REVIEW ARTICLE

Antioxidants Role Against Acrylamide Toxicity on Urogenital System: An Overview

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ABSTRACT

Acrylamide (AA) is a chemical substance which is used as a soil stabilizing agent and in the production of copolymers and polymers since 1970. The presence of an AA adduct in food was observed in rats fed with fried food which led to a substantial increase in levels of hemoglobin adduct. Foods that are rich in carbohydrate when prepared at high temperature (above 120 C) by baking, toasting, frying, roasting or cooking results in the production of AA by the reaction of the amino acid with glucose present in it. Several studies observed AA toxicity on nervous system, reproductive system, and immune system. To justify this toxicity there is not a clear mechanism described. In this review article the mechanisms of AA toxicity on urogenital system and role of antioxidants against its toxicity has been reviewed. According to previous studies the main factor that induces AA toxicity is oxidative stress. AA treated groups revealed degeneration of the kidney's epithelial lining and the glomerular tuft. Adverse effect on reproductive system by AA has been evidenced by sperm-head abnormalities, dominant lethal effects, and testicular epithelial tissue degeneration. Therefore, it is advised that modifying of food processing methods and consuming lot of vegetables and fruits containing antioxidants. These antioxidants give us some supports to the cells of our body organs against the AA sources which cause cell defects.
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Keywords: Acrylamide, Toxicity, Antioxidant, Urogenital system, Reproductive system, Oxidative stress

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INTRODUCTION

Acrylamide (AA) is a chemical substance which is toxic and is mainly used in several industrial fields, and it is also present in certain cosmetic products. In room temperature AA presents as an odorless chemical, and as a white crystalline solid substance. C3H5NO is the molecular formula of AA. In 2002, Swedish scientists first found the presence of AA in some food substances. Maillard reaction results in the production of AA. By this reaction AA is formed by the interaction of the amino acid asparagine with glucose. Foods that are rich in carbohydrate when prepared at high temperature (above 120 C) by baking, toasting, frying, roasting or cooking, the amino acid asparagine reacts with glucose present in the food substance and produces AA due to the Maillard reaction (1).

The International Agency for Research on Cancer (IARC) has classified AA as "probably carcinogeni¬c to humans" (2). In 2001 the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) discovered that AA displays toxic effects on nervous system, reproductive system, immune system and also inherent toxic properties genotoxicity and carcinogenicity. Sweden'¬s national food administration added AA to the neo-formed contaminants list (NFCs) in 2002 after it was detected in several carbohydrates-rich heat-processed foods, such as bread, potato chips, and coffee (3).

The federal limit of AA in an eight-ounce glass of water is around 0.12 micrograms. 60 micrograms of AA is found in a six-ounce serving of french fries, or about five hundred times over the limit that is allowed. All the potato chips product exceeds the federal limit of AA by minimum of 39 times to maximum of 910 times! (4). Tolerable daily intake of AA to produce neurotoxicity and cancer was estimated to be 40µg/kg /day and 2.6µg/kg/day respectively (6). As AA has wide exposure on various systems, we focused to review the impact of AA on urogenital and reproductive system and the role of antioxidants against its toxicity in this article. High level of AA is found in heated carbohydrate rich foods

with a range of 150-4000µg/kg. Examples of such foods are potato, potato products, crip bread etc. Moderate amount of AA is observed in heated protein-rich foods with a range of 5-50µg/kg. Low level of AA is observed in unheated control or boiled foods with a range of <5µg/kg (5).

Concentration of AA in popular banana-based snacks in Malaysia was determined due to the concern of its toxicity. Banana fritter (Pisang goreng) had a quite high concentration of AA when compared to other types of banana snacks [banana chips, sweet banana chips, banana cake and banana balls]; The reason of increased concentration of AA in banana fritter could be due to reuse of the oil or duration of frying process or dough formulation procedure. (7) The coated fried chicken can possibly cause a health risk as the hazard quotient (HQ) value was more than 1 in it when compared to the other samples (fried sweet potato, French fries, fried banana, anchovies fritter) whose values were less than 1. Based on individual excess lifetime cancer risk (IELCR) calculation, cancer risk of coated fried chicken is higher (3 Ч 10-2) compared to fried sweet potato (5.81 Ч 10-4), french fries (1.89 Ч 10-4) and anchovies fritter (5.4 Ч 10-5) (8). The temperature and the duration of frying process of tapioca chips showed a positive correlation with AA levels. AA formation highly takes place at the initial stages of frying which was proved by the difference in AA levels formed at smaller concentration when it was fried in the high range between 180 °C and 210 °C compared to the smaller frying range 120 °C to 180 °C. It showed 90% difference in the AA level production with this temperature change. AA formation significantly reduced when tapioca was vacuum fried compared to the traditional frying method (9).

