Elucidate the Neuro-Pharmacodynamic Actions of 3-Hydroxypterostilbene

By

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Abstract

Pterostilbene (dimethyl ether analog of resveratrol) is a metabolically stable natural bioactive and has exhibited substantial pharmacological activities. 3-Hydroxypterostilbene is a natural pterostilbene analog and an active metabolite of Pterostilbene. The current literature reveals antimicrobial (anti-fungal), anti-obesity, and anti-cancer (skin, leukemia, and colon) activities. However, there are no reports on the actions of 3-Hydroxypterostilbene on the central nervous system. Consequently, there is a void in the neuropharmacological effect of 3-Hydroxypterostilbene. Therefore, this study investigated the pharmacodynamic effect of 3-Hydroxypterostilbene on the dopaminergic and hippocampal neurons. Additionally, *in-silico* analyses were performed to validate its neuro-pharmacodynamic effects. The *in-silico* studies revealed its ability to cross the blood-brain barrier and *in-vitro* studies established the ability to significantly inhibit the dopaminergic and hippocampal neuronal viability. 3-Hydroxypterostilbene induced significant neurotoxicity (hippocampal and dopaminergic neuronal death) by enhancing apoptosis (Caspase-3 activity) and by inhibiting tyrosine hydroxylase activity without inducing oxidative stress and mitochondrial dysfunction.

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List of Abbreviations

RES Resveratrol

Nrf2 Nuclear factor erythroid 2-related factor 2

NF-Kb Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)

sICAM1 soluble intercellular adhesion molecule 1

MCP-1 Monocyte chemoattractant protein-1

sE selectin-Serum levels of E-selectin

ERS Endoplasmic reticulum stress

eIF2a ERS-related proteins eukaryotic translation initiation factor 2a

ICAM1 Intercellular adhesion molecule 1

MMP9 Matrix metallopeptidase 9

GRP78 Glucose-regulated protein 78

TNF alpha Tumour Necrosis Factor-alpha

STZ Streptozotocin

(HO-1) heme oxygenase-1

DMBA Dimethylbenzaanthracene

LPS Lipopolysaccharide

SD Sprague Dawley (SD)

NLRP3 NLR family pyrin domain containing 3

MOMP Mitochondrial outer membrane permeabilization)

EGFR Epidermal growth factor receptor

MGMT O6-6-methylguanine-DNA methyltransferase (MGMT

COX-1/2 Cyclooxygenase1/2

3-hps 3-hydroxypterostilbene

5-LOX 5-Lipoxygenase

CNS Central nervous system

CICI Chemotherapeutics induced cognitive impairment

1. Introduction to natural bioactive compounds:

Natural bioactive compounds are generally considered substances/products that are obtained from plants/botanicals, animals, and microorganisms (bacteria and fungi). These can be the major or secondary metabolites with a well-defined chemical structure attributed to their diverse pharmacological or toxicological effects on humans and animals. Currently, the Secondary metabolites from botanicals and microbes are of primary focus due to their structural diversity and potency as drug candidates. The use of natural bioactive metabolites started as far back as 2600 BC, and in the following years, secondary metabolites have been used as pharmaceuticals, food additives, and cosmetic ingredients. There are four primary classes of metabolites (Figure1), Terpenes, Phenolics, N-containing compounds, and S-containing compounds (Saxena, Saxena et al. 1995, Hasler and Blumberg 1999, Velu, Palanichamy et al. 2018, Twaij and Hasan 2022).

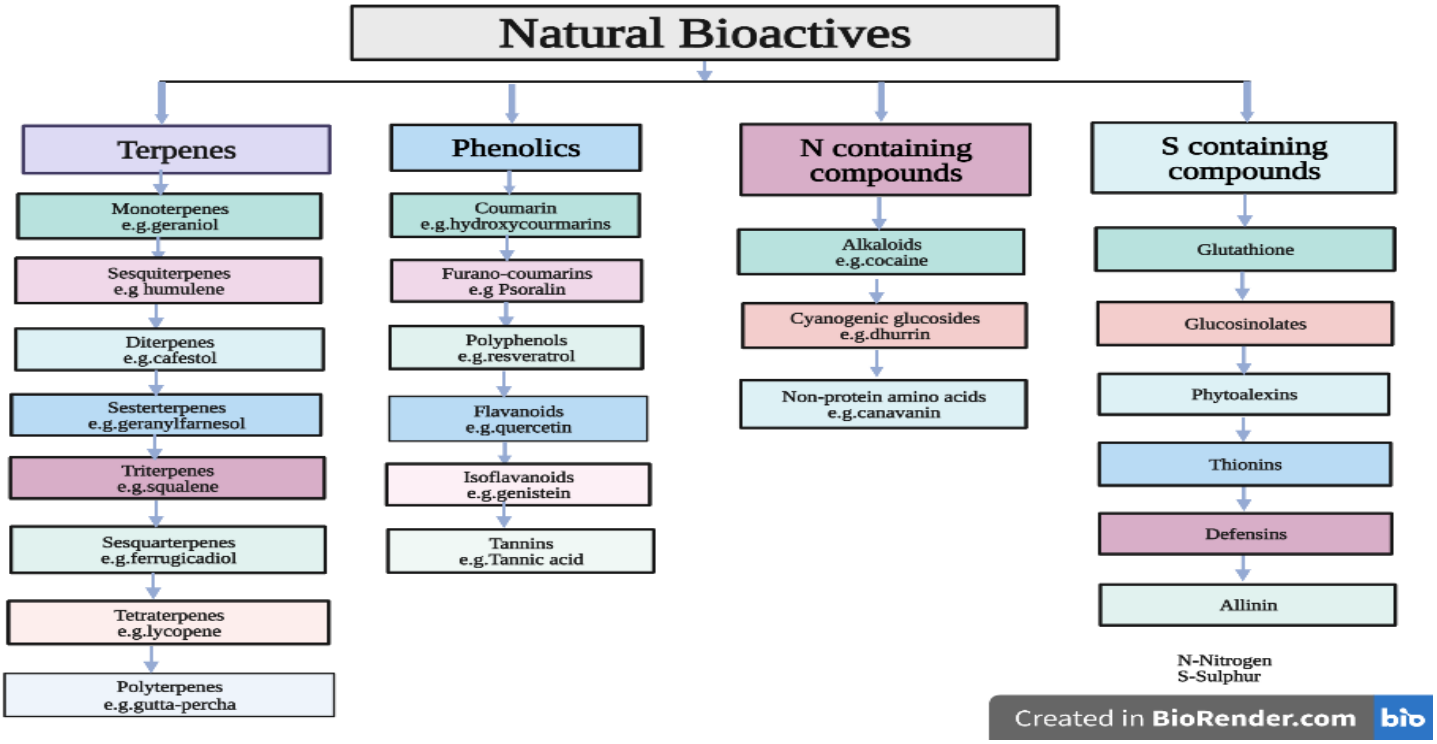


Figure 1: Classification of Natural bioactive

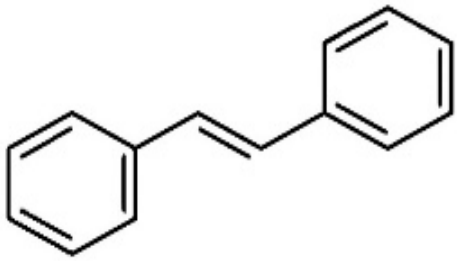
Among the various secondary metabolites, the phenolic metabolites have several pharmacodynamic properties, such as antioxidant, anti-carcinogenic and anti-inflammatory effects.

1.1. Pharmacodynamic profile and Synthesis of Polyphenols and Stilbenes:

Polyphenols are the largest group of phytochemicals, most of which have been recognized in plant-based natural bioactives (nutraceuticals) and food. Polyphenol-rich diets show many health benefits. Polyphenolic compounds are known antioxidants and anti-carcinogenic and are used in the treatment of neurological disease and cancer chemoprophylaxis. Furthermore, polyphenols can reduce mortality from coronary heart disease by raising high-density lipoprotein levels and preventing platelet aggregation. Considering these findings, polyphenolic compounds have become the recent focus of research. Therefore, in recent years, research on polyphenols has established an essential role in preventing degenerative diseases, particularly cancers, cardiovascular diseases, and neurodegenerative diseases (Tsao, 2010).

Stilbenes are small, naturally occurring compounds that are phytochemicals with a molecular weight of approximately 200-300 g/mol, a subclass of polyphenolic compounds, and are known to exert multiple beneficial properties (Tsai et al., 2017). Most plants synthesize flavonoids, but only a few synthesize stilbenes (S. M. Poulose et al., 2015). Stilbene's name was derived from the Greek word "stilbos," which means shining. They exist in two isometric forms:(E)-stilbene(trans-stilbene), which is not hindered sterically,

and (Z)-stilbene(cis-stilbene), which is hindered sterically and therefore less stable (Avendaño & Menéndez, 2015). The central chemical structure of stilbene compounds is 1,2-diphenylethylene (Figure 2).



1,2-diphenylethylene

Figure 2: The central chemical structure of stilbenes

In the late 1980s, French epidemiologists found that, despite having high dietary cholesterol and saturated fat intake, France had a low incidence and mortality rate due to coronary heart disease and certain types of cancer. This finding gained popularity, and this phenomenon was coined as the "French Paradox. In 1992, it was hypothesized that compounds found in wine, i.e., resveratrol, may be accountable for the French Paradox (Shibu M. Poulose et al., 2015). Stilbenes (Figure 3), including resveratrol, oxyresveratrol, pterostilbene, and piceatannol, are widely available in various fruits, vegetables, edible plants, and dietary supplements and play an essential role in plant's defense against pathogen attacks, ultraviolet radiation, and disease (Tsai et al., 2017). Resveratrol (3,5,4'-trihydroxy-trans-stilbene) (RES/RSV) is a naturally occurring plant non-flavonoid polyphenol that was detected first in the roots of white hellebore (*Veratrum grandiflorum*).

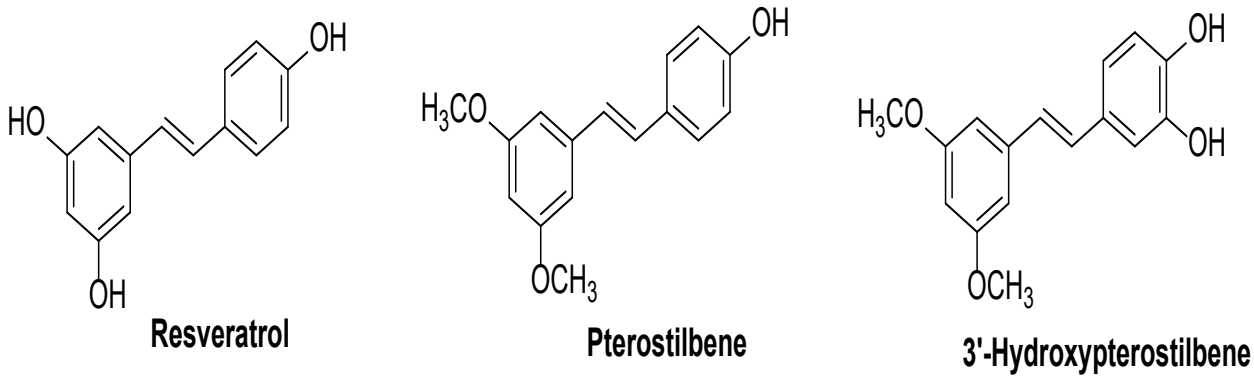


Figure 3: The most used stilbenes

Still, RES is isolated from more than 70 plant species present in various food sources such as grapes, berries, peanuts, red wine, chocolate, and other foodstuffs (Shibu M. Poulose et al., 2015). It is also present in foods such as itadori tea, soy, red fruits, and a large variety of flowers and leaves such as Gnetum, butterfly orchid tree, white hellebore, corn lily, eucalyptus, and spruce (Ahmadi & Ebrahim Zadeh, 2020). Resveratrol (phytoestrogen) has chemical features (structural similarity) that permit it to bind to estrogen receptors and exerts intrinsic signaling through the associated pathways, inducing modifications of kinase activity, transcription of mRNA, or other critical cellular functions (Ahmadi & Ebrahim Zadeh, 2020). Resveratrol is biosynthesized by many plants in response to UV radiations and injuries, especially when the plant is attacked by the pathogens such as bacteria, fungi, or mechanical damage (Ahmadi & Ebrahim Zadeh, 2020). It has a broad range of desirable health benefits, which include antioxidant, anti-cancer, estrogenic, anti-aging, anti-Alzheimer's, anti-hyperglycemic, anti-viral, anti-osteoporosis, anti-obesity, neuroprotective, cardioprotective activities and many biological activities that are consistent with cancer chemoprevention (Ahmadi & Ebrahim Zadeh, 2020). Approximately

50-98% of absorbed RES is bound non-covalently to albumin, low-density lipoprotein, and hemoglobin. A pharmacokinetic study of RES in human and animal models showed that phase-II enzymes rapidly metabolize RES in the intestine and liver (Shibu M. Poulose et al., 2015). However, recent references suggested that chronic dosing can achieve biologically active concentrations of resveratrol. However, resveratrol displays low oral bioavailability and endures speedy first-pass metabolism, Glucuronide, and Sulfate conjugation. Among the many pharmacological activities of RES and despite its limitations, it gained tremendous attention as a promising multi-target anti-cancer agent because of its potential use in chemoprevention and chemotherapy in various tumors such as breast, colon, lung, ovarian, pancreatic, and prostate cancers, mediated by affecting on cell growth, apoptosis, angiogenesis, and metastasis (Ahmadi & Ebrahim Zadeh, 2020). Inadequate oral bioavailability and speedy metabolism are not uncommon amongst polyphenols. So, researchers started to modify the functional groups, thereby increasing their bioavailability and preventing metabolism.

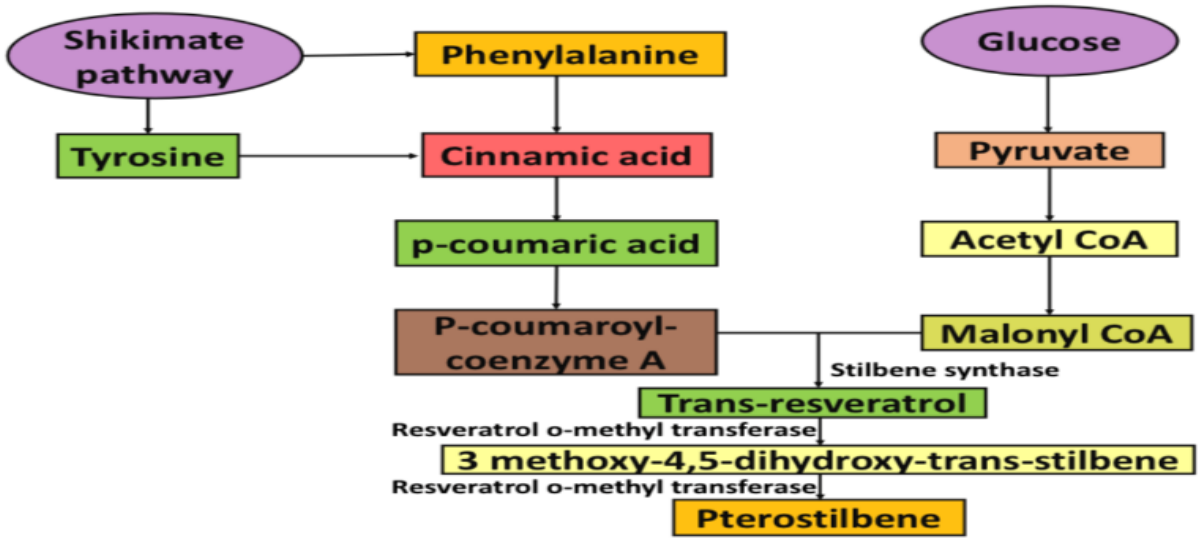


Figure 4: General biosynthesis pathway for resveratrol and stilbenes(Poulose, Thangthaeng et al. 2015)

The biosynthetic pathway of stilbenes (Figure 4) starts with phenylalanine which undergoes multiple enzymatic reactions to produce p-coumaroyl-CoA; then, in the presence of malonyl CoA and stilbene synthases, RES is formed via aldol reaction (a means of forming carbon-carbon bonds). RES is converted to pterostilbene through an O-methyltransferase-facilitated reaction (S. M. Poulose et al., 2015). By contrast, methylated polyphenols appear to show excellent intestinal absorption and inflated hepatic stability.

1.2. Pharmacological effects and therapeutic applications of Pterostilbene:

Pterostilbene (3,5-dimethoxy-4'-hydroxy-trans-stilbene), a naturally occurring dimethyl analog of resveratrol, was first isolated from red sandalwood (*Pterocarpus santalinus*) and, together with resveratrol, it has been identified in the grape berries of *Vitis vinifera*, which is the most important species which is grown worldwide for grape and wine production (Tolomeo et al., 2005). It is phytoalexin-like resveratrol and is engendered by plants in response to stressful conditions like microbial infestation or exposure to ultraviolet light, low soil fertility, high/low temperatures, and severe drought or grazing pressure. Pterostilbene appears to have greater bioavailability because of its lipophilic nature with two methoxy groups, and it possesses cancer chemopreventive activity and other resveratrol-like health benefits (Tsai et al., 2017). Methoxylation on hydroxyl groups of pterostilbene prevents metabolism and shows better pharmacokinetic characteristics than resveratrol. Resveratrol and pterostilbene are well-known stilbenes that are enormously studied because of their biological properties and potential therapeutic and preventive

application. Pterostilbene has more vigorous anti-fungal activity than resveratrol ((Liu, You et al. 2020). Pterostilbene shows powerful growth-inhibitory effects on cancer cells (Tsai et al., 2017). Pterostilbene was more potent than resveratrol in preventing colon tumorigenesis by activating the Nrf2-mediated signaling pathway. Interestingly, pterostilbene was highly efficient compared to resveratrol in preventing colon carcinogenesis *in vitro* (HT-29 human adenocarcinoma cells). In several research findings, pterostilbene was shown to be an effective apoptotic and autophagic agent that can inhibit cancer cell viability, induce cell cycle arrest, alter apoptosis expression gene, promote autophagy-related proteins, and inhibit cancer cells from metastasizing (Tsai et al., 2017). Pterostilbene exerts its bioactivities through different mechanisms. Pterostilbene exerts antitumor, neuroprotective role, antioxidant, anti-inflammatory, lipid-lowering, and anti-fungal activities. A complete knowledge of the bioactivities and pharmacodynamic action can aid in assessing the prospective remedial purposes of pterostilbene.

a. Neuroprotective activity against ischemia:

According to Zhou et al. (Zhou et al., 2015), pterostilbene improved motor performance before and after ischemia in a time and concentration-dependent manner after oral treatment in the mouse model of middle cerebral artery occlusion. In a rodent model of middle cerebral artery occlusion, pterostilbene significantly reduced the infarct volume and lessened the toxic effect on the blood-brain barrier subsequent to ischemic reperfusion perfusion. The most effective dose was 10mg/kg within 1 hour of ischemia-reperfusion (Zhou, Zhang et al. 2015). This protective effect might partially relate to the prevention of oxidative stress and neuronal death in the cortex's penumbra. Another study using a

similar model came to the same conclusion ((Liu, Wu et al. 2019). However, the pharmacological action of pterostilbene was attributed to the inhibition of NF-κB nuclear translocation and phosphorylation, lowering astrocyte-mediated inflammation and oxidative stress after ischemia-reperfusion (Liu et al., 2019). Pterostilbene decreased mitochondrial oxidative damage induced by cerebral ischemia-reperfusion by triggering the heme oxygenase-1 (HO-1) signaling pathway. According to these findings, pterostilbene may help treat neurological abnormalities following cerebral ischemia-reperfusion(Liu, You et al. 2020).

b. Alzheimer's disease:

Pterostilbene can improve learning and memory deficits brought on by lipopolysaccharide (LPS). By suppressing doublecortin expression and enhancing neuronal nuclear antigen expression, pterostilbene alleviated LPS-induced learning and memory deficits (Liu, You et al. 2020).

c. Antitumor activity:

The antitumor activity of pterostilbene is the focus of the current research. In various *in vitro* studies, Pterostilbene hindered the proliferation of various tumor cells, encompassing the oral cavity, breast, lung, liver, stomach, pancreas, lymph, colon, prostate, melanoma, leukemia, and myeloma tumor cells (Table1). In the *in vivo* studies, pterostilbene inhibited tumor occurrence and metastasis and exhibited few toxic effects. Pterostilbene has a less harmful impact on normal hemopoietic stem cells than leukemia cells (Liu, You et al. 2020).

Model	Dose	Signaling Pathway	References
Urethane-induced lung tumor	250mg/kg	By inhibiting the EGFR, Akt/mTOR, stat3, ERK1/2 pathway	(Chen, Tsai et al. 2012)
Breast cancer cells (MDA-231 and ZR-751)	75μM	By the reduction of cell proliferation and JAK/STAT3 signaling pathway	(McCormack, Schneider et al. 2011)
MDA-MB-231 bearing NOD mice	10mg/kg	By inhibiting the Src/Fak signaling pathway	(Su, Lee et al. 2015)
T24 human bladder cancer cell	66.58μM	Autophagy was triggered by inhibiting active human protein kinase/the mammalian TOR/p70S6K pathway and activating the extracellular signal-regulated kinase pathway.	(Chen, Ho et al. 2010)
Human EC109 and TE1 esophageal cancer cells	150μM	Activation of ERS signaling pathway. It upregulated the pro-apoptosis-related protein PUMA and downregulated the anti-apoptosis-related protein Bcl-2 while promoting the translocation of cytochrome c from mitochondria to cytosol and the activation of caspase 9 and caspase 12	(Feng, Yang et al. 2016)
HepG2 cells	100μM	It induced ROS generation, which was attributed to the p53-mediated downregulation of SOD2.	(Guo, Tan et al. 2016)
MDA-MB-231 cells	10μM	Suppression of cell migration and invasion through blocking NF-κB-mediated uPA expression and Rac1/WAVE/Arp2/3 pathway.	(Ko, Kim et al. 2014)
Human osteosarcoma cell line (SOSP-9607)	1.81μM	Inhibition of JAK2/STAT3 signaling	(Liu, Wang et al. 2013)
Non-small cell lung cancer cell(A549)	21μM	Activation of ATM/CHK/P53 pathway	(Lee, Kim et al. 2016)

Table 1: Signaling pathway of the antitumor effect of pterostilbene

d. Anti-inflammatory effect:

The anti-inflammatory effect of pterostilbene is another critical point of focus. In the *In vitro* studies, it decreases the adherence of U937 monocytes to umbilical vein endothelial cells of humans and lowers the production of the cytokines soluble intercellular adhesion molecule-1(sICAM1), IL-8, monocyte chemoattractant protein-1(MCP-1), and serum levels of E-selectin (sE-selectin) ((Ma, Zhang et al. 2019). Thus, pterostilbene considerably reduced inflammatory response. Additionally, under endoplasmic reticulum stress (ERS), pterostilbene decreased the expression of ERS-related proteins eukaryotic translation initiation factor 2a(eIF2a), intercellular adhesion molecule 1(ICAM1), matrix metallopeptidase 9 (MMP9), and glucose-regulated protein 78 (GRP78), significantly decreasing the inflammation of vascular endothelial cells ((Ma, Zhang et al. 2019). In the HT-29 human adenocarcinoma cells, pterostilbene was a more potent anti-inflammatory chemical than resveratrol to prevent colon cancer development (Tsai, Ho et al. 2017).

Pterostilbene demonstrated its potential anti-inflammatory effect *in vivo* by lowering IL-6 and TNF-α mRNA levels induced by lipopolysaccharide in the rat hippocampal region ((Liu, You et al. 2020). The reduction of inflammatory cytokines (IL-1, TNF-α, and IFN-γ) in mice with hyperglycemia caused by streptozotocin (STZ) showed that pterostilbene therapy could considerably reduce the inflammatory response (Li, Li et al. 2018). It was discovered that pterostilbene therapy decreased NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, indicating that pterostilbene may alleviate early brain injury

following subarachnoid hemorrhage by reducing NLRP3 inflammatory bodies, indicating that pterostilbene has the potential to be an anti-inflammatory drug(Liu, You et al. 2020).

e. Antioxidant activity:

Pterostilbene's antioxidant effect is the basis for its use in the treatment of a variety of central and peripheral diseases. Nuclear transcription factor (Nrf2) acts as the "main regulator" of cytoprotective and antioxidant genes. During pterostilbene treatment in the Streptozotocin (STZ)-induced diabetic mellitus model, Nrf2 activation and downstream target gene expression were observed, and oxidative damage to pancreatic tissue was reduced. (Zhou, Zhang et al. 2015). As an effective Nrf2 activator, pterostilbene protects human keratinocytes from arsenic-induced cytotoxicity and apoptosis (Table 2)(Liu, You et al. 2020).

