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Review

Ameliorative and protective effects of ginger and its main constituents against natural, chemical and radiation-induced toxicities: A comprehensive review

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ABSTRACT

Fatal unintentional poisoning is widespread upon human exposure to toxic agents such as pesticides, heavy metals, environmental pollutants, bacterial and fungal toxins or even some medications and cosmetic products. In this regards, the application of the natural dietary agents as antidotes has engrossed a substantial attention. One of the ancient known traditional medicines and spices with an arsenal of metabolites of several reported health benefits is ginger. This extended literature review serves to demonstrate the protective effects and mechanisms of ginger and its phytochemicals against natural, chemical and radiation-induced toxicities. Collected data obtained from the *in-vivo* and *in-vitro* experimental studies in this overview detail the designation of the protective effects to ginger's antioxidant, anti-inflammatory, and anti-apoptotic properties. Ginger's armoury of phytochemicals exerted its protective function *via* different mechanisms and cell signalling pathways, including Nrf2/ARE, MAPK, NF-ƙB, *Wnt*/β-catenin, TGF-β1/Smad3, and ERK/CREB. The outcomes of this review could encourage further clinical trials of ginger applications in radiotherapy and chemotherapy regime for cancer treatments or its implementation to counteract the chemical toxicity induced by industrial pollutants, alcohol, smoking or administered drugs.

1. Introduction

Exposure to either natural or synthetic chemicals represents a worldwide public health problem. Humans or animals could be exposed to toxic substances in air, soil, food, fruits, vegetables, or even pharmaceutical and cosmetic products *via* inhalation, ingestion, or direct contact. Of course, these toxic agents can produce hazardous toxicities including non-organ directed (carcinogenesis, endocrine disruption, and teratogenicity) or either single or multiple organ-directed noxiousness on liver, kidney, brain, heart, and reproductive system. Nevertheless, the sensitivity to these toxins is affected by exposure times and received doses, as well as the individual factors such as age, illness, diet, or pregnancy. Certain populations like children and pregnant women are more vulnerable to poisoning. With this in mind, the fatal poisoning is embroiled worldwide in almost 4% of infant deaths and ranked 13th among teenagers (Branche et al., 2008). Additionally, the unintentional toxicity may range from nausea, vomiting, burns, and diarrhoea up to death. For instance, in 2000, around 300,000 deaths with about 23% in children up to 14 years old were reported, according to the World Health Organisation (WHO) estimates (WHO, 2004). Also, 0.5% of total deaths in England and Wales between 2000 and 2011 were due to poisoning with about 3000 cases annually (Handley and Flanagan, 2014). In a related vein, a recent study of the fatal poisoning in Brazil (2009–2013) has reported more than 50% fatalities occurred upon unintentional exposures to toxins, while the medications followed by the pesticides were regarded as the main fatal

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poisonous agents (Magalhães and Caldas, 2018).

Toxins are either natural; produced by living cells such as bacteria, fungi, snake venom … etc., or chemical agents. A variety of these toxic chemicals have been synthesized to be used as pesticides, herbicide, fungicide or even either medication as well as the environmental pollutants like heavy metals or that produced during the industrial processes. Meanwhile, the protective effects against toxic agents in different organs have been reported for several herbs, including curcuma (Hosseini and Hosseinzadeh, 2018), black cumin (Tavakkoli et al., 2017), milk thistle (Fanoudi et al., 2018), cinnamon (Dorri et al., 2018), barberry (Mohammadzadeh et al., 2017), and green tea (Rameshrad et al., 2017). This may shed the light on the importance of the herbal antidotes, which might be accentuated by the global market surge of herbal supplements consumption as driven by the evidence-based benefits offered by herbs against diverse illnesses and pathological conditions (GLobal-industry-analysts-Inc; Traditional medicine).

Herbal medicines are considered a fundamental source for novel pharmacological active lead compounds, where about 11% of basic medications in the 21st century are derived exclusively from plant origin (Veeresham, 2012). Accordingly, this augments further studies for the prophylactic and therapeutic effects of herbs or herbal combinations against toxic agents.

One of the herbs widely employed for many ailments is ginger. Several health benefits have been reported for ginger extracts and preparations since antiquity (Srinivasan, 2017) for inflammation (Ezzat et al., 2018), gastrointestinal disorders, diabetes (Zhu et al., 2018), cancer (de Lima et al., 2018), obesity and metabolic syndromes (Wang et al., 2017a). Ginger (*Zingiber officinale* Roscoe) belongs to family zingiberaceae and regarded as white ginger variety, which is one of the most commonly used spices in food and beverages. Other members of the ginger family include the red ginger (*Zingiber officinale* var. Rubra) and bitter ginger (*Zingiber zerumbet*). All are native to the Indian continent and southern Asia. Ginger (*Zingiber officinale* Roscoe) rhizome contains volatile oils (monoterpenes [β-phellandrene, (+)-camphene, cineole, geraniol, curcumene, citral, terpineol, and borneol] and sesquiterpenes [α-zingiberene (30–70%), β-sesquiphellandrene (15–20%), β-bisabolene (10–15%), (E-E)-α-farnesene, curcumene, zingiberol]). It also contains diterpenes and ginger glycolipids. The pungency of fresh ginger is attributed to the phenolic gingerols, with 6-gingerol as a major pungent principle, but the dried ginger pungency is due to shogaols derived from gingerols. Zingerone is a less pungent drying by-product of gingerol as well. Paradols (6-deoxy gingerol) and methyl paradols are also detected in the fresh ginger rhizomes (Ali et al., 2008).

Herein, we will evaluate the protective effects of ginger and its main components against a wide range of biological, chemical and radiation-induced toxicities, followed by the description of the antidotal mechanism of action.

2. Methods

Relevant publications have been retrieved from Web of Science, PubMed, Ovid, and Scopus databases on 30th March 2018. While search descriptors include “Protective, or ameliorative”, “toxin, toxicity, toxic, radiation, hepatotoxic, nephrotoxic, cardiotoxic, or neurotoxic” combined with, “ginger”, “gingerol”, and “shogaol” were searched. No time limitation was considered, and both *in-vitro,* as well as *in-vivo* studies were included in this review. The white and red ginger varieties together with the bitter ginger (*Zingiber zerumbet*) extracts, fractions or constituents were included, but the term ‘ginger’ is only indicated, without Latin name throughout this work to indicate *Zingiber officinale* Roscoe (white ginger).

The search strategy identifies 1586 publications from Ovid [825], PubMed [188], Web of Science [213], and Scopus [360] databases. Four hundreds and forty-seven references were excluded for duplication, and the remaining studies were evaluated with the exclusion of 980 references did not meet the search criteria of ginger antidotal effects against the three sources of noxiousness covered in this review. Moreover, 159 publications were included, and the ameliorative effects of ginger were classified into three main headings against natural, chemical, and radiation-induced toxicities.

3. Discussion

3.1. Effects of ginger on radiation-induced toxicity

The daily exposure to ultraviolet radiation of sunlight may be associated with skin cancer, aging, immunosuppression, cataracts, and macular degeneration as well. Moreover, many therapeutic and diagnostic applications require the exposure to gamma ionizing radiation. Herein, the protective effects of ginger and its main metabolites against UV and gamma radiation are detailed.

3.1.1. Solar ultraviolet radiation

One of the substantial burdens on the human skin is the solar ultraviolet (UV) radiation. It is composed of UVA irradiation (λ = 320–400 nm) which comprises approximately 95% of the solar UV irradiation alongside with the UVB (λ = 290–320 nm) and UVC (λ = 100–290 nm). Unlike the UVC, which is mostly screened out by the ozone layer, both UVA and UVB reach the earth's surface. Several deleterious effects can be elicited by the human skin exposure to UV irradiation. These adverse effects include DNA damage, oxidative stress, inflammation, gene mutation and immunosuppression with a result of premature skin aging, wrinkles and high skin cancer incidence (Gallagher and Lee, 2006; Hart and Norval, 2018; Savoye et al., 2018; Gies et al., 2018).

Ginger extracts and its components gingerol, shagaol, zingerone and zerumbone have been shown to effectively ameliorate the UV induced toxicity and reactive oxygen species (ROS) production in both *in-vivo* and *in-vitro* preclinical models (Yang et al., 2018; Thongrakard et al., 2014; Lee et al., 2018a; Kim et al., 2007; Guahk et al., 2010; Kamel et al., 2017). This skin protective effect may be linked to the increased antioxidant capacity accompanied by inclined nuclear translocation of nuclear factor erythroid2-related factor 2 (Nrf2) and elevated antioxidant response element (ARE) luciferase activity. The Nrf2/ARE signalling cascade contributed to the inclined production of Nrf2 dependent antioxidant genes such as heme oxygenase-1 (HO-1), NADPH quinone oxidoreductase 1, and γ-glutamyl cysteine ligase (γ -GCLC) genes with increased glutathione level (Yang et al., 2018) and upregulation of diverse antioxidant systems, including thioredoxin 1 (Thongrakard et al., 2014). Also, zingerone upregulated the declined proliferative genes (PCNA, and VEGF), and anti-senescence related genes (TERT, HDAC1, and DNMT1) in UVB-challenged (30 mJ/cm^2) keratinocytes stem cells (KSCs) with suppression of the UVB-induced cell cycle-arrest gene (p21). As illustrated in Fig. 1, zingerone's UVB protective effects may be mediated by p38, p42/44 mitogen-activated protein kinase (MAPK) inhibition (Lee et al., 2018a). Overall, the anti-inflammatory effect of ginger and its components (Lee et al., 2018a; Kim et al., 2007; Guahk et al., 2010) alongside with the anti-senescence, and the antioxidant effects have augmented its skin protective and anti-photoaging effect against UV radiation (Table 1).

3.1.2. Gamma radiation

Radiotherapy is a proven treatment for malignancies' control. At certain point of cancer treatment course, approximately 70% of patients receiving radiotherapy (Baliga et al., 2012). Human exposure to the ionizing radiation resulted in adverse hematopoietic, gastrointestinal and neurovascular side effects. These adverse effects augment the use of radioprotective agents especially the natural ones which elicited less toxic effects compared to the synthetic radioprotectors (Kamran et al., 2016). Ginger and its components possess anti-inflammatory and antioxidant effects, which play an important role in its radioprotective effect. For example, the gastrointestinal induced injuries in mice upon

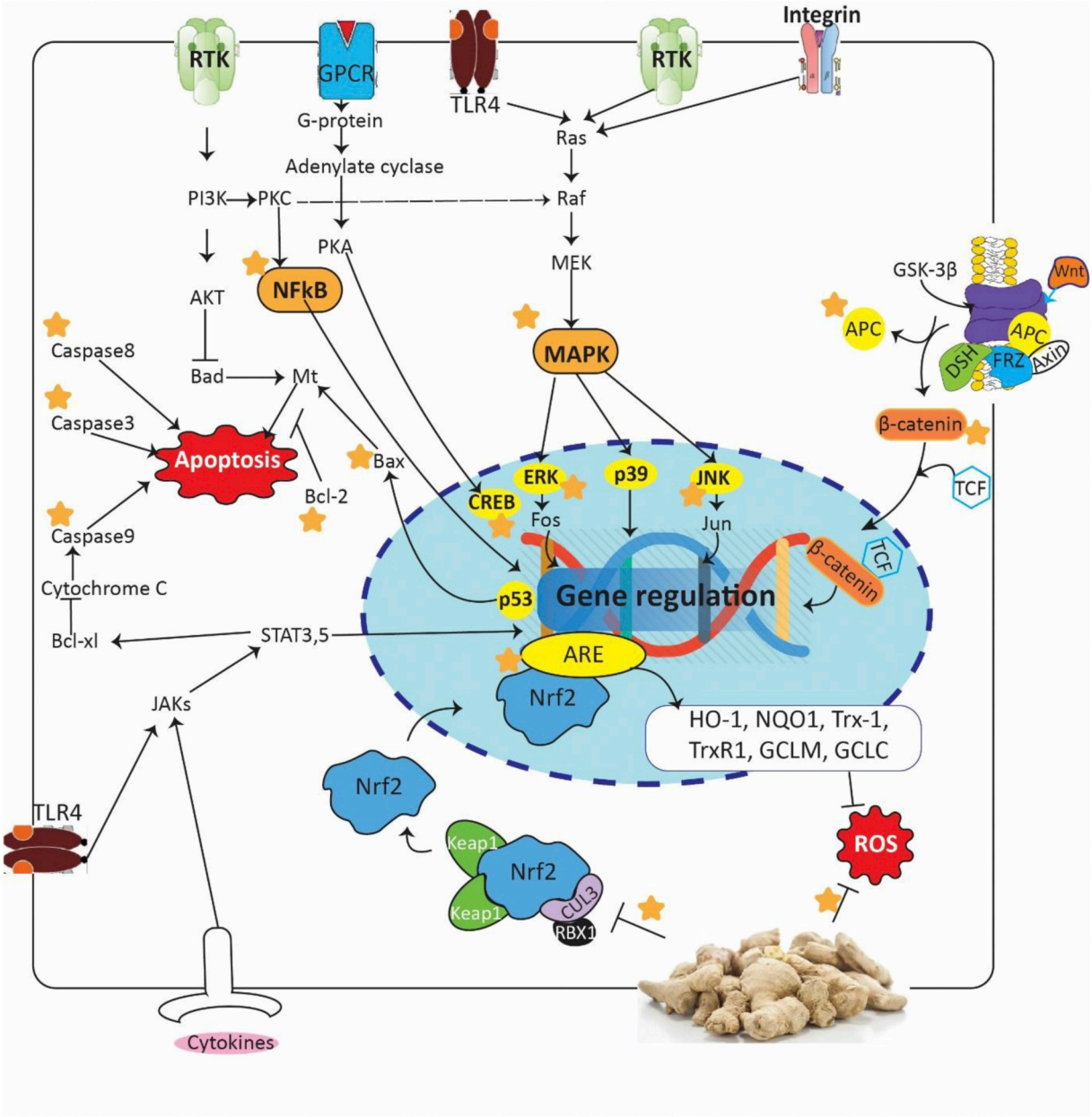

Fig. 1. Protective mechanisms and pathways signalling of ginger and its components
APC; Adenomatous polyposis coli, ARE; Antioxidant response element, ERK; extracellular signal-regulated kinases, CUL3; Cullin-3, GCLC; Glutamate-cysteine ligase catalytic, GCLM; Glutamate-cysteine ligase modifier, GPCR; G protein–coupled receptors, HO-1; heme oxygenase-2, JAKS; Janus kinases, JNK; c-Jun N-terminal kinases, Keap1; Kelch-like ECH-associated protein 1, MAPK; mitogen-activated protein kinase, NF-ƙB; nuclear factor kappa-light-chain-enhancer of activated B cells, NQO-1; NAD(P)H: quinone oxidoreductase 1, Nrf2; Nuclear translocation of nuclear factor erythroid2-related factor 2, RBX1; E3 ubiquitin ligase, ROS; reactive oxygen species, RTK; Receptor tyrosine kinases, STATS; Signal Transducer and Activator of Transcription proteins, TLR4; Toll-like receptor 4, Trx-1; Thioredoxin 1, TrxR-1; Thioredoxin reductase 1, Orange star (★); indicates the pathways affected by ginger's phytochemicals. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

abdomen gamma (γ)-irradiation (15 Gy) were alleviated by 6-shogaol with a reduction in bacterial translocation and endotoxin levels (Wang et al., 2017b). Also, the radiation protection was significantly achieved by using 20 mg/kg/day oral zingereone for five days and single 100 mg/kg intraperitoneal (i.p.) dehydrozingerone in mice before exposure to 10 Gy dose of γ-radiation. The lethal dose expected to kill half the mice in 30 days (LD50/30) inclined by 1.8 and 0.9 Gy, and the dose reduction factor (DRF) of 1.09 and 1.2 were reported for zingerone and dehydrozingerone, respectively (Rao et al., 2009; Parihar et al., 2007). Additionally, zingerone (25 mg/kg/day for 3 weeks) given by intragastric intubation ameliorated the γ radiation-induced cardiotoxicity (20 mg/kg) in rats upon single whole body exposure to 6 Gy on the 21st day of treatment. It recovered the cardiac histopathological abnormalities, and the biochemical indicators of cardiotoxicity (lactate dehydrogenase; LDH, cardiac Troponin-T; cTnT, creatine kinase MB isoenzyme; CK-MB, and B-natriuretic peptide; BNP). Also, it suppressed both inflammation, and oxidative stress markers (malonaldehyde; MDA, and myeloperoxide; MPO, respectively). Moreover, it down-regulated the overexpressed tumour necrosis factor alpha (TNF-α), cyclooxygenase-2 (COX-2), and the apoptotic caspase-3 as well. Remarkably, zingerone showed a selective protection to the normal cells against radiation when applied to tumour-bearing mice (Baliga et al., 2012). Furthermore, the ginger oleoresin pre-treatment reduced the cytotoxicity and ROS production in human mesenchymal stem cells

Table 1
Radioprotective effects of ginger and its constituents.

