



Exploring phytotherapeutic approach in the management of valproic acid-induced toxicity

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Abstract

The antiepileptic drug, valproic acid (VPA), also used for treating psychiatric disorders, is hampered by its toxicity. Its associated adverse effects include hepatotoxicity, nephrotoxicity, central nervous system (CNS) depression, respiratory failure, acute pancreatitis, thrombocytopenia, hyperammonaemia, bone marrow suppression, and teratogenicity. Currently, no antidotes exist for treating VPA toxicity and therapeutic management is majorly supportive while modifying drug disposition. The lack of effective treatment has prompted evaluating plant-derived products to manage this challenge since studies show their protective potential against drug-induced toxicities. This review investigates purported mechanisms and the protective capacity of plants products against VPA-induced toxicity. The compiled studies revealed that VPA causes hepatotoxicity, nephrotoxicity, ocular toxicity, teratogenicity and reproductive toxicity among others. Further findings highlighted the oxido-inflammatory and apoptotic pathway as crucial mechanisms of VPA-induced organ toxicities. Extracts of *Apium graveolens* L., *Bacopa monniera*, *Green tea*, *Kaempferia parviflora*, *Korean red ginseng*, *Ocimum sanctum*, *Oryza sativa*, *Withania somnifera* and plant-derived compounds, including diammonium glycyrrhizinate, sulforaphane, vitamin U, B6, E, diallyl trisulfide, curcumin, α -tocopherol, quercetin, piperine, resveratrol, hesperitin, thymoquinone, caffeic acid and asiatic acid exhibited protection against VPA-induced toxicities. From these observations, it is suggested that further studies should target evaluating more plant products as well as identifying and isolating specific compounds from such, and others demonstrating protective effect against toxicities induced by VPA.

Keywords Phytotherapy · Antioxidants · Oxido-inflammatory · Valproic acid toxicity · Oxidative stress

Abbreviations

VPA	Valproic acid
CNS	Central nervous system
GABA	γ -Aminobutyric acid
DNA	Deoxyribonucleic acid
ROS	Reactive oxygen species

MDA	Malondialdehyde
GSH	Reduced glutathione
SOD	Superoxide dismutase
CAT	Catalase
GPX	Glutathione peroxidase
Nrf2	Nuclear factor E2-related factor 2
ARE	Antioxidant response elements
TNF- α	Tumor necrosis factor- α
IL-1 β	Interleukin-1 β
IFN- γ	Interferon gamma
iNOS	Inducible nitric oxide synthase
NF- κ B	Nuclear factor-kappa B
COX-2	Cyclooxygenase-2
Bax: Bcl-2	Associated X protein
ROS	Reactive oxygen species
pNf-kB	Phosphonuclear factor kappa B
Keap1	Kelch-like ECH-associated protein 1
NTDs	Neural tube defects
ASD	Autism spectrum disorder
HDAC	Histone deacetylase

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PARP	Poly (ADP-ribose) polymerase
Bcl-2	B-cell lymphoma protein 2l
ATP	Adenosine triphosphate
mtDNA	Mitochondrial DNA
MEK	Mitogen-activated protein kinase
ERK	Extracellular regulated kinase
MPT	Mitochondrial permeability transition
LH	Luteinizing hormone
FSH	Follicle stimulating hormone
MDA	Malondialdehyde
GST	Glutathione-S-transferase
GPX	Glutathione peroxidase
GR	Glutathione reductase
MPP	Mitochondrial permeability transition pore
ALT	Alanine amino transaminases
AST	Aspartate amino transaminases
ALP	Alkaline phosphatase
LDH	Lactate dehydrogenase
DTA	Diallyl trisulfide
TJ-960	Shosaiko-to-go-keishikashakuyaku-to
H ₂ O ₂	Hydrogen peroxide
HO-1	Heme oxygenase 1

Introduction

Valproic acid (VPA, valproate, Fig. 1); a drug used originally in clinical practice as an antiepileptic drug, is also being used for the treatment of bipolar disorder, migraine, schizoaffective disorders, neuropathic pain and social phobias (Mangewala et al. 2013). The most understood mechanism of action of VPA is the enhancement of γ -aminobutyric acid (GABA) synthesis, inhibition of GABA metabolism as well as interruption of GABA reuptake into nerve endings (Manoguerra et al. 2008; Monti et al. 2009). Despite the fact that VPA is generally tolerated by most patients, cases of adverse reactions following chronic usage have been reported, these include hepatotoxicity, hyperammonaemic encephalopathy, bone marrow suppression, haemorrhagic pancreatitis and teratogenicity (Lheureux et al. 2005; Brotzmann et al. 2020). VPA poisoning from intentional or accidental ingestions is on the increase because it is now being used in the

treatment of psychiatric disorders. Although such poisonings usually lead to mild central nervous system (CNS) depression; severe toxicity leading to fatal cases have been recorded (Lheureux et al. 2005; Manoguerra et al. 2008). The increasing rate of VPA-induced adverse effect might be attributed to the lack of a definite antidote or effective and generalised common treatment to ameliorate the toxic effects of the drug since limited improvements have been observed following known medical treatments, including L-carnitine, activated charcoal, haemodialysis or haemofiltration and the use of antioxidants (Lheureux et al. 2005).

The major effects of VPA poisoning include hepatotoxicity, renal failure, CNS depression, respiratory failure, acute pancreatitis, leucopenia, drowsiness and thrombocytopenia (Meek et al. 2004). Strategies in the management of VPA poisoning is mainly supportive, involving the modification of the disposition of the drug by either hampering its absorption or increasing its elimination, using procedures, such as administration of oral absorbents (activated charcoal), induced haemodialysis and haemoperfusion (Meek et al. 2004; Lheureux et al. 2005). To prevent the increased rate of VPA-induced foetal disorders, reduced dose is often recommended in addition to taking folic acid (Morceau et al. 2010), while VPA-induced decreases in fertility can be prevented, to a large extent, by administration of folic acid, 5-formyltetrahydrofolate, and S-adenosylmethionine (Ubeda-Martin et al. 1998).

Since the most understood mechanism via which VPA induces its toxic effects is oxidative stress and activation of inflammatory responses, antioxidants and antiinflammatories have been investigated as potential therapeutic options. More so, in the past few decades, there has been a renewed interest in plant products, based on the fact that some products have been developed into new drugs, and even huge chances of many more new drugs being developed. Plant products have been used in the management and treatment of a number of diseases, including diabetes, cancer and malaria, because of their presumed efficacies and relative safety compared to synthetic molecules. However, there is little or no consolidated information on the efficacy of plant products in the prevention and amelioration of VPA-induced toxicities. This review, therefore, investigates the protective capacity of plants products against VPA-induced toxicity. Identification, characterisation and isolation of specific compounds with ameliorative effect against VPA-induced toxicity from the plants may help resolve the drawback associated with the usage of this important drug. Scientific databases including Google Scholar, Mendeley, PubMed and ScienceDirect were searched for relevant information on plant products having protective activity against valproic acid-induced toxicities. The keywords used included valproic acid,

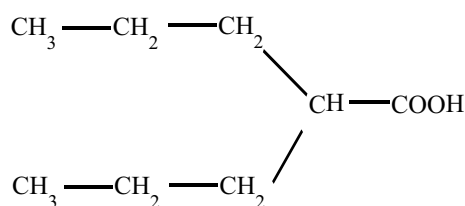


Fig. 1 Structure of Valproic acid

valproate, valproic acid-induced, valproate-induced, plants extract and extract.

Phytotherapeutic preparations

Phytotherapeutic preparations are extracts obtained from plants; they are obtained by various extraction methods and they have varied bioactive components (Sharma et al. 2017). It has been observed that skepticism still exists about the reliance on phytotherapeutic approach in the management and treatment of diseases. This is because phytotherapeutic approach is sometimes seen to have more academic value rather than real-time or real-life clinical application, considering the unharmonized and mis-standardized practices prevailing in medicine systems relying on phytotherapeutic approach. Thus, there are always serious unanswered questions with phytotherapeutic approach due to insufficient knowledge of their mode of action, possible adverse reactions, contraindications, and interactions with existing conventional pharmaceuticals and functional foods (Ekor 2014). However, the use of phytotherapeutic agents or herbal medicinal products is as old as man, and it is even on the increase over the past few decades with about 80% of people worldwide depending on them for some part of primary healthcare (Bodeker et al. 2005; Ekor 2014), including developed countries such as the UK and the rest of Europe, as well as Australia and North America (Calapai 2008; Braun et al. 2010; Anquez-Traxler 2011; Ekor 2014). Studies have also shown that about 25 percent of medicines have originated from plant products, thus medicinal plants represent unlimited, interesting, and attractive sources of new bioactive compounds to identify and investigate for therapeutic purposes (Varoni et al. 2015; Luiz and Piazza 2019). This review is thus intended to compile information on plant products that have been shown to exhibit protective potentials against VPA-induced toxicities, as discussed in the following sections.

