Counteracting arsenic toxicity: curcumin to the rescue?

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Abstract

Arsenicosis leads to various irreversible damages in several organs and is considered to be a carcinogen. The effects of chronic arsenic poisoning are a result of an imbalance between pro- and antioxidant homeostasis, oxidative stress, as well as DNA and protein damage. Curcumin, the polyphenolic pigment extracted from the rhizome of *Curcuma longa*, is well-known for its pleiotropic medicinal effects. Curcumin has been shown to have ameliorative effects in arsenic-induced genotoxicity, nephrotoxicity, hepatotoxicity, angiogenesis, skin diseases, reproductive toxicity, neurotoxicity, and immunotoxicity. This review aims to summarize the scientific evidence on arsenic toxicity in various organs and the ameliorative effects of curcumin on the arsenic toxicity.

1. Introduction

Heavy metals are characterized as metallic elements with a relatively high atomic weight such as arsenic (As) which may harm living organisms at small concentrations [1]. As one of the most abundant natural elements and environmental toxicants, As is considered as a critical human health hazard [2]. Various manifestations of chronic As poisoning (arsenicosis) are due to the imbalance between pro- and antioxidant homeostasis and its high affinity for thiol groups on proteins. As is categorized usually as a metalloid, due to its both metallic and non-metallic features [3].

As is ubiquitous in the environment, earth's crust and the biosphere [4, 5]. Human exposure to As usually occurs by air, soil, drinking water, inhalation, skin contact during occupational situations, contaminated food and medicines [6]. More than 100 million peoples worldwide are exposed to a higher than safe recommended level of As in drinking water as recommended by the World Health Organization (<10 μg/L) [7].

As is water-soluble and exists as elemental (0), trivalent (+3 oxidation; arsenite), As (III) and pentavalent (+5 oxidation; arsenate), As (V). When As combines with elements such as oxygen, chlorine and sulfur, it forms the inorganic arsenic (iAs) whereas when it binds with hydrogen and carbon, it forms organic As. Notably, As (III) has been considered to be more toxic compared to As (V) and iAs are more toxic compared to the organic forms (Figure 1) [8-10]. As (V) is an analogue of phosphate and therefore disrupts several pivotal cellular events such as oxidative phosphorylation and ATP synthesis [11]. Arsenate reductase enzyme converts the As (V) to As (III) as a part of detoxification. The half-life of As is nearly 4 days, but As (III) have a lower half-life compared to As (V) [12]. Generally, the bioavailability of iAs is 60% to 87% [13, 14], and the majority of iAs and its metabolites are excreted through the urine and bile. iAs is easily absorbed by the gastrointestinal tract and after being metabolized in the liver and becomes methylated As. As interferes with several normal body

activities and affects the central nervous system, reproductive system, the hematopoietic system, cardiovascular system, respiratory system, ophthalmic system and the gastrointestinal system (Figure 2, 3) [15, 16].

Arsenicosis causes a myriad of irreversible injuries in several organs in the prenatal period, early childhood and later in life and is considered as a carcinogen. The mechanisms by which As induces carcinogenesis include oxidative stress (OS), DNA damage and chromosomal abnormalities, altering of gene expression and epigenetic modifications [17, 18]. As affects the cellular function of several enzymes, particularly those involved in the heme synthesis and degradation [19]. As compounds have also been implicated in the inactivation of endothelial nitric oxide synthase (eNOS) via connecting with the thiol groups leading to an increase in reactive nitrogen species (RNS) which together with the reactive oxygen species (ROS) causes extensive lipid peroxidation (LPO) and apoptosis [20].

There is a growing interest in establishing a safe and effective treatment for iAs exposure. The use of plant and natural products for the remedy of human diseases is as old as the humankind. The main advantages of medicines based on phytochemicals seem to be their high efficacy, little side effects and a low cost [21]. Curcumin (CUR), the yellowish and water-insoluble polyphenolic pigment extracted from the rhizome of *Curcuma longa* (Zingiberaceae), is well-known as a pleiotropic medicinal herb [22, 23]. However, there is little known about the protective effects of CUR against hazardous effects induced by the exposure to As, including those associated with damage to the nervous system, DNA, kidneys and liver. The purpose of this review is to summarize the scientific evidence concerning the organ toxicities induced by As, and the ameliorative role of CUR.

2.   Molecular mechanisms involved in arsenic toxicity

1.   *Signal transduction*

As affects the regulation of several cellular signal transduction pathways (Figure 3). As activate a series of downstream signaling cascades and disrupts various signaling pathways associated with cell growth, proliferation and apoptosis [24]. As can damage DNA and triggers the cell arrest at G or G/M phase [25, 26]. Arsenic trioxide (As2O3) can attenuate the steady-state levels of CDK/cyclin complexes, such as CDK2, CDK6, cyclins A, D1 and E, in different tumor cells [27, 28]. As2O3 arrests the cell cycle by the suppression of cdc2-associated kinase and CDK2/6-associated kinases in compliance with the decrement of cdc25B/C phosphatases and the Rb protein hypophosphorylation, respectively [27, 28]. It has been found that p53 signaling pathway have a important role in As-created cell cycle arrest [29].

As exposure can induce apoptosis through disturbance of signal transduction, activation of activator protein-1 (AP-1), deactivation of constitutive nuclear factor-kappa B (NF-κB) and by inhibition of PI3K/Akt signaling. As causes imbalances in intracellular oxidation/reduction reactions which induce signaling axis that modulate early response genes. Transcription factors (TFs) related to stress response, i.e. AP-1 and NF-κB mediate the transcription of multiple downstream target genes [30]. Since upstream proteins which regulate AP-1, NF-κB, and nuclear factor (erythroid-2 related) factor 2 (Nrf2) and nitric oxide synthase (NOS) all have reactive thiols, their oxidative modification through ROS, produced during As exposure, maybe the crucial step in various cellular responses and toxicity [31]. As stimulate ROS generation, a mitochondrial OS, which in turn decreases the matrix metalloproteinases (MMPs). The disrupted MMP increases the leakage of cytochrome c and induction of the caspase cascade resulting in apoptosis [32].

Mitogen-activated protein kinases (MAPKs) consist of a family of regulatory serine/threonine phosphorylating proteins which regulate the signal transductions against different extracellular stimuli and mediate the regulation of gene amplification, mitosis, motility, metabolism, and apoptosis [33]. The MAPK family encompasses important members such as extracellular signal-regulated kinases (ERKs), c-Jun amino-terminal kinase 3(JNK) and p38 [33]. ERKs transduce the signaling which causes cell differentiation, proliferation and transformation, whereas JNKs and p38 kinase react to stressful events, which leads to the cell cycle arrest and cell apoptosis [34]. As has an impact on various biological pathways since it can induce proteins such as ERK2, p38 and JNK [35-37]. Thereore, the Ras-MAPK/ERK pathway seems to be sensitive to As damage [38].

