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REVIEW

Review of natural antioxidant plants to overcome the neurotoxic effects of methamphetamine

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Keywords
Aronia melanocarpa
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Abstract

Background: Methamphetamine (METH) is a psychostimulant substance known for its substantial abuse potential and neurotoxic properties. METH is a second-line drug in certain conditions such as Attention Deficit Hyperactivity Disorder (ADHD), severe obesity, or narcolepsy. **Objective:** This study aims to compare natural plant antioxidants to overcome neurotoxicity caused by methamphetamine. **Method:** The authors used a literature review method and collected articles from "PubMed", "Google Scholar", "ScienceDirect", "Scopus" from 2010 - 2023 without excluding old works that are often cited and trusted using the terms "Methamphetamine", "Neurotoxicity", "*Ipomoea batatas* L.", "*Scutellaria baicaleinsis Georgi* ", "*Cinnamomum cassia*", "*Laurus nobilis* L.", "*Aronia melanocarpa*", "*Tripterygium wilfordii* Hook. f.", "*Gingko biloba* L.", "*Centella asiatica* (L.)", "*Curcuma longa* Linn.", "*Brassia oleracea* L." as inclusion criteria. **Result:** Several reviewed natural antioxidant plants exhibit pathways and substantial evidence from both in vivo and in vitro studies addressing methamphetamine-induced neurotoxicity. However, *Aronia melanocarpa* demonstrates a superior LD50 profile, making it the safest choice for consumption. **Conclusion:** *Aronia melanocarpa* had the highest LD50 value at 5 g/kg of body weight. Further research is needed to investigate the efficacy of *Aronia melanocarpa* in addressing methamphetamine-induced neurotoxicity.

Introduction

Methamphetamine (METH) is a psychostimulant substance known for its substantial abuse potential and neurotoxic properties (Panenka *et al.,* 2013). METH is a second-line drug in certain conditions such as Attention Deficit Hyperactivity Disorder (ADHD), severe obesity, or narcolepsy. However, because of its higher booster potency, amphetamine is more frequently prescribed for this condition than METH (Moszczynska & Callan, 2017). Its primary action mechanism is to increase extracellular monoamine neurotransmitters, including dopamine, serotonin, and norepinephrine (Der-Ghazarian *et al.,* 2019).

Based on data from the 2017 National Survey on Drug Use and Health (NSDUH), it is estimated that more than 14.7 million individuals, which accounts for 5.4 percent of the population, have experimented with methamphetamine at least once. Additionally, the survey reveals that nearly 1.6 million people used methamphetamine within the year preceding the survey. This indicates that methamphetamine remains one of the most frequently misused stimulant drugs globally (Nida, 2021). The neurotoxic effects of METH are a matter of significant concern, and the investigation of the mechanisms responsible for this neurotoxicity has become a prominent area of research in recent years (Xie *et al.,* 2018).

The United States National Institute on Drug Abuse (NIDA) and European researchers have recognised the importance of finding effective treatments for methamphetamine dependence as a priority. The complex neural mechanisms underlying methamphetamine dependence have led to the identification of several pharmacological approaches that could potentially be beneficial in addressing this issue (Karila *et al.,* 2010). The neurotoxic mechanisms of METH are intricate and involve multiple pathways. Oxidative stress has been identified as a significant

contributor to cellular toxicity. METH stimulates the production of various reactive oxygen species (ROS), including hydroxyl radicals (OH-), hydrogen peroxide (H2O2), and superoxide anions (O2-), by enhancing the oxidation of dopamine. These ROS play a crucial role in the neurotoxic effects of METH (Yang *et al.,* 2018).

Through technological developments and research, we review natural plants with antioxidant content that can potentially reduce neurotoxic levels of methamphetamine. The exploration of natural antioxidant plants to counter the neurotoxic impact of methamphetamine holds paramount significance in contemporary research and healthcare. Methamphetamine abuse is a pressing concern globally, causing severe neurological damage and cognitive impairments.

Natural antioxidants derived from plants offer promising therapeutic potential due to their ability to mitigate oxidative stress, a primary mechanism contributing to methamphetamine-induced neurotoxicity (Zeng *et al*., 2022). Understanding and identifying specific plants with potent antioxidant properties could pave the way for developing adjunctive treatments that protect against methamphetamine's detrimental effects on the brain. (Kasote *et al.,* 2015). This review is crucial as it seeks to unveil potential botanical solutions, potentially offering novel avenues for mitigating the devastating consequences of methamphetamine abuse on the nervous system (Yu *et al.,* 2015).

Methods

We used a literature review method and collected articles from "*PubMed*", "*Google Scholar*", "*ScienceDirect*", "*Scopus*" from 2010-2023 without excluding old works that are often cited and trusted using the terms "*Ipomoea batatas* L.", "*Scutellaria baicaleinsis* Georgi", "*Cinnamomum cassia", "Laurus nobilis* L.", "*Aronia melanocarpa*", "*Tripterygium wilfordii* Hook. f.", "Gingko biloba L.", "*Centella asiatica* (L.)", "*Curcuma longa* Linn.", "*Brassia oleracea* L." as inclusion criteria.

Results

The results of the conducted literature review can be observed in Table I.