Model	Dose	References
Human keratinocytes, mouse epidermal cells	3.75,7.5,15μM	(Zhou, Ci et al. 2019)
Streptozotocin-nicotinamide-induced type 2 diabetes mellitus in Wistar rats	40mg/kg for 6 weeks	(Satheesh and Pari 2010)

Table 2: Model and dose of antioxidation activity of pterostilbene

f. Anti-lipidemic activity:

Pterostilbene exerts its lipid-lowering activity by reducing the amount of white adipose tissue and increasing the amount of brown adipose tissue. Koji et al. found that pterostilbene inhibits the accumulation of white adipose tissue by enhancing energy metabolism and partially inhibiting adipogenesis in obese Otsuka Long–Evans Tokushima fatty rats. Pterostilbene can also induce the browning of white adipose tissue (Liu, You et

al. 2020). Pterostilbene is an agonist of the peroxisome proliferator-activated receptor and has the same activity as fibrate antihyperlipidemic medications, according to a study by Rimando et al. For the treatment of dyslipidemia, pterostilbene may be a better option because it is a more potent hypolipidemic molecule (Liu, You et al. 2020).

g. Anti-microbial activities:

The current research has indicated the anti-fungal action, pterostilbene at a concentration of 60g/mL, prevented the germination of the conidia of *Botrytis cinerea*. Additionally, pterostilbene demonstrated a potent bacteriostatic impact against the important periodontal pathogen, *Fusobacterium nucleatum*. The anti-bacterial effect of pterostilbene involved inducing cell contents to leak out, reducing bacterial cell viability. Pterostilbene is used in the treatment of periodontitis as adjuvant therapy (Zakova, Rondevaldova et al. 2018). This reference has been overused. Can you find another reference?

1.3. Pharmacological effects and therapeutic applications of 3-hydroxypterostilbene:

3-hydroxypterostilbene(trans-3,5-dimethoxy-3',4'-dihydroxypterostilbene) (3-HPS), one of the metabolites of pterostilbene (a novel natural pterostilbene analog) has been isolated from the plant, *Sphaerophysa salsula*, *Pterocarpus marsupium,* and in honeybee propolis which is used in Chinese folk medicine to treat hypertension. It is widely available in Central Asia and Northwest China (Tsai et al., 2017). The presence and position of the hydroxyl groups of 3′-hydroxypterostilbene are directly related to the significant difference in biological activity compared with pterostilbene (Koh et al., 2021). Oxidative stress is of clinical importance not only because oxidants are common in inflammation but disruption

of mitochondrial energy metabolism can lead to the initiation of inflammation. Moreover, disturbance of colonocytes may also impair the ability to combat free oxygen radicals responsible for cell damage. Current drug therapies like corticosteroids and immunomodulators exacerbate the disease and exert numerous adverse drug reactions, so there is a need for new and novel treatments to manage drug treatments with minimal adverse effects (Takemoto et al., 2015). Natural bioactives can be widely used as they show low adverse effects and multiple pharmacodynamic actions. 3-hydroxypterostilbene acts as an antioxidant and anti-inflammatory agent. Structural features that enhance pharmacodynamic action include a 3-hydroxyl group on the B-ring and/or hydroxyl group on the C3 position. The hydroxyl group is mainly responsible for antioxidant capacity. Researchers found that 3-hydroxypterostilbene acts as an activator and inhibitor of SIRT1, depending on the concentration used (Takemoto et al., 2015). Recent research showed that 3-hydroxyterostilbene was more potent than pterostilbene against human colon cancer cells (Tsai et al., 2017).

Molecular targets for 3-hydroxypterostilbene (3-hps)

a. Effect of 3-hps on Phase-I metabolizing enzymes: 3-hps exhibited a chemopreventive effect during DMBA (7,12-Dimethylbenzaanthracene)-induced initiation of skin carcinogenesis through the inhibition of CYP1A1 and CYP1B1 gene expression but not the induction of detoxification in HaCaT cells (Figure 5) (Lee et al., 2021).

b. Effect of 3-hps on IL-6/JAK/STAT-3 pathway:

The IL-6/JAK/STAT-3 is aberrantly hyperactivated in many types of cancer, and such activation leads to poor clinical prognosis. In the tumor microenvironment, IL-6/JAK/STAT-3 signaling drives tumor cell proliferation, survival, and metastasis while strongly suppressing the antitumor immune response (Johnson, O'Keefe, and Grandis 2018). In the study by Lee et al. (2021), a significant reduction in phosphorylation (Tyr705) of STAT3 was observed, which suggests that 3-hydroxypterostilbene suppresses tumor proliferation (Lee et al., 2021). Inhibition of STAT3 was also reported by Lai et al. (2017), also showed the suppressive effect of 3-hydroxypterostilbene on colitis-associated tumorigenesis (Figure 5) (Lai et al., 2017)

c. Effect of 3-hps on the 5-lipoxygenase (5-LOX) pathway:

Leukotrienes, synthesized from the 5-lipoxygenase (5-LOX), have a significant role in the inflammatory process (Martel-Pelletier et al., 2003). The inhibition of 5-LOX is known for the treatment of asthma. However, initial investigations have revealed an up-regulation of LOX enzymes following myocardial ischemia/infarction, which may contribute to cardiac hypertrophy, myocyte apoptosis, and fibrosis (Boccellino et al., 2019).

In 2019, it was elucidated that lipoxygenase (LOX) could be inhibited effectively by 3-hydroxypterostilbene, and it could play a crucial factor in the improvement of hypoxia-induced toxicity in H9c2 cardiomyocytes. LOX can produce oxidized eicosanoids, which function as a sign of myocardial ischemia/ infarction. This study revealed that 3-hydroxypterostilbene inhibited the activity of 5-LOX via direct docking/binding on the

enzyme. Hydroxyl and methoxy groups might contribute to the strong interaction with 5-LOX (Figure 5) (Koh,Ho, and Pan 2021b).

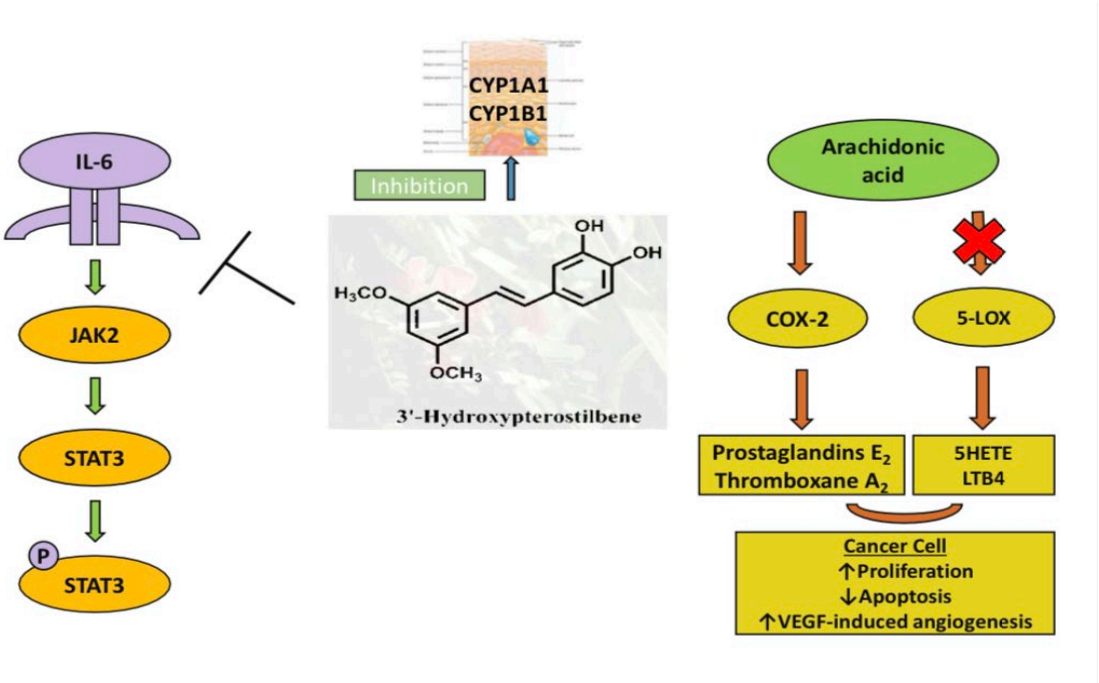


Figure 5: 3-hydroxypterostilbene targets and their associated pathway

Effect of 3-hps on various organs

a. Effect of 3-hps on the central nervous system:

There are very minimal studies related to the effect of 3-hps on the central nervous system.

b. Effect of 3-hps on the Ophthalmic system:

A study by Majeed and his colleagues elucidated the chronic effect of 3-hps on the ophthalmic functions (visual response) in Sprague Dawley rats. 3-hps had no treatment-related abnormalities on the visual response (Majeed et al., 2017).

b. Effect of 3-hydroxypterostilbene on the Auditory system:

A study by Majeed and his colleagues elucidated the chronic effect of 3-hps on the auditory response in Sprague Dawley rats. 3-hps had no treatment-related abnormalities in the auditory response (Majeed et al., 2017).

c. Effect of 3-hps on the Gastrointestinal system:

Molecular analysis revealed that 3-hps has anti-inflammatory properties because it significantly reduces the levels of IL-6, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) and thus contributes to their chemopreventive activity in suppressing colitis-associated colorectal cancer (CRC). Furthermore, dietary 3-hps has been shown to significantly reduce IL-6/STAT-3 signals in inflamed colonic tissue (Lai et al., 2017; Shahini&Shahini, 2022).

d. Effect of 3-hps on inflammation and Cardiopulmonary disease:

Takemoto and his colleagues in this study elucidated that 3-hps was prepared at 1 to 250g/mL in DMSO concentrations. As a control, ibuprofen was used. COX expression varies from one tissue to the next. COX-1 participates in normal cell function, most notably mucosal integrity. COX-2 is also expressed after being activated by mitogenic stimuli (cytokines, phorbol esters, lipopolysaccharides), which contributes to its involvement in neoplastic and inflammatory conditions. COX-2 is essential in the biosynthesis of prostaglandins during acute inflammatory conditions. Because of the complications

associated with current treatments, an alternative agent for reducing COX-mediated inflammation is required, making Phytotherapeutic agents such as polyphenols potentially appealing alternatives. Inflammation reduction can aid in the prevention of certain cancers, cardiopulmonary diseases, and other chronic conditions. 3-hps appears to inhibit both COX-1 and COX-2. At 1,10 and 250g/mL, 3-hps inhibits COX-1 better than Ibuprofen. In comparison to deracoxib, 3-hps inhibits COX-2 at 1g/ml (Takemoto et al., 2015).

e. Effect of 3-hps on Skin:

Zakova and his colleagues showed that 3-hps had a more potent anti-bacterial effect on *Staphylococcus aureus* and thus can be a novel anti-staphylococcal agent for the topical treatment of skin infections (Zakova et al., 2018).

f. Effect of 3-hps on Sexual organs:

In males, 3-hps treatment induced a slight increase in the number of seminiferous tubules in the testes. In females, one uterus had significant eosinophil infiltration of endometrial tissues (Majeed et al., 2017).

g. Effect of 3-hps on Pregnancy:

Male and female (pre-mating) body weight was increased due to 3-hps administration, but the administration of 3-hps during the gestation and lactation period did not affect female body weight. In females, 3-hps revealed no abnormalities in the ovaries' epididymides. Females' absolute organ weight (ovaries and uterus were not affected and were found to be comparable with the control group). The average number of implants, corpora lutea,

pregnancies, dams littered, gestation length, or days of pregnancy are unaffected by daily oral exposure to 3-hps (Majeed et al., 2017)

h. Effect of 3-hps on Bones:

Inflammation or Inflamm-aging is linked to various horse ailments, including laminitis and osteoarthritis, and are commonly treated with NSAIDs. Although NSAIDs effectively treat acute inflammatory problems, long-term use can have adverse side effects. 3-hps in horses decreases lymphocyte production of IFN-gamma (IFN- γ) and TNF- α (Pro-inflammatory cytokines) (Zakova et al., 2018).

i. Toxicity profile of 3-hps:

3-hps was freshly prepared and given orally daily in corn oil (mg/kg/bwt) in Sprague dawley (SD) rats aged 6-8 weeks for 90 days. Repeated oral exposure to 3-hps was deemed safe and had no observed adverse effect level (NOAEL) (Majeed et al., 2017).

Role of caspases in apoptosis:

Caspases are a family of cysteinyl aspartate-specific proteases that function as central regulators of apoptosis in multicellular organisms. Caspase-3, a caspase family member, has been identified as an essential mediator of apoptosis in neuronal cells. For activating the caspase cascade in mammals, two major pathways have evolved (Figure 6):

i. Mitochondrial pathway (Intrinsic pathway)
ii. Death receptor pathway (Extrinsic pathway)

Mitochondrial outer membrane permeabilization (MOMP) is a significant event in the intrinsic pathway. BCL-2 family members play a critical role in MOMP. These proteins are distinguished by the presence of one or more BCL-2 homology (BH) domains and are classified as pro-apoptotic (BAX, BAK, etc.) or anti-apoptotic (BCL-2, BCL-XL) proteins. BAX and BAK undergo conformational changes and oligomerization as a result of apoptotic stimuli, and they cause MOMP by destabilizing the lipid bilayer, creating pores, or interacting with channels. MOMP causes the release of cytochrome c into the cytoplasm, which activates Apaf-1 in the presence of dATP, resulting in the formation of an Apaf-1-containing macromolecular complex known as the apoptosome. In turn, this complex binds to and activates procaspase 9. When mitochondria are damaged, mature caspase-9 is continuously bound to the apoptosome, recruiting and activating executioner caspase 3 or caspase-7, released from the intermembranous space (D'Amelio et al., 2010).

Signaling from a cell surface receptor is involved in the extrinsic pathway. Fas is the most well-studied death receptor; Fas ligand binding causes receptor trimerization and the recruitment of specific adaptor proteins. In its cytoplasmic region, the Fas receptor includes a death domain (DD) that combines with the adaptor protein, Fas-associated DD protein (FADD), to form a death receptor-induced signaling complex (DISC). FADD, like DD, has a death effector domain (DED), which recruits the DED-containing procaspase-8 into the DISC. Procaspase-8 is prototypically activated, resulting in enzymatically active caspase-8, which activates downstream effector caspases. In this case, the mitochondrial pathway is activated by the caspase-8-mediated cleavage of Bid, a pro-apoptotic member of the Bcl-2 family. Truncated Bid (t-Bid) translocate to the mitochondria, which induces

cytochrome c release, an essential step in the mitochondrial pathway. Caspase-3, along with other effector caspases (such as caspase-7 and caspase-6), orchestrates the dismantling of various cell structures (D'Amelio et al., 2010). More research is being conducted to investigate caspase-3's non-apoptotic function in the central nervous system (D'Amelio et al., 2010).

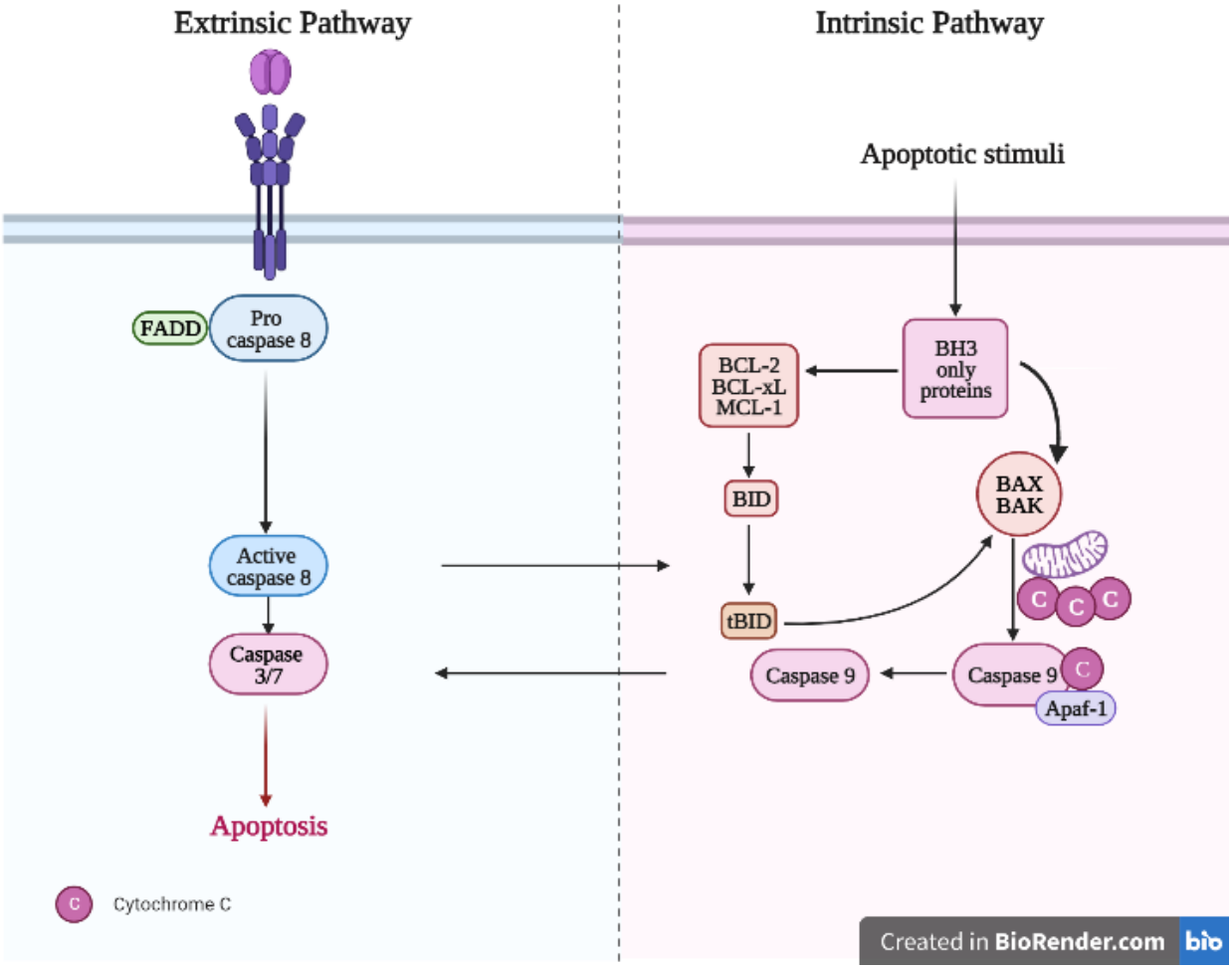


Figure 6: Extrinsic and Intrinsic pathway of apoptosis

2. Introduction to cancer:

Cancer is a disease involving abnormal growth of cells that can subjugate and metastasize other body parts. It has become a leading cause of death globally, causing nearly 10 million deaths in 2020. In 2018, approximately 9.6 million people died due to cancer. Cancer is a multifactorial disease, and various factors, such as diet, lifestyle, exposure to radiation, and hormonal factors, can contribute to the development of this fatal disease (Kamal et al., 2022).

a. Classification of different types of cancer:

Cancer is classified into different types based on organ and cell/tissue (Table 3).

Organ Based	
Appendix Cancer	Malignant cells in the appendix
Bile Duct Cancer	Cancer in the bile tubes through the liver
Adrenocortical Carcinoma	Cancer of the adrenal cortex
Bladder Cancer	Cancerous tumors begin in the bladder
Retinoblastoma	Cancer, which begins in the eye's retina, is common in children
Bronchial Tumors	A type of cancer begins in the mucus sacs of the lungs or "bronchi."
Cervical Cancer	A cancerous tumor that can form in the cervix, usually preventable by a pap smear
Cholangio Carcinoma	Cancer in the bile tubes through the liver
Chordoma	A type of bone cancer in the spine
Colorectal Cancer	A cancerous growth in the rectum or colon region
Esophageal Cancer	The cancerous growth of the esophagus is usually caused by smoking or poor control of acid reflux
Esthesio neuroblastoma	Cancer of the roof of the nose affects the tiny nerve cells
Fallopian Tube Cancer	Sporadic cancer grows in the tube that connects the ovaries, and the uterus called the fallopian tube
Gastric Cancer	Cancer that forms in the stomach is usually caused by smoking and salty foods
Testicular Cancer	Cancerous cells are found in the germ cells of the testicles
Head and Neck Cancer	Smoking contributes to cancer of the nose, throat, mouth, and

	sinuses
Hepatocellular Cancer	Cancer forms in the liver and is most common in people with liver disease
Hodgkin Lymphoma	Cancer of the lymphatic system affects the body to fight off infection
Hypopharyngeal Cancer	Cancer found in the throat is attributed to head and neck cancer
Laryngeal Cancer	Cancer is found in the larynx or voice box and is attributed to head and neck cancer
Lip and Oral Cavity Cancer	Cancerous growths in the mouth, including lips and gums, are usually attributed to smoking and strong alcohol use
Liver Cancer	Cancer is formed in the liver
Lung Cancer	Cancer, found in the lungs, is most common in those who smoke; these cancers include non-small cell, small cell, pleuropulmonary blastoma, pulmonary inflammatory myofibroblastic tumor, and tracheobronchial tumor
Nasal Cavity and Paranasal Sinus Cancer	Cancer that forms in the nasal cavity and paranasal sinuses is associated with head and neck cancer
Neuroblastoma	Rare cancer is most found in the adrenal glands; it can also develop in the belly, chest, and bones
Ovarian Cancer	A disease that allows cancer cells to form in the ovaries of females usually goes undetected until it spreads to the pelvis and belly
Pancreatic Cancer	Cancer begins in the pancreas; symptoms include unexplained weight loss and loss of cancer forms appetite
Parathyroid Cancer	Cancer forms in the parathyroid gland
Penile Cancer	Cancer forms in the tissues of the penis
Pituitary Tumor	A tumor that stays within the skull is present in the pituitary gland
Prostate Cancer	Cancer forms in the male's prostate right below the bladder
Rectal Cancer	A cancer of the rectum or colon, people over the age of 50, are at a higher risk for this disease
Salivary gland Cancer	Rare cancer is when cancer cells form in the salivary glands.
Oropharyngeal Cancer	A cancer type is found in the oropharynx or middle part of the pharynx
Thymoma and Thymic Carcinoma	A disease where cancer cells form in the thymus
Urethral Cancer	Cancer that is found in the urethra and a history of bladder cancer can increase the risk of this disease
Vaginal Cancer	A disease that includes malignant cells forming in the vagina
Male Breast Cancer	Rare cancer forms in the breasts of men
Gastrointestinal Tumor	A cancerous tumor that forms in the lining of the gastrointestinal tract, often in the small intestine or appendix
Atypical Teratoid/Rhabdoid Tumor	An aggressive embryonal central nervous system tumor of infants

Carcinoid Tumor	A slow-growing tumor can affect multiple parts of the body
Embryonal tumors of the central nervous system	A cancerous tumor starts in the embryonic stage of the brain
Ewing Sarcoma	A sporadic cancer of the bones, usually in children and young adults
Bone Cancer	Tumors that grow in bones; some can be non-cancerous. These can sometimes come from abnormal healing of the bone from an injury
Gastrointestinal Carcinoid Tumor	A cancerous tumor forms in the gastrointestinal tract lining, often in the small intestine or appendix

Table 3: Classification of cancers based on organs type

Cell/Tissue-Based	
Breast Cancer	Abnormal growth of cells in the breast is most common in females but can occur in males
Anal Cancer	Cancer cells form in the anus tissues
Acute Lymphoblastic Leukemia	Cancer of the red blood cells and bone marrow affects white blood cells
Acute Myeloid Leukemia	Cancer of blood cells and bone marrow with excess white blood cells
Kaposi Sarcoma	A disease that causes lesions in the soft tissues
AIDS-related lymphoma	Malignant cells forming in the lymph system in AIDS patients
Astrocytoma	Brain tumors originate from astrocytes
Basal Cell Carcinoma of the Skin	Skin cancer begins in basal cells
Brain Tumors	Abnormal growth of cells in the brain that can be cancerous or non-cancerous
Burkitt Lymphoma	A form of non-Hodgkin's lymphoma where cancer starts in B-cells
Cardiac Tumors	A cancerous or non-cancerous abnormal growth of cells in the heart
Medulloblastoma	The most common type of brain cancer in children is a tumor in the lower back of the brain called the cerebellum
Germ Cell Tumors	A disease in which a growth of cells forms from reproductive cells
Chronic Lymphocytic Leukemia	Cancer of the bone marrow or blood develops from B-cell white blood cells
Chronic Myelogenous Leukemia	Cancer in the blood cell is rare, and the cause is unknown
Chronic Myeloproliferative Neoplasms	A disease in which the bone marrow makes too many red blood cells, platelets, or white blood cells, usually worsens over time
Craniopharyngioma	A benign brain tumor forms near the pituitary gland and does not

	spread to other brain or body parts
Cutaneous T-Cell Lymphoma	T-cells are a type of cancer that begins in specific kinds of white blood cells
Ductal carcinoma In situ	Abnormal growth of cells in a milk duct of the breasts is considered the earliest form of breast cancer
Endometrial Cancer	A cancerous growth that begins in the lining of the womb
Ependymoma	A central nervous system tumor begins in the spinal cord
Extracranial Germ Cell Tumor	Abnormal growth of germ cells in areas other than the brain
Extragonadal Germ Cell Tumor	Abnormal growth of germ cells everywhere except the gonads
Intraocular Melanoma	In a disease where cancer cells form in the eye's tissue, fair-skinned and older individuals are at higher risk
Ovarian germ cell Tumor	A disease where cancer cells are found in the ovary's germ cells
Gestational Trophoblastic Disease	Rare cancer that forms tumors during abnormal pregnancies forms in the tissues surrounding the egg
Hairy Cell Leukemia	Cancer in which there is a more significant production of lymphocytes by the bone marrow
Histiocytosis	A condition where too many histiocytes or white blood cells build up in organs and tissues like skin, bones, liver, lungs, lymph nodes, and spleen
Pancreatic Neuroendocrine Tumors	A tumor that is found in the pancreas, more specifically, the islet cells or hormone-making cells of the pancreas
Renal Cell Cancer	Cancer is found in the kidneys
Langerhans Cell Histiocytosis	Rare cancer can cause lesions to form anywhere on the body
Leukemia	Cancer of the blood-forming tissues, preventing the body from fighting off infection properly
Melanoma	A type of skin cancer where the cells producing pigment become cancerous
Merkel Cell Carcinoma	Rare and aggressive skin cancer often appears as a blueish-red nodule
Mesothelioma	A cancerous tumor that can cover the lungs, stomach, and other organs; it is sporadic
Metastatic Cancer	Cancer spreads from where it started to another part of the body
Metastatic Squamous Neck Cancer	Cancer threads from an unknown origin to the lymph nodes in the neck
Midline Tract Carcinoma with NUT Gene Changes	A change in chromosomes causes cancer
Multiple Endocrine Neoplasia Syndromes	Cancer can affect the endocrine glands, which could lead to tumors in the thyroid, adrenal, and parathyroid glands
Plasma Cell Neoplasms	A cancer of plasma cells
Mycosis Fungoides	A rare form of T-cell lymphoma in the skin
Myelodysplastic	A disorder that disrupts the creation of blood cells

Syndromes	
Myelogenous Leukemia	It is a type of cancer that begins in the bone marrow and affects the blood cells
Nasopharyngeal Cancer	A disease where cancer forms in the nasopharynx tissue

Table 4: Classification of cancers based on cell/tissue type

b. CNS:

In 1669, Nicolaus steno quoted that the brain, the masterpiece of creation, is almost mysterious to us (El-Habashy et al., 2014). After centuries, the amazingly complex organ mystery seeks attention to unravel. The Edwin Smith Papyrus is an ancient Egyptian medical text where the word brain appeared for the first time (Kamp et al., 2012; Stiefel et al., 2006; Sullivan, 1996). In this papyrus, the description of the CNS was first known and detailed (Cunha, 1949; Jex, 1951). The CNS is a delicate central system controlling every aspect of the biological routines and interaction with the surrounding in mammals. The brain plays a critical role in regulating and controlling most body functions, including sensibility, consciousness, movements, notion, articulation, emotion, learning, and memory (Mineta et al., 2003; Packer et al., 2010). The brain, a vital organ, has 644 kilometers of blood vessels that remove carbon dioxide, provide energy, oxygen, metabolites, and provide nutrients to neurons/glia (cells in the brain), and remove other metabolic wastes (A. Alahmari, 2021; Kisler et al., 2017). The brain acquires 20% of the body's glucose and oxygen while contributing to 2% of total body mass, supplying blood and oxygen to its active areas through neurovascular coupling (AbeerAlahmari, 2021; Iadecola, 2013).