AA induces apoptosis due to oxidative stress by the following mechanism. AA can generate reactive oxygen species (ROS) by affecting the cellular redox chain. Then AA reacts with glutathione (GSH) by the help of glutathione s transferase (GST) (10, 11). After AA reacts with glutathione it gets oxidized to glycidamide. Nucleophiles group in cells like –SH, –NH2 or –OH interact with AA and its metabolite glycidamide. AA then rapidly gets absorbed in intestine and after absorption from intestine, AA results in the depletion of cellular GSH stores by conjugating non enzymatically and enzymatically with GSH (12). The reduction in GSH levels may enhance the levels of ROS, which are widely known as key mediators of cell function (13). Activity of GST and SOD increases due to the increase in the concentration of AA and that results in the depletion of GSH count (10, 11). The production of ROS showed the activation of mitogen activated protein kinase (MAPK)-JNKs. The MAPK plays a very important role in the regulation of apoptosis (13). Intestinal cell death and signaling of apoptosis in intestinal cells are influenced by cellular glutathione redox imbalance which was proved in several studies.

Therefore, cellular oxidative stress and apoptosis is caused by decreased GSH levels which could be suggested as a potential mechanism for AA toxicity.

METABOLISM OF AA IN THE BODY

AA once ingested is readily absorbed into the circulation and thereafter it is distributed to various organs which then react with cellular DNA, haemoglobin, nerve cells and enzymes (14). According to Miller et al. (1982), AA is largely excreted as metabolites in urine and bile. Within few hours two-thirds of the absorbed dose is excreted with a half-life. However, protein bound AA or AA metabolites in the blood and possibly in the nervous system have a half-life of about 10 days. The total serum protein, albumin, and globulin levels decreases with AA exposure due to retarded protein synthesis or changes in protein metabolism (15) (Figure 1).

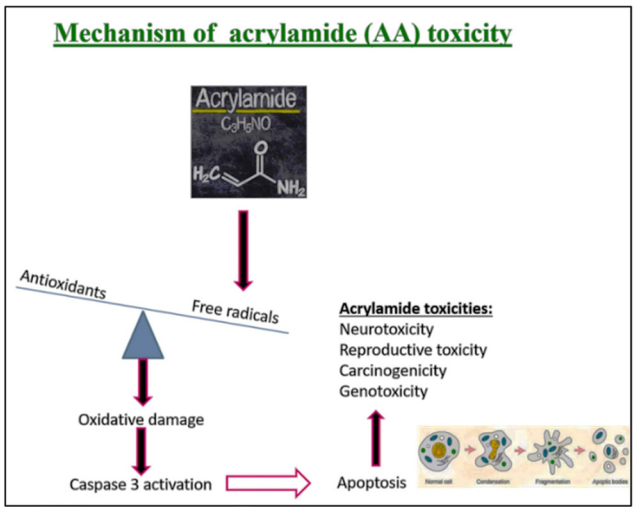

Figure 1: Diagram showing the mechanism of acrylamide toxicity in the body

High concentration of polyphenols can protect the epithelium of intestines from the potential oxidative stress which could be induced by AA (16, 17). In humans oxidative stress might be induced by dietary intake of AA over a chronic period. After exposure to AA there is increased ROS formation and GSH oxidation observed in isolated human monocyte (18).

A prospective cohort study showed a positive association between dietary AA and risk for renal cell cancer, but there is no association was seen with dietary AA and risk for bladder cancer. So, the food industries should continue striving to lower the concentration of acrylamide in foods (19-21).

Urea

Urea is the nitrogenous breakdown of protein nitrogen balance. The measurement of urea helps in evaluating the metabolism of amino acids and proteins through the urea cycle. The blood urea level was found to be

elevated in the rats treated with acrylamide at the level of 50mg/kg which suggests kidney damage.

