INTRODUCTION

Generally, alcohol is any organic compound with the hydroxyl functional group bound to a saturated carbon atom. It is grouped into three, primary, secondary and tertiary alcohols. Alcohols do not ionise in water and are neutral to litmus. Alcohol is an organic solvent that could be oxidised to aldehydes and ketones. Globally, alcohol is the most socially accepted addictive drug and the consumption of alcohol in excess is the third leading cause of preventable death in the United States. Alcohol undergoes oxidation to yield aldehydes, ketone or carboxylic acids which mediate cell damage, hence are implicated in a number of disease conditions. In particular, alcohol could trigger a cascade of acute health problems, characterised by central nervous system damage resulting in impaired brain activity, poor motor coordination and general behavioural changes. Central nervous system damage following excessive alcohol intake may also be due to adverse effects of alcohols on the synthesis and release of neurotransmitters. The disturbing aspect of alcohol-induced adverse effects is that on the focus, which may be compounded since many women that drink alcohol may continue without realising they are pregnant. Indeed, alcohol-induced teratogenic effects have been reported and generally result to an irreversible condition known as foetal alcohol syndrome (FAS) or foetal alcohol spectrum disorder (FASD), characterised by neurological symptoms including mental retardation/learning disabilities.

Preventing and/or mitigating the adverse effect of excessive alcohol exposure could reduce the associated risk, hence is advocated. In particular, the risk associated with maternal alcohol use during pregnancy, could be ameliorated through a good understanding of the mechanisms of alcohol-induced teratogenic effects on various tissues. Maternal ethanol (a representative of alcohol) ingestion caused foetal injury by two mechanisms. These are the direct mechanisms involving damage on the foetus following direct contact with ethanol and its product acetaldehyde and the indirect mechanisms via alcohol-induced damage of the placenta.

L-arginine is a synthetic precursor for nitric oxide (NO), and also for proline, ornithine and other glutamate family of amino acids. NO plays important physiological roles in neurotransmission,
vasodilation, cytotoxicity and immunity. L-arginine affected organ histology and markers of organ function including the brain, heart, liver and even testis. It also improves markers of metabolic syndrome related to renal function. L-arginine also improves markers of oxidative stress, glucose metabolism and nitric oxide synthesis. These warranted the present review, alcohol-induced teratogenesis: biochemical basis, management strategies and possible ameliorative role of L-arginine. The review could provide basis for detailed further studies in animals. The outcome of such studies could help in managing and/or controlling alcohol-induced teratogenesis in women who drink alcohol prior to and/or during pregnancy.

**ALCOHOL METABOLISM**

Alcohol metabolism essentially occurs in the liver and to a lesser extent in the stomach. Alcohol metabolism in non liver tissues is dependent on cytochrome P450 (CYT P450), catalase and alcohol dehydrogenase. The metabolism and resultant effects of alcohol on various tissues, including liver, depend on the concentration of alcohol and that of its metabolites in the blood over time. During the ADH dependent oxidation of alcohols, reduction of nicotinamide adenine dinucleotide (NAD⁺) to NADH results in the production of acetaldehyde a highly reactive and toxic metabolite that contribute to tissue damage, including damage to the signalling pathway as it (acetaldehyde) could cross the blood brain barrier and concomitant generation of highly reduced cytosolic environment in the liver (and other) cells. Therefore, any mechanism that could inhibit alcohol built up could lower its side effects through this mechanism.

**TERATOGENS AND POSSIBLE MEANS OF ALCOHOL-INDUCED TERATOGENESIS**

Generally, a teratogen is any agent that could induce or enhance the incidence of congenital malformation. It could be any chemical, infectious agent, physical condition or deficiency that can alter foetal morphology or subsequent functions. Essentially, teratogenic effects depend on the ability of the teratogen to cross the placenta. The possibility of a teratogen crossing the placenta is likely to be higher when the concentration of the teratogen is high. This also implies that reduction in the built up of any teratogen is important in the prevention of teratogenesis. The underlying processes of teratogenesis are not fully understood, however, genetic factor as well as the time, concentration and even the duration of teratogen exposure are essential in attempting to understand the processes of teratogenesis. Thus, the following possible mechanisms of alcohol-related teratogenesis were developed.

**Teratogenesis via Necrosis and Apoptosis**

Alcohol exposures results to cell death which could either be necrotic, the accidental cell death from exposure to a toxic agent or are apoptotic that involves programmed death and removal of unwanted cells. Thus, according to Deniaud et al., excessive cell death following abnormal apoptosis as could result from alcohol abuse could produce malformation of susceptible tissues and especially the embryos by overwhelming the capacity such tissues and the embryo to repair. This situation could result to damage to the foetus since apoptosis destroyed vital protein in cells.