The BBB is a dynamic, semi-permeable, and immensely selective tissue in the cerebral microvessels of most vertebrates. It plays a primary role in regulating the transport of required substances for brain function by controlling homeostasis via regulating molecule transport into and out of the CNS, thereby preventing blood cells, plasma components, and pathogens that enter the brain by creating tightly regulated neurovascular unit (NVU) that encompasses endothelial cells, pericytes, and astrocytes, all of them in conjunction conserve the neural environment to make the brain function normally(Harati et al., 2012; Zhao et al., 2015). The blood capillaries in the brain are distinctive in two aspects.:

- ✓ First, tight junctions, the vital barrier component, tie the endothelial cells that line capillaries walls together. Physically it creates a barrier that prevents paracellular diffusion of polar or large molecules into the brain through the blood-brain barrier. Functionally, it protects the brain against unwanted exogenous and endogenous agents.

- ✓ Second, astrocytes surround these vessels acting as a partly effective barrier regulating the homeostasis of the brain. At the same time, pericytes control the formation and differentiation and help maintain the integrity of the blood-brain barrier (O'Brown et al., 2018).

Efflux transporters are another main functional barrier of BBB. They significantly limit brain accumulation of several classes of drugs (Anti-cancer, anti-viral, anti-bacterial, anti-epileptic, and analgesics (Begley, 2004; Deeken&Löscher, 2007; El-Habashy et al., 2014; Löscher&Potschka, 2005; Shen et al., 2010; Smith, 1993). Some examples of efflux

transporters are P-glycoprotein (P-gp, ABCB1), breast cancer-resistant protein (BCRP, ABCG2), multidrug-resistant proteins (MRP, ABCC1-6), organic anion transporter, concentrative nucleoside transporter (CNT-2) (Begley & Brightman, 2003). Doxorubicin and paclitaxel are the most common chemotherapeutics subjected to active efflux transport mechanisms, including P-gp, BCRP, and MRP expressed on the luminal BBB surface (Löscher&Potschka, 2005; Thomas et al., 2009).

Another functional barrier is the degradative enzymes in BBB, such as phosphatase enzymes. These enzymes aid in the biotransformation or inactivation of several molecules, including peptides and neuropeptides (Brownlees & Williams, 1993; Minn et al., 1991; Witt et al., 2001) as they attempt to cross the BBB to enter the brain parenchyma. Despite such functional and physical barriers that protect the brain from the entry of unwanted agents, the brain vasculature presents other pathways, thereby facilitating the penetration of wanted compounds, including polar and large molecules, across the BBB. This pathway maintains the normal and healthy status of the brain by the uptake of required minerals and nutrients to the brain.

The other significant pathway is the influx transporters that translocate various polar nutrients (glucose, amino acids, and monocarboxylic acids), vitamins, or hormones from the blood into the brain across the BBB (Oldendorf, 1971; Tamai & Tsuji, 2000; Tsuji & Tamai, 1999). Indispensable compounds such as glucose and amino acids utilize carrier-mediated transporters such as GLUT1(glucose transmembrane transporter 1), LAT (L-

amino acid transporter), cationic amino acid transporter, and lactate transporter to enter the brain parenchyma (Pardridge, 2003).

The other pathway is receptor-mediated transport, which transports various macromolecules (Ex: Insulin, leptin, transferrin, etc.,) across the BBB (Karkan et al., 2008; Pardridge, 2008). For example, insulin is transported by the insulin transporter (Laron, 2009), and iron utilizes the transferrin receptor (Boado et al., 2009), which is highly expressed in the capillary endothelium of the brain. The brain contains billions of cells for physiological and psychological processes which define us as individuals.

Brain cancer is a tumor that starts and stays in the brain. The tumor present in the brain cells alter the functional landscape of the brain, leading to specific molecular abnormalities that are fatal in both children and adults (Nilsson & Cunningham, 2018). Brain tumors, also named neoplasms (abnormal tissue mass), originate primarily in the brain or secondary tumors involving the brain as a metastatic site. The World Health Organization (WHO) recognized four categories in the 2007 classification of central nervous system tumors (grade I to grade IV) based on the type, the degree of malignancy, and location. Grade-I and grade II are low-grade gliomas, and grade 3 and grade 4 are high-grade gliomas (Figure 7) (Louis et al., 2016; Zhang et al., 2012). High-grade gliomas are related to poor prognosis.

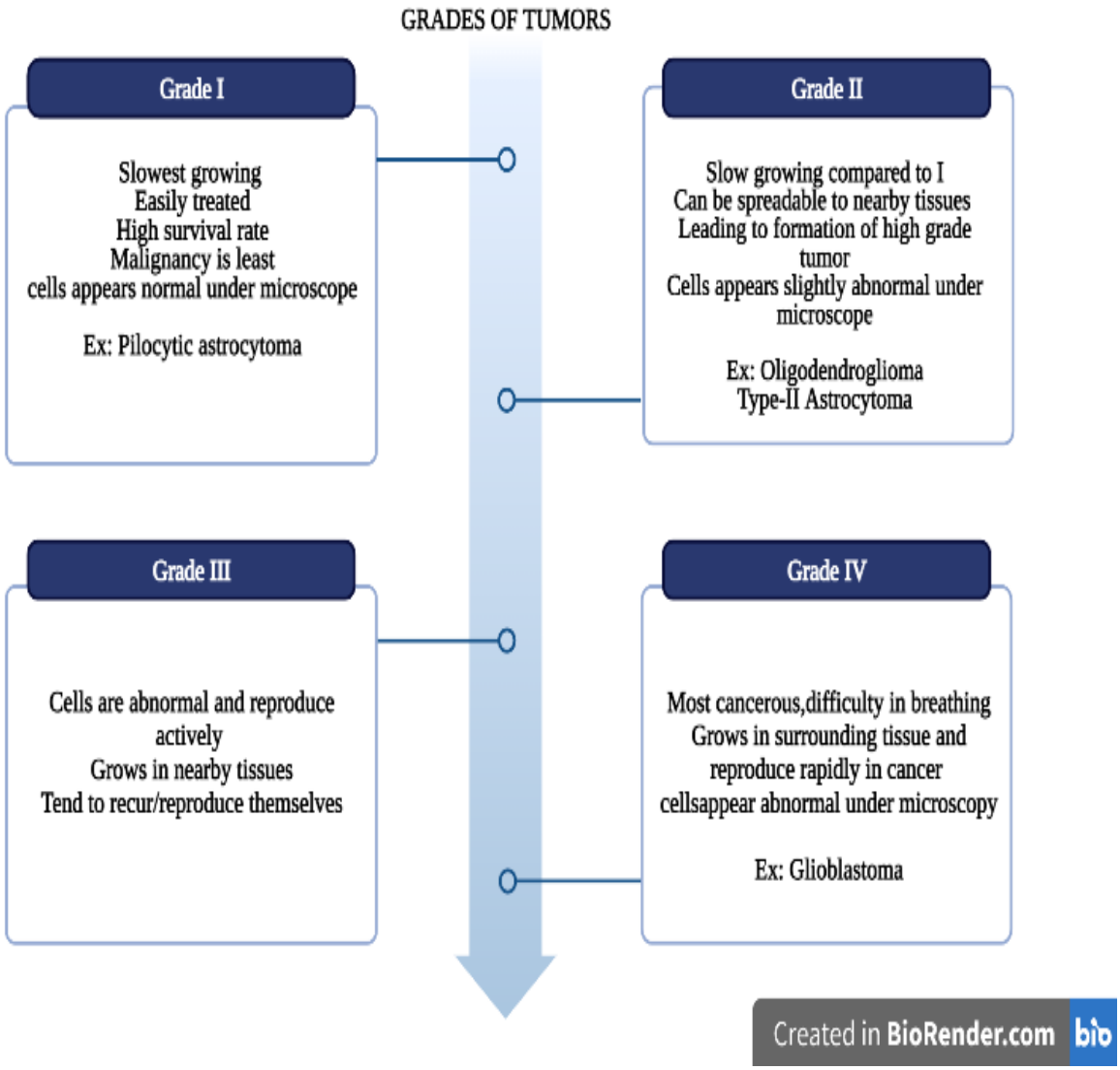


Figure 7: The classification of central nervous system tumors by the world health organization (WHO)

Around 80% of primary malignant brain tumors are collectively called gliomas (the most common brain tumor), the general name for the tumor that originates from the glial cells or precursor cells (astrocytes, oligodendrocytes, and ependymal cells), which supports and

nourishes the brain and then develops into astrocytoma, oligodendroglioma, ependymoma or oligoastrocytoma (Ostrom et al., 2018; Zhang et al., 2012).

c. Classification of primary brain cancer: Primary brain cancer is classified into various types (Figure 8).

The

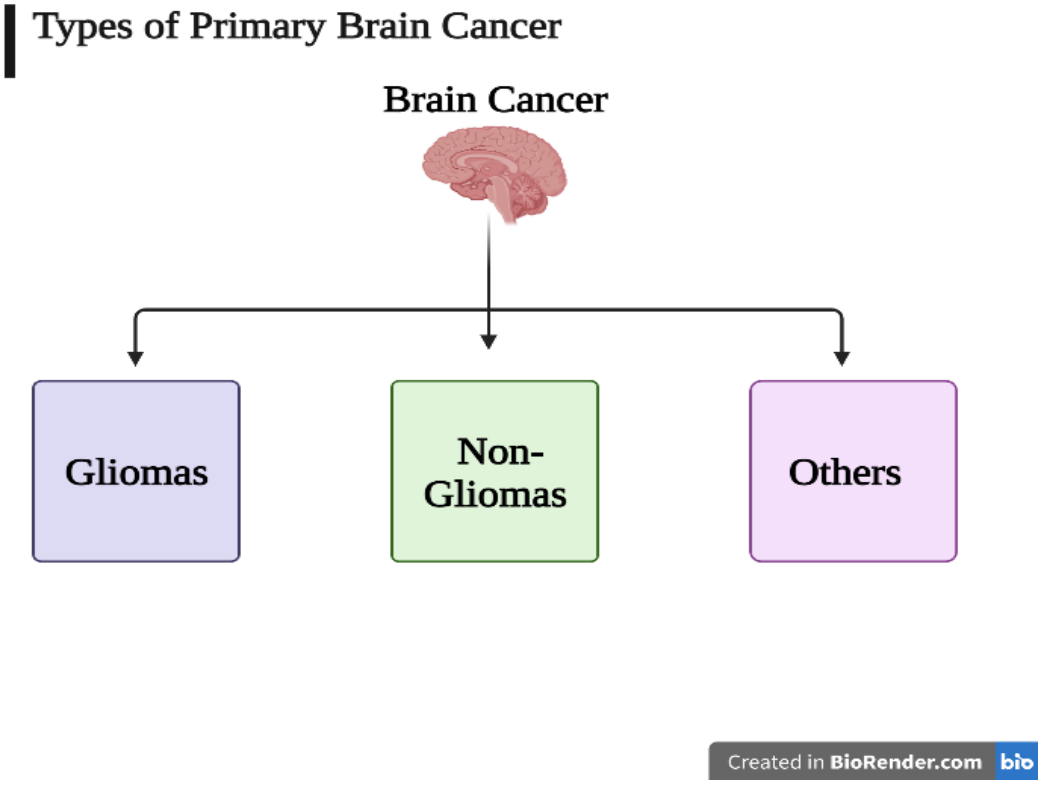


Figure 8: Classification of primary brain cancer

1. Gliomas:

It is a tumor arising from glial cells (supportive or glue-like tissues of the brain), and also it referred to as a "glioma." Three types of glial cells give rise to tumors:

i. Astrocytes

ii. Oligodendrocytes

iii. Ependymal cells

These cells, in general, support and nourish the brain. Gliomas are widespread brain tumors and account for approximately 45-50% of all primary brain tumors.

2. Astrocytoma

The tumors are derived from astrocytes (star-shaped cells) found in the cerebrum part of the brain. It is graded from I to IV (Pilocytic astrocytoma-grade-I; Diffuse astrocytoma-grade II; Anaplastic astrocytoma-grade III and Glioblastoma multiforme (most aggressive type)-grade IV (Table 4).

Types of Astrocytoma	**Grades**
Pilocytic astrocytoma	I
Diffuse astrocytoma	II
Anaplastic astrocytoma	III
Glioblastoma multiforme	IV

Table 5: Different types of astrocytoma with grades

Pilocytic astrocytoma, also called juvenile pilocytic, is a slow-growing tumor that is often benign and responsible for 5-6% of gliomas, primarily seen in children and young adults of age 20. It occurs in the optic nerve (an "optic glioma"), the optic chiasm near the

hypothalamus, thalamus, basal ganglia, cerebral hemispheres, and the cerebellum (i.e., a cerebellar astrocytoma). This group has an evident incidence of alterations in the BRAF oncogenes, leading to its activation by different mechanisms, but the most common one is fusion with the KIAA1549 gene (Cohen & Colman, 2015; Jones & Baylin, 2007). Patients with loss of the NF1(Neurofibromatosis type 1) gene and alterations in the TP53(Tumor suppressor) gene showed increased susceptibility to develop pilocytic astrocytoma (Benítez et al., 2008).

Diffuse astrocytoma-grade II arises in the cerebrum region of the brain. It is also reported in the basal ganglia, brain stem, cerebellum, spinal cord, and other areas of the CNS. It is a monomorphic tumor, which represents 1.7% of all primary brain tumors of the CNS. The survival rate of patients with this tumor is between 5-10years after diagnosis. Grade-II tumors affect young adults. Genetic pathways associated with the initiation of grade-II astrocytoma are: loss of neurofibromatosis type 1 gene (NF1), loss of tumor suppressor gene (TP53), and/or mutations in its DNA binding domain, which is found in 60% of all grade-II tumors and considered most frequent genetic abnormality in these tumors (Sonoda et al., 2001). Another abnormality in this type of tumor is the over-expression of both platelet-derived growth factor receptors and its ligand (PDGFR/PDGF) (Maher et al., 2001; Zhu & Parada, 2002). There is an increased incidence of these tumors in a familial syndrome (Li-Fraumeni) with a genetic predisposition to the loss of NF1 and TP53. These tumors can further progress to more malignant grade (Anaplastic astrocytoma).

Anaplastic astrocytoma-grade III, also called malignant astrocytoma, comprises a mixture of cells and commonly occurs in males of age 45 or older than females. Grade-III astrocytoma shows a similar TP53 mutation rate compared to grade-II astrocytoma. The most common alterations in these tumors are abnormalities in the Rb pathway, loss of Cyclin-dependent kinase 4 inhibitor 2A (CDKN2A) (which encodes p16), or Cyclin-dependent kinase 4 inhibitor 2A (CDKN2B) (which encodes p15). CDKN2A andCDKN2B is tumor suppressor genes, and their loss leads to cancer progression.

Glioblastoma multiforme (GBM, most aggressive type)-grade IV is a fast-growing tumor and represents 20% of all primary brain tumors of the CNS and appears in lobes of the brain (frontal, temporal, parietal, and occipital lobes) usually in adults in a range of 50-70 years age group. These usually harbor Isocitrate dehydrogenase mutations (IDH1 or IDH2), frequently associated with Alpha thalassemia X-linked mental retardation (ATRX) mutation. Physiologically, IDH1 is a metabolic enzyme that acts on the substrate isocitrate and converts it to α-ketoglutarate. Glioma-associated IDH1 mutations alter the activity and cause the formation of 2-hydroxyglutarate, which severely varies epigenetic mechanisms to alter the profile of DNA methylation (Cohen & Colman, 2015). Approximately 30% of primary GBM have mutations in TP53 and over-express the MDM2 (mouse double minute 2) protein, which inhibits transcriptional activation of p53 (Maher et al., 2001). Another common alteration in primary GBM is the loss of the long arm of chromosome 10q, where the tumor suppressor PTEN gene is localized. This alteration is present in more than 30% of all primary GBMs. The Phosphatase and tensin homolog (PTEN) loss results in the activation of mTOR (mammalian target of rapamycin), a downstream protein activated by

PI3K signaling, leading to cancer progression. Secondary glioblastomas arise from anaplastic astrocytoma by accumulative mutations.

3) oligodendroglia tumor is formed from oligodendrocytes (These are cells that form a protective coating around the neurons). It is mainly seen in young and middle-aged adults and rarely in children. Oligodendrogliomas have a high incidence of IDH1 and IDH2 mutations synchronous with 1p19q co-deletion (Archer et al., 2018). Patients with oligodendroglia tumors are quick to respond to chemotherapeutics and have a safer scenario than tumors devoid of 1p19q co-deletion.

4) Ependymomas are tumors originating from ependymal cells (line the spinal cord, fluid-filled cavities, and brain ventricles) (Malhotra et al., 2015). The occurrence of ependymomas is rare in adults and children. It contributes to 17% of tumors and is classified as grade IV by the World health organization (WHO). It is the 12th leading cause of cancer-related deaths (accounts for 3-4%) in the United States, with 6.5 per 1 lakh newly diagnosed cases/year and 4.3 per 100,000 deaths/year, and 4-5% of 5-year survival rate with inferior prognosis (Chen et al., 2015).

Ependymomas are classified into four types and are graded from I to III:

I. Sub Ependymomas (Grade-I): Occur near the ventricles of the brain.
II. Myxopapillary ependymomas (Grade-I): Occur in the spinal cord lower part.
III. Ependymomas (Grade-II): Occur in a ventricular system in the posterior fossa and spinal cord.

IV. Anaplastic Ependymomas (Grade-III): Occurs in adults' brains and posterior fossa in children.

Astrocytoma (Low-grade) arises mainly in young children, but around 50% of all high-grade astrocytoma and GBM occur in adults. The most aggressive form of malignant primary brain tumor is GBM, and it contributes to 17% of central nervous system tumors with an occurrence of 2-3 cases per 100,000-person life-years in Europe and North America (Bleeker et al., 2012). It elevates incidence with age and affects a more significant number of males than females. GBM is presented as primary GBM (90-95% of GBM developing directly from precursor cells (most likely radial glia) or evolving from lower grade astrocytoma as a secondary GBM (5-10%) (Chen et al., 2015). It tends to be found in adults aged 45 and younger and is characterized as malignant, mitotically active, and predisposed to necrosis and is highly infiltrative (A process whereby inflammatory or other types of disease spread throughout an organ) in nature, bears cellular heterogeneity and primarily affecting the cerebral hemisphere of the brain. With regard to age, GBM in children are minimal (only 3%). Primary GBMs exemplify a high degree of genetic instability with numerous cytogenetic abnormalities, DNA copy number gains/losses, and mutations. Genetic alterations include amplification of Epidermal growth factor receptor (EGFR) or Platelet-derived growth factor receptor A(PDGFRA) and mutation or loss of Tumor suppressor protein (TP53), Neurofibromatosis type 1(NF1), Phosphatidylinositol 3-Kinase regulatory subunit (PIK3R1), or Phosphatase and tensin homolog (PTEN).

Further, the genetic mutations significantly affect p53, PI3K/MAPK, and p16/CDK4/RB pathways. The major pathway includes the methylation of the promoter and reduced effect of O6-6-methylguanine-DNA methyltransferase (MGMT), leading to decreased DNA repair. This mechanism is correlated with enhanced sensitivity to alkylating chemotherapeutics (temozolomide), thus resulting in a superior prognosis. (Carlsson et al., 2014).

However, apart from brain tumors originating from glial cells, non-glioma primary brain tumors exist (Figure 9), such as

1) Medulloblastomas, a tumor located in the cerebellum part of the brain. It is a growing tumor that spreads to other parts of the CNS. It contributes to 3% of adults and 13% of children.

2) Pituitary adenoma tumors originate from the pituitary gland.

3) Meningioma tumors develop from the meninges (the membrane that covers the brain) and spinal cord (Carlsson et al., 2014). It represents 38% of primary brain tumors, is prevalent in middle-aged women, and is further classified into three grades.

Grade-I: A benign meningioma-slow-growing tumor (Carlsson et al., 2014).
Grade-II A typical meningioma-faster growing tumor having a reoccurrence tendency
Grade-III Anaplastic or malignant meningiomas-malignant have a tendency to happen and expand to adjacent tissues

2. Brain stem glioma:

It commonly appears in the brain stem. It affects the upper region of the brain stem (midbrain or tectum), the middle region of the brain stem (pons), and the lower region of the brain stem (cervico-medullary). It is widely prevalent in children and adults aged 5-40 (Shah & Kochar, 2018).

3. Craniopharyngioma:

The tumor evolves from tiny groups of cells located close to the pituitary stalk. The two types of craniopharyngioma are:

I. Adamantinomatous

II. Papillary craniopharyngioma

Craniopharyngioma contributes to 2-5% of all primary brain cancer in adults after age 45 and is also seen in children (Shah & Kochar, 2018).

4. Germ cell tumors: These tumors occur in the brain's pineal or suprasellar regions. It contributes to 1-3% of children and is found in young adults ranging from 11-30 years of age. It is the only primary tumor that can be diagnosed using markers (Placental Alkaline Phosphatase (PAP) and Human Chorionic Gonadotropin (HCG) markers used for diagnosing germ cell tumors), located in cerebrospinal fluid and blood alpha-fetoprotein (AFP) (Shah & Kochar, 2018).

5. Recurrent tumors: The tumors that recur even after surgery due to incomplete removal of the tumor; such tumors are called recurrent tumors, Ex: Astrocytoma and Meningiomas (Shah & Kochar, 2018).

6. Miscellaneous: Apart from the above tumors, there are other brain tumors, including acoustic neuroma, atypicalteroidrhabdoidtumor (ATRT), chondroma, chondrosarcoma, Chordoma, Choroid plexis tumors, etc. (Shah & Kochar, 2018).

