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An Overview on Arsenic Trioxide-Induced Cardiotoxicity

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Abstract
Arsenic trioxide (ATO) is among the first-line chemotherapeutic drugs used in oncological practice. It has shown substantial efficacy in treating patients with relapsed or refractory acute promyelocytic leukaemia. The clinical use of ATO is hampered due to cardiotoxicity and hence many patients are precluded from receiving this highly effective treatment. An alternative to this would be to use any drug that can ameliorate the cardiotoxic effects and allow exploiting the full therapeutic potential of ATO, with considerable impact on cancer therapy. Generation of reactive oxygen species is involved in a wide range of human diseases, including cancer, cardiovascular, pulmonary and neurological disorders. Hence, agents with the ability to protect against these reactive species may be therapeutically useful. The present review focuses on the beneficial as well as harmful effects of arsenic and ATO, the mechanisms underlying ATO toxicity and the possible ways that can be adopted to circumvent ATO-induced toxicity.

Keywords Arsenic trioxide · Cardiotoxicity · Reactive oxygen species · Chemotherapy · Phytochemicals

Introduction

Arsenic trioxide (ATO) has been recommended as the front-line agent for treatment of relapsed or refractory acute promyelocytic leukaemia (APL), due to its substantial anti-cancer effect [1, 2]. Numerous clinical reports have indicated that chronic exposure to a therapeutic dose of ATO could cause cardiotoxicity and evoke severe side effects such as ventricular arrhythmia resulting in sudden cardiac death in certain cases [3–5]. This has become increasingly relevant concern due to the extended survival time of APL patients and increased likelihood of long-term exposure to ATO resulting in cardiovascular disease. Thus, a prophylactic treatment is required for managing the consequent cardiotoxicity in clinical applications of ATO. A better understanding of the potential mechanism by which ATO induces cardiotoxicity would be of great significance for developing specific and effective preventive measures. The main reasons that make cardiomyocytes more prone to oxidative stress is the low antioxidant defences [6] and enrichment of mitochondria [7, 8] compared to other cells. This review focuses on the useful and adverse effects of arsenic and ATO, the mechanisms underlying ATO-induced cardiotoxicity in chemotherapy and the possible ways to overcome/circumvent it.

Human Exposure to Arsenic and Its Health Effects

Arsenic is a naturally occurring metalloid that exists in practically all environmental media, such as air, soil and water. It exists in inorganic and organic forms and in different oxidation states (−3, 0, +3, +5). In the case of environmental exposure, toxicologists are primarily concerned with arsenic in the trivalent [As(III)] and pentavalent [As(V)] oxidation state [9] with the trivalent exhibiting more toxic effects than the pentavalent compound [10]. There are various sources of ingested arsenic, such as food (mainly in fish and seafood, algae and cereals), air (coal-fired power generation and smelting) and water [11]. Arsenical species tend to remain in solution even at high concentrations (tens of µg/L) at

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near-neutral pH [12]. As a result, arsenic exposure through drinking water and inhalation of particulate matter is considered the cause of the largest mass poisoning worldwide [13, 14].

Exposures of human populations to arsenic-contaminated drinking water can cause anaemia, neuropathies, hyper-pigmentation, and irritations of the skin, mucous membranes and gastrointestinal tract. Chronic exposures can lead to hyperkeratosis and loss of skin pigmentation [15, 16]. Given its daily and widespread consumption, occurrence of arsenic in drinking water has been recognized as a major public health concern in several regions of the world [17–19]. Drinking of groundwater contaminated with naturally occurring inorganic arsenic in Bangladesh represents one of the largest mass poisoning of a population in history [20]. Worldwide, an estimated 160 million people live in regions with naturally elevated levels of arsenic in drinking water, due to the presence of arsenic-rich geological formations [19]. The World Health Organization (WHO), as well as the United States Environmental Protection Agency (EPA), has reduced the allowable arsenic concentration in drinking water from 50 to 10 ppb in the past two decades [21, 22].

Arsenic compounds are used for agricultural applications, such as insecticides, fertilizers and fungicides [23]. ATO is a form of inorganic arsenite found in nature and a common by-product of copper smelting. In addition, ATO is commonly used as a raw material for manufacturing other arsenic compounds used as wood preservatives, insecticides and herbicides [24].

Long-term exposure to low doses of inorganic arsenic compounds has been associated with the increased incidence of several cancer types including skin, lung, liver, bladder, kidney and prostate cancers [25]. The transcription of the reverse transcriptase subunit of the human telomerase gene (hTERT) is inhibited by arsenic. Telomerase is an enzyme that maintains the length of chromosomal ends or telomeres, which otherwise would progressively shorten after each cell division [26]. Interestingly, cells lacking telomerase are prone to genomic instability and carcinogenesis [27]. Paradoxically, telomerase activity is frequently found in advanced cancer cells and is important for continuous cancer cell proliferation [28]. The metabolic toxicity of ATO may also be attributed to the exquisite sensitivity of accessible thiol groups in key enzymes or to enzymes such as pyruvate dehydrogenase, which uses the dithiol lipoic acid as a cofactor [29].

Ethnic Medicinal Use of Arsenic

While arsenic compounds are regarded as potent toxin and carcinogen, they have also been medically used for over 2000 years in diverse treatments (e.g. leukaemia, leishmaniosis, trypanosomiasis) [30–32]. Arsenic was used as a "healing agent" by Greek physicians such as Hippocrates. Later on, Fowler's solution, a 1% potassium arsenite ($KAsO_2$) preparation, was widely used during the nineteenth century. The indications were leukaemia, skin conditions (psoriasis, dermatitis herpetiformis and eczema), stomatitis and gingivitis in infants and Vincent's anginas. Long-term use of Fowler's solution caused haemangiosarcoma, angiosarcoma of the liver and nasopharyngeal carcinoma. Arsenic was the primary treatment for syphilis until World War II (arsphenamine, neoarsphenamine: 30%) and some protozoan infections [33, 34].