Many family members of receptor tyrosine kinase (RTK), have emerged as a main regulators of important cellular processes, like cell proliferation, differentiation, metabolism, survival, propagation, and cell-cycle control [39]. Exposure of the cells to As promoted total cellular tyrosine phosphorylation possibly through direct interact with EGFR molecules to induce the conformational changes or the dimerization of EGFR, and eventually EGFR activation [40]. As might activate EGFR via the production of ROS which stimulated the conformational altrations in the receptor [41]. As exposure also produces dose-dependent toxicity through stimulation of epidermal growth factor receptor (EGFR) pathway intermediates, cSrc, Rac1, Shc, Grb2, MAPK or ERK kinases (MEK)1/2 and ERK1/2 [42, 43]. As-mediated ERK1/2 induction reversely regulates DNA polymerase beta expression and over-expresses heme oxygenase 1 (HO-1) at toxic concentrations [42]. As also can induce carcinogenesis and can promote tumor growth [44]. Generally, the ERK1⁄2 cascade is activated by mitogens like growth factors. Aberrant regulation of the ERK1⁄2 cascade can cause susceptible cells to undergo tumorigenesis [42]. As induces tumorigenesis also through

the abrogation of p53 pathway causing uncontrolled proliferation [24]. Evidence also suggests a connection between As exposure and inhibited acetylcholinesterase (AChE) activity [45], generation of acetylcholine (ACh) and action of choline acetyltransferase [46].

The protein kinase C (PKC) family includes different isoenzymes with identical structures; all of which regulate various cellular actions. Three known PKC forms (PKCα, PKCε, and PKCδ) were found to mediate As-induced cellular signal transduction resulting in AP-1 induction [47]. As induced translocation of PKC isoforms from the cytosol to membranes, where these isoenzymes mediate As-induced AP-1 activation via various MAPK (ERKs, JNKs, and p38) pathways [47].

Autophagy flux disturbance has also been observed in As models. Sodium arsenite (NaAsO2) causes to an accumulation of LC3-II and p62 proteins in female mice. The LC3-II is an crucial protein for elongation and fold of the phagophore in the autophagosome membranes. Whereas, p62 is a receptor protein, which binds to the specific cargo, eventually leads to the cargo's degradation whitin autophagolysosomes [48, 49]. The This phenomenon is related with ERK overinduction, via SOCS3-dependent IL-6/STAT3 signaling cascade inhibition [50].

Angiotensin II Type I receptor (AT$_1$R) as a G protein-coupled receptor coordinate most of the physiological or pathological roles of AngII as a part of renin–angiotensin system [51, 52]. NaAsO2 increases the expression of AT$_1$R by ROS-mediated induction of the JNK pathway. Long-time As exposure can enhance the pathogenic roles of AngII via modulating a deviant AT$_1$R signaling pathway, resulting in hypertension [53].

2. Receptor pharmacology

As can disrupt the hormone-induced gene expression mediated via the glucocorticoid receptor (GR) [54]. Glucocorticoids activate a different biological process that is mediated

via their connection with the cytosolic steroid hormone receptor GR. GR coordinates various metabolic and homeostatic functions in almost all tissues [55]. It has been shown that non-toxic concentrations of As can interact directly with GR complexes and specifically inhibit GR-mediated transcription [56].

It has been shown that As can cause male infertility by suppression of androgen receptor (AR) transcriptional activity via inhibiting the recruitment of AR to promoters of its target gene [57]. As have also been found to be an active endocrine disruptor of estrogen receptor (ER)-mediated gene expression, both *in vivo* and *in vitro* [58].

As can also interrupt the function of the hypothalamic-pituitary-adrenal (HPA) axis. As increases serum corticosterone concentrations, decreases levels of corticotropin-releasing factor receptor 1 in offspring hippocampus, and raises dorsal hippocampal serotonin 5-hydroxytryptamine receptor as well as receptor-effector coupling [59]. It has been reported that As (III) affects thyroid hormone levels and interrupts thyroid function via alterings the expression of TR-associated genes. As exposure change the expression of thyroid hormone receptor (TR) response element as well as the endogenous TR-regulated type I deiodinase gene [60].

The transient receptor potential melastatin 4 (TRPM4) is a voltage dependent non-selective cation channel [61]. TRPM4 is mainly found in the heart, and CNS, as well as its expression also found in endothelial cells (ECs) from various vascular tissues [62]. As2O3 over-express the both transcription and translationsl levels of TRPM4 through entering the cell membrane, TRPM4 channels is over-activated in endothelial cells (ECs). The activated TRPM4 channels causes to unlimited Na^+ influx which leads cell membranes depolarization and Ca^{2+} overload, eventually the ECs are injured [63].

3.   Biochemistry

As can substitute phosphate in various biochemical reactions due to their identical structure and characteristics [64]. For instance, arsenate interacts with glucose and gluconate [65] to generate glucose-6-arsenate and 6-arsenogluconate, respectively. These elements are similar to glucose-6-phosphate (G6P) and 6-phosphogluconate, respectively. During the glycolysis, glucose-6-arsenate is a substrate for glucose-6-phosphate dehydrogenase (G6PD) and can suppress hexokinase, as does G6P [66, 67].

The metabolomic investigations demonstrated that alteration in the metabolism of energy, amino acid, purine, choline as well as degradation of membrane phospholipids is implicated in the cell apoptosis in As-induced toxicity [68]. As enforces allosteric inhibition of pyruvate dehydrogenase complex which catalyze the oxidative decarboxylation of pyruvate to synthesis acetyl-COA via NAD+. Therefore, the cellular energy system is disrupted and results in apoptosis [12]. The As toxicity could be via its interaction with sulfhydryl groups related to proteins and enzymes and via boost of the ROS in the cells leading to cell damage [69]. In addition, As activate unstable mitochondrial metabolism, reduced withdrawal of ROS, attenuate protein production and changing membrane lipid polarity and fluidness resulting in the mitochondrial oxidative injury [70].

Furthermore, As can also lead to thiamine deficiency through mitigating its availability and also cause lactic acidosis via increasing the amount of lactic acid [12]. NaAsO2 increased LPO, DNA fragmentation, triacylglycerides, total cholesterol and low-density lipoprotein cholesterol (LDL-C), while antioxidant status and high-density lipoprotein cholesterol (HDL-C) were found to be decreased [71].

As regulate the expression of the heat shock proteins (Hsps) families. Hsp are regulated via a complex regulatory mechanism, which needs the integration of most signal pathways. This stress response is an adaptive phenomenon in organisms [72]. For instance, Hsp90 is involved in the regulation of cellular redox status. Redox-regulated communications between cytochrome c and cytoplasmic Hsp90 are implicated in apoptosis. These interplays can be inhibited by high doses of NaAsO2 in a purified system [73].

