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Ins and outs of cadmium-induced carcinogenesis: Mechanism and prevention

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ABSTRACT

Cadmium (Cd) is a heavy metal and a highly toxic pollutant that is released into the environment as a byproduct of most modern factories and industries. Cd enters our body in significant quantities from contaminated water, cigarette smoke, or food product to many detrimental health hazards. Based on causal association all the Cd-related or derived compounds have been classified as carcinogens. In this study, we present an overview of the published literature to understand the molecular mechanisms for Cd-induced carcinogenesis and its prevention. In acute Cd poisoning production of reactive oxygen species is a key factor. However, chronic Cd exposure can transform cells to become more resistant to oxidative stress. Also, as an epigenetic mechanism Cd acts indirectly on DNA repair mechanisms via alteration of reactions upstream. Those transformed cells acquire resistance to apoptosis and deregulation of calcium homeostasis. Leading to uncontrolled carcinogenic cell proliferation and inherent DNA lesions. Flavonoids commonly found in plant foods have been shown to have a protective effect against Cd-induced carcinogenicity. A wide variety of tumorigenic mechanisms involved in chronic Cd exposure and the beneficial effects of flavonoids against Cd-induced carcinogenicity necessitate further investigations.

1. Introduction

Cadmium (Cd) is a toxic metallic widely present in the environment, as a pollutant i.e. water, air, and soil. Cd is a non-biodegradable stable divalent cation that persists in the environment for several decades. Cd is utilized in the commercial production of several common use electronics such as television screens, lasers, and batteries, as well as in paint pigments, cosmetics, and galvanizing solutions. In the United States alone, approximately 600 metric are produced annually and about 150 metric are imported [1]. Currently, many developed countries are effortlessly trying to reduce the industrial use of Cd, however, in developing countries; it continues to be a major public health problem.

We are normally exposed to low levels of Cd either at the workplace or by ingesting contaminated water and food [2]. However, smoking tobacco or cigarettes is the most significant source of high-dose Cd exposure. This finding was confirmed by observing consistently higher Cd levels in blood and urine in smokers compared to nonsmokers [2]. Also, occupational inhalation due to industrial exposure is significant. Depending on particle size, approximately 10–15% of inhaled or ingested Cd is absorbed; however, the absorption through skin contact is negligible. Also, the intestinal absorption could be greater if coexist with iron, calcium, or zinc deficiency [1].

The most dangerous characteristic of Cd is that it is an accumulative toxicant due to its long biological half-life and low excretion levels [3]. USA National toxicology program and International Agency for Research on Cancer classified Cd exposure as a type I carcinogen. Population-based studies have suggested that long-term Cd exposure was positively correlated to increased risk of developing lung, liver, breast, colon, and genitourinary cancers [4,5]. Itai-Itai syndrome, in which there is severe bone pain, osteomalacia, osteoporosis, and kidney shut down, is a classic example of chronic Cd poisoning affecting human health. This disease was reported in the Chubu region of western Japan [6,7].

In this review article, we aimed to summarize the current knowledge regarding the molecular mechanisms of the Cd-induced carcinogenesis; Cd-induced common cancer types and we also discussed the protective

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response against Cd insult.

2. Methods

In this review, we narrate all the published literature related to Cd-induced carcinogenesis until the year 2020. To search for appropriate studies, several scientific databases (SCOPUS, Ovid, PubMed, and Web of Science) were searched using the following MeSH terms: "cadmium" with "cancer," "carcinogenesis,", "malignancy" or "toxicity". The references of the filtered studies were searched manually to identify additional relevant researches.