Radiation	Model	Constituents	Results	References
Ultraviolet radiation				
UVA	HaCaT cells and mice	Zerumbone	Decreased UVAinduced cytotoxicity, ROS production, and LDH release.	(Yang et al., 2018)
UVB	HaCaT cells	Ginger dichloromethane extract	Reduced the UV-induced caspase dependent cellular apoptosis and DNA damage with increased thioredoxin 1 expression.	(Thongrakard et al., 2014)
	KSCs	Zingerone	Inhibited the UVB-induced cytokines (IL-6, IL-1β, and TNF-α), and the p21 gene expression. Also, upregulated proliferation-related genes (PCNA, and VEGF) and anti-senescence-related genes (TERT, HDAC1, and DNMT1).	(Lee et al., 2018a)
	HaCaT cells and mice	6-gingerol	Inhibited the UV-induced COX-2 expression and NF-ƙB translocation.	(Kim et al., 2007)
	HaCaT cells and Mice	Aqueous ginger extract, gingerol, and shogaol	Inhibited the UVB-induced cytokines (IL-6, IL-8, IL-1β, and TNF-α).	(Guahk et al., 2010)
Solar irradiation	Mice	LCC of diosmin and ginger essential oils	Improved the sun protective, anti-wrinkling and anti-photo-aging effect of diosmin.	(Kamel et al., 2017)
Gamma radiation				
γ-radiation	HEK 293 cells	Zerumbone	Reduced cell apoptosis and DNA damage by activating Keap1/Nrf2/ARE pathway.	(Tang et al., 2011)
	IEC-6 cells and Mice	6-shogaol	Improved animal survival and intestinal function after abdomen irradiation. Curtailed the induced pro-inflammatory cytokines (INF−-γ, TNF-α, and iNos mRNA).	(Wang et al., 2017b)
	hMSCs cells	Ginger oleoresin	Reduced the cytotoxicity, ROS production and DNA strands break *via* Nrf2 activation.	(Ji et al., 2017)
	Mice	Ginger methanolic extract	Elevated the GSH, GPx and declined the MDA, IL-1β, IL-6, TNF-α, PLA2 levels.	(Abd El-Salam and Hassan, 2017)
	Mice	Ginger essential oil	Improved the haematological, immunological parameters and antioxidant enzymes levels (SOD, CAT and GPx). LD50/30 increased by 3.02 Gy (DRF = 1.42).	(Jeena et al., 2016)
	HepG2 cells	6-gingerol	Prevented the cytotoxicity and GSH depletion with declined expression of both p53 and Bax and increased Bcl-2.	(Chung et al., 2015)
	Rats	Ginger hydro-alcoholic extract	Blocked the saccharin avoidance response.	(Haksar et al., 2006; Sharma et al., 2005)
	Mice	Ginger hydro-alcoholic extract	Reduced gastrointestinal and bone marrow-related mortalities, with significant lipid peroxidation reduction and GSH level elevation.	(Jagetia et al., 2003, 2004)
	Rats	Zingerone	Ameliorated the induced biochemical indices (LDH, cTnT, CK-MB, and BNP). Reduced the TNF-α, COX-2, caspase3 expression with increased expression of the declined antioxidant defences (SOD, CAT, and GSH).	(Soliman et al., 2018)
	Mice	Zingerone	Reduced mortality and lipid peroxidation with increased antioxidant parameters (GST, GSH, CAT and SOD), and normalised histological and hematopoietic parameters. LD50/30 increased by 1.8 Gy (DRF = 1.2).	(Rao et al., 2009)
	Mice	Dehydrozingerone	Increased antioxidant parameters (SOD, GST and GSH) and normalised the hematopoietic parameters with LD50/30 increased by 0.9 Gy (DRF = 1.09).	(Parihar et al., 2007)

ARE; Antioxidant response element, BNP; B-natriuretic peptide, CAT; catalase, cTnT; cardiac troponin-T, CK-MB; creating kinase MB isoenzyme, COX; cyclooxygenase, DNMT1; DNA cytosine-5 methyltransferase1, DRF; dose reduction factor, GPx; Glutathione peroxidase, GSH; Glutathione, GST; Glutathione-s-transferase, HDAC1; histone deacetylase 1, HaCaT; human Keratinocyte cells, hMSCs; human mesenchymal stem cells, IL; interleukin, INF; interferon, KSCs; keratinocyte stem cells, LCC; lipoid colloidal carrier, LDH; Lactate dehydrogenase, LD50/30; dose expected to kill half of the exposed population within 30 days, MDA; malonaldehyde, Nrf2; Nuclear translocation of nuclear factor erythroid2-related factor 2, ROS; Reactive oxygen species, PLA2; Phospholipase A2, PCNA; proliferating cell nuclear antigen, SOD; superoxide dismutase, TERT; telomerase reverse transcriptase, TNF-α; tumour necrosis factor-α, UVA; ultraviolet A, VEGF; vascular endothelial growth factor.

exposed to 4 Gy γ-rays. Coupled with, the Nrf2 target genes activation, which encodes for the cytoprotective proteins such as intracellular redox balancing and phase II detoxifying enzyme (Ji et al., 2017). Both HO-1 and NQQ-1 proteins' upregulation was also reported by 5–20 μM of zerumbone pre-treatment, which significantly protected the HEK 293 cell from 4 Gy γ-radiation-induced death in a dose dependent manner (Tang et al., 2011). Equally important, zerumbone was not only reported for its normal cell line's protective potentiality but also, it sensitized the prostatic cancer cell lines to the ionizing radiation (Chiang et al., 2018). The pre-treatment of 5 μM 6-gingerol reduced the HepG2 cells' death upon exposure to 5 Gy γ-radiation. 6-gingerol inclined the levels of glutathione (GSH) and the anti-apoptotic protein; B-cell lymphoma-2 (Bcl-2) and declined the expression of the γ-radiation-induced pro-apoptotic protein p53 and Bcl-2-associated X (Bax) (Chung et al., 2015). The oral administration of 100 and 500 mg/kg/day oleoresin of ginger protected irradiated mice (6 Gy) from DNA damage and chromosomal aberrations. In this case, the LD50/30 was increased by 3.02 Gy and DRF 1.42 (Ji et al., 2017). The radioprotective effect was also reported for the hydro-alcoholic extract of ginger in γ-irradiated mice both orally (Jagetia et al., 2004) and intraperitoneally (Jagetia et al., 2003). While, 37.5% and 33% survival rates alongside with a DRF of 1.2 and 1.15 were respectively, indicated for the oral dose of 250 mg/kg/day and intraperitoneal dose of 10 mg/kg/day for five days before exposure to 10 Gy γ-radiation. Additionally, the hydro-alcoholic extract of ginger offered a behavioural radioprotection at a dose of 200 and 250 mg/kg for male and female rats, respectively emphasizing its potentiality to block γ radiation-induced conditioned taste aversion (CTA) (Haksar et al., 2006; Sharma et al., 2005). These preclinical studies of ginger and its components reinforced the promising radioprotective effect against hematopoietic, intestinal and behavioural injuries through anti-inflammatory, antioxidant and anticlastogenic effects. Moreover, the proliferative and anti-senescence related genes were also regulated (Table 1).

3.2. Effects of ginger on natural-induced toxicity

The ameliorative effect of ginger and its components against natural-induced toxicities such as bacterial and fungal toxins in multiple organ toxicity in various preclinical models is reported and evaluated here.

3.2.1. Mycotoxins

Mycotoxins are toxic secondary metabolites produced by a series of filamentous fungi as *Fusarium*, *Asperigillus* and *Penicillium*. It has been reported not only for its carcinogenic, teratogenic, hepato- and nephrotoxic adverse effects, but also for the economic losses upon its occurrence in food products and feed chain (Luo et al., 2018). Aflatoxins, ochratoxins, patulin, fumonisins, zearalenone occur among the common mycotoxins types in foods.

3.2.1.1. Aflatoxins. Aflatoxins are regarded as precarious food contaminants. These sorts of mycotoxins are mainly produced by *Asperigilus flavus* and *Aspergilus parasiticus*. Of all aflatoxins kinds, aflatoxin B_1 (AFB_1) is recognised as the most toxic and widely distributed in a variety of foods, including sorghum, rice, milk, oils and maize. The intoxication with AFB_1 may result in hepatotoxicity, carcinogenesis, mutagenesis and epigenetic alteration (Dai et al., 2017). The bio-activation of AFB_1 by the cytochrome P450 produces AFB_1–exo-8 and 9-epoxide forms, which in turn increase the ROS production. Ginger extract was reported to inhibit the AFB_1-induced cytotoxicity and hepatotoxicity (Table 2) in both *in-vivo* and *in-vitro* models (Vipin et al., 2017). In brief, the phenolic-rich extracts of ginger had effectively protected the HepG2 cell line from AFB_1-induced cytotoxicity, which is mediated by the oxidative stress and DNA damage. This cytoprotective effect is mainly due to the antioxidant activity of ginger phenolics (Vipin et al., 2017). Furthermore, ginger ameliorated the AFB_1-induced hepatotoxicity (200 mg/kg/day for 28 days) in rats. The serum enzymes such as aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and LDH are released into the plasma upon liver damage by AFB_1. But, the oral ginger administration (100, 250 mg/kg/day for 28 days) improved the hepatocytes physiological integrity and normalised the serum levels of these liver markers significantly. Moreover, the phenolic rich ginger extract had declined the hepatic lipid peroxidation marker; MDA and increased the hepatic antioxidants levels GSH, glutathione S-transferase (GST), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx). These antioxidant defence systems may be utilised for AFB_1 detoxification and liver protection from injury *via* ROS neutralisation and upregulation of Nrf2/HO-1 pathway (Vipin et al., 2017).

3.2.1.2. Patulin. Patulin is a common mycotoxin contaminant in fruits and fruits-based products like apple, pears, grapes, peaches, and berries. It is produced by many species of *Penicillium*, *Aspergillus* and *Byssochlamys*. It was reported for its carcinogenic, mutagenic and genotoxic properties. The patulin-induced DNA strand breaks and micronuclei formation in HepG2 cell lines were significantly declined by pre-treatment with 10 μM of 6-gingerol. Furthermore, 6-gingerol suppressed the patulin-induced ROS production, 8-hydroxydeoxyguanosine (8-OHdG) and GSH depletion (Yang et al., 2011).

3.2.2. Bacterial toxins

3.2.2.1. Lipopolysaccharide. Bacterial lipopolysaccharide (LPS) is found in the outer membrane of gram-negative bacteria. It elicits a systematic inflammatory response, sepsis and multiple organ dysfunctions upon infection.

3.2.2.1.1. Lung-protective effects. The LPS-induced acute lung injury in mouse models was ameliorated by 6-shogaol (10, 20, or 40 mg/kg, i.p.), zingerone (10, 20, or 40 mg/kg) or zerumbone (0.1, 1, or 10 mmoL/kg, i.p.), while the pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 were suppressed (Ho et al., 2017; Wang et al., 2016a; Xie et al., 2014). Moreover, zerumbone suppressed the inducible nitric oxide synthase (iNOS) and COX-2 expression and inhibited the activation of both the nuclear factor-kappa B (NF-κB) and Protein kinase B (Akt) pathways (Ho et al., 2017). Similarly, the Zingerone inhibited the MAPK and NF-κB pathways by hindering the phosphorylation of extracellular-signal-regulated kinase (ERK), p38/MAPK and IκBα, NF-κB/P65 (Xie et al., 2014). Additionally, 6-shogaol was reported to fit in the NF-ƙB's active site *in-silico* (Wang et al., 2016a). Additionally, both 6-shogaol and zingerone significantly improved the histopathological lung conditions in a dose-dependent manner and attenuated the LPS-induced neutrophils and macrophages in the bronchoalveolar lavage fluid (BALF) with a declined MPO activity, which serves as an important marker of neutrophil influx into the tissues (Wang et al., 2016a; Xie et al., 2014). Therefore, the lung protective effect of ginger's phytochemicals against LPS-induced acute lung injury might be attributed to the anti-inflammatory activity *via* the attenuation of the NF-κB pathway.

3.2.2.1.2. Hepatoprotective effects. The LPS-induced hepatic injuries in mice were attenuated by zingerone (0.18, 0.36 or 0.72 mg/kg), which was intravenously (i.v.) administered 12 h after LPS (15 mg/kg, i.p). The zingerone administration had reduced the mortality rate in a dose-dependent manner. Also, zingerone significantly declined not only the serum levels of the ALT and AST hepatic markers, but also the inflammatory cytokines (TNF-α, IL-6 and interferon beta; IFN-β). The inhibition of the LPS-induced Toll-like receptor-4(TLR-4) signalling and the attenuation of the myeloid differentiation primary response-88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF) dependent signalling pathways of the TLR system were reported. In addition, the NF-κB and MAPKs activation were also inhibited. These pathways were found to be activated in hepatic failure by LPS and significantly inhibited by zingerone (Lee et al.,

Table 2
Hepatoprotective effects of ginger and its constituents against chemical or natural toxins.

Toxin	Model	Constituents	Results	References
LPS	Mice	Zingerone	Decreased the mortality, ALT, AST, TNF-α, IL-6, IFN-β, TLR4 expression and inhibited the MyD88 signalling.	(Lee et al., 2018b)
	Mice	Aqueous ginger extract	Decreased the expression of IFN-γ, IL-6 and iNOS with inhibition of the NF-*k* B activation.	(Choi et al., 2013)
AFB_1	HepG2 And rats	Phenolic rich ginger extract	-Reduced the cytotoxicity on HepG2, declined ROS production and DNA strand break. -Reduced the ALT, AST, ALP and LDH serum levels -Upregulated Nrf2/HO-1 pathway, as well as GSH, GST, CAT, SOD and GPx levels in liver.	(Vipin et al., 2017)
Mercury	Rats	Ginger aqueous extract and 6-gingerol	Reversed the toxic effect on liver function parameters (ALT, AST, ALP, LDH, albumin, bilirubin, protein, GGT, TG and C) and increased antioxidant parameters (GSH, SOD, CAT, GR, GST and GPx).	(Joshi et al., 2017)
Arsenic	Mice Hepatocyte pancreatic β-cells	6-Gingerol	Reduced the cell death and reversed the arsenic toxic effects on oxidation defence systems (CAT, SOD, GPx, GSH) , and inflammation (TNF-α and IL-6) parameters.	(Chakraborty et al., 2012)
	Calves	Ginger powder	Reduced the induced liver markers (serum ALT and AST) with increased antioxidant parameters (SOD and CAT).	(Biswas et al., 2017)
Aluminium	Rats	Gingerol	Reversed the perturbations in the, liver histoarchitecture, biochemical parameters (ALT, AST, protein, TG and TC), antioxidant parameters; GSH and lipid peroxidation in liver homogenate.	(Shrivastava, 2015)
Iron	Rats	70% Methanolic ginger extract	Normalised both histopathological and liver function parameters (AST, ALT, ALP, LDH, bilirubin, protein, albumin. TG, C).	(Gholampour et al., 2017)
Cadmium	Rats	Garlic, ginger and nutmeg mixture aqueous extract	Decreased the liver function parameters (ALT, AST, TC and bilirubin).	(Ugwuja et al., 2016)
	Rabbits	Ginger powder	Decreased the induced genes (apoptotic; Caspase3, proliferative; MKI67 and proto-oncogene; C-fos) and increased the expression of GST and the anti-apoptotic; Bcl2 in the hepatocytes.	(Baiomy and Mansour, 2016)
Lead	Rats	Aqueous *Z. officinale* extract	Decreased the ALT, AST, and increased GSH, SOD, CAT, GST and GPx levels.	(Mohamed et al., 2016)
Carbendazim	Rats	6-Gingerol-Rich fraction of *Z. officinale*	Decreased the ALT, AST, bilirubin, H_2O_2 and MDA levels and increased the GSH, SOD, CAT, GST and GPx levels in liver. Alleviated toxic histopathological effect.	(Salihu et al., 2016)
Phosphamidon	Rats	Ginger polyphenol-rich ethanolic extract	Reversed the phosphamidon-dysregulated levels of MDA, AST, ALT, ALP, CAT, GSH, GST, SOD, GPx, and, apoptotic markers.	(Mukherjee et al., 2015)
Malathion	Rats	Ginger and Zinc chloride	Ameliorated the histopathological liver changes such as oedema, congestion, and leucocytic infiltrations.	(Baiomy et al., 2015)
Doxorubicin	Rats	50% Ethanolic or aqueous ginger extract	Ameliorated the histopathological toxicity parameters of doxorubicin. Reversed the perturbations in (ALT, AST, MDA and SOD).	(Ahmed, 2013; Sakr et al., 2011)
Acetaminophen	Rats	Ginger powder	Reversed the perturbations in the serum biochemical, histopathological and lipid peroxidation parameters.	(Abdel-Azeem et al., 2013)
	Mice/Rats	6-Gingerol, ethanolic, essential oil extracts of ginger	Reversed the perturbations in the hepatic histo-architecture, serum biochemical hepatic markers (ALT, AST, LDH, SDH, ALP and GDH), and lipid peroxidation. Inclined the antioxidant parameters (SOD, CAT, GR, GST, GPx, and GSH) as well.	(Sabina et al., 2011; Ajith et al., 2007a; Yemitan and Izegbu, 2006)
Diclofenac	Rats	6-Shogaol and 6-gingerol	Decreased the levels of biochemical parameter (ALT, AST, ALP, bilirubin)in serum and MDA in liver homogenate.	(Alqasoumi et al., 2011)
Atorvastatin	Rats	50% Ethanolic ginger extract	Reversed the perturbations in the liver histoarchitecture, the serum biochemical indices (ALT, and AST), lipid peroxidation (MDA), and antioxidant (SOD, CAT) parameters.	(Heeba and Abd-Elghany, 2010)
Estradiol valerate	Rats	6-Gingerol	Decreased the COX-2 expression alongside with, the restoration of biochemical hepatic (ALT, AST, ALP) and antioxidant (SOD, CAT, GPx) parameters.	(Pournaderi et al., 2017)
Ethanol	Rats	Ginger *n*-hexane extract	Decreased the levels of serum ALT, AST, TG, TC and hepatic MDA, where GSH, GST and SOD normal levels were restored.	(Nwozo et al., 2014)
	Rats	Ginger powder	Reversed the ethanol toxic effect on the level of MDA and antioxidant parameters (SOD, CAT, GSH, GPx).	(Mallikarjuna et al., 2008)
	Mice	Ginger essential oils	Restored the histopathological, serum biochemical and antioxidant parameters alongside with the perturbed metabolites levels of D-glucurono-6,3-lactone, glycerol-3-phosphate, pyruvic acid, lithocholic acid, 2-pyrocatechuic acid, and prostaglandin E_1.	(Liu et al., 2013)
	Mice	Aqueous ginger extract	Ameliorated the perturbations in the biochemical (ALT, AST, GGT and others), oxidative stress (NO and MDA) and antioxidant (GPx, and GST) parameters.	(Shati and Elsaid, 2009)
Hydrogen peroxide	Mice hepatocyte	Aqueous ginger extract	Reduced the cell apoptosis, intracellular ROS, and the liver enzymes levels (ALT, AST, LDH) *via* the overexpression of HO-1 and HSP72.	(Oh et al., 2012)

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Table 2 (*continued*)