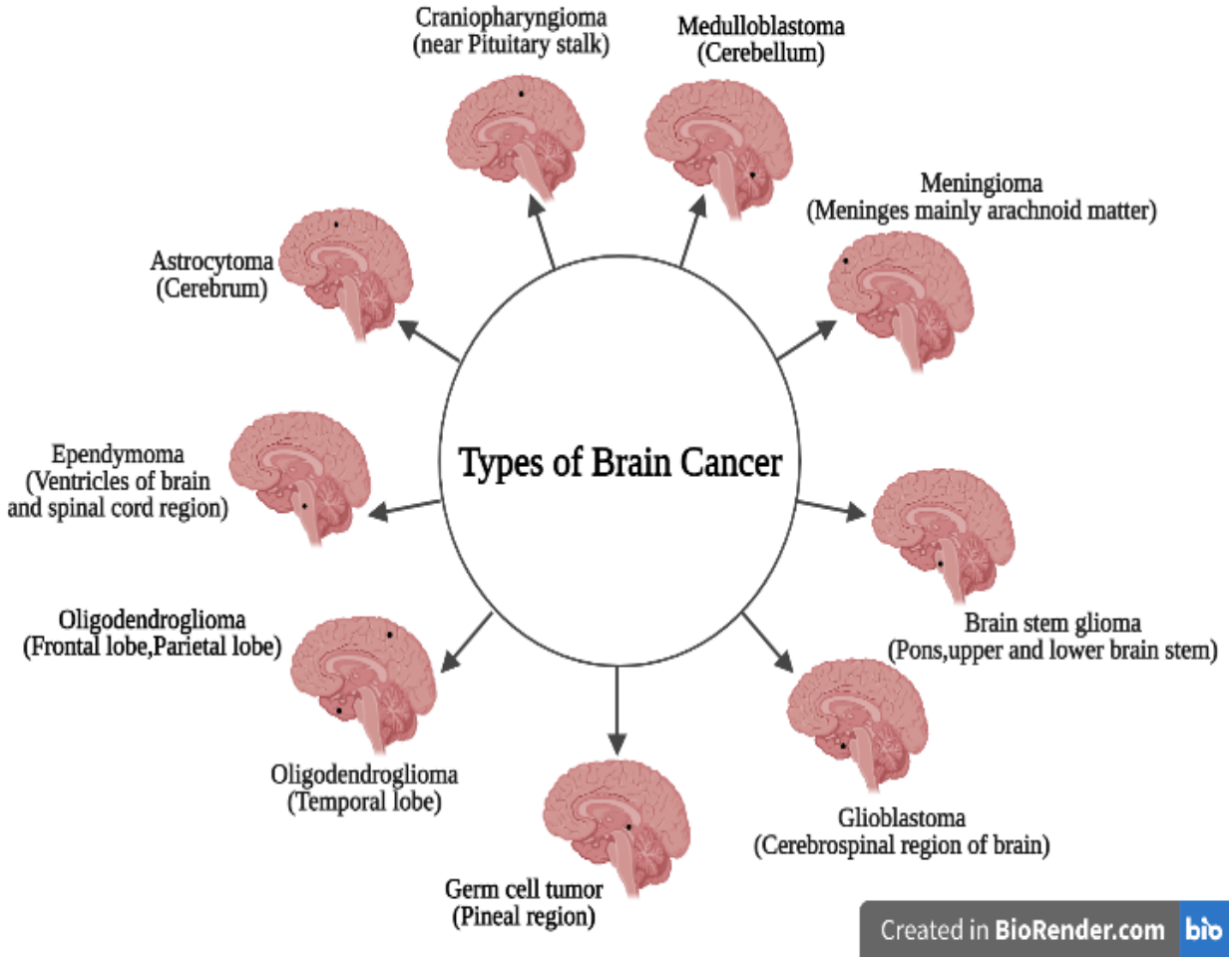


Figure 9: Types of primary brain cancer (Black dot represents the location of the tumor)

f. Symptoms associated with brain cancer:

Symptoms of brain cancer vary from person to person depending on the tumor type, size, and location in the brain. A patient with brain cancer could suffer the following symptoms (Figure 10) (Shah & Kochar, 2018):

I. Behavioral change

II. Changes in speech

III. Depressing or personality changes

IV. Elevated intracranial pressure resulting in headaches, vomiting, drowsiness,

V. Hearing or vision problems

VI. Loss of consciousness and general irritability

VII. Loss of strength in one side of the body,

VIII. Memory-related problems

IX. Seizures

X. Strange feeling in head and odd smells

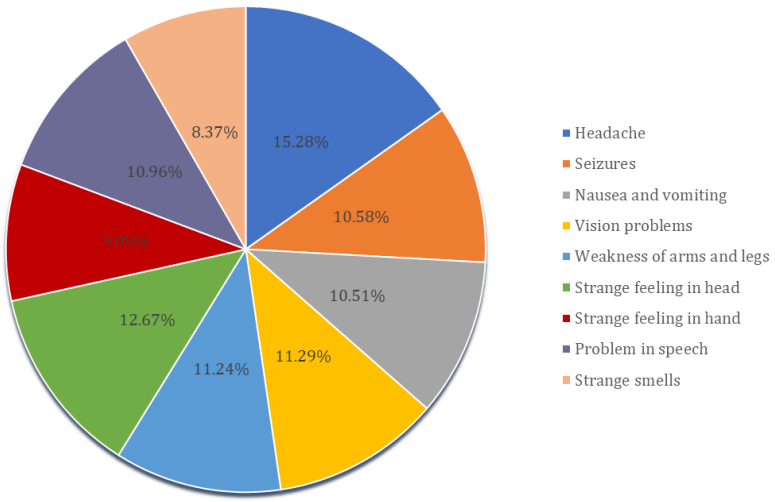


Figure 10: Symptoms associated with brain cancer

2. 1. Classification of chemotherapeutic agents to treat cancer: (Table 5).

Classification	Drugs
Alkylating Agents	Altretamine, Bendamustine, Busulfan, Carmustine, Chlorambucil, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Procarbazine, Streptozocin, Temozolomide, Thiotepa, Trabectedin
Platinum Coordination Complexes	Carboplatin, Cisplatin, Oxaliplatin
Antibiotics, Cytotoxic	Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, Mitoxantrone, Plicamycin, Valrubicin
Antimetabolites	Antifolates: Methotrexate, Pemetrexed, Pralatrexate, Trimetrexate
	Purine Analogues: Azathioprine, Cladribine, Fludarabine, Mercaptopurine, Thioguanine
	Pyrimidine Analogues: Azacitidine, Capecitabine, Cytarabine, Decitabine, Floxuridine, Fluorouracil, Gemcitabine, Trifluridine
Biologic Response Modifiers	Aldesleukin (IL-2), Denileukin Diftitox, Interferon Gamma
Histone Deacetylase Inhibitors	Belinostat, Panobinostat, Romidepsin, Vorinostat
Hormonal Agents	Antiandrogens: Abiraterone, Apalutamide, Bicalutamide, Cyproterone, Enzalutamide, Flutamide, Nilutamide
	Antiestrogens (including Aromatase Inhibitors): Anastrozole, Exemestane, Fulvestrant, Letrozole, Raloxifene, Tamoxifen, Toremifene
	Gonadotropin Releasing Hormone Analogues: Degarelix, Goserelin, Histrelin, Leuprolide, Triptorelin
	Peptide Hormones: Lanreotide, Octreotide, Pasireotide
Monoclonal Antibodies	Alemtuzumab, Atezolizumab, Avelumab, Bevacizumab, Blinatumomab, Brentuximab, Cemiplimab, Cetuximab, Daratumumab, Dinutuximab, Dostarlimab, Durvalumab, Elotuzumab, Gemtuzumab, Inotuzumab Ozogamicin, Ipilimumab, Mogamulizumab, Moxetumomab Pasudotox, Necitumumab, Nivolumab, Ofatumumab, Olaratumab, Panitumumab, Pembrolizumab, Pertuzumab, Ramucirumab, Rituximab, Tositumomab, Trastuzumab

Protein Kinase Inhibitors	Abemaciclib, Acalabrutinib, Afatinib, Alectinib, Alpelisib, Axitinib, Binimetinib, Bortezomib, Bosutinib,Brigatinib, Cabozantinib, Carfilzomib, Ceritinib, Cobimetinib, Copanlisib, Crizotinib, Dabrafenib, Dacomitinib, Dasatinib, Duvelisib, Enasidenib, Encorafenib, Entrectinib, Erdafitinib, Erlotinib,Fedratinib, Gefitinib, Gilteritinib, Glasdegib, Ibrutinib, Idelalisib, Imatinib, Ivosidenib, Ixazomib,Lapatinib, Larotrectinib, Lenvatinib, Lorlatinib, Midostaurin, Neratinib, Nilotinib, Niraparib, Olaparib, Osimertinib, Palbociclib, Pazopanib, Pexidartinib, Ponatinib, Regorafenib, Ribocicib, Rucaparib,Ruxolitinib, Selumetinib, Sonidegib, Sorafenib, Sunitinib, Talazoparib, Trametinib, Vandetanib,Vemurafenib, Vismodegib, Zanubrutinib
Taxanes	Cabazitaxel, Docetaxel, Paclitaxel
Topoisomerase Inhibitors	Etoposide, Irinotecan, Teniposide, Topotecan
Vinca Alkaloids	Vinblastine, Vincristine, Vinorelbine
Miscellaneous	Asparaginase (Pegaspargase), Bexarotene, Eribulin, Everolimus, Hydroxyurea, Ixabepilone, Lenalidomide, Mitotane, Omacetaxine, Pomalidomide, Tagraxofusp, Telotristat, Temsirolimus, Thalidomide, Venetoclax

Table 6: Classification of chemotherapeutic agents

2.2. Chemotherapeutics induced adverse effects:

Classification of Antineoplastic agents		**Adverse effects**	**References**
Alkylating Agents	**Cyclophosphamide**	✓ Common-Anorexia, nausea, and vomiting, myelosuppression, particularly leukopenia, bladder cancer, thrombocytopenia, anemia, hemorrhagic cystitis ✓ CNS- Neurotoxicity	(Germanas and Pandya 2002)

	Chlorambucil	✓ Common-Bone marrow suppression, acute myelogenous leukemia, gastrointestinal disturbances such as nausea, vomiting, diarrhea, and oral ulceration ✓ CNS: -Tremors, muscular twitching, confusion, agitation, ataxia, flaccid paresis, and hallucinations	(Germanas and Pandya 2002)
	Busulfan	✓ Common-Intestinal mucosal damage, alopecia, pancytopenia, anemia, amenorrhea, impaired spermatogenesis, and increased risk of malignancy. ✓ CNS: -Neurotoxicity, specifically causing seizures	(Germanas and Pandya 2002)
	Ifosfamide	✓ Common -Myelosuppression, nausea, vomiting ✓ CNS: Confusion, drowsiness, depressive psychosis, hallucinations, rarely seizures	(Missailidis 2008)
	Altretamine	✓ Common-Gastrointestinal tract ✓ CNS-Seizures, dizziness, depression	(Solimando 1999, Missailidis 2008)
	Dacarbazine	✓ Common-Anorexia, nausea, vomiting, diarrhea, skin reactions, phototoxicity, alopecia, flu-like syndrome, headache, blurred vision, vascular toxicity ✓ CNS-Seizures	(Missailidis 2008)
	Procarbazine	✓ Common-Leucopenia, thrombocytopenia, gastrointestinal symptoms like nausea and vomiting, diarrhea, dry mouth, stomatitis, abdominal pain ✓ CNS: Frequent nightmares, depression, insomnia, headache, nervousness, hallucinations	(Missailidis 2008)

	Carmustine	✓ Common-Intestinal mucosal damage, alopecia, pancytopenia, anemia, amenorrhea, impaired spermatogenesis, increased risk of malignancy, inherent nephrotoxicity ✓ CNS: CSF leakage, intracranial abscess formation, cerebral edema, and hydrocephalus	(Bock, Puchner et al. 2010, Izzedine and Perazella 2017)
	Lomustine	✓ Common-Delayed myelosuppression, lethargy, ataxia, dysarthria, pulmonary toxicity, nausea, vomiting ✓ CNS- Disorientation, dysarthria, ataxia, lethargy	(Missailidis 2008)
	Trabectedin	✓ Common- Fatigue, nausea, and/or vomiting. ✓ CNS-Headache and dizziness	(Vet—QL01CX01 2003, Carter and Keam 2007)
Platinum Coordination Complexes	**Cisplatin**	✓ Common-Nephrotoxicity, ototoxicity, hepatotoxicity, gastrointestinal toxicity ✓ CNS-Neurotoxicity	(Dowd 2007, Ghosh 2019)
Antibiotics, Cytotoxic	**Bleomycin**	✓ Common -Lung toxicity, alopecia ✓ CNS: Central nervous system toxicity, aggressive behavior, disorientation, weakness	(Yamamoto 2006, Ciccone 2013)
Anti-Metabolites (Pyrimidine analogues)	**Azacitidine**	✓ Common-Myelosuppression, renal tubular toxicity ✓ CNS- Aside from hepatic coma, disorientation, and a depressed level of consciousness	(Kintzel 2001, Watanabe, Doki et al. 2015)
	Capecitabine	✓ Common-Lymphopenia, anemia, diarrhea, hand-and-foot syndrome, nausea, fatigue, hyperbilirubinemia, dermatitis, and vomiting ✓ CNS-Neurotoxicity, fatigue, headache, dizziness, insomnia	(Wagstaff, Ibbotson et al. 2003, Ciccone 2013)

	Cytarabine	✓ Common-Myelosuppression. gastrointestinal disturbances, stomatitis, conjunctivitis, reversible hepatic enzyme elevation, and dermatitis. ✓ CNS-Cerebellar toxicity includes ataxia and slurred speech, while cerebral toxicity are seizures and dementia, confusion, drowsiness, headache	(Ciccone 2013, Faruqi and Tadi 2022)
	Decitabine	✓ Common-Cytopenia and cytopenia-related infection, anemia, neutropenia, and thrombocytopenia ✓ CNS-Cognitive impairment, lethargy, confusion, insomnia, fatigue, and depression	(Je-Hwan, Jun Ho et al. 2011, Ciccone 2013)
	5-Fluorouracil	✓ Common- Diarrhea, nausea, vomiting, mouth sores, poor appetite, photosensitivity, metallic taste, neutropenia, and thrombocytopenia. ✓ CNS-Neurotoxicity	(Dowd 2007)
	Tipracil	✓ Common-Neutropenia, anemia, and leukopenia ✓ CNS-Low neurotoxicity	(Zukas and Schiff 2017, Chan, Hochster et al. 2019)
	Gemcitabine	✓ Common-Bone marrow suppression, hemolytic uremic syndrome ✓ CNS-Headache, epileptic crisis, focal brain signs, nausea, vomiting.	(Kintzel 2001, Cioffi, Laudadio et al. 2011)
Anti-Metabolites (Purine analogues)	**Cladribine**	✓ Common-Myelosuppression, nausea, vomiting, alopecia, skin rash, or abnormal renal or hepatic function ✓ CNS-Neurotoxicity, fatigue, headache, dizziness, insomnia, malaise, weakness	(Bryson and Sorkin 1993, Ciccone 2013)
	Fludarabine	✓ Common-Myelosuppression, nausea, and vomiting ✓ CNS-Neurotoxicity	(Ross, McTavish et al. 1993, Krisl and Doan 2017)
Anti-Metabolites (Antifolates)	**Pralatrexate**	✓ Common-Mucositis, fatigue, nausea, vomiting, anorexia,	(Wood and Wu 2015, Zukas and Schiff 2017)

		skin toxicity, epistaxis, and anemia. ✓ CNS-Fatigue	
Biologic Response Modifiers	**Aldesleukin**	✓ Common-Renal dysfunction characterized by oliguria increased serum creatinine and uremia ✓ CNS- Neuropsychiatric effects can also be appreciated and vary from mild confusion to frank psychosis.	(Kintzel 2001, Amaria, Reuben et al. 2015)
	Denileukin Diftitox	✓ Common-Hypoalbuminemia, fever/chills, acute hypersensitivity reactions, nausea/vomiting, and asthenia ✓ CNS-Headache, dizziness, confusion, insomnia, nervousness, weakness	(Figgitt, Lamb et al. 2000, McCann, Akilov et al. 2012, Ciccone 2013)
	Interferon Gamma	✓ Common-Flu-like symptoms (fever, fatigue, myalgia/arthralgia), gastrointestinal symptoms (nausea, emesis, diarrhea, weight loss, anorexia, leucopenia, thrombopenia dizziness, depression, proteinuria, acute renal failure ✓ CNS-Neurotoxicity	(Grassegger and Höpfl 2004, Bock, Puchner et al. 2010, Hashioka, G McGeer et al. 2015)
Histone Deacetylase Inhibitors	**Belinostat Panobinostat Romidepsin Vorinostat**	✓ Common- Cardiac conduction abnormalities ✓ CNS-Confusion, disorientation, ataxia, vertigo, and somnolence, status epilepticus, fatigue	(Subramanian, Bates et al. 2010, Zukas and Schiff 2017)
Hormonal Agents (Anti-androgens)	**Abiraterone**	✓ Common-Increased risk of cardiac orders abnormalities in liver function ✓ CNS-Fatigue and perceived cognitive impairment	(Jeong, Choi et al. 2007, Gartrell and Saad 2015, Lee, Chen et al. 2021)
	Enzalutamide	✓ Common- Increased risk of hypertension	(Wang, hui et al. 2020, Lee, Chen et al. 2021)

		✓ CNS- Fatigue and perceived cognitive impairment, seizure	
	Bicalutamide	✓ Common-Interstitial lung disease ✓ CNS- Hallucinations, dizziness, seizures, weakness, headache, insomnia	(Ciccone 2013, Lee, Chen et al. 2021)
	Apalutamide	✓ Common- Fatigue, rash, arthralgia, falls, fractures, and hypothyroidism. ✓ CNS- Seizures.	(Boukovala, Spetsieris et al. 2020)
Hormonal Agents (Antiestrogens)	**Anastrozole**	✓ Common-Asthenia, Hot flashes, headaches, and back pain ✓ CNS-Headache, weakness, dizziness	(Higa and Khouri 1998, Ciccone 2013)
	Goserelin	✓ Common-Hot vaginal dryness, headaches, and loss of libido ✓ CNS-Lethargy, memory disturbances, severe fatigue, and depression.	(Perry and Brogden 1996, Zukas and Schiff 2017)
	Leuprolide	✓ Common-Mood changes, skin rash, acne vulgaris, seborrhea, vaginal discharge, vaginal hemorrhage, pain, flushing, hot flashes, ✓ CNS-Headaches, and migraines.	(Swayzer and Gerriets 2021)
Monoclonal Antibodies	**Anti-VEGF (Bevacizumab)**	✓ Common-Hypertension ✓ CNS-Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	(Grant 2009)
	EGFR-targeted inhibitors (Cetuximab, Erbitux), and Panitumumab)	✓ Common-Fatigue, diarrhea, and the development of dermatological toxicities like rash and hand-foot syndrome ✓ CNS-Fatigue and malaise are the most common neurological complaints	(Grant 2009, Zukas and Schiff 2017)
	Avelumab	✓ Common-Fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash,	(Palla and Doll 2018, Jacques, Nicholas et al. 2021)

		decreased appetite, peripheral edema, acute kidney injury, anemia, abdominal pain, ileus, asthenia, and cellulitis. ✓ CNS- Seizure	
	Blinatumomab	✓ Common-Neutropenia, thrombocytopenia, and elevated transaminases ✓ CNS-Pyrexia, headache, edema, febrile neutropenia, nausea, tremor, and rash.	(Przepiorka, Ko et al. 2015)
	Ofatumumab,	✓ Common-Anemia, Headache, Hypertension, Insomnia, sinusitis, tachycardia, cough] ✓ CNS-Headache, Insomnia	(Lemery, Zhang et al. 2010)
	Trastuzumab	✓ Common-Nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, ✓ CNS-Headaches, dizziness, pain, depression	(Solimando 1999, Keam 2020)
Protein Kinase inhibitors	**Ibrutinib**	✓ Common-Diarrhea, upper respiratory tract infection, bleeding, fatigue, cardiac side effects, severe bleeding severe. ✓ CNS - Fatigue, dizziness, and headaches	(Zukas and Schiff 2017, Paydas 2019)
	Ivosidenib	✓ Common-Edema, chest pain, hypotension, fatigue, arthralgia, myalgia, fever ✓ CNS: Headache, neuropathy	(Lohr 2018)
	Lenvatinib	✓ Common-Hypertension, diarrhea, fatigue, decreased appetite, and proteinuria ✓ CNS- Low neurotoxicity	(Zukas and Schiff 2017, Koyama, Miyake et al. 2018)
	Olaparib	✓ Common-Fatigue, nausea, vomiting, diarrhea, dyspepsia, headache, altered taste, decreased appetite and dizziness, anemia,	(Goulooze, Cohen et al. 2016, Zukas and Schiff 2017)

		neutropenia, thrombocytopenia, and lymphopenia ✓ CNS-Neurotoxicity is minimal, with the most common toxicity being fatigue	
	Palbociclib	✓ Common-Neutropenia ✓ CNS-Mild neurotoxicity such as myalgia, fatigue, and dysgeusia.	(Zukas and Schiff 2017, Kanbayashi, Sakaguchi et al. 2021)
	Pazopanib	✓ Common-Diarrhea, rash, hand-foot syndrome, fatigue, the elevation of liver enzymes, hepatotoxicity ✓ CNS- Hallucinations associated with its use as well as PRES	(Keisner and Shah 2011).
	Regorafenib	✓ Common: HFSR (hand skin foot reactions), rash, fatigue, diarrhea, and hypertension, stomatitis, liver dysfunction ✓ CNS-Low neurotoxicity	(Krishnamoorthy, Relias et al. 2015, Zukas and Schiff 2017)
	Rucaparib	✓ Common-Gastrointestinal events, fatigue/asthenia, myelosuppression-related events, increased blood creatinine, dizziness ✓ CNS-Neurotoxicity is minimal, with the most common toxicity being fatigue, mild dysgeusia	(Zukas and Schiff 2017, Shirley 2019)
	Sonidegeb	✓ Common: Nausea, dysgeusia, muscle spasms, myalgia, alopecia, diarrhea, weight loss ✓ CNS- Neurotoxicity like dysgeusia, myalgia, and muscle spasms	(Kish and Corry 2016) (Zukas and Schiff 2017)
	Vismodegib	✓ Common: Muscle cramps, alopecia, dysgeusia, nausea ✓ CNS-Neurotoxicity like dysgeusia, myalgia, and muscle spasms	(Cirrone and Harris 2012, Zukas and Schiff 2017)

Taxanes	**Cabazitaxel, Docetaxel, Paclitaxel**	✓ CNS: Central neurotoxicity characterized by cognitive impairment and encephalopathy	(Dowd 2007, da Costa, Passos et al. 2020)
Topoisomerase Inhibitors	**Irinotecan Teniposide Topotecan Etoposide**	✓ Common-Diarrhea, dizziness, and insomnia, as well as occasional episodes of dysarthria ✓ CNS-Neurotoxicity	(Dowd 2007, Newton 2012)
Vinca Alkaloids	**Vinblastine**	✓ Common one-Paralytic ileus, alopecia ✓ CNS-Neurotoxicity	(Dowd 2007, Missailidis 2008, Arora and Menezes 2022)
	Vinorelbine	✓ Less common-Neuropathy and constipation, nausea, vomiting, diarrhea, and stomatitis are less frequent ✓ CNS- Cranial neuropathies	(Missailidis 2008, Arora and Menezes 2022)
	Vincristine	✓ Common-Leucopenia, thrombocytopenia, alopecia ✓ CNS- Cranial neuropathies	(Missailidis 2008, Arora and Menezes 2022)
	Mitotane	✓ Common-Gastrointestinal symptoms include diarrhea, nausea, vomiting, and anorexia ✓ CNS-Effected central nervous system and produced neuromuscular manifestations, including ataxia, speech disturbance, confusion, somnolence, depression, decreased memory, muscle tremors, polyneuropathy, and dizziness	(Corso, Acco et al. 2021)
	Omacetaxine	✓ Common- Cytopenia and infections. ✓ CNS-Intracerebral hemorrhage	(Zukas and Schiff 2017, Winer and DeAngelo 2018)
	Venetoclax	✓ Common- Tumor lysis syndrome (TLS), hematologic toxicities such as neutropenia. ✓ CNS-Neurotoxicity is limited to low-grade fatigue and headache	(Juárez-Salcedo, Desai et al. 2019, Pinzi, Galvan et al. 2019)

Table 7: Adverse effects associated with chemotherapeutics

2.2. Chemotherapeutics-induced cognitive impairment (CICI) in the brain:

Chemotherapy is the most primarily implemented strategy in cancer treatment in conjunction with radiotherapy, surgery, or hormonal therapy. Although chemotherapy is beneficial against several malignancies, it also affects healthy cells causing adverse effects (Table 6), among which central nervous system (CNS) toxicity, including cognitive impairment, is of particular concern. This cognitive impairment, often referred to as chemo-brain, chemo-fog, or chemotherapy-induced cognitive impairment (CICI), is characterized by the impairment of the patient's memory, learning, attention, concentration, reasoning, processing speed, and executive functions. This cognitive impairment varies widely among transient patients with mild reversible manifestations (occurring during and after discontinuation of chemotherapy) in most cases. However, it can last for years with more severe progressive manifestations, deleteriously impacting patient quality of life. A specific chemotherapeutic to induce CICI and CNS toxicity requires numerous components, such as the structural attributes, affinity towards the efflux pumps, dose, dosage (route of administration), occurrence of anatomical lesions in the brain, exposure to prior or concurrent irradiation, and drug-drug interactions.

3.1. Therapeutic strategies to treat brain cancer:

A significant number of people around the world are affected by different types of CNS disorders, such as brain tumors, epilepsy, cerebrovascular diseases, Parkinson's disease, Alzheimer's disease, and other neurological/neurodegenerative diseases. Despite the

ongoing research being so advanced, the number of mortalities because of CNS diseases immeasurably exceeds the number of patients suffering from different types of systemic cancer and other cardiovascular disorders (Ferraris et al., 2020; Verheggen et al., 2020). Developing techniques that can elevate the delivery of drugs to the brain across the BBB plays a significant role in treating different CNS disorders. The preventative and therapeutic approaches are mainly targeted to eradicate the tumor and alleviate cancer symptoms by diminishing the tumor.