4.   Immunity

As has been shown to lead immunotoxicity, skin lesions and suseptibility to developing malignancy (Figure 3)[74, 75]. In difernent experimental model, As exposing has been found to attenuate IgM/IgG antibody-forming cell response [76, 77] as well as repress delayed type of hypersensitivity response to phytohemagglutinin [78]. NaAsO2 can change immune cell populations causing to functional altrations in immune response particularly decreament of cutaneous contact hypersitivity response [79].

Immunosuppressive features of As lead to inability of innate immune system to eradicate various bacterial and viral infection such as HIV-1 [80] and influenza A (H1N1) infection[81]. In Bangladesh, people who expose to As, more vulnerable to lower respiratory tract infections and diarrhea [82-84]. Neutrophil and macrophages as a main regulator of innate immunity have been reported to be a major cellular target population of As toxicity[85, 86]. For instance, As prompts apoptotic cell death in neutrophils and change phenotype of Macrophages. Remarkable loss of cell adhesion capability, reduce NO generation, and reduce chemotactic/phagocytic dysfunction and reduced regulation of CD54/F-actin with these immune cells [87-89]. iAs inhibits the differentiation of monocytes to functionally active macrophages through suppressing survival signaling pathways [90]. Additionally, As can alters the phenotypic and genotypic properties

of mature macrophages [87, 91, 92]. iAs significantly changes the expression of a large number of correspounding genes particuarly activated or inhibited whitin the differentiation process, possibly via an oxidative stress-associated mechanism [91, 92]. Indeed, As also mitigate cystic fibrosis transmembrane conductance regulator (CFTR)-mediated chloride secretion; so abolished clearance of respiratory pathogens [93].

There are remarkable negative correlation between long-time As exposure and the number and action of T regulatory cells in adults [94]. It has been shown that maternal As exposure during pregnancy was related with a reduction in the frequency of pan T cells in the placenta in spite of increased inflmmatory cytokines amounts, as well as reduced thymic size and function in infants and elevated morbidity from infectious diseases[84, 95, 96].

iAs can also markedly alter development, induction and proliferation of T cells [97]. Actually, iAs-dependent suppression of peripheral T cell proliferation is mainly related with inhibition of interleukin-2 (IL-2) secretion which is necessary cytokine for induction of T cells and their progression to the cell cycle [98]. As2O3 enormously impaires the releasing of IL-12 and IL-23 from activated dendritic cells and reduce the activation of T helper (Th) cells [99, 100]. Altogether, these evidences indicated that As may change both the action and the number of T cells, which are of important for cell-mediated immunity [90, 101].

3. Curcumin

Curcumin [1,7-bis(4-hydroxy-3-methoxy phenol)-1,6-heptadiene-3,5-dione], is an alkaloid and the active component of turmeric and ginger [102]. Since at least 2500 years ago, turmeric root has been extensively used to add color and flavor in cooking and as a remedy in traditional medicine. CUR showed various biological advantageous such as anti-microbial, antioxidant, lipid-lowering, hypoglycemic, anti-inflammatory and anti-ageing properties [103-108]. Molecular targets of CUR are numerous including transcription factors,

transporters, enzymes, microRNAs, pro-inflammatory cytokines, apoptotic proteins, growth factors, hormones and receptors [109-113].

CUR as a chain-breaking antioxidant which gives H from the phenolic moiety [114]. The aromatic ring systems (phenols) are linked via 2 α,β-unsaturated carbonyl groups. Furthermore, CUR can inhibit LPO and quenching hydroxyl and superoxide radicals through the phenolic OH group and the CH2 group of the β-diketone section [115, 116]. Multiple molecular targets in different cell types, i.e. NF-kB, P38, hypoxia-inducible factor (HIF-1α), peroxisome proliferator-activated receptor-γ (PPARγ) and AKT, are involved in the anti-inflammatory effect of CUR [117, 118].

In another pathway, CUR exerts anti-oxidative functions through activation of antioxidant responses via Nrf2 activation and effectively suppresses a host of factors which contributes to inflammation [119]. CUR can decrease the expression of genes implicated in apoptosis, proliferation, and transformation [120].

CUR reduces N-nitrosodiethylamine (DEN)-caused hepatotoxicity by modulating the enzymes involved in the oxidant stress, liver function, lactate dehydrogenase A (LDHA), alpha-fetoprotein (AFP) and the cyclooxygenase (COX)-2/Prostaglandin E2 (PGE2) cascade [121]. CUR has been shown to have ameliorative effects in the As-induced genotoxicity [122, 123], nephrotoxicity [124], hepatotoxicity [125], angiogenesis [123], dermatological disorders [126], reproductive intoxication [127], neurotoxicity [128] and immunotoxicity (Figure 4) [129]. It has been reported that CUR also can used as a co-treatment with chelating agents in a synergistic way for the treatment of As intoxication[130].

4. Effect of curcumin on arsenic-induced toxicity

4.1. Nephrotoxicity

Acute tubular necrosis with acute renal failure has been observed in patients with acute As poisoning. Some of these cases can progress to cortical necrosis and ultimately chronic kidney disease. The kidney injury can be due to the hypotensive shock, direct impacts of As on tubule cells resulting in tubular damage and hemoglobinuria or myoglobinuria which can lead to proteinuria. Acute tubulointerstitial nephritis has also been considered as a clinical presentation of acute As intoxication [131].

NaAsO2 causes shrinkage of the glomerulus, disturbed glomerular integrity, and a reduction in the glomerular area as well as an increase in the Bowman's space due to the of glomerular atrophy. Collagen is the important protein ingredient of glomerular basement membrane and is necessary for glomerular integrity [132]. As affects cell antioxidant defense system to activate LPO and the disturbance of cell polyunsaturated fatty acid. As also suppress protein synthesis [133]. Simultaneous treatment with CUR plus NaAsO2 ameliorated the side effects of As on the glomerulus and proximal tubule, glomerular area, serum total antioxidant capacity and the circulating levels of malondialdehyde (MDA) [134]. It has been shown that CUR reduced the As-induced increase in bilirubin, urea and creatinine (Cr) in an experimental model of As toxicity [46, 135, 136]. The elevated amount of serum Cr after As2O3 exposure is because of the increased formation of metabolic waste product related to metabolism of musclse. Moreover, Cr is anhydride of creatine. Muscle consists phosphocreatine which endores involuntary cyclization with miss of inorganic phosphorous to constitute creatine. Transformation of creatine into Cr is a non-enzymatic immutable procedure. Since, affinity for thiol group of different proteins exist in the cell membrane of muscles, As harms the cells due to which the enzyme, creatine phosphokinase, released from the cells which is acounted for the transformation of phosphocreatine in to creatine. Therefore enhances the value of Cr [137]. Ameliorative role of CUR against As induced pathologies could be due to the antioxidant potency of this natural agent. The protective roles of *Curcuma*

aromatica leaf extract were shown on the nephrotoxicity of As2O3 in the albino rats. As2O3 poisoning significantly increased the serum level of uric acid, blood urea nitrogen, and Cr because of renal dysfunction. *Curcuma aromatica* (50 mg/kg BW) normalized the serum levels of uric acid, blood urea nitrogen and Cr [137]. *Curcuma aromatica* inhibits tubular necrosis and back-leak of filtrate as well as normalize serum urea consentration by antioxidant features [137].