Creatinine

Creatinine was the other metabolite that was assessed in the study. One of the excretory products of the muscle activity is creatinine which circulates in the blood stream. Creatinine is exclusively eliminated by kidneys so there is a correlation between kidney function and level of creatinine. Having said that kidneys will eliminate most of the creatinine which will be filtered freely in the renal glomerulus mainly and a small fraction of the creatinine will be filtered by the renal tubular component, which serves as a good indicator of renal-glomerular function.

Blood urea nitrogen (BUN)

BUN was also significantly reduced like urea and creatinine in rats which received acrylamide at the dose of 25mg/kg body weight and 50mg/kg body weight. This clearly indicates that there is damage in the kidney. BUN is defined as the quantity of nitrogen that circulates in the form of urea through the bloodstream. In a normal healthy animal, the renal glomerulus filters the urea from the plasma. This filtered urea will come back to the blood stream through the tubules of kidney, but majority of this urea will be excreted via urine. However, if the kidneys are not functioning well then, the amount of urea that should be filtered from plasma will be reduced resulting in higher blood urea nitrogen levels which fluctuates under many physiological conditions like dehydration, urinary tract obstruction, fever, infection, congestive heart failure or recent heart attack, gastrointestinal bleeding, shock, severe burns, poisoning, high protein diet and certain medications like some antibiotics. To identify if renal damage is the reason for increased blood urea nitrogen level it should be considered together with serum creatinine level too. Direct nephrotoxic agents, disseminated vascular coagulation, proteolytic enzymes and vasoactive substances that act on the kidneys may be the pathophysiological factors that can be related to renal failure. When the neurotoxin dose increases there is an increase in the concentration of analyte. The rats that received AA showed evident changes at renal level and it was dose dependant while the levels of vehicle-treated rats were within the normal range.

The toxicological effects of acrylamide on the renal system at the metabolic level have been proved. The metabolism in rats is 15-20 times higher than the human who is at resting stage. Therefore, negative effects on health in humans can be produced even with lower concentrations of acrylamide in food.

When the histological sections of kidney were assessed, it showed glomerular tuft degeneration and degeneration of the kidney's epithelial lining of the brush border membrane in all the groups treated with acrylamide. Congestion in the blood vessels were noted in the kidneys. Degenerative changes and pathophysiological disturbance were observed in mild and high doses. Wistar rats which was treated with various concentrations of AA showed a significant decrease in the body weight when compared to the control group.

In a study conducted to compare the effects of AA intake and fried potato chips the kidney histology showed marked changes. The group of rats that was treated with AA showed dense peritubular inflammatory cellular infiltration. Swelling of the tubular lumina is noted along with degeneration of their epithelial lining. The bowman's space was occupied due to the increase of cellularity and swelling of glomeruli. Cellular granulomatous lesions were formed in between the tubules due to the accumulation of inflammatory cells. This results in obliteration leading to degeneration of the tubules. Both the peri-glomerular and peri-tubular regions has dispersed inflammatory cells.

AA TOXICITY ON REPRODUCTIVE SYSTEM

Adverse effect on reproductive system by AA was identified by very dominant lethal effects, sperm-head abnormalities & testicular epithelial tissue degeneration. Apart from the above-mentioned adverse effect there are also other adverse effects of AA noticed in somatic cells producing chromosomal damage and also mutagenesis and disturbance in genomic imprinting during spermatogenesis. It also has adverse effects on male reproductive system, endocrine system and showed prenatal lethality in rats.

AA treated rat groups growth was reduced but there is no significant difference seen in the weights of testis and epididymis while comparing to the body weight. It also suggests partial depletion of germ cells as a result of significant decrease in the epididymal sperm reserve. In addition to this, histological lesions were noticed in the testes of AA fed rats. In AA fed rats distinct expression patterns of sGC (soluble Guanylyl Cyclase) heterodimers were observed which suggests different physiologic roles in spermiogenesis and steroidogenesis by sGC subunits (22).

Concentration of testosterone and prolactin in male rats reduced when AA was injected intraperitoneally in a dose-dependence manner (23). It was revealed that the oral doses of AA significantly reduced weight of the body and also reproductive organs as dose dependent. There was also reduction in the number of corpus lutea and serum progesterone concentrations in a dose dependent manner (24).