Arsenic also has a rich history as a cancer chemotherapeutic. As reported by Antman [35], pharmacology texts from the 1880s described the use of arsenical pastes for the treatment of skin and breast cancer. In 1878, it was found that Fowler's solution could be effective in lowering the white blood cell count in leukaemia patients [35]. Also in traditional Chinese medicine, ATO was often used to treat tooth marrow disease (devitalizing agent), malaria, psoriasis, syphilis and rheumatosis [34, 36].

Arsenic as a Chemotherapeutic Agent

ATO is among the first-line chemotherapeutic drugs used in oncological practice [37, 38]. It has shown substantial efficacy in treating patients with relapsed or refractory acute promyelocytic leukaemia (APL) [39, 40]. It is also found to be effective in certain other hematologic malignancies, such as myelodysplastic syndrome, multiple myeloma and non-Hodgkin's lymphoma and some solid tumours, such as esophageal, gastric, lung, colon, hepatic, breast, gallbladder carcinoma and neuroblastoma [38, 41] in a dose-dependent way. ATO is available in injectable form and is widely known by the trade name Arsenox™ or Trisenox™.

Mechanism of Action of ATO on APL Cell

APL is characterized by a chromosomal translocation involving the retinoic acid receptor-alpha (RARα) gene on chromosome 17. In majority of the cases of APL, RARα gene on chromosome 17 is involved in a reciprocal translocation with the promyelocytic leukaemia (PML) gene on chromosome 15. The RAR receptor depends on retinoic acid for regulation of transcription. The fusion of PML and RARα genes results in the expression of a hybrid protein (PML-RARα oncoprotein) with altered functions [42, 43]. This fusion protein binds with enhanced affinity to sites on the cell's DNA, blocking transcription and differentiation of granulocytes arresting maturation at the promyelocytic stage of myeloid development causing accumulation of

PML cells. It does so by enhancing interaction of nuclear co-repressor molecule and histone deacetylase. Phosphatidyl inositol 3 kinase (PI3K)/Akt signalling is frequently activated in blast cells in Acute myeloid leukaemia patients, which contributes strongly to the proliferation, survival and drug resistance of these cells. The endogenous PML protein in normal cells has shown to be localized to a novel macromolecular structure in the nucleus, the nuclear body. Expression of the PML-RARα fusion protein in leukemic cells disrupts the nuclear bodies, and the PML protein is dispersed into smaller fragments of these structures [44–46].

Down-regulation of the PML-RARα oncoprotein by ATO overcomes the maturation blockade. ATO induces apoptosis and partial differentiation of APL cells [47]. ATO triggers a cellular protein called SUMO to 'tag' the fusion protein, earmarking it for destruction [48]. Arsenic binds to zinc finger region of the PML moiety of PML-RARα which is rich in cysteine residues and initiate the degradation of PML-RARα in a proteasome-dependent way leading to activation of repressed genes (Fig. 1). Studies report that the binding of arsenic to this region causes several protein molecules to join together as an oligomer through cross-linking and conformational changes. ATO facilitates the clearance of leukaemia-initiating cells (LIC) of APL. The new research has shown that when ATO is added to cell extracts containing the fusion protein, the protein becomes insoluble and the arsenic is associated with the insoluble fraction [49].

In the 1970s, ATO was introduced into the treatment of APL and showed immense success in China. The clinical complete remission rate with ATO treatment (10 mg/dl, intravenous infusion for 28–60 days) was in the range from 65.6 to 84% [50, 51]. ATO is widely used to induce remission in patients with APL based on its mechanism of induction of apoptosis specifically in tumour cells [52–54]. Chen et al. determined that, at low concentrations (0.1–0.5 μmol/L), ATO promotes differentiation of APL cells and, at higher concentrations (1–2 μmol/L), triggers apoptosis and down-regulates Bcl-2 expression [55].

Pharmacokinetics and Distribution of ATO

In most preclinical and clinical studies, the ATO dosage has been 10 or 0.15 mg/kg/day until achieving complete remission or maximum for 60 days [1, 56, 57]. Pharmacokinetic parameters of ATO in blood are clinically significant and have a direct relation to its dosage. At low dose (0.08 mg/kg), ATO had the same effect as the conventional dosage with decrease in the occurrence of some toxic events and the mechanism seemed to primarily induce differentiation of APL cells [58]. The pharmacokinetics and metabolism of ATO has been widely studied [58–60].

The principal route for arsenic elimination is renal in animals and human and appears to be very similar [61]. Though significant amounts of arsenic are detected in bile, very little is excreted in faeces, indicating its extensive absorption. 24-h arsenic content in urine accounted for 1–8% of the daily administered dose [62, 63]. Nearly 32–65% of the total arsenic injected is excreted into the urine. Speciation analysis of the urine samples in patients intravenously injected with ATO revealed the presence of monomethylarsonous acid [MMA(III)], dimethylarsinous acid [DMA(III)], monomethylarsonic acid [MMA(V)] and dimethylarsinic acid [DMA(V)] [59]. The proportion of inorganic arsenic to methylated metabolites found in urine decreased as time post dose increases. Approximately 50% of arsenic found in urine is dimethylarsenic acid and approximately equal amounts of methylarsonic acid and inorganic arsenic. The sum of inorganic and methylated arsenic species in urine is an established biomarker of recent and ongoing arsenic exposure studies [61].