Table I: Natural antioxidant plants

Natural plants	LD 50	Compounds	Methods	Pathway	Result	References
Ipomoea batatas L.	Greater than 5,000 mg/kg	Anthocyanins	Animal model: male Wistar rats Dosage: 3 mL/day Route: Intragastric only	Increasing Bcl-2 expression and decreasing Bak expression. (See Figure 1)	The treatment group exhibited elevated Bcl-2 expression in comparison to the control group. Furthermore, the treatment group demonstrated reduced levels of cytochrome c and caspase-3.	(Adnyana *et al.,* 2018)
Scutellaria baicaleinsis Georgi	286.15 mg/kg	Baicalein	Animal model: Male ICR mice Dosage:0,1- 3.0 mg/kg Route: intraperitoneally (IP)	Inhibit myeloperoxidase (MPO) activity and ROS production induced by METH. (See Figure 2)	Baicalein demonstrated dose-dependent neuroprotection within the 0.1–1.0 mg/kg range but was ineffective at 3.0 mg/kg. Notably, higher baicalein doses did not show a dose-dependent neuroprotective response against striatal DAT loss.	(Wu *et al.*, 2006b)
Cinnamomum cassia	2000 mg/kg	Cinnamal dehyde (CA)	Animal model: male Wistar rats Dosage: 20, 40 and 80 mg/ kg) Route: intraperitoneally (IP)	CA reduces phosphorylated ERK1/2 levels in the hippocampus, disrupts the MEK1/2-ERK1/2 signalling pathway (See Figure 3)	Cinnamon exhibits potential in preventing neurodegenerative diseases by offering protection against neuroinflammation. However, our study's outcomes revealed that at a dosage of 80 mg/kg, CA did not ameliorate memory impairment or alter the expression of phosphorylated ERK1/2.	(C. Zhang *et al.,* 2019)

Natural plants	LD 50	Compounds	Methods	Pathway	Result	References
Laurus nobilis L.	1100 µg/mL	Spirafolide	Cells: SH-SY5Y neuroblastoma cells of human origin Dosage: The cells were subjected to treatment with different concentrations (0.08, 0.4, 2, 10, 25, and 50 µM) of spirafolide for an additional 48 hours.	Spirafolide suppressed apoptosis and the generation of reactive oxygen species (ROS) in neuronal SH-SY5Y cells exposed to DA (dopamine) treatment. (See Figure 4)	In the group treated with 600 µM DA alone, the total percentage of Annexin V+ / PI and Annexin V+ / PI+ cells was measured at 30.3 ± 2.9%. In contrast, in the spirafolide-treated groups, this percentage decreased to 19.3%, 12.2%, and 9.7% at concentrations of 0.4 µM, 2 µM, and 10 µM, respectively. These findings demonstrate that varying concentrations of spirafolide can effectively attenuate DA-induced apoptosis.	(Ham *et al.,* 2010b)
Aronia melanocarpa	5 g/kg	Anthocyanins	Animal model: male Wistar rats Dosage: 3 mL/day Route: Intragastric only	Increasing Bcl-2 expression and decreasing Bak expression. (See Figure 1)	The treatment group exhibited elevated Bcl-2 expression in comparison to the control group. Furthermore, the treatment group demonstrated reduced levels of cytochrome c and caspase-3.	(Adnyana *et al.,* 2018)
Tripterygium wilfordii Hook. f.	Ranged from 608 to 858 mg/kg	Celastrol	Cells: Cells (PC12) and SH-SY5Y cells Dosage: Cells were pretreated with or without celastrol at 1 µM or Mito-TEMPO at 10 µM for 1 h.	Celastrol effectively inhibited the Cd-induced reduction in p-AMPKα (Thr172) levels and caspase-3 cleavage in PC12 cells, SH-SY5Y cells, and primary neurons. (See Figure 5)	The administration of 1 µM celastrol effectively reduced Cd-induced apoptosis in PC12 cells, SH-SY5Y cells, and primary neurons. This protective effect was achieved by preventing Cd-induced inactivation of AMPK, subsequently inhibiting the activation of mTOR in these cells. Additionally, celastrol treatment significantly reduced the excessive production of reactive oxygen species (ROS) in neuronal cells exposed to Cd.	(R. Zhang *et al.,* 2017)
Gingko biloba L..	4947.2 mg/kg.	Ginkgolide B	Cells: BV2 cells Treatment ginkgolide: Ginkgolide B was introduced 2 hours prior to the Meth incubation. After 12, 24, and 48 hours of treatment, total protein was extracted for subsequent experiments.	Ginkgolide B (GB) demonstrated a significant reduction in the expression of pro-inflammatory cytokines, specifically TNF-α, IL-1β, and IL-6, which were induced by Meth in BV2 cells. GB exhibited inhibitory effects on the expression of TLR4 and phosphorylated NF-κB (p-NF-κB), (See I Figure 6)	Ginkgolide B has the ability to inhibit the upregulation of TLR4 expression induced by 1000 µM Meth and also attenuates the activation of p-NF-κB that is induced by 1000 µM Meth.	(Sun *et al.,* 2006)
Centella asiatica (L.)	2000 mg/kg	Asiatic acid	Animal model: Male Sprague-Dawley rats Dosage: 300 mg/kg and 500 mg/kg of body weight over a period of 21 days. Route: Subcutaneous injections	CAE can significantly alter SOD2 manganese superoxide dismutase II expression by removing superoxide and oxidative attenuation emphasize and increase microRNA-	There was a significant increase in SOD2 expression in the METH-exposed group (Group II) and in the groups exposed to METH and treated with CAE (Caffeic Acid Ethyl Ester) at doses of 300 mg/kg (Group V) and 500 mg/kg (Group VI) compared to the control group. The results	(Shamsuddin *et al.,* 2023)