Toxin	Model	Constituents	Results	References
CCl_4	Rats	Alcoholic ginger extract	Decreased the perturbations in the biochemical (ALT, AST, ALP, GGT, bilirubin, C, And TG) and histopathological parameters.	(Jaffat et al., 2016; Atta et al., 2010)
	Rats	Ginger, rosemary extracts and its combination	Alleviated the toxic effects on the biochemical indices (ALT, AST and ALP, TC, TG, CYP, globulin, bilirubin, and MDA) upregulated GPx, GST, SOD and CAT with improved hepatocyte histo-architecture.	(Essawy et al., 2018)
	Rats	*Z. officinale* in corn oil extract	Decreased the ALT, AST, TNF-α and downregulated NF-ƙB/IƙB and TGF-β1/Smad3 pathways.	(Hasan et al., 2016)
	Rats	Zingerone	Decreased the induced levels of ALT, AST, MDA, TNF-α, IL-1β, COX-2, and iNOS, as well as, downregulated the NF-ƙB expression.	(Cheong et al., 2016)
	Rats	Ginger and/or curcumin	Decreased the induced levels of ALT, AST, and MDA, as well as elevated the declined levels of SOD, CAT, GSH.	(Abd-Allah et al., 2016b)
	Rats	Ethanolic ginger extract	Reversed the perturbations in the hepatic histo-architecture, and serum biochemical hepatic markers (ALT, AST, LDH, SDH, ALP and GDH).	(Yemitan and Izegbu, 2006)
Dimethyl- nitrosamine	Rats	Zingerone	Reduced the elicited hydroxyproline, hepatic stellate cell activation, and phosphorylation of extracellular signal-regulated kinases (c-Jun NH2-terminal kinase, and MAPKs) as well as the hepatic biochemical markers (ALT, and AST).	(Cheong et al., 2016)
Diethyl-nitrosamine and CCl_4	Rats	90% Ethanolic ginger extract	Normalised the induced serum hepatic tumour markers (AFP and CEA), the hepatic hydroxyproline content, and the hepatic growth factors (VEGF, TGF-β1, and FGF). Increased the declined hepatic level of endostatin and metallothonein.	(Mansour et al., 2010)
Bromobenzene	Rats	90% Ethanolic ginger extract	Alleviated the toxic effect on the biochemical (AST, ALT, bilirubin and protein), oxidative stress (NO, and MDA) and antioxidant (SOD, GPx, and GSH) parameters.	(El-Sharaky et al., 2009)
Paraben	Mice	Aqueous ginger extract	Decreased the level of MDA and increased the antioxidant parameters (SOD, GPx, CAT, ascorbic acid and GSH). Ameliorated cholesterol, carbohydrate and all protein types levels in liver.	(Asnani and Verma, 2009; Verma and Asnani, 2007)
Thioacetamide	Rats	Ginger ethanol extract	Ameliorated the histopathological, biochemical (Albumin, bilirubin, globulin, protein, MDA, ALP, AST, ALT and GGT) and antioxidant (SOD) parameters.	(Abdulaziz Bardi et al., 2013)
Chromate	Rats	Ginger powder 2%	Recovered the biochemical parameters (ALT, AST, bilirubin, TC and TG), and GSH.	(Krim et al., 2013)
Streptozotocin	Rats	Free and bound ginger polyphenols	Reversed the perturbed biochemical (ALT, AST, albumin and bilirubin) and antioxidant (SOD, CAT, GPx, GSH) parameters.	(Kazeem et al., 2013)
	Mice	95% Ethanolic ginger extract	Increased the declined antioxidant defences (SOD, CAT, GPx, GR, GSH) with declined MDA level in liver.	(Ramakrishna et al., 2015)

AFP; α-fetoprotein, AFB1; Aflatoxin B1, ALP; Alkaline phosphatase, ALT; alanine aminotransferase, AST; aspartate aminotransferase, CAT; catalase, CCl_4; Carbon tetra chloride, CEA; carcinoembryonic antigen, COX-2; cyclooxygenase-2, CYP; cytochrome P450, FGF; basic fibroblast growth factor, GDH; glutamate dehydrogenase, GGT; gamma glutamyl transferase, GSH; glutathione, GST; Glutathione S-transferase, GPx; Glutathione peroxidase, GR; glutathione reductase, HO-1; heme oxygenase-1, HSP; heat shock protein, IL; interleukin, INF; interferon, LDH; lactate dehydrogenase, LPS; Lipopolysaccharide, MDA; malonaldehyde, MAPKs; mitogen-activated protein kinases, MyD88; myeloid differentiation primary response gene 88, NF-ƙB; nuclear factor-kappa B, NO; nitric oxide, ROS; Reactive oxygen species, SDH; sorbitol dehydrogenase, SOD; superoxide dismutase, TG; triglyceride, TGF-β1; transforming growth factor-beta1, TLR; toll-like receptor, TNF-α; tumour necrosis factor- α, VEGF; vascular endothelial growth factor.

Table 3
Nephroprotective effects of ginger and its constituents against chemical or natural toxins.

Toxin	Model	Constituents	Results	References
Nicotine	Rats	Ginger selenium nanoparticles with or without low dose of ionising radiation	Reduced MDA, serum inflammatory markers (TNF-α and VCAM-1) and both COX-2 and caspase-3 expression. Increased the antioxidant parameters (GSH, GST, and GPx). Restored the biochemical indices (Cr, urea, sodium and potassium).	(Zahran et al., 2017)
Ethanol	Rats	70% ethanolic ginger extract	Reversed the renal histopathological parameters and the biochemical indices (urea, Cr, Crc, cystatin, C/Cr ratio, and 8-OHdG).	(Shirpoor et al., 2016)
	Rats	95% ethanolic ginger extract	Significantly increased the renal GSH, GST, CAT, SOD, GR and GPx with improved the histo-architecture of the kidney.	(Ramudu et al., 2011a; Shanmugam et al., 2010)
Mercury	Rats	Ginger aqueous extract and 6-gingerol	Reduced the elevated levels of kidney function parameters in plasma (urea, Cr, uric acid and BUN) and increased the level of antioxidant parameters (GSH, SOD, CAT, GR, Gpx and GST) in kidney tissue. Improved the renal histo-architecture.	(Joshi et al., 2017)
Arsenic	Calves	Ginger powder	Reduced the induced kidney markers (serum BUN and Cr) with increased antioxidant parameters (SOD and CAT).	(Biswas et al., 2017)
Iron	Rats	70% Methanolic ginger extract	Reversed the kidney function parameters in urine (Cr, Crc, FENa, and UN) and the histopathology of the kidney.	(Gholampour et al., 2017)
Cadmium	Rats	Garlic, ginger and nutmeg mixture	Decreased the toxic effect on kidney function parameters (uric acid, urea and Cr) in serum.	(Ugwuja et al., 2016)
	Rats	Ginger powder	Reversed the cadmium-induced effect on the kidney weight and the levels of ACP, ALP, PAP and MDA.	(Onwuka et al., 2011)
	Rabbits	Ginger powder	Decreased the overexpressed genes (apoptotic; Caspase3, proliferative; MKI67 and proto-oncogene and C-fos) and increased the expression of GST and the anti-apoptotic; Bcl2 in the tubular epithelial cells.	(Baiomy and Mansour, 2016)
Lead	Rats	Ethanolic ginger extract	Reversed the lead-induced reduction of GSH, GST, CAT, and GPx levels in the kidney and restored the normal histoarchitecture.	(Reddy et al., 2014)
Aluminium	Rats	Gingerol	Improved the kidney histo-architecture, biochemical variables (urea and creatinine in serum), and GSH.	(Shrivastava, 2015)
Carbendazim	Rats	6-Gingerol-Rich Fraction of *Z. officinale*	Decreased the urea and Cr plasma levels, and kidney oxidation parameters (H_2O_2 and MDA), where increased the GSH, SOD, CAT, GST and GPx levels in the kidney. Improved histo-architecture of kidney.	(Salihu et al., 2016)
Malathion	Rats	Ginger and Zinc chloride	Improved cloudy swelling in the kidney tissue and hydropic degeneration of the renal tubules.	(Baiomy et al., 2015)
Paraben	Mice	Aqueous ginger extract	Ameliorated the toxic effect on the cholesterol, carbohydrate and all protein types levels in kidney.	(Verma and Asnani, 2007)
Chromate	Rats	Ginger powder	Decreased the induced biochemical parameters (TG, TC, urea, Cr and uric acid) and increased the GSH level in the kidney.	(Krim et al., 2013)
Cisplatin	Rats	Aqueous ginger extract	Reversed the induced histopathological damage, biochemical renal markers (BUN, and Cr), and pro-apoptotic Bax protein.	(Ali et al., 2015)
	Rats	Zingerone	Reduced the histopathological renal damage, the biochemical renal indices (BUN, LDH, and Cr) in serum, and renal MDA level, while increased the antioxidant parameters (GSH,SOD, CAT and GPx) in kidney tissue.	(Alibakhshi et al., 2018)
	Mice	70% Ethanolic ginger extract	Reduced the level of the biochemical renal parameters in serum (Urea and Cr), and renal MDA level with increased antioxidant parameters (GSH, SOD, CAT, and GPx) in kidney tissue.	(Ajith et al., 2007b)
Doxorubicin	Rats	50% Ethanolic ginger extract	Decreased MDA, and the induced renal failure markers (urea and Cr in serum), with increased antioxidant parameters (GSH, GST, GPx, SOD, and CAT).	(Ajith et al., 2008)
Gentamycin	Rats	6-Gingerol	Normalised the BUN, serum Cr, TBARS, HSP47 and Caspase 3 and GSH levels with improved histological parameters.	(Hegazy et al., 2016)
	Rats	Gingerol rich fraction	Decreased the gentamycin-induced level of MDA, nitrites in kidney tissue with downregulated gene expression of TNF-α, IL-1β, IL-2 and INF-γ. Reversed the perturbation in the biochemical kidney parameters (Serum Cr, Crc, urea, urinary protein and uric acid) and increased antioxidant parameters (GSH and SOD).	(Rodrigues et al., 2014)
	Rats	Ginger powder	Decreased the renal damage biomarkers in plasma (Cr, urea, BUN and uric acid) and MDA, while increased the antioxidant parameters (CAT, GST, GPx, SOD and GSH).	(Ademiluyi et al., 2012)
	Rats	80% Ethanolic ginger extract	Prevented the gentamycin-induced renal tubular degeneration.	(Nasri et al., 2013)
CCl_4	Mice	Zingerone	Decreased the induced levels of TNF-α, IL-1β, IL-2 and the apoptotic caspase-3 and caspase-9. Reversed the perturbations in the biochemical kidney indices (Cr, and BUN) in serum, while increased antioxidant parameters (GSH, GST, CAT, and SOD) in the kidney tissue.	(Safhi, 2018)
Streptozotocin	Mice	80% Ethanolic ginger extract	Declined the induced parameters in kidney tissue (caspase-3, cytochrome *c*, TNF- α, IL-1β, and IL-6), inclined antioxidant defence (GSH, CAT, and SOD). Ameliorated the degenerative histopathological parameters of kidney tissue.	(Al Hroob et al., 2018)
	Mice	95% Ethanolic ginger extract	Reversed the altered mitochondrial enzymes in the kidney tissue (G6PD, SDH, GDH, MDH, and LDH) and histological parameters.	(Ramudu et al., 2011b)

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Table 3 (*continued*)

Toxin	Model	Constituents	Results	References
Chronic fructose consumption	Rats	Ethanolic ginger extract	Decreased the overexpressed renal pro-inflammatory markers (TNF-α, IL-6, TGF-β, PAI-1, MCP1, CCR-2, CD68 and F4/80). Restored uPA/PAI-1 ratio, the biochemical (plasma TG, TC, BUN and Cr) and histopathological parameters.	(Yang et al., 2014)

8-OHdG; 8-Oxo-2′-deoxyguanosine, ALP; alkaline phosphatase, ACP; acid phosphatase, BUN; blood urea nitrogen, CAT; catalase, CCR-2; chemokine (−C-C motif) receptor-2, CD68; macrophage accumulation marker, Cr; creatinine, CrC; creatinine clearance, FENa; fractional excretion of sodium, F4/80; macrophage accumulation marker, G6PD; glucose-6-phosphate dehydrogenase, GDH; glutamate dehydrogenase, GPx; Glutathione peroxidase, GR; glutathione reductase, GSH; glutathione, GST; Glutathione S-transferase, IL; interleukin, INF; interferon, LPO; lipid peroxidation, MCP-1; monocyte chemoattractant protein-1, MDH; malate dehydrogenase, PAI-1; plasminogen activator inhibitor, PAP; prostatic acid phosphatase, SDH; succinate dehydrogenase, SOD; superoxide dismutase, TBARS; thiobarbituric acid reactive substances, TGF-β; transformer growth factor beta, TNF-α; tissue necrosis factor alpha, UN; urea nitrogen, uPA; urokinase-type plasminogen activator, VCAM-1; vascular cell adhesion molecule 1.

2018b). On the other hand, oral administration of the aqueous ginger extract (100 or 1000 mg/kg/day for three days) reduced the LPS (35 mg/kg, i.p.) induced pathological changes in mice's liver with a declined expression of inflammatory cytokines (INF-γ and IL-6) *via* the inhibition of the NF-κB activation with subsequent decreased expression of iNOS and COX-2 (Choi et al., 2013). Finally, the aforementioned hepatoprotective effects (Table 2) may be attributed to the inhibition of the TLR mediated inflammatory pathway with attenuated NF-κB and MAPKs activation (Lee et al., 2018b; Choi et al., 2013).

3.2.2.1.3. Neuroprotective effects. Ginger and gingerol-related compounds showed neuroprotective activity against LPS in BV2 microglia cell model (Table 4). Particularly, 6-shogaol, at a concentration of 20 μM inhibited the induced nitric oxide (NO), prostaglandin-E_2 (PGE_2), COX-2, pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and their mRNA levels *via* blocking both the NF-ƙB and MAPKs activation (Ho et al., 2013; Ha et al., 2012). But, the neuroprotective effect of fresh ginger was mainly correlated to 10-gingerol (Ho et al., 2013). Furthermore, significant neuroprotection of 6-shogaol was reported in transient global ischemic rats *via* the microglia inhibition (Ha et al., 2012). Notably, 6-shogaol (10 μM) showed a neuroprotective effect in LPS- treated astrocytes *via* the up-regulation of brain-derived neurotrophic factor (BDNF) (Shim et al., 2012).

3.2.2.2. Streptozotocin. Streptozotocin (STZ) is an alkylating antineoplastic agent, that was discovered in *Streptomyces achromogenes* strain in soil. Due to its toxicity to the beta cells of pancreatic islets, STZ is usually used to induce diabetes in animal models and study the diabetic complications in liver, kidney, brain and eye. Also, it is approved for pancreatic islets cancer (Kouvaraki et al., 2004) under the generic name of Zanosar®. Accordingly, the protective effects of ginger against STZ-induced multi-organ toxicity will be discussed later under the chemotherapeutic agents section (3.3.3.4).

3.3. Effects of ginger on chemical-induced toxicity

Ginger's armoury of phytochemicals protected the liver (Table 2), kidney (Table 3), brain (Table 4), gastrointestinal tract (Table 5), heart (Table 6) and reproductive organs (Table 7) against chemical toxicity. Ameliorative potentiality of ginger versus the chemical toxic agents such as heavy metals, pesticides, pollutants, drugs and recreational drugs will be reviewed in the following sections.

3.3.1. Heavy metals-toxicities

3.3.1.1. Mercury. Renal, hepatic, nervous, hematologic and reproductive disorders may be elicited upon environmental or occupational exposure to mercury (Hg) (Bernhoft, 2012). Hepatorenal toxicity was reported by acute intoxication of mercuric chloride (12 μM/kg, i.p., once) in rats, alongside with oxidative stress and declined oxidation defence systems (Tables 2 and 3). These detrimental effects on the liver and kidney's biochemical parameters and histoarchitecture were reversed by oral administration of the ginger aqueous extract (125 mg/kg) or 6-gingerol (50 mg/kg) for three days after 24 h of mercury exposure (Joshi et al., 2017). This may represent a worthwhile candidate against acute mercury poisoning.

3.3.1.2. Arsenic. Arsenic (As) causes acute and chronic toxicities to many organs of humans or animals such as dermal, renal, hepatic, nervous, endocrine and cardiovascular systems (Abdul et al., 2015; Sattar et al., 2016). It has been classified as a class I carcinogen (Hettick et al., 2015). However, ginger showed a protective potentiality against arsenic induced toxicity both *in-vivo* and *in-vitro* (Tables 2 and 3). Chronic hepatorenal toxicity of orally administered sodium arsenite (1 mg/kg) in calves for 90 days was ameliorated by oral doses of ginger powder (10 mg/kg) starting from 46th day. The As adverse effects on the biochemical, haematological and antioxidant parameters were reversed with increased arsenic excretion in faeces and urine and subsequently reduced As levels in the plasma and hair (Biswas et al., 2017). Furthermore, 50 and 75 μg/ml of 6-gingerol attenuated the

Table 4
Neuroprotective effects of ginger and its constituents against chemical or natural toxins.