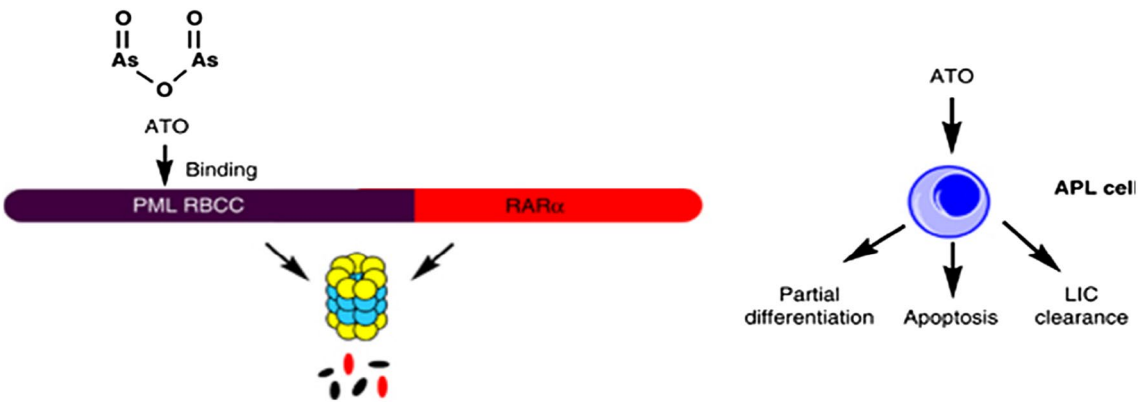

Fig. 1 Mechanism of ATO on APL cells [49]

The pharmacokinetic parameters such as plasma maximal concentration, peak time, plasma distribution half-time, elimination half-time, apparent distribution volume and system clearance in intravenously ATO administered patients vary depending on the type and severity of carcinoma [57, 63, 64]. Arsenic accumulation in hair and nail increased continuously which were declined gradually after drug withdrawal [63].

Proposed Mechanism of ATO on Other Cancer Cells

Although several hypotheses have been proposed, the exact role that ATO plays in the sequence of reactions leading to the death of the cancer cells has not yet been clearly defined. Observations of the clinical utility of ATO in APL have prompted investigations into the mechanisms of action by which arsenic produces clinical benefit. Considerable preclinical evidence supports the potential of ATO against a number of different malignancies.

The proposed major mechanisms by which ATO induces apoptosis in cancer cells include generation of reactive oxidative species (ROS), chromosomal damage, perturbation of DNA methylation patterns, inhibition of DNA repair, modulation of signal transduction pathways and gene expression, interactions with growth factors or cell proliferation [65, 66], inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), caspase activation [67] and down-regulation of hTERT transcription [27]. Signalling pathways include mitogen-activated protein kinases (MAPK) [68], RAS signalling activation [69], c-Myc overexpression [70] and acquisition of androgen independence [71]. It could also determine promotion/progression of gene amplification, suppression of p53, as well as global DNA hypomethylation or malignant transformation [72, 73]. Malignant transformation of human urothelial cells by arsenic is associated with epigenetic changes in histone acetylation and DNA methylation in gene promoter regions [74]. ATO has also been shown to suppress the action of oestrogen through regulation of oestrogen receptor-α expression in breast cancer cell lines [75, 76]. ATO could also cause apoptosis in proliferating layers of human umbilical vein endothelial cells and prevent capillary tubule and branch formation under in vivo and in vitro assay conditions [77], raising the possibility of inhibiting metastasis. However, significant induction of apoptosis in cell systems other than APL sometimes require high concentration ATO (5–10 μM), a dose difficult to be achieved in vivo. Arsenic compounds have the ability to replace physiological metals (e.g. zinc, selenium) from their binding sites in molecules, and therefore, interferes with many physiological processes [78].

Cardiotoxicity Due to Cancer Therapy

Unfortunately, the clinical use of ATO is hampered by side effects in healthy tissue, most notably in the form of cardiotoxicity and subsequent decline of cardiac function [67]. Cardiotoxicity, including QT prolongation, torsades de pointes (TdP) and sudden cardiac death, has been reported with ATO treatment [79, 80]. Due to these limitations, some patients are precluded from receiving this highly effective treatment. Long-term biological safety is another issue that needs clarification in the future.

New anti-cancer therapies have led to long life expectancy for many patients but treatment-related co-morbidities have become an issue for cancer survivors. Cancer chemotherapy aims to induce rapid apoptosis or necrosis in proliferating cancer cells, often in union with growth deprivation, suppression of angiogenesis, or both. When these mechanisms are enacted in the heart, the result can be a terminally differentiated organ of limited proliferative potential, cell death and organ dysfunction.

In a U.S. National Health and Nutrition Examination survey of 1,807 cancer survivors followed for 7 years, 33% died of heart diseases and 51% of cancer [81]. Certain statistical studies report that in any patient, heart disease and cancer are likely to overlap [82]. During cardiotoxicity, mild electrocardiograph (ECG) changes to serious arrhythmias, myocarditis, pericarditis and myocardial infarction may occur that may ultimately lead to heart failure. Thus, the heart muscle cannot pump with enough force to supply the body with blood containing essential O_2 and nutrients.