3. Mechanism of cadmium transport across the cells

Many studies have reported a nonspecific route of Cd entry into the cell. It was suggested that Cd ions diffuse into the cells through channel proteins in addition to the transporter proteins specific for other metal ions. Divalent metal ion transporter type I (DMT1), which is usually required to transport iron into the cells, was reported to be a major carrier protein for Cd import [7]. Moreover, zinc ion symporters such as ZRT/IRT-like protein 8 (ZIP8) and ZIP14 were also reported to have affinities for Cd. In support of that, the uptake of Cd ions from the luminal side of proximal kidney tubule cells was inhibited by the knockdown of ZIP8, ZIP14, or DMT1[7]. Changes in Cd and Zn metabolism due to ZIP8 polymorphism was also reported to be involved in several human diseases [8]. Upon intestinal absorption, Cd can bind to intravascular proteins to form a Cd-protein complex. Of those proteins metallothionein (MT), megalin, cystic fibrosis transmembrane conductance regulator, multidrug-resistant protein 1 (MRP1), and tubulin are helping Cd to enter cells via receptor-mediated endocytosis. In the plant cells, overexpression of OsNRAMP5 transporter protein increases Cd uptake and accumulation [9], and *OsNramp5* mutant cells prevent Cd accumulation [10]. Also in human cells, Cd ions can penetrate through the cell membranes of electrogenic cells using *L*-or *N*-type voltage-dependent calcium channels. However, store-operated Ca^{2+} channels might be used in non-electrogenic cells [11,12]. Subsequently, Cd is inducing oxidative stress-mediated cytotoxicity. Once entered in the cell, Cd leads to protein unfolding and malfunction and eventually causes endoplasmic reticulum stress and cell death [13].

4. Oxidative stress induced by cadmium

Cd-induced cytotoxicity is due to oxidative stress via reactive oxygen species (ROS) production leading to mitochondrial damage, cellular respiration inhibition, and membrane lipid peroxidation [14,15]. Nevertheless, interestingly, Cd does not generate ROS by itself; rather it displaces other metallic ions such as copper, iron, and zinc from their respective protein complexes, which in turn induces oxidative stress [16]. Later this increased oxidative stress initiates tumor development and growth by inducing mutations [17].

Cd is also shown to inhibit mitochondrial complex III, resulting in the accumulation of unstable semi ubiquinones, which then transfer an electron to molecular oxygen, resulting in the formation of superoxide [18]. On the other hand, Cd also induces oxidative stress via interference with the thiol groups of antioxidant enzymes such as catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase [19]. This oxidative stress leads to oxidative DNA damage. The formation of a key marker for oxidative stress and carcinogenesis, 8-hydroxy-2′-deoxyguanosine (8-OHdG), is the crucial link between Cd-induced production of ROS and DNA damage. On top of that Cd prevents the repair of DNA damage [16]. An association between Cd, the formation of 8-OHdG, and the progression of cancer tissue has been proven in glass production workers as well as in animal models [20].

Mismatch repair, base excision repair, and nucleotide excision repair are the main component of the DNA repair system [21]. Cd is responsible for obstructing all DNA repair systems; this will disturb the repair of DNA damage generated by Cd-induced ROS [16,22]. DNA repair pathways remove the most delirious damage caused by normal metabolic activities, and if the DNA repair system were inactivated and ineffective, the accumulation of DNA damage could result in the development of cancer (Fig. 1).

5. Adaptive mechanisms after chronic or low dose cadmium exposure

Low doses of Cd exposure activate intracellular defense mechanisms via metallothionein, glutathione, and transcription factor nuclear factor E2-related factor 2 (Nrf2), in addition to other antioxidant molecules. Of these targets, the Nrf2 transcription factor plays a key role in protecting against the chronic Cd toxic effects [23]. Besides that, NF-κB and AP-1 pathways are activated as an adaptive response to Cd-induced oxidative stress [24]. All of these have integrated functions to induce resistance against oxidative stress in Cd-treated cells. Metallothionein is a Cd-binding protein, which plays an important role in protecting against the Cd-induced toxicity by sequestering ROS or by scavenging free radicals. However, due to chronic exposure a marked elevation of metallothionein leads to resistance to apoptosis and ROS in Cd transformed cells [25]. Glutathione is the first line of defense against Cd toxicity. Marked elevations of tissue GSH levels are often observed after chronic Cd exposure which diminishes oxidative damage. But after an acute Cd exposure, there is significant depletion of GSH level [26].