Toxin	Model	Protective agent	Results	References
Scopolamine	Mice	Supercritical fluid ginger extract	Improved the impaired memory with elevated NGF, synaptophysin (SYN) and PSD-95 *via* NGF-induced ERK/CREB activation.	(Lim et al., 2014)
Scopolamine $A\beta_{1-42}$	Mice	Fermented ginger extract	Improved cognition and memory impairments.	(Huh et al., 2018)
$A\beta_{1-42}$	Mice	6-Shogaol	Reduced the microgliosis and astrogliosis and ameliorated the induced memory impairment with elevated NGF.	(Moon et al., 2014)
	HT22 and Mice	6-Shogaol	Ameliorated the behavioural deficit in mice *via* CysLT1R/cathepsin B inhibition and decreased the cytotoxicity on the HT22 cells.	(Na et al., 2016)
Aβ and Aluminium	Rats	Ginger root extract	Reversed behavioural dysfunction, increased SOD and CAT level, while decreased the MDA, NF-ƙB, and IL-1β levels.	(Zeng et al., 2013)
Aluminium	Rats	Gingerol	Inclined the downregulated GSH, ALAS and AChE in the brain and improved histo-architecture.	(Shrivastava, 2015)
AF64A	Rats	Ethanolic extract of *Cyperus rotundus* and *Zingiber officinale* (1:5)	Spatial memory enhancement with increased neuronal density, SOD, and CAT, while declined both the AChE activity and MDA level in the hippocampus with activated p-ERK1/2	(Sutalangka and Wattanathorn, 2017)
MSG	Rats	Ginger powder Or aqueous ginger extract	Decreased the MSG-induced 8-OHdG, E, NE, DA, 5-HT, glutamate, Aβ, NO and MDA levels with increased SOD, CAT and GSH and improved histological parameters in the brain.	(Hussein et al., 2017; Waggas, 2009)
H_2O_2 or 6-OHDA	PC12 cells	6-shogaol or 6-Dehydrogingerdione	Declined LDH and caspase-3 level with inclined total thiols, GSH, Trx-1, TrxR-1, HO-1 and NOQ-1 mediated by Nrf2 activation.	(Peng et al., 2015; Yao et al., 2014)
6-OHDA	Mice	Zingerone	Prevented the striatal DA reduction with enhanced the free radical scavenging activity.	(Kabuto et al., 2005)
PTZ	Mice	80% Ethanolic ginger extract	Increased the PTZ-induced seizure threshold for the myoclonic, generalized clonic, and tonic extension phase seizures in acute and chronic dose administrations.	(Hosseini and Mirazi, 2014, 2015)
MPP^+/MPTP	Mesencephalic cells and mice	6-Shogaol	*In-vitro*; increased TH-IR neurons with decreased TNF-α and NO levels. *In-vivo*, reversed the altered motor coordination and bradykinesia with inhibition of the induced levels of TNF-α, NO, iNOS, and COX-2 in both SNpc and ST with increased TH-positive cell number.	(Park et al., 2013)
LPS	BV2 microglial cells	Gingerols, shogaols and 90% ethanolic fresh ginger extract	Reduced the LPS-induced NO, IL-1β, IL-6, PGE_2, COX-2, TNF-α, P38 MAPK and NF-ƙB expression.	(Ho et al., 2013; Ha et al., 2012)
	Murine astrocytes	6-Shogaol	Attenuated LPS-induced death with increased BDNF, Bclxl and Bcl-2/Bax expression ratio.	(Shim et al., 2012)
Streptozotocin	Rats	Ginger powder	Declined the overexpressed iNOS, TNF-α, AChE, GFAP and caspase 3.	(El-Akabawy and El-Kholy, 2014)
	Rats	Ethanolic ginger extract	Recovered the hippocampus histo-architecture with upregulated Cyclin D1 ($P = 0.049$).	(Molahosseini et al., 2016)
	Rats	95% Ethanolic ginger extract	Upregulated the declined SOD, CAT, GPx, GR, GSH in rat brain, also declined the MDA level.	(Shanmugam et al., 2011)
	Mice STZ	Gingerol	Increased the α-secretase activity with a declined cerebral Aβ-42, β- secretase, APH1a activity and COX-2.	(Halawany et al., 2017)
Ethanol	Rats	*Z. zeurmbet* extracts	Ethyl acetate extract increased the serum and brain levels of antioxidant parameters (SOD, CAT, GPx, and GSH) and reduced the MDA and protein carbonyl levels in the brain homogenate.	(Hamid et al., 2018)
MDMA	Rats	70% Ethanolic ginger extract	Decreased MDMA-induced spatial memory impairment, caspase 3,8 and 9 expression in hippocampus and increased Bcl-2/Bax expression ratio.	(Asl et al., 2013; Mehdizadeh et al., 2012)
Chlorpyrifos	Rats	6-Gingerol-Rich fraction of ginger	Declined the induced inflammatory (MPO, NO, and TNF-α), oxidative stress (H_2O_2, and MDA), and apoptotic (caspase-3) markers. Also increased GPx, SOD, CAT, GST, and GSH antioxidant defences in the rats' brain.	(Abolaji et al., 2017)
Dichlorvos and/or Lindane	Rats	Dried ginger juice	Reduced the induced level LPO and increased the downregulated level of GSH, GPx, GST, SOD, CAT, GR and QR.	(Sharma and Singh, 2012)
Iron (Fe2 +)/$Na_2[Fe(CN)_5NO]$	Rat brain in-vitro	Aqueous extract of white and red ginger	Both extracts inhibited the AChE activity in a dose dependent manner and reduced the induced MDA in the brain tissue homogenate.	(Oboh et al., 2012a, 2012b)

5-HT; serotonin, 6-OHDA; 6-hydroxydopamine, Aβ; Amyloid $beta_{1-42}$, ALAS; δ-Aminolevulinic acid synthase, AF64A; ethylcholine azirinium ion, AChE; acetylcholinesterase, APH1a; anterior pharynx-defective 1a, Bcl-2; B-cell lymphoma-2, Bcl-xl; B-cell lymphoma-extra-large, BDNF; brain-derived neurotrophic factor, CysLT1R; cysteinyl leukotriene-1 receptor, CREB; cyclic AMP response element-binding protein, CAT; catalase, COX-2; cyclooxygenase 2, DA; Dopamine, E; epinephrine, ERK; extracellular-signal-regulated kinase, GFAP; glial fibrillary acidic protein, GPx; Glutathione peroxidase, GR; glutathione reductase, GST; glutathione-s-transferase, GSH; Glutathione, HT22; Mouse hippocampal cells, HO-1; heme oxygenase-2, H_2O_2; hydrogen peroxide, IL-6; interleukin-6, IL-1β; interleukin-1β, iNOS; Inducible nitric oxide synthase, LPO; lipid peroxidation, LPS; Lipopolysaccharide, MDA; malonaldehyde, MPP^+; 1-methyl-4-phenylpyridinium, MPTP; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MSG; monosodium glutamate, MPO; myeloperoxidase, $Na_2[Fe(CN)_5NO]$; sodium nitroprusside, NE; norepinephrine, NF-ƙB; nuclear factor-ƙB, NGF; nerve growth factor, NO; nitric oxide, NQO-1; NAD(P)H: quinone oxidoreductase 1, Nrf2; Nuclear translocation of nuclear factor-E2-related factor-2, PC12; pheochromocytoma cell line, p-ERK1/2; Phospho extracellular-signal-regulated kinase-1/2, PSD-95; postsynaptic density protein 95, PTZ; pentylenetetrazole, QR; quinine reductase, SNpc; substantia nigra pars compacta, SOD; superoxide dismutase, ST; stratum, SYN; synaptophysin, TNF-α; tumour necrosis factor alpha, TH-IR; tyrosine hydroxylase immunoreactive, TrxR-1; thioredoxin reductase 1, Trx-1; thioredoxin 1.

sodium arsenite (10 μM) induced oxidative stress in murine pancreatic β-cells and hepatocytes. Whereas, inclined antioxidant parameters (CAT, SOD, GPx, GSH) and declined pro-inflammatory cytokines (TNF-α and IL-6) were reported with upregulation of insulin signalling molecules impaired by arsenic intoxication (Chakraborty et al., 2012).

3.3.1.3. Aluminium. Oxidative stress-mediated neurotoxicity (Wang et al., 2018), Alzheimer's disease (AD) (Mathiyazahan et al., 2015), reproductive (Yousef and Salama, 2009), and heptorenal (Shrivastava, 2015) toxicities are among the adverse effects of Aluminium (Al), which is found in water, food products, antacids and antiperspirants. 6-gingerol (25, 50, and 100 mg/kg/day, p.o. for three days) ameliorated the aluminium nitrate (32.5 mg/kg, i.p., once) induced toxicity in rat liver, kidney and brain (Tables 2–4). The different doses significantly reversed the toxic effects on the histoarchitecture, serum biomarkers (ALT, AST, urea, creatinine, cholesterol and triglycerides), lipid peroxidation and glutathione (GSH) levels in the liver, kidney and the brain tissues. Moreover, the Al exposure decreased δ-Aminolevulinic acid dehydratase (ALAD) in the blood, δ-aminolevulinic acid synthase (ALAS) in the brain, and acetylcholine esterase (AChE) in the fore-, mid- and hind-brain tissue. These perturbations were attenuated by different oral doses of 6-gingerol (Shrivastava, 2015). Both ALAS and ALAD are essential rate-limiting enzymes for heme biosynthesis. Likewise, ginger extract (50 mg/kg/day) normalised the haematological parameters of Al-intoxicated rats (Aluminium chloride 50 mg/kg/day) when both were orally administered for 60 days (Kalaiselvi et al., 2015). Also, the oral co-administration of ginger powder (40 mg/kg) protected the male rats against reproductive toxicity of Al (Aluminium chloride 34 mg/kg/day for 60 days) (Moselhy et al., 2012). Furthermore, the ginger root extract effectively reversed AD-like symptoms induced by oral Al-intoxication for four weeks after single intra-cerebroventricular (i.c.v.) injection of amyloid β–protein (Aβ) in rats (Zeng et al., 2013). Overall, ginger phytochemicals offered *in-vivo* protection to not only liver, kidney, nervous and reproductive systems, but also showed hemato-protective effect against Al exposure.

3.3.1.4. Cadmium. Long term exposure to cadmium (Cd) contaminated water and food (Aziz et al., 2015; Huang et al., 2017) results in extreme hepatotoxicity (Baiomy and Mansour, 2016; Garcia-Nino and Pedraza-Chaverri, 2014), and nephrotoxicity (Ugwuja et al., 2016; Baiomy and Mansour, 2016) *via* oxidative stress in blood, liver, and kidney (Matović et al., 2015). Cd occurred generally in cigarettes and industrial products with kidney as its chronic toxicity target organ. However, spice mixture formed of ginger, garlic and nutmeg (300 mg/kg, p.o, for 2 weeks) showed both therapeutic and prophylactic hepatorenal protective potentiality in Cd intoxicated rats (25 mg/kg, p.o., for 4 weeks) (Ugwuja et al., 2016). Likewise, the oral co-administration of ginger powder (400 mg/kg) protects the rabbit kidney and liver from the genotoxic effect of cadmium chloride (200 mg/kg/day for 12 weeks). Notably, it declined the induced mRNA expression of the apoptotic Caspase3, proliferative; MKI67 and proto-oncogene; c-Fos. Too, it increased the expression of GST and the anti-apoptotic; Bcl2 in both kidney and liver tissue (Baiomy and Mansour, 2016). Additionally, the cadmium-induced toxicity (3 mg/kg/day for 28 days) was ameliorated by ginger powder co-administered in a dose of 0.5 g/kg in rats. While, a significant reversal of the levels of acid phosphatase (ACP), ALP, prostatic acid phosphatase (PAP) and MDA levels in both kidney and testis were achieved, together with the normalisation of the perturbed haematological parameters (Onwuka et al., 2011).

3.3.1.5. Lead. Lead (Pb) is a common environmental pollutant particularly after the industrial revolution in the 18th century. Its oxidative stress mediated toxicity affects the nervous, reproductive, cardiovascular and the hematopoietic systems, as well as the kidney and liver (Matović et al., 2015). These toxic effects augmented the global trend to phase the leaded petrol out. Ginger showed an obvious protective effect against Pb-induced hepatotoxicity, especially, in the early stages without affecting Pb accumulation in rats' liver upon Pb-intoxication with 1 ppm/day for 6 weeks in drinking water. As the pre- and post-treatments with aqueous ginger extract (350 mg/kg, p.o.) decreased the liver transaminases (ALT and AST) and inclined the downregulated antioxidant molecules (Table 2) in liver tissue (Mohamed et al., 2016). Another study investigated Pb-induced renal toxicity in rats treated with ethanolic ginger extract (150 mg/kg) with lead nitrate (300 mg/kg) daily for 3 weeks in rats. It reversed not only the Pb-induced depletion in the renal antioxidant (Table 3) molecules but also restored the normal kidney histoarchitecture (Reddy et al., 2014). Moreover, ginger ameliorated not only the testicular degenerative alterations in spermatogenic tubules and germ cells (Mustafa, 2015) but also recovered the testosterone level (Riaz et al., 2011) in Lead-challenged rats (Table 7).

3.3.1.6. Iron. Iron (Fe) is an essential heavy metal found in myoglobin, haemoglobin, and cytochrome enzymes. However, its overloading results in a hepatotoxicity, heart failure, anaemia and other oxidative stress related disorders (Pari et al., 2015). Notably, the effect of ginger against Fe-intoxicated rats (30 mg/kg/day for 2 weeks as Ferrous sulphate) was evaluated. Ginger methanolic extract (400 mg/kg/day) ameliorated the hepato-renal functional and histological injuries (Tables 2 and 3), alongside with the attenuation of the MDA level in both liver and kidney tissue (Gholampour et al., 2017). Also, the aqueous extracts of both red ginger and white ginger attenuated the Fe-mediated lipid peroxidation (Oboh et al., 2012a; Akinyemi et al., 2013) in the heart and brain homogenate of rats *in-vitro*. In addition, the ginger extracts inhibited the iron-induced AChE (Oboh et al., 2012b) and the angiotensin-I converting enzyme (ACE-I) (Akinyemi et al., 2013) activity in brain and heart homogenate, respectively (Tables 4 and 6). These results augment the protective effects of ginger, which may be mediated by both iron chelating and free radical scavenging capacity of ginger phenolics with its antioxidant inducing capability.

3.3.2. Insecticide, pesticide, herbicide and/or fungicide toxicities

3.3.2.1. Carbendazim. Carbendazim (CBZ) is a widely used fungicide in agriculture and veterinary. CBZ is controversially used to control plant diseases on arable crops and as preservative in paint, paper and leather industries. A maximum residue limit of 1 mg/kg and acceptable daily intake (ADI) of 0.02 mg/kg b.w. are indicated for CBZ in fruits, vegetable or drinking water (Liu et al., 2016a). High CBZ exposure may result in testis, liver, kidney, and hematologic injuries. The oral co-administration of the 6-gingerol rich fraction (6-GRF) in 50, 100, and 200 mg/kg doses successfully attenuated the CBZ-induced adverse effect (50 mg/kg, p.o.) in rats. It inhibited the CBZ-mediated oxidative damage, and augmented the antioxidant enzymes (SOD, CAT, GST and GPx) and GSH level in kidney, liver and testis (Tables 2, 3 and 7). 6-GRF significantly declined the increased plasma levels of liver (ALT, AST, ALP, GGT, and bilirubin) and kidney markers (urea, and creatinine) in a dose dependent manner. Also, it reversed the CBZ-toxic effect on the follicle stimulating hormone (FSH), testosterone, thyrotropin, triiodothyronine and tetraiodothyronine, levels in CBZ-treated rats. Furthermore, significant enhancement was also reported for the sperm characteristics and CBZ-histological-induced damage to the testes, epididymis, liver and kidney (Salihu et al., 2016, 2017). Additionally, the CBZ-mediated haematological toxicity to the total white blood cells, neutrophils, lymphocytes, and platelet counts were normalised by 6-GRF intervention (Salihu et al., 2016).

3.3.2.2. Phosphamidon. Phosphamidon is an organophosphorus insecticide, and classified as WHO hazard class Ia with ADI of 0.0005 mg/kg b.w. (Menard et al., 2008). Its toxicity is mediated by the inhibition of the AChE activity and the oxidative stress induction (A.Caldas et al., 2018). Ginger polyphenol-rich ethanolic extract (1 mg/

Table 5
Gastroprotective effects of ginger and its constituents against chemical or natural toxins.

Toxin	Model	Constituents	Results	References
Methotrexate	Rats	Ginger!	Ameliorated the induced ileum injury, improved the number of goblet cells and the length of the ileum brush border with intact villi.	(Abdul-Hamid and Salah, 2016)
Indomethacin	Rats	50% Ethanolic ginger extract	Declined the induced ulceration, MDA and histamine in the gastric mucosa increased the GSH, NO, and SOD.	(Zaghlool et al., 2015)
	Rats	Cuttlebone complex, including ginger	Decreased the gastric ulcer lesions and the induced PEG-2 in the gastric mucosa.	(Chien et al., 2015)
Aspirin	Rats	Ginger powder	Ameliorated the induced ulcers, mucosal haemorrhage, submucosal oedema and leukocyte infiltration *via* reducing the Bax and iNOS levels and increasing HSP70.	(Salah Khalil, 2015)
	Rats	Ginger powder, 6-gingerol or 6-shogaol	Ameliorated the aspirin induced haemorrhagic ulcer by reducing the level of iNOS, TNF-α and IL-1β levels.	(Wang et al., 2011)
Aspirin and pylorus ligation	Rats	Ginger oil	Reversed the perturbations in gastric mucus, acidity and juice volume with improved ulcer index score and decreased serum γ-GTP.	(Khushtar et al., 2009)
Ethanol	Rats	Ginger essential oils	Inhibited the induced gastric ulcer by 85.1% and increased the antioxidant parameters (GSH, GPx, SOD, and CAT).	(Liju et al., 2015)
	Rats	Aqueous ginger extract	Inhibited the induced gastric ulcer by 77.0% and both the *H. pylori* (MIC of 300 ± 38 μg), and H^+, K^+-ATPase activity, while recovered the damaged gastric mucin.	(Nanjundaiah et al., 2011)
	Rats	Ginger powder	Reversed the ethanol-induced decrease in the antioxidant enzymes (CAT, SOD, GR and GST) and the mucin content in both gastric and intestinal mucosa.	(Prakash and Srinivasan, 2010)
Ethanol, ammonia and sodium deoxycholate	Rats	Zerumbone	Ameliorated the gastric epithelial cells deformation and abscission. Increased antioxidant defences (SOD, CAT, and GSH) with declined oxidative stress in the gastric tissue *via* upregulated HO-1 and Nrf-2 expression.	(Li et al., 2017)
Acetic acid	Rats	Ginger essential oils	Reduced the colon ulceration area, index, and severity.	(Rashidian et al., 2014)
	Rats	Ginger powder	Improved histopathological colon parameters with declined both the colonic total peroxides and cytokines (IL-10, and TNF-α), alongside with the serum 5-HT levels.	(Abd Allah et al., 2016a)
	Rats	Ginger extract	Reduced the ulcerated area, NO, MPO and MDA in the gastric mucosa with pro-inflammatory protein expression downregulation (TNF-α, IL-1β, MIP-2 and CINC-2α).	(Ko and Leung, 2010)
Dextran sulphate sodium	Mice	6-Gingerol	Improved colonic antioxidant (SOD, CAT, GPx, GST, and GSH) and regulated both inflammatory (p38, NF-ƙB, TNF-α, COX-2, iNOS, RANTES, MCP-1,IL-10, and IL-1β) and *Wnt* signalling proteins (*β*-catenin and APC).	(Ajayi et al., 2018)

!; undefined ginger form, 5-HT; serotonin, APC; adenomatous polyposis coli, CAT; catalase, CINC-2α; cytokine-induced neutrophil chemoattractant, γ-GTP; gamma glutamyl transpeptidase, GPx; glutathione peroxidase, GR; glutathione reductase, GSH; glutathione, GST; glutathione-s-transferase, HO-1; Heme oxygenase-1, HSP70; heat shock protein 70, IL; interleukin, iNOS; Inducible nitric oxide synthase, MCP-1; Monocyte chemoattractant protein-1, MDA; malonaldehyde, MIC; minimum inhibitory concentration, MIP-2; macrophage inflammatory protein-2, MPO; mucosal myeloperoxidase, NF-ƙB; nuclear factor kappa-light-chain-enhancer of activated B cells, NO; nitric oxide, Nrf-2; Nuclear translocation of nuclear factor erythroid2-related factor 2, PGE_2; PorstaglandinE-$_2$, RANTES; regulated on activation normal T cell expressed and secreted, SOD; superoxide dismutase, TNF-α; tissue necrosis factor alpha, XO; xanthine oxidase.

