with decreased viability of the granulosa cells, corpora lutea, and production of progesterone in their ovaries[57]. When rats were administered 60 mg/kg/day, the mating index and fertility index showed considerable decreases among studied subjects. Male systemic toxicity was found in this investigation at dosage rates of 15, 30,45, and 60 mg/kg/day, with bodyweight alterations, occurring during the dosing period. In addition, a substantial association between systemic toxicity and reproductive consequences has also been documented in the available literature[54].

Immunotoxicity

There is no comprehensive review of the literature on acrylamide-induced immune toxicity. An experiment using rats exposed to acrylamide at 50 mg/kg body weight, daily for ten days, reported a reduction in the weight of their thymus and spleen. The lymph nodes in the mesenteric region significantly decreased in size[60]. Additionally, acrylamide was discovered to be immunotoxic in Balb/c female mice, with pathological variations in the thymus, lymph nodes, and spleen, along with decreased body weights, spleen, and thymus weights and lymphocyte numbers. Furthermore, it inhibits the production of interleukin 6, which regulates the immune system, as well as the proliferation of splenocytes[15].

Hepatotoxicity

Although acrylamide is metabolized in the liver, there have been few human reports of hepatotoxicity. In various animal studies, dietary acrylamide has been shown to cause oxidative stress in the liver. The administration of a dose of (25 mg/kg) acrylamide given to adult rats for 21 days led to a substantial drop in liver GSH levels as well as a significant reduction in overall antioxidant level. In addition, acrylamide also increases liver enzyme levels in the serum. It also decreases the activity of catalase and superoxide dismutase and increases levels of malondialdehyde[5].

It has been reported to cause significant pathological alterations in the liver, including hypertrophied kupffer cells, hazy edema or hydropic degeneration of hepatic cells, dilated congested blood vessels, and hepatic sinusoids. Necrotic alterations were also observed. Moreover, round cell infiltration was also found in the portal and interstitial tissues[48]. Acrylamide has been found to change the composition of plasma membranes and increase the permeability of the liver parenchymal membrane, which causes active retention of enzymes in the extracellular environment before they enter the blood[10].