6. Cadmium-induced carcinogenesis

At concentrations lower than environmental levels, Cd can transform normal epithelial cells into malignant cancerous cells, which might not be due to increased cellular ROS levels [27,28] (Fig. 2). Cd might be

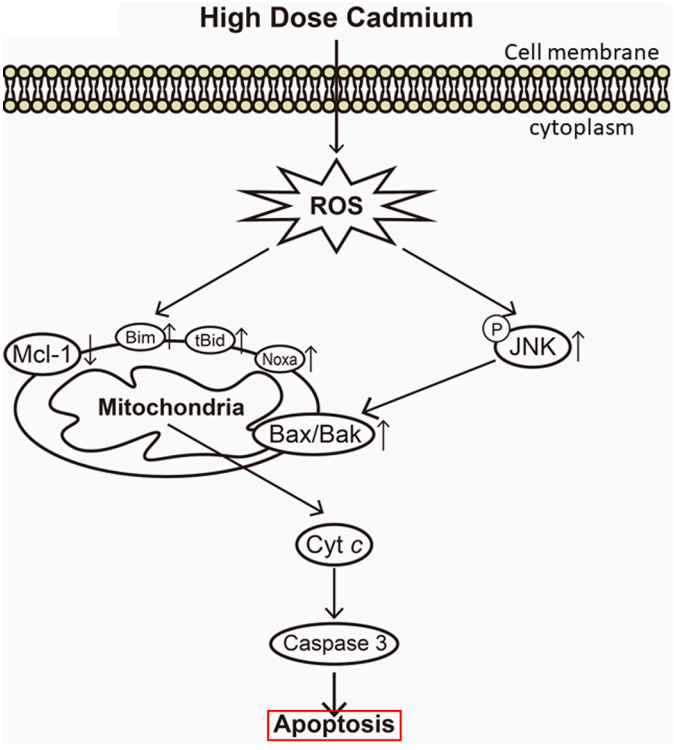

Fig. 1.. Molecular mechanism involved in the pro-apoptotic effects of acute Cd toxicity. At a high dose, Cd induces ROS generation which leads to apoptosis via JNK activation, up-regulation of pro-apoptotic proteins (Bim, Noxa, and tBid), and down-regulation of anti-apoptotic protein Mcl-1. Cd-induced increase in intracellular Ca^{2+} concentration is also responsible for inducing apoptosis via ROS generation and JNK activation.

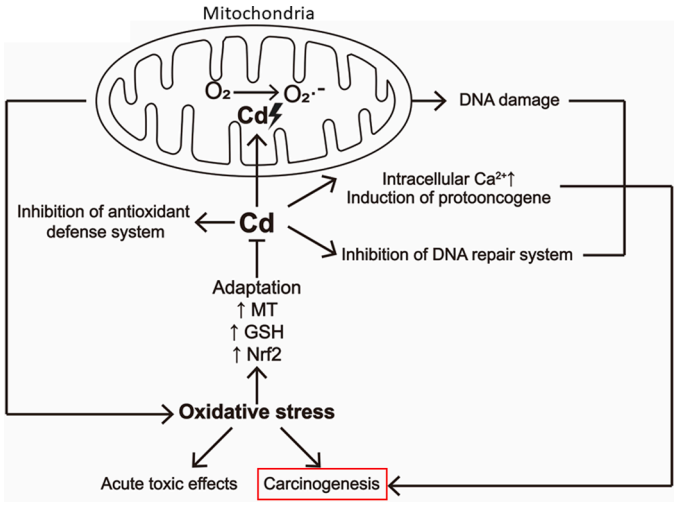

Fig. 2.. Molecular mechanism involved in the carcinogenesis caused by cadmium (Cd). Cd can induce oxidative stress via mitochondria and by inhibition of antioxidant defense mechanisms. Chronic Cd exposure can trigger adaptive mechanisms for oxidative stress. Cd-induced inhibition of DNA repair system and disturbance in intracellular Ca^{2+} homeostasis plays a role in Cd-induced carcinogenesis.

acting indirectly via epigenetic mechanisms by altering the molecular signals upstream of DNA repair and apoptosis [22]. Making these Cd-transformed cells more tolerant to oxidative stress probably via epigenetic activation genes related to adaptation response and cell growth. Epigenetic inactivation of p53's was reported to cause the development of tumors due to the alteration of response to the DNA damage. Also, Cd affects the structure and function of p53 through various mechanisms reported earlier [29]. Cd can substitute zinc or bind to the thiol group in the structure of p53. These changes result in the impairment of p53 function reducing the cell's ability to respond to DNA lesions [30]. Along with resistance to apoptosis, chronic low dose exposure to Cd induces DNA hypermethylation via an increase in DNA methyltransferase activity [31]. Hence the apoptotic resistance happens in Cd-induced malignancy, as DNA-damaged cells will be able to evade apoptosis and proliferate with inherent DNA lesions, eventually progressing to the malignant phenotype.