OS is a hallmark of As-induced liver, renal and neuronal injury [138]. As is not a redox metal, however, is a potent disruptor of the cell signaling pathways through inducing reactive oxygen and nitrogen radical production, where superoxide anion radical is the main species that is turned to hydrogen peroxide and finally to hydroxyl radical [139]. Hydroxyl radical can interact with macromolecules resulting in OS, LPO, DNA damage and extensive changes in the cellular regulatory mechanisms [139-141].

Several enzymatic antioxidants such as superoxide dismutase (SOD), catalase (Cat), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST) and G6PD are the first line of intracellular defence against OS induced by As exposure [142]. SOD and Cat are considered to be the two preliminary subcellular defence of antioxidant system against free radical production with As exposure. SOD catalysis the conversion of superoxide anion to hydrogen peroxide (H2O2), whereas Cat or GPx converts H_2O_2 to a water molecule. Glutathione (GSH) associated enzymes such as GPx and GR acts directly or indirectly against oxidation, but GST is also involved in the metabolic detoxification. GSTs maintain a shield against As via conjugation or decrement with GSH as well as relief the OS and subsequent LPO induced by As [143]. GST and GPx decrease the organic hydroperoxides in the membranes and lipoproteins accompanied by GSH. GSH as a tripeptide non-enzymatic antioxidant has a crucial role in the free radical quenching and acts as a co-factor for numerous enzymes participating in the general antioxidant defence [144]. In

addition, GSH inhibits the oxidation of SH-groups [145]. Hence, these antioxidant enzymes reduce the deleterious effects of ROS.

The protective role of CUR against As could be through free radical scavenging, which would inhibit the oxidation of SH-group (Figure 4) [146]. The renoprotective effect of CUR is due to the scavenging of ROS and inhibition of hydrogen peroxide-induced oxidative injury in a renal cells [147]. Furthermore, CUR can potentially inhibit the thiol depletion and improves the renal GSH amount [136]. Thiols (SH-group) considered to be a main protector of cells against ROS. Furtheremore, thiols as a target site for As-induced cellular injury can remarkably decrease SH-group content. CUR enhances the activities of antioxidant enzymes (SOD, Cat, GSH, GR, GPx, and GST). Simultaneous administration of NaAsO2 with CUR decreased the levels of thiobarbituric acid-reactive substances (TBARS), whereas augmented the actions of the antioxidant enzymes, and the amount of SH-groups [148].

Sankar *et al*. reported that As exposure through drinking water (25 ppm; 42 days) led to OS and tissue injury in kidneys of rats. However, nanoparticle-encapsulated CUR (NP-CUR) treatment remarkably increased the GSH level (60%), GR function (67%) in kidneys as well as reduced the LPO in the rats exposed to As [135].

4.2.DNA damage

As is categorized as a group 1 human carcinogen as per the epidemiological surveys [15]. It has been shown that As have genotoxic effects such as induction of OS, enhancing the number of micronucleus (MN) and chromosomal aberrations, DNA strand break, cross-links between DNA and protein, reduction of proliferation index, suppression of DNA repair along with production of 8-hydroxy-20-deoxyguanosine (8-OHdG) as an indicator of OS to DNA caused by As [149-151]. The ROS-related DNA damage 8-oxoguanine is removed through 8-oxoguanine DNA glycosylase, which encodes through *OGG1* gene. It has been shown that *OGG1* gene expression is significantly associated with chronic exposure to As [152]. As

prevents the enzymes contributed in repair, so causing to the change of DNA replication and repair mechanisms. Suppression of DNA is because of the inihibitory effect of As (III) on DNA ligase II/I [153]. As (III) can produce NO to damage DNA, which thus induce ADP-ribosylation [153].

CUR has a protective effect against the As-induced DNA lesions through combating ROS production and LPO, promotion the activities of numerous antioxidant enzymes, i.e. Cat, SOD, GPx, GR, GST and GSH [122]. CUR also induces over-expression of the polymerase, an enzyme responsible for DNA repair [153].

In another study, CUR effectively restored the genotoxic effect of As by decreasing the number of structural aberrations and hypoploidy (Figure 4) [154]. CUR also suppressed the 8-OHdG and *OGG1* regulation and activated the DNA repair enzymes in the repair pathways at the protein and gene levels [155]. The protective effects of CUR against As-induced genotoxicity may be due to its antioxidant and free radical scavenger properties [156]. CUR can trap the free radicals and induce O6-methylguanine-DNA methyltransferase (MGMT), a protective genome protein [157, 158], and HO-1 activity which donates H from phenolic OH group and suppresses the iNOS induction resulting in protection of DNA [159]. Biswas *et a.l.* reported that treatment of Swiss albino mice with CUR prevented the NaAsO2-induced DNA lesions through decreasing the comet tail moment of whole blood and MN population in the cultured splenic lymphocytes [160]. Findings of *in vitro* and the field trials among Indian populations exposed to chronic groundwater As demonstrated that NaAsO2 can induce DNA damage and generates ROS which was efficiently ameliorated by CUR [161].

4.3. Neurotoxicity

Metals can cross the blood-brain barrier (BBB) and deposit in the brain resulting in neurobehavioral disorders [162]. Deposition of As in the central nervous system impairs the neuronal activities, reduces the neuronal migration, prevents the neural progenitor cells

proliferation and maturation together with altered dopaminergic, cholinergic, serotonergic and glutamatergic systems functions [162-164]. Children who are chronically exposed to As have difficulties in cognitive development and verbal intelligence [165, 166]. As related-neurotoxicity occurs by the promotion of apoptosis via activating p38 mitogen-activated protein kinase and JNK3 pathways along with activation of caspase-9, an initiator of apoptosis [167]. Degenerative lesions and vascular engorgement was found in brain tissues demonstrate the possible of the As to enforce neurotoxicty. As-induced production of free radicals and following OS is one of the main mechanisms which mediate conversion in these tissues [168]. Although, brain is more sensitive to As due to that has an inefficient oxidative system [169]. Additionally, brain possess a high levels of polyunsaturated fatty acid [170].

CUR can inverse neuroleptic-created tardive dyskinesia in rats [171]. CUR also exhibited significant neuroprotection in focal cerebral ischemia via suppressoing of LPO and regulating antioxidant enzymes [172]. It was also reported to be has potential in decreasing the peroxynitrite generation in cerebral ischemia [173]. A decrease in As amounts in brain tissues, CUR [174] that may have possibly reduced the load of As.

