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A neuroprotective potential of berberine in Acrylamide induced neurotoxicity

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ABSTRACT: -
Neurotoxicity refers to the harmful effects on the nervous system, including its normal functions like neuronal transmission, connectivity, and survival. Various substances, such as drugs, toxins, and food additives, can induce neurotoxicity. Acrylamide (ACR), also known as 2-propenamide, is a colorless, odorless, water-soluble crystalline solid with a low molecular weight. It has been widely synthesized for many years. One of the primary culprits of neurotoxicity is oxidative stress and mitochondrial dysfunction. Acrylamide toxicity impacts both the peripheral and central nervous systems. Berberine, an isoquinoline alkaloid derived from different Berberis species, is frequently used in the treatment of neurological and neurodegenerative disorders like Alzheimer's, Huntington's disease (HD), Parkinson's disease, mental depression, schizophrenia, anxiety, and certain stroke conditions. Berberine is a small molecule that easily crosses the blood-brain barrier (BBB). Numerous clinical and preclinical studies have demonstrated the positive effects of berberine on a range of health issues, including metabolic, neurological, and cardiovascular problems. This review seeks to outline the potential neuroprotective properties of berberine against ACR-induced neurotoxicity.

Keywords: - neurotoxicity, berberine, acrylamide, mitochondrial dysfunction, oxidative stress.

I. INTRODUCTION: -

Neurotoxicity is the result of harmful agents affecting the normal functioning of the nervous system, including processes like neuronal transmission, connectivity, and survival. Various substances, including drugs, toxins, and food additives, can potentially induce neurotoxicity [1]. Both experimental research in animals and observations in industrial settings involving humans have indicated that Acrylamide (ACR) toxicity has detrimental effects on both the peripheral and central nervous systems. Human exposure to ACR can occur through inhalation, ingestion (via the diet), and skin absorption, leading to neurological symptoms [2]. The neurotoxic impact of ACR is progressive, affecting both the peripheral and central nervous systems, with cumulative damage observed. Repeated exposure to ACR can initially manifest with mild symptoms that can progress to severe impairment and irreversible harm [3].

ACR, also known as 2-propenamide, is a crystalline solid characterized by its colorless, odorless, and water-soluble properties. Figure No. 01 Shows the **Physico-Chemical Properties**of ACR. This low-molecular-weight substituted alkene has been produced extensively for many years and is commonly used as an intermediate in organic compound manufacturing and as a monomer in polyacrylamide production [4-5]. ACR also finds applications in the cosmetics and textile industries, laboratories, and as a soil conditioner in wastewater treatment [6-8]. A significant source of ACR is the cooking of carbohydrate-rich foods with asparagine and low sugar content at temperatures above 120°C and with limited moisture [9-10]. Dietary intake is the primary source of exposure for the general population, though exposure from cosmetics can also contribute. The estimated chronic daily dietary intake for the average person ranges from 0.3 to 0.7 grams per kilogram of body weight (g/kg BTW) [11-12]. Common dietary sources of ACR include French fries (averaging 308 g/kg), potato chips (averaging 389 g/kg), bread (averaging 42 g/kg), cookies (averaging 265 g/kg), and coffee (averaging 522 g/kg in dry coffee). Notably, ACR has also been found in significant amounts in cigarette smoke, ranging from 497 to 169 nanograms per cigarette [13]. Children's ACR intake tends to increase with age, peaking between