Proposed mechanisms of VPA-induced toxicity

The metabolism of VPA takes place primarily in the liver via cytochrome P450, fatty acid and β -oxidation. Thereafter, it is conjugated to yield active and inactive metabolites some of which are highly reactive and toxic, such as 2, 4-diene-VPA which can form glutathione conjugate altering glutathione homeostasis and other metabolites which are capable of binding to embryonic or fetal nucleic acids leading to disruption of normal growth and development, hypoglycin as well as pantoic acid, which inhibits β -oxidation strongly associated with hepatotoxicity (Silva et al. 2008; Chen et al. 2014; Akhondian et al. 2015; Nazmy et al. 2016). Although the mechanism of VPA-induced organ toxicity is still not entirely clear, evidences from studies using different

experimental models have suggested that oxidative stress and induction of inflammatory cytokines (Tong et al. 2005a, b; Kiang et al. 2011; Jin et al. 2014) are key factors, with resultant organ injury. Up-regulation or expression of pro-inflammatory cytokines as well as apoptotic biomarkers have also been associated with increased oxidative stress in such organs exposed to VPA (Fig. 2). Most often, the consequence of these happenings especially when sustained for a reasonable duration is damage to DNA.

In the prognosis of VPA-induced teratogenesis, damage accumulated within foetuses due to excess reactive oxygen species (ROS) most frequently results in the failure of the neural tube to completely close during organogenesis (spina bifida) and may lead to reduced post-natal cognitive function (Tung and Winn 2011). The increase in malondialdehyde (MDA) levels and corresponding decreases in reduced glutathione (GSH) levels and intracellular antioxidants superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) in cerebellum, astrocytes and other type of brain cells have also been reported in the neurotoxicity of VPA as a mechanism underlying its teratogenic effects (Hamzawy et al. 2018). Consequently this increase in ROS favours the formation of DNA double strand breaks and impairs its repair (Servadio et al. 2018). There is also evidence showing a link between elevated levels of ROS and the transcription factor nuclear factor E2-related factor 2 (Nrf2) which subsequently induces expression of antioxidant response elements (ARE)-containing genes. VPA has been shown to induce gene transcription in an ARE-dependent manner for these same genes (Kawai and Arinze 2006; Hamzawy et al. 2018).

An oxido-inflammatory mechanism is also reported in VPA modelled autism with severe changes in serum inflammatory cytokines: tumor necrosis-alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6) and elevations in apoptosis in differentiating hippocampal neurons and astrocytes. This corroborates well documented evidences that autistic individuals are more vulnerable to neuroinflammation accompanied with altered inflammatory response. This may be due to over activation of the monocytic (increased IL-1RA) and Th-1-like (increased IFN-gamma) in the inflammatory response system (Wang et al. 2011; Hamzawy et al. 2018). Increased nuclear factor-kappa B (NF- κ B) and p53 levels as well as expression of its target genes, hyperacetylation of p53, and markers of the intrinsic apoptotic pathway in neurulation and midorganogenesis murine limbs has also been observed with VPA-induced embryotoxicity (Dawson et al. 2006; France-Hélène and Barbara 2015). During VPA-induced hepatic toxicity, the mitochondrial oxidant stress depletes GSH whilst increasing levels of ROS and inhibiting the antioxidant function of SOD in murine hepatic microsomal systems (Santos et al. 2008; Komulainen et al. 2015; Li et al. 2015). This alteration in antioxidant defence

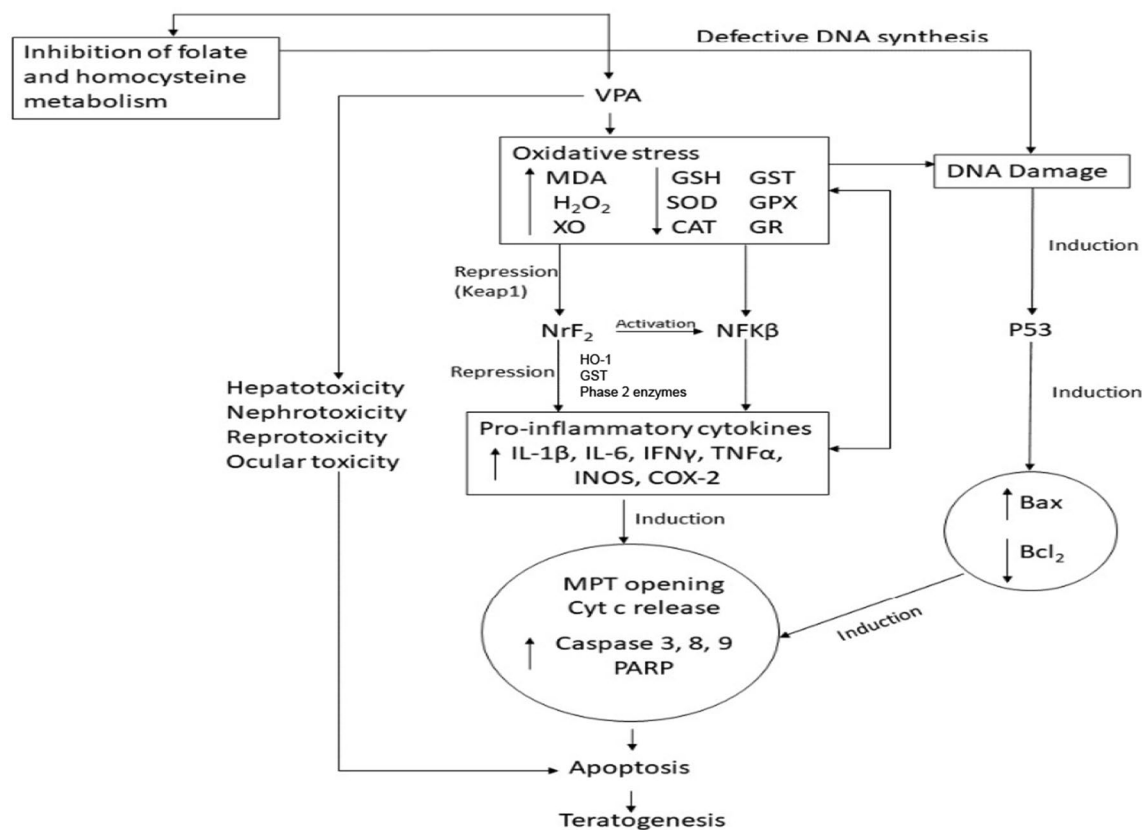


Fig. 2 Schematic representation of the oxido-inflammatory and apoptotic pathway of VPA-induced organ toxicity. VPA: valproic acid; MDA: malondialdehyde; H_2O_2 : hydrogen peroxide; XO: xanthine oxidase; GSH: reduced glutathione; SOD: superoxide dismutase; CAT: catalase; GST: glutathione-S-transferase; GPX: glutathione

peroxidase; GR: glutathione reductase; Nrf2: nuclear factor erythroid 2-related factor 2; HO-1: heme oxygenase 1; NF κ B: nuclear factor kappa-light chain-enhancer of activated B cells; IL: interleukin; IFN γ : interferon gamma; TNF α : tumor necrosis alpha; iNOS: inducible nitric oxide synthase

is likely associated with VPA-induced mitochondrial DNA damage and subsequent apoptosis (Li et al. 2015). The redox sensitive transcription factor NF- κ B is also reportedly crucial to the ROS-mediated apoptosis associated with VPA hepatotoxicity. The relationship between an oxido-inflammatory induced apoptotic pathway exhibited by VPA could be as a result of its suppression of Nrf2 with subsequent depletion of antioxidant defenses. This enhances NF- κ B levels which increases expression of inflammatory markers cyclooxygenase-2 (COX-2), TNF- α , IL-1 β and IL-6 initiating inflammation and triggering apoptosis with evidence of increased levels of BCL-2 associated X protein (Bax), caspase 3 and decreased Bcl-2 (Jin et al. 2014). In another study the accumulation of p53 protein expression which triggered apoptosis was shown by positively stained terminal deoxynucleotidyl transferase-mediated nick end-labeling (TUNEL) hepatic cells (Ahmed et al. 2016).