Accumulating evidence suggests that As-induced neurotoxicity is neutralized by CUR through modulating the OS and dopaminergic functions. NaAsO2 (20 mg/kg BW) reduce the levels of dopamine (28, 51 and 35%), norepinephrine (54, 22 and 35%), epinephrine (46, 47 and 29%), serotonin (44, 25 and 54%), 3,4 dihydroxyphenylacetic acid (20, 34 and 37%) and homovanillic acid (31, 41 and 46%) in the corpus striatum, frontal cortex and hippocampus, respectively. CUR can modulates the levels of NO and brain biogenic amines in As-contaminated rats [128].

NaAsO2 (20 mg/kg BW) and CUR (100 mg/kg BW) therapy led to an increased locomotor function and grip force as well as promoted the rota-rod task in As treated rats. A remarkable

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improvement in behavioral, neurochemical and immunohistochemical indices in the rats which concurrent received As and CUR demonstrates the neuroprotective potential of CUR [163]. CUR potentially crosses the BBB and reduce senile plaques and cerebrovascular amyloid angiopathy as well as decreases amyloid accumulation and neuroleptic-created tardive dyskinesia [171, 175]. Jahan-Abad and coworkers provided evidence on the preventive effect of CUR combating the toxic effects of As on the viability, telomerase activity and cell death of neural stem cells [176]. CUR effect on elevating telomerase activity might be mediated via upgrading the stability of telomerase structure and successively enhancing the halflife of the enzyme [177]. Cell damage/death in As-treated neural stem cells happen via caspase-dependent apoptosis and CUR attenuated caspase processing[176]. As can also induce white matter lesions and damage the brain hippocampal CA1 area. Co-treatment with antioxidants (N-acetylcysteine and CUR) reverse these changes and protect cells against inflammation through decreasing the levels of MMP-2, -9 and TNF-α inflammatory factors[178].

It has been shown that As can disturb the maturity of the pre- and post-synaptic signaling proteins related to the dopaminergic axis in the corpus striatum. The concurrent exposure to CUR led to the amelioration of the As-induced changes in the regulation of DAD2 receptors, pPP1α, PKA, pCREB and pDARPP32. Moreover, modulation in the regulation of pGSK3β and BDNF in the corpus striatum via CUR demonstrates the significance of the neuronal survival cascade in As-stimulated dopaminergic dysfunction [179]. In similar in vivo and in vitro experiment, administration of CUR alleviated the NaAsO2-induced variances in the levels of N-methyl-D-aspartate (NMDA) receptors and its subunits along with synaptic proteins (pCaMKIIa, PSD-95 and SynGAP). CUR also compensated for the NaAsO2-induced reduction the levels of pAkt, pGSK3β, pERK1/2, BDNF and pCREB. Interestingly, CUR exerts its neuroprotective effects against NaAsO2 in the hippocampus via

regulating PI3K/Akt/GSK3β pathway [180]. As-induced decreament in brain acetylcholinesterase action were also observed to be mitigated after CUR treatment in rats [46].

NaAsO2 (5 mg/kg BW) remarkably mitigated the function of the brain and plasma AChE and levels of plasma total protein, albumin and HDL-C, while increased the levels of urea, Cr, bilirubin, cholesterol, total lipid, LDL-C, triglyceride and glucose which were reversed by the administration of CUR (15 mg/kg BW) in rats [46].

4.3.1. Cholinergic dysfunctions

As exposure possibly lead to cholinergic dysfunctions linked with the activity of the brain AChE and disturbed learning and memory in experimental models [181, 182]. It has been reported that iAs has major effects on brain primary cultures obtained from transgenic Tg2576 mice, which increased the expression of amyloid precursor protein (APP) and are associated to the early development of Alzheimer's disease (AD)[183]. Chronic As exposing induces the JNK3 and p38 MAPK related with the construction of neurotic plaques (NFs) and neurofibrillary tangles(NFTs) [184] which are associated with the AD [185]. It has been shown that CUR can reverse As-induced brain cholinergic deficits [186]. CUR decreased the vasoactive peptide endothelin1-created cell death of hippocampal neurons through diminishing of cleaved caspase-3, decreament the activity of caspases 3/7 via inhibiting the elevation in c-Jun amounts [187].

Concurrent supplementation of rats with NaAsO2 (20 mg/kg BW) and CUR (100 mg/kg BW) enhanced the learning and memory execution related with the over binding of [3H]quinuclidinyl benzylate ([3H]-QNB) and the activity of AChE in the hippocampus and frontal cortex versus the As group. An increase in the transcription, translation and immunoreactivity of choline acetyltransferase, an index of cholinergic neurons, as well as

binding of cholinergic–muscarinic receptors (MAChR), Nissl-stained hippocampus was also observed in the As+CUR than As group [186].

Similarly, treatment with both As (20 mg/kg BW) and CUR (100 mg/kg BW) protected against the alterations in the mitochondrial membrane integrity, function of mitochondrial complexes and a reduction in the CHRM2 receptor gene in specific brain regions of rats along with regulating the amplification of brain pro- and anti-apoptotic proteins which are induced by As [188].

4.4. Hepatotoxicity

The liver is the most common site for the metabolism and methylation of As [189]. The As methylated metabolites produced in the hepatocytes, methylarsinic acid (MMA) and dimethylarsinic acid (DMA), are primarily excreted through urine as a detoxification and elimination system (Figure 2, 3) [190]. Furthermore, the liver is also considered as one of the main targets of As toxicity. Histopathological changes in the liver tissue, abnormal liver function tests with gastrointestinal manifestations and an increase in serum enzymes are frequent during acute and chronic arsenicosis [191, 192]. It has been shown As intoxication remarkably discharge delta-aminolevulinic acid dehydratase (ALAD) activity in liver tissues of mice [193]. It has been suggested that the leakage of enzymes due to the liver damage is prohibited through the liver cell membrane stabilizing activity of CUR. It has been shown that CUR potentially can enhance the As methylation and excretion through urine [125]. Due to its polyphenolic structure and β-diketone functional group, CUR has powerful antioxidant potencies compared to other flavonoids with only one phenolic hydroxyl group [194].

As2O3 administration causes the production of reactive ROS, As accumulation, and attenuation of various antioxidant enzymes in the liver of adult male Wistar rats. CUR administration (15 mg/kg BW) had hepatoprotective effects from the As induced-worsening of antioxidant levels and OS. CUR also led to a remarkable reduction in the hepatic As

accumulation and serum marker enzymes including aspartate transaminase (AST), alanine transaminase (ALT) and ALP [195]. CUR administration also (0.4 mg/kg BW) significantly reduced the intracellular ROS generation via promoting the activity of GR and ROS scavenging enzymes (GST, GPx, SOD and Cat) in the hepatic tissue of adult male Swiss Albino Mice exposed to As2O3 [127]. Similarly, As-induced elevation of serum ALT and AST, hepatic MDA, as well as the decrements of serum and hepatic GSH concentrations were all also reversed by administration of CUR[125].