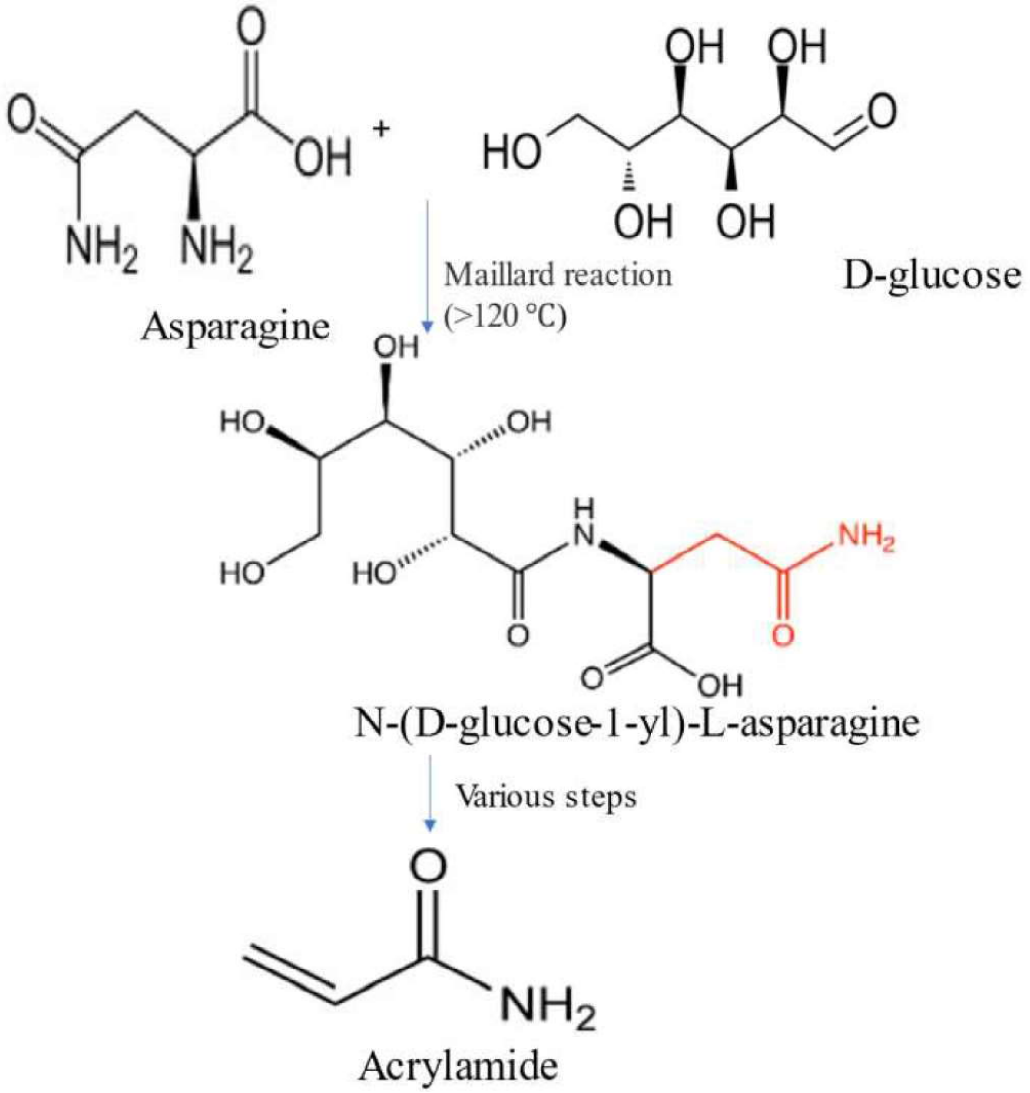

Fig. 2 : Formation of Acrylamide

Cardiotoxicity

Acrylamide-induced cardiac abnormalities have not yet been studied in epidemiological studies. In addition, there are only a few studies that suggest cardiotoxicity. There is no denying that acrylamide (2.8 mM for 6 weeks) has the potential to cause cardiotoxicity. Heart tissue histopathology observed hemorrhaging of myocardial muscle fibers as well as degeneration and striation loss, which indicates cardiotoxicity[38]. In terms of cardiac toxicity, long-term exposure to acrylamide may alter the properties of rat cardiomyocytes, such as cell morphology, cell-cell communication, and contraction patterns[55].

Researchers have investigated how 0.2, 0.4, and 0.6 mg doses of acrylamide affect the development of heart of a chick embryo. Dose-dependent changes in heart tissue were observed: 0.2 mg caused mild deterioration, 0.4 mg caused degenerative and necrotic changes, and 0.6 mg caused defective myocardium. GSH S-transferase, Superoxide dismutase, GSH peroxidase and catalase activity were all reduced, indicating a reduction in antioxidant defence[50].

Haematotoxicity

Acrylamide binds to haemoglobin when absorbed and is then transported to various organs *via* body fluid[24]. It binds to reduced glutathione to form conjugates (GSH). Glycidamide is then formed by metabolizing the complex form by using the cytochrome P450 pathway[32]. The final metabolite is genotoxic, causing haemoglobin and glycidamide DNA adduct formation[20]. Furthermore, acrylamide disrupted haematological parameters, decreased erythrocyte membrane resistance, and prevented Hb synthesis[47]. The haematotoxicity was reported on acrylamide administered *via* gavage to Swiss albino mice at three different dose levels (10,15,25mg/kg/day). A significant decrease in haemoglobin, TLC, DLC, and total protein levels, as well as a highly significant