Studies have shown that Cd could stimulate cell proliferation by enhancing the level of intracellular calcium signaling pathways. This elevated intracellular calcium then induces *in vitro* and *in vivo* overexpression of several proto-oncogenes like c-fos, c-jun, and c-myc. These genes constitute the AP-1 transcription factor and several other genes which are involved in cell growth and division [12,32,33]. Ca^{2+} elevated by Cd can stimulate the phosphorylation of CaMKII [34]. CaMKII is a multifunctional serine/threonine-protein kinase that is involved in processes causing major tumor progression, including cell cycle regulation, apoptosis, differentiation, and cancer cell metastasis [35]. These studies suggest dysregulation of calcium homeostasis is also plays an important role in Cd-induced carcinogenesis.

7. Cadmium-induced multiple cell death mechanisms

Cd is known to induce multiple intracellular death signals, such as autophagy, necroptosis and apoptosis [36]. Of these, the production of ROS plays an important role in Cd-induced apoptosis. ROS-induced mitochondrial damage releases cytochrome c into the cytosol, which activates the caspase cascade and ultimately induces apoptosis. Acute Cd toxicity is associated with an increased intracellular ROS which activates JNK and induces apoptosis via mitochondrial dysfunction, down-regulation of anti-apoptotic protein Mcl-1, and up-regulation of pro-apoptotic proteins Bim, tBid, Noxa which activates Bax/Bak and thus promote the release of cytochrome *c* [37]. The chronic low dose of Cd develops cellular apoptotic resistance by modulating the balance between anti-apoptotic protein Mcl-1 and pro-apoptotic proteins Bim, tBid, and Noxa [37]. The inhibition of apoptosis following prolonged Cd exposure makes the cells more susceptible to the accumulation of mutated or neoplastic transformation.

Calcium ions also play an important role in Cd-induced apoptosis (Fig. 1). In neuronal cells, Cd-induced intracellular Ca^{2+} elevation leads to apoptosis via mitogen-activated protein kinase (MAPK) and mTOR signaling pathways [38,39]. Cd-induced Ca^{2+} is shown to be responsible for ROS generation in neuronal cells [38]. The JB6 Cl 41–5a epithelial cell lines from primary cultures of neonatal BALB/c mice treated with Cd showed JNK and p53-mediated apoptosis in addition to disruption of intracellular Ca^{2+} homeostasis [40]. Moreover, the human embryonic kidney cells (HEK293) cells upon Cd treatment showed increasing concentrations of intracellular Ca^{2+} levels that also activate Calpain proteins. These proteins belong to a family of non-lysosomal cysteine-bearing proteolytic enzymes that functions as pro-apoptotic [41]. Given this information, we believe that Cd can act as a double-edged sword, which can cause cell death by apoptosis in acute exposure, but inhibition of apoptosis and increased survival in chronic exposure. Such hyper-proliferation will transform cells to become more tumorigenic [37,38,42].

Necroptosis is initially considered as a secondary cell death pathway after apoptosis where caspases are not principal regulators. Pathologically evidence suggests that necroptotic cell death can cause various diseases, and may lead to cancer [43]. In general, concentrations of greater than 50 μM Cd initiate necrotic death by ROS production, depletion of antioxidant defenses, and enzyme inhibition [43]. High parenteral Cd exposure causes necrosis in prostate and testicular tissue [44]. Acute oral administration causes necrosis of the gastric and intestinal mucosa [45]. Further studies at high concentrations are warranted to achieve insight into Cd-induced necroptosis in carcinogenesis.

Autophagy refers to the sequestration of cytoplasmic and organelle-derived material within double-membraned autophagosomes [43]. Human stem cells treated with Cd for 48 h showed evidence of mitochondrial damage and the presence of prominent autophagosomes/autophagolysosomes [46]. Autophagy initialized by transient Cd treatment disrupts the levels of p62 and LC3-II in normal rat kidney cells. But the main damage seems to occur at the final steps of the autophagic machinery at the interference at autophagosome-lysosome fusion due to lysosomal dysfunction [47]. Hence, the Cd exemplifies the accumulation of ubiquitinated proteins and damaged organelles leading to enhanced carcinogenesis.