Natural plants	LD 50	Compounds	Methods	Pathway	Result	References
				to-regulate neuroprotection by regulating genes related to mitigating reactive oxygen species (ROS) in mitochondria. (See Figure 7)	demonstrate that treatment with CAE alone (Groups III and IV) elevated the expression of miR-34a compared to the control group.	
Curcuma longa Linn.	1000 mg/kg	Curcumin	Animal model: male Wistar rats Dosage: 100 and 200 mg/kg Route: intraperitoneally (IP)	Curcumin can increase SOD and GSH, is protective against oxidative damage and curcumin can decrease peroxide TNF-α and MDA because it can increase methamphetamine-induced neurotoxicity. (See Figure 8)	The levels of SOD (Superoxide Dismutase) were significantly decreased in the methamphetamine group compared to both the control and DMSO groups.	(Hadizadeh-Bazaz *et al.*, 2021)
Brassia oleracea L.	2000 mg/kg	Sulforaphane and hexyl isothiocyanate (6-HITC)% lysolecithin in normal saline	Cells: tissue obtained from the anterior striatum in fetal Wistar rats cultures were incubated with a 6-HITC injection to the corpus callosum and straviuom on the right-hand side of the brain by stereo-static	These findings demonstrate that 6-HITC triggers the intracellular defence system against oxidative stress, specifically involving the Nrf2–ARE pathway. (See Figure 9)	In our cell cultures, pre-treatment with 0.01 – 1 µM sulforaphane or 0.01 – 1 µM 6-HITC mitigated the cytotoxic effects induced by H2O2 and paraquat. These findings suggest that sulforaphane and 6-HITC instigate intracellular defence mechanisms against oxidative stress, including the Nrf2–ARE pathway.	(de Paula Faria *et al.*, 2014)

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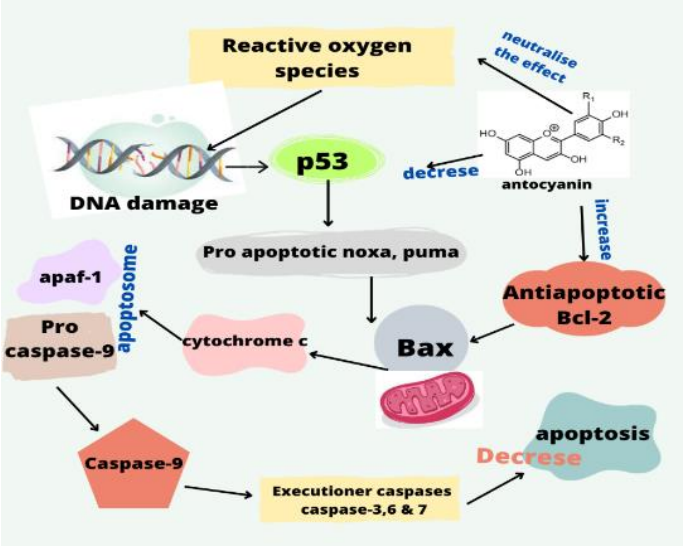
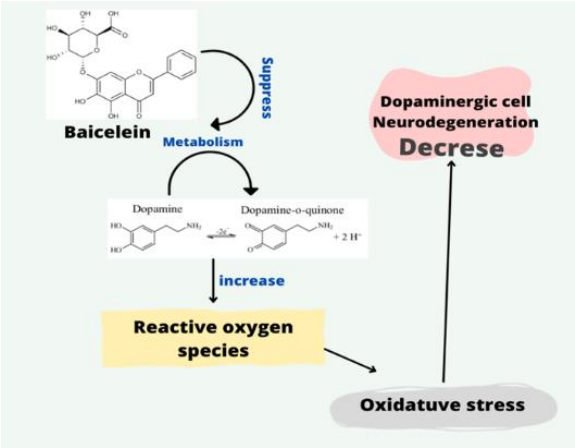


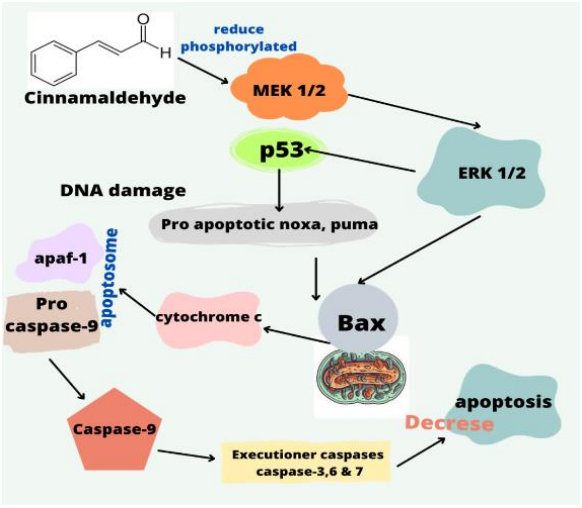
Anthocyanin increases Bcl-2 expression as antiapoptotic and decreases Bak expression to reduce apoptotic.

Figure 1: Mechanism of anthocyanin to overcome neurotoxic-induced methamphetamine



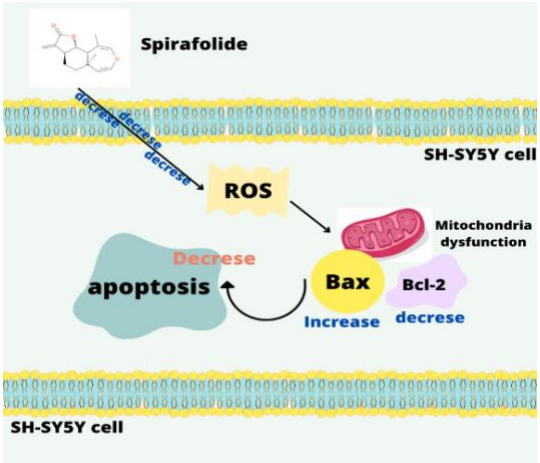
Baicalein inhibits ROS production induced by METH, so neurodegeneration of dopaminergic cells is reduced.

Figure 2: Mechanism baicalein to overcome neurotoxic induced methamphetamine.



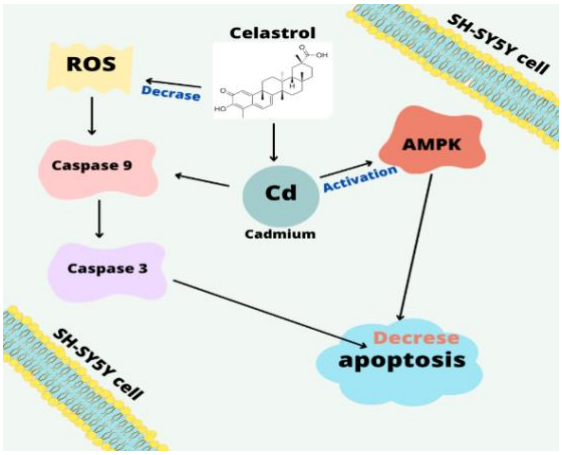
CA reduces phosphorylated ERK1/2 levels in the hippocampus and disrupts the MEK1/2-ERK1/2 signalling pathway.