Mechanism of AA toxicity on female reproductive system

Cumulus cells are very important for the maturation of oocyte, including the meiotic arrest process and resumption. Toxic effects of AA results in apoptosis and increases the caspase-3 expression in cumulus cells.

(25). The serum progesterone concentrations were reduced by AA and the reduction is dose dependent. According to the review, it was suggested that the mechanism of AA toxicity could be the oxidative stress (26) which further results in apoptosis (Figure 2).

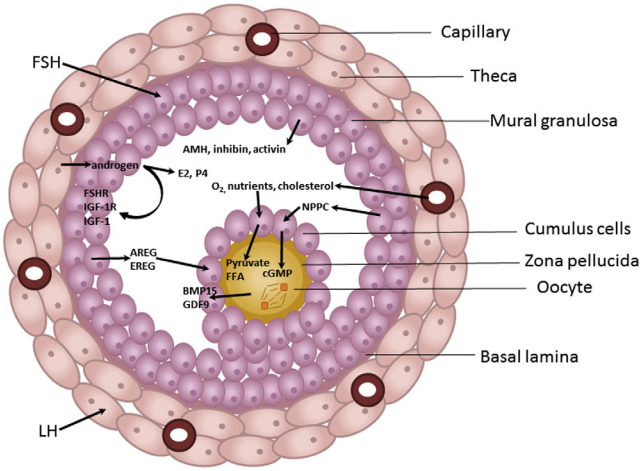

Figure 2: Diagram showing the structure of a mature ovarian follicle

Mechanism of AA toxicity on male reproductive system

Reproductive toxicity of AA in males may be due to the following reasons. Interference with kinesin motor proteins which is found in flagella of sperm affects sperm motility and fertilization events (27) (Figure 3). AA reduces the level of serum testosterone and prolactin (23) which will result in atrophy of the testis and affects the development of sperm and the motility of the sperm (28). Exposure to AA and glycidamide will reduce the viability of the cell and increases the oxidative stress which will result in apoptosis of both interstitial cells of leydig and sertoli cells (29). Peripheral neuropathies (like reduced function of hind limb) were induced by AA which can affect the copulatory behavior, mounting responses and intromission (30) which further affects the proper deposition of sperm in the female reproductive tract (vagina and uterus) and the hormonal changes resulting from it (31).

AA toxicity on developing fetus and childhood

A study reported histological abnormalities in the maternal tissues which occurs due to the intake of AA or fried potato chips. The mother's epiphyseal cartilage exhibited highest drastic alterations of cell structures.

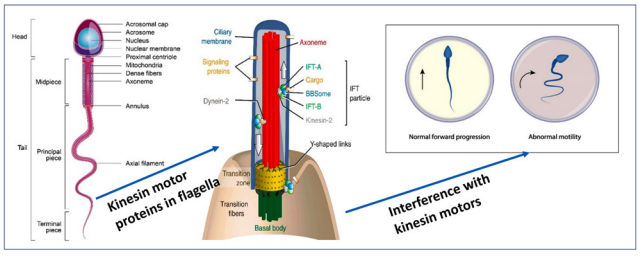

Figure 3: Diagram showing the structure of kinesin motors in flagella of the sperm and the result of interference with these kinesin motors.

Histological examination of liver showed erosion of endothelial cells, hepatic cords destruction with dilated sinusoids containing hypertrophied Kupffer cells in their wall. The cell boundaries of the hepatocytes were ill defined. In the group fed with fried potato chips there were hypertrophy of some of the hepatocytes manifesting early phase of hyperplasia. Both AA-intake and fried potatoes chips supplementation increased the neonatal mortality and the abortion rate. The newly born that was maternally fed with potato chips showed marked reduction in weight than the one fed with AA which also caused some amount of weight reduction (32).

The newborn of both experimental groups showed gross morphological changes. Of which the group that was fed with fried potato chips showed a higher rate of gross abnormalities than the group fed with AA. Some of the congenital abnormalities that were noted are unilateral and bilateral malformation of both the limbs, kinky tail, superficial hematomas, kyphotic body, missing sternebrae, partial or complete non-ossified digital phalanges for limbs and reduced neck region. The regular consumption of fried potato chips in childhood should be taken into serious consideration in order to keep proper bone growth and in pregnancy too for having healthy pregnancy by preventing adverse effects of AA on foetus growth (32).