8. Cadmium-induced most common cancers

Epidemiological surveys suggest that long-term exposure to Cd is strongly correlated with an increased risk of prostate, breast, and lung carcinoma in humans [48,49]. The most definitively established and studied Cd-induced malignancy is lung cancer. However, Cd exposure has been more commonly associated with the development of cancers of the prostate and breast (Table 1).

Prostatic cancer is a very lethal disease of indeterminate etiology. Long-term Cd exposure to human prostate cells induces malignant transformation, and these transformed cells give rise to aggressive tumor growth in nude mice [50]. However, the molecular mechanisms are only partially known. In another study, Cd-treated rats showed significantly higher Lysophosphatidic acid-1 (LPA-1) expression, involved in a variety of cell growth processes, in dysplastic lesions compared with that in the normal prostate epithelium in controls [51]. Furthermore, Cd toxicity has been shown to inhibit the DNA repair process in various in vitro models of prostate cancer [51]. Interestingly, short-term treatment of normal prostate epithelial cells with Cd-induced apoptosis, however, after chronic exposure those cells eventually become resistant to apoptosis [52,53]. Analysis of molecular signaling revealed that the

Table 1.
Summary of cadmium-induced cancer types and their mechanisms.

Cancer types	Mechanisms	References
Prostate cancer	■ Increased Lysophosphatidic acid ■ Inhibition of DNA repair system ■ Increased resistance to apoptosis	[50–54]
Breast cancer	■ Estrogen-receptor mediated increase cell growth and survival ■ Development of more aggressive cancer phenotype ■ Upregulation of pro-survival genes	[55–57]
Lung cancer	■ Increased DNA damage ■ Inhibition of DNA repair system ■ Increased tumorigenicity potential ■ Elevation of matrix metalloproteinase activity ■ Downregulation of p16 ■ Upregulation of Cyclin D1	[58,59]

Table 2.
Summary of protection strategies against cadmium-induced carcinogenesis.

Protective agent	Mechanism of action	References
Flavonoids	■ Decreases Cd absorption ■ Increases Cd elimination ■ Targets intravascular Cd ■ Acts as ROS scavenger ■ Restores antioxidants ■ Increases GSH activity ■ Protects cellular proteins and DNA strands ■ Direct Cd chelation	[37, 52–58]
Arthrospira maxima	■ Antioxidant potentials ■ Reduces Cd-induced genotoxicity	[61]
Piper betel	■ Antioxidant potentials	[62]
Catechins	■ Antioxidant potentials	[63]
Melatonin	■ Antioxidant potentials	[64–66]
N-acetylcysteine	■ Antioxidant potentials	[67]

(Cd: Cadmium; ROS: reactive oxygen species; GSH: Glutathione).

Bcl-2/Bax ratio was 5 times higher in the short-term treated cells [53]. Several markers of stress and inflammatory responses were also upregulated in Cd-treated prostate epithelial cells [54].

Breast cancer is the most frequent malignancy in women worldwide. Cd is known as metalloestrogen and is associated with the development of breast cancer. Short-term exposure to Cd promotes estrogen receptor (ER)-mediated growth and survival of breast cells [55]. Cd-treated MCF-7 cells show increased cell growth, cell migration, and invasion, hence, development of more aggressive cancer phenotype [56]. In the presence of Cd, the anti-cancer drug 5-fluorouracil (5-FU) fails to induce apoptosis in MCF-7 cells. Likewise, even a very low Cd concentration (as low as 1 μM), induces significant cell proliferation in ERα-positive breast cancer cell lines and was associated with the upregulation of pro-survival genes. Later, the silencing of the ERα or blocking the receptor with a competitive antagonist mitigated the stimulatory effect of Cd, thus suggesting the role of ERα in mediating the cellular effects of Cd [57].