Figure 3: Mechanism CA to overcome neurotoxic induced methamphetamine.



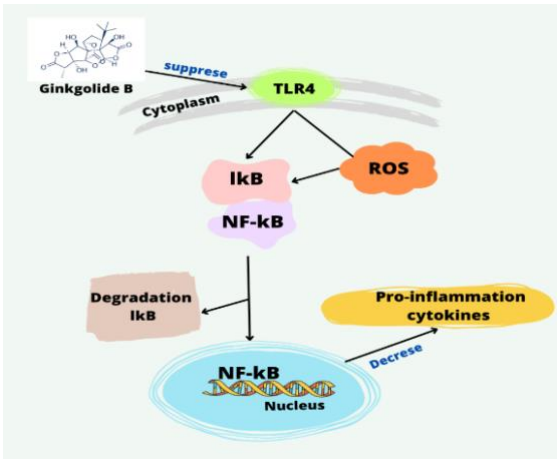
Spirafolide suppressed apoptosis and the generation of reactive oxygen species (ROS) in neuronal SH-SY5Y cells exposed to DA (dopamine) treatment.

Figure 4: Mechanism spirafolide overcome neurotoxic induced methamphetamine.



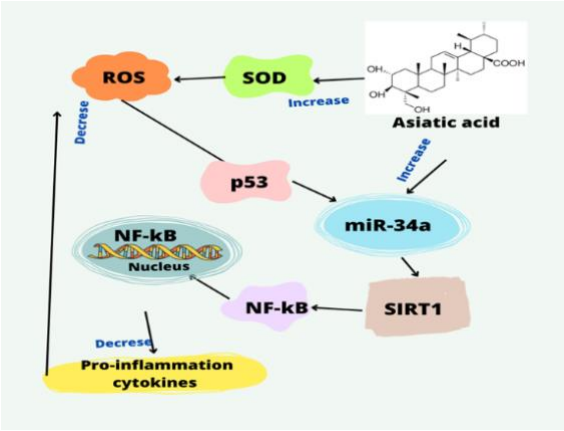
Celastrol effectively inhibited the Cd-induced reduction in p-AMPKα (Thr172) levels and caspase-3 cleavage in PC12 cells, SH-SY5Y cells, and primary neurons.

Figure 5: Mechanism of celastrol to overcome neurotoxic induced methamphetamine.



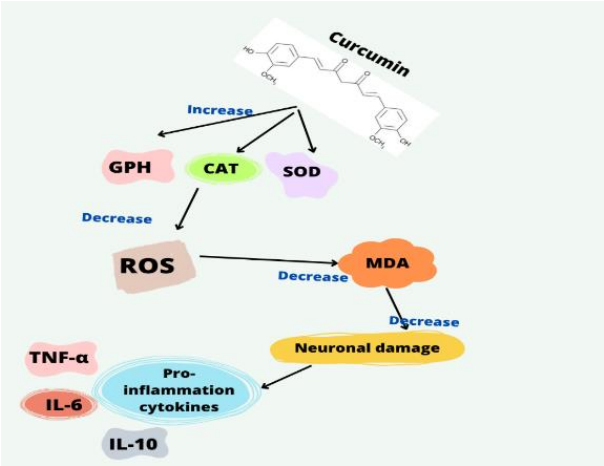
GB demonstrated a significant reduction in the expression of pro-inflammatory cytokines, specifically TNF-α, IL-1β, and IL-6, which were induced by Meth in BV2 cells. GB exhibited inhibitory effects on the expression of TLR4 and phosphorylated NF-κB (p-NF-κB).

Figure 6: Mechanism Ginkgolide B (GB) to overcome neurotoxic induced methamphetamine.



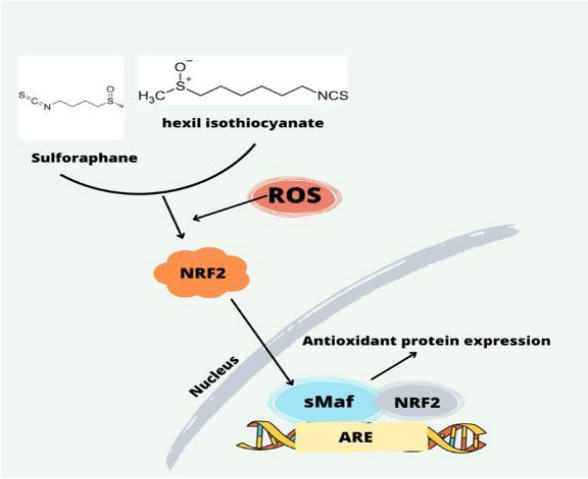
Asiatic acid can significantly alter SOD2 manganese superoxide dismutase II expression by removing superoxide and oxidative attenuation emphasize and increase microRNA-to-regulate neuroprotection by regulating genes related to mitigating reactive oxygen species (ROS) in mitochondria.

Figure 7: Mechanism asiatic acid to overcome neurotoxic induced methamphetamine.



Curcumin can increase SOD and GSH, is protective against oxidative damage and curcumin can decrease peroxide TNF-α and MDA because it can increase methamphetamine-induced neurotoxicity.

Figure 8: Mechanism Curcumin to overcome neurotoxic induced methamphetamine.



These components trigger the intracellular defence system against oxidative stress, specifically involving the Nrf2–ARE pathway.

Figure 9: Mechanism sulforaphane and hexil isothiocyanate to overcome neurotoxic induced methamphetamine.