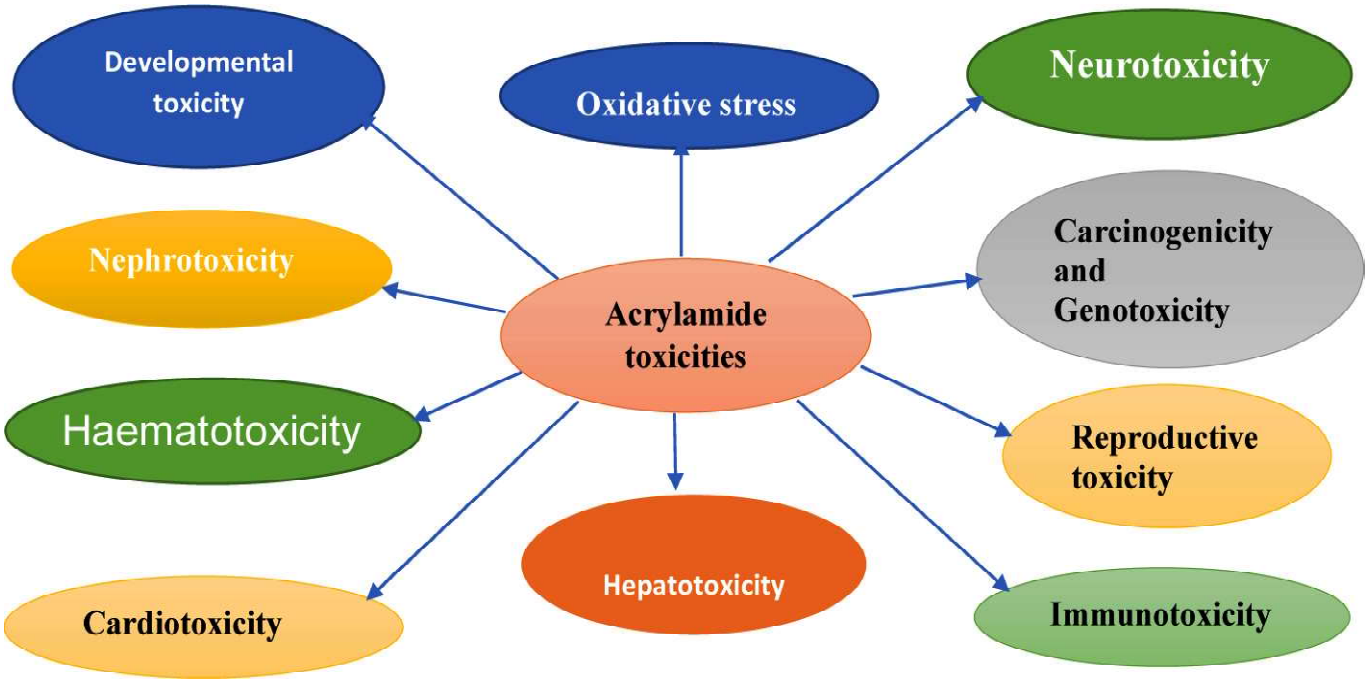

Fig. 3 : Acrylamide toxicities

increase in SGOT and SGPT activity, was observed when compared to the control group[31]. It also affects porcine granulopoiesis at doses of 0.5 and 5 gm/kg of body weight day[22].

Nephrotoxicity

Acrylamide is also absorbed into the circulatory system through skin contact and accumulates in the kidneys[23]. A high level of acrylamide exposure has been associated with a decrease in antioxidant function, detoxification capacity, and cellular impairment of visceral organs[8]. Exposure to acrylamide causes vacuolization, infiltration of inflammatory cells and edema in the periglomerular region in renal tubular cells[53]. Acrylamide has been shown to stimulate the expression of inflammatory cytokines including interleukin-1 beta, tumor necrosis factor-alpha, and malondialdehyde [13].

Among the health effects of Acrylamide, are a decrease in glutathione (GSH) as well as a decrease in levels of enzymatic oxidant and an increase in renal function markers such as blood urea nitrogen and creatinine, which have also been associated with kidney damage[11]. The administration of acrylamide has also been shown to increase levels of renal proinflammatory cytokines, uric acid, creatinine and serum urea in rats, as well as cause lipid peroxidation and DNA[1].

Developmental toxicity

The efficacy of acrylamide on human development has not been studied. According to some reports, these chemicals may be distributed in fetal tissues during pregnancy[17]. There have been studies that indicate the effects of acrylamide during pregnancy. Because acrylamide and glycidamide are water-soluble, they pass easily through the placenta[49]. When embryos of zebra fish were exposed to different concentrations of acrylamide 10,30,100 and 300 mg/L after 6 hours of fertilization in a medium for 114 hours, it caused developmental toxicity including swim bladder deficiency, body curvature, and scoliosis and retention of yolk. It also affected activities that involve locomotion, as measured by distance and speed traveled while swimming[43].

The availability of information regarding the developmentally harmful effects of acrylamide in rodents is inadequate due to the associated costs. As a result, zebrafish have become increasingly used to study developmental toxicity[9].