**Teratogenesis via Oxidative Stress and Mitochondrial Dysfunction**

Alcohol-induced oxidative stress by the formation of ROS and by the reduction of the intracellular antioxidant capacity via the reduction of glutathione peroxidise enzyme. Free radicals are implicated in the aetiology of several human diseases. It is formed from various biochemical reactions in the cell involving oxygen and is known as reactive oxygen species (ROS). ROS and other free radicals are scavenged by antioxidants in the cells. However, as the level of the ROS exceeds that of the antioxidants, oxidative stress occurs with the attendant susceptibility of cells to damage. ROS also interferes with the functions of the mitochondria which play a vital role in energy generation, storage and regulation of calcium in the cells that is critical to neuron communication. In other words, mitochondrial dysfunction and calcium imbalance may result from alcohol-induced production of ROS. These could ultimately overwhelm the cell activities and activate apoptotic pathway, which results in teratogenic effect as suggested above.

**Teratogenesis via Growth Factors Inhibition**

The activities of cells depend on the growth factors which are important in the formation of organs in the body and in the development of an embryo. Cells activities in embryo exposed to alcohol are altered, leading to significant reduction in new cells formation and growth. This could be due to alcohol-induced inhibition of normal cell activities including cell migration, differentiation and growth that could result to cell death even in the foetus brain.

**Retinoic Acid Imbalance**

Retinol and ethanol are alcohols that are metabolised by the same enzyme, alcohol dehydrogenase that oxidise ethanol to acetaldehyde and retinol to retinaldehyde. Retinoic acid that could result from retinol plays an important positive role in neural crest development by ensuring the proper positioning of cells during the development of the embryo. Ethanol competitively inhibits, hence
reduces, retinoic acid in target tissues during embryonic development.\(^1\) Retinoic acid reduction may result to cell death to reduction of the signalling pathways,\(^2\) which may adversely affect the forming embryo.

**OTHER EFFECTS OF ALCOHOL**

Evidence abound that excess alcohol consumption impaired the central nervous system and overall behaviour,\(^4\) altered neural crest development and deformation of the facial characteristics of the foetus.\(^5,7\) Ethanol disrupted the L1 cell adhesion molecules function which results to abnormal brain development.\(^30,40\) Hepatomegaly and raised level of serum transaminases following alcohol consumption over time have been reported.\(^28\) In particular, alcohol could affect glucose transport and uptake. This is interesting because glucose metabolism is the chief source of energy for the brain cells and a significant reduction in the uptake and utilization of glucose by rat foetal astrocytes culture was reported.\(^41\) The disruption of glucose uptake and utilisation in the brain would affect the function and survival of the brain cells\(^18\) and this disruption may be by decreasing the levels of the principal glucose transporters.

Alcohol is also interfered with neurotransmission by reducing excitatory neurotransmission activity of glutamate.\(^8\) Excitatory actions of glutamate do result in the influx of calcium ion to the nitric oxide synthetic medium to enhance the nitric oxide synthesis.\(^12\) In the CNS, glutamate is very important for maintenance of calcium homeostasis and as a neurotransmitter it plays significant role in synaptic plasticity and in learning.\(^15\) As it were, calcium influx is a vital regulator of the activity and function of the neurons, as such rise in the intracellular calcium could lead to cell death by apoptosis and necrosis.\(^24\)

**MANAGEMENT STRATEGIES FOR ALCOHOL-INDUCED TERATOGENESIS AND POSSIBLE ROLES OF L-ARGININE**

**Antagonising the Effect of Alcohol on L1-mediated Cell Adhesion**

Alcohol-induced teratogenesis could be managed by antagonising the effect of alcohol on L1-mediated cell adhesion\(^44\) and by using serotonin agonist since alcohol is known to alter serotonin functions.\(^35,46\) Previously, administration of serotonin agonists (ipratropine and busipirone) exerted protective effect on alcohol-induced effects.\(^47\)

**Using Appropriate N-methyl-d-Aspartate Receptor (NMDAR) Antagonists**

Also, alcohol-induced teratogenesis could be managed at the level of NMDAR, using appropriate NMDAR antagonists. This is because NMDAR plays functional roles in brain development, ranging from the excitatory neurotransmission to learning and memory.\(^49\) Interestingly, NMDAR is characterised by high affinity for glutamate and high calcium permeability.\(^25\) Furthermore, calcium permeability to this receptor is the basis for the regulation of synaptic plasticity which is the brain’s ability to change to external stimuli such as learning and memory.\(^40\) Excessive activation of NMDAR resulted in excitotoxic effects while the NMDAR antagonists protected the neurons from the effects by blocking the excessive NMDAR activation.\(^29\) Glutamate, an excitotoxin, is known to exert its excitotoxic activity by way of release of calcium ion that complexes with a specialised protein, calmodulin to trigger the nitric oxide synthase that catalyses the synthesis of nitric oxide which could be toxic at abnormal physiological concentration.\(^13\) L-arginine is very important in the regulation of nitric oxide synthesis, thus we speculated that regulating the availability of L-arginine, the sole precursor to nitric oxide synthesis, could be useful in managing alcohol-induced teratogenesis. L-Arginine prevented ethanol-induced inactivation of NMDAR related increase in the intracellular calcium level\(^24\) perhaps through the product, NO, which plays an important role in cell signalling in the brain, and as an unconventional neurotransmitter, NO does not mediate its action by binding to membrane associated receptors but diffuses from one neuron to another and acts directly on intracellular components.\(^29\)