Several studies have observed oxidative stress in germ cell toxicity of VPA as evidenced in the increase of ROS such as MDA with decrease in total antioxidant potential, GSH and SOD in testes and epididymis (Glanzner et al.

2016; Ourique et al. 2016). One of such reports sperm DNA damage associated with oxidative stress in sodium valproate treated Swiss mice (Khan et al. 2011). Induction of inflammation and apoptosis has also been linked to VPA-induced oxidative testicular toxicity as VPA was found to increase oxidative stress parameters and the expressions of phospho-nuclear factor kappa B (pNF- κ B) and caspase 3 (Savran et al. 2020).

VPA has also been shown to elicit damage to the kidneys and ocular lens via generation of ROS, reduction in the level GSH and non-protein thiol, reduction in activities of the triad of glutathione antioxidants GST, GR and GPX, activities of SOD and catalase and an increase in lipid peroxidation product; MDA and protein carbonyl (Tunali 2014; Chaudhary and Ganjoo 2015; Gad 2018). In lens epithelial cells, VPA induced overexpression of Kelch-like ECH-associated protein 1 (Keap1) which decreased Nrf2 levels, thereby abolishing the Nrf2 dependent antioxidant protection. This might be responsible for lenticular protein oxidation and cataract formation (Palsamy et al. 2014). The association of inflammation and apoptosis with VPA-induced

oxidative stress in kidneys was also observed with increased TNF- α , IFN- γ , NF- κ B/p65, iNOS and caspase-3 expressions (Gad 2018).

Thus far in this review, the redox sensitive transcription factors NF- κ B, Nrf2 and p53 have been implicated in VPA-induced organ toxicities. In the oxido-inflammatory pathway that involves NF- κ B activation, NF- κ B functions as a link between oxidative stress and inflammation. This factor transduces oxidative stimuli to the nucleus to modulate the expression of target genes including those involved in inflammatory responses e.g. iNOS, COX-2, TNF- α , IL-1 β and IL-6 (Liu et al. 2017). A simultaneous occurrence of oxidative stress and apoptosis is also possible as seen in the toxicity studies of VPA, with NF- κ B appearing to be involved in the execution of apoptosis through an inflammatory response with changes in the levels/expression of pro-apoptotic markers Bax, Bcl-2, caspase 9 and 3 (Jin et al. 2014; Gad 2018; Savran et al. 2020).

The role of Nrf2-ARE pathway is also associated with oxidative stress. However, repression of Nrf2 in VPA-induced toxicity in the face of oxidative stress may be associated with changes in DNA methylation patterns, increasing Keap1 expression and Nrf2 suppression (Palsamy et al. 2014; Wolters et al. 2017). This leads to decrease in intracellular antioxidants as well as those of the ARE (HO-1, GSTs, etc.). Oxidative stress can also activate p53 in response to DNA damage leading to either its repair or apoptosis if DNA repair mechanism falters (Ashley B. Williams and Schumacher 2016).

With an understanding of the oxido-inflammatory pathway of VPA toxicity, plants/plant products with dual potentials of antioxidant, anti-inflammatory and possibly apoptotic activity could be a choice in the phytotherapeutic management of VPA-induced organ toxicities.

Some effects of VPA-induced toxicity

Some of the toxic effects of VPA include teratogenicity, hepatotoxicity, reproductive toxicity and nephrotoxicity which are now discussed in detail.

Teratogenicity

The teratogenic effect of VPA is thought to occur during early organogenesis, at a period highly susceptible to interference with neural tube closure by its metabolite (Brotzmann et al. 2020). Major anomalies reported include cardiac abnormalities, neural tube defects (NTDs) commonly manifesting as spina bifida, cleft lip/palate, skeletal/limb malformation, reduced cognitive function, behavioural problems, decreased verbal intelligence with communication problem of the autism spectrum disorder (ASD) (Lloyd 2013).

Several hypotheses suggest the molecular mechanisms of the teratogenic effect of VPA may include drug accumulation within the foetus, increased fetal oxidative stress particularly in the brain, folate antagonism and histone deacetylase (HDAC) inhibition. HDAC inhibition and formation of reactive oxygen species (ROS) are particularly influential in the first trimester of pregnancy when DNA dysregulation has the largest impact on foetal organ development (Lloyd 2013).

In the majority of cases, VPA accumulates in the circulation of the embryo, reaching a higher concentration than in the maternal blood; this may be responsible for causing toxicity and increased risk (approximately three-fold) of teratogenicity (Vajda 2012).

On another hand, as a result of an immature defence system of the foetus at the first trimester of pregnancy, ROS generated by VPA bioactivation interferes with the electron transport chain in the production of energy causing limited detoxification and increasing ROS interactions with biomolecules like DNA (Tung and Winn 2011; Lloyd 2013). VPA has been shown to induce DNA double strand breaks (DSBs) and increase homologous recombination as the differential expression of several genes involved in DSB repair (*Rad51*, *Brca1*, and *Brca2*) is altered following exposure to VPA in post-implantation mouse embryos (Lamparter and Winn 2014). This may contribute to increased apoptosis evidenced by increased expression of p53 target genes, cleaved caspase 9, caspase 3 and cleaved-poly (ADP-ribose) polymerase (PARP) (France-Hélène and Barbara 2015).

VPA has also been proven to exacerbate folate deficiency by inhibiting key enzymes within the folate metabolism pathway during embryogenesis resulting in teratogenicity (Lloyd 2013). Associated detrimental effects include interference with epigenetic control of gene expression, hyperhomocysteinemia, induction of oxidative stress and disruption of critical proteins (Lloyd 2013). Folate deficiency has been associated with impaired homocysteine metabolism with resultant activation of nuclear factor-kappa B (NF- κ B) and induction of apoptosis mediated by oxidative stress (Lloyd 2013).

VPA inhibition of HDACs is thought to occur through direct binding of VPA (or its active metabolites) to the active site of the enzyme, preventing the hydrolytic removal of acetyl groups from DNA. The open, uncondensed chromatin is then exposed to numerous transcription factors that can induce the transcription of potentially damaging genes, such as B-cell lymphoma protein 2 (Bcl-2) and *Hoxa1* (Ornoy 2009), increasing the regulation of apoptosis and reducing morphogenesis (obligatory for organ differentiation) and cell proliferation, respectively.

Hepatotoxicity

The proposed mechanism of VPA-induced hepatotoxicity supports the generation of reactive intermediates that causes mitochondrial dysfunction by inhibiting β -oxidation resulting in steatosis. VPA-induced mitochondrial dysfunction is reportedly associated with decrease in oxygen consumption and adenosine triphosphate (ATP) levels, reduced expression of DNA polymerase gamma, which plays a major role in mitochondrial DNA (mtDNA) replication and repair (Li et al. 2015), diminished hepatic mitochondrial membrane potential (Komulainen et al. 2015), respiratory control ratio and increased mitochondrial swelling with altered calcium flux (Natarajan et al. 2006).

It is reported that in VPA-induced intracellular fat accumulation (steatosis), VPA-triggered over-regulation of cluster of differentiation 36 (CD36), an important fatty acid transporter, and diacylglycerol acyltransferase 2 (DGAT2) in liver cells. This remarkably enhanced the efficiency of fatty acid uptake mediated by CD36, while increased DGAT2 expression as a result of the inhibition of mitogen-activated protein kinase (MEK)—extracellular regulated kinase (ERK) pathway enhanced triglyceride synthesis (Bai et al. 2017). Further investigation on VPA-induced mechanisms of steatosis suggests changing patterns of methylation in nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) which plays a role in mitochondrial dysfunction and steatosis development. Mitochondrial dysfunction leads to spontaneous bursts of ROS generation which is likely due to VPA mediated opening of the mitochondrial permeability transition (MPT) pore, mitochondrial cytochrome c release and caspase 9 activation, which triggers mitochondria mediated apoptosis (Li et al. 2015; Zhang et al. 2016).

Reprotoxicity

Valproate (VPA) has been claimed to induce endocrine disorders in both sexes in humans. In female rats, VPA is reported to affect steroidogenesis in ovarian follicular cells; inhibiting the conversion of testosterone to estradiol (Sveberg et al. 2002). This is corroborated by other studies that record a reduction in estradiol levels leading to significantly increased testosterone/estradiol ratio. Luteinizing hormone (LH), follicle stimulating hormone (FSH) and progesterone levels have also been reported as reduced in females (Hassan et al. 2019). In males, reduced androgen receptor levels in testis and epididymis have been reported (Iamsaard et al. 2017) with increases in FSH and LH concentrations too (Sveberg et al. 2002).