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12 and 18 years, reflecting greater consumption of fast-food items like potato chips or French fries [11-12].Various regulatory bodies have set permissible limits for ACR in drinking water, with the World Health Organization (WHO) at 1 gram per liter (g/l), the US Environmental Protection Agency at 0.5 g/l, and the European Union at 1 g/l. Occupational exposure limits for ACR in ambient air have been established at 0.3 milligrams per cubic meter (mg/m3) for time-weighted averages of 8 hours (Occupational Safety and Health Administration) or 10 hours (National Institute for Occupational Safety and Health) [14-15]. The discovery of ACR in food prompted numerous international conferences, bringing together scientists to assess the implications of these findings. Regulatory agencies such as the US Federal FDA, the UK Foods Standard Agency, Health Canada, and the Swedish National Food Administration all issued statements following these discussions. The broad spectrum of foods potentially containing ACR residues and the prospect of eliminating specific items from diets raise concerns regarding health risks associated with dietary choices. In addition, foodborne illnesses impact millions annually, causing thousands of fatalities. Over 200 research projects have been initiated to gain a better understanding of the risks associated with ACR exposure in humans (EFSA, 2005; FAO/WHO, 2005). In early 2005, a WHO/FAO meeting further examined these findings in the context of food safety (JECFA, 2005). The Risk Assessment section of this document includes some of the meeting's remarks and recommendations [16].Berberine is a natural alkaloid compound found in various plants, including goldenseal, barberry, and Oregon grape. It has been traditionally used in various traditional medicine practices, particularly in Chinese and Ayurvedic medicine, for its potential health benefits. Berberine has gained attention in modern research due to its diverse pharmacological properties, including Neuroprotective Effects, Anti-inflammatory, Antimicrobial, and Antioxidant effects.

Table 01: - Physico-Chemical Properties

S.NO.	CLASS	PROPERTIES
1.	**Molecular formula**	C_3H_5NO
2.	**IUPAC Name**	2-propenamide
3.	**Molecular Weight [g/mol]**	71.078
4.	**Physical characteristics**	White, Crystalline solid at room temperature
5.	**Density**	30 ºC 1.127 g/cm3
6.	**Melting Point**	84 - 84.5 ºC
7.	**Boiling Point**	125 ºC at 3.3 Pa
8.	**Vapour Pressure**	0.9 Pa at 25 ºC
9.	**log POW**	0.67 to 1.65
10.	**Water Solubility**	2.155 g/l at 30 ºC

Factors responsible for ACR toxicity: -

One of the primary factors contributing to ACR toxicity is its formation during certain cooking processes. ACR is produced when carbohydrate-rich foods, such as potatoes and cereals, are cooked at high temperatures, typically above 120°C, in the presence of amino acids, particularly asparagine, and reducing sugars. Common cooking methods like frying, baking, and roasting can trigger the Maillard reaction, a complex chemical process that generates ACR as a byproduct. As a result, a wide range of commonly consumed foods can contain ACR residues. ACR is a highly reactive organic chemical that polymerizes and finds use in a variety of industries [17-19]. ACR is frequently utilized in the cosmetics industry and molecular biology research for wastewater treatment [20]. It can be ingested or be exposed to us through our diet or our surroundings, both of which are mentioned further below [21-22].Figure 01 Different sources of exposure to Acrylamide.

Dietary Exposure: -

The occurrence of ACR in our regular meals or foods is a main source of concern. Diet plays a significant role in ACR exposure for the general population. Consuming foods like French fries, potato chips, bread, cookies, and coffee, all of which can contain notable ACR levels, contributes

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to daily ACR intake. Additionally, exposure through dietary supplements and other sources must be considered when assessing ACR toxicity. Overheating, pH, water content, and the reactivity of the different components can all contribute to the formation of ACR. [20] Elevated temperatures increase the formation of ACR along with the time of heating separately or jointly. ACR is formed at temperatures of 190 degrees or higher, as evidenced by the rise in ACR concentrations in French fries after cooking [23]. ACR is found in breast milk, and up to 50% of it is transferred from a pregnant mother to the growing foetus through the placenta [24].

Environmental Exposure

Environmental ACR primarily originates from industrial processes, including the production of plastics, wastewater treatment, cosmetics and textile industries, cigarette smoke, and other sources. It is used as an intermediate in organic compound manufacturing and as a monomer in the production of polyacrylamide, a polymer widely employed in various industries. ACR can also be found in the waste streams of these processes, potentially contaminating soil and water [25,26] ACR can be ingested, inhaled, or comes into contact with the skin**.** A single cigarette includes around 1 µg of ACR. Snuff, tobacco strips, and other tobacco products contain ACR in the range of 100 to 367 ng/g dry weight [27].

Occupational exposure: -

Inhalation or direct contact with skin or mucous membranes are the most common methods of occupational exposure. Furthermore, some personal care products (for example, cosmetics) include free ACR, which can be absorbed through dermal contact; however, estimating dermal exposure is challenging [28].