Acrylamide and oxidative stress

Oxidative stress occurs when there is an imbalance in the number of free radicals (or reactive oxygen species, ROS, and antioxidants) in our bodies. Free radicals are molecules with an uneven number of electrons that can react with other molecules in our bodies, causing them to oxidise[51]. A variety of cell types are cytotoxic after exposure to acrylamide, and this is associated with increased levels of 3-nitrotyrosine and ROS and activates NOS and Cox 23[6].

Orally administered acrylamide caused an increase in thiobarbituric acid reactive substances in rats[59]. The rats exposed to the superoxide anion showed

elevated levels of SOD activity in the liver, kidney, testes, and brain in response to the increased rate of superoxide anion throughout the body[59]. When animals are exposed to acrylamide, their GSH levels are frequently reduced. When consumptions include Chemicals such as hydrogen peroxide, GSH depletion is seen to be significantly higher[63].

Conclusion

Acrylamide is one of the most prevalent toxins in the human diet. It can be found in relatively high concentrations in asparagine-rich foods that have been cooked at a high temperature. Many international organizations, including WHO and the Food and Drug Administration, currently classified acrylamide as a food-borne toxin. The toxic effects of acrylamide could be concluded as neurotoxicity, carcinogenicity and genotoxicity, reproductive toxicity, immunotoxicity, hepatotoxicity, cardiotoxicity, hematotoxicty, nephrotoxicity, and developmental toxicity. Acrylamide toxicity can be caused by a disruption in the antioxidant system. Furthermore, it is widely utilized in industries and is prevalent in dietary foods, so it is not possible to avoid exposure to it. Antioxidant compounds may help reduce acrylamide synthesis in food during processing. To reduce the formation of acrylamide in foods, it is beneficial to modify the processing methods of dietary foods, particularly in carbohydrate-rich foods including potato fries and chips. Further research is needed on the molecular mechanisms of acrylamide toxicity.

References

1. Abdel-Daim MM, Abd Eldaim MA, Hassan AG. *Trigonella foenum-graecum* ameliorates acrylamide-induced toxicity in rats: roles of oxidative stress, proinflammatory cytokines, and DNA damage. *Biochem Cell Biol.* 2014; **93**(3):192–198.
2. Ali SF, Hong JS, Wilson WE, Uphouse LL, Bondy SC. Effect of acrylamide on neurotransmitter metabolism and neuropeptide levels in several brain regions and upon circulating hormones. *Arch Toxicol.* 1983; **52**(1):35-43.
3. Alzahrani HA. Protective effect of l-carnitine against acrylamide-induced DNA damage in somatic and germ cells of mice. *Saudi J Biol Sci .*2011; **18**(1):29-36.
4. Annola K, Karttunen V, Keski-Rahkonen P, Myllynen P, Segerback D, Heinonen S, Vahakangas K. Transplacental transfer of acrylamide and glycidamide are comparable to that of antipyrine in perfused human placenta. *Toxicol Lett* .2008; **182**(1-3):50-6.
5. Ansar S, Siddiqi NJ, Zargar S, Ganaie MA, Abudawood M. Hepatoprotective effect of Quercetin supplementation against Acrylamide-induced DNA damage in Wistar rats. *BMC Complement Altern Med* .2016; **16**(1):327.
6. Bradley WG, Asbury AK. Radioautographic studies of Schwann cell behavior. Acrylamide neuropathy in the mouse. *J Neuropathol Exp Neurol.* 1970; **29**(3):500-6.
7. Claus A, Carle R, & Schieber A. Acrylamide in cereal products. A review. *Journal of Cereal Science .* 2008; **47**(2) :118–133.
8. Dasari S, Gonuguntla S, Yellanurkonda P, Nagarajan P, Meriga B. Sensitivity of glutathione S-transferases to high doses of acrylamide in albino wistar rats: affinity purification, biochemical characterization and expression analysis. *Ecotoxicol Environ Saf.* 2019;**182**: 109416.
9. de Esch C, Slieker R, Wolterbeek A, Woutersen R, de Groot D. Zebrafish as potential model for developmental neurotoxicity testing: A mini review. *Neurotoxicol. Teratol.* 2012; **34**(6): 545–553.
10. El- Kholy TA, Khalifa NA, Alghamidi AK. Badereldin AM. A trail of using green tea for competing toxicity of acrylamide on liver function. *J Am Sci.* 2011; **7**(12): 815 – 821.
11. Elhelaly AE, AlBasher G, Alfarraj S, Almeer R, Bahbah EI, Fouda MMA, Bungau SG, Aleya L, Abdel-Daim MM. Protective effects of hesperidin and diosmin against acrylamide-induced liver, kidney, and brain oxidative damage in rats, *Environ Sci Pollut Res Int.* 2019; **26**(34): 35151–35162.
12. Erdemli ME, Turkoz Y, Altinoz E, Elibol E, Dogan Z. Investigation of the effects of acrylamide applied during pregnancy on fetal brain development in rats and protective role of the vitamin *E. Human & Experimental Toxicology.* 2016; **35**(12): 1337–1344.