Table 6
Cardioprotective effects of ginger and its constituents against chemical or natural toxins.

Toxin	Model	Constituents	Results	References
Doxorubicin	Rats	50% Ethanolic ginger extract	Reduced the induced levels of AST, serum LDH and cardiac MDA.	(Ajith et al., 2016)
Cisplatin	Rats	Zingerone	Ameliorated the induced biochemical indices (LDH, cTnT, CK-MB, and BNP). Reduced the TNF-α, COX-2, caspase3 expression with increased expression of the declined antioxidant defences (SOD, CAT, and GSH).	(Soliman et al., 2018)
Streptozotocin	Rats	Hydroalcoholic Ginger extract	Restored the normal levels of C-reactive protein, homocysteine, cathepsin G, leptin, apo A and B.	(Ilkhanizadeh et al., 2016)
	Rats	6-Gingerol	Declined the induced myocardial indices (serum LDH, CK-MB, and AST) with increased antioxidant parameters (SOD), and declined the induced both Bax/Bcl-2 ratio and caspase-3 expression in heart tissue.	(Yu et al., 2017)
Ethanol	Rats	99.9% Ethanolic ginger extract	Reversed the alcohol-induced abnormalities in the lipid profiles and cardiac biomarkers (LDH, AST, CK-MB, cTn-T and cTn-I).	(Subbaiah et al., 2017)
	Rats	70% ethanolic ginger extract	Ameliorated the toxic effect on the gene expression of MHC isoforms and reduced the inclined 8-OHdG and NADPH oxidase levels, while increased the downregulated paraoxonase enzyme.	(Shirpoor et al., 2017)
Isoproterenol	Rats	80% Ethanolic ginger extract	Reduced the induced levels of cardiac biomarkers (CK-MB, cTn-I, ALT, AST and LDH), increased antioxidant parameters (SOD, CAT, GPx), and improved cell membrane cell integrity.	(Amran et al., 2015; Ansari et al., 2006)
Iron (Fe2+), sodium nitroprusside and ACE-I	*In-vitro* on rat hearts	Aqueous white and red ginger extracts	Decreased lipid peroxidation (MDA) and inhibited ACE-I activity.	(Akinyemi et al., 2013)

8-OHdG; 8-Oxo-2′-deoxyguanosine, ACE-I; Angiotensin-I converting enzyme, ALT; alanine aminotransferase, APO; Apolipoproteins, AST; aspartate aminotransferase, Bax; Bcl-2-associated X, Bcl-2; B-cell lymphoma-2, BNP; B-natriuretic peptide, CAT; catalase, CK-MB; creating kinase MB, cTn-I; cardiac Troponin-I cTnT; cardiac Troponin-T, GPx; Glutathione peroxidase, LDH; lactate dehydrogenase, MDA; malonaldehyde, MHC; myosin heavy chain, SOD; superoxide dismutase.

kg/day, p.o.) ameliorated the phosphamidon-induced hepatotoxicity (2 mg/kg/day, i.p.) in rats (Table 2). While, the elevated lipid peroxidation marker (MDA) and the biochemical liver markers (ALT, AST, and ALP) were declined. In addition, the downregulated antioxidant enzymes (CAT, SOD, and GPx) and GSH were recovered and the DNA fragmentation alongside with the apoptotic nuclei were effectively attenuated as well (Mukherjee et al., 2015).

3.3.2.3. Malathion. Malathion is an organophosphorus insecticide, widely used in pest control for not only the agricultural crops, but also, it was approved in the pediculosis treatment. Sub-chronic rat exposure to malathion (20 ppm for four weeks) was reported to induce lipid peroxidation and oxidative stress (Ahmed et al., 2000). Nevertheless, the dietary feeding of *Z. officinales* Rosc. (1% w/w) significantly attenuated the increased serum MDA and the declined oxidative defence systems (SOD, CAT, GPx in the erythrocytes, and both GR, and GST in the serum and GSH in whole blood) (Ahmed et al., 2000). Moreover, the malathion administration (100 mg/kg.bw/day) in rats for four months resulted in congestion, oedema and leucocytic infiltration in livers, and both cloudy swelling, and tubules degeneration in the kidneys. However, the concomitant administration of ginger (400 mg/kg.b.w/day) and zinc chloride (300 mg/L) mixture, ameliorated the malathion-induced hepatorenal histopathological changes in rats (Baiomy et al., 2015).

3.3.2.4. 1-Methyl-4-phenylpyridinium (MPP+). MPP^+ was used in the 1970s as a herbicide. Though, it is no longer used, its analogue; paraquat is still widespread. Its prodrug is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), where both are used as neurotoxins causing symptoms of Parkinson's disease (PD) in preclinical models. 6-shogoal demonstrated a neuroprotective effect against both the MPP + or MPTP in *in-vitro* and *in-vivo* PD models. Whereas, 6-shogoal (0.01 moL/L and 10 mg/kg/day, p.o.) significantly increased the MPP^+/or MPTP-induced reduction in tyrosine hydroxylase immuno-reactive (TH-IR) neurons in the mesencephalic cells and in mice, respectively. Additionally, it improved the motor deficits and bradykinesia in MPTP-challenged mice with significant attenuation of the MPTP-induced levels of inflammatory factors (TNF-α, NO, iNOS, and COX-2) in both substantia nigra para compacta and stratum (Park et al., 2013). In summary, the dopaminergic neurons could be effectively protected against MPP^+/or MPTP-induced neurotoxicity *via* the 6-shogoal neuro-inflammatory inhibition responses.

3.3.2.5. Dichlorvos and lindane. Dichlorvos and lindane are organophosphate and organochlorine agricultural insecticides respectively. A brain tissue damage was reported in rats received 8.8 mg/kg/day of dichlorvos, lindane, or their combination for two weeks *via* oxidative stress induction. But, the post-treatments with ginger juice (100 mg/kg/day) significantly ameliorated the lipid peroxidation and increased the levels of the downregulated the antioxidant armoury (GSH, GPx, GST, SOD, CAT, GR and QR) (Sharma and Singh, 2012). Furthermore the concomitant diet of ginger (1% w/w) ameliorated the lindane-induced lipid peroxidation and antioxidant defences (Ahmed et al., 2008).

3.3.2.6. Chlorpyrifos. Chlorpyrifos (CPF) is an organophosphate pesticide with wide household and agricultural applications. Adverse toxic effects have been reported for CPF on reproductive (Farag et al., 2010), nervous (Xu et al., 2015) systems alongside with liver (Goel et al., 2005) and heart (Bas and Kalender, 2011) in animals. Still, the potent anti-inflammatory, antioxidant, and anti-apoptotic properties of ginger could ameliorate the CPF-induced neuro- and reproductive toxicities in rats. However, the 6-GRF of *Z. officinale* reversed the CPF-induced alterations in the brain, ovary, and uterus tissues of rats. The levels of inflammatory (MPO, NO, and TNF-α), oxidative stress (H_2O_2, and MDA), and apoptotic (caspase-3) markers were elevated in

Table 7
Reproductive system protective effects of ginger and its constituents against chemical or natural toxins.

Toxin	Model	Constituents	Results	References
Lead	Rats	Ethanolic ginger extract	Ameliorated the induced degenerative alterations in testicular histoarchitecture.	(Mustafa, 2015)
	Rats	Ginger!	Increased the lead-declined level of T.	(Riaz et al., 2011)
Cadmium	Rats	Ginger powder	Reversed the cadmium-induced effect on the testes weight and the levels of ACP, ALP, PAP and MDA.	(Onwuka et al., 2011)
Aluminium	Rats	Generic ginger tablets	Reversed the induced effects on the levels of T testicular MDA, testicular histological degenerative changes and testicular DNA fragmentation.	(Moselhy et al., 2012)
Cisplatin	Rats	Zingerone	Suppressed the induced FSH, E2, oxidative stress (8-OHdG), apoptotic (caspase-3), and inflammatory (NF-κB, TNF-α, IL-1β, IL-6, COX-2, and iNOS) markers. Upregulated the SOD, CAT, GPx, and Bcl-2 levels.	(Kaygusuzoglu et al., 2018)
	Rats	70% Ethanolic ginger extract	Restored testis' normal histoarchitecture, decreased the induced apoptotic cells in testicular tissue and in the sperms. Recovered the sperm motility and epididymal sperm count with reduced sperm abnormality.	(Amin and Hamza, 2006; Amin et al., 2008)
Cyclophosphamide	Rats	50% Ethanolic ginger extract	Improved testicular histo-architecture and increased serum T level and total antioxidant capacity.	(Mohammadi et al., 2014)
	Rats	1:1 Ginger and pumpkin seed extract	Improved sperm, epididymal tissue parameters with inclined total antioxidant capacity.	(Aghaie et al., 2016)
Estradiol valerate	Rats	6-Gingerol	Attenuated induced adverse effects on the ovarian weight, ovarian cysts, serum-sex hormones (FSH, LH, E2, P4, and T), and declined the induced COX-2 gene expression.	(Pournaderi et al., 2017)
Dextran sulphate sodium	Mice	6-Gingerol	Reversed the declined LH, FSH, and T alongside with the induced testicular biochemical indices (LDH, ALP, and ACP) Oxidative stress, pro-inflammatory markers (IL-1β, TNF-α, NO, and MPO) and apoptotic caspase-3 activity. It augmented antioxidant defences (SOD, CAT, GPx, and GSH) with improved sperm parameters and testicular histo-architecture.	(Farombi et al., 2018)
Gentamycin	Rats	Ginger powder	Declined gentamycin-induced apoptotic cell percentage in rat testes utilising the TUNEL method.	(Zahedi et al., 2012)
Carbendazim	Rats	6-Gingerol-rich fraction of ginger	Reversed the plasma hormonal disruptions (FSH, T, thyrotropin, triiodothyronine and tetraiodothyronine). Restored the antioxidant defences (SOD, CAT, GST, GPx, and GSH), the normal testes weights, and both the sperm quality and quantity.	(Salihu et al., 2017)
Chlorpyrifos (CPF)	Rats	6-Gingerol-rich fraction of ginger	Declined the CPF-induced inflammatory (MPO, NO, and TNF-α), oxidative stress (H_2O_2, and MDA), and apoptotic (caspase-3) markers. Increased GPx, SOD, CAT, GST, and GSH antioxidant defences in ovary and uterus.	(Abolaji et al., 2017)
Ethanol	Rats	Ethanolic ginger extract	Ameliorated the ethanol-induced testicular tHct and MDA levels with inclined testicular antioxidant parameters (SOD, CAT, and GPx) and restored the normal testes weights.	(Akbari et al., 2017)
Sulphite	Rats	50% Ethanolic ginger extract	Reversed the adverse effect of sulphite on T level, spermatogenesis, sperm parameters, MDA level and antioxidant defence systems (GR, CAT, and GPx).	(Afkhami Fathabad et al., 2017)
Di (*n*-butyl) phthalate	Rabbits	Ginger!	Ameliorated the induced abnormalities on testis and prostate weights, testicular MDA level, and sperm parameters (count, mass, live sperm percentage, and motility).	(Oda and Waheeb, 2017)

!; undefined ginger form, 8-OHdG; 8-hydroxydeoxyguanosine, ACP; acid phosphatase, ALP; alkaline phosphatase, CAT; Catalase, COX-2; cyclooxygenase-2, E2; Estradiol, FSH; Follicle stimulating hormone, GR; glutathione reductase, GPx; Glutathione peroxidase, GSK; Glutathione, GST; Glutathione S-transferase, IL; interleukin, iNOS; Inducible nitric oxide synthase, LH: Luteinizing hormone, MDA; Malonaldehyde, MPO; myeloperoxide, NF-κB; Nuclear factor-kappa B, NO; Nitric oxide, P4; Progesterone, PAP; prostatic acid phosphatase, SOD; Superoxide dismutase, T; Testosterone, THct; total homocysteine, TNF-α; Tumour necrosis factor alpha, TUNEL; Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labelling.

brain, ovary and uterus upon CPF administration (5 mg/kg/day for 35 days) in rats. However, the concurrent administration of 6-GRF through gavage in a dose of 50 or 100 mg/kg significantly, declined the CPF-induced markers. Moreover, it induced the CPF-declined antioxidant arsenal (GPx, SOD, CAT, GST, and GSH) in the brain, ovary and uterus tissues (Abolaji et al., 2017).

3.3.2.7. Lambda-cyhalothrin. Lambda-cyhalothrin (LCT) is a pyrethroid insecticide formed of a mixture of cyhalothrin isomers, and widely used in pest control *via* sodium channels' disturbance. Despite being more toxic to fish and aquatic invertebrates, its multiple organ toxicity was reported in rats and mice (Al-Sarar et al., 2014; Aouey et al., 2017; El-Demerdash, 2011; Fetoui et al., 2009). The provoked toxicity may be attributed to the induced oxidative stress and the upregulated pro-inflammatory mediators (Aouey et al., 2017). Nonetheless, the toxic LCT-induced thyroid toxicity was ameliorated *via* the concurrent oral administration of aqueous extract of *Z. officinale* R. (24 mg/ml) and LCT (1/100 LD_{50}) for 3 days per week for 4 weeks (Al-Amoudi, 2018). The protective effect of ginger was indicated against the histological thyroid damage. Also, it closely normalised the biochemical parameters (T3, T4, TSH, and SOD) in plasma samples with declined oxidative stress and DNA damage in the thyroid gland (Al-Amoudi, 2018).

3.3.3. Drug-induced toxicities

Noxious, and unintended toxic effects may be experienced following the drug administration. This may be attributed to on-target binding in an inappropriate concentration, and/or suboptimal kinetics or even either off-target binding or due to its toxic metabolites. The ginger phytochemicals were able to ameliorate some of these drugs-induced toxicities as summarised in Tables 2–7 These protective effects may be accredited to its anti-inflammatory, and antioxidant properties.

3.3.3.1. Acetaminophen. Acetaminophen (N-acetyl-*p*-amino phenol; N-APAP) also known as paracetamol is a widely used as an over the counter (OTC) analgesic and antipyretic drug. Its overdose (> 4g/day) may result in severe hepatotoxicity and acute liver failure (Bessems and Vermeulen, 2001; Yoon et al., 2016; Castaneda-Arriaga and Galano, 2017). However, ginger extracts and its individual components successfully reversed the N-APAP-induced perturbations in the biochemical, histopathological, antioxidant and lipid peroxidation parameters in animal studies (Abdel-Azeem et al., 2013; Sabina et al., 2011; Ajith et al., 2007a; Yemitan and Izegbu, 2006). In details, the pre-treated rats with ginger powder (100 mg/kg/day, p.o., for 14 days) before the acute liver injury induction using 600 mg/kg, i.p. A single dose of N-APAP, substantially decreased the N-APAP-induced hepatic marker enzymes (ALT, AST, ALP, and arginase) and total bilirubin in plasma. Additionally, it remarkably ameliorated the N-APAP-induced alterations in the hepatic histoarchitecture and oxidative status (Abdel-Azeem et al., 2013). These protective effects were also indicated after single oral administration of 3 g/kg p.o of N-APAP in rats protected with a single oral dose of 200 and 400 mg/kg 50% ethanolic ginger extract. Additionally, the 400 mg/kg dose, significantly increased the N-APAP-declined antioxidant defences (SOD, GPx, GST and GSH) (Ajith et al., 2007a). Moreover, both the ethanol extract of ginger essential oil pre-treatments (Yemitan and Izegbu, 2006) and 6-gingeral (30 mg/kg) post-treatments (Sabina et al., 2011) have protected against acetaminophen induced acute liver injuries in rats and mice, respectively. It declined the induced both liver marker enzymes (ALT, AST, LDH, ALP, SDH, and GDH) and lipid peroxidation with increased antioxidant capacity as well. These results obviously demonstrate the promising hepato-protective effect of ginger against acetaminophen toxicity.

3.3.3.2. Nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are a group of medications used to relief the pain, fever, and inflammation by blocking cyclooxygenases, which are responsible for prostaglandins (PGs) production. PGs control many processes, including the inflammation, blood flow and blood clot formation.

3.3.3.2.1. Diclofenac. Diclofenac sodium and potassium salts are widely used NSAIDs in different systematic and topical preparations, albeit its well-documented hepatotoxicity (Kaplowitz, 2005). 6-Gingerol and 6-shogoal reversed the diclofenac-induced alterations in serum biochemical markers (ALT, AST, and ALP), oxidative stress marker (MDA) in liver homogenate, and the hepatic histo-architecture (Alqasoumi et al., 2011).