Cardiotoxicity due to cancer drugs are of two types: (1) acute or subacute cardiotoxicity—alteration of ventricular repolarization phase, duration of QT, arrhythmias, ischemia, acute heart failure, myocarditis-pericarditis-like syndrome; (2) chronic (early/late) cardiotoxicity—asymptomatic left ventricular dysfunction, systolic and/or diastolic dysfunction, severe form of dilated cardiomyopathy, cardiac death [83]. The factors influencing cardiotoxicity due to drug are type of drug, dose administered during each cycle, electrolyte imbalance, combination of other cardiotoxic drugs, associated radiotherapy, patient's age, presence of cardiovascular risk factors, previous cardiovascular disease [84]. A lethal dose of ATO can lead to multiorgan systems failure, coma and death. The acute minimal lethal dose varies from animal to animal. In adult humans, the acute minimal lethal dose is 100–300 mg [34]. As per the Risk Assessment Information System database, the acute lethal dose of inorganic arsenic to humans is about 0.6 mg/kg/day [34]. In humans, environmentally relevant doses (100-several hundred ppb) of arsenic may evoke subacute toxicity resulting in carcinogenesis, heart disease, neuronal damage or other disease conditions.

QT Prolongation

The QT interval on the surface ECG is measured from the beginning of the QRS complex to the end of the T wave (Fig. 2). QT interval is the electrocardiographic demonstration of ventricular depolarization and repolarization. The electrical activity of the heart is mediated through channels and complex protein within the myocardial cell membrane that regulate the flow of ions in and out of cardiac cells. The rapid inflow of positively charged sodium (Na^+) and calcium (Ca^{2+}) ions results in normal myocardial depolarization. When this inflow is exceeded by outflow of potassium (K^+) ions, myocardial repolarization occurs. Malfunction of ion channels, which can result from drugs, electrolyte abnormalities or other factors, leads to an intracellular overload of positively charged ions by way of an inadequate outflow of K^+ ions or excess inflow of Na^+ ions. This intracellular excess of positively charged ions extends ventricular repolarization and results in QT interval prolongation [85]. Normal QT interval range: 350–420 ms; QT interval prolongation: > 460 ms in women and > 440 ms in men; High risk patients: > 500 ms.

ATO-induced QT prolongation is capable of causing polymorphic ventricular tachycardia, i.e. TdP which may trigger ventricular fibrillation and sudden death in the worst case [79, 80, 86]. It has been demonstrated that ATO prolongs the action potential duration of guinea pig ventricular myocytes via two independent molecular mechanisms. ATO increases cardiac Ca^{2+} currents, which regulate the plateau phase of the cardiac action potential and also reduces surface expression of the cardiac K^+ current human ether-a-go-go-related gene (hERG), which is crucial to later stages of cardiac repolarization [87]. The hERG encodes the alpha-subunit of the human K^+ channels. The blockers of hERG channel are well known to prolong cardiac APD and lead to long QT syndrome [88]. The mechanism of sudden death with hERG blockage has been diagrammatically illustrated in Fig. 3.

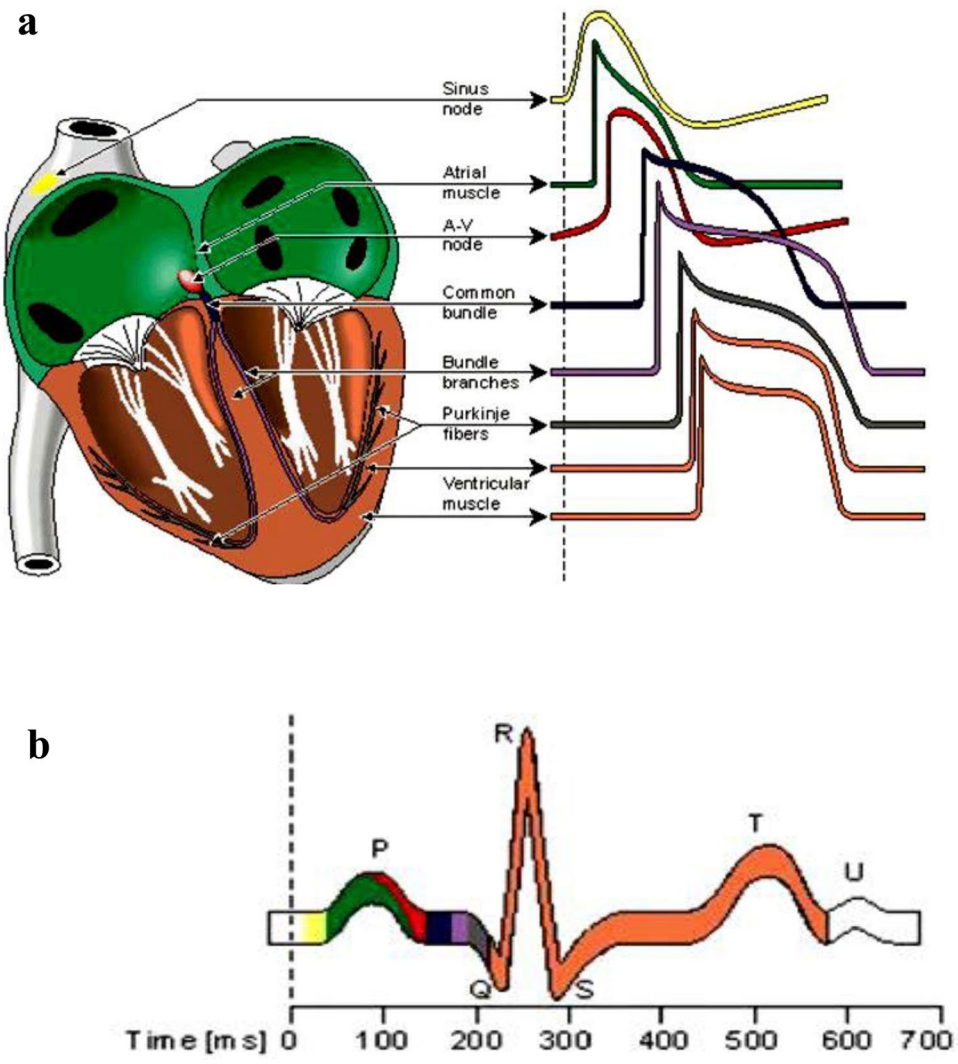

Fig. 2 ECG waveform in detail. **a** Action potential derived from different parts of the heart, **b** relationship between action potential duration and ECG Adopted from http://ecggu ru.com/ecg/ecg-waveform-illus tration