13. Erhan E, Salcan I, Bayram R, Suleyman B, Dilber M, Yazici GN, Coban TA, Altuner D, Suleyman H. Protective effect of lutein against acrolein-induced ototoxicity in rats, Biomed. *Pharmacother.* 2021; **137** :111281.

14. Exon JH. A review of the toxicology of acrylamide. *J Toxicol Environ Health B Crit Rev.* 2006; **9**(5):397-412.

15. Fang J, Liang CL, Jia XD, Li N. Immunotoxicity of acrylamide in female BALB/c mice. *Biomed Environ Sci.* 2014; **27**(6): 401-409.

16. Friedman M. Chemistry, biochemistry and safety of acrylamide. A review. *Journal of Agricultural and Food Chemistry*. 2003; **51**(16): 4504–4526.

17. Friedman MA, Tyl RW, Marr MC, Myers CB, Gerling FS, Ross WP. Effects of lactational administration of acrylamide on rat dams and offspring. *Reprod. Toxicol.* 1999; **13**(6): 511-520.

18. Fullerton PM, Barnes JM. Peripheral neuropathy in rats produced by acrylamide. *Br J Indust Med.* 1966; **23**(3):210-21.

19. Gedik S, Erdemli ME, Gul M, Yigitcan B, Bag HG. Hepatoprotective effects of crocin on biochemical and histopathological alterations following acrylamide-induced liver injury in Wistar rats. *Biomed Pharmacother.* 2017; **95**: 764-770.

20. Ghanayem BI, McDaniel LP, Churchwell MI, Twaddle NC, Snyder R, Fennell TR, Daniel R. Doerge. Role of CYP2E1 in the epoxidation of acrylamide to glycidamide and formation of DNA and haemoglobin adducts. *Toxicol Sci.* 2005; **88** :311-8.

21. Ghanayem BI, Witt KL, El Hadri L, Hoffler U, Kissling GE, Shelby MD, Bishop JB. Comparison of germ cell mutagenicity in male CYP2E1-null and wildtype mice treated with acrylamide: evidence supporting a glycidamide mediated effect. *Biol Reprod.* 2005; **72**(1): 157-163.

22. Grzybowska D, Snarska A. Acrylamide-induced changes of granulopoiesis in porcine bone marrow. *J Vet Res.* 2021; **65**: 323-327.

23. Hamdy SM, Shabaan AM, Abdel Latif AKM, Abdel-Aziz AM, Amin AM. Protective effect of hesperidin and tiger nut against acrylamide toxicity in female rats. *Exp Toxicol Pathol.* 2017; **69**(8) :580–588.

24. Hashimoto K, and Aldridge NW. Biochemical studies on acrylamide, a neurotoxic agent. *Biochemical Pharmacology.* 1970;**19**(9): 2591-2604.

25. Hopkins AP. The effect of acrylamide on the peripheral nervous system of the baboon. *J. Neurosurg. Psyehiatr.* 1970; **33**(6):805-16.

26. International Agency for Cancer Research. Acrylamide. IARC Monog. Eval. Carcinogen. *Risks Hum.* 1994; **60**: 389–433.

27. Johnson KA, Gorzinski SJ, Bodner KM, Campbell RA, Wolf CH, Friedman MA, Mast RW. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. *Toxicol Appl Pharmacol.* 1986; **85**(2):154–168.

28. Kang DE, Lee HU, Davaatseren M, Chung MS. Comparison of acrylamide and furan concentrations, antioxidant activities, and volatile profiles in cold or hot brew coffees. *Food Science and Biotechnology.* 2020; **29**:141-148.