3.3.3.2.2. Indomethathin. Indomethacin is an NSAID, commonly used as analgesic, antipyretic, and anti-inflammatory for joint diseases. Like other non-selective COX inhibitors, its excessive use may lead to peptic ulcers. The possible mechanisms of indomethacin-induced gastric ulcers include ROS-mediated mitochondrial damage, gastric mucosa apoptosis alongside with the inhibition of PGE_2 synthesis. However, the pre-treated rats with ginger (50% ethanolic extract, 100 mg/kg/day for 14 days) suppressed the indomethacin-induced gastric ulceration (single dose, 20 mg/kg, i.p.). Ginger has alleviated the biochemical and histopathological ulcerogenic alterations induced by indomethacin, where, increased the antioxidant defences (GSH, and SOD), and declined both lipid peroxidation (MDA), and histamine release in the gastric mucosa were reported (Zaghlool et al., 2015). On the other hand, the Cuttlebone complex (CBC) including fresh ginger roots demonstrated a protective potentiality against indomethathin-induced gastric ulcer in rats. The oral CBC administration (310, 620, and 930 mg/kg) reduced the gastric ulcerous lesions and increased the indomethacin-declined PGE_2 levels in the stomach in a dose dependent manner (Chien et al., 2015). In summary, the antioxidant properties, histamine release inhibition, and increased PGE_2 may account for the gastro-protective effects of ginger against indomethacin-induced gastric ulcer (Table 5).

3.3.3.2.3. Aspirin. Acetyl-salicylic acid (ASA) or aspirin is the most commonly used analgesic, antipyretic, and anti-inflammatory NSAIDs. Its low doses used to be administered as blood thinner and antiplatelet medication. Nevertheless, it is contraindicated for individual with peptic ulcer and haemophilia or people at risk of gastrointestinal bleeding (Rodriguez et al., 2001; Roderick et al., 1993). However, ginger showed a gastro-protective effect against aspirin-induced ulceration in rats (Khalil, 2015; Khushtar et al., 2009; Salah Khalil, 2015; Wang et al., 2011). The oral administration of ginger oil for five days (0.5 and 1 g/kg/day) alleviated the induced gastric damage by co-administered aspirin (200 mg/kg/day, p.o.) and pylorus ligation in rats, with a reversal of the declined gastric wall mucus and gastric juice volume were indicated. It significantly declined the increased ulcer score indices, total acidity and, serum level of gamma glutamyl transpeptidase (γ-GTP) in a dose dependent manner as well (Khushtar et al., 2009). Furthermore, rats received 200 mg/kg/day ginger powder ameliorated the gastric ulcer and, mucosal haemorrhage induced by aspirin (400 or 200 mg/kg) co-administered orally for five days. It significantly reduced the aspirin-induced overexpression of iNOS, TNF-α, IL-1β, and Bax (Salah Khalil, 2015; Wang et al., 2011). These overexpressed mediators except for the Bax were also significantly reduced by 6-gingrol (2 or 1 mg/kg/day) or 6-shogaol (1 or 0.5 mg/kg/day) in a dose dependent manner. Shortly, the overexpression of inflammatory mediators, apoptotic proteins and neutrophil infiltration play an important role in the pathogenesis of aspirin-induced gastric damage, which was significantly declined by the co-treatment of ginger or its components with ameliorated ulcer area and mucosal haemorrhage (Table 5).

3.3.3.3. Estradiol valerate. Estradiol (E2) is the most active estrogenic female sex hormone, and is used in the hormonal therapy for menopausal symptoms. Unbalanced oestrogen level alongside with other hormones, like luteinising hormone (LH) and follicle stimulating hormone (FSH), was noticed in polycystic ovary syndrome (PCOS). The female infertility, premenstrual syndrome, and

weight gain are common in women with PCOS, and many of these symptoms are attributable to oestrogen dominance (Edmondson, 2018). However, 6-gingerol (0.2 or 0.4 mg/kg/day for 14 days) represents a promising treatment in PCOS rat model induced by subcutaneous injection of estradiol valerate (4 mg/day for 28 days). It declined the COX-2 induced gene expression alongside with significant reduction of the elevated hepatic enzymes (ALT, AST, and ALP), and sex hormones (FSH, LH, testosterone, and E2) in serum. Additionally, it induced the antioxidant parameters (SOD, CAT, and GPx) in a dose dependent manner. In fact, the anti-inflammatory and antioxidant properties of 6-gingerol can represent a useful treatment to improve the PCOS *via* the reduction of COX-2, LH, FSH, oestrogen, and testosterone production (Pournaderi et al., 2017).

3.3.3.4. Chemotherapeutic agents

3.3.3.4.1. Doxorubicin (Adriamycin®). Doxorubicin (DOX) is anthracycline antineoplastic drug widely used in cancer treatment regimens. However, Its cardio- and hepatorenal-toxicities could limit its clinical expediency (Pugazhendhi et al., 2018; Jasra and Anampa, 2018; Saad et al., 2001; El-Sayyad et al., 2009). At the same time, the protective effect of ginger was reported against DOX both *in-vivo* and *in-vitro* (Tables 2, 3 and 6). For example, 50% ethanol ginger extract (250 mg/kg/day, p.o., for 2 weeks) ameliorated the DOX-induced pathological hepatic damages (2.5 mg/kg, six i.p. injections) in rats (Ahmed, 2013). Same results were also reported for the aqueous ginger extract (24 mg/ml/day, p.o. for 6 weeks) in DOX-challenged rats (2 mg/kg, i.p., once weekly for 6 weeks). It reduced the inclined liver enzymes (serum ALT, and AST) and increased the antioxidant SOD enzyme with declined oxidative stress (MDA level) in liver tissue (Sakr et al., 2011). By the same token, nephroprotective effect against DOX (15 mg/kg, i.p., single dose) was reported in pre-treated rats with a single dose of ginger 50% ethanol extract (200 or 400 mg/kg) by oral gavage 1 h before DOX injection. As, it prevents the DOX-induced decline in renal antioxidants (GSH, GST, GPx, SOD, and CAT), and normalised not only, the serum urea and creatinine level but also, the renal MDA level (Ajith et al., 2008). This extract, in the same doses, declined the oxidative stress and cardiac MDA level in DOX-challenged rats (Ajith et al., 2016). Interestingly, herbal combination containing ginger (nigella, liquorice, and ginger) exhibited a protective effect against DOX-induced toxicity in h9c2 cardio-myocyte *via* reducing the oxidative stress and inhibiting the apoptotic induction processes (Hosseini et al., 2014). Thus, the DOX-induced cardio- and hepatorenal-toxicities could be amended *via* the antioxidant capability of the co-administered ginger.

3.3.3.4.2. Cisplatin. Cisplatin (CP) is a widely used component in breast, prostate, ovarian, neuroblastoma, lung, and colorectal chemotherapy regimens. Its clinical use may be compromised by multiple organ toxicities (Soliman et al., 2018; El-Sayyad et al., 2009; Gómez-Sierra et al., 2018) *via* the triggered pro-inflammatory mediators and oxidative stress cascades, alongside with the apoptotic Bax activation (Neamatallah et al., 2018). On the other hand, ginger and its phytochemicals showed an ameliorative potentiality against CP-induced toxicities (Tables 3, 6 and 7). For instance, the protective effect was indicated for zingerone against CP-induced cardiotoxicity, nephrotoxicity, and ovarian toxicity. Briefly, zingerone administration (25 or 50 mg/kg/day for 7 days) ameliorated the uterine and ovarian CP-induced toxicities upon single CP injection (7 mg/kg, i.p.) on the first day in female rats. It suppressed the CP-induced sex hormones (FSH, and E2), inflammatory markers (NF-κB, TNF-α, IL-1β, IL-6, COX-2, and iNOS), and both apoptosis (Caspase3), and oxidative stress (8-OHdG) markers. Also, increased the antioxidant enzyme level (SOD, CAT, and GPx) and upregulated the expression of the cellular survival promotor Bcl-2 (Kaygusuzoglu et al., 2018). These anti-inflammatory and antioxidant effects of zingerone (50 mg/kg/day, p.o., for 7 days) facilitated its protective effect against CP-induced rat nephrotoxicity upon single CP intraperitoneal injection of 7.5 mg/kg, on the 4th day of the study (Alibakhshi et al., 2018). In like manner, zingerone (25 mg/kg/day for 3 weeks) given by intragastric intubation significantly ameliorated the CP-induced cardiotoxicity (20 mg/kg) in rats upon single intraperitoneal injection on the 21st day. It not only recovered the cardiac histopathological abnormalities, and biochemical indicators of cardiotoxicity (LDH, cTnT, CK-MB, and BNP) but also, suppressed both inflammation, oxidative stress markers (MDA, and MPO, respectively). Moreover, it downregulated the overexpressed TNF-α, COX-2, and the apoptotic caspase-3 as well (Soliman et al., 2018). Furthermore, the 70% ethanol extract of *Z. officinale* R. (1 gm/kg/day for 26 day) improved the CP-induced testicular damage upon single CP dose (10 mg/kg, i.p) on the 21st day of the experiment. It enhanced sperm motility and declined sperm abnormality. Besides, it significantly increased the epididymal sperm count and declined the apoptotic cells in testicular tissue and in sperm (Amin and Hamza, 2006; Amin et al., 2008) *via* oxidative stress suppression. On the other hand, both aqueous and 70% ethanol ginger extract offered a nephroprotective effect against CP-induced nephrotoxicity in rats and mice, respectively (Ali et al., 2015; Ajith et al., 2007b). Since, it enhanced the renal histo-architecture and inhibited the induced renal biochemical parameters (BUN, urea, and Cr) in serum and the apoptotic Bax protein. It suppressed the renal oxidative stress with an inclined antioxidant arsenal (SOD, CAT, and GPx) as well. Therefore, the antioxidant, anti-inflammatory, anti-apoptotic properties of ginger phytochemicals augment its protective potentiality against CP-induced multiple organ toxicities.

3.3.3.4.3. Cyclophosphamide. Cyclophosphamide (CPP) is an alkylating anticancer and potent immunosuppressant agent. Unfortunately, the CPP-induced hepatorenal-, neurological-toxicities, alongside with the reproductive system induced toxicity may limit its clinical application (Tong et al., 2017; Liu et al., 2016b; Zhai et al., 2018). However, 70% ethanolic extract of ginger and pumpkin seed mixture (300, 600 mg/kg/day for 6 weeks) ameliorated CPP-induced testicular damage in rats upon single intraperitoneal administration of 100 mg/kg of CPP at the beginning of the study. Both sperm and epididymis histological parameters have been improved with increased total antioxidant capacity (Aghaie et al., 2016). The same results were also reported for 50% ethanolic ginger extract within the same doses and experimental conditions, where the CPP-declined testosterone serum level was significantly inclined by ginger treatment, as well (Mohammadi et al., 2014). This augments the potentiality of ginger to counteract the CPP-induced testicular toxicity (Table 7). This could represent a base for more preclinical and clinical studies of the protective effects of ginger and its co-administrations in chemotherapeutic regimens containing cyclophosphamide.

3.3.3.4.4. Methotrexate. Methotrexate (MTX) is a chemotherapy and immunosuppressive agent, which is structurally related analogue of folic acid that interferes with the nucleic acid synthesis. Its clinical application is often limited by nausea, vomiting, gastrointestinal ulceration and other adverse effects. Ginger intervention may ameliorate the oxidative stress mediated pathogenesis of MTX-induced intestinal damage (Table 5). Briefly, ginger (200 mg/kg/day for 24 days) administered by gastric intubation ameliorated the MTX-induced ileum injury in rats (10 mg/kg/day, i.p., in the last four days of the experiment) as shown by immunohistochemical, histological and ultrastructural investigations (Abdul-Hamid and Salah, 2016).

3.3.3.4.5. Streptozotocin (Zanosar®). The protective effect of ginger extracts and its polyphenols was indicated in STZ-associated toxicities in liver, kidney, brain, and heart. The polyphenol extract of ginger, and 95% ethanol extract of ginger upregulated the STZ-declined antioxidant defences in liver (SOD, CAT, GPx, GR, GSH) and recovered the inclined oxidative stress marker; MDA and the biomedical liver function indices (Kazeem et al., 2013; Ramakrishna et al., 2015) (Table 2). Furthermore, elevated cytokines (TNF-α, IL-6, and IL-1β) and apoptotic caspase-3 with perturbed mitochondrial enzymes (glucose-6-phosphate dehydrogenase; G6PD, succinate dehydrogenase; SDH, glutamate dehydrogenase; GDH, malate

dehydrogenase; MDH, and LDH) was reported for the STZ-injured kidney tissue in mice. The ethanolic ginger extract significantly reversed the STZ-induced perturbations in kidney tissue together with declined oxidative stress and improved histo-architecture (Al Hroob et al., 2018; Ramudu et al., 2011b) (Table 3). Moreover, it curtailed the overexpressed iNOS, TNF-α, AChE, glial fibrillary acidic protein (GFAP) and the apoptotic caspase 3 (El-Akabawy and El-Kholy, 2014) in the brain tissue with maintaining the antioxidants haemostasis (Shanmugam et al., 2011). In addition, improved cognition was reported for gingerol (10 and 20 mg/kg/day, i.p., for one week) in mice received 3 mg/kg STZ intracerebroventricularly (Halawany et al., 2017) by affecting the amyloidogenic pathway and hampering the STZ-induced neuro-inflammation. Combined Extract of *Zea mays* and ginger ameliorated the STZ-induced retinopathy in mice. Ginger increased the neurons number in the ganglion cell layer with inclined thickness of retina and its nuclear layer (Thiraphatthanavong et al., 2014) (Table 4). In the same way, ginger extract significantly reduced the STZ-induced heart structural abnormalities in rats, which may be correlated with amended serum levels of C-reactive protein, apolipoproteins, leptin, cathepsin G, and homocysteine (Ilkhanizadeh et al., 2016; Shirpoor, 2014). The STZ-disturbed myocardial indices in rats were also restored with declined apoptotic caspase and Bax/Bcl-2 ratio in heart tissue upon 6-gingerol co-administration (Yu et al., 2017). To summarise, the STZ-induced multi-organ toxicity is associated with oxidative stress and inflammation and could be ameliorated effectively with the concomitant administration of ginger.

3.3.3.5. Atorvastatin. Atorvastatin (AT) belongs to the statins group, which used for hyperlipidaemia treatment. Statins-induced liver problems were reported in animal and preclinical studies. However, its hepatotoxicity is controversial and the temporary asymptomatic incline of transaminases may be due to lowered cholesterol level, where no development of chronic liver diseases, with acute liver failure of 0.5–1.0 cases per million was reported in United States (Antonelli et al., 2018). Anyway, the hepatic oxidative stress and the histopathological damage as reported by inclined plasma transaminases in rat received AT orally (20 or 80 mg/kg/day) for 4 weeks were successfully ameliorated by co-administered hydro-alcoholic extract of ginger (400 mg/kg/day) orally (Heeba and Abd-Elghany, 2010). This reported hepato-protection (Table 2) with the antihyperlipidemic effect of ginger could encourage more preclinical studies for its synergistic combination with statins.

3.3.3.6. Gentamycin. Gentamycin (GM) is a well-established antibiotic with common adverse effects as ototoxicity and nephrotoxicity (Hayward et al., 2018). However, therapeutic and prophylactic ameliorative effects were indicated for ginger against GM-induced toxicity (Tables 3 and 7). The pre-treated rats with 2 or 4% ginger in diet for a month ameliorated GM-induced nephrotoxicity (100 mg/kg/day for the last 3 days of the study). It significantly reversed the inclined renal damage biomarkers in plasma (Cr, urea, BUN, and uric acid) with declined renal oxidative stress and increased antioxidant parameters (SOD, CAT, GST, GPx, and GSH) (Ademiluyi et al., 2012). This nephroprotective effect was also indicated for gingerol rich fraction (GRF) in GM-challenged rats (100 mg/kg/day, i.p.) for 7 days and received GRF (25 mg/kg/day) on the fifth day of the study. While declined gene expression of pro-inflammatory mediators (TNF-α, IL-1β, IL-2 and INF-γ) was reported, as well (Rodrigues et al., 2014). 6-gingerol declined the GM-induced apoptotic caspase-3 and anti-heat shock protein 47 (HSP47) as oxidative damage marker in the renal cortex of rats (Hegazy et al., 2016) The GM-induced degeneration in the renal tubules was prevented by pre-treatment of ginger 80% ethanolic extract (Nasri et al., 2013). Ginger co-administration declined the apoptotic cell percentage in rats' testicular tissue (Zahedi et al., 2012).

3.3.3.7. Scopolamine (Hyoscine). Scopolamine (SCP) is an anti-muscarinic, solanaceous alkaloid used in motion thickness, colic, and post-operative nausea or vomiting. Its anti-cholinergic effects contribute to its implementation in dementia models for neurodegenerative diseases. Indeed, ginger extracts were reported to improve the SCP-induced amnesia in mice (Lim et al., 2014; Huh et al., 2018). Briefly, ginger extract (100 mg/kg, intraorally) improved the impaired memory recognition in SCP-challenged mice (1.1 mg/kg, i.p., 30 min before the acquisition of the behavioural test) using novel object recognition test (NORT) and Y-maze tasks. Notably, more time was spent in the novel objects exploration for mice received either fermented or non-fermented ginger extracts (fermented with *Schizosaccharomyces pombe*). In fact, the anti-amnesic effect of fermented ginger extract exceeded that of donepezil-treated mice. In addition, ginger extracts significantly increased the SCP-declined spontaneous alterations proportions in Y-maze task. In both tasks, slight memory improvement was reported for the fermented ginger extract compared from the non-fermented one (Huh et al., 2018). This result was in agreement with the cognitive enhancing effect of super critical fluid extracted ginger (5, 25, and 125 mg/kg) in both normal mice and SCP-induced memory deficit model. The underlying molecular mechanism of memory enhancement may be attributed to the synaptogenic effect of ginger, where it significantly increased pre- and post-synaptic markers (synaptophysin and PSD-95) with inclined nerve growth factor (NGF) levels in the mouse hippocampus and rat glioma C6 cells. The elevated expression of NGF and subsequent phosphorylation of ERK-1/2 and cyclic AMP response element-binding protein (CREB). ERK-1/2 and CREB signalling pathways are involved in the synaptic remodelling, memory formation and consolidation (Lim et al., 2014). In conclusion, memory enhancing, and synaptogenic effects of ginger were reported *via* NGF induced ERK/CREB activation with superior effect of fermented ginger extract (Table 4). These effects might be implemented in the amelioration of the anticholinergic-induced memory deficits.