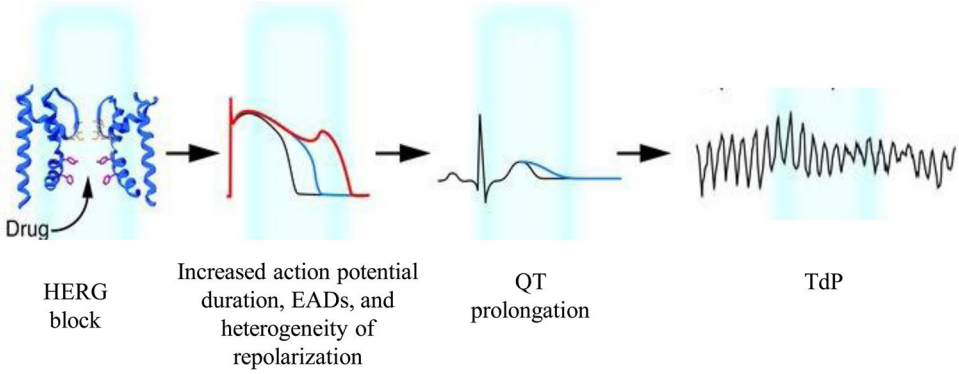

Fig. 3 Mechanisms of sudden death with hERG blockade. Drug blockade of the hERG channel (left) produces prolongation (blue) and an early after depolarization (EAD, red) in the cardiac action potential. These changes, which are heterogeneous across the ventricular wall, generate QT interval prolongation through torsade de pointes (right). Source: Roden and Viswanathan [91]

Table 1 Drugs causing QT prolongation

Drug	Treatment
Terfenadine (Seldane®)	Antihistamine/removed in 1997
Chlorpromazine (Thorazine®)	Anti-psychotic
Arsenic trioxide (Trisenox®)	Anti-cancer/leukaemia
Erythromycin (Erythrocin®)	Antibiotic
Fluoxetine (Prozac®, Sarafem®)	Anti-depressant
Haloperidol (Haldol®)	Anti-psychotic/schizophrenia

Enhanced outward currents and accelerated deactivation kinetics have been reported as a result of hERG modulation by ROS [89, 90] and are compatible with the property of ATO to induce oxidative stress by increasing ROS.

Drug-induced QT interval prolongation is one of the most common causes of the withdrawal of hundreds of drugs in the past decade [92]. Over 100 marketed pharmaceutical agents cause interference in ventricular repolarization, and QT prolongation is mentioned in the US Food and drug administration (FDA)-approved labelling as a known action of the drug (Table 1).

Patho-Physiology of Cardiotoxicity Induced by ATO

Generation of ROS

Oxidative stress is the term referring to the imbalance between generation of ROS and the activity of the antioxidant defences. ROS are characterized by their high chemical reactivity and include radical species (with one or more unpaired electrons) such as superoxide ($O_2^{\bullet-}$) and hydroxyl radicals ($OH^{-\bullet}$), and non-radical species such as hydrogen peroxide (H_2O_2), which cause damage to cellular components, including DNA, lipids, proteins and ultimately apoptosis [93, 94]. A free radical is any species capable of independent existence that contains one or more unpaired electrons occupying an atomic orbital by itself. This situation is energetically unstable making such species highly reactive and short-lived. Stability is achieved by the removal of electrons from (i.e. oxidation) or addition of electrons to (i.e. reduction) surrounding molecules to produce an electron pair. Under normal physiological conditions in cardiomyocytes, several types of ROS are formed inside the cells at very low concentrations which can be easily detoxified by normal cellular mechanisms. If the concentration of ROS is increased, they will escape from the cellular scavenging machineries and propagate by chain reaction leading to superfluous boost in ROS concentration in the cells leading to oxidative stress [95]. In case of antioxidant targets, the resultant radical has low reactivity and the chain is broken.

The ROS is generated endogenously by enzymatic or non-enzymatic means. The former includes the biological processes like mitochondrial respiratory chain, phagocytosis, prostaglandin synthesis and detoxification by cytochrome P450 system [96]. The non-enzymatic causes include the ionizing radiations that can form most of the ROS by the photolysis of water in the presence of oxygen (O_2) [97]. In cardiac health, there is a balance between ROS generation and the activity of enzymatic and non-enzymatic antioxidant systems that scavenge or reduce ROS concentrations. Generation of ROS has been proved to be one of the major causes behind DNA damage induced by ATO in various types of cells [98–101].

Role of Mitochondria in ROS Generation

The mitochondrial electron transport chain (ETC) is a very efficient system but the nature of the alternating redox reactions it catalyzes, predispose each electron carrier to side reactions with O_2 [102]. For example, as ubiquinone within the ETC cycles between the quinone (fully oxidized) to semiquinone (one-electron reduction product) to quinol (fully reduced by two electrons) states, there is a tendency for an electron to pass to O_2 directly (generating $O_2^{\bullet-}$) instead of the next electron carrier in the chain. Several iron–sulphur clusters within the respiratory chain are also subject to such toxic $O_2^{\bullet-}$ generating side reactions with O_2. It has

been estimated that about 1–3% of O_2 respired is converted to $O_2^{\bullet-}$, a rate that increases during periods of increased energy metabolism [103]. Thus, mitochondrial generation of $O_2^{\bullet-}$ represents the major intracellular source of oxygen radicals under physiological conditions. With estimates of 1–2% of the total daily O_2 consumption going to mitochondrial $O_2^{\bullet-}$ generation, a 60-kg woman would produce some 160–320 mmol of $O_2^{\bullet-}$ each day from mitochondrial respiration alone (based on an O_2 consumption of 6.4 l/kg/day) and an 80-kg man would produce some 215–430 mmol of $O_2^{\bullet-}$ per day [104].