In women, VPA medication is associated with hyperandrogenism, polycystic ovary/polycystic ovarian syndrome, menstrual disorders and ovulatory failure. Men on VPA therapy show abnormalities in androgens blood levels, sperm

motility and erectile dysfunctions (Verrott et al. 2016). These observations of alterations in reproductive hormone levels indicate that the drug exerts its effect primarily at the gonadal level.

Oxidative stress has also been shown to be involved in VPA-induced reproductive toxicity with consequent apoptosis in both small and medium-sized follicles and testes as well as damage to sperm DNA (Taubøll et al. 2009; Khan et al. 2011). Involvement of the redox sensitive transcription factor NF- κ B which mediates inflammation has also been reported (Savran et al. 2020).

Nephrotoxicity

Experimental and clinical studies have shown that VPA induces oxidative stress, mitochondrial deficits, carnitine deficiency and inflammation and fibrosis in renal tissue in mice and in vitro studies (Hamed 2017). Increased levels of malondialdehyde (MDA), a measure of lipid peroxidation; protein carbonyl and xanthine oxidase activity, markers of oxidative stress; reduction of glutathione concentration and non-protein thiol level, antioxidant markers; and altered activities of glutathione-S-transferase (GST), GPX and glutathione reductase (GR), glutathione metabolizing enzymes activity markers, were reported in kidney tissue of mice fed with sodium valproate (Gezginci-oktayoglu et al. 2016) and in vitro studies (Chaudhary and Ganjoo 2015). Mitochondrial deficits with impairment of mitochondrial succinate dehydrogenase activity (SDA), mitochondrial permeability transition pore (MPP), glutathione, ATP and increased mitochondrial reactive oxygen species and lipid peroxidation are also suggested mechanisms of kidney injury induced by VPA (Heidari et al. 2018).

Furthermore, increase in TNF- α , IL-1 β , interferon gamma (IFN- γ), inducible nitric oxide synthase (iNOS) expressions, NF- κ B/p65, monocyte chemoattractant protein-1 levels, and adenosine deaminase activity, indicating inflammation and increase in transforming growth factor- β , collagen-1 levels, and arginase activity in the renal tissue indicating fibrosis, were observed in the renal tissue of animals injected with VPA (Gezginci-oktayoglu et al. 2016; Gad 2018). VPA also activated notch signaling cascade and increased caspase-3 expression (Gad 2018). In another study VPA induced marked chromosomal aberrations, alterations in mitotic index; evident of its genotoxic potential and histopathological changes in kidney tissue (Sanaa et al. 2014). Fanconi syndrome is also reported with VPA therapy especially in children with epilepsy and it is due to dysfunction of the proximal renal tubules caused by VPA.

Plants products with potential for ameliorating VPA-induced organ toxicities: molecular and cellular protective mechanisms of action

Evidences from several studies have shown that the therapeutic effects of plant products on VPA-induced toxic effects are mainly mediated by properties related to antioxidant, antiinflammatory, antiapoptotic, antifibrotic and modulation of detoxifying enzymes. In this section, the key molecular mechanisms associated with these effects are highlighted.

Hepatotoxicity

Diammonium glycyrrhizinate

Diammonium glycyrrhizinate (DG) is a popular compound isolated from liquorice root, and has been shown to have antioxidant and antiinflammatory properties (Yang et al. 2017; Wang et al. 2020). Simultaneous treatment of animals with VPA (100 mg/kg, oral) and DG (60 mg/kg, oral) protected the liver against inflammation and oxidative stress (Jin et al. 2014). DG treatment was observed to attenuate VPA-induced liver dysfunction, hepatic structural damage, decrease in antioxidant enzymes and depletion of reduced glutathione (GSH). DG prevented VPA-induced reduction of cytosolic Nrf2 and suppression of nuclear translocation of Nrf2 and, in turn, up-regulated phase II and antioxidant enzymes system. A similar result on the effects of VPA and DG on the expression of Nrf2 was also obtained in an in vitro model using HepG2 cells where VPA-induced increase in the nuclear levels of NF- κ B and inflammatory cytokines including IL-1 β , IL-6 and TNF α were inhibited by DG. These results show that the effectiveness of DG in the treatment of VPA-induced liver toxicity may be attributed to its inhibition of oxidative stress as well as activation of Nrf2-dependent antioxidant pathways, inhibition of NF- κ B expression and pro-inflammatory cytokines (IL-1 β , IL-6, TNF α .) (Tong et al. 2005a).

Sulforaphane

Sulforaphane is a thiol compound found abundantly in cruciferous plants, with many reported therapeutic properties. Co-treatment of animals with VPA (700 mg/kg, i.p) and sulforaphane (0.5 mg/kg, orally) protected the liver against VPA-induced oxidative stress and inflammation (Nazmy et al. 2016). Sulforaphane was observed to significantly boost liver functions biomarkers including reduction of VPA-elevated serum alanine amino transaminases (ALT), aspartate amino transaminases (AST), alkaline phosphatase

(ALP), restoration of serum albumin and hepatic architecture. It was observed that sulforaphane attenuated oxidative stress induced by VPA, as evidenced by lower level of MDA and increased levels of GSH and HO-1 content. The attenuative effect of sulforaphane on inflammation was also observed in the lower level of TNF- α contents in sulforaphane-treated animals when compared with VPA group. The results from this study indicate the effectiveness of sulforaphane in the treatment of VPA poisoning mainly by modulating oxidative stress and inflammatory responses (Nazmy et al. 2016).

Vitamin U

Vitamin U (S-methyl methionine sulphonium chloride), a compound present in plants such as tomatoes, spinach, corn, celery and garlic, has been reported to have protective effect against VPA-induced toxicity (Watanabe et al. 2000). The administration of vitamin U (50 mg/kg/day, gavage) along with VPA (500 mg/kg/day, i.p) for 15 days was shown to protect against VPA-induced liver injury as substantiated by the significant decreases in liver ALT, AST, ALP, myeloperoxidase, lactate dehydrogenase (LDH), sorbitol dehydrogenase, xanthine oxidase and glutamate dehydrogenase activities and MDA level as well as increased level of GSH compared to VPA-treated group (Bilgin et al. 2012).

Garlic

Gallic has been a long-time dietary spice in many cultures, with its extracts used in many traditional medicinal prescriptions. The protective ability of diallyl trisulfide (DTS), the main component of garlic oil, was investigated in rats co-treated with VPA [(DTS; 80 mg/kg, orally), (VPA; 500 mg/kg, orally)] for 2 weeks (Shaaban and El-agamy 2017). Results showed that DTS counteracted VPA-induced hepatic damage, as evidenced by reduction in VPA-induced elevated serum AST, ALT, ALP, and preservation of liver histopathology. The antioxidative ameliorative and protective ability of DTS against VP-induced oxidative stress was evidenced by reduction in the level of VPA-induced increase in MDA and significant increase in VPA-induced reduction of total antioxidant content, level of GSH and activity of SOD. This study also revealed significant activation of NF- κ B, increased expression of COX-2, overproduction of proinflammatory cytokines, including TNF- α , IL-1 β , IL-6, increased levels of Bax and caspase-3, but decreased level of Bcl2 following VPA administration; administration of DTS however counteracted all of these molecular events, showing that this phytochemical may offer protection against VPA-induced hepatic damage via antioxidant, antiinflammatory, and antiapoptotic activities (Shaaban and El-agamy 2017).

Curcumin

Curcumin, the major curcuminoid from turmeric, has been credited with several important pharmacological properties, such as antiinflammatory, antioxidant, antimutagenic, and antitumour activities. In rats treated simultaneously with VPA (250 mg/kg i.p 3 times daily) and curcumin (200 mg/kg/day, orally once daily) for one week, curcumin ameliorated VPA-induced liver injury as evidenced by significant decreases in activities of serum AST and ALT compared to rats treated with VPA, curcumin also abolished VPA-induced steatosis, necrosis and inflammation in hepatic tissue histology (Said and El-Agamy 2010). Curcumin's protective effect against VPA-induced hepatic damage could be linked to its through anti-inflammatory and possibly antioxidant potential in hepatic tissue (Said and El-Agamy 2010).

Nephrotoxicity

Alpha-tocopherol

Alpha-tocopherol has been shown to ameliorate VPA-induced renal injury in an in vitro experimental model. Rat hepatocyte cultures co-treated with VPA (500 µg/ml) and varying doses of α -tocopherol (1.0 to 4.0 µM) was protected from injury by α -tocopherol as revealed by reduction of LDH release into the culture media; indicating that VPA toxicity can be prevented by simultaneous administration of α -tocopherol, a potent free-radical scavenger (Buchi et al. 1984).