29. Krishnakumar T, Visvanathan R. Acrylamide in Food Products: A Review. *J Food Process Technol.* 2014; **5**:7.

30. Kuperman AS. Effects of acrylamide on the central nervous system of the cat. *J Pharmacol Exp Ther.* 1958; **123**(3): 180- 92.

31. Lal R, Arora M, Sharma A. Acrylamide caused haematotoxicity on *Mus musculus* through gavage. *Indian Journal of Fundamental and Applied Life Sciences.* 2011; **1**(4): 330-334.

32. Lee JG, Wang YS, Chou CC. Acrylamide-induced apoptosis in rat primary astrocytes and human astrocytoma cell lines. *Toxicol In Vitro.* 2014; **28**(4):562-70.

33. Li J, Li D, Yang Y, Xu T, Li P, He D. Acrylamide induces locomotor defects and degeneration of dopamine neurons in *Caenorhabditis elegans. J Appl Toxicol.* 2016; **36**(1):60-7.

34. Liu Z, Song G, Zou C. Acrylamide induces mitochondrial dysfunction and apoptosis in BV-2 microglial cells. *Free Radic Biol Med.* 2015; **84**:42-53.

35. LoPachin RM. The changing view of acrylamide neurotoxicity. *Neurotoxicology.* 2004; **25**(4): 617–630.

36. Lyn-Cook Jr. L.E, Tareke E, Word B, Starlard-Davenport A, LynCook BD, Hammons GJ. Food contaminant acrylamide increase expression of Cox-2 and nitric oxide synthase in breast epithelial cells, *Toxicol. Ind. Health.* 2011; **27**(1): 11-18.

37. Manjanatha MG, Aidoo A, Shelton SD, Bishop ME, McDaniel LP, Lyn-Cook LE, Doerge DR. Genotoxicity of acrylamide and its metabolite glycidamide administered in drinking water to male and female Big Blue mice. *Environ Mol Mutagen.* 2006; **47**(1): 6-17.

38. Mansour MK, Ibrahim E, El-Kholy MM, El-Madawy SA. Antioxidant and histopathological effect of catechin and neem leaves extract in acrylamide toxicity of rats. *Egypt J Comp Path Clin Path.* 2008; **21**:290-313.

39. McCollister DD, Oyen F, Rowe VK. Toxicology of acrylamide. *Toxicol Appl Pharmacol.* 1964; **6**:172-8.

40. Mesias M, Delgado-Andrade C, Holgado F, Morales FJ. Impact of the consumer cooking practices on acrylamide formation during the preparation of French fries in Spanish households. *Food Additives & Contaminants: Part A* 2020; **37**(2):254- 266.

41. Murray SM, Waddell BM, Wu CW. Neuron-specific toxicity of chronic acrylamide exposure in *C. elegans. Neurotoxicology and teratology Neurotoxicol Teratol.* 2020; **77**: 106848.

42. Obon SM, Lujan BL, Travis RC, Freisling H, Ferrari P, Severi G, Baglietto L, Boutron-Ruault MC, Fortner RT, Ose J, Boeing H, Menéndez V, Sánchez-Cantalejo E, Chamosa S, Castaño JM, Ardanaz E, Khaw KT, Wareham N, Merritt MA, Gunter MJ, Trichopoulou A, Papatesta EM, Klinaki E, Saieva C, Tagliabue G, Tumino R, Sacerdote C, Mattiello A, Bueno-de-Mesquita HB, Peeters PH, Onland-Moret NC, Idahl A, Lundin E, Weiderpass E, Vesper HW, Riboli E, Duell EJ. Acrylamide and glycidamide haemoglobin adducts and epithelial ovarian cancer: a nested case-control study in nonsmoking postmenopausal women from the EPIC cohort. *Epidem Biomar.* 2016; **25**:127–34.

43. Park JS, Samanta P, Lee S, Lee J, Cho JW, Chun HS, Yoon S, Kim WK. Developmental and Neurotoxicity of Acrylamide to Zebrafish. *Int. J. Mol. Sci.* 2021; **22**(7) 3518.

44. Pelucchi C, Galeone C, Levi F, Negri E, Franceschi S, Talamini R, Bosetti C, Giacosa A, La Vecchia C. Dietary acrylamide and human cancer. *Int J Cancer.* 2006; **118**(2):467-71.