The preventative and therapeutic chemotherapeutic predominantly depends on factors such as the (V. Shah & P. Kochar, 2018):

I. Type of Cancer/Tumor
II. Size of the Tumor
III. Location of Cancer/Tumor,
IV. Patient's age
V. Patient's medical history
VI. Patient's general status of health
VII. Types of symptoms
VIII. Iatrogenesis

1. Surgery:

The surgical removal of the benign tumor at the initial tumor stages while retaining the brain's neurological function is the primary strategy. Surgery Provides a complete cure for the low-grade tumor. Surgical treatment also provides relief from intracranial pressure

built by tumors, thereby reducing the symptoms of cancer. It is the easiest and safest process with the least or no side effects. The main limitation of surgery is that it is possible only when the tumor is in a specific location that can be reached without damaging essential brain functions. Adverse effects resulting from surgery include headache, weakness, tiredness, brain swelling, or fluid that may build up in the brain, and brain damage can be a severe significant problem. Surgery also leads to seizures and thinking, speech, and vision problems.

2. Radiation therapy:

Radiation therapy mainly involves using X-rays, gamma rays, and proton beams to kill or destroy the cancerous cells resulting in tumor shrinkage. Radiation therapy is usually given five days a week for six weeks. Radiation therapy is classified into various classes:

I. External radiation therapy comprising stereostatic radiosurgery (SRS), which involves delivering a high amount of radiation in a single treatment, and fractioned stereostatic radiosurgery consists in providing a low dose of radiation at each treatment

II. Whole brain radiotherapy delivers radiation doses to the entire brain.

III. At the same time, internal radiation therapy involves implant-based radiation therapy or brachytherapy.

Side effects after radiation therapy include fatigue, headache, swelling, nausea, possible hair loss, and changes in your sensations or movement

3. Chemotherapy:

This treatment strategy involves the use of chemotherapeutics for treating cancer. These agents primarily disrupt the cell division process or block the blood supply to tumor cells, resulting in the death of abnormal cells and, thereby, tumor shrinkage. The limitation is that it also damages normal cells/tissues. Common side effects include nausea, fatigue, dehydration, weakness, and reduced WBC counts, which increase the risk of infection (Shah & Kochar, 2018).

3.2. Novel strategies employed for treating brain cancer/tumor:

Brain tumor is proven extremely difficult to treat, and patients have poor prognoses. The standard of care for brain cancer patients consists of surgery, radiation, and chemotherapy. However, not all brain tumors are operable, and the recurrence rate can be extremely high (Adib et al., 2021; Faustino et al., 2020). While radiation can be effective, the cumulative exposure dose is limited due to neurotoxic effects (Kim et al., 2008; Shaw et al., 2000; Smart, 2017). The effectiveness of anti-cancer agents administered systemically is hindered by the blood-brain barrier, which severely limits the molecular transport into the brain (N. J. Abbott et al., 2010; Abbott & Romero, 1996; Abbott et al., 2006; Arvanitis et al., 2020; BlumlingIii & Silva, 2012; van Vliet et al., 2014). Due to the high recurrence rate and lack of treatment options, most patients diagnosed with primary brain tumors succumb to the disease within two years (Gilbert et al., 2014; Gilbert et al., 2013; Ostrom et al., 2017; Stupp et al., 2009; Stupp et al., 2005). Therefore, there is a critical necessity for novel methods to treat brain tumors and significantly reduce mortality effectively.

1. Reversible BBB Opening:

The blood-brain barrier hinders the transportation of most drugs to the brain, thus inhibiting their effectiveness against serious neuropathologies. Scientists have explored different approaches for opening the vascular barrier temporarily, and the use of focused ultrasound (FUS) combined with stabilized microbubbles has emerged as a promising therapeutic strategy. Prof. Kullervo Hynynen and his group pioneered FUS-mediated blood-brain barrier opening in the early 2000s (Hynynen et al., 2001). The brain drug delivery methods consist of three components, Low-intensity FUS, an intravenous administration of encapsulated microbubbles, and a drug of interest. The microbubbles used for BBB opening are currently FDA-approved as ultrasound contrast agents. The microbubbles are micrometer-sized particles that typically consist of a lipid or protein shell that encapsulates a gaseous core, typically perfluoro propane or sulfur hexafluoride. During the BBB opening process, FUS transmits acoustic waves through the skull, which oscillate circulating microbubbles in targeted brain regions. The blood-brain barrier is subjected to forces generated by the oscillating microbubbles, which can create defects in the endothelial cells and promote vesicle formation (Sheikov et al., 2004). As a result of these reversible cellular changes, the permeability of BBB is increased temporarily. The extent and duration of FUS-mediated BBB opening have been explored using computational modeling and various imaging modalities, optical imaging, magnetic resonance imaging, and positron emission tomography. It was reported that cavitating microbubbles open the BBB immediately and reseal within four hours depending on FUS parameters (N Joan Abbott et al., 2010; Cho et al., 2011; Marty et al., 2012; Samiotaki et al., 2012; Ye et al., 2018). This method has been used to improve the delivery of anti-cancer agents to brain tumors. Furthermore, a study

reported that multiple sessions of chemotherapy combined with FUS-mediated BBB opening increased the volume of drug distribution in brain tumors and destroyed cancers entirely in most of the treated animals (Aryal et al., 2013; Fan et al., 2013; McDannold et al., 2019; Wei et al., 2013). In addition to that, the safety of opening the BBB repeatedly with FUS has been demonstrated in preclinical models, including non-human primates (Abrahao et al., 2019; Aryal, Park et al., 2015; Aryal, Vykhodtseva et al., 2015; Lipsman et al., 2018; McDannold et al., 2012; Rezai et al., 2020).

2. Targeted therapy:

It focuses on specific cellular elements involved in the growth of cancerous cells. It uses a specific element as a target ex: Tyrosine Kinase inhibitor (TKI) therapy and anti-vasculature endothelial growth factor (VEGF) therapy. Targeted biological therapy, referred to as biotherapy or immunotherapy, where the immune system plays a significant role in fighting cancer, is a novel approach in treating cancer (Viral Shah & Pratiksha Kochar, 2018).

3. Electric field treatment:

This therapy involves using a device called voTTFTM (by Novicure), which is placed on the scalp. The electric current or electrodes destroy tumor cells without harming the normal cells (Viral Shah &Pratiksha Kochar, 2018).

4. Viral therapy:

Oncolytic viruses are a form of immunotherapy that uses viruses to infect and destroy cancer cells. As infected cancer cells are destroyed by oncolysis, they release new infectious virus particles to help eliminate the remaining tumor. Adenoviruses have been extensively studied due to their prevalence and easy manipulation (Xu et al., 2020).

5. Vaccine therapy:

In this therapy, the patient's immune system plays a significant role. The substances derived from brain tissues are responsible for restoring the body's natural defense system to cure disease (Viral Shah &Pratiksha Kochar, 2018).

6. Gene therapy:

This therapy involves the introduction of engineered genes to cancerous cells to eradicate them. It also stimulates the body's immune system to fight against cancer (Viral Shah &Pratiksha Kochar, 2018).

Immunotherapy	Oncolytic agents	Gene transfer
Stimulating the immune system to target and destroy cancer cells	Oncolytic vectors are designed to infect cancer cells and cause cell death through viral replication, cytotoxic protein expression, and cell lysis.	A new process in which a foreign gene is introduced into a cancer cell or surrounding tissue. Suicide genes (genes that cause cellular death when expressed), anti-angiogenesis genes, and cellular stasis genes have all been proposed as candidates for this type of therapy.
Limitation: cancer cells evolve mechanisms to avoid immune detection	Limitation: The rates of viral particle production in infected cancer cells must exceed the growth rates in uninfected cancer cells.	Earlier gene transfer trials were plagued by gene silencing, which meant that even if the gene was successfully introduced into the cell, it was either not expressed or was only expressed for a short period of time. Despite these obstacles, solid tumors like prostate, lung, and pancreatic cancer have been successfully treated in animal models using a variety of genes.

Table 8- Difference between different types of therapies

3.3 Drugs to treat chemotherapy-induced cognitive impairment

Memory impairment is common in patients with brain tumors, brain-directed therapies, and after systemic chemotherapy (Karschnia, Parsons et al. 2019).

1. Methylphenidate: It is a CNS stimulant that has emerged as a potential intervention in the treatment of chemotherapy-induced cognitive dysfunction in children with cancer. Methylphenidate influences the frontostriatal network, which regulates attention, and is commonly used to treat attention deficit hyperactivity disorder (Karschnia, Parsons et al. 2019).

Mechanism of action**:** It inhibits the reuptake of two neurotransmitters, norepinephrine (NE) and dopamine, in presynaptic neurons. It inhibits explicitly these neurotransmitter transporters, increasing the concentration of dopamine and norepinephrine in the synaptic cleft. Increased dopamine levels can provide neuroprotection in certain conditions, such as Parkinson's disease. This effect is achieved through transporter inhibition and indirect regulation of the vesicular monoamine transporter 2(Verghese and Abdijadid 2022).

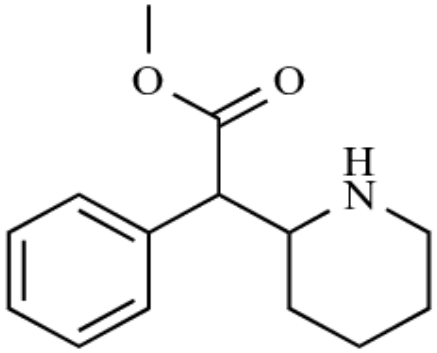


Figure 11: Structure of Methylphenidate
(Methylphenidate structure - Bing images)

2. Memantine, an N-methyl-D-aspartate receptor (NMDA) antagonist, is an anti-dementia drug and is a treatment option for Alzheimer's and dementia with Lewy bodies (Karschnia, Parsons et al. 2019).

Mechanism of action: Memantine is an uncompetitive antagonist of glutamate receptors of the NMDA subtype in the CNS. The NMDA receptor is a voltage-gated cation channel that is blocked by magnesium ions in the physiologic unstimulated state. The displaced magnesium allows calcium influx and activation. Pathologic overstimulation of the receptor causes it to be chronically active in Alzheimer's disease. Memantine aids in the reduction of

overstimulation. Memantine also inhibits the serotonergic type 3 (5-HT3) and nicotinic acetylcholine receptors(Kuns, Rosani et al. 2022).

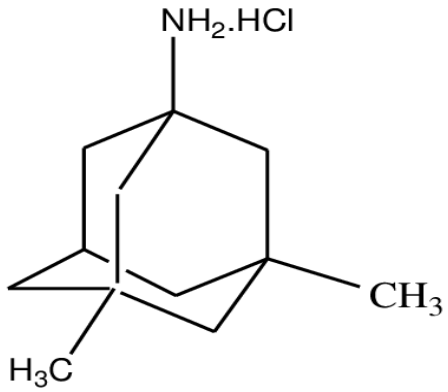


Figure 12: Structure of Memantine
(memantine structure - Bing images)

3. Donepezil: Donepezil is an acetylcholinesterase inhibitor and one of the few drugs approved by the FDA for treating Alzheimer's disease. Donepezil slows the atrophy of the basal forebrain cholinergic system, which projects to the cortex, entorhinal cortex, and hippocampus ((Kumar, Gupta et al. 2022).

Mechanism of action: Donepezil hydrochloride is a piperidine derivative that acts centrally to inhibit acetylcholinesterase and is reversible. The enzyme acetylcholinesterase degrades acetylcholine after it is released from the presynapse. Donepezil binds reversibly to acetylcholinesterase and inhibits acetylcholine hydrolysis, increasing acetylcholine availability at synapses and enhancing cholinergic transmission. Donepezil upregulates the nicotinic receptors in the cortical neurons, adding to neuroprotective properties(Kumar, Gupta et al. 2022).

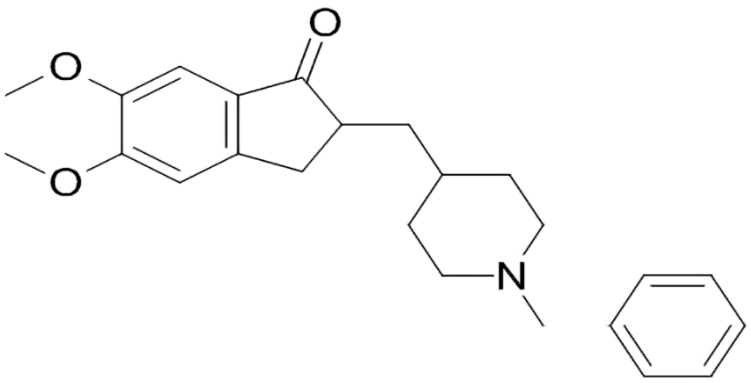


Figure 13: Structure of Donepezil
(donepezil structure - Bing images)

4. Fluoxetine: It is a selective serotonin reuptake inhibitor (SSRI) primarily reported to improve patients' memory function by increasing extracellular serotonin levels within the brain by inhibiting its reuptake by serotonin transporters. According to Wigmore and colleagues, SSRIs such as fluoxetine may be beneficial in reducing chemotherapy-induced cognitive impairments ((Lyons, Elbeltagy et al. 2012). In particular, healthy rats who were given fluoxetine (10mg/kg/day in drinking water) prior to and throughout treatment with 5-Fluorouracil chemotherapy performed better on object location recognition than those who were given 5FU alone (Lyons, Elbeltagy et al. 2012).

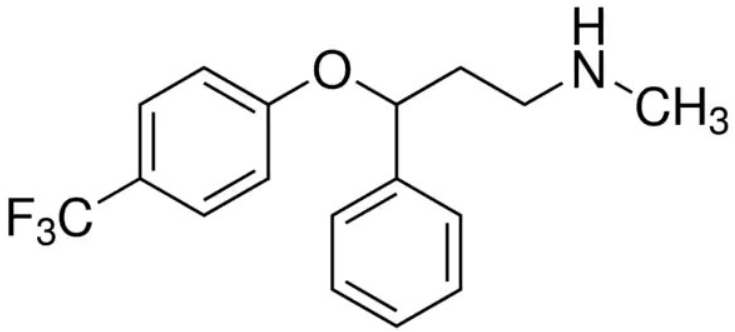


Figure 14: Structure of fluoxetine
(fluoxetine structure - Bing images)

5. Ricolinostat (ACY-1215): Scientists found that the histone deacetylase 6 inhibitor, ACY-1215, improved established cisplatin-induced cognitive impairment by restoring mitochondrial and synaptic damage. However, these relevant clinical trials are still lacking. Clinical trials of lithium, pioglitazone, ramipril, docosahexaenoic acid, ibuprofen, and other drugs for CICI are also ongoing. To sum up, no specific drugs can prevent and treat CRCI. More prominent, reproducible experimental studies are needed in this area(Lv, Mao et al. 2020).

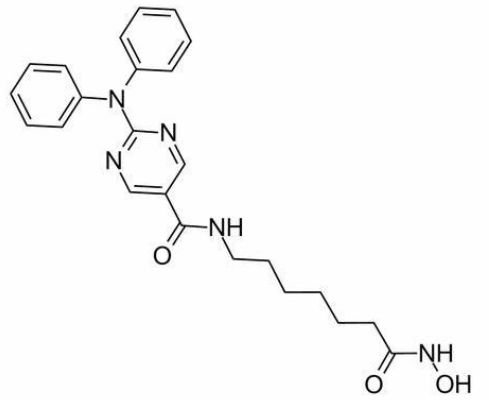


Figure 15: Structure of ACY-1215
Ricolinostat structure - Bing images

3.4. Significance of Markers:

Oxidative stress arises when reactive oxygen species production exceeds the intrinsic antioxidant defenses (GJ 2011). Antioxidants reduce oxidative stress, which is crucial because it plays a significant role in neuroprotection (Mandal et al., 2019). Additionally, it is well-recognized that an elevated oxidative stress can cause apoptosis, DNA damage, mitochondrial dysfunction, and neuronal death. Another significant proxidant produced by mitochondria is hydrogen peroxide, which is capable of neuronal damage.

Glutathione, the brain's significant antioxidant, primarily protects against intracellular ROS damage through detoxification. In addition to the antioxidant effects, glutathione is essential for neutralizing cysteine (Cys) in the brain. This function is crucial because, at high concentrations, cysteine is linked to the formation of ROS and the excessive activation of excitatory N-methyl-D-aspartate receptors, both of which cause excitotoxicity and, ultimately lead to neuronal death (Duffy et al. 2014). Previous research has shown that increased mitochondrial oxidative stress levels degrade mitochondrial integrity, damage the mitochondrial electron transport system, and accelerate cellular energy depletion in animal models (Apaijai et al., 2020). Disturbance of cognitive processes depending on the hippocampus, such as memory and learning, is influenced by mitochondrial activity (Khacho et al., 2017).

Exposure to natural bioactives usually is expected to reduce oxidative stress, apoptosis, excitotoxicity, inflammation and increase mitochondrial function leading to neuroprotection. Additionally, the effect of active metabolites of the natural bioactive are usually structural congeners and are expected to exert actions similar to the parent compounds. However, there are natural bioactives and their active metabolites that cross the blood brain barrier and are not substrates of p-glycoprotein and exhibit neurotoxic effects. Based on the existing literature and the gap in the current literature, this study was performed to elucidate the neuro-pharmacodynamic actions of the active natural bioactive metabolite, 3-hydroxypterostilbene.

Chapter II: Materials and methods

I. Chemicals and reagents:

Thiazolyl Blue Tetrazolium Bromide (MTT) was purchased from Tokyo Chemical Industry America (Portland, OR). Dulbecco's Modified Eagle Medium (DMEM), and Trypsin-EDTA solution, were purchased from Cytiva life sciences, and the Penicillin-Streptomycin solution was purchased from VWR (North America). Fetal bovine serum (FBS) from Sigma Aldrich (St. Louis, MO). 2 mM L-glutamine, and 1 mM sodium pyruvate from Cellgro. Thermo Scientific Pierce 660nm Protein Assay reagent kit was purchased from Thermo Scientific (Pierce, Rockford, IL) for protein quantification. Bovine serum albumin (BSA), Phosphate buffer saline (PBS), and Dimethyl sulfoxide (DMSO) were purchased from VWR (North America), Nicotinamide adenine dinucleotide (NADH) was purchased from Sigma Aldrich (St. Louis, MO),2',7-dichlorofluorescein diacetate (DCF-DA) were purchased from Thermo Scientific (Pierce, Rockford, IL), O-phthalaldehyde (OPT)were purchased from BTC Company. Serine-like protease(Z-GGL-AMC) and Hydrogen peroxide, Levodopa, Tetrahydrobiopterin (BH_4), Ferrous sulfate, Sodium periodate were purchased from Sigma Aldrich (St. Louis, MO).AC-DEVD-AMC (Caspase-3 substrate) and Griess reagent was purchased from Enzo life sciences (Farmingdale, NY). Cryopreserved human primary hepatocytes and hepatocyte media were purchased from Thermo Fisher Scientific (Waltham, MA) and Triangle Research Labs (Research Triangle, NC) (Table 1).

Chemicals	Catalog No	Links
Thiazolyl Blue Tetrazolium Bromide (MTT)	D0801	Tokyo Chemical Industry Co., Ltd. (APAC)
Dulbecco's Modified Eagle Medium (DMEM)	SH30243.01	Hy Clone Dulbecco's Modified Eagle Medium (DMEM) with high glucose: Liquid | Cytiva (cytivalifesciences.com)
Trypsin-EDTA protease solution	SH30236.01	Hy Clone Trypsin Protease | Cytiva (cytivalifesciences.com)
Penicillin-Streptomycin solution	45000-652	https://us.vwr.com/store/product/10243589/penicillin-streptomycin-solution-corning-100x#order
Fetal bovine serum (FBS)	F2442	sigmaaldrich.com/US/en/product/sigma/f2442
Thermo Scientific Pierce 660nm Protein Assay reagent kit	22660	Thermo Fisher Scientific - US
Bovine serum albumin (BSA)	90604-29-8	Bovine Serum Albumin (BSA) | VWR
Phosphate buffer saline (PBS)	97063-658	Phosphate Buffered Saline, Ultra-Pure Grade, VWR Life Science | VWR
Dimethyl sulfoxide (DMSO)	BDH1115-1LP	Dimethyl sulfoxide ≥99.9% ACS, VWR Chemicals BDH® | VWR
β-Nicotinamide adenine dinucleotide (NADH)	43410-1G	https://www.sigmaaldrich.com/US/en/product/sigma/43410
2',7-dichlorofluorescein diacetate (DCF-DA)	B24717.06	2,7-Dichlorofluorene, 97%, Thermo Scientific™ (thermofisher.com)
Hydrogen peroxide	H1009	Hydrogen peroxide 30 (w/w) H2O, contains stabilizer 7722-84-1 (sigmaaldrich.com)
Levodopa	PHR1271	Levodopa Pharmaceutical Secondary Standard; Certified Reference Material 59-92-7 (sigmaaldrich.com)
Tetrahydrobiopterin (BH_4)	D0387	Tetrahydrobiopterin | Sigma-Aldrich (sigmaaldrich.com)
Ferrous sulphate	215422	Iron sulfate | Sigma-Aldrich (sigmaaldrich.com)
Sodium periodate	311448	Sodium periodate | Sigma-Aldrich (sigmaaldrich.com)
Griess reagent	ALX-400-004-L050	Griess Reagent - ALX-400-004 - Enzo Life Sciences
O-phthalaldehyde (OPT)	223690-10G	BTC Company
Serine like protease (Z-GGL-AMC)	SCP0225	Scp0225 | Sigma-Aldrich (sigmaaldrich.com)
AC-DEVD-AMC	ALX-260-031-M005	https://www.enzolifesciences.com/ALX-260-031/ac-devd-amc/

Table 9: Chemicals purchased from companies with catalog numbers

II*. In silico* analysis:

Good absorption, distribution, metabolism, and elimination (ADME) properties of drug molecules have been recognized as primary indicators of successful candidate molecules in drug discovery and development. QikProp Schrodinger's software was employed in this study to determine several pharmacokinetic and pharmacodynamic properties of Pterostilbene and 3-hydroxypterostilbene. To examine permeability, metabolism, and activity, the QikProp set of descriptors (SASA, FOSA, FISA, PISA, number of metabolites (#metab), CNS distribution, QPlogBB, Donor HB, Accept HB, CLogP, %Human oral absorption, Rule of 3 and Rule of Five) were preferred. Swiss ADME software was also used for *in silico* analysis of a compound's pharmacokinetic and pharmacodynamic properties.

III. Methods

1. Cell culture:

1a. HT-22 mouse hippocampal neurons & N27 rat dopaminergic neurons:

HT-22 mouse hippocampal neurons and N27 rat dopaminergic neurons were cultured in Dulbecco's Modified Eagle Medium (DMEM), supplemented with Fetal bovine serum (10%), Penicillin-Streptomycin (1%). For the cell viability assay, HT-22 mouse hippocampal neurons and N27 rat dopaminergic neurons were grown and harvested via trypsinization. The HT-22 mouse hippocampal neurons and N27 rat dopaminergic neurons were then seeded into 96 well plates at 1 x 10^5 cells/well density. HT-22 mouse hippocampal neurons and N27 rat dopaminergic neurons were incubated at 37°C and supplemented with 5% CO_2.

1b. Why HT-22 mouse hippocampal neurons?

Hippocampus is associated with learning and memory. The common adverse effect of chemotherapeutics in CNS is neurotoxicity leading to cognitive impairment. So, HT-22 mouse hippocampal neurons are the valid model to study the effect of 3-hydroxypterostilbene.

1c. WhyN-27 rat dopaminergic neurons?

Dopamine is associated with movement disorders. The common adverse effect of chemotherapeutics in CNS is neurotoxicity also leading to loss of dopaminergic neurons. So, N27 rat dopaminergic neurons are the valid model to study the effect of 3-hydroxypterostilbene.

1d. LS174T human colon cancer cells and HepG2 cancer cells:

LS174T human colon cancer cells and Hep G2 were obtained from the American Type Culture Collection and grown in Dulbecco's Modified Eagle's Medium supplemented with 10% Fetal bovine serum,100 µg/ml Penicillin and 100 µg/ml Streptomycin, 2 mM L-glutamine, and 1 mM Sodium pyruvate. The assay media included phenol red-free Dulbecco's Modified Eagle's Medium supplemented with 5% charcoal/dextran-treated FBS. The donor information for the hepatocytes is provided in Table 2. The hepatocytes were cultured by following the manufacturer's instructions and our published protocol. Briefly, the hepatocytes were maintained for 6 h in Williams' medium E without phenol red, supplemented with 5% Fetal bovine serum, cell maintenance cocktail, and 500 nM dexamethasone, in collagen-coated 24 well culture plates in an atmosphere of 5% CO2 at

37°C for 12 h. The cells were treated with the vehicle or drugs for 24 hours (Pondugula, Flannery et al. 2015).

Identification Number	Sex	Race	Age (years)
Thermo Fisher Scientific			
Hu8210	Male	Caucasian	51
Hu8164	Male	Caucasian	23
Triangle Research Laboratories			
HUM4111A	Male	Caucasian	29
HUM4113	Male	Caucasian	29
HUM4119E	Female	African American	30
HUM4122B	Male	Asian	35

Table 10: Identification number, sex, race, and age of the hepatocyte donors

2. Treatment strategies:

Prior to each experiment,3-hydroxypterostilbene was freshly prepared and dissolved in 100% dimethyl sulfoxide (DMSO). To evaluate the hippocampal and N27 rat dopaminergic neuronal viability, different concentrations of 3-hydroxypterostilbene were obtained by serial dilution in DMSO. For the cell viability assay, Specific doses of 3-hydroxypterostilbene (0.01μM,0.1μM,1μM,10μM,100μM) were incubated with HT-22 mouse hippocampal neurons and N27 rat dopaminergic neurons for 24 hours. With regard to control, HT-22 mouse hippocampal neurons and N27 rat dopaminergic neurons were treated with 1% DMSO.