Caffeic acid

Caffeic acid is a natural phenolic compound found in many plants, including apple, blueberry, carrot, potato, strawberry and tomato (Chao et al. 2010). Caffeic acid (50 mg/kg, orally), simultaneously administered with VPA (500 mg/kg, i.p) daily for 2 weeks, attenuated biochemical and molecular alterations of kidney damage as indicated by reduced levels of urea, creatinine, MDA, TNF- α , IFN- γ , NF- κ B/p65 and transforming growth factor beta (TGF- β), suppression of caspase-3 and inducible nitric oxide synthase expressions, inhibition of activated Notch signaling cascade, as well as increased GSH level (Gad 2018). Thus this phytochemical protects against VPA-induced nephrotoxicity via its antiinflammatory, antioxidant and antiapoptotic mechanisms by increasing GSH level, reducing the levels of MDA, TNF- α , IFN- γ , NF- κ B/p65 and TGF- β and suppressing the expression of caspase-3 and iNOS (Gad 2018).

Quercetin

Quercetin, a member of the flavonoid family is one of the most studied dietary antioxidant. It is ubiquitously found in foods and vegetables and has biological activities including antiinflammatory, antioxidant, antiallergic, antitumor and antibacterial activities (Barcelos et al. 2011). Quercetin has been shown to attenuate VPA-induced nephrotoxicity in rat kidney tissue preparation (39). The protective effect of quercetin after VPA-induced kidney injury in rats was associated with its antioxidative property by reducing MDA and protein carbonyl levels, increasing the level of GSH, as well as increasing the activities of GST, GPX and GR (Chaudhary and Ganjoo 2015).

Vitamin U

Also, pre-treatment with vitamin U 1 h prior to treatment with VPA prevented renal injury as shown by a significant reduction in histopathological changes, MDA level and xanthine oxidase activity, as well as increases CAT and SOD activities and the level of GSH (Gezginci-oktayoglu et al. 2016). The protective ability of vitamin U against VPA-induced renal injury occurs through its inhibition of oxidative stress and its antiinflammatory property, as shown by a decrease in TNF- α , IL-1 β , monocyte chemoattractant protein-1 level and adenosine deaminase activity (Lamparter and Winn 2014). Its antifibrotic effect was via its ability to reduce the levels of TGF- β , collagen-1 levels and arginase activity (Gezginci-oktayoglu et al. 2016).

Ocular toxicity

Vitamin B6

Various studies have reported that usage of VPA for the treatment of epilepsy causes the development of cataract; this is associated with the interference of VPA with the antioxidative protection system of the lens, leading to oxidation of lens protein with consequent formation of cataract (Palsamy et al. 2014). VPA was shown to induce ER stress signals, leading to overproduction of reactive oxygen species and cell death, suppression of Nrf2, CAT, and GR expressions with significant increases in Keap1; overexpression of Keap1 decreases the Nrf2 level, thereby abolishing the Nrf2 dependent antioxidant protection (Palsamy et al. 2014). Vitamin B6 treatment (50 mg/kg, oral) for 7 days simultaneously with VPA (500 mg/kg, i.p) ameliorated VPA-induced changes in the levels of GSH, MDA and activities of GST, GPx, GR, aldose reductase and SOD (Tunali 2014). These results indicate that vitamin B6 may protect the lens against VPA-induced damage by decreasing oxidative stress.

Reprotoxicity

Vitamin E and resveratrol

Many studies have reported the toxicity of VPA on the male reproductive system, for example, VPA treatment (500 mg/kg/day, i.p) for 10 days induced histological changes and reduced androgen receptor levels of testis and epididymis (Iamsaard et al. 2017). Co-treatment with vitamin E (50 mg/kg) abrogated VPA-mediated (400 mg/kg/day, oral) oxidative stress following 28 days administration. VPA-induced decrease in sperm motility accompanied with testicular and epididymal depletion of GSH and a decrease in total reactive antioxidant potential were abrogated by vitamin E, thus, vitamin E protects the male reproductive system from the VPA-induced damage (Glanzner et al. 2016). Also, co-administration of resveratrol (10 mg/kg/day, i.p) and VPA (400 mg/kg/day, oral) for 28 days prevented decrease in sperm motility, increase in oxidative damage to lipids and proteins, depletion of GSH and decrease in total antioxidant potential in testes and epididymides of Wistar rats, suggesting that resveratrol might be a valuable phytochemical for the management of VPA-induced reproductive impairment (Ourique et al. 2016). These studies thus associate the protective effects of vitamin E and resveratrol on VPA-induced toxic effect on the male reproductive system in rats, to their antioxidant properties (43, 44).

Apium graveolens L. (Celery)

In a study that investigated the protective effect of *Apium graveolens* L. (celery) against the VPA-induced testis injury in rats, pre-treatment with AG extract (200 mg/kg/day) 23 days before administration of VPA (500 mg/kg/day) and 7 consecutive days post-VPA administration ameliorated VPA-induced degeneration of seminiferous tubules and depletion of germ cells, increased levels of MDA, reduced activity of SOD (Hamza and Amin 2007). The major compound in *A. graveolens* *A. graveolens* was shown to be apigenin, a flavonoid, also present in other fruits and vegetables and has long been shown to possess various bioactivities, including antioxidant, antiinflammatory and anticancer activities (Hamza and Amin 2007; Ju et al. 2015). However, the roles of other constituents of *A. graveolens* need to be investigated in the relation to prevention of VPA-induced toxicity. The protective property of celery extract was through antioxidative effect shown by its ability to lower the level of MDA and increase the activity of SOD (Hamza and Amin 2007).

Ellagic acid

In a study evaluating the protective effect of ellagic acid, a flavonoid component of numerous fruits and vegetables, on VPA-induced sperm abnormalities in male Wistar rats,

results showed that ellagic acid ameliorated VPA-induced sperm abnormalities by increasing sperm count and sperm motility, reducing sperm abnormalities as well as prevented degeneration and desquamation of germinal cells in the epithelium (Girish et al. 2014).

Teratogenesis and neurotoxicity

Ocimum sanctum

Administration of *Ocimum sanctum* extract (1000 mg/kg/day, p.o) for 14 days was shown to ameliorate VPA-induced (370 mg/kg/day, p.o) memory impairment and oxidative stress, as evidenced by decreased lipid peroxidation and higher GSH level in experimental animals (Sarangi et al. 2017). *Ocimum sanctum*, a commonly used herb in Traditional Medicine, has been shown to possess anticancer, antispasmodic, antidiabetic, hepatoprotective, cardioprotective and analgesic properties, with the pharmacological effects of the plant attributed mainly to eugenol, although the presence of ursolic acid and oleanolic acid in the extract were also reported (Prakash and Gupta 2005; Sarangi et al. 2017; Garabadu and Sharma 2019).

TJ-960

TJ-960 (Shosaiko-to-go-keishikashakuyaku-to) is a traditional Japanese medicinal preparation of nine medicinal herbs, including, *Paeoniae radix*, *Cinna momi cortex*, *Bupleuri radix*, *Zingiberis rhizoma*, *Glycyrrhizae radix*, *Ginseng radix*, *Scutellariae radix*, *Pinelliae tuber* and *Zizyphi fructus* (Minematsu et al. 1990). Co-treatment of animals with TJ-960 (< 3000 mg/kg/day) and VPA (400 mg/kg) prevented VPA-induced teratogenic indices, as revealed by protective effects of TJ-960 against VPA-induced anomalies in embryonic resorption, fetal body weight, ossification and skeletal variations (Minematsu et al. 1990).

Asiatic acid

Asiatic acid, a naturally occurring triterpenoids from *Centella asiatica*, is used in traditional medicine for the management of cancer, wound healing and neurodegenerative diseases (Fizur et al. 2018). In relation to VPA-induced toxicity, administration of asiatic acid (30 mg/kg/day, p.o) 1 week before VPA (300 mg/kg, twice daily, i.p) and co-administration for 14 days post-VPA administration prevented VPA-induced impairments of spatial working memory and neurogenesis (Welbat et al. 2016).