Discussion

Mechanism of methamphetamine-induced neurotoxicity

In its entirety, methamphetamine neurotoxicity involves the interplay of several mechanisms. These mechanisms encompass hyperthermia, oxidative stress, excitotoxicity, neuroinflammation, microglial activation, Blood-brain Barrier (BBB) dysfunction, and the activation of apoptotic pathways. These processes collectively contribute to the damaging effects on the nervous system caused by methamphetamine (Primatanti & Jawi, 2019). Methamphetamine leads to the formation of reactive oxygen species (ROS), including hydroxyl radicals (OH-), hydrogen peroxide (H_2O_2), and superoxide anions (O^{2-}), via enhanced dopamine auto-oxidation. Elevated ROS levels contribute to oxidative stress by increasing markers such as lipid peroxidase and triggering protease activation, leading to cell death. Simultaneously, there is a dysfunction in mitochondrial metabolism, inhibiting the Krebs cycle and the electron transport chain. This mitochondrial dysfunction adds to the observed neurotoxicity. In addition, the neurotransmitter glutamate, the main excitatory neuron, plays an important role in neurotoxicity. Glutamate accumulation causes an influx of calcium, causing an increase in intracellular Ca++ levels. This high intracellular Ca++ level initiates an intracellular cascade, activating protein kinases, phosphatases, and nitric oxide synthase (NOS) to produce nitric oxide (NO). This process causes endoplasmic reticulum stress

and activation of the apoptotic pathway. Furthermore, inflammation occurs as a result of methamphetamine-induced activation of NFKB, leading to the transcription of proinflammatory cytokines in microglia. This increases levels of IL-6, IL-1β, TNF-α, MCP-1, and ICAM-1 (Primatanti & Jawi, 2019).

Methamphetamine exerts its pharmacological actions by interacting with multiple receptors and transporters, namely the dopamine transporter (DAT), serotonin transporter (SERT), noradrenaline transporter (NET), and N-methyl-D-aspartate (NMDA) receptors. These receptors are integral membrane proteins situated on the cell surface. Furthermore, the drug interacts with vesicular monoamine transporter-2 (VMAT-2), which is embedded in vesicular membranes. These interactions collectively modulate monoamine neurotransmitters' release and reuptake processes, ultimately giving rise to the drug's stimulating properties and potential neurotoxic effects. (Shrestha *et al.,* 2022).

Clinical methamphetamine-induced neurotoxicity

Individuals who abuse METH are at an increased risk of developing various neuropsychiatric and cognitive conditions, including Parkinson's Disease (PD), depression, schizophrenia, psychosis, and other related sequelae. These conditions are largely attributed to the neurotoxicity induced by METH (Yang *et al.,* 2018). In the brain, substantial doses of methamphetamine (METH) have been demonstrated to induce neuronal apoptosis and activate glial cells. These glial cells are crucial to the brain's immune response and tissue repair mechanisms (Moratalla *et al.,* 2017).

The immediate physiological consequences of methamphetamine use encompass a range of symptoms, such as diminished appetite, heightened heart rate (tachycardia), elevated blood pressure (hypertension), accelerated respiration (tachypnea), dilated pupils (mydriasis), and an increase in body temperature. At higher dosages, individuals may experience symptoms like fever, perspiration, migraines, impaired vision, dizziness, abdominal discomfort, muscle weakness, chest pains, tremors, desiccation, queasiness, and emesis. In instances of extremely high doses, the adverse effects can include hyperthermia, irregular cardiac rhythms (cardiac arrhythmia), seizures, cerebral haemorrhage, renal failure, muscular breakdown (rhabdomyolysis), and profound wakefulness, potentially culminating in temporary blindness, coma, or fatality. Even when administered as prescribed by medical professionals, methamphetamine doses can yield undesirable effects like dysphoria, insomnia, and tremors, with the potential for addiction. The smallest dosage (5 mg; equivalent to 0.06 to 0.08 mg per kilogram of body weight) can induce favourable drug responses.

Prolonged methamphetamine abuse, particularly at elevated dosages, is associated with a variety of physiological repercussions affecting the cardiovascular, gastrointestinal, and neurological systems, which encompass conditions like cerebral vasculitis and various types of cerebral haemorrhage, including intracerebral, subarachnoid, or intracranial bleeding. The behavioural outcomes of chronic usage involve addiction, cognitive deficits, anxiety, depression, aggressive behaviour, insomnia, repetitive behaviours (stereotypy), and psychosis. Withdrawal symptoms entail cognitive deficits, disrupted sleep patterns, depression, anxiety, and intense cravings for the drug, which may precipitate thoughts of self-harm. Additionally, individuals engaged in chronic methamphetamine use may be at an elevated risk of developing Parkinson's disease due to the toxic effects of the drug on the nigrostriatal dopamine pathway (Moszczynska, 2016).

Antioxidant plants that have the potential to overcome the neurotoxicity of methamphetamine

Ipomoea batatas L.

In the 16th century, purple sweet potatoes were believed to be introduced to Spain and disseminated to various regions, including Tahiti, the Guam Islands, Fiji, and New Zealand. These potatoes eventually spread globally, particularly to nations characterised by tropical climates (Saludung *et al.,* 2020). Purple Sweet potato contains anthocyanins with a stronger DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity compared to anthocyanins obtained from red cabbage, grape skins, elderberry, or purple corn. Moreover, among the eight major anthocyanin components found in purple sweet potato, its antioxidant activity surpasses ascorbic acid (Panda & Sonkamble, 2012). Anthocyanin has exhibited neuroprotective effects against apoptosis caused by mitochondrial oxidative stress (MOS). It has shown efficacy similar to glutathione (GSH) in safeguarding cerebral granule neurons (CGNs). Inhibition of Bcl-2 results in a considerable reduction in mitochondrial GSH, a process that is counteracted by anthocyanin. This shows that anthocyanins can reduce neurotoxicity due to methamphetamine (Kelsey *et al.,* 2011).