Tobacco exposure: -

In tabaco, more than 8,000 compounds have been discovered, with more than 60 of them being recognized to be carcinogenic [29]. Hazardous substances were tested in both mainstem and side stream smoke. Tobacco pyrolysis also produces ACR, and tobacco use is a major source of ACR exposure [30].

Acrylamide in Processed Food:

Acrylamide in food is mostly formed during baking and frying by heat-induced interactions between the amino group of the free amino acid asparagine and the carbonyl group of reducing sugars such as glucose. Plant-based foods high in both precursors include potatoes and cereals (barley, rice, and wheat), but not animal meals like chicken, meat, and fish. High-acrylamide processed foods include French fries, potato chips, tortilla chips, bread crust, crispbread, and many baked products and cereal formulations However, the observed wide variations in acrylamide levels in different food categories as well as different brands of the same food category (e.g., French fries, potato chips) appear to be due to changes in processing circumstances (e.g., temperature, time, nature of frying oil, nature of food matrix). **Table 02 shows the Content of Acrylamide in Food Products**

Table 01: - The Content of Acrylamide in Food Products:

THE PRODUCTS TYPE	THE ACRYLAMIDE CONTENT (µG/KG)
Bread (rolls, bread, bagels)	70-430
Potato chips	<50–3500
Potato fries	200-2287
Boiled potatoes	48
Cookies, crackers, biscuits	<30-3200
Rusks	80-1200
Cereals	30-1400
Gingerbread cookies	<50-100
Chocolate (powder)	64-457
Nuts, peanut butter	64-457
Meat, poultry	30-64
Baked asparagus	143

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ACR and oxidative stress

In the pathology of chemical-induced neurodegeneration, oxidative stress is a critical event. When the rate of production of free oxygen radicals (ROS) exceeds the rate of neutralization, oxidative stress occurs. Excessive free radicals can cause biological molecules to oxidize, such as lipid peroxidation, enzyme oxidation, and DNA base oxidation. This results in cell organelle damage, slowed cell metabolism, DNA fragmentation, and cell death [31-33]. According to some experimental evidence, it also shown that ACR-induced oxidative stress is characterized by increased lipid peroxidation (LPO) and protein carbonyl content, as well as a decrease in enzymic and non-enzymic antioxidants[34]. Studies also investigate the negative effects of ACR on PC12 cells. [35].In the brain tissues of rats exposed to 40 mg/kg ACR for four weeks, the level of MDA (an important biomarker of oxidative stress and lipid peroxidation) increased significantly, while the content of GSH (a biologically important intracellular thiol acting as a free radical scavenger) and the activities of SOD and GSH-Px (two important antioxidant enzymes) decreased significantly [36].

1.6 ACR and mitochondrial dysfunction

Mitochondria are the organelles that generate 90 percent of cellular ATP. The function of mitochondria is especially important in nerve cells specified for ATP generation [37]. The neurons are specific cell which requires the higher energy to support the cell activities, especially in the synaptic region. Mitochondria is the main site for ROS production, which is involved normally under physiological conditions, that is mainly produced at the site of mitochondrial enzyme complex I and III in the respiratory chain of mitochondria. Some studies reported that the mitochondrial complexes II are also involved in ROS production [38 - 40]. ACR showed a concentration-dependent reduction in cell viability and induced apoptosis. ACR toxicity was also observed due to impairment in the mitochondrial respiratory chain, aerobic glycolysis, and lower expression of the complex I, III, and IV subunits. The activation of mitochondrion-driven apoptotic signalling is triggered by a decrease in mitochondrial membrane potential and the ratio of Bcl-2/Bax. Increased NF-kB expression, as well as downstream inducible nitric oxide synthase (iNOS) and nitric oxide production, suggest that ACR has a pro-inflammatory effect.[41] ACR-induced mitochondria-dependent apoptosis was mediated by the mitogen-activated protein kinases (MAPK) and Nrf2 signalling pathways [42]. [43-45]. Currently ACR-induced cellular toxicity has been shown to inhibit proliferation and differentiation, activate mitochondrial-mediated apoptosis, and downregulate antioxidant signalling pathways in neurons [46- 48].