**Antioxidant Activities**

Generally, oxidative stress is a key mechanism and manifestation of diseased state and cells/organisms damage, including alcohol-induced damages. Oxidative stress results from the imbalance between the generated ROS and antioxidant, implying that antioxidants can mitigate alcohol-induced effects, including teratogenic effects.\(^26\) Thus, intake of antioxidant rich foods by alcohol drinking pregnant women could provide a good level of protection to the foetus. Depending on the concentration, nitric oxide is an antioxidant and it is readily synthesised following exogenous supply of L-arginine.\(^44\) Hence, L-arginine may improve alcohol-induced teratogenesis \textit{via} its capacity to serve as the sole precursor in the synthesis of nitric oxide, a potent antioxidant.

**Maintaining Neurotrophic Factors Balance**

Neurotrophic factors are important for the differentiation, maturation and survival of neurons in the brain, especially during initial development stage.\(^45\) The four identified neurotrophic factors, nerve growth factor, the brain-derived neurotrophic factors\(^4\) are known to reduce following alcohol intake.\(^49\) Thus, maintaining the neurotrophic factors optimal level may mitigate alcohol-induced teratogenesis. L-arginine, particularly through it sole synthetic product, nitric oxide, may enhance the maintenance of the neurotrophic factors balance.
OTHER POSSIBLE ROLES OF L-ARGININE IN AMELIORATING ALCOHOL-INDUCED EFFECTS

Generally, ethanol reduces the activity of NOS via modulation of the conformation and stability of the enzyme possibly by preventing calcium ion built up and consequently preventing the formation of calciun-calcmodulin complex that activates the NOS. As stated earlier, prenatal alcohol exposure altered glucose uptake and its utilisation. L-Arginine could ameliorate this effect possibly by regulating the release and utilization of glucose. L-Arginine enhances the production and release of insulin. Furthermore, inhibition of NOS in pregnant rat precipitated preeclampsia-like symptoms that was reversed by infusing L-Arginine, suggesting that supplementation of L-arginine could improve the foetal utilization of glucose in alcohol taking pregnant women. L-Arginine could improve/protect the liver and other organs of high metabolic capacity, including the brain, heart and lung. Alcohol intake when low L-Arginine availability resulted in the reduction of the biological activity of NO and consequent production of peroxynitrites that mediate cell damage. This was reversed upon supplementation of L-arginine suggesting that exogenous supply of L-arginine could modulate alcohol-induced adverse effects.

CONCLUSION

Alcohol as a teratogen could induce foetal malfunction, generally referred to as foetal alcohol spectrum disorder (FASD), by mechanisms involving the dehydrogenases, cytochrome P4502E1 and catalase enzymes that result in the concomitant ROS generation and the resultant ROS-related damage. The alcohol-induced teratogenesis (and even other alcohol-induced adverse effects) are generally mediated via and/or characterised by oxidative stress, cell death, mitochondrial dysfunction, interference with the activity of growth factors and retinoid acid (RA) imbalance. Alcohol-induced generation of ROS could overwhelm cellular activities by inactivating electron transport chain complex hence decreasing the production of mitochondrial energy and activating the apoptotic pathway. On the other hand, the use of N-methyl-D-aspartate receptors antagonists, antioxidants and neurotrophic factors seemingly attenuated alcohol-induced teratogenesis, hence served as its management strategies. L-arginine, an amino acid that plays central role in the synthesis of nitric oxide, NO, improved foetal regulation of glucose release, transport and utilisation which were fundamental to alcohol-induced damage. These suggested the possible ameliorative role of L-arginine on alcohol-induced teratogenesis and other adverse effects of alcohol. Detailed further studies perhaps in animals are warranted as the outcome of such studies could help in managing and/or controlling alcohol-induced teratogenesis in women on alcohol prior to and/or during pregnancy as well as other adverse effects of alcohol in humans.

REFERENCES


Statement of originality of work: The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and that each author believes that the manuscript represents honest and original work.

Author contribution: UOM conducted the literature search and writing of the manuscript while ACCE supervised, proof read and corrected the manuscript.

Sources of funding: None.

Competing interest / Conflict of interest: The author(s) have no competing interests for financial support, publication of this research, patents, and royalties through this collaborative research. All authors were equally involved in discussed research work. There is no financial conflict with the subject matter discussed in the manuscript.

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