3.3.3.8. Isoproterenol (Isoprenaline). Isoproterenol (ISO) is a non-selective *β*-adrenergic agonist used in the treatment of bradycardia, and heart block. In large doses may cause myocardial infarction and cardiac injury *via* the induced oxidative stress and hypoxia due to myocardial hyperactivity. However, the 80% ethanolic extract of ginger pre-treated rats (100, 200, and 400 mg/kg/day, p.o., for 28 days) showed a myocardial protective effect against ISO-induced alterations upon the subcutaneous administration of ISO (85 mg/kg/day) for the subsequent 2 days. In brief, the 400 mg dose of ginger extract significantly ameliorated the biochemical and histological ISO-induced perturbations more or less comparable with the positive control (propranolol, 10 mg/kg/day for 28 days). It significantly not only reduced the induced cardiac biomarkers (CK-MB, cardiac troponin-T; cTn-I, ALT, AST, and LDH), but also increased the antioxidant defences (SOD, CAT, and GPx) with improved cell membrane integrity (Amran et al., 2015; Ansari et al., 2006).

3.3.3.9. Dextran. Dextran is a branched glucan used medicinally as antiplatelet, plasma expander in hypovolaemia, and lubricant in eye drops. Although, its medicinal use associated side effects are rare, it still may be serious. Already, dextran sulphate sodium (DSS) is used to induce chronic ulcerative colitis in mice using 2.5% DSS in the drinking water for 3 cycles (7 days each, followed by 2 weeks of normal drinking water). However, a protective effect against the DSS-induced colitis and its mediated testicular damage in mice were reported upon oral co-administration of 6-gingerol (100 mg/kg/day) for the DSS- treated water during the three cycles (Ajayi et al., 2018; Farombi et al., 2018). It reduced the overexpressed cytokines (TNF-α, and IL-1β), and chemokines (Regulated on activation normal T cell expressed and secreted [RANTES], and monocyte chemoattractant protein-1 [MCP-1]) and other inflammatory cellular targets such as NF-ƙB, iNOS, COX-2 and p38 in the colonic tissue. It enhanced IL-10 and adenomatous polyposis coli expression (APC), alongside with the colonic antioxidant

defences (SOD, CAT, GPx, GST, and GSH) (Ajayi et al., 2018). Furthermore, 6- gingerol normalised the induced abnormalities in the reproductive hormones (LH, FSH and testosterone), testicular biochemical indices (ALT, ALP, and ACP), with improved sperm parameters and testicular histo-architecture. To conclude, the antioxidant and anti-inflammatory mechanisms with the preservation of *Wnt*/β-catenin signalling pathway mediated the ameliorative effect of 6-gingerol against DSS-induced toxicities (Tables 5 and 7).

3.3.4. Recreational drugs

3.3.4.1. Alcohol (ethanol). Alcohol overconsumption is a leading morbidity and mortality cause worldwide (Antonelli et al., 2018), it is considered a causal factor in over 200 diseases or clinical impairments (Wang and Ren, 2018; Davis and Bajaj, 2018; Henriques et al., 2018; Tapia-Rojas et al., 2017; Singh et al., 2017). Notably, ginger extracts and fractions offered a protective effect against alcohol-induced toxicities in liver, kidney, heart, brain, and testis in preclinical *in-vivo* models (Tables 2–7). For example, the concurrent oral administration of either *n*-hexane (200 mg/kg/day for 4 weeks) or aqueous (500 mg/kg/day for 2 weeks) ginger extracts ameliorated the ethanol-induced hepatotoxicity in rats and mice, respectively. Not only the liver biochemical markers in serum with the hepatic antioxidant defences were recovered, but also it declined hepatic oxidative stress markers (Nwozo et al., 2014; Shati and Elsaid, 2009). Also, the 1% dietary ginger reversed the hepatotoxic effect of alcohol (2 g/kg/day for 4 weeks) on the antioxidant status in rats (Mallikarjuna et al., 2008). These hepato-protective effects of ginger were also augmented by serum metabolomics study of the ginger essential oil against alcohol-induced fatty liver in mice, where it significantly reversed all the perturbed metabolites (Liu et al., 2013). On the other hand, alcohol-induced renal histopathological degenerations, oxidative damage, and perturbed kidney indices were reversed by concurrent administration of 70 or 95% ethanolic ginger extracts in rats (Shirpoor et al., 2016; Ramudu et al., 2011a; Shanmugam et al., 2010). Furthermore, ginger not only inhibited the alcohol induced gastric ulcers, but also inclined the gastric mucin in rats (Liju et al., 2015; Nanjundaiah et al., 2011; Prakash and Srinivasan, 2010). These gastroprotective effects may be also mediated by ginger's antimicrobial activity against, *H. pylori* and the inhibition of H^+, K^+-ATPase activity (Nanjundaiah et al., 2011) alongside with significant reduction of alcohol-induced oxidative stress. Moreover, the ethanol-induced heart abnormalities in rats were found to be associated with the declined expression of both the alpha/beta myosin heavy chain ratio (α-MHC/β-MHC) in heart tissue, and the plasma level of paraoxonase enzymes level. The paraoxonase is a calcium-dependent esterase located on HDL, which play an important role in the HDL antioxidant ability against LDL oxidation. Besides, it inclined the DNA degradation marker (8-OHdG) and NADPH oxidase level in the heart tissue. While the NADPH oxidase derived ROS played a key role in cardiovascular abnormalities. These ethanol-induced effects in rats received 20% ethanol (4.5 g/kg/day for 6 week) were significantly ameliorated by co-administered ginger 70% ethanolic extract (50 mg/kg/day) intragastrically by gavage. Thus, the ethanol induced heart abnormalities, which may be associated with the dysregulated expression of MHC isoforms and mediated by oxidative stress can be alleviated with the antioxidant capacity of ginger extracts (Shirpoor et al., 2017). Further study, reported the ginger's ability to mitigate the ethanol-induced abnormalities in lipid profiles and plasma cardiac biomarkers (Subbaiah et al., 2017). Last but not least, the antioxidant mediated protective effect against ethanol induced toxicity in the rats' brain and testicular tissue was reported for *Z. zerumbet* L. (Hamid et al., 2018) and *Z. officinale* R (Akbari et al., 2017) extracts, respectively. Overall, ginger extracts can effectively ameliorate the hazardous effects of alcohol abuse, which is one of the main cofactors in various diseases.

3.3.4.2. 3,4-Methylene-dioxy-methamphetamine (MDMA). It is a psychoactive drug, commonly known as ecstasy and consumed for recreational purposes. Though, it is widely banned due to its neurotoxicity and spatial memory impairments, it has been granted a breakthrough designation by the U.S. Food and Drug Administration (FDA) for posttraumatic stress disorder (PTSD) (Kupferschmidt, 2017). Also, a neuroprotective effect was reported for ginger on the MDMA-induced spatial memory impairments in rats upon daily intraperitoneal administration of 10 mg/kg of MDMA for one week. Briefly, ginger 70% ethanolic extract (100 mg/kg/day, i.p., 4hr before MDMA administration for one week) declined the MDMA-induced expression of the apoptotic Bax, caspases-3, 8, and 9 in the hippocampus with inclined anti-apoptotic Bcl-2 (Asl et al., 2013; Mehdizadeh et al., 2012).

3.3.4.3. Nicotine. Nicotine is a parasympathomimetic tobacco alkaloid, which is commonly consumed for its stimulant effects as in chewing tobacco, cigarette, or e-cigarette. Medicinally, it is primarily used in nicotine dependence treatment as gum or dermal patches. Nicotine exposure in tobacco or electronic cigarette results in oxidative injury with the depletion of free radical scavengers, alongside with the promoted inflammatory stresses (Cai and Wang, 2017). Liver, Kidneys, and lungs are targets of the nicotine toxicity. Renal dysfunction in rats was induced by nicotine (0.5 mg/kg/day over 4 weeks) as identified by the abnormalities in kidney function biomarkers (creatinine, urea, sodium, and potassium) with increased renal oxidative stress (MDA), serum inflammatory markers (TNF-α, and vascular cell adhesion protein 1[VCAM-1]) and overexpressed COX-2 and caspase-3. A nephron-protective effect was indicated for the selenium nanoparticle of ginger aqueous extract (0.1 mg/kg/day) administered concomitantly with nicotine. It not only reversed the aforementioned abnormalities, but also increased the antioxidant defences (GSH, GST, and GPx) (Zahran et al., 2017). These antioxidant and anti-inflammatory effects of ginger selenium nanoparticles in a relatively small dose of enhanced nano-formula, can be recommended for smokers against nicotine-induced nephrotoxicity.

3.3.5. Miscellaneous

3.3.5.1. Parabens. It is *p*-hydroxy-benzoates and its esters, which is widely used as preservatives in cosmetic and pharmaceutical products as well. Unfortunately, it has been manifested as being estrogenic and disturbing to the normal oxidative stress status. Concurrent administration of ginger aqueous extract ameliorated the paraben –induced hepatorenal toxicity in mice. It increased the antioxidant defences (SOD, GPx, CAT, ascorbic acid and GSH) in the liver. Besides, it alleviated the paraben-induced abnormalities in the hepatorenal biochemical markers in serum samples (Asnani and Verma, 2009; Verma and Asnani, 2007). Also, declined the paraben-induced lipid peroxidation *in-vitro* in both kidney and liver homogenate (Asnani and Verma, 2007).

3.3.5.2. Monosodium glutamate (MSG). It is generally recognised as safe (GRAS) flavour enhancer by FDA, but subject to the quantitative limits in the European Union. It elicited neurotoxicity in rats received 100 mg/kg/day of MSG for 2 months as manifested by inclined DNA oxidative marker; 8-OHdG, NO and lipid peroxidation as well as accumulated β-amyloid proteins and alternation of the neurotransmitter levels in the brain tissue. Nonetheless, the concurrent oral administration of ginger powder (500 mg/kg/day, for 8 weeks) suppressed MSG-induced alteration with inclined antioxidant defences (SOD, CAT and GSH) (Hussein et al., 2017). Also, the aqueous ginger extract (100 mg/kg/day, i.p., for 30 days) increased the declined neurotransmitters (epinephrine [E], norepinephrine [NE], dopamine [DA] and serotonin [5-HT]) in rat cerebellum, brainstem, striatum, cerebral cortex, hypothalamus and hippocampus upon MSG treatment (4 mg/kg/day, i.p., for 30 days) (Waggas, 2009).

3.3.5.3. Carbon tetrachloride. Carbon tetrachloride (CCl_4) is a volatile organic solvent used in the halogenation reactions, nuclear magnetic resonance (NMR), and infrared (IR) spectroscopy. As a potent hepatotoxin it is widely used in the research of the hepato-protective agents, as well. Hepatoprotective properties were indicated for different extracts of *Z. officinale R*. and its combinations with either rosemary (Essawy et al., 2018) or curcumin (Abd-Allah et al., 2016b) as well as the pure zingerone compound (Cheong et al., 2016). Ginger treatments successfully reversed the CCl_4-induced histopathological hepatic damage and inclined serum hepatic indices and oxidative stress, while increased the declined antioxidant enzymes (Jaffat et al., 2016; Essawy et al., 2018; Hasan et al., 2016; Cheong et al., 2016; Abd-Allah et al., 2016b). These protective effects may be mediated *via* the downregulation of NF-κB/IκB and transforming growth factor-beta-1 (TGF-β1/Smad3) pathways (Hasan et al., 2016; Cheong et al., 2016). On the other hand, CCl_4 induced a renal-toxicity in rats as manifested by the inclined inflammatory markers (TNF-α, IL-1β, IL-2, and iNOS), kidney biochemical indices (Creatinine, and BUN) in serum, as well as the apoptotic caspase-3 and caspase-9 overexpression. Moreover, it inclined the oxidative stress marker (thiobarbituric acid reactive substance; TBARS) and declined renal antioxidant enzymes as well. While, the rats received zingerone pre-treatments (100 mg/kg/day, p.o., for 15 days) significantly reversed all the CCl_4-induced abnormalities in the kidney tissue (Safhi, 2018).

3.3.5.4. Di-alkyl nitrosamine. It is a group of highly toxic organic chemicals and well-known carcinogens. This group includes diethylnitrosamine (DEN) and dimethylnitrosamine (DMN), which found in tobacco smoke or as a by-product of several industrial processes, respectively. Orally administered zingerone in rats (10 and 20 mg/kg/day) ameliorated the DMN-mediated liver fibrosis. It declined the DMN-induced phosphorylation of extracellular signal-regulated kinase (c-Jun NH2-terminal kinase, and MAPKs). It significantly reversed the DMN-induced hepatic histopathological abnormalities and inclined hepatic biochemical markers (ALT, and AST), as well as the liver fibrosis marker (hydroxyproline), and the hepatic stellate cells activation (Cheong et al., 2016). Likewise, the 90% ginger extract (90 mg/kg/day, p.o., for 8 weeks) reported a hepatoprotective effect against the premalignant stages of the DEN-initiated and CCl_4-promoted hepatocarcinogenesis model in rats. It also normalised the induced serum hepatic tumour markers (α-fetoprotein [AFP] and carcinoembryonic antigen [CEA]), the hepatic hydroxyproline content, and the hepatic growth factors (VEGF, TGF-β1, and basic fibroblast growth factor [FGF]) as well. Moreover, it increased the declined hepatic level of the antiangiogenic factor (endostatin), and the metallothonein, which is responsible for metal binding and oxidative stress control (Mansour et al., 2010).

3.3.5.5. Bromobenzene. Bromobenzene (BB) is a volatile reagent used in organic synthesis for phenyl group introduction into other compounds. It may be released into the environment during its production or its use in motor oil as an additive and solvent. Though its low detection levels in food samples, its metabolites are highly hepatotoxic and nephrotoxic, however, ginger ethanolic extract (100, 200, and 300 mg/kg/day for 3 weeks) alleviated the BB-induced hepatotoxicity (460 mg/kg/day during the third week) in rats. It reversed the elevated liver biochemical markers (AST, ALT, bilirubin and protein), and recovered the antioxidant parameters (SOD, GR, GST, GPx and GSH) as well as, declined oxidative stress, caspase-3 and COX-2 expression (El-Sharaky et al., 2009).

3.3.5.6. Chromate. It is a coloured salt of chromium used as a pigment before being discouraged by environmental regulation. It used as titrant in redox chemical reaction due to its oxidizing power, which accounts for its toxicity and carcinogenicity especially when airborne. Then again, ginger 2% in the diet ameliorated the chromate-induced hepatorenal toxicities in rats. It decreased the induced hepato-renal biochemical indices and increased the GSH level in both liver and kidney tissue (Krim et al., 2013).

3.3.5.7. Gasoline. Both lipid and protein oxidation markers were elevated in blood and eyes samples of rats exposed to leaded gasoline vapours (18.18 ppm for 3, 6, 9, and 12 h/day for 14 days) with declined GSH level, as well. This gasoline induced oxidative stress in rats was significantly reversed upon concurrent oral administration of 100 mg/kg/day ginger power (El-Hak et al., 2015).

3.3.5.8. Dioxin. Dioxins and dioxin-like compounds are extremely toxic and persistent organic pollutants, which are produced as by-products of various industrial processes, metal production, waste incineration, and both fossil-fuel and wood combustion. For instance, the 2,3,7,8-tetracholorodibenzo-p-dioxin (TCDD)-induced a colon cancer initiation in rats. But, the co-administered poly-lactic-*co*-glycolic acid (PLGA) encapsulated *Zingiber officinale* nanoparticles significantly enhanced the declined antioxidant defences (SOD, CAT, GPx, and GST) with inclined anti-apoptotic Bcl-2 expression and downregulated the TCDD-overexpressed apoptotic Bax and p53 genes (Abdu et al., 2017).

3.3.5.9. Di-n-butyl phthalate (DBP). It is a common synthetic plasticiser of phthalate ester's family, which is disturbing the normal reproductive organ growth. The protective effect of concomitant oral administration of ginger (400 mg/kg b.w.) was studied in rabbits received an oral DBP dose of 520 mg/kg b.w. All the treatments were given three times a week for seven weeks. The induced abnormalities on testis and prostate weights with declined testicular MDA level were ameliorated. Also, the co-administered ginger improved the sperm parameters (count, mass, live sperm percentage, and motility) (Oda and Waheeb, 2017).

3.4. The protective mechanisms of ginger and relevant constituents

The antioxidant, anti-inflammatory and anti-apoptotic properties of ginger and its constituents may be the major contributors in its protective effects versus toxic agents. On one hand, the reactive oxygen species (ROS) played a vital role in regulating normal cellular processes *via* signalling cascades regulation, such as JNK, ERK, and MAPK pathways (Droge, 2002). This will be followed by the modulation of fundamental transcription factors such as NF-ƙB, Nrf2, AP1, and p53 (Hamanaka and Chandel, 2010; Trachootham et al., 2008). On the other hand, higher levels of ROS may trigger various diseases include cancers, this will be also toxic to the cancer cells, but detoxified through the maintained higher levels of antioxidants in cancer cells (Nogueira and Hay, 2013). Thus far, a balance between the intracellular ROS and quenching mechanisms will be required.