POSSIBLE WAYS TO REDUCE AA TOXICITY IN OUR DAILY LIFE

Besides, to avoid slightly hazardous consuming other fried food stuffs containing low rates of AA, lot amounts of vegetables and fruits shall take to provide us with a source of antioxidants. These give us some supports to cells of our body organs against the AA sources which cause cell defects (32). AA is produced in the potato products mainly due the processing procedure of the potatoes especially the frying and baking processes at high temperature which will eventually results in an adverse change in the product leading to the formation of AA. Some techniques proposed certain ways to reduce the formation of free asparagine or reducing sugars by changing other ingredients or cooking time or temperature which will help to reduce the chance of cancer risk. Reducing AA in food and protecting the other aspects related to the quality is a major challenge, and it will set as a scope for future research (33). It has been proved that grape leaves reduced the toxic effect of AA on thyroid hormones and led to improvement of physiological activity in experimental rats by improving the hormonal activity (34).

Antioxidants

One of the possible ways to reduce AA toxicity is by increasing the intake of antioxidant food materials. Antioxidants are the one that disposes the free radicals by scavenging them and suppressing either their formation or opposing their actions. Every normal cell will

have a balance between pro-oxidant and antioxidant. When this balance is affected, it can lead to oxidative stress resulting in the shift towards pro-oxidant which mainly occurs due to the increase in the production of oxygen species or reduction in the level of antioxidants. This may lead to serious cell damage. This cell damage can be prevented by the antioxidants by preventing or slowing down the oxidation process and helps to increase the life of the oxidizable matter. Figure 4 shows the classification of antioxidants.

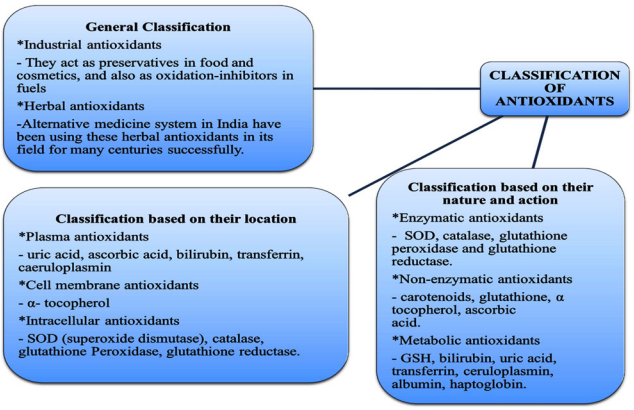

Figure 4: Diagram showing the classification of antioxidants based on different criteria

Free radicals

Free radicals (oxidants) cause oxidative stress which results in majority of the diseases/disorders. Free radicals have very short half-life. They are highly reactive and has damaging action towards DNA, proteins and lipids. The reactive oxygen species (ROS) that circulates in the body reacts with the electron of other molecules in the body which affects the various systems particularly the enzyme activity resulting in damage that further can lead to diseases like tumor, arthritis, ischemia etc. The free radicals may be derived either from oxygen or Nitrogen. The most common oxygen derived radicals include superoxide anion (O2), hydrogen peroxide (H2O2), peroxyl radicals (ROO) and reactive hydroxyl radicals (OH). The common nitrogen derived free radicals are nitric oxide (NO), peroxy nitrite anion (ONOO), Nitrogen dioxide (NO2) and Dinitrogen trioxide (N2O3) (35).

There are two main sources to produce ROS. They are exogenous (Cosmic & UV radiation, drugs, pollutants, smoking, toxins etc) and endogenous (Xanthine oxidase, transition metals, mitochondria etc).

Antioxidants mechanism of action

There are two main mechanisms of action

1. Chain breaking mechanism - In this mechanism an electron is donated to the free radical which is in the systems as beta-carotene and vitamins C and E by the primary antioxidant. Or else the primary antioxidant simply decays it into a harmless product.

2. Preventive – The intracellular antioxidant enzymes like superoxide dismutase etc. reduces the rate of chain initiation and thus prevents oxidation. Oxidation can be prevented by stabilizing copper and iron which are the transition metal radicals.

Antioxidants are used to protect the food deterioration by acting as food additives. Prevention of food deterioration can be done by keeping it in the dark and by sealing it by wax coating as exposure to oxygen and sunlight are the two main factors that results in oxidation of food particles. Oxygen is very important for respiration of plants so if plant materials are stored in anaerobic conditions for a longer time, it will cause unpleasant flavors and unappealing colors. Unsaturated fats are the most affected molecules by oxidation which causes them to turn rancid. So, this is usually prevented by smoking, salting, or fermenting the product.