$O_2^{\bullet-}$ is produced by phagocytic cells (neutrophils, monocytes, macrophages, eosinophils) also and helps them to inactivate viruses and bacteria [105]. When these cells encounter a phagocytable particle, their O_2 consumption increases tremendously ('respiratory burst') with the activation of a membrane-located enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (or Noxs) which catalyse the reduction of O_2 into $O_2^{\bullet-}$ [106]. Recent studies provide confirmatory evidence of the fundamental roles of Noxs in human disease [107, 108]. $O_2^{\bullet-}$ can participate in the production of $OH^{-\bullet}$, hypochlorite and chloramines. $O_2^{\bullet-}$ is also generated by a variety of cytosolic and membrane-bound enzymes, including xanthine oxidase (XO), cytochrome P450 complex and phospholipase A2 [109].

In addition to these toxic ETC reactions of the inner mitochondrial membrane, the mitochondrial outer membrane enzyme monoamine oxidase catalyses the oxidative deamination of biogenic amines that contributes to an increase in the steady-state concentrations of reactive species in the mitochondrial matrix and cytosol. H_2O_2 is able to diffuse across biological membranes, whereas $O_2^{\bullet-}$ does not. As well as arising from dismutation of $O_2^{\bullet-}$, H_2O_2 is produced by the action of several oxidase enzymes in vivo, including amino acid oxidases and XO [110]. The major by-product of these oxidases is H_2O_2, thus explaining the high level of catalase (CAT) present in peroxisomes which detoxifies H_2O_2 to H_2O. Much of the toxicity of $O_2^{\bullet-}$ and H_2O_2 involves formation of $OH^{-\bullet}$ which is the most reactive free radical in vivo. Various studies have revealed that mitochondrial dysfunctions play crucial roles in ATO-mediated cardiotoxicity via inducing excessive production of ROS [7, 111].

Innate Antioxidant System

Cellular redox homeostasis is carefully maintained by an elaborate endogenous antioxidant defence system, which includes endogenous antioxidant enzymes such as superoxide dismutase (SOD), CAT, glutathione peroxidase (GPx) and reduced glutathione (GSH) that are directly involved in the neutralization of ROS (Fig. 4) [112]. The human antioxidant defence is complex. They minimize the levels of ROS while allowing useful roles of ROS to perform cell signalling and redox regulation [109]. SOD is a cytoplasmic and mitochondrial enzyme, which accelerates the dismutation of $O_2^{\bullet-}$. The SOD exists in three forms: extracellular and intracellular copper/zinc (Cu/Zn) SOD and mitochondrial, manganese (Mn) SOD. These catalyse the dismutation of $O_2^{\bullet-}$ to H_2O_2 and work in association with H_2O_2-removing enzymes. CAT, an exclusively peroxisomal enzyme in most tissues, converts H_2O_2 to water and O_2. However, the most important H_2O_2-removing enzymes are the GPx enzymes which remove H_2O_2 by using it to oxidize GSH to oxidized glutathione (GSSG). GSH is a tripeptide composed of cysteine, glycine and glutamic acid. It is the major antioxidant in the non-lipid portion of cells (most of the cytoplasm). Glutathione reductase converts GSSG to GSH, with simultaneous conversion of NADPH to NADP. GPx also catalyse the reduction of unstable hydroperoxides at the expense of GSH [113]. Excessive generation of ROS during ATO therapy leads to disruption of the endogenous antioxidant system [7, 100, 114] in cardiac cells particularly because these cells are highly susceptible to oxidative stress damage due to low amounts of antioxidants compared to other organs and production of high amounts of basal pro-oxidants [6].

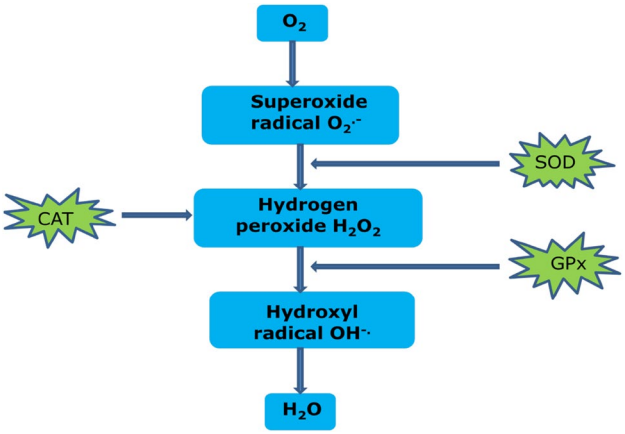

Fig. 4 Endogenous antioxidant system

Ca^{2+} Signalling

Ca^{2+} is a universal second messenger and its disruption can activate pathways that can lead to apoptosis [115]. Evidence demonstrates that Ca^{2+} handling abnormalities play an important role in the patho-physiology of heart diseases, such as heart failure and cardiomyopathies [116]. To survive, living cells need to maintain a tight control over intracellular calcium ($[Ca^{2+}]i$) that ranges from basal levels of 100 nM to signalling levels up to millimolar concentrations [117, 118]. The Ca^{2+} signalling theory affirms that the increase in $[Ca^{2+}]i$ can be due to (1) Ca^{2+} entry from the extracellular