The results of the research (Damayanti *et al.,* 2022) showed that a test animal group of female mice (*Mus musculus*) Swiss Webster strain, aged between six to eight weeks weighing 25 to 30 g treated with purple sweet potato aqueous extract, showed mild macrophage accumulation, slight vacuolisation of tubular epithelial cells, mild blood vessel dilatation, and

mild hydrophilic degeneration in the early phase. In later phases, macrophage accumulation was observed at moderate levels. The LD50 of purple sweet potato extract was determined to be greater than 5,000 mg/kg body weight. The findings of this study indicate that administering purple sweet potato extract at doses is guaranteed to be safe and does not cause death. In addition, evaluation of the toxicity of purple sweet potato water extract on kidney tissue showed minimal chemical effects.

Scutellaria baicaleinsis georgi

This plant species is native to several East Asian countries and the Russian Federation and has been grown in numerous European nations. For over 2000 years, the Chinese employed the dried root of this medicinal plant as a traditional medicine known as Huang-Qin. It has now gained official recognition in the Chinese Pharmacopoeia (Zhao *et al.,* 2016). Baicalein is a phenolic flavonoid found in the dried roots of *Scutellaria baicalensis* Georgi. This compound has been reported to exhibit various biological properties, including antioxidative activities (He *et al.,* 2015). Neurotoxicity is marked by the depletion of dopamine transporter (DAT) levels. Baicalein can potentially mitigate the loss of DAT induced by methamphetamine by inhibiting the elevation of neutrophils and lipid peroxidation caused by neutrophil-derived reactive oxygen species in the striatum (Wu *et al.,* 2006). Acute toxicity research in Qi et al*.* (2009) was carried out randomly with 30 mice (15 females and 15 males) *on Scutellaria baicaleinsis* Georgi extract, namely Wogonin, dissolved in normal saline (NS), and the mice were injected intravenously with a dose of 120 each. mg/kg, 60 mg/kg, and 30 mg/kg for groups I, II, and III for 90 days and monitoring on days 45 and 90. The LD50 value of wogonin determined by the Bliss method was obtained at 286.15 mg/kg, with 95% confidence limits ranging from 278.27 to 295.26 mg/kg.

Cinnamomum cassia

Cinnamomum cassia originates from China, primarily in the provinces of Guangxi, Guangdong, Fujian, and Hainan. This plant has been distributed within China and to countries like India and Vietnam. In various Asian regions, Cinnamon cortex is commonly employed for medicinal purposes, particularly in traditional Chinese medicine. Cinnamon cortex is a well-recognised component of traditional Chinese medicine and has been included in the Pharmacopoeia of the People's Republic of China since 1963. It is a key ingredient in over 500 different formulations used to address a wide range of health conditions, including cardiovascular diseases, chronic gastrointestinal disorders, gynaecological ailments, and inflammatory conditions (C. Zhang *et al.,* 2019). Cinnamaldehyde (CA) is the predominant and essential organic compound found in the essential oil extracted from the stem bark of *Cinnamomum cassia*. It is responsible for the characteristic taste and aroma of the essential oil. Trans-cinnamaldehyde (TCA), extracted from cinnamon, exhibits a well-known neuroprotective effect against METH-induced cytotoxicity in PC12 cells. The neuroprotective action involves inhibiting apoptotic DNA fragmentation and reducing the generation of reactive oxygen species (ROS). Additionally, TCA increased glutathione levels in cells, further contributing to its neuroprotective properties (Rashidi *et al.,* 2021). In a 13-week repeated-dose oral toxicity study from Yun et al*.* (2018) conducted on healthy male ICR mice (eight weeks old), daily oral administration of cinnamon extract at doses of 500, 1000, and 2000 mg/kg BW for three days was performed. The study revealed that mice's body weight returned to normal after receiving doses of up to 2000 mg/kg of cinnamon extract. However, high doses of cinnamon extract (2000 mg/kg) demonstrated potential nephrotoxicity and hepatotoxicity in both men and women. This was substantiated by an increase in kidney and liver weight and a statistically significant, slight elevation in total cholesterol levels. The comprehensive findings from genetic toxicity testing, which included the Ames test, in vitro mammalian cell micronucleus test, and in vivo bone marrow micronucleus test, collectively indicate that cinnamon extract does not possess mutagenic or clastogenic properties. Cinnamon extract has the potential to induce nephrotoxicity and hepatotoxicity at doses higher than the recommended daily safe dose of 2000 mg/kg BW/day. This recommended human dose can be extrapolated to 324 mg/kg/day.

Laurus nobilis L.

The laurel tree, scientifically known as *Laurus nobilis* L., is an evergreen tree or shrub that falls under the Lauraceae family. It originates from southern Europe and the Mediterranean region and is extensively grown in numerous countries within this geographical area. In traditional Iranian medicine, the leaves of this tree have been employed to address conditions such as epilepsy, neuralgia, and parkinsonism (Caputo *et al.,* 2017). Spirafolide, a sesquiterpene lactone derived from *Laurus nobilis* leaves, has been identified as an inhibitor of intracellular reactive oxygen species (ROS) and apoptosis in dopamine-induced SH-SY5Y neuroblastoma cells. This discovery holds significance as excessive ROS levels are associated with nervous system abnormalities seen in conditions like Alzheimer's disease and Parkinson's disease. Given

these findings, spirafolide from *L. nobilis* appears to be a promising candidate for potential therapeutic intervention in the treatment of methamphetamine-induced neurotoxicity (Ham *et al.,* 2010). The study from Kazeem et al. (2015) assessed the toxicity of Laurus nobilis extract using a brine shrimp (Artemia salina) bioassay. Brine shrimp eggs are hatched in a salt solution, and the resulting larvae (nauplii) are collected. Extracts were tested at 10, 100, and 1000 µg/mL concentrations, with ten nauplii in each of the three replicates. After 24 hours, the results showed an LD50 of 1100 µg/mL higher than 100 µg/mL in the brine shrimp lethal test, indicating that the extract was non-toxic and safe for consumption.