3. Cell viability assay:

The MTT assay was used to evaluate the effect of different doses of 3-hydroxypterostilbene on HT-22 mouse hippocampal neurons and N27 rat dopaminergic neurons at 24 hours**.** The mitochondria of viable cells reduce the MTT (3-(4,5-dimethylthiazol-2)-2,5-diphenyltetrazolium bromide), which is yellow color is converted to form insoluble blue crystal formazan by mitochondrial NADH dehydrogenase enzyme. After adding the MTT reagent to the 96 well plates, the plates were incubated for 2 hours and then aspirated the medium; subsequently, 200ul of DMSO was added to dissolve the crystal formazan. The resulting crystal formazan was measured calorimetrically at 544nm. The Results are expressed as (%) change compared to the Control, Mean ± SEM. Cell viability of LS174T colorectal cancer cells and HepG2 cancer cells was measured using the CellTiter-Glo Luminescent Cell viability assays. Depending on the cell viability assay, mouse hippocampal neurons were used. Two different doses, one non-toxic and another low-toxic, were finalized for further experiments (Biochemical assays).

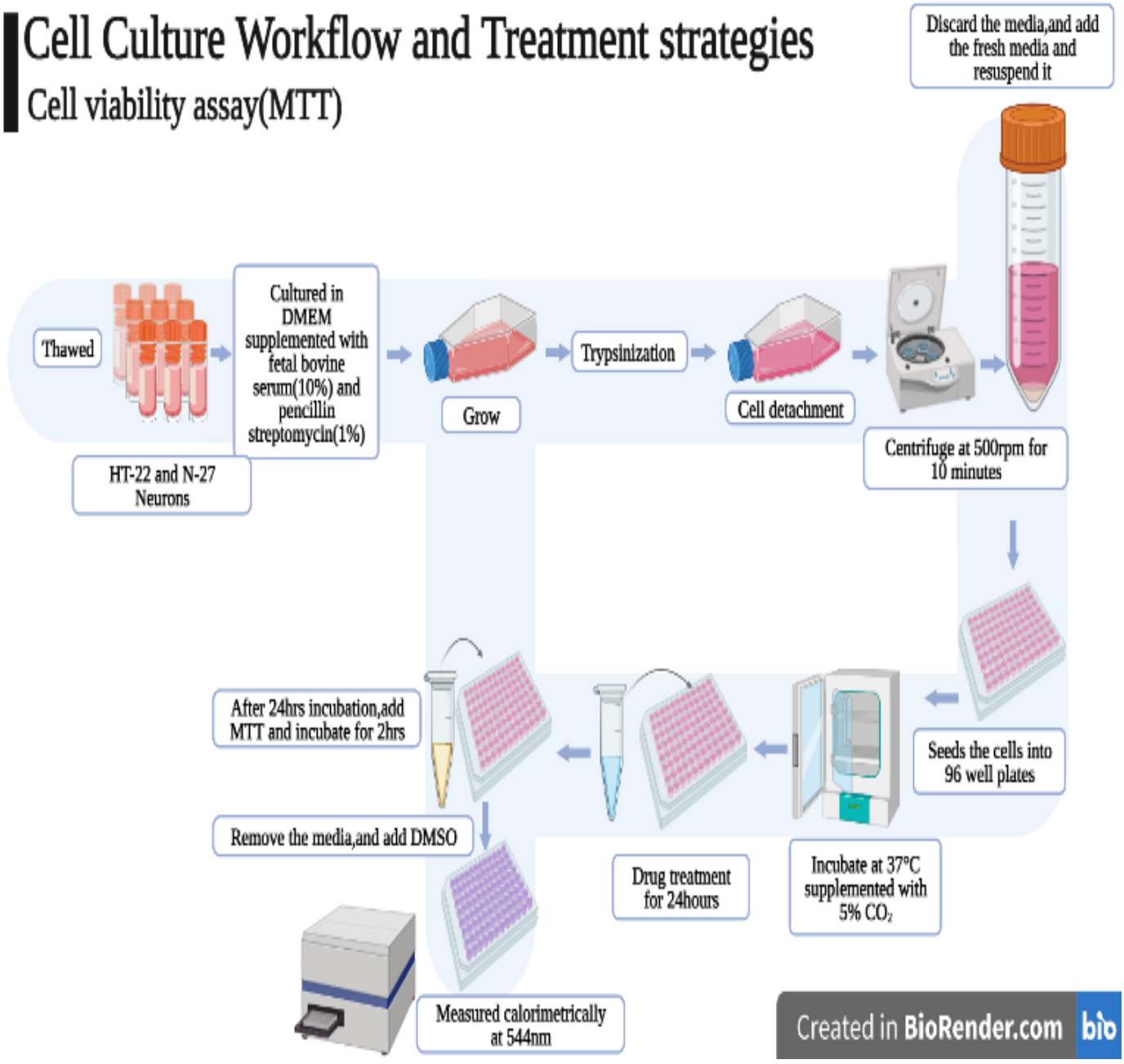


Figure 16: Cell culture workflow and treatment strategies

4. Protein Quantification:

Protein quantification was done by using Thermo Scientific Pierce 660nm protein assay reagent kit. Bovine serum albumin (BSA) was used as a standard for protein quantification.

5. Determination of ROS content:

The reactive oxygen species (ROS) content in control and 3-hydroxypterostilbene-treated hippocampal neurons were estimated spectrofluorometerically by measuring the conversion of non-fluorescent chloromethyl-DCF-DA (2′, 7′- Dichlorofluorescin diacetate, DCF-DA) to fluorescent DCF using an excitation wavelength of 460nm and an emission wavelength of 528nm using BioTek Synergy HT plate reader (BioTek, VT, USA). ROS content was normalized to total protein content and reported as relative fluorescence intensity/mg protein. (Ahuja et al., 2017; Bhattacharya et al., 2020; Majrashi et al., 2021).

6. Determination of Nitrite content:

Nitrite content was measured spectrophotometrically using the commercially available Griess reagent (Promega). The Griess method depends on nitrite reaction with sulfanilamide under acidic conditions, producing diazonium ions. The diazonium ion formed and then combines with N-(1-naphthyl) ethylenediamine to form a chromophoric azo product, which was measured Spectrophotometrically at 545nm using the BioTek Synergy HT plate reader, BioTek, VT, USA. The results were expressed as nitrite nmoles/mg protein (Bhattacharya et al., 2020).

7. Determination of hydrogen peroxide content:

Hydrogen peroxide content in control and 3-hydroxypterostilbene treated neurons were quantified by spectrophotometric method at 240nm. A standard curve obtained using hydrogen peroxide was used, and the results were expressed as hydrogen peroxide nmoles/mg protein.

8. Determination of glutathione content:

O-phthalaldehyde (OPT) reacts with glutathione (GSH) to form a fluorescence product that can be assessed spectrofluorometrically at an excitation wavelength of 340nm and an emission wavelength of 420nm. A GSH standard curve was prepared from commercially acquired GSH, and the results were expressed as glutathione μmoles/mg protein (Pondugula et al., 2022; Zheng et al., 2014).

9. Determination of Caspase-3 activity:

The spectrofluorimetric method was used to measure the caspase-3 activity. AC-DEVD-AMC was used as a substrate for measuring caspase-3 activity, and the AMC product formed from cleavage of AC-DEVD-AMC substrate by caspase-3 was measured at 360 nm/460nm using the BioTek Synergy HT plate reader, BioTek, VT, USA. Caspase-3 activity in control and 3-hydroxypterostilbene treated neurons were expressed as relative fluorescence intensity (RFU)/mg protein (Bhattacharya et al., 2020; Majrashi et al., 2021; Pondugula et al., 2022).

10. Determination of Serine-like protease Activity:

The spectrofluorimetric method using the BioTek Synergy HT plate reader, BioTek, VT, USA, was to measure the protease activity. Z-GGL-AMC (Carbobenzoxy-Gly-Gly-Leu-7-amido-4-methyl coumarin) was used as a substrate for measuring protease activity, and the AMC product formed from cleavage of the substrate by serine-like protease was measured at 380/440nm. Protease activity was expressed as the relative fluorescence intensity (RFU)/mg protein (Pondugula et al., 2022; Usha et al., 2000).

11. Determination of Mitochondrial Complex-I activity:

Complex-I (NADH dehydrogenase) catalyzes the oxidation of NADH to NAD＋ in an electron transport chain. The NADH oxidation in control and 3-hydroxypterostilbene-treated neurons was measured spectrophotometrically by the decrease in absorbance at 340 nm. A standard curve was composed of commercially obtained NADH, and the results were expressed as NADH oxidized μmoles/mg protein (Majrashi et al., 2021).

12. Determination of NADH content:

NADH in control and 3-hydroxypterostilbene-treated neurons were quantified by the spectrophotometric method at 340nm. A standard curve obtained using NADH was used, and the results were expressed as NADH μmoles/mg protein.

13.Determination of Tyrosine Hydroxylase activity:

Tyrosine hydroxylase is the rate-limiting enzyme in the synthesis of dopamine, norepinephrine, and epinephrine. The substrate, tyrosine was added to the control and 3-

hydroxypterostilbene treated N-27 neurons and incubated for 30 min induces the formation of levodopa by tyrosine hydroxylase present in the sample. Following the above reaction, sodium periodate was added to the solution. The formed L-dopa in the control and 3-hydroxypterostilbene treated neurons reacts with sodium periodate to form dopaquinone. Dopaquinone was measured spectrophotometrically at 475 nm.

IV. Statistical analysis:

Data was reported as Mean ± SEM. Statistical analyses were accomplished using a one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test ($p<0.05$) and was determined to be statistically significant. The Statistical analyses were performed using Prism-V software (La Jolla, CA, USA).

Chapter III: Results

I. *In-silico* analysis

a. QikProp assessment:

The pharmacokinetic and pharmacodynamic properties of Pterostilbene and 3-hydroxypterostilbene were analyzed using QikProp, the Schrodinger software.

A molecule's solvent-accessible surface area (SASA) is defined as its surface area in contact with the solvent in the biological system. Lower scores of SASA mean that a greater amount of the molecule interacts with a biomolecule like a protein or a membrane, and most of it will remain in unionized form. Therefore, greater absorption and bioavailability. In addition, higher SASA scores indicate that more of the molecule is interacting with the solvent, such as the aqueous medium of the stomach (stomach acid). Most of it will likely stay ionized, thus lowering absorption and bioavailability. The total solvent accessible surface area (SASA) acceptable range for a compound is (300-1000); likewise, FOSA: a hydrophobic component of SASA acceptable range is (0.0-750.0), FISA: hydrophilic component of SASA acceptable range is(7.0-330.0), PISA: π, carbon and attached hydrogen components of the SASA acceptable range is (0.0-450.0),#metab: number of metabolic reactions(1-8), CNS-2(Inactive) to +2(active), QPlogBB: (-3.0 to -1.2) are defined as the acceptable ranges, polar compounds have larger negative values, and the pterostilbene and 3-hydroxypterostilbene show SASA values within the acceptable range. Other parameters like hydrophobic components of the SASA(FOSA), hydrophilic components of the SASA(FISA), and carbon and attached hydrogen components of the SASA (PISA) values of Pterostilbene and 3-hydroxypterostilbene are within the acceptable range. Regarding metabolic reaction prediction(#metab), Pterostilbene has a lower number of metabolic

reactions than 3-hydroxypterostilbene. However, they are in an acceptable range. Less negative QPlog BB values indicate accessibility into the blood-brain barrier and better CNS activity. Pterostilbene have lesser negative QPlog BB value than 3- hydroxypterostilbene. However, they are in an acceptable range. Other parameters like HB donor, HB accept, cLogP, %Human oral absorption, Rule of 3, and Rule of 5 are within an acceptable range of drug bioavailability. The permissible ranges are as follows: Mol weight: (130-725), Hydrogen bond (HB) Donor: (0.0-6.0), Hydrogen bond (HB) Acceptor: (2.0-20.0), cLogP: (-2.0-6.5), % Human oral absorption: >80% high, <25% low, Rule of 3(maximum 3), Rule of 5(maximum 4)

Compound	SASA (Å)	FOSA (Å)	FISA (Å)	PISA (Å)	#Metab	CNS	QPlog BB
Pterostilbene	529.72	199.53	54.63	275.56	3	0	-0.31
3-Hydroxypterostilbene	541.67	199.71	101.88	240.09	4	-1	-0.82

Table 11: Pharmacodynamic effects of Pterostilbene and 3-hydroxypterostilbene

Compound	Molecular weight	HB Donor	HB Accept	cLogP	%Human oral absorption	Rule of 3	Rule of 5
Pterostilbene	256.30	1	2.25	-4.201	100	0	0
3-Hydroxypterostilbene	272.3	2	3	-4.154	100	0	0

Table 12: Pharmacodynamic effects of Pterostilbene and 3-hydroxypterostilbene

b. Swiss ADME Assessment:

To succeed as a preventive or therapeutic ligand, the "molecule of interest" must reach its target (central or peripheral) in the body at the optimum concentration and remain in a bioactive state for a certain amount of time to elicit expected pharmacological actions. Effective ADME (absorption, distribution, metabolism, and elimination) qualities in drug molecules are the most critical determinants of successful candidate molecules in drug discovery and development. Molecular weight, rotatable bonds, molar refractivity, total polar surface area, log p octanol/water (o/w), log S, log Kp, drug-likeness, PAINS, Brenk, Lead likeness, and synthetic accessibility were chosen to describe this aspect of the compound's ADME in this study. SwissADME, a web tool used in computational analysis, provides free access to a pool of compounds. The size of the molecule significantly influences the molecular weight of a compound. To be considered a preventive or therapeutic ligand, the molecular weight of a substance should range from 150 to 500 g/mol.

Drug molecules with beneficial absorption, distribution, metabolism, and elimination (ADME) properties are the foremost indicators of flourishing candidate molecules in drug discovery and development. In this study, SwissADME assesses the pharmacokinetic and pharmacodynamic properties of pterostilbene and 3-hydroxypterostilbene. For saturation, the ratio of sp3 Hybridized carbons over the total carbon count of the molecule should be at least 0.25. Any single non-ring bond attached to a non-terminal, non-hydrogen atom is called a rotatable bond (not more than nine rotatable bonds) and is used to predict the flexibility and polarity of the drug, which is essential in determining the oral bioavailability of the drugs. Molar refractivity measures the total polarizability of a substance's mole. The

polar surface area (PSA) is calculated using a fragmental technique called topological polar surface area (TPSA). PSA usually uses medicinal chemistry metrics to optimize a drug's ability to permeate cells. For polarity, the TPSA should be between 20 and 130 Å. Greater than 140 Å tend to be poor at permeating cell membranes. PSA less than 90 Å is usually needed for a molecule to penetrate the blood-brain barrier.

In the research, design, and development of pharmaceuticals, the physiochemical parameter for lipophilicity is the n-octanol/water partition coefficient (log P o/w). For solubility in water, Log S is intended; it shouldn't be greater than 6. The Log Kp defines the skin permeability coefficient. The less permeant the molecule is to the skin, the more negative value of log Kp. Drug similarity was determined from structural or physiochemical analyses of created substances thought to be candidates for oral drugs. In the early stages of high-volume drug discovery screening, biologically active molecules called PAINS (Pan-assay interference compounds) pose as prospective therapeutic candidates. When a PAIN warning was present in a substance, it was a PAINS, which are chemical compounds that frequently provide false-positive findings in high-throughput screening. Brenk is issuing a caution regarding potentially dangerous, unstable, and reactive structural fragments. These alerts will come up if any of the substructures of the target compounds exhibit hazardous properties. A compound must meet specific criteria to be considered similar to "lead." Lead is the phrase used in the drug development process to describe a chemical molecule with therapeutic or pharmacological action but a suboptimal structure that needs to be modified.

The following requirements are made by SwissADME: similarity to lead, 350 molecular weights, XLOGP of 3.5, and 7 rotatable bonds. On a scale of 1 to 10, a compound's synthetic

accessibility is determined by how easily it can be made. It establishes how similar the target substance and accessible molecules are (Table 13).

The major difference is that 3-hydroxypterostilbene is not a substrate for p-gp. So, 3-Hydroxypterostilbene can't get effluxed by P-gp drug transporter.

		Pterostilbene	**3-Hydroxypterostilbene**
Physicochemical properties	Formula	C16H16O3	C16H1604
	Molecular weight	256.30 g/mol	272.30 g/mol
	Num. heavy atoms	19	20
	Num. arom. heavy atoms	12	12
	Fraction Csp3	0.12	0.12
	Num. rotatable bonds	4	4
	Num. H-bond acceptors	3	4
	Num. H-bond donors	1	2
	Molar Refractivity	76.82	78.84
	TPSA	38.69 A^2	58.92 A^2
Lipophilicity	LogPo/w (iLOGP)	3.02	2.84
	LogPo/w(XLOGP3)	3.78	3.51
	LogPo/w(WLOGP)	3.36	3.07
	LogPo/w(Mlogp)	2.76	2.18
	LogPo/w (SILICOS-IT)	3.61	3.13
	Consensus Log Po/w	3.31	2.94
Water solubility	Log S(ESOL)	-4.01	-3.92
	Solubility	2.48e-02 mg/ml,9.69e-05 mol/l	3.28e-02 mg/ml;1.20e-04 mol/l
	Class	Moderately soluble	soluble
	Log S (Ali)	-4.29	-4.43
	Solubility	1.33e-02 mg/ml;5.17e-05	1.01e-02 mg/ml;3.71e-05 mol/l

		mol/l	
	Class	Moderately soluble	Moderately soluble
	LogS (SILICOS-IT)	-4.69	-4.11
	Solubility	5.24e-03mg/ml; 2.05e-05 mol/l	2.11e-02mg/ml;7.76e-05 mol/l
	Class	Moderately soluble	Moderately soluble
Pharmacokinetics	GI absorption	High	High
	BBB permeant	Yes	Yes
	P-gp substrate	No	No
	CYP1A2 inhibitor	Yes	Yes
	CYP2C19 inhibitor	Yes	Yes
	CYP2C9 inhibitor	Yes	Yes
	CYP2D6 inhibitor	Yes	Yes
	CYP3A4 inhibitor	No	Yes
	log Kp (cm/s)	-5.18 cm/s	-5.47cm/s
Drug likeness	Lipinski	Yes; 0 violation	Yes; 0 violation
	Ghose	yes	yes
	Veber	yes	yes
	Egan	yes	yes
	Muegge	yes	yes
	Bioavailability Score	0.55	0.55
Medicinal chemistry	PAINS	0 alert	1alert: catechol_A
	Brenk	1 alert: stilbene	2 alerts: catechol, Stilbene
	Leadlikeness	No; 1 violation: XLOGP>3.5	No; 1 violation: XLOGP>3.5
	Synthetic accessibility	2.29	2.35

Table 13: *In-silico* evaluation of ADME parameters of Pterostilbene and 3-Hydroxypterostilbene by SwissADME.

II. Effect of 3-hydroxypterostilbene on HT-22 mouse hippocampal neuronal viability:

In the present study, the dose-dependent effect of 3-hydroxypterostoilbene on HT-22 mouse hippocampal neuronal viability was investigated using MTT based colorimetric method at 24 hours. 3-hydroxypterostilbene dose-dependently decreased the neuronal viability significantly at 0.1μM,1μM,10μM, and 100μM as compared to the control (n = 121, **p < 0.01, ***p<0.001). Nevertheless, a statistically significant HT-22 cell toxicity of 3-hydroxypterostilbene was observed from a lower dose of 0.1uM.

Figure 17: Effect of different doses of 3-hydroxypterostilbene on HT-22 mouse hippocampal neurons at 24 hours:

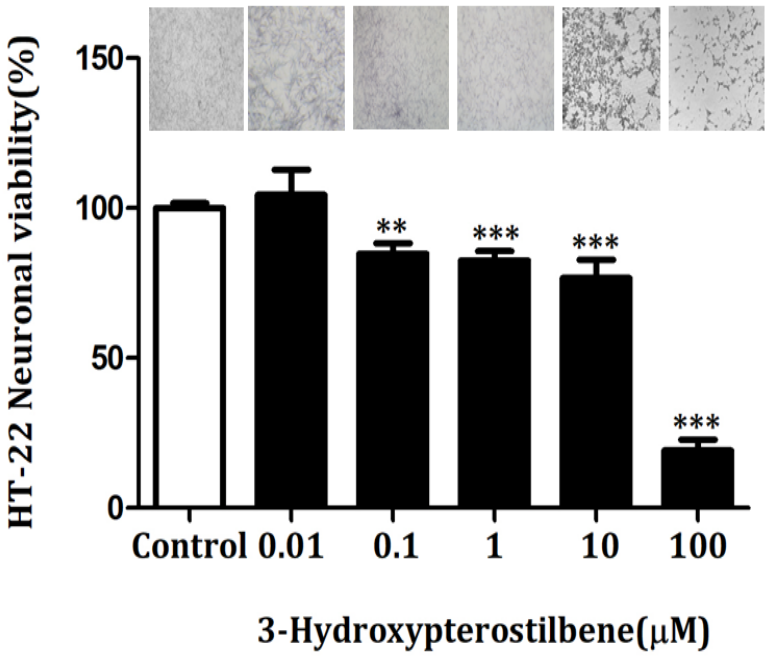


Figure 17: HT-22 mouse hippocampal neurons were treated with different concentrations of 3-hydroxypterostilbene and incubated for 24 hours. MTT assay was used to evaluate neuronal viability. Results are expressed as (%) change as compared to the control; Mean ± SEM.3-hydroxypterostilbene dose-dependently decreased the neuronal viability significantly at 0.1μM,1μM,10μM,100μM as compared to the control (n = 121, **p < 0.01, ***p<0.001).a compared to the 0.01μM (n=15).b compared to the 0.1μM (n=87,).c. compared to the 1μM (n=84).d. compared to the 10μM (n=36).

III. Effect of 3-Hydroxypterostilbene on N27 rat dopaminergic neuronal cell viability:

The present study investigated the dose-dependent effect of 3-hydroxypterostoilbene on N27 rat dopaminergic neuronal viability using the MTT-based colorimetric method at 24 hours.3-hydroxypterostilbene dose-dependently decreased the neuronal viability significantly at 1μM,10μM,100μM as compared to the control (n = 121, **p < 0.01, ***p<0.001). Nevertheless, a statistically significant N-27 cell toxicity of 3-hydroxypterostilbene was observed from a lower dose of 1uM at 24 hours.

Figure 18: Effect of different doses of 3-hydroxypterostilbene on N27 rat dopaminergic neurons at 24 hours:

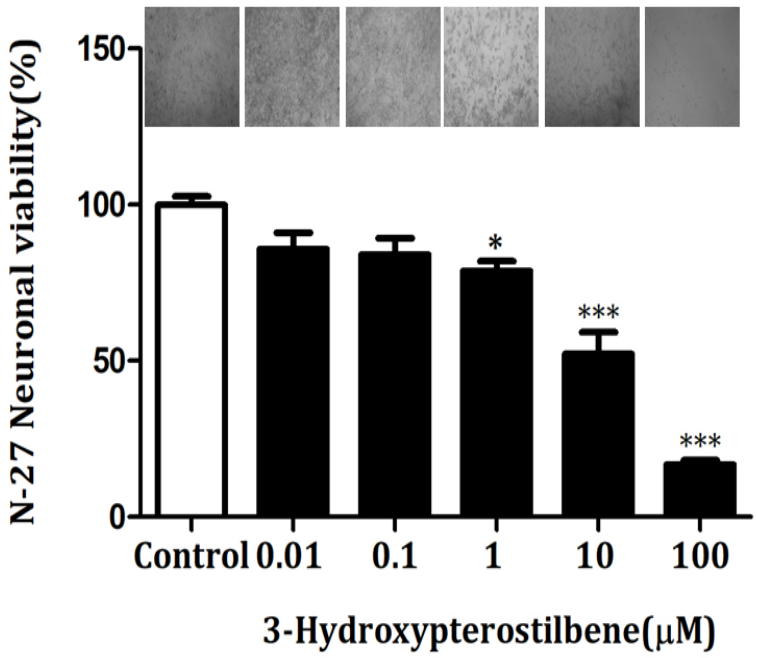


Figure 18: N27 rat dopaminergic neurons were treated with different concentrations of 3-hydroxypterostilbene and incubated for 24 hours. MTT assay was used to evaluate neuronal viability. Results are expressed as (%) change as compared to the control; Mean ± SEM.3-hydroxypterostilbene, dose-dependently decreased the neuronal viability significantly at 1μM,10μM,100μM compared to the control (n = 27, *p < 0.05, ***p < 0.001).a compared to the 0.01μM (n=15).b. compared to the 0.1μM (n=15).c. compared to the 1μM (n=8).d. compared to the 10μM (n=12).

IV. Effect of different doses of hydrogen peroxide on HT-22 hippocampal neurons:

The endotoxin hydrogen peroxide (the positive control) induced a significant dose-dependent decrease in neuronal viability.