space, through channels in the plasma membrane or from (2) $[Ca^{2+}]$i stores. Drugs could activate phospholipase C causing hydrolysis of phosphatidylinositol (4,5) biphosphate to release the signalling molecule inositol-1,4,5-trisphosphate (IP3) in cells. The receptor for IP3 located on the cell membrane and at the internal stores functions as a ligand-gated Ca^{2+} channel. Its activation by IP3 leads to the opening of Ca^{2+} conducting channels and thus an increase in $[Ca^{2+}]$i [118, 119]. The return of $[Ca^{2+}]$i to resting level is done by (1) plasma membrane pumps or exchangers or through (2) re-entry to the Ca^{2+} stores (mitochondria, sarcoplasmic reticulum (SR)) via Ca^{2+}-ATPases [120]. $[Ca^{2+}]$i could also be bound by Ca^{2+}-buffering proteins that can further modulate $[Ca^{2+}]$i levels. One of the most important events resulting from the Ca^{2+} signalling is the activation of biological events that are modulated by binding of Ca^{2+} to Ca^{2+}-sensor proteins [118, 119].

Abnormal Ca^{2+} signalling leading to cytoplasmic Ca^{2+} overload is thought to be critical and perhaps common mechanism underlying cardiac dysfunctioning. Carefully regulated Ca^{2+} cycling is critical for cardiac function, which depends on the Ca^{2+} concentration surrounding the myofilaments rising and falling in a cyclic manner in response to membrane depolarization [121]. Insufficient Ca^{2+} delivery to the myofilaments results in a weak contraction, whereas excessive Ca^{2+} delivery carries the risk of contracture, activation of proteases and other maladaptive Ca^{2+}-sensitive pathways that lead to cell death. A variety of ion channels, ATP-dependent pumps and transporter proteins serve as the major control points of Ca^{2+} regulation in the heart [122, 123].

A considerable amount of Ca^{2+} released from the SR has been taken by mitochondria and this helps to maintain the physiological level of Ca^{2+} in the heart. Regulation of $[Ca^{2+}]$i level by mitochondria also regulates synthesis of ATP in the cell. During mitochondrial dysfunction, $[Ca^{2+}]$i in the mitochondrial matrix increases. This promotes opening of mitochondrial membrane permeability transition pore (mPTP) and thereby cell death occurs in ATO-induced cardiotoxicity [124, 125].

Signalling Pathways Affected by ATO Interfering Cardiac Function

Long-term exposure to inorganic arsenic may cause various cardiovascular disorders such as atherosclerosis, hypertension, ischemic heart diseases and ventricular arrhythmias [36, 55, 126]. The cytotoxicity of ATO is mediated mainly through generation of ROS and oxidative stress [127, 128]. Apoptosis induced by ATO is also associated with generation of ROS [129]. ATO is found to be genotoxic in human cells [130]. In addition, a few studies have shown that exposure to arsenic increases the frequency of micronuclei, chromosome aberrations and sister chromatid exchanges both in humans and animals [131].

ATO induces gene expression of a number of stress response proteins, such as ubiquitin, that has resulted in alteration of the DNA repair mechanisms causing DNA damage [132]. GSH is known to provide good protection against xenobiotics and its depletion below a critical concentration allows enhancement of lipid peroxidation evoked by endogenous substances. ATO is reported to deplete cellular GSH levels and to induce oxidative stress leading to induction of ROS that play a key role in DNA damage [133]. This could result in induction of ROS affecting DNA repair mechanisms, leading to DNA damage [134]. The presence of ATO in the body activates antioxidants, such as SOD and CAT, to metabolize the ROS [135].

Arsenite stimulates Noxs present in the plasma membrane of vascular endothelial cells and vascular smooth muscle cells (VSMC) increasing the generation of ROS such as $O_2^{\bullet-}$ and H_2O_2 [136, 137]. ROS generated during arsenite exposure couples with nitric oxide (NO) to form peroxynitrite, a strong oxidant implicated in the upregulation of inflammatory mediator such as cyclooxygenase-2 [138]. It increases the expression of atherosclerosis-related genes such as hemeoxygenase-1, monocyte chemo-attractant protein (MCP-1), and interleukin-6 (IL-6) and thus its exposure promotes the attachment, penetration and migration of monocytes in VSMC [139]. Arsenic alters focal adhesion proteins in VSMCs leading to their proliferation and migration [140].

Arsenic increases the synthesis of inflammatory mediators such as leukotriene E_4 and prostacyclin, tumour necrosis factor-alpha (TNF-α) and NF-κB in vascular endothelial cells to induce the pathogenic process of atherosclerosis [138, 141]. Moreover, arsenic causes neurogenic inflammation of the blood vessel by increasing the release of substance P and endothelial neurokinin-1 [142]. Arsenic also activates protein kinase C alpha, causing phosphorylation of beta-catenin and thus reverses the association between vascular endothelial cadherin and beta-catenin, along with the formation of actin stress fibres resulting in increased intercellular gap formation and permeability of the endothelium [143]. Arsenite has been reported to decrease the activity of endothelial nitric oxide synthase (eNOS) and Akt/protein kinase B, which subsequently decreases the bioavailability of NO that may lead to vascular endothelial dysfunction and associated cardiovascular complications [144, 145]. Arsenite mediates vasoconstriction of the blood vessels by phosphorylating myosin light chain kinase and increases Ca^{2+} sensitization leading to hypertension [146].

ATO develops ventricular arrhythmia by inducing prolonged QT interval and action potential duration [126, 147]. ATO interferes with hERG trafficking by inhibition of hERG–chaperone complexes and increases Ca^{2+} currents

by a faster cellular process. Ficker et al. proposed that an increase in cardiac Ca^{2+} current and reduced trafficking of hERG channels to the cell surface caused QT prolongation and TdP in patients treated with ATO and that Ca^{2+}-channel antagonists may be useful in normalizing QT prolongation during ATO therapy [87].