Aronia melanocarpa

Black chokeberry, scientifically known as *Aronia melanocarpa*, originally hails from the eastern regions of North America. The primary centre of its distribution can be found in the northeastern states of the United States of America and the Great Lakes region, with its range extending into the higher elevations of the Appalachian Mountains. During the 20th century, the cultivation of the Aronia plant expanded to several European countries. These countries include Eastern European states, such as Poland (with approximately 1600 hectares of cultivation and an annual production of 14,000–15,000 tons), as well as Germany, Finland, Sweden, and Norway. In addition to the widely recognised commercial black chokeberry cultivars like 'Viking' in Finland and 'Nero' in the Czech Republic, several other cultivar types have been developed, such as 'Aron' in Denmark, Polish 'Galicjanka,' Swedish 'Hugin,' Russian 'Rubina,' and 'Fertödi' in Hungary (Jurikova *et al.,* 2017). Aronia melanocarpa is rich in various antioxidants, the main one being anthocyanin.

Anthocyanins and related compounds, such as cyanidin-3-glycosides, can cross the blood-brain barrier, enabling them to reach the brain. Once in the brain, these compounds exhibit neuroprotective properties by effectively reducing neuroinflammation and oxidative stress (Ahles *et al.,* 2020). The antioxidant effects of aronia extract encompass the inhibition of reactive oxygen species/reactive nitrogen species (ROS/RNS) formation, restoration of antioxidant enzyme expression and activity, and alterations in cellular signalling that lead to an enhancement in antioxidant defences (Dietrich-Muszalska *et al.,* 2014). A toxicity assessment was carried out by Niedworok & Brzozowski (2001) using the LD50 method to determine the toxic threshold for anthocyanin, *Aronia melanocarpa* extract. Anthocyanin was tested on mice at a dose of 10 mg/kg body weight for six weeks through oral administration. The results showed that the characteristics were not toxic and caused toxic manifestations. Administration of 5 g/kg body weight as an aqueous solution does not cause toxic manifestations. There is no interference with the excretory and digestive systems.

Tripterygium wilfordii Hook. F.

This species is native to a region from southern China to northeastern Myanmar and includes Taiwan. It is characterised as a scrambling shrub or liana and predominantly thrives in the temperate biome (Song *et al.,* 2020). Celastrol is a prominent bioactive compound found in *Tripterygium wilfordii* Hook. f., exhibits a diverse array of biological activities. Its pharmacological properties include anti-inflammatory, antioxidant, immunosuppressive, anti-cancer, and neuroprotective effects. Celastrol exerts an inhibitory effect on abnormally active astrocytes because astrocytes play an important role in maintaining central nervous system (CNS) homeostasis. They regulate reactive oxygen species (ROS) levels, maintain the integrity of the blood-brain barrier (BBB), and prevent or reverse Cd-induced oxidative stress and neuronal apoptosis in neurodegenerative diseases. Together, by targeting abnormally active astrocytes, celastrol may assist in modulating the CNS environment, potentially leading to a reduction in inflammation, oxidative stress, and preservation of BBB function, thereby potentially counteracting the neurotoxic effects of methamphetamine (Liu *et al.,* 2022).

LD50 for single administration of *Tripterygium wilfordii* Hook extract ranged from 608 to 858 mg/kg. Subacute toxicity testing by Tao & Lipsky (2000) in mice, using doses equivalent to one-sixteenth to one-fourth of the LD50, for six months, showed various pathological changes in the lymphatic system, including reduced numbers of follicles and lymphocytes in the lymph nodes, spleen, and intestines. In addition, a decrease in the number of spermatozoa and varying degrees of damage were observed in the testicles. No pathological changes were noted in the heart, liver, kidneys, or ovaries. These findings suggest that the main target organs of subacute toxicity are the lymphatic system and reproductive tract.

Gingko biloba L.

Ginkgo biloba, which is the sole surviving species in the Ginkgophyta division, is an ancient tree that originates from China. While it was once widely distributed across the world, it is now primarily found in the northeast Asian region (Yuan *et al.,* 2017). *Gingko biloba* contains antioxidant compounds that inhibit lipid peroxidation (H-290/51) H-290/51 has the ability to reduce methamphetamine-induced neurotoxicity through its ability to reduce oxidative stress (Sharma *et al.,* 2015).

In the acute study by Sun et al. (2006), 60 mice were randomly divided into six groups, each consisting of ten animals. Treatment was administered through gavage using a stainless-steel feeding needle, with varying dose levels of 1, 2, 4, 8, and 16 g/kg. The negative control group received tap water via gavage. After dosing, the animals were returned to an ad libitum diet, and any fatalities occurring within two weeks were documented. The acute toxicity concentration of ginkgo extract that caused mortality in 50% (LD50) of the Wistar rats within a two-week timeframe was determined to be 4947.2 mg/kg.

Centella asiatica (L.)

Centella asiatica (CA), also known as pegaga, Indian pennywort, Gotu kola, or breed, is a native herb that belongs to the Apiaceae family. This herbaceous plant, characterised by its small size, is extensively distributed in Southeast Asian countries, including Malaysia, Thailand, and Indonesia. The antioxidant effect is capable of activating antioxidant response pathways, involving triterpenes as the main bioactive constituents, namely asiatic acid, asiaticosside, medacassic acid, and madecassoside. These constituents have demonstrated a protective role on dopaminergic neurons by exhibiting antioxidant activity. Additionally, antioxidant compounds like quercetin and catechins act as scavengers of reactive oxygen species (ROS) by inhibiting the formation of free radicals and scavenging methamphetamine-induced superoxide radicals (Shamsuddin *et al.,* 2023). LD50 was carried out by Yadav et al. (2019) on Ethanol *Centella asiatica* extract (CEA) was orally administered to mice at doses of 200, 400, 800, 1600, and 2000 mg/kg. The animals were then observed for 72 hours. In the evaluation of acute toxicity, a single oral dose of both extracts was given to mice at doses of 300, 600, 1200, and 2000 mg/kg, and the animals were monitored for 14 days. In a sub-acute study, the extract was orally administered to mice for 28 days at 300, 600, 1200, and 2000 mg/kg doses. Oral administration of *C. asiatica* ethanol extract did not induce any mortality in LD50, acute, or sub-acute toxicity assessments. These doses did not result in fatality in either acute or subacute toxicity investigations. Furthermore, histopathological examination of the kidney, liver, heart, and brain tissues revealed no alterations in tissue morphology.