In another study, for enhancing the bioavailability of CUR, encapsulated CUR in chitosan nanoparticles (ECNPs) have been shown to have a superior antagonistic effect against As-induced toxicity than free CUR. Co-treatment with CUR or ECNPs with As significantly ameliorated the alterations in the hepatic OS markers. As exposure led to ROS generation and an increase in LPO, which was significantly reduced after CUR administration [196]. Sankar *et al.* studied the efficacy of the NP-CUR from NaAsO2-related hepatic oxidative injuries in rats. Hepatotoxicity of As was manifested by an elevation of the serum ALT and AST activities and led to related histological changes in the liver. As elevated LPO and reduced the activities of SOD, Cat, GPx and GR in the liver. CUR administration resulted in a significant improvement of the As-induced effects and to a greater extent by CUR-NP. These findings imply that when CUR given in a nano-encapsulated form has better efficacy on As related toxicities compared to free CUR[197].

CUR reduced the toxic biochemical responses of As through lowering the acid phosphatase activity (43-70%), alkaline phosphatase (ALP) activity (40-63%) and GSH activity (27-41%) as these enzymes are markers for As-induced toxicity in Swiss Albino Mice [198].

Recently, CUR has been suggested to have chemopreventive effects via the induction of Nrf2. NF-E2 related factors (Nrfs) are a group of transcription factors which modulate the

cellular stress response to OS via the *cis*-acting antioxidant response element (ARE). Usually, ARE-dependent genes are responsible for mediating the redox homeostasis of cells and inhibit oxidative injury. Under OS, Nrf2 and/or Nrf1 bind and activates the expression of detoxifying genes [199]; NAD(P)H:quinone oxidoreductase 1 (*NQO1*), *GSTs*, Gama-glutamylcysteine synthetase heavy subunit (γ-*GCS$_h$*) and light subunit, HO-1, glutamate-cysteine ligase catalytic (*GCLC*) and regulatory (*GCLM*) subunits, and peroxiredoxin 1 [200].

It has been shown that the effects of CUR against the As-induced hepatic damages are potentially mediated through activation of the Nrf2 pathway. Post CUR administration, both the hepatic Nrf2 protein and two primary Nrf2 downstream genes including NADP(H) quinine oxidoreductase 1 (NQO1) and HO-1, were over-expressed. Considering the potent antioxidative and detoxifying capacities of HO-1 and NQO1, their up-regulation may, in turn, reduce the As-induced OS [125].

NaAsO2 reduces the cell viability and induction of apoptosis via an increase in the number of cells with ROS generation, loss of mitochondrial transmembrane integrity, changing the function of cytochrome c oxidase and citrate synthase, increasing the cell population with sub-G1 DNA content and DNA fragmentation in murine splenocytes. Co-treatment of CUR with NaAsO2 resulted in a significant improvement in cell viability and attenuation of the As induced apoptosis-associated molecular alterations [201].

Tetrahydrocurcumin (THC), one of the main metabolites of CUR, in certain biosystems, was shown to have a higher antioxidant function compared to CUR. Muthumani and co-workers administrated As (5 mg/kg BW) with THC (80 mg/kg BW) for 28 days in a rat model. As treatment-induced hepatotoxicity as evidenced by elevated activities of serum AST, ALT, ALP and bilirubin as well as worsened the lipid peroxidative parameters, TBARS. As also worsened serum lipid levels, reduced the antioxidant activities of SOD, Cat, GPx and GSH

along with mitochondrial enlargement, suppression of cytochrome c oxidase, Ca2+ATPase and a diminution of mitochondrial calcium accumulation. Pre-treatment with THC significantly mitigated the toxic effects of As in the rat liver as well as scavenged the As-related free radicals [202]. Supporting those findings, long time exposure to NaAso2 resulted in increased in the levels of AST, ALT, ALP and lactate dehydrogenase (LDH), decreased activities of membrane-bound ATPases, enzymatic antioxidants including SOD, Cat, GPx, GST, GR and G6PD along with non-enzymatic antioxidants like reduced GSH, total SH-groups, vitamins C and E. Administration of THC showed a significant inhibition of As-induced hepatotoxicity [203]. Accumulating evidence shows that As can trigger ROS such as singlet oxygen, superoxide anion, hydrogen peroxide, hydroxyl radical, and peroxyl radicals [204].

The *HER-2* gene is a putative oncoprotein which is up-regulated in many types of human tumors. Interestingly, it has been reported that As could induce the over-expression of HER-2 and other oncoproteins; and CUR, as a chemopreventive and therapeutic agent has the inhibitory activity on HER-2-overexpressed hepatocellular carcinoma. Based on these results, it could be proposed that CUR has the potential to be developed as a complementary anti-cancer agent to treat hepatocellular carcinoma. Besides, CUR can protect hepatic cells from As-toxicity damage [205].

4.5. Dermal disorders

iAs exposure increases the susceptibility to different dermal pathologies such as hyperkeratosis and skin tumor. Immunohistochemical evidence indicated that the appearance of 8-oxo-deoxyguanosine(8-oxodG) in keratosis and healthy tissues of As induced skin malignancies [206].

CUR can lead to Nrf2 activation, Nrf2 protein nuclear accumulation and over-expression of ARE-target genes in the HaCaT keratinocytes. CUR at high doses also enhanced the

translation of the Nrf2. Administration of low doses of CUR increased the viability of HaCaT cells from the iAs-intoxication and also mitigated the Asi-induced transcription of cleaved caspase-3 and PARP. On the other hand, the expression of Nrf2 is under the control of Kelch-like ECH-associated protein 1 (KEAP1) via ubiquitination and proteasomal degradation. Interestingly, the transcription of *KEAP1* was also increased by CUR, indicating possible feedback from Nrf2 to KEAP1. Notably, KEAP1 knockdown remarkably weakened the cytoprotection of CUR [126]. It may be since NRF2 was already fully activated owning to the absence of *KEAP1*, and thus maximum protection against iAs was already in place, as pointed via the significant right-ward shift of the response curve observed in the untreated cells. Thus, CUR treatment did not further activate NRF2 and hence, no further protection [126].

4.6. Other arsenic induced-pathologic conditions

Chorionic exposure to As disturbs the action of several cellular immune components including leukocytes and macrophages thereby affects cellular immune responses resulting in immunosuppression [84, 207]. Different mechanisms for the effect of As on the immunity have been proposed. Apoptosis has been found as an major mechanism of As-induced immunosuppression in human [208]. A study on peripheral blood mononuclear cells of cases which drinking water with low/moderate As levels revealed modulations in expression of T cell receptor (TCR), T cell cycle regulation, and apoptosis [209]. Anemia and leucopenia are among the most common effects of toxicity from acute or chronic As exposure. It has been reported that the *Haridra* (turmeric root) attenuates the experimentally As-induced reduction of hemoglobin level, red blood cell count and white blood cell count in calves [210]. CUR can reverse the haematological alterations through restoration of enzymes related to haem biosynthesis, elevating feed intake and promoting the excretion of As via urine and faeces [210].