Figure 19: Effect of different doses of endotoxin hydrogen peroxide on HT-22 hippocampal neurons at 24 hours:

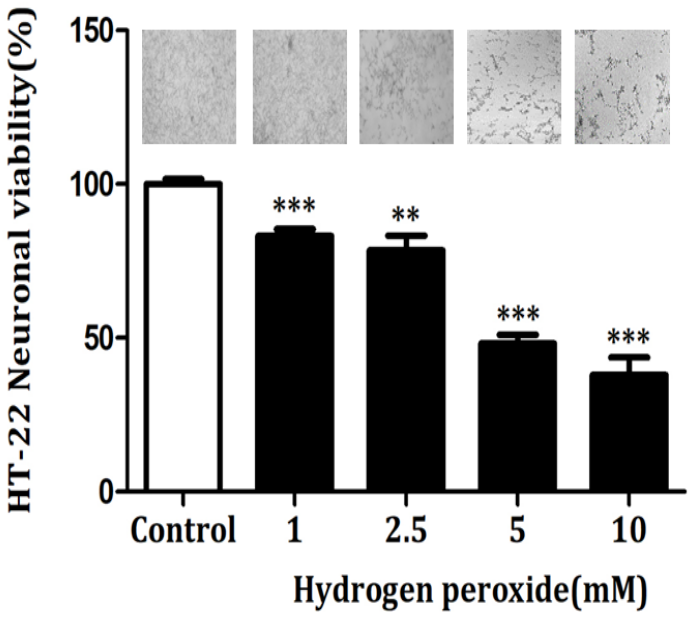


Figure 19: HT-22 neurons were treated with different doses of hydrogen peroxide for 24 hours. Neuronal viability was evaluated through the MTT reduction assay. Results are

expressed as (%) change, Mean ± SEM. Note (*) indicates a statistically significant difference when compared to controls (**p < 0.01, ***p<0.001 n=121)

V. Effect of 3-Hydroxypterostilbene on Hep G2 cancer cell viability:

The present study investigated the dose-dependent effect of 3-hydroxypterostoilbene on Hep G2 cancer cells using the CellTiter-Glo Luminescent Cell viability assays at 24 hours.3-hydroxypterostilbene dose-dependently decreased the cancer cell viability significantly at 30μM and 50μM as compared to the control (n = 6, **p < 0.01, ***p<0.001). Nevertheless, a statistically significant Hep G2 cancer cell toxicity of 3-hydroxypterostilbene was observed from a lower dose of 30μM at 24 hours.

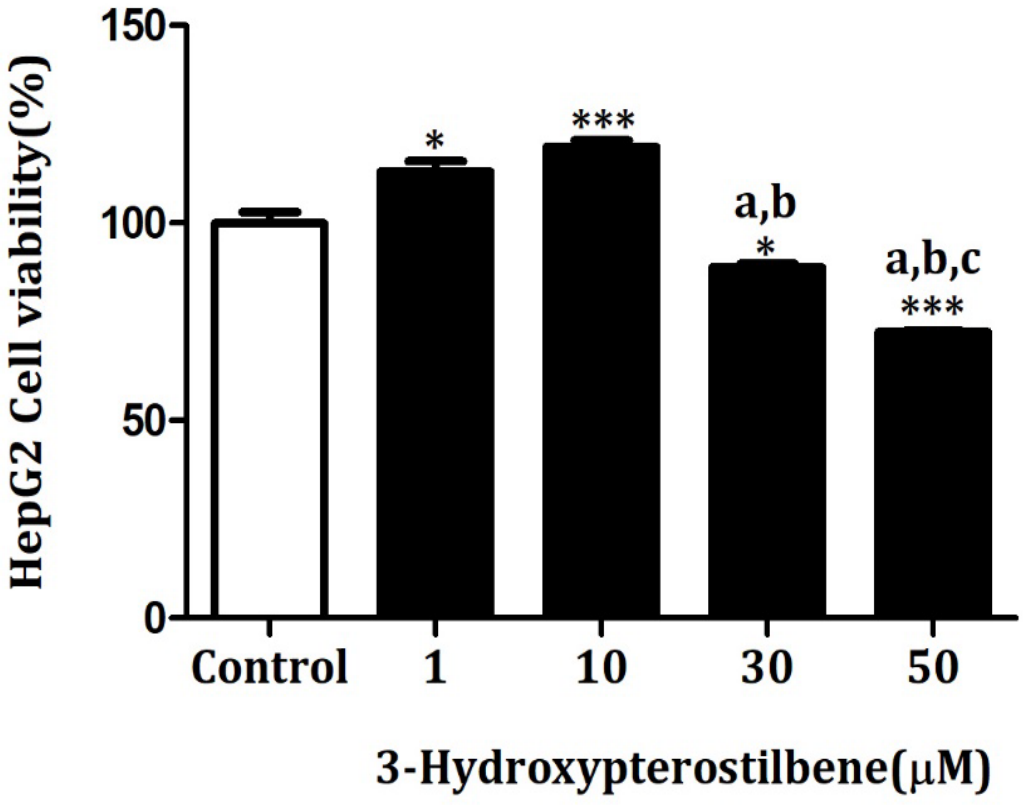


Figure 20: Effect of different doses of 3-Hydroxypterostilbene on HepG2 cancer cells at 24 hours

Figure 20: HepG2 cancer cells were treated with different concentrations of 3-hydroxypterostilbene and incubated for 24 hours. Cell titer glow assay was used to evaluate cell viability. Results are expressed as (%) change as compared to the control; Mean ± SEM.3-hydroxypterostilbene, dose-dependently decreased the cell viability significantly at 30μM and 50μM compared to the control (n = 6, *p < 0.05, ***p < 0.001). a compared to the 1μM (n=3). b. compared to the 10 μM (n=3). c. compared to the 30μM (n=3).

VI. Effect of 3-Hydroxypterostilbene on LS174T colorectal cancer cell viability:

The present study investigated the dose-dependent effect of 3-hydroxypterostoilbene on LS174T colorectal cancer cells using the CellTiter-Glo Luminescent Cell viability assays at 24 hours.3-hydroxypterostilbene decreased the cell viability significantly at 50μM as compared to the control (n = 6, ***p<0.001). Nevertheless, a statistically significant LS174T colorectal cancer cell toxicity of 3-hydroxypterostilbene was observed from a dose of 50uM at 24 hours.

Figure 21: Effect of different doses of 3-Hydroxypterostilbene on LS174T Colorectal Cancer cells at 24 hours:

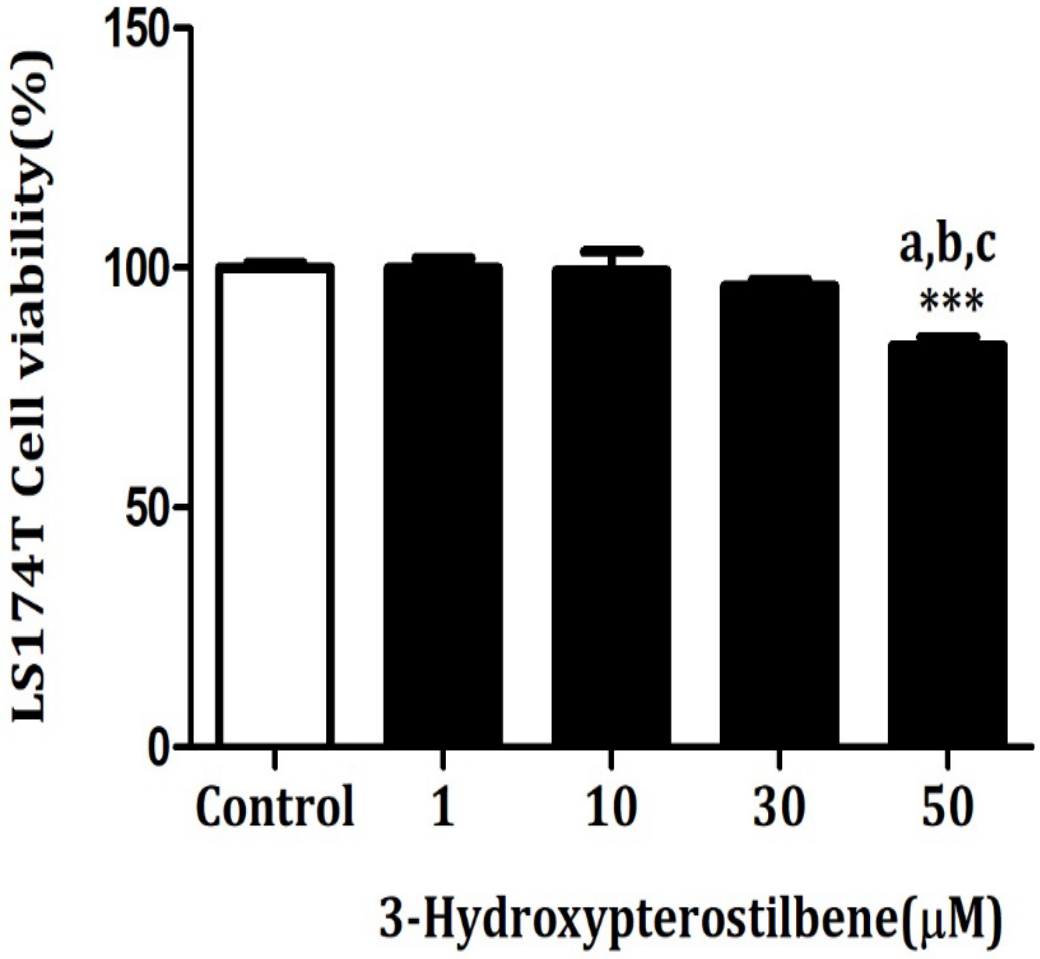


Figure 21: LS174T cancer cells were treated with different concentrations of 3-hydroxypterostilbene and incubated for 24 hours. Cell titer glow assay was used to evaluate cell viability. Results are expressed as (%) change as compared to the control; Mean ± SEM.3-hydroxypterostilbene, decreased the cell viability significantly at 50μM compared to the control (n = 6, ***p < 0.001). a compared to the 1μM (n=3). b. compared to the 10 μM (n=3). c. compared to the 30μM (n=3).

VII. Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on various pro-oxidant markers in the HT-22 neurons:

a. Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on reactive oxygen species (ROS) content

ROS generation in control and two different doses of 3-hydroxypterostilbene treated HT-22 neurons was measured based on the conversion of non-fluorescent substrate DCF (2',7'-Dichlorofluorescin diacetate) to the fluorescent product that was quantified spectrofluorometrically. The generation of ROS was significantly decreased in a dose-dependent manner in 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) treated neurons as compared to the control (**$p<0.01$, $n=5$). Reactive oxygen species were measured as relative fluorescence units (495/527nm)/mg protein, Mean ± SEM.

Figure 22: Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on ROS content

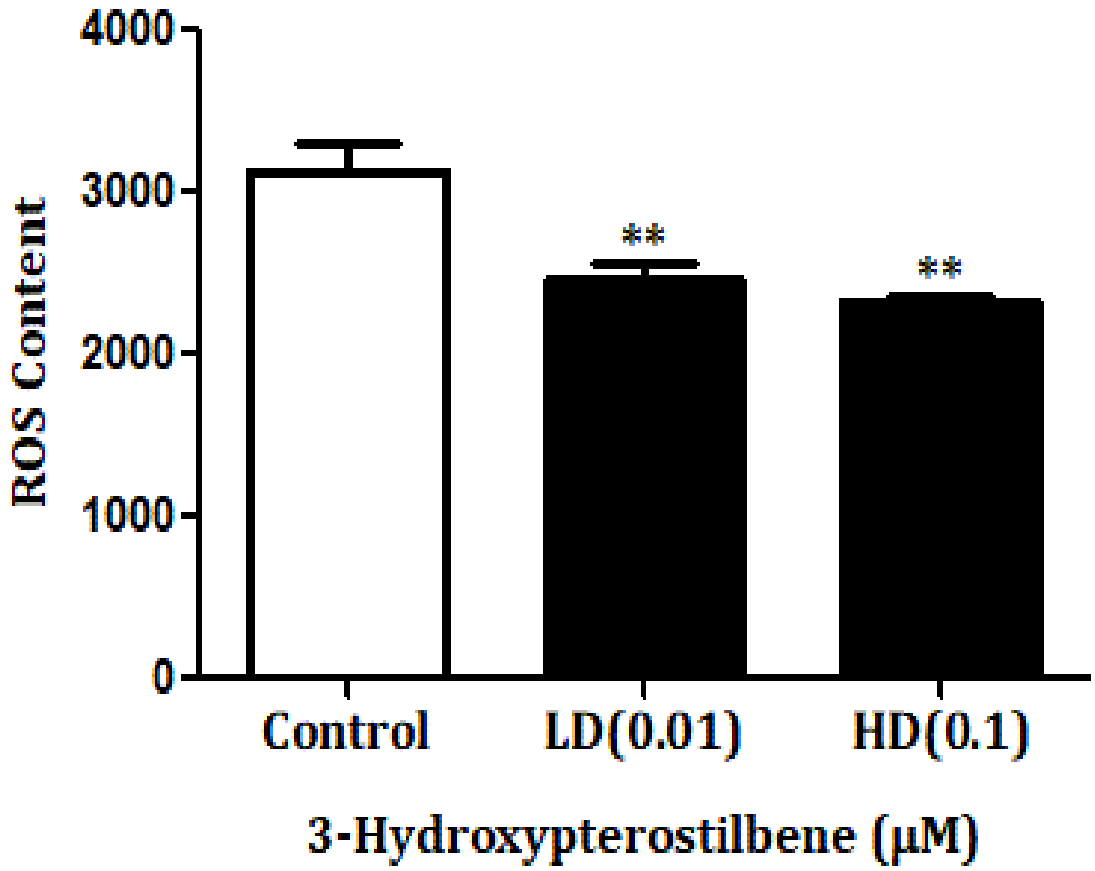


Figure 22: Reactive oxygen species was measured spectrofluorimetrically at (495nm / 527nm). Results are expressed as Mean ± SEM, the relative fluorescence units/mg protein. 3-hydroxypterostilbene induced a significant dose-dependent decrease in reactive oxygen species content compared to the control (**$p < 0.01$, $n = 5$).

b. Effect of 3-hydroxypterostilbene (LD-0.01μM and HD-0.1μM) on Nitrite content

Nitrite content in the control and different doses of 3-hydroxypterostilbene treated HT-22 neurons was quantified calorimetrically based on the formation of the azo product by the nitrite content reacting with the Griess reagent. 3-hydroxypterostilbene (LD-0.01μM and

HD-0.1μM) did not affect nitrite content compared to the control (n=5). Results are expressed as (nmoles/mg protein), Mean ± SEM

Figure 23: Effect of 3-Hydroxypterostilbene (LD-0.01μM and HD-0.1μM) on nitrite content

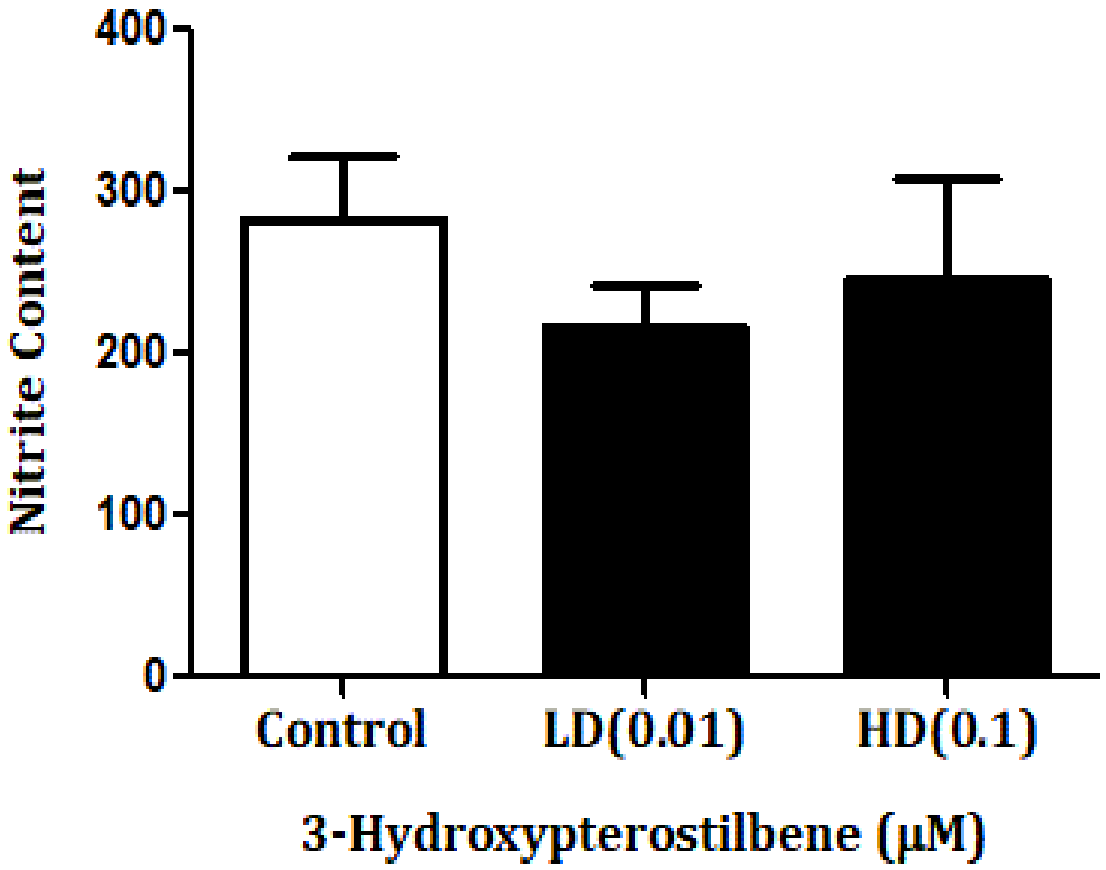


Figure 23: Nitrite content was measured spectrophotometrically at 540nm.3-hydroxypterostilbene did not affect nitrite content compared to the control (n = 5). Results are expressed as Mean ± SEM, nitrite content nmoles/mg protein.

c. effect of 3-Hydroxypterostilbene (LD-0.01μM and HD-0.1μM) on hydrogen peroxide content.

Hydrogen peroxide content in control and two different doses of 3-hydroxypterostilbene treated HT-22 neurons was quantified by the spectrophotometric method.

3-hydroxypterostilbene did not affect hydrogen peroxide as compared to the control (n=5). Results are expressed as (nmoles/mg protein), Mean ± SEM.

Figure 24: Effect of Effect of 3-Hydroxypterostilbene (LD-0.01μM and HD-0.1μM) on Hydrogen Peroxide(H_2O_2) content

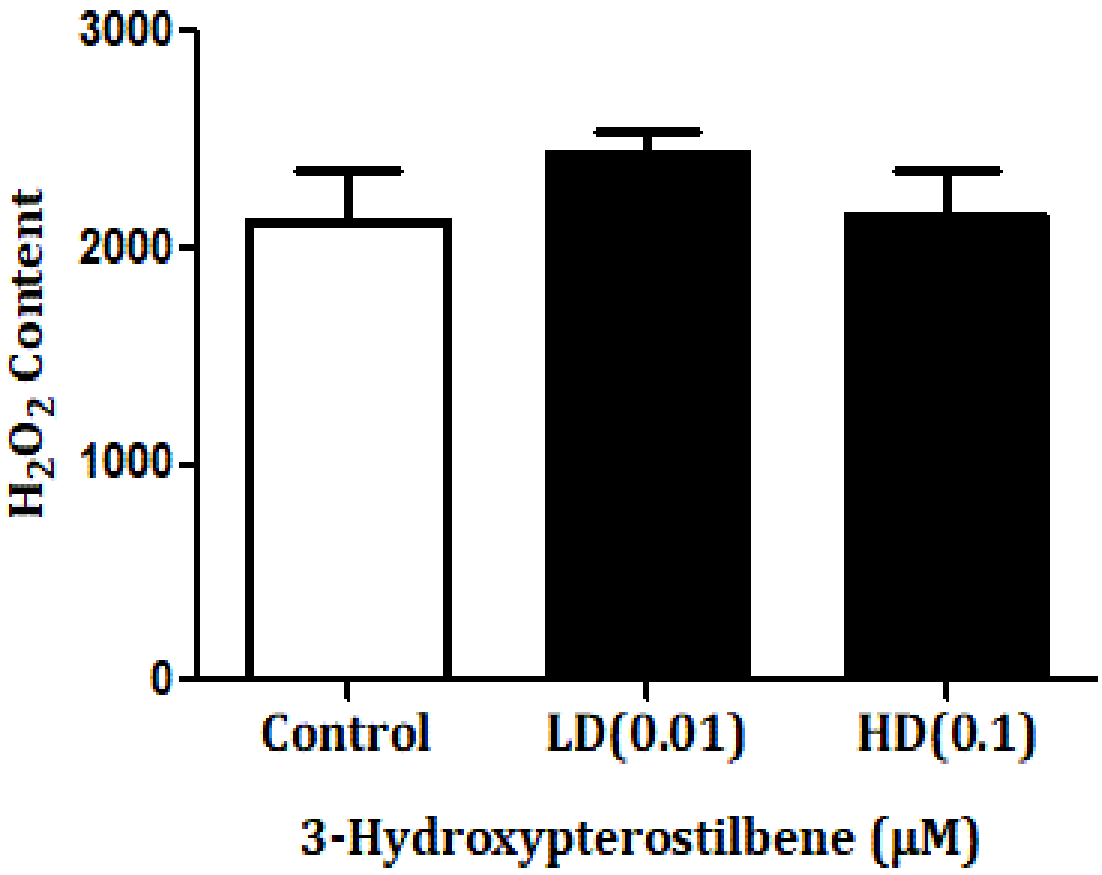


Figure 24: H_2O_2 content was measured spectrophotometrically at 240nm.3-hydroxypterostilbene did not affect H_2O_2 Content compared to the control (n = 5). Results are expressed as Mean ± SEM, H_2O_2 content nmoles/mg protein

VIII. Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on Antioxidant markers in the HT-22 neurons:

1. Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on glutathione content:

   Glutathione content in control and 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) treated neurons was quantified by the spectrofluorimetric method. 3-hydroxypterostilbene did not affect Glutathione content compared to the control (n = 5). Results are expressed as (nmoles/mg protein), Mean ± SEM.

   Figure 25: Effect of 3-Hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on GSH content

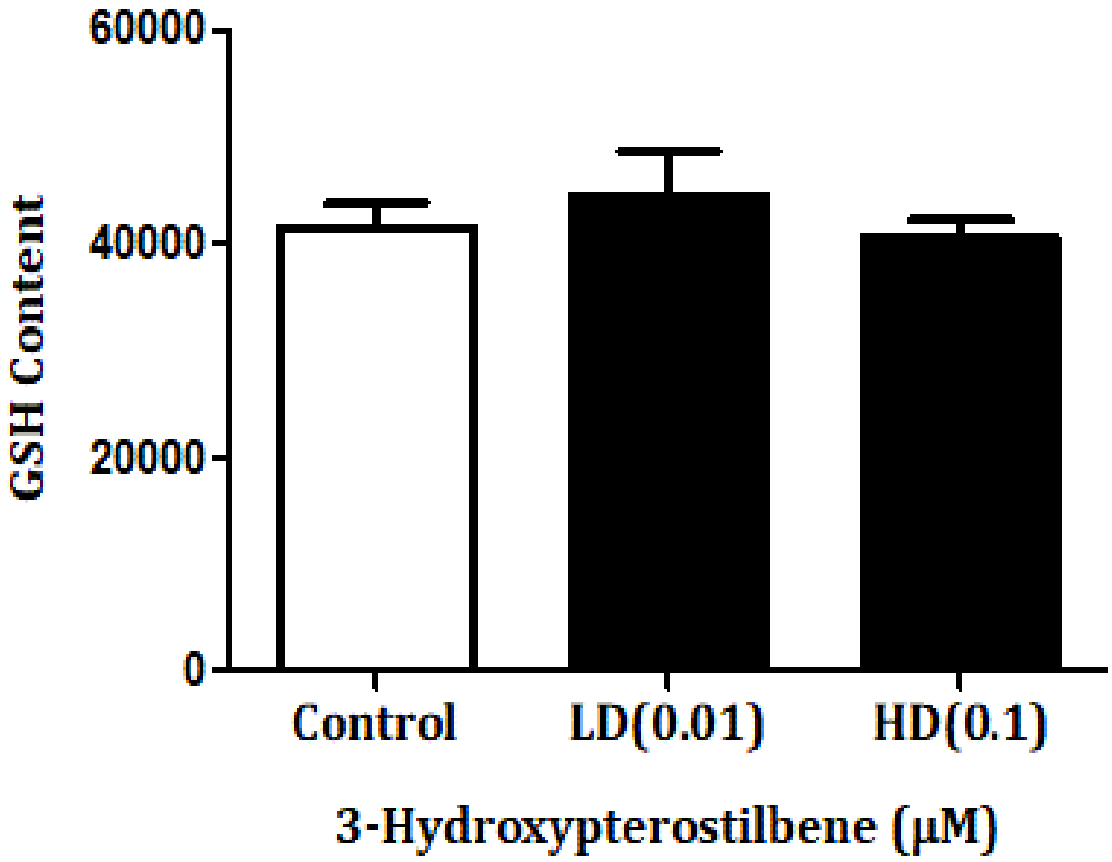


Figure 25: Glutathione content was measured spectrofluorimetrically at 337/423nm. 3-Hydroxypterostilbene did not affect GSH Content compared to the control (n = 5). Results are expressed as Mean ± SEM, GSH Content nmoles/mg protein.