Ginger and its natural products ameliorated the oxidative and/or nitrosative damage with the accompanied inflammation induced upon the exposure to radiation (Table 1), or either chemical or natural toxic agents as summarised in (Tables 2–7). The protective effect against oxidative stress could be mediated *via* Nrf2 transcription factor activation by 6-gingerol (Lee et al., 2011) zerumbone (Tang et al., 2011) ginger's oleoresin (Ji et al., 2017) shogaol, or dehydrogingeridone (Peng et al., 2015; Yao et al., 2014). Briefly, Nrf2 is regulated by Kelch-like ECH-associated protein 1 (Keap1), and an adaptor subunit Cullin 3 (Cul3)-Rbx E3 ubiquitin ligase, which mediated the nrf2-degradation by proteasomes. Conformational changes to this complex upon exposure to ROS or specific binding of ginger's phytochemicals with cysteine residue of Keap1 will lead to Nrf2 activation (Fig. 1). The activated Nrf2 will be translocated to the nucleus to bind the antioxidant response element (ARE) in the Nrf2 target genes with synchronised activation of detoxifying antioxidant enzymes expression and GSH synthesis (SOD, CAT, GST, and GPx). Moreover, the upregulated phase II enzymes will facilitate xenobiotic metabolism and excretion of the toxic agents with the inclined cell survival, proliferation and DNA repair (Bellezza et al.,

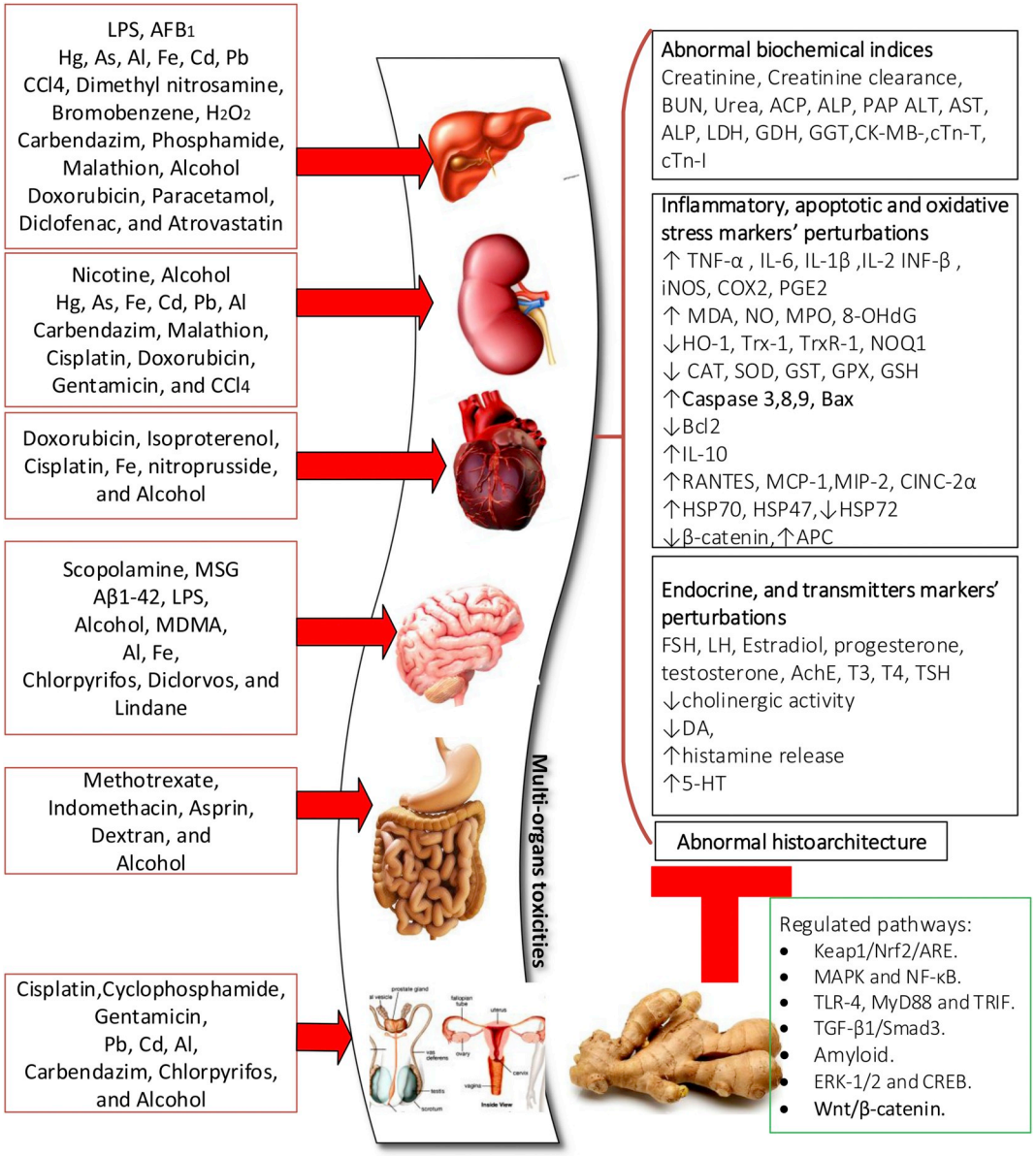

Fig. 2. Protective effects of ginger against biological and chemical-induced toxicities

5-HT; serotonin, 8-OHdG; 8-hydroxydeoxyguanosine, Aβ; Amyloid β-protein, AChE; Acetylcholinesterase, ACP; Acid phosphatase, Al; Aluminium, ALP; Alkaline phosphatase, APC; Adenomatous polyposis coli, ARE; Antioxidant response element, As; Arsenic, AST; Aspartate aminotransferase, Bax; Bcl-2-associated X, Bcl2; B-cell lymphoma-2, BUN; Blood urea nitrogen, Cd; Cadmium, CAT; Catalase, CCl_4; Carbon tetrachloride, CINC-2α; cytokine-induced neutrophil chemoattractant, CK-MB; Creatine kinase MB isoenzyme, COX-2; Cyclooxygenase-2, CREB; Cyclic AMP response element-binding protein, Ctn-T; cardiac troponin-T, Ctn-I; cardiac troponin-I, DA; Dopamine, ERK; Extracellular signal-regulated kinases, Fe; Iron, FSH; Follicle stimulating hormone, GDH; Glutamate dehydrogenase, GGT; gamma glutamyl transferase, GSH; Glutathione, GST; Glutathione-s-transferase, GPX; Glutathione peroxidase, H_2O_2; Hydrogen peroxide, Hg; Mercury, HO-1; Heme oxygenase-1, HSP; Heat shock protein, IL; Interleukin, INF-β; Interferon-β, iNOS; Inducible nitric oxide synthase, LDH; Lactate dehydrogenase, AFB1; Aflatoxin B1, LH; Luteinising hormone, LPS; Lipopolysaccharide, Keap1; Kelch-like ECH-associated protein 1, MAPK; Mitogen activated protein kinase, MPO; Myeloperoxidase, MCP-1; Monocyte chemoattractant protein-1, MDA; Malonaldehyde, MDMA; 3,4-Methylene-dioxy-methamphetamine, MIP-2; macrophage inflammatory protein-2, MSG; Monosodium glutamate, MyD88; Myeloid differentiation primary response-88, NF-ƙB; Nuclear factor-kappa B, NOQ1; NADPH quinone oxidoreductase 1, NO; Nitric Oxide, Nrf2; Nuclear translocation of nuclear factor erythroid2-related factor 2, PAP; Prostatic acid phosphatase, ALT; Alanine transaminase, PEG2; Prostaglandin E2, Pb; Lead, RANTES; Regulated on activation normal T cell expressed and secreted, SOD; Superoxide dismutase, T3; Triiodothyronine, T4; Thyroxine, TGF-β1; transforming growth factor-beta1, TLR-4; toll-like receptor-4, TNF-a; Tumour necrosis factor alpha, TRIF; TIR-domain-containing adapter-inducing interferon-β, Trx-1; Thioredoxin reductase 1, TrxR-1; Thioredoxin reductase 1, TSH; Thyroid stimulating hormone, *Wnt*/β-catenin; Wingless/integrated beta catenin pathway.

2018; Rojo de la Vega et al., 2018). Furthermore, 6-gingerol inhibited the excess production of ROS by a mechanism related to autophagy induction (Wang et al., 2016b). Additionally, ginger's phytochemicals attenuated the lipid peroxidation induced by the exposure to either radiation or toxic agents in both *in-vitro* and *in-vivo* models. As it declined the lipid peroxidation maker; MDA in the liver (Salihu et al., 2016; Mukherjee et al., 2015; Alqasoumi et al., 2011; Mallikarjuna et al., 2008; Shati and Elsaid, 2009; Essawy et al., 2018; Cheong et al., 2016; Abd-Allah et al., 2016b; El-Sharaky et al., 2009; Asnani and Verma, 2009; Verma and Asnani, 2007), kidney (Salihu et al., 2016; Zahran et al., 2017; Onwuka et al., 2011; Alibakhshi et al., 2018; Rodrigues et al., 2014), brain (Zeng et al., 2013; Sutalangka and Wattanathorn, 2017; Abolaji et al., 2017), heart (Ajith et al., 2016), GIT (Zaghlool et al., 2015; Ko and Leung, 2010), and testis (Akbari et al.,

2017; Afkhami Fathabad et al., 2017; Oda and Waheeb, 2017) of the challenged animals (Fig. 2).

Another key protective point of ginger's natural compounds to be considered is the ability to significantly reverse the toxins-induced pro-inflammatory and apoptotic responses (Fig. 1). Inflammation is playing a central role to eliminate the damaged cells and the original insult-inducing toxins for the initiation of tissue repair. Besides, the toxin-induced cellular stress may lead to programmed cell death or in other term; apoptosis. Ginger constituents suppressed the toxin-induced cytokines (TNF-, α, IL-6, IL-8, IL-2 and IL-1β), PLA2, iNOS, COX2, and PGE_2 (Tables 1–7). Additionally, ginger extracts reduced acetic acid induced chemokines such as macrophage inflammatory protein 2-alpha (MIP2-α) and Cytokine-induced neutrophil chemoattractant-2-alpha (CINC-2α) (Ko and Leung, 2010). Both are powerful chemoattractant of neutrophils and are involved in many immune responses. Alongside with 6-gingerol inhibitory effect on other chemokines such as RANTES, and MCP-1 (Ajayi et al., 2018). The exhibited anti-inflammatory activity of ginger phytochemicals may be attributed to NF-KB pathway attenuation (Kim et al., 2007; Xie et al., 2014; Ho et al., 2013; Ha et al., 2012; Ajayi et al., 2018) and inhibiting the phosphorylation of MAPKs, ERK1/2, p38 MAPK and c-Jun N-terminal kinase (Lee et al., 2018a, 2018b; Xie et al., 2014; Cheong et al., 2016). It also increased the anti-inflammatory cytokine; IL-10 (Wang et al., 2016b). Additionally, ginger's constituents increased the anti-apoptotic proteins such as Bcl-2 with declined apoptotic proteins like caspase-3 (Thongrakard et al., 2014; Soliman et al., 2018; Baiomy and Mansour, 2016; Safhi, 2018), caspase 8, caspase 9 (Safhi, 2018; Asl et al., 2013; Mehdizadeh et al., 2012) and Bax. It downregulated the proto-oncogene; C-fos (Baiomy and Mansour, 2016) together with the vital apoptosis regulatory Bax/Bcl-2 ratio (Chung et al., 2015; Shim et al., 2012; Ali et al., 2015; Asl et al., 2013; Mehdizadeh et al., 2012; Yu et al., 2017).

Other signalling pathways were also involved in the protective effect of ginger against toxic agents. For instance, the hepato-protective effect of ginger was accompanied with the downregulation of TGF-β1/Smad3 pathway (Hasan et al., 2016). Also, the gastroprotective effect (Table 5) was associated with the preservation of *Wnt*/β-catenin pathway, where it declined the induced β-catenin and increased its destruction complex APC (Ajayi et al., 2018). The β-catenin and APC balance is vital for intestinal haemostasis (Ajayi et al., 2016) and its dysregulations were reported in colon cancer and colitis (Cosin-Roger et al., 2013; Shenoy et al., 2012). Moreover, These gastroprotective effects of ginger may be also mediated by ginger's antimicrobial activity against, *H. pylori* and the inhibition of H^+, K^+-ATPase activity (Nanjundaiah et al., 2011). By the same token, neuroprotective effect (Table 4) was reported for ginger and its components, by regulating the amyloidogenic pathway (Halawany et al., 2017) and hampering the neuro-inflammation. Additionally, it improves the induced amnesia in mice (Lim et al., 2014; Huh et al., 2018). The memory enhancing, and synaptogenic effects of ginger were reported *via* NGF induced ERK/CREB activation (Lim et al., 2014). These effects might be implemented in the amelioration of the induced memory deficits by anticholinergic medications.

Selective protection offered by ginger's phytochemicals to the normal cells against radiotherapy (Baliga et al., 2012; Chiang et al., 2018) with behavioural radioprotection (Haksar et al., 2006; Sharma et al., 2005) were reported together with its antidotal effect in chemotherapeutic regimens containing cyclophosphamide, doxorubicin, and cisplatin. This could represent a base for more preclinical and clinical studies of the protective effects of ginger's phytochemicals as not only radioprotective agents, but also in the chemotherapy adverse effects amelioration, together with its antiproliferative, antitumor, and anti-invasive effects as an extra bonus (de Lima et al., 2018). Protective and detoxifying effect of enhanced nano-formulations of ginger or fermented ginger (Huh et al., 2018) in a relatively small doses (0.1 mg/kg/day) (Zahran et al., 2017) can be recommended for smokers, over alcohol consumers, or patient exposed to other toxic agents.

4. Conclusion

Numerous investigations demonstrated the prophylactic and therapeutic protective effect of ginger and its arsenal of metabolites such as 6-gingerol, 6-shogaol, zingerone, and zerumbone. The antidotal effects of ginger were summarised against a wide range of toxins such as environmental pollutants, heavy metals, pesticides, radiation, drugs, bacterial and fungal toxins in both *in-vitro* and *in-vivo* models. Furthermore, the mechanisms of protection were scrutinised, which may be attributed to its antioxidant, radical scavenging, and the regulation of the apoptotic and inflammatory responses. Ginger's armoury of phytochemicals exerted its protective function *via* different mechanisms and cell signalling pathways. This extensive review highlights the importance of ginger's constituents in cancer treatment regime, not only as a radioprotective agent with selective protection to the normal cells but also due to its ameliorative effect of the chemotherapy-induced toxicities. The protective effects of ginger and its components could offer some benefits to smokers, over alcohol consumers and/or elderly patients who are receiving multiple medications or human and/or animal exposed to toxic agents. The findings of this review have provided preclinical evidence to support ginger's protective effects in a diverse range of radiation-, natural- and chemical-induced toxicities. Clinical investigations into its uses in these areas are warranted.

Acronyms and abbreviations

5-HT	Serotonin
6-GRF	6-gingerol rich fraction
8-OHdG	8-hydroxydeoxyguanosine
Aβ	Amyloid β–protein
ACE-I	Angiotensin-I converting enzyme
AChE	Acetylcholinesterase
ACP	Acid phosphatase
ADI	Acceptable daily intake
AFB1	Aflatoxin B1
Akt	Protein kinase B
Al	Aluminium
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Adenomatous polyposis coli
ARE	Antioxidant response element
AST	Aspartate aminotransferase
As	Arsenic
BALF	Bronchoalveolar lavage fluid
Bax	Bcl-2-associated X
Bcl-2	B-cell lymphoma-2
BDNF	Brain-derived neurotrophic factor
BNP	B-natriuretic peptide
BUN	Blood urea nitrogen
b.w.	Body weight
CAT	Catalase
Cd	Cadmium
CINC-2α	Cytokine-induced neutrophil chemoattractant 2α
COX-2	Cyclooxygenase-2
CREB	Cyclic AMP response element-binding protein
cTnT	cardiac troponin-T
CTA	conditioned taste aversion
CK-MB	Creatine kinase MB isoenzyme
DA	Dopamine
DNMT1	DNA cytosine-5 methyltransferase1
DRF	Dose reduction factor
E2	Estradiol
ERK	Extracellular signal-regulated kinases
FDA	Food and drug administration
Fe	Iron
FSH	Follicle stimulating hormone

G6PD	Glucose-6-phosphate dehydrogenase
γ -GCLC	Gamma-glutamyl cysteine ligase
γ-GTP	Gamma glutamyl transpeptidase
GDH	Glutamate dehydrogenase
GFAP	Glial fibrillary acidic protein
GGT	Gamma glutamyl transferase
Gy	Gray
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Glutathione
GST	Glutathione-s-transferase
HDAC1	Histone deacetylase 1
Hg	Mercury
HO-1	Heme oxygenase-1
HSP	Heat shock protein
INF	Interferon
iNOS	Inducible nitric oxide synthase
i.p.	intraperitoneal
i.v.	Intravenous
Keap1	Kelch-like ECH-associated protein 1
LD50/30	Lethal dose expected to kill half the mice in 30 days
LDH	Lactate dehydrogenase
LH	Luteinising hormone
LPS	lipopolysaccharide
MAPK	Mitogen activated protein kinase
MAD	Malonaldehyde
MCP-1	Monocyte chemoattractant protein-1
MDMA	3,4-Methylene-dioxy-methamphetamine
MDH	Malate dehydrogenase
MHC	Myosin heavy chain
MIP-2	Macrophage inflammatory protein-2
MPO	Myeloperoxidase
MyD88	Myeloid differentiation primary response-88
NQQ-1	NADPH quinone oxidoreductase 1
NF-κB	Nuclear factor-kappa B
NGF	Nerve growth factor
NO	Nitric Oxide
NORT	Novel object recognition test
Nrf2	Nuclear translocation of nuclear factor erythroid2-related factor 2
NSAID	Non-steroidal anti-inflammatory drugs
PAP	Prostatic acid phosphatase
Pb	Lead
PCNA	Proliferating cell nuclear antigen
PCOS	Polycystic ovary syndrome
PGE_2	Prostaglandin E_2
p.o.	Per oral
PSD-95	postsynaptic density protein 95
PTSD	Posttraumatic stress disorder
QR	Quinine reductase
RANTES	Regulated on activation normal T cell expressed and secreted
ROS	Reactive oxygen species
SDH	Succinate dehydrogenase
SOD	Superoxide dismutase
T3	Triiodothyronine
T4	Thyroxine
TBARS	Thiobarbituric acid reactive substance
TERT	Telomerase reverse transcriptase
TGF-β1	Transforming growth factor-beta1
TLR-4	Toll like receptor-4
TNF-α	Tumour necrosis factor alpha
TRIF	TIR-domain-containing adapter-inducing interferon-β
Trx-1	Thioredoxin reductase 1
TrxR-1	Thioredoxin reductase 1
TSH	Thyroid stimulating hormone
UV	Ultraviolet
VCAM-1	Vascular cell adhesion protein 1
VEGF	Vascular endothelial growth factor
WHO	World health Organisation
Wnt/β-catenin	Wingless/integrated beta catenin pathway

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