It has been shown that CUR can protect against immune dysfunction due to the As exposure. Considering spleen weight as an indicator of splenic dysfunction, As reduced the splenic lymphocyte proliferation, delayed-type hypersensitivity response and secondary antibody response to a specific antigen which was reversed by CUR [129]. CUR has a protective effect against As-related apoptosis in the rat thymocytes through its free radical scavenging potential [211].

An excess of ROS can be implicated in several reproductive disorders such as polycystic ovary syndrome. Wang and colleagues established an animal model of the ovarian OS by injection of NaAsO2 to examine the inhibitory role of CUR against OS damage. CUR therapy significantly elevates SOD, whereas reducing the ROS and MDA in the ovary. Immunohistochemistry of the ovarian tissues demonstrated that the higher value of atretic follicles and the suppression of granular cells proliferation under OS would be abrogated via CUR treatment. In addition, the OS-induced p66Shc over-expression would be mitigated after CUR therapy. Altogether, these findings demonstrate that CUR can scavenge free radicals and provide the antioxidant circumstances in ovarian tissue upon modulating the expression of p66Shc [212]. NaAsO2 inhibited the actions of the uterine enzymatic antioxidants including SOD, Cat, and peroxidase. The circulating levels of vitamin B12 and folic acid were reduced followed by an elevated serum LDH, homocysteine level and hepatic metallothionein-1 in As-treated rats. Uterine tissue necrosis with the disturbance of ovarian steroidogenesis was manifested in As-administrated rats with an over-expression of uterine NF-κB and IL-6 as well as an increase in serum TNF-α levels. Oral supplementation of CUR (20 mg/kg BW/day) in As-treated rats reversed these abnormalities by detoxifying As. The underlying mechanism of As detoxification might be implicated in the stabilization of the S-adenosine methionine (SAM) pool by maintaining the circulating levels of vitamin B12, folate, and homocysteine [213].

NaAsO2 directly affects the antioxidant enzymes (SOD, Cat, GPx, and GST) and regulation of antioxidant genes (SOD1, Cat, and GPx1) in embryonic fibroblast cells and caused oxidative damage through increasing the cellular levels of hydrogen peroxide, hydroxyl radical and LPO. It has been found that CUR potentially improved antioxidant system genes and enzymes to defend the fibroblast cell toxicity created by NaAsO2 [214].

5. Conclusion and future prospective

The gold standard treatment of As poisoning is by 'chelation therapy' though chelating drugs are limited by different side effects and reduced selectivity and specificity. Accumulating evidence supports that CUR administration is effective in combating As-mediated toxicity in Wistar rats and Swiss albino rats. However, most of the studies discussed does not demonstrate the capability of CUR in reducing the body burden of As nor any efficacy in humans with chronic arsenic poisoning. In addition, no placebo-controlled trials with this natural agent have been performed nor the efficacy of their long-term use has been assessed. The benefits of CUR at the cellular level should be validated in human subjects with chronic As toxicity. The beneficial effects of CUR should be assessed in arsenecosis through endpoint evaluations such as changes in the As concentrations in blood, nail and faeces, changes in urine As metabolites, size of keratotic lesion or scoring of palmar arsenical keratosis. Suggested markers for evaluation of the effect of CUR in As-associated kidney damage among arsenicosis patients are expression levels of kidney injury molecule (KIM) and changes in the activities of enzymes-related with carbohydrate metabolism such as hexokinase, LDH, G6PD and malate dehydrogenase. Additionally, It was observed that As disrupts the normal levels of metabolic enzymes in the body which are robust biomarkers of toxicity, and could be used as screening markers for As-induced tissue damage in human beings.

It has been suggested that co-treatment with CUR and arsenate chelator may offer advantageous effects in a synergistic manner on the adverse alterations in the oxidative stress induced by As. The development of novel pharmaceutical delivery approaches of CUR may have higher efficacy compared to its conventional administration. CUR intervention may be a promising approach for the prevention of As-induced damage and should be tested in clinical studies. Therefore, CUR, a spice once associated with the kitchen shelf, will be promoted to the clinic and may accept to be "Curecumin"[215].

Figures legends:

Figure 1. **Structure of arsenic compounds**.

Figure 2. Toxicity of Arsenic in different organs. Abbreviations: micronucleus (MN), 8-hydroxy-20deoxyguanosine (8-OHdG), p38 mitogen-activated protein kinase(MAPK), reactive oxygen species (ROS), oxidative stress (OS)

Figure 3. **Molecular mechanism of arsenic toxicity in different organs**. Abbreviations: heme oxygenase 1 (HO-1), activation of activator protein-1 (AP-1), reactive oxygen species (ROS).

Figure 4. Ameliorative effects of curcumin against arsenic-induced toxicity. Arsenic exposure leads to ROS generation which results in oxidative stress and deactivation of the cellular signaling pathway, and ultimately DNA damage, apoptosis and organ dysfunction. Curcumin reverses the arsenic-induced ROS generation and activates the antioxidant enzyme. Abbreviations: NAD(P)H:quinone oxidoreductase 1 (NQO1), GSTs, Gama-glutamylcysteine synthetase heavy subunit (γ-GCSh) and light subunit, heme oxygenase 1 (HO-1), nuclear factor (erythroid-2 related) factor 2(Nrf2), superoxide dismutase (SOD), catalase (Cat), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), and glucose-6-phosphate dehydrogenase (G6PD), reactive oxygen species (ROS), c-Jun amino-terminal kinase (JNK).