IX. Effect of 3-Hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on markers of apoptosis in the HT-22 neurons:

a. Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on caspase-3 activity:

Caspase-3 activity in control and 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) treated neurons was measured fluorometrically at 360/460nm. 3-hydroxypterostilbene induced a significant dose-dependent increase in the caspase-3 activity compared to the control(n=5)

Figure 26: Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on Caspase-3 activity

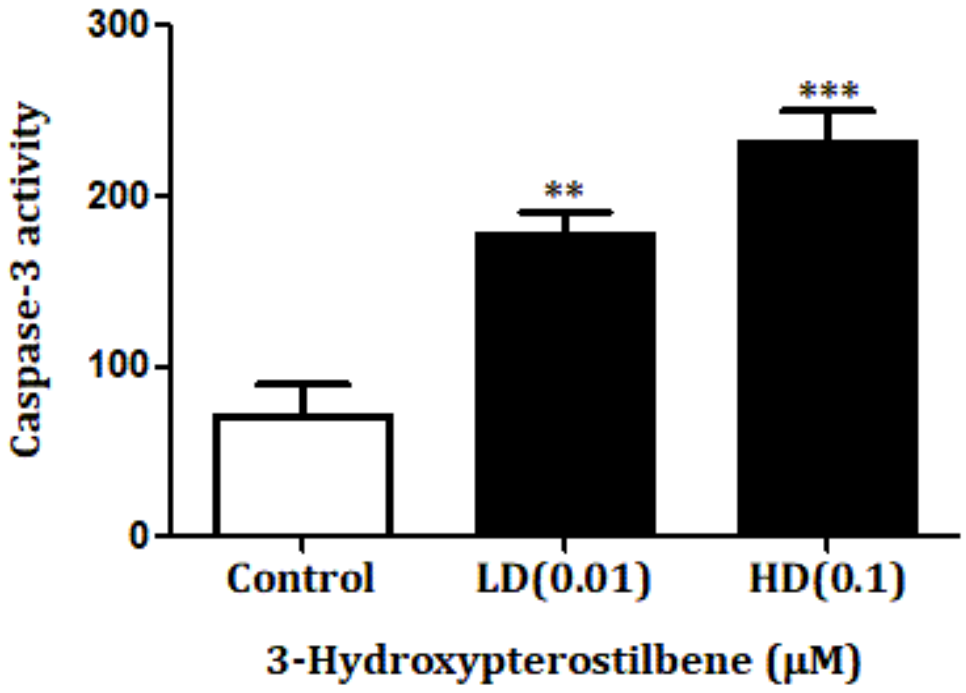


Figure 26: Caspase-3 activity was measured fluorometrically (360/460nm). 3-hydroxypterostilbene induced a significant dose-dependent increase in caspase-3 activity compared to the control (**p < 0.01, ***P<0.001, n = 5). Results are expressed as Mean ± SEM, AMC formed / mg protein.

b. Effect of 3-Hydroxypterostilbene (LD-0.01μM and HD-0.1μM) on Serine-like protease activity:

Serine-like protease activity in the control and 3-hydroxypterostilbene (LD-0.01μM and HD-0.1μM) treated neurons was measured fluorometrically at 360/460nm. 3-hydroxypterostilbene did not affect protease activity compared to the control(n=5). Results are expressed as (RFU/mg protein), Mean ± SEM.

Figure 27: Effect of 3-hydroxypterostilbene (LD-0.01μM and HD-0.1μM) on Serine-like protease activity

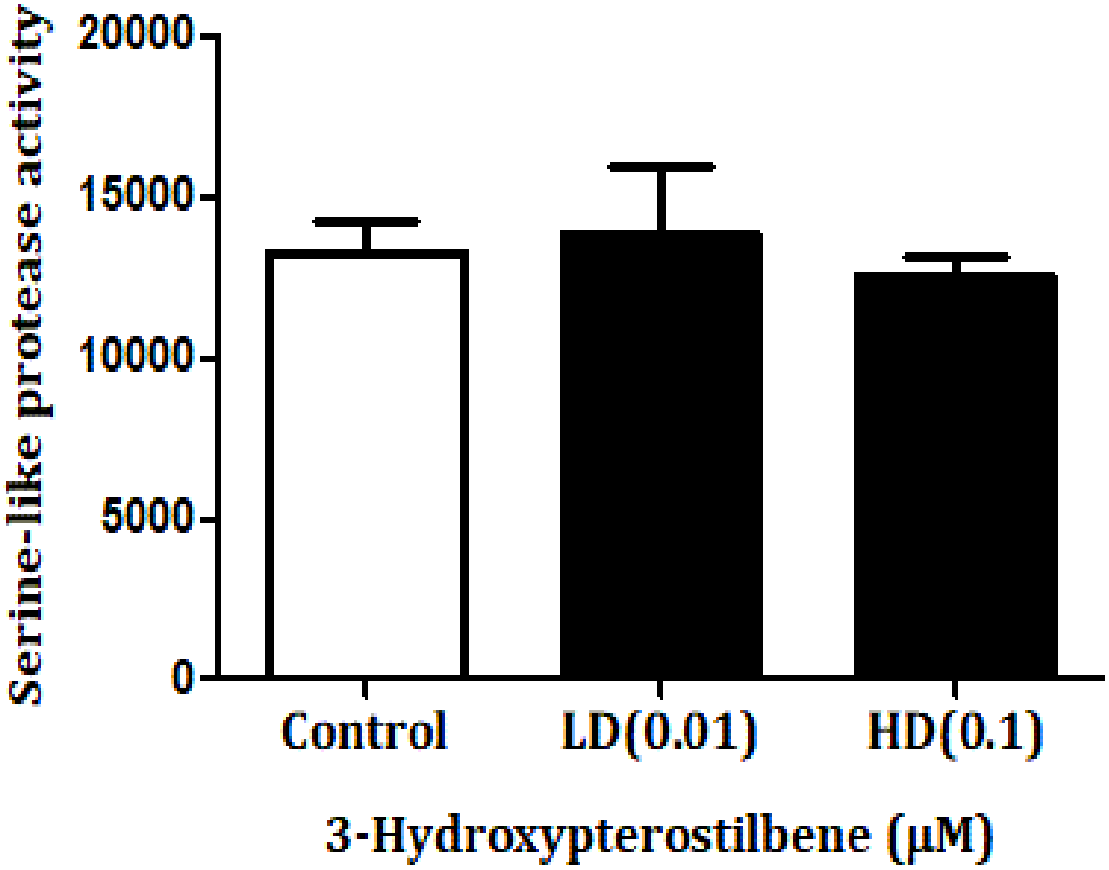


Figure 27: Serine-like protease activity was measured fluorometrically (360/460nm). 3-Hydroxypterostilbene did not affect Protease activity compared to the control (n = 5). Results are expressed as Mean ± SEM, AMC formed / mg protein.

X. Effect of 3-Hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on mitochondrial function in the HT-22 neurons:

1.Effect of 3-Hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on mitochondrial Complex-I activity:

Mitochondrial Complex-I activity in the control and 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) treated neurons was measured at 340nm. 3-hydroxypterostilbene did not affect mitochondrial Complex-I activity compared to the control(n=5). Results are expressed as NADH oxidized (nmoles/mg protein), Mean ± SEM.

Figure 28: Effect of 3-Hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on Mitochondrial Complex-I activity

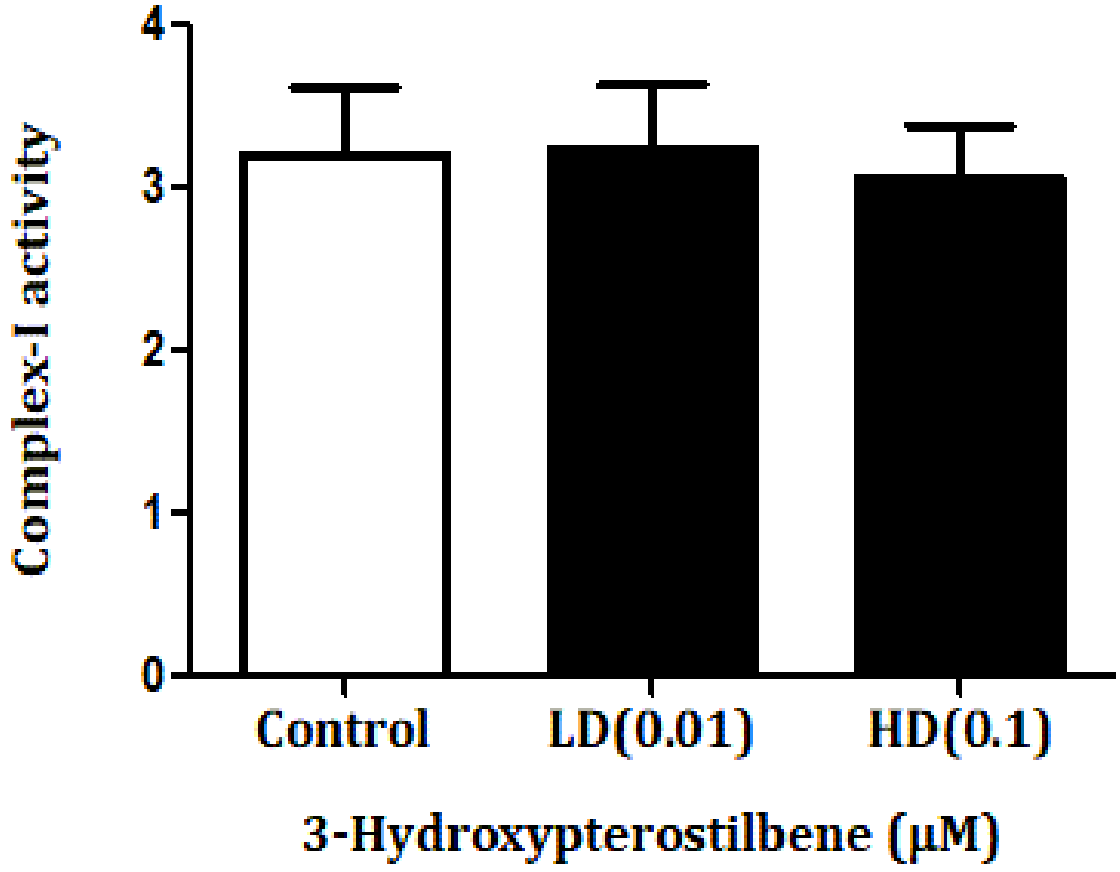


Figure 28: Mitochondrial Complex I activity was based on NADH oxidation **and** was measured spectrophotometrically (340nm). Results are expressed as Mean ± SEM, NADH

oxidized (nmoles/mg protein).3-hydroxypterostilbene did not affect Complex-I activity compared to the control (n = 5).

2.Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on NADH Content:

NADH Content in control and 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) treated neurons was measured spectrophotometrically at 340nm. 3-hydroxyptrostilbene did not affect NADH content compared to the control(n=5). Results are expressed as NADH Content (nmoles/mg protein), Mean ± SEM.

Figure 29: Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on NADH Content

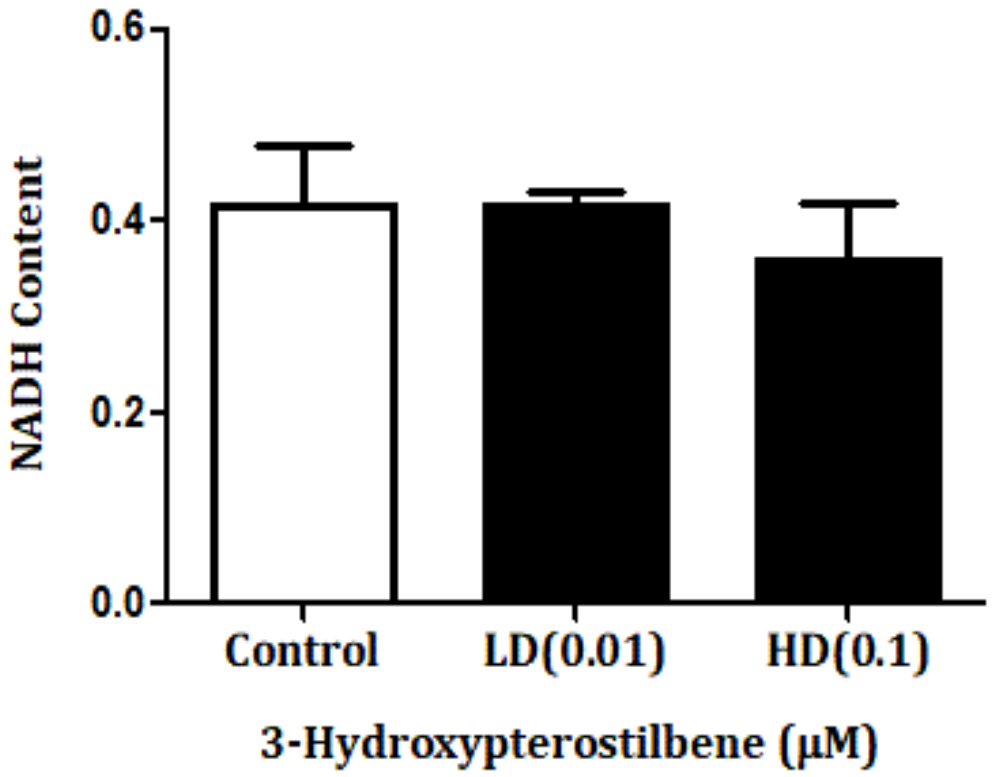


Figure 29: NADH Content was measured spectrophotometrically at 340nm. 3-hydroxypterostilbene did not effect on NADH content compared to the control (n = 5). Results are expressed as Mean ± SEM, NADH Content (moles/mg protein).

XI. Effect of 3-Hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on Tyrosine Hydroxylase activity in the N-27 neurons:

1.Effect of 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on Tyrosine Hydroxylase activity:

Tyrosine hydroxylase in control and 3-hydroxypterostilbene (LD-0.01µM and HD-0.1µM) treated neurons was measured spectrophotometrically at 475nm. 3-hydroxyptrostilbene significantly inhibited Tyrosine hydroxylase activity compared to the control(n=6). Results are expressed as (%) as compared to control, Mean ± SEM.

Effect of 3-Hydroxypterostilbene (LD-0.01µM and HD-0.1µM) on Tyrosine Hydroxylase activity:

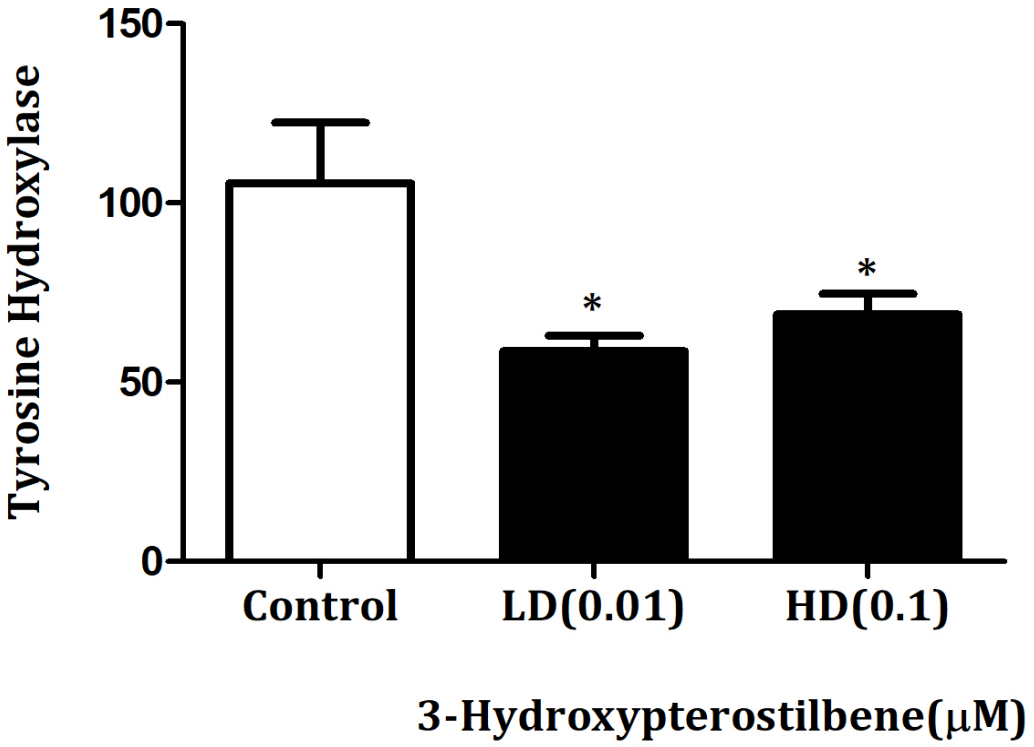


Figure 30: Tyrosine hydroxylase activity was measured spectrophotometrically at 475nm.3-Hydroxypterostilbene significantly inhibited tyrosine hydroxylase activity compared to control ($^{*}p < 0.05$, $n = 6$). Results are expressed as (%) change as compared to the control, Mean ± SEM

XII. Effect of 3-Hydroxypterostilbene (LD-0.01μM and HD-0.1μM) on markers of apoptosis in the N-27 neurons:

a. Effect of 3-hydroxypterostilbene (LD-0.01μM and HD-0.1μM) on Caspase-3 activity:

Caspase-3 activity in control and 3-hydroxypterostilbene (LD-0.01μM and HD-0.1μM) treated neurons was measured fluorometrically at 360/460nm. 3-hydroxypterostilbene induced a significant increase in the caspase-3 activity compared to the control(n=6)

Figure 31: Effect of 3-hydroxypterostilbene (LD-0.01μM and HD-0.1μM) on Caspase-3 activity

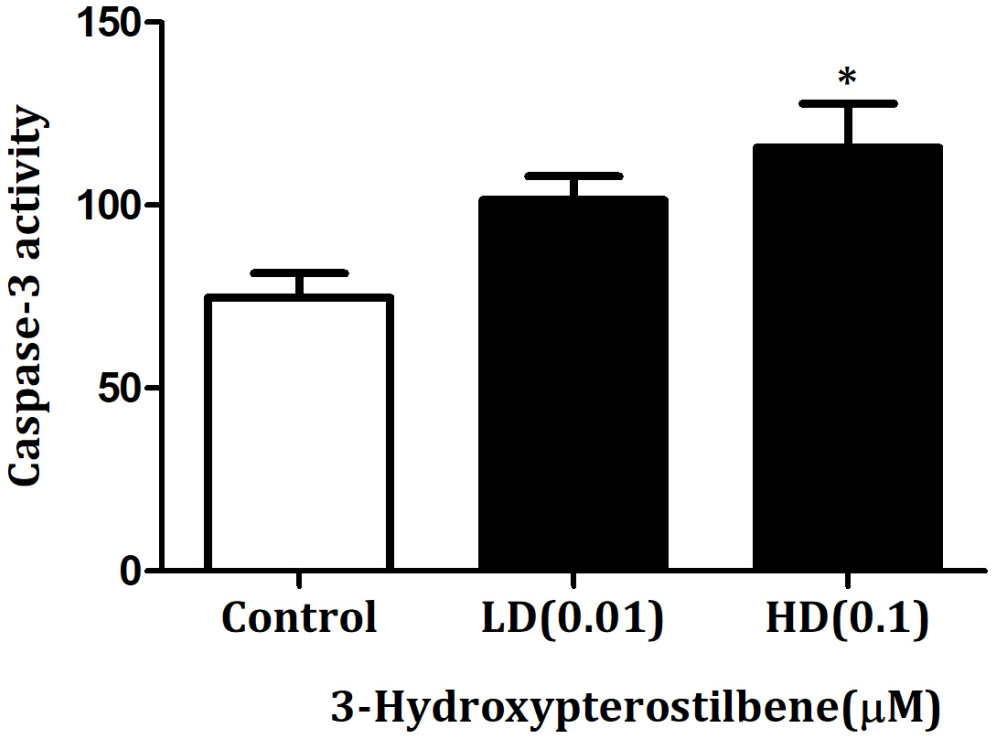


Figure 31: Caspase-3 activity was measured spectrofluorometrically at 360/460nm. 3-hydroxypterostilbene showed an significant increase in Caspase-3 activity compared to the control (n = 6). Results are expressed as Mean ± SEM, AMC formed/mg protein.

Discussion:

The chemical characteristics of a natural bioactive determine the target for the pharmacodynamic effects and also contribute to its ADME profile. The naturally occurring bioactive substances found in fruits, vegetables, and other plant-based foods—commonly

referred to as "phytochemicals"—can be divided into various groups. More than 5000 phytochemicals have been extracted and researched, despite the theory that many plant-derived beneficial substances are still undiscovered. These naturally occurring bioactive substances can be divided into phenolics, carotenoids, alkaloids, phytosterols, nitrogen compounds, and sulfur. Among them, polyphenolics have undoubtedly received the most significant research. These are by-products of a plant's secondary metabolism and frequently affect its development, reproduction, and metabolism, giving fruit and vegetables their distinctive color. They also help protect the plant from bacteria and other parasites(Chen, Drew et al. 2021). Polyphenols present in fruit and vegetables exhibit antioxidant and anticarcinogenic properties. These natural bioactives contribute to the daily amount of fiber and are high in micronutrients (vitamins and minerals). Natural bioactive substances are organic substances that have significant effects on biological tissues(Chen, Drew et al. 2021). Thus, the small amounts of natural bioactives not only have nutritional value but also have the potential to be a prophylactic or therapeutic agent to prevent and treat various central and peripheral diseases. As a result, scientists have focused their efforts on developing safe and effective neuroprotective agents. Numerous categories of natural and synthetic neuroprotective agents have been reported. Synthetic neuroprotective agents, on the other hand, are thought to have higher adverse drug effects such as dry mouth, tiredness, drowsiness, sleepiness, anxiety or nervousness, difficulty balancing, and so on. As a result, researchers are now interested in researching natural bioactives that can act as safe neuroprotective agents.

Natural products, including antioxidants and anti-neuroinflammatory agents, have been proven to have neuroprotective effects. Compounds known as antioxidants can interact with free radicals and change them into harmless forms. Numerous studies have linked oxidative stress to the onset and progression of the disease, and antioxidants have been shown to be effective in preventing these effects. Antioxidants are divided into two categories based on how frequently they occur in nature: natural antioxidants and synthetic antioxidants, with the majority of synthetic antioxidants coming from natural sources(Chen, Drew et al. 2021).

The hydroxyl groups replaced on the aromatic rings of these phenolic and polyphenolic compounds, in particular, give them the ability to carry out their antioxidative action. Flavonoids, the most prevalent polyphenolic chemicals, have a wide spectrum of antioxidative effects on cancers, inflammation, and cell signaling caused by free radicals. It is not unexpected that several natural flavonoids, derivatives of flavonoids, and natural sources rich in flavonoids are being widely examined for the treatment of neurological diseases, given that this defective cell communication may cause many neurological diseases. Flavonoids- antioxidative abilities, which can limit the generation of free radicals by modifying the cell signaling pathways involved in the expression of antioxidant proteins, glutathione synthesis, and cell proliferation, are partially responsible for their neuroprotective effects(Chen, Drew et al. 2021). Non-flavonoids, the other type of phenolic compound, have slightly more variable structures than flavonoids. Non-flavonoids with high antioxidant activity include phenolic acids, tannins, lignans, stilbenes, quinones, coumarins, and curcuminoids, particularly phenolic acids. Dietary polyphenols have been shown in vitro and in vivo to prevent neuron damage and apoptosis by lowering ROS levels,

a major mechanism for reducing the oxidative stress involved in the onset and progression of neurological disease(Chen, Drew et al. 2021). Phenolic compounds and their natural sources have recently received a lot of attention for their antioxidant capacities as neuroprotective agents for better neurological disease management(Chen, Drew et al. 2021).

In general, the natural bioactives play a crucial role in the development and halting of a number of diseases, including cardiovascular conditions, cancer, diabetes, Alzheimer's disease, and chronic kidney disease, both when consumed as fresh food and when taken orally as supplements. These organic bioactive substances appear to have anti-inflammatory, antioxidant, and antibacterial activities and hypoglycemic, antihypertensive, cardioprotective, neuroprotective, and hepatoprotective qualities. Numerous substances have more than one of these effects. The growing research suggests that natural bioactives are becoming more widely accepted for the prevention and treatment of various ailments.

Many neurological diseases occur due to specific neuronal death or neurodegeneration in a particular region of the brain. Endogenous and exogenous natural and synthetic ligands have been shown to exert significant neurotoxicity. Paralytic shellfish toxins (PSTs) are a class of neurotoxic PSTs which can be further classified as hydrophilic or hydrophobic and further subdivided based on substituent side chains such as carbamate, sulfate, hydroxyl, hydroxybenzoate, or acetate. Each moiety then adds a different level of toxicity. Similarly, many cyanobacteria produce compounds with high toxicological activity. With regard to iatrogenesis (drug-indued neurotoxicity), Chemotherapeutics have shown to induce significant neuronal death. Chemotherapeutics have significantly improved the survival of

patients suffering from other common cancers like breast, prostate, and lung cancer. However, as a result of treatment, the patients experience cognitive impairment, which may last for many years after completion of the treatment due to neurotoxicity. 3-hydroxypterostilbene, has been shown to significantly affect dopaminergic and hippocampal neuronal growth by inducing apoptosis.

Summary:

Natural bioactive compounds are substances derived from natural sources like plants, animals, microorganisms. The chemical nature of natural products are attributed to pharmacological or toxicological effects on humans and animals. Pterostilbene a dimethyl analog of resveratrol exhibited the pharmacological activities like Neuro-protective activity, Antioxidant activity, Anti-inflammatory activity, Anti-lipidemic activity and Anti-fungal activity.3-Hydroxypterostilbene an active metabolite of pterostilbene have no studies on central nervous system and hepatic carcinoma. To Study the effect of 3-hydroxypterostilbene on central nervous system, HT-22 neurons and N-27 neurons were used and analysed by Cell viability (MTT assay) and Hydrogen peroxide was used as positive control. To study the effect on hepatic carcinoma, HepG2 cancer cells was used, and LS174T colon cancer cells were used as positive control. Celltiter gloassay was used for cell viability assay