Vegetables, nuts, fruits, wholegrains, eggs, some fish, poultry etc contain good amount of antioxidant in it. But when they are stored for long-term or cooked for long duration then the vitamins in it can get destroyed particularly vitamin A, C and E. When compared to fresh foods and uncooked foods the antioxidant is less found in the processed foods as the preparation process usually exposes the food particles to oxygen and heat resulting in oxidation.

ROLE OF ANTIOXIDANTS ON ACRYLAMIDE TOXICITY

"CIAA toolbox for acrylamide" (36) and some other review studies (37–39) have fully discussed the control of AA content in foods using mitigating strategy with the help of organic acids, mono and divalent cations and amino acids as additives. Each antioxidant according to its unique structure can reduce the formation of AA by playing a specific role. Some have reported that even though curcumin is a potential antioxidant that can reduce the formation of AA. But a recent study showed that curcumin can even facilitate the production of AA due to the presence of carbonyl moieties in it, which will react with asparagine and can lead to the production of AA. Surprisingly, a weak antioxidant naringenin, reacts with the amide group strongly and helps in blocking the AA formation particularly when the formation of AA happens during the Maillard reaction (39–41).

Opposite results for the same kind of agent can happen because there are some other parameters which influences the production of AA like reaction condition, concentration, solubility, and antioxidants preparation method (40, 42, 43). In both in vitro and in vivo studies one of the possible mechanisms to reduce the AA toxicity is the antioxidative activity by the phenolic-containing herbal medicines.

DISCUSSION

AA is found to be excreted mainly by two ways which as bile in one way and as metabolites in urine as another way. Two-third of absorbed AA dose is excreted with a few hours of half-life. However, AA which is bound to protein and AA metabolites in blood have a half-life of about ten days. In animal models, AA has been shown to have negative effects on a variety of systems, including the neurological, urogenital, and immunological systems. Although many types of research studies have been conducted in the past to study in detail the effect of AA on different systems of the body, further research in this area is needed to focus on a better understanding of the dose-response of health effects corresponding to dietary intake. The toxic effect of AA mainly occurs either due to the disturbance it makes in the antioxidant system in the body or may be due to the induction of apoptosis of the cells. Normally the antioxidant substances are beneficial in reducing the rate of synthesis of acrylamide or by preventing the formation of AA in food mainly during food processing.

This study tries to focus the effect of AA toxicity on urogenital system as it is affecting our major body functions. This study also emphasis the mechanism of AA toxicity on the urogenital system specifically on the male and female reproductive system so that it will be helpful to direct in attaining the preventive and treatment measures exactly. Significance of antioxidant role on AA toxicity have been specified in this study which will lead to expand the research more on this area.

LIMITATIONS

There are several studies which has proved the toxicity of AA on different systems of the body but there are only few studies that finds a solution to prevent or treat the AA toxicity. Another limitation regarding AA toxicity is majority of the studies have been conducted only on animal models.

FUTURE DIRECTIONS

There are two ideas related to this topic in which the future research can be directed. Firstly, there is no strong evidence of AA toxicity proven in human studies, hence more research must be conducted on human samples to ensure the toxicity of AA on different systems so that the exact effect of toxicity on the humans can be understood clearly to proceed further to prevention and treatment directions. Secondly, lot of animal studies have proven the toxic effects of AA on different organs, but its preventive and treatment methods are not discussed much so far. It will be a great area to expand the research on preventive and treatment methods of AA toxicity as AA is one of the unavoidable substances in our day-to-day life.

CONCLUSION

To minimize the effects of AA on our body it is highly recommended to reduce the consumption of processed food particularly the food items that are rich in carbohydrates especially for the children to maintain their regular bone growth and for pregnant women to avoid the adverse effect on the fetus growth. In addition to avoiding AA containing foods, it is advised to consume a lot of vegetables and fruits that are rich in antioxidants which will provide support to our body organs against the effect of AA. The novelty of this study is to analyze the studies conducted so far on the toxic effects of AA on urogenital system and to find out the limitations and future directions of the research related to this toxicity.

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