Table 1. Effect of curcumin on arsenic induced-toxicity in different organs.			
Arm	**Experimental model**	**Consequence**	**Ref.**
Neurotoxicity			
NaAsO2(20 mg/kg BW; 28 days) + CUR (100 mg/kg BW; 28 days)	-female Wistar rats	-increase in the activity of GPx, SOD, GSH and decrease of MDA in frontal cortex, corpus striatum and hippocampus -increase of binding of striatal dopamine receptors and tyrosine hydroxylase expression	[163]
NaAsO2 (20 mg/kg BW; 28 days) + CUR(100 mg/kg BW; 28 days)	-female Wistar rats	-elevated levels of catecholamines and their metabolites as well as serotonin -reduced levels of NO in brain regions	[128]
NaAsO2 (2 mg/kg) and ECNPs (1.5 or 15 mg/kg)	-male Wistar rats	-ameliorated alterations in hepatic OS markers and restoration of blood GSH	[196]
NaAsO2 (20 mg/kg BW) + CUR (100 mg/kg BW)	-female Wistar rats	-increased learning and memory execution related to over binding of [3H]-QNB and activity of AChE in hippocampus and frontal cortex -elevation of choline acetyltransferase and binding of cholinergic–MAChR, Nissl-stained hippocampus	[186]
As (20 mg/kg BW) +CUR (100 mg/kg BW) 28 days	-male rats of Wistar rat	-defend against alterations in the mitochondrial membrane integrity, function of mitochondrial complexes and reduction in the CHRM2 receptor gene in specific brain regions together with regulating the amplification of brain pro- and anti-apoptotic proteins	[188]
NaAsO2 (20 mg/kg BW) +CUR (100 mg/kg BW) 28 days	-male rats of Wistar rat	-protection of arsenic-caused changes in the regulation of DAD2 receptors, pPP1α, PKA, pCREB, and pDARPP32 -modulation in the regulation of pGSK3β and BDNF in corpus striatum	[179]
Genotoxic effects			
NaAsO2 (1.4 µM)+ CUR (1.7 µM),	-peripheral blood lymphocytes	-decreasing the number of structural aberrations, and hypoploidy	[154]
CUR (500 mg twice daily for 3 month)	-peripheral blood lymphocytes	-combating ROS production and lipid peroxidation -promotion the activities of numerous antioxidant enzymes i.e. Cat, SOD, GPx, GR, GST and GSH	[122]
CUR (500 mg twice daily 3 months)	-peripheral blood lymphocytes	- suppression of the 8-OHdG value and OGG1 regulation -activation of DNA repair enzymes participated in the repair pathways at protein and genetic levels	[155]
NaAsO2 (25 ppm)+CUR-NP (100 mg/kg BW)	-rat	-attenuated chromosomal aberrations, micronuclei formation, DNA damage	[156]
NaAsO2 (500 µg/l)+ CUR(5, 10 and 15 mg/kg BW/daily)	-Normal male Swiss albino	-prevented NaAsO2-induced DNA lesions through decreasing comet tail moment of whole blood and MN population in cultured spleenic lymphocytes	[160]
As2O3 (0.1, 0.2, 0.5, 1, 2.5, and 5 mg/l)+ CUR(1, 2, 5, 10, 20, and 50 µM)	-neural precursor cells	-promoted telomerase activity of neural stem/progenitor cells -decreased arsenic-created apoptosis (by inactivation of caspases) and-ROS generation	[176]
NaAsO2 (100, 250, 500 and 1000 µM) + CUR(10, 25 and 50 µM)	-peripheral blood lymphocytes	-reduction in comet tail moment -quenching the OS -regression in DNA damage	[161]
Hepatoprotective			

As2O3 (4 mg/kg BW; 45 days+CUR(15 mg/kg BW)	-male Wistar rats	-decrement in hepatic arsenic accumulation and serum marker enzymes including AST, ALT and ALP	[195]
As+ CUR	-female Kunming mice	-enhance arsenic methylation and urinary excretion -overexpression of hepatic Nrf2 protein and its downstream genes (NQO1 and HO-1)	[125]
As2O3(0.4 mg/kg BW) +CUR(0.4 mg/kg BW)	-adult male Swiss Albino Mic	- decreased intracellular ROS generation via promoting the activity of GSH generating enzyme GR and ROS scavenging enzymes (GST, GPx, SOD and Cat) in hepatic tissue	[127]
CUR-NP (100 mg/kg BW)	-male Wistar rats	-decreased LPO -increased the activities of SOD, Cat, GPx and GR in liver	[197]
NaAsO2(5 μM) + CUR (5 and 10 μg/ml)	-albino Swiss mice	-mitigated the effects of arsenic on cell viability, ROS generation, loss in MTP, and hypodiploid DNA content	[201]
As(5 mg/kg BW)+ THC (80 mg/kg BW) 28 days	-male albino Wistar rats	-decreased the levels of AST, ALT, ALP and LDH -increased the activities of membrane bound ATPases, enzymatic antioxidants including SOD, Cat, GPx, GST, GR and G6PD along with non-enzymatic antioxidants like reduced GSH, total SH-groups, vitamins C and E.	[203]
As2O3 (5 mg/kg BW) +THC (80 mg/kg BW)	-adult male albino Wistar rats	-decreased values of AST, ALT, ALP and bilirubin	[202]
Oxidative damage			
As2O3 (5 mg/kg BW) +CUR (15 mg/kg BW)	- male Sprague–Dawley rats	- reduced the induction in the levels of TBARS -induced the reduction in the activities of antioxidant enzymes and the SH-groups levels	[148]
As2O3 (25 ppm)+CUR-NP(100 mg/kg)	-male Wistar rats	-elevated the GSH level in renal and brain -enhanced GR function in renal and brain tissues -reduced the LPO	[135]
- As2O3 (8 mg/kg)+CUR(0, 100, 150, or 200 mg/kg)	-female Kunming mouse	- elevate SOD -decrease ROS and MDA in the ovary -abrogating both higher value of atretic follicles and suppression of granular cells proliferation under OS -mitigating the OS-induced p66Shc over-expression	[212]
Nephrotoxicity			
NaAsO2 (5 mg/kg)+CUR(100 mg/kg)	- adult male NMRI mice	-increase the diameter of glomerulus and proximal tubule, glomerular area, total antioxidant capacity -decrease serum concentration of MDA	[134]
As2O3+ *Curcuma aromatic(*50 mg/kg BW)	- male Wistar albino rats	-increament of the serum level of uric acid, blood urea nitrogen, and creatinine because of renal dysfunction -normalization of the serum levels of uric acid, blood urea nitrogen and creatinine	[137]
As2O3(5 mg/kg BW)+ CUR (15 mg/kg BW)	-male Wistar rats	-mitigates the elevation of liver function enzymes, lipid and protein profile, and indices of renal injury	[46]
Dermal disease			

iAs (30 μM) + CUR(20 μM)	-human keratinocytes (HaCaT cells)	-elevated the viability of HaCaT cells -mitigated Asi-induced transcription of cleaved caspase-3 and PARP	[126]
Other pathologies			
As (20 ppm)+ CUR(100 mg/kg BW)	-adult male Wistar rats	- inhibit arsenic-related apoptosis in rat thymocytes by its free radical scavenging	[211]
CUR-NP (100 mg/kg BW) + As2O3 (25 ppm)	-male Wistar rats	-decreased the spleen weight -increased the splenic lymphocyte proliferation - induced type hypersensitivity response and secondary antibody response to specific antigen	[129]
Abbreviations: alanine transaminase (ALT), alkaline phosphatase (ALP), arsenic (As), aspartate transaminase (AST), body weight (BW), catalase (Cat), curcumin (CUR), encapsulated curcumin nanoparticles (ECNPs), glucose-6-phosphate dehydrogenase (G6PD), glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), heme oxygenase-1 (HO-1), inorganic arsenic (iAs), lactate dehydrogenase (LDH),lipid peroxidation (LPO), Malondialdehyde (MDA), Micronucleus (MN), mitochondrial transmembrane potential (MTP), muscarinic receptors (MAChR), NADP(H) quinine oxidoreductase 1 (NQO1), nanoparticles encapsulated curcumin (CUR-NP), oxidative stress (OS), sulfhydryl groups (SH-groups), superoxide dismutase (SOD), tetrahydrocurcumin (THC), thiobarbituric acid-reactive substances (TBARS), [3H]quinuclidinyl benzylate ([3H]-QNB), 8-hydroxy-2'-deoxyguanosine (8-OHdG).			

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