45. Pelucchi C, Galeone C, Negri E, Bosetti C, Serraino D, Montella M, Talamini R, La Vecchia C. Dietary acrylamide and the risk of endometrial cancer: an Italian case control. *Nutr Cancer.* 2016; **68**: 187-192.

46. Pelucchi C, Rosato V, Bracci PM, Li D, Neale RE. Dietary acrylamide and the risk of pancreatic cancer in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol.* 2016; **28**(2): 408-414.

47. Rawi SM, Marie SM, Sohair R, Fahmy SR, El-Abied SA. Hazardous effects of acrylamide on immature male and female rats. *Afr J Pharm and Pharmacol.* 2012; **6**(18):1367-86.

48. Sahai V. Histological changes in liver of albino mice due to chronic administration of acrylamide. *Ind J Fund App Life Sci.* 2012; **2**(3): 51- 54.

49. Sorgel F, Weissenbacher R, Kinzig-Schippers M, Hofmann A, Illauer M, Skott A, Landersdorfer C. Acrylamide: increased concentrations in homemade food and first evidence of its variable absorption from food, variable metabolism and placental and breast milk transfer in humans. *Chemotherapy.* 2002; **48**(6): 267-274.

50. Swamy MV, Subbaiah KV, Bukke S, Raju KT. Toxic effect of acrylamide on body weight, the study of antioxidants and histoarchitecture of heart in the developing Chick embryo. *Indian J Appl Res.* 2013; **3**:27-30.

51. Tabeshpour J, Mehri S, Abnous K, Hosseinzadeh H. Role of Oxidative Stress, MAPKinase and Apoptosis Pathways in the Protective Effects of Thymoquinone Against Acrylamide-Induced Central Nervous System Toxicity in Rat. *Neurochem Res.* 2020; **45**(2):254-67.

52. Tareke E, Rydberg P, Karlsson P, Eriksson S, Tornqvist. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. *J Agric Food Chem.* 2002; **50**(17): 4998-5006.

53. Totani N, Yawata M, Ojiri Y, Fujioka Y. Effects of trace acrylamide intake in Wistar rats. *J Oleo Sci.* 2007; **56**(9):501–516.

54. Tyl RW, Marr MC, Myers CB, Ross WP, Friedman MA. Relationship between acrylamide reproductive and neurotoxicity in male rats. *Reprod Toxicol.* 2000; **14**(2):147-57.

55. Walters B, Hariharan V, Huang H. Dietary levels of acrylamide affect rat cardiomyocyte properties. *Food Chem Toxicol.* 2014; **71**:68-73.

56. Wang H, Huang P, Lie T, Li J, Hutz RJ, Li K, Shi F. Reproductive toxicity of acrylamide-treated male rats. *Reprod Toxicol.* 2010; **29**(2):225-30.

57. Wei Q, Li J, Li X, Zhang L, Shi F. Reproductive toxicity in acrylamide-treated female mice. *Reprod Toxicol.* 2014; **46**:121- 8.

58. WHO Summary report of the sixty-fourth meeting of the joint FAO/WHO expert committee on food additives (JECFA). Rome, Italy. 2005. The ILSI Press International Life Sciences Institute, Washington, DC. 2005:1–47.

59. Yousef MI, El-Demerdash FM. Acrylamide induced oxidative stress and biochemical perturbations in rats. *Toxicology.* 2006; **219** (1-3):133-41.

60. Zaidi SIA, Raisuddin S, Singh KP, Jafri A, Husain R, Husain MM, Mall SA, Seth PK, Ray PK. Acrylamide Induced Immunosuppression in Rats and Its Modulan by 6-MFA, An Interferon Inducer. *Immunopharm Immunot.* 1994;**16**: 247-260.

61. Zamani E, Shokrzadeh M, Fallah M, Shaki F. A review of acrylamide toxicity and its mechanism. *Pharm Biomed Res.* 2017; **3**(1):1-7.

62. Zenick H, Hope E, and Smith MK. Reproductive toxicity associated with acrylamide treatment in male and female rats. *J Toxicol Environ Health.* 1986; **17**(4):457-472.

63. Zhu YJ, Zeng T, Zhu YB, Yu SF, Wang QS, Zhang LP, Guo X, Xie KQ. Effects of acrylamide on the nervous tissue antioxidant system and sciatic nerve electrophysiology in the rat. *Neurochem Res.* 2008;**33**(11):2310-7.