Neurotransmitter and neurotoxicity

ACR causes neurotoxicity by covalently binding to critical pre-synaptic protein thiol groups, resulting in a reduction in neurotransmitter release. Furthermore, ACR has been shown to affect DA receptor density, DA uptake, and dopamine release [49-50], some studies have shown that considerable decrease in the neurotransmitter's dopamine and norepinephrine in the brains of rats and zebrafish. [51-52].Some studies also revealed that the increased AChE activity inhibits cell proliferation and promotes apoptosis. ACR caused a significant increase in neurotransmission markers in the brain, such as AChE activity [53].

Neuromodulator alteration&Inflammation

Upregulation of glial fibrillary acidic protein (GFAP), an astrocytic marker, has been reported in all types of central nervous system injury. Exposure to be ACR increase the expression of GFAP [54] BDNF is an important neurotrophic brain development factor that promotes neuron growth, synaptic function, and neural plasticity during brain development. The most important functions of BDNF are neuron protection from toxic effects and neuron survival [55]. A current study has also discovered that giving ACR to pregnant rats reduces foetal brain BDNF levels [56-58].

Role of berberine in various disease: -

Berberine is a yellow alkaloid which occurs in numerous plants [59, 60]. Berberine is the principal component for many popular medicinal plants,such as Coptidis chinensis Franch. (family Ranunculaceae), PhellodendronchinenseSchneid. (family Rutaceae), and Mahonia bealei (Fort.) Carr. (family Berberidaceae) [62].BBR was found to be a small molecule with a molecular weight of only 371.8 Da [63]. BBR has been used clinically to treat bacterial diarrhea, hypercholesterolemia, type 2 diabetes, cardiac disease, cancer, and more [63-68]. Several therapeutic effects of berberine have been identified against cancer, obesity, congestive heart failure,[69] inflammation, atherosclerosis,

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neurodegenerative diseases,[70] rheumatoid arthritis, cardiovascular diseases,[71] and metabolic disorders, such as dyslipidemia, impaired fasting glucose, metabolic syndrome, and diabetes [69,72–74].Historically, berberine has also been used as a yellow dye, due to its yellow color.In tradition, the main activity of berberine has been evidenced to possess antimicrobial properties against various bacteria, fungi, protozoans, helminths, chlamydia, and viruses [75-78].Berberine has also been evaluated as a treatment for hypercholesterolemia, via reducing serum triglycerides, cholesterol, and low-density lipoprotein (LDL) cholesterol [79–81] Multiple studies have indicated that berberine has been found to be beneficial to cancer,[82] obesity, atherosclerosis,[83] rheumatoid arthritis, cerebrovascular diseases, fever, headaches, high blood pressure, immune system, irritable bowel syndrome, leukemia, leukopenia, liver disease (alcoholic), osteoporosis and respiratory disorders.

Therapeutic role of Berberine on neurotoxicity

Berberine has been found to possess multiple neuroprotective effects and improve survival, development, and function of neurons, while protecting these electrically excitable brain cells[84] Furthermore, there has been strong evidence that berberine has a close relationship with neurodegenerative diseases,[85] includingAlzheimer's disease(AD),[86] Parkinson's disease (PD)[87] and Huntington's disease(HD) [88].

II. CONCLUSION

In conclusion, this review highlights berberine's excellent neuroprotective ability against neurotoxicity generated by acrylamide. The comprehensive analysis of existing literature reveals that berberine exerts its protective effects through multifaceted mechanisms, including the attenuation of oxidative stress, modulation of apoptosis, and suppression of inflammatory responses in neural tissues. The observed neuroprotective properties position berberine as a promising candidate for mitigating the detrimental impact of Acrylamide on the nervous system. These insights not only contribute to the understanding of berberine's pharmacological actions but also highlight its potential therapeutic value in preventing or ameliorating neurotoxicity associated with Acrylamide exposure, warranting further exploration in clinical contexts.

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Conflict of interest
The author declares that there are no conflicts of interest regarding the publication of this manuscripts.

Ethical approval
This article does not contain any studies with human participants or animals performed by any of the author**.**

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List of abbreviation:
BBR :- Berberine
AD :- Alzheimer's disease
PD :- Parkinson's disease
ROS :- Reactive oxygen species
ACR :- Acrylamide
SOD :- Superoxide dismutase
LPO: Lipid peroxidation
WHO: World Health Organization

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