Curcuma longa Linn.

The turmeric rhizomes have the highest curcumin content at 11.3%, surpassing other plants that contain curcumin, such as those with 5.95% curcumin or black curcumin with 2.80% (Yustinianus *et al.,* 2019). Curcumin demonstrates a high degree of effectiveness in preventing lipid peroxidation and exhibits a significant capacity to enhance the levels of antioxidant enzymes, including Superoxide Dismutase (SOD) and Glutathione (GSH), following the induction of neurotoxicity by methamphetamine. The neurotoxic effects associated with methamphetamine usage led to an increased production of Reactive Oxygen Species (ROS) within the brain. These elevated ROS levels trigger a sequence of oxidative stress responses, such as lipid peroxidation and the activation of proteases, which serve as the initial steps in the cellular apoptosis cascade. Malondialdehyde (MDA) is a biomarker for evaluating oxidative stress, reflecting the generation of free radicals and tissue damage. Antioxidant enzymes like SOD and GSH play a protective role against oxidative damage, as reported by Davidson et al. (2001), offering defence mechanisms that promote the survival of aerobic organisms. SOD catalyses the decomposition of superoxide anions into oxygen and hydrogen peroxide (H2O2), while GSH safeguards cells against damage caused by ROS, including free radicals and peroxides (Hadizadeh-Bazaz *et al.,* 2021).

In the assessment of acute toxicity from (Yadav *et al.,* 2019), female albino mice in groups two to four were orally administered with different doses of C. longa, specifically 250 mg/kg, 500 mg/kg, and 1000 mg/kg of body weight. Remarkably, no fatalities were observed in any of the mouse groups within the initial 48-hour period. Consequently, it can be inferred that the LD50 for this substance exceeds 1000 mg/kg. In the course of the acute toxicity investigations, the administration of C. longa at a dose of 1000 mg/kg did produce some noticeable physiological effects. These effects included initial excitability, mild depression, lethargy, reduced respiration rate, and decreased Spontaneous Motor Activity (SMA). The findings suggest that, despite containing various pharmacologically significant active components, higher doses of *C. longa*, specifically at 1000 mg/kg, exhibit a mild level of toxicity.

Brassia oleracea L.

Cabbage originated from the Western European continent and then spread to various countries with good agriculture. SFN isothiocyanate, an organosulfur compound, originates from identified glucosinolate precursors within *Brassia oleracea* cabbage. This implies that SFN modulates various cellular antioxidant defence mechanisms, resulting in a significant augmentation of intracellular Glutathione (GSH) levels. Elevated GSH levels play a crucial role in safeguarding the SH-SY5Y neuroblastoma cell line against chemical-induced oxidative damage, characterized by the disruption of intracellular redox equilibrium and cellular demise. The neurotoxin 6-hydroxydopamine (6-

OHDA) is commonly employed to establish models of dopaminergic (DA) neuron degeneration resembling Parkinson's disease (PD). Following exposure to 6-OHDA, SFN effectively diminishes intracellular oxidative stress by reducing antioxidant capacity and mitigating the formation of reactive oxygen species (ROS) (Mizuno *et al.,* 2011).

Research from Thounaojam et al. (2011) conducted a safety assessment of acute and sub-chronic oral toxicity in Swiss albino mice. Administration of a single dose of *Brassica oleracea* or Red Cabbage (RC) extract at various concentrations (1000, 2000, 3000, 4000, or 5000 mg/kg body weight) did not result in toxicity or significant adverse behavioural changes. Additionally, chronic administration of RC extract (1000, 2000, and 3000 mg/kg body weight) over 28 days showed no side effects. Parameters such as fluid intake, organ weight, plasma lipid profile, plasma markers (creatine kinase-MB, lactate dehydrogenase, aspartate transaminase, alanine transaminase, creatinine), electrolytes, calcium levels, and total blood count showed insignificant changes. Nevertheless, mice treated with 3000 mg/kg body weight for 28 days showed a significant reduction in body weight gain, food intake, red blood cell count, and increased haemoglobin content, alkaline phosphatase, bilirubin, and urea levels. No deaths occurred even at the highest dose administered, namely 5000 mg/kg body weight, so it is not practical to determine the lethal dose (LD50) of RC extract, which can be assumed to exceed 5000 mg/kg. The observed level of side effects was identified at a dose of 2000 mg/kg body weight for RC extract. Therefore, consuming RC extract for various medicinal purposes is considered safe.

Conclusion

Based on a literature review of plants with the potential to mitigate methamphetamine-induced neurotoxicity through in vitro and in vivo studies, including *Ipomoea batatas* L., *Scutellaria baicalensis* Georgi, *Cinnamomum cassia*, *Laurus nobilis* L., *Aronia melanocarpa, Tripterygium wilfordii* Hook f., *Gingko biloba* L., *Centella asiatica* (L.), *Curcuma longa* Linn., and *Brassica oleracea*, we found that *Aronia melanocarpa* had the highest LD50 value at 5 g/kg of body weight. Further research is needed to investigate the efficacy of *Aronia melanocarpa* in addressing methamphetamine-induced neurotoxicity.

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