Cell Death by ATO

Studies have demonstrated that low doses of ATO induce apoptosis, whereas high doses lead to necrosis [148]. Apoptosis plays an important role in the progression of heart failure [149]. Nerheim et al. also reported that apoptosis provided a potential pathogenetic mechanism of the cardiac rhythm [150]. In addition, ATO increases LDH leakage from cytoplasm and consequently causes necrosis in cardiomyocytes [149].

There are, however, studies which suggest higher concentrations of arsenic cause oxidative stress [151, 152], increased ROS, inhibits enzyme and mitochondrial function and induces several stress genes [153]. Finally, it alters cellular signal transduction, such as activation of transcription factors, changes of gene expression and induction of apoptosis [117]. The inhibition of apoptosis by Ac-DEVD-CHO, a caspase-3 inhibitor, indicates that the caspase-3 activation pathway is a major cause of ATO-induced H9c2 cell apoptosis [154].

Activation of caspase-3 is mediated by two different pathways, extrinsic pathway and intrinsic pathway. The intrinsic pathway is activated by intracellular stresses that cause mitochondrial membrane depolarization and cytochrome C release [155]. Mitochondria impairment has been reported to cause collapse of mitochondrial transmembrane potential (Ψm) that leads to release of cytochrome C causing the activation of caspase-3. It has been reported that oxidative stress leads to opening of mPTP and activates caspase-3 [156]. Taken together, these data suggest that ATO-induced cardiomyocyte apoptosis is mediated through ROS formation, increased $[Ca^{2+}]$ and then caspase-3 activation. The Bcl-2 family is major regulators of mitochondrial cytochrome C release and caspase-3 activation and play an important role in the regulation of cardiomyocyte apoptosis. The extrinsic pathway is triggered by extracellular stresses that cause the activation of caspase-3 [156].

Nutraceuticals and Cardiovascular Disorders

An alternative to the adverse effects on cardiac functioning posed by ATO would be to use any drug that can ameliorate the cardiotoxic effects and allow exploiting the full therapeutic potential of ATO, with a considerable impact on cancer therapy. Generation of ROS is involved in a wide range of human diseases, including cancer, cardiovascular, pulmonary and neurological diseases. Hence, agents with the ability to protect against these reactive species may be therapeutically useful such as any synthetic scavenger of ROS or an antioxidant. In this context, nutraceuticals are emerging as attractive alternative for the prevention and management of cardiovascular diseases because of their antioxidant properties. A "nutraceutical" is any non-toxic food or part of a food that has scientifically proven medical or health benefits for both the treatment and prevention of disease [157]. More than 50% of FDA-approved drugs are from natural products and their derivatives [158]. The search for novel phytomedicines is becoming more popular because they are easily available, cost effective, possess less adverse effects and have multifaceted activities [159]. Various clinical, experimental and epidemiological studies revealed that nutraceuticals are effective in the management of cardiovascular diseases and ATO toxicity, and consumption of diet rich in fruits and vegetables are inversely associated with the risk of cardiovascular diseases due to the abundance of different bioactive compounds present in it [7, 114, 160–162].

Antioxidants and Phytochemicals

Antioxidants are chemicals that interact with and neutralize free radicals, thus preventing them from causing damage. Antioxidants are also known as "free radical scavengers". The body makes some of the antioxidants and uses it to neutralize free radicals. These antioxidants are called endogenous antioxidants. They play an important role in cellular homeostasis, mitosis, swelling, differentiation and signalling [163]. The damaging effects of ROS are reduced by antioxidants in normal physiological conditions. A series of defence mechanisms are developed on exposure to free radicals from a variety of sources. The defence mechanisms against free radical induced oxidative stress involve (i) preventative mechanisms, (ii) repair mechanisms, (iii) physical defences and (iv) antioxidant defences. The body relies on exogenous sources, primarily the diet, to obtain the rest of the antioxidants it needs called dietary antioxidants. Fruits, vegetables and grains are rich sources of dietary antioxidants. Some dietary antioxidants are also available as dietary supplements [163, 164]. Dietary antioxidants include beta-carotene, lycopene and vitamins A, C and E.

In recent years, we have seen an increasing interest in dietary compounds contained in food towards health benefits. The growing list of phytochemicals and their biological activities has become the focus of intensive research. Numerous epidemiological studies have established the protective and preventive effects of phytochemicals in cardiovascular diseases [165, 166]. Administration of antioxidant phytochemicals such as curcumin [167], resveratrol [168],

phloretin [7] α-lipoic acid [169], salvianolic acid B [170] and arjunolic acid [171] attenuated the ATO-induced toxicity and the reported mechanisms for protection against cardiotoxicity was via their antioxidant-related effects [172].

Conclusion

Cardiotoxicity has a rising relevance in the present scenario as a consequence of the global improvement in cancer therapy and management, which has led to better survival of cancer patients. It is therefore critical to limit the co-morbid illnesses associated with chemotherapy. ATO is a highly effective therapeutic drug used in the treatment of APL. The reported adverse effects associated with ATO treatment in cancer patients include QT prolongation, torsades de pointes and sudden cardiac death. The overall reviewed literature indicates that cardiotoxicity is mainly due to the effect of ATO on cardiac ion channels, excessive free radical production, intracellular calcium overload, mitochondrial dysfunctioning and depletion of antioxidant status causing an imbalance in the redox state and subsequently leading to an oxidative stress in the cell. Therefore, strategies targeting to reduce the oxidative stress hold great significance in circumventing the adverse effects caused by ATO.

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Compliance with Ethical Standards

Conflict of interest There is no conflict of interest existing among the authors.

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