Resveratrol

The teratogenicity of VPA, involving neurotubular defects (NTDs), anencephaly, lumbosacral meningomyelocele, and leg dysfunction due to spina bifida aperta is associated with its oxidative effects, including downregulation of the levels of SOD, GSH, HDAC and folate, and upregulation of hydrogen peroxide (H_2O_2) and homocysteine (Hsieh et al. 2012). Resveratrol treatment (2.0 μ M) prevented VPA-induced (60 μ M) teratogenicity via antioxidative mechanism, evidenced by suppression of serum homocysteine and S-adenosylhomocysteine concentrations, downregulation of cervical muscular carnitine, H_2O_2 , MDA, IL-6 and upregulation of GSH expression (Hsieh et al. 2014); as well as inhibition of VPA-induced modulation of several genes associated with hemorrhagic myoliposis in chicken embryos (Chen et al. 2014).

Oryza sativa

The extract of purple rice (*Oryza sativa*), has been shown to exhibit antioxidant and neuroprotective effects. The administration of purple rice extract [50, 100, and 200 mg/kg (orally) mixed with *Bombyx mori* extract (6:1) for 27 days post-VPA (400 mg/kg/day, s.c.)-induced autism-like behaviours was shown to partially reduce autism-like behaviours, reduced Purkinje cell loss and ameliorated oxidative stress as evidenced by significant decrease in MDA level and increase activities of catalase and GR (Morakotsriwan et al. 2016). The partial protective effect of purple rice extract on VPA-induced autism-like behaviours was related to reducing Purkinje cell loss and antioxidative mechanism (Morakotsriwan et al. 2016).

Withania somnifera

In a study that evaluated the ameliorating effect of *Withania somnifera* on VPA-induced autism in BALB/c mice, *W. somnifera* (100 and 200 mg/kg, p.o) ameliorated the autistic-like behaviours and oxidative stress induced by VPA (400 mg/kg, s.c). This was evidenced by significant improvement in behavioural alterations, oxidative stress status and restoration of histo-architecture of cerebellum when compared with VPA group; indicating the anti-anxiety, antioxidant and neuroprotective properties of this plant against VPA-induced toxic effect (Veeresh et al. 2016). *W. somnifera*, commonly referred to as Indian ginseng, is an important medicinal herb in the Ayurveda medical system. The active components responsible for the pharmacological activities of *W. somnifera* include alkaloids, such as isopelletierine and anferine, steroidal lactones, such as withanolides and

withaferins, and saponins (Ganzera et al. 2003), however, the role of these constituents in alleviating VPA-induced autism-like behaviours needs to be investigated.

Piperine

The autism-like behaviours and oxidative stress induced by VPA (400 mg/kg s.c.) in BALB/c mice were significantly ameliorated by administration of piperine (20 mg/kg p.o.) (Pragnya et al. 2014). Piperine improved the behavioural alterations, lowered oxidative stress markers, and restored histo-architecture of cerebellum (Pragnya et al. 2014). Piperine, an alkaloid that is present in long pepper (*Piper longum*) and black pepper (*Piper nigrum*), has been used in traditional medicine for the treatment of seizure disorders.

Green tea (*Camellia sinensis*)

Daily administration of green tea (*Camellia sinensis*) extract (300 mg/kg, p.o) from post natal day 13 to 40 ameliorated oxidative stress and prevented histological degeneration of the sagittal sections of the cerebellum induced by VPA (400 mg/kg, s.c) administration (Banji et al. 2011). The protective effect of green tea extract against VPA-induced neuronal toxicity is attributed to its antioxidant action (Banji et al. 2011). Green tea is known to be an important source of dietary polyphenols, mainly flavonoids, including, (–)-epigallocatechin (EGC) and (–)-epigallocatechin-3-gallate (EGCG), flavonols such as kaempferol, myricetin and quercetin and other compounds like gallic acid, chlorogenic acid and caffeic acid (Cabrera et al. 2006). Green tea polyphenols have been shown to cross the blood brain barrier (Hong et al. 2000; Levites et al. 2001), possess excellent antioxidant activity (Yang et al. 2007) and antiinflammatory action (Meki et al. 2009).

Kaempferia parviflora

Kaempferia parviflora is a herbal plant used in traditional medicine; with experimental validation of its antidepressant, learning and memory improving properties (Surget et al. 2008). The protective effect of *K. parviflora* extract against VPA-induced impairments in cognition and hippocampal neurogenesis in Sprague Dawley rats have been reported (Umka et al. 2016). *K. parviflora* extract (100 mg/kg, p.o) was administered for 21 days while VPA (300 mg/kg, i.p) was administered twice daily from days 8 to 21. Co-treatment of *K. parviflora* and VPA prevented the impaired cognition and reduction in proliferating cells caused by VPA (Umka et al. 2016). The main active component of *K. parviflora* are the methoxyflavones (Chen et al. 2018). The antioxidative and antiinflammatory properties of the

methoxyflavones have been shown by their inhibitory effect on the expression of prostaglandin E2, nitric oxide, TNF- α , COX-2, IL-1 β , and IL-6 (Horigome et al. 2017; Chen et al. 2018). However, the effects of the different methoxyflavones isolated from *K. parviflora* on VPA-induced toxicity need to be investigated.

Korean red ginseng

In a study that evaluated the effects of Korean red ginseng extract on prenatal valproic acid (VPA)-induced model of autism spectrum disorder, Korean red ginseng extract (20, 50, 100 and 200 mg/kg/day, p.o) ameliorated VPA-induced (400 mg/kg, i.p) impairment in social interactions, abnormal locomotor and crooked tail phenotypes in experimental animals in a dose dependent fashion (Kim et al. 2013). Korean ginseng, a popular herbal medicine, belongs to the *Araliaceae* family and it is known to exhibit numerous pharmacological activities including antioxidant, antiinflammatory, immunomodulatory, antihyperglycemic, antihypertensive, antidiabetic, and anticancer effects, as well as effects on central nervous system and the cardiovascular system (Sathishkumar et al. 2012). The main bioactive components of ginseng are the ginsenosides, although other active compounds such as polysaccharides, fatty acids, peptides and poly acetylene alcohols are also present in this plant. The ginsenosides are triterpene saponins, a group of important natural known for numerous pharmacological activities (Karmazyn and Gan 2020).

Bacopa monniera

Bacopa monniera, a well-known plant in Ayurvedic medicine is useful in several neurological disorders. In pregnant rats challenged with VPA (600 mg/kg, i.p.) and treated with *B. monniera* (300 mg/kg/p.o.), *B. monniera* ameliorated the VPA-induced autistic behaviour; evidenced by improved behavioral alterations, and decreased oxidative stress markers; evidenced by decreased total nitrite levels and increased GSH and catalase activities, and restored histo-architecture of cerebellum (Sandhya et al. 2012). *B. monniera* extract is known to contain bacosides, a class of compounds belonging to the dammarane-type triterpenoid saponins known for their various neurological and neuropsychological effect (Russo and Borrelli 2005; Mathew et al. 2010; Sandhya et al. 2012). The underlying mechanisms of improved behavior by *B. monniera* on VPA-induced autistic behaviour was associated with decreased oxidative and nitrative stress (Sandhya et al. 2012).