Lastly and most importantly, studies have reported that exposure to Cd can induce lung cancer in both, rodents and humans [58]. In human bronchial epithelial cells, chronic Cd exposure is not inducing mutagenesis directly, chronic Cd treatment may cause DNA damage also decreases DNA repair capacity. Although the mechanisms are only partially known, studies have used specific cell lines to understand the specific mode of Cd-induced lung adenocarcinoma. non-tumorigenic immortalized bronchial epithelial (BEAS-2B) cell lines are commonly used as an in vitro model to study lung carcinogenesis. These cells treated with Cd resulted in tumorigenic phenotype by showing a significant increase in cell migration and invasion. Also, a special lung epithelial cell line (CCT-LC cell line) generated by applying over 20 weeks of Cd exposure, displayed marked elevation of MMP activity, enhanced metastasis, and colony formation. These cells also showed downregulation of p16 and upregulation of cyclin D1, which was attributed to increased cell survival [59].

9. Protection strategies against Cd insult

Cd-induced cytotoxicity is via activation of several cell death pathways. As mentioned earlier, the main mechanisms involved in Cd-induced carcinogenesis are oxidative damage-mediated cell apoptosis or interactions between essential trace elements. Population-based studies have shown that a diet rich in vitamins, fibers, and flavonoids, which could be obtained from vegetables, fruits, and especially beans, could reduce the harmful Cd-induced effects on the human body [51]. Plant-based flavonoids can be found either as bound or free-state flavonoid aglycones. Several studies have reported the ability of flavonoids to scavenge ROS, hence preventing oxidative stress and regulates body metabolism [52,53].

Several mechanisms have been reported (Table 2). The flavonoids in the alimentary tract can directly chelate Cd ions reducing their absorption and enhancing elimination. Cd ions if absorbed will be a direct target of flavonoids and their metabolites in the circulation [37]. Flavonoids inhibit the free radical chain reactions by scavenging ROS reducing cell membrane lipid peroxidation [54,55]. Also, flavonoids can restore the depleted antioxidants by acting as an antagonist to Cd on antioxidant enzymes and increasing GSH activity [56-58]. Furthermore, flavonoids and their derivatives isoflavones have shown protective effects towards cellular proteins and DNA strands from free radical-induced damages [56]. Accumulation of free Cd ions is a key factor to cause toxicity and natural flavonoids, such as quercetin, ability to directly chelate Cd ions reduces its accumulation [56,57]. In various biological models, Cd has different mechanisms of injury, hence, further studies are needed to explore all the possible beneficial effects of flavonoids against Cd-induced cell toxicities.

Medicinal plant extracts and biological compounds that are protective against Cd intoxication are considered natural antioxidants [60]. *Arthrospira maxima* (Spirulina) had shown to exhibit antioxidant potential by significantly reducing Cd-mediated genotoxic effects [61]. *Piper betel* leaf extract also showed protective effects against Cd-induced oxidative stress [62]. Catechins in green tea extracts demonstrated antioxidant potential in Cd intoxicated cells [63]. Furthermore, recently numerous studies showed a beneficial role of hormones like melatonin and antioxidant such as N-acetylcysteine against Cd-induced cytotoxicity [64–67].

10. Conclusion

Cd is highly prevalent in the environment, which is largely introduced by industries and other human activities such as cigarette smoking. Cd-induced free radical production is probably mediated by several complex intracellular mechanisms, but Cd itself is not an active redox agent. However, long-term exposure to low doses of Cd affects cell proliferation and differentiation but might not be associated with ROS accumulation or carcinogenicity. Suggesting cellular responses to adapt against Cd-induced toxicity. So, then it is the acute exposure to high levels of Cd which might have induced oxidative damages to DNA or aberrant epigenetic changes to the promoter regions of tumor-associated genes. Hence, activation and integration of several carcinogenic pathways might be the main cancer progression factor. Hence, the most important preventive strategy or therapeutic regimen would depend on the identification of the main intracellular pathway and key molecules involved. Naturally, occurring flavonoids can be considered as a potential source for identifying compounds that might work effectively against Cd-induced cytotoxicity. To the best of our knowledge role of flavonoids has just been studied superficially, and a detailed investigation in future research could help us in finding the best key molecule to unlock the toxic side effects of Cd-induced carcinogenesis.

Ethical approval

None sought.

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Author contribution statement

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Kanwal Ahmed: Writing- Reviewing and Editing

Syed Faisal Zaidi: Writing- Reviewing and Editing

Jibran Sualeh Muhammad: Conceptualization, Writing- Original draft preparation, Writing- Reviewing and Editing

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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