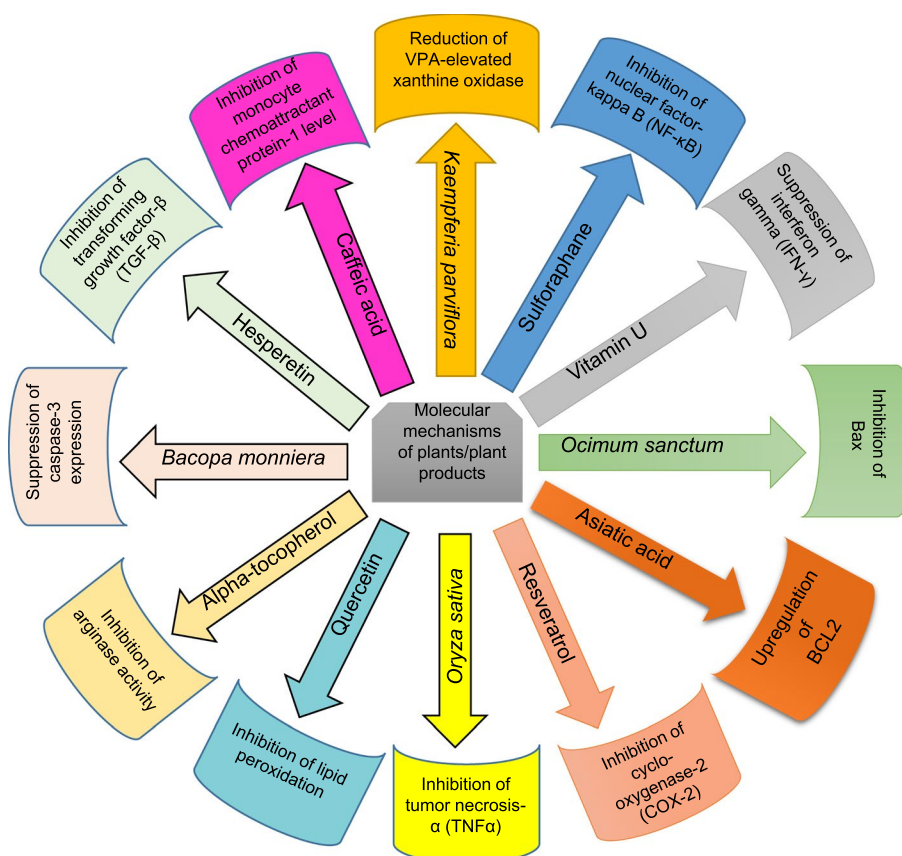
Hesperetin

Pre-treatment of pregnant Wistar rats with hesperetin, as well as nano-hesperetin (10 and 20 mg/kg/day, p.o) for 12 days before treatment with VPA (500 mg/kg, i.p) and 18 days afterwards showed the neuroprotection of hesperetin against VPA-induced autistic behaviours (Khalaj et al. 2018). This was demonstrated by improved behavioral disorder (reduced anxiogenic-like behaviour and improved social interaction), reduced oxidative stress in the brain (reduced MDA level and increased SOD activity) and ameliorated inflammatory indices (decreased level of plasma IL-6 and TNF- α) (Khalaj et al. 2018). Hesperetin is a flavonoid found many plant sources, especially citrus fruits, and earlier studies have confirmed the pharmacological activities of hesperetin, via its effect on signaling pathways such as induction of HO-1 via ERK/Nrf2 signaling pathway, and gene expression of antioxidant enzymes such as CAT, SOD, and GPx (Chen et al. 2010; Roohbakhsh et al. 2015; Su et al. 2019). The neuroprotection by hesperetin against VPA-induced autistic behaviours was potentially mediated via anti-oxidative and anti-inflammatory mechanisms (Khalaj et al. 2018).

Effect of phytotherapeutic agents on the pharmacokinetics of VPA

VPA is obtainable as oral preparations or as an intravenous formulation, and the therapeutic daily doses range from 1 to 2 g in adults, and from 15 to 60 mg/kg in children (Lheureux et al. 2005). From all the experimental studies reviewed, doses of VPA used ranged between 100 and 750 mg/kg body weight/day. Compared to therapeutic adult doses (1 to 2 g/kg), the experimental doses (of between 100 and 750 mg/kg body weight/day) used in most studies reported in this review seems to be within the range for adult therapeutic doses, as such the observed toxicities elicited in these studies could not have been said to be from overdose. VPA is a simple branched chain carboxylic acid with a pKa 4.8 and a reported volume of distribution ranging from 0.1 to 0.5 L/kg (Sztajnkrzyer 2002). After therapeutic dosing, VPA is rapidly absorbed from the gastrointestinal tract, with peak serum levels occurring 1–4 h after ingestion, and the range of therapeutic serum concentrations range from 50 mg/mL to between 100 and 150 mg/mL; with controversial serum peak occurrence and concentrations in cases of overdose (Ge et al. 2017). It was observed that most of the studies covered in this review did not investigate the effects of the various therapeutic agents on the pharmacokinetics of VPA. To fully understand the protective effects of these phytotherapeutic agents for possible translation to real-time clinical applications, the influences of these agents on the pharmacokinetics of VPA need to be investigated. From such studies, questions

Fig. 3 Summary of the protective mechanisms of medicinal plants against VPA-induced toxicity



such as whether or not the plant extracts or compounds administered in combination with VPA affect chemico-biological and chemico-chemical interaction aspects of the drug, like the degree of protein binding exhibited by the drug could be answered. Also, questions as to whether or not the plant extracts or compounds administered in combination with VPA inhibited its primary effects, including treating epilepsy, bipolar disorder, migraine, schizoaffective disorders, neuropathic pain, etc., besides curbing the negative effects were not addressed by these studies.

Summary

This review discusses the experimental evidences and the mechanisms involved in the protective effects of plant-derived products against VPA-induced toxicities (Fig. 3).

In recent years, there has been an interest in traditional medicinal plant products, because they have been scientifically validated to be rich in several bioactive components, including those with antioxidant and antiinflammatory properties that can be exploited as pharmaceutical agents. Plant-derived compounds with protective potentials against VPA-induced toxicity include saponins, isothiocyanate, vitamins, organosulfur compounds, polyphenols, triterpenes and alkaloids, through augmentation of systemic antioxidant defence as well as modulation of inflammatory responses (Table 1). Although most of these studies were conducted in animal models, similar effects are expected in human subjects. It is apparent that only limited studies have examined the effectiveness of individual compounds in the treatment and prevention of VPA-induced toxicity and the effects of these phytotherapeutic agents on the pharmacokinetics of VPA. Also, the studies

Table 1 Effects of plant extracts on Valproic acid-induced toxicities

Name of plant/traditional medicine	Main bioactive component	Experimental model	Result	References
Hepatotoxicity Liquorice root	Diammonium glycyrrhizinate	BALB/C mice VPA: 370 mg/kg/day, p.o Diammonium glycyrrhizinate (60 mg/kg, oral) for 14 days	Amelioration of VPA-induced liver injury by inhibiting translocation of nuclear levels of NF- κ B and decreasing levels of inflammatory cytokines	(Jin et al. 2014)
<i>Garlic</i>	Diallyl trisulfide	Male Sprague–Dawley rats VPA: 500 mg/kg, p.o Diallyl trisulfide (80 mg/kg, oral) for 14 days	Counteracted VPA-induced hepatic damage by reducing VPA-induced elevated serum AST, ALT, ALP, preserving liver histopathology, reducing MDA levels, ameliorating total antioxidant content, level of GSH and activity of SOD, significantly inhibiting NF κ B, expression of COX-2, proinflammatory cytokines, including TNF- α , IL-1 β , IL-6, and levels of Bax and caspase-3, and increasing level of Bcl-2	(Shaaban and El-agamy 2017)
Turmeric	Curcumin	Sprague–Dawley rats VPA (250 mg/kg i.p 3 times daily) curcumin (200 mg/kg/day, orally once daily) for 7 days	Ameliorated VPA-induced liver injury shown by significant decreases in activities of serum AST and ALT, abolishing steatosis, necrosis and inflammation in hepatic tissue histology	(Said and El-Agamy 2010)
NA	<i>Alpha-tocopherol</i>	Rat hepatocyte cultures VPA (500 μ g/ml) α -tocopherol (1.0 to 4.0 μ M)	Protected hepatocytes from injury by reduction of LDH release into the culture media	(Buchi et al. 1984)
NA	Sulforaphane	Sprague–Dawley rats VPA (700 mg/kg, i.p) Sulforaphane (0.5 mg/kg, orally for 7 days)	Protected against liver damage by reduction of serum ALT, AST and ALP, restoration of serum albumin and hepatic architecture, lowered level of MDA, increased levels of GSH and HO-1, and lower level of TNF- α contents	(Nazmy et al. 2016)

Table 1 (continued)

Name of plant/traditional medicine	Main bioactive component	Experimental model	Result	References
NA	Vitamin U	Sprague Dawley rats VPA: 500 mg/kg/day, i.p Vitamin U (50 mg/kg/day, gavage) for 15 days	Protected against liver injury by decreased liver ALT, AST, ALP, myeloperoxidase, LDH, sorbitol dehydrogenase, xanthine oxidase and glutamate dehydrogenase activities and MDA level, increased level of GSH, prevented histopathological changes, xanthine oxidase activity, increased CAT and SOD activities, displayed antiinflammatory property, shown by decrease in TNF- α , IL-1 β , monocyte chemoattractant protein-1 level and adenosine deaminase activity. Also displayed antifibrotic effect shown by a decrease in transforming growth factor- β (TGF- β), collagen-1 levels and arginase activity	(Bilgin et al. 2012; Gezginci-oktayoglu et al. 2016)
Nephrotoxicity NA	Caffeic acid	Sprague–Dawley rats VPA: 500 mg/kg, i.p Caffeic acid (50 mg/kg, orally) daily for 2 weeks	Attenuated kidney damage as shown by reduced serum levels of urea, creatinine, MDA, TNF- α , IFN- γ , NF- κ B/p65 and TGF- β , suppressed expressions of caspase-3 and iNOS, inhibited activated Notch signaling cascade and increased GSH level	(Gad 2018)
NA	Quercetin	Post nuclear supernatant of Wistar rats kidney VPA: 20 mg Quercetin:05 mM for 1 h	Attenuated nephrotoxicity as revealed by reduced levels of lipid peroxidation and protein carbonyl, increased level of GSH and non protein thiol, increased the activities of GST, GPX, and GR	(Chaudhary and Ganjoo 2015)
Ocular Toxicity	Vitamin B6	Sprague–Dawley rats VPA: 500 mg/kg, i.p Vitamin B6: 50 mg/kg, p. o for 7 days	Protected the lens against oxidative stress as shown by changes in the levels of GSH, MDA and activities of GST, GPX, GR, aldose reductase and SOD	(Tunali 2014)

Table 1 (continued)

Name of plant/traditional medicine	Main bioactive component	Experimental model	Result	References
Reprotoxicity <i>Nigella sativa</i>	Thymoquinone (TMQ)	Male Sprague-Dawley rats VPA: 500 mg/kg/day, for 14 days VPA plus TMQ (50 mg/kg/day), for 14 days	Protected against VPA-induced testicular toxicity shown by ameliorated spermatogenic and interstitial degenerations induced by VPA, decreased total oxidant status (TOS) and oxidative stress indices (OSI), and increased total antioxidant status (TAS), decreased expressions of p-Nf-kB, caspase 3 and NADPH-oxidase 2	(Savran et al. 2020)
<i>Apium graveolens</i> L	Apigenin	Male Wistar rats VPA: 500 mg/kg/day, i.p Seed extract of <i>A. graveolens</i> 200 mg/kg/day (gavage) 23 days before administration of VPA and 7 consecutive days post-VPA administration	Ameliorated VPA-induced reproductive toxicity as revealed by prevention of the degeneration of seminiferous tubules and depletion of germ cells, reduced levels of MDA, and increased activity of SOD	(Hamza and Amin 2007)
NA	Vitamin E	Wistar rats VPA: 400 mg/kg p.o Vitamin E: 50 mg/kg intraperitoneally for 28 days	Protected the reproductive system from damage, revealed by restored antioxidant status in the testes and epididymides, and restored sperm motility	(Glanzner et al. 2016)
NA	Resveratrol	Wistar rats VPA: 400 mg/kg p.o Resveratrol: 10 mg/kg i.p for 28 days	Minimized reproductive impairment by preventing decrease in sperm motility, oxidative damage to lipids and proteins, depletion of GSH and decrease in total antioxidant potential in testes and epididymis	(Ourique et al. 2016)
NA	Ellagic acid	Wistar rats VPA: 400 mg/kg, p.o Ellagic acid 50 mg/kg for 10 days	Protected against testicular and spermatozoal damage	(Girish et al., 2014)
Teratogenesis and Neurotoxicity <i>Bacopa monniera</i>	Triterpenoid saponins, mainly bacosides	Rats VPA: 600 mg/kg, i.p on postnatal day 21 Whole plant extract of <i>Bacopa monniera</i> 300 mg/kg/p.o.) from postnatal day 21 to 35	Ameliorated VPA-induced autistic behaviour, decreased oxidative stress markers, improved behavioural alterations, decreased total nitrite levels, increased GSH and CAT activities, and restored histology of cerebellum	(Sandhya et al. 2012)
NA	Asiatic acid	VPA: 300 mg/kg, i.p Sprague Dawley rat Asiatic acid: 30 mg/kg/day for 28 days	Prevented impairments of spatial working memory and neurogenesis	(Welbat et al. 2016)

Table 1 (continued)

Name of plant/traditional medicine	Main bioactive component	Experimental model	Result	References
<i>Piper longum</i> and <i>Piper nigrum</i>	Piperine	BALB/c mice VPA: 400 mg/kg s.c. Piperin: 20 mg/kg p.o. post natal day 13–40	Improved behavioural alterations, lowered oxidative stress markers, and restored histo-architecture of cerebellum	(Pragnya et al. 2014)
<i>Ocimum sanctum</i>	Eugenol, ursolic acid and oleanolic acid	Wistar rat VPA: 370 mg/kg, p.o. Standardised extract of <i>O. sanctum</i> (1000 mg/kg/day, p.o) for 14 days	Amelioration of VPA-induced memory impairment and oxidative stress, decreased lipid peroxidation and increased GSH level	(Sarangi et al. 2017)
TJ-960 <i>Paeoniae radix</i> , <i>Cinna momi cortex</i> , <i>Bupleuri radix</i> , <i>Zingiberis rhizome</i> , <i>Glycyrrhizae radix</i> , <i>Ginseng radi</i> , <i>Scutellariae radi</i> , <i>Pinelliae tube</i> and, <i>Zizyphi fructus</i>	Flavonoids, triterpenes, baicalein	Rat VPA: 400 mg/kg TJ-960 < 3000 mg/kg/day, p.o days 7–17 of gestation	Prevented VPA-induced teratogenicity, prevented anomalies in embryonic resorption, protected against fetal skeletal variations	(Minematsu et al. 1990)
<i>Oryza sativa</i>	Anthocyanins	Rats VPA: 400 mg/kg, s.c on post natal day 14 Combined extract of purple rice and silkworm pupae (5, 100, 200 mg/kg, p.o) daily from post natal day 14 to 40	Ameliorated VPA-induced neurotoxicity, reduce autism-like behaviours, reduced Purkinje cell loss, decrease in malondialdehyde levels, and increased activities of CAT and GPX	(Morakotsriwan et al. 2016)
<i>Withania somnifera</i>	Alkaloids, steroidal lactones and saponins	BALB/C mice VPA: 400 mg/kg, s.c Aqueous root extract of <i>W. somnifera</i> 100 and 200 mg/kg, p.o	Reduced autistic behavioural indices, oxidative stress status and restored histo-architecture of cerebellum, improved locomotor and nociceptive responses, increased GSH level, and reduced MDA level	(Ganzera et al. 2003), (Veeresh et al. 2016)
<i>Camellia sinensis</i> (Green tea extract)	Flavonoids	Albino mice VPA: 400 mg/kg, s.c Green tea extract (75 and 300 mg/kg, p.o, 13 to 40 days post natal	Reduced autistic behavioural indices, oxidative stress status, improved mid-air righting, improved nociceptive response, reduced MDA level, and prevented histo-architecture of the cerebellum	(Banji et al. 2011)
<i>Kaempferia parviflora</i>	Methoxyflavones	Sprague Dawley rat <i>K. parviflora</i> rhizome extract 100 mg/kg, p.o was administered for 21 days VPA: 300 mg/kg, i. p administered twice daily from days 8 to 21	Prevented VPA-induced cognition impairment, and improved spatial working memory	(Umka et al. 2016)
Korean red ginseng	Ginsenosides	Sprague Dawley rats VPA: 400 mg/kg, i.p Korean red ginseng extract 20, 50, 100 and 200 mg/kg/day, p.o	Reduced impairment in social interactions, abnormal locomotor and crooked tail phenotypes	(Kim et al. 2013)

Table 1 (continued)

Name of plant/traditional medicine	Main bioactive component	Experimental model	Result	References
NA	Hesperetin	Wistar rat VPA: 500 mg/kg, i.p Hesperetin and nano-hesperetin (10 and 20 mg/kg/day, p.o) for 12 days	Improved behaviour: reduced anxiogenic-like behaviour and improved social interaction. Reduced oxidative stress in the brain: reduced MDA level and increased SOD activity. Abated inflammatory indices: decreased level of plasma IL-6 and TNF- α	(Khalaj et al. 2018)

involving extracts do not indicate whether the protective effects provided by the extracts against VPA-induced toxicity are attributable to any particular compound or synergism of the component compounds of such extracts. From earlier studies and observations, it is however rational to conclude that additive, synergistic, or potentiating effects between two or more compounds yields better protection and ameliorative effects against drug-induced toxicities. It is however important to point out that there are many therapeutic approaches to treat epilepsy, and if VPA elicits adverse effects in a patient, the approach is to reduce the dose and/or frequency administration, or administer another class of anti-epileptic drug. Notwithstanding, this study showed that plant products can offer modest protection against VPA-induced toxicities, and further studies should be targeted towards evaluating the protective effects of more phytochemicals against VPA-induced toxicity, and also at identifying and isolating specific compounds from plant extracts that have been shown to have protective or ameliorative effects toxicity induced by this drug.

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Data availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethical statement This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

Conflict of interest Kayode Ezekiel Adewole has no conflict of interest. Alfred Francis Attah has no conflict of interest. Sharon Oluchi Osawe has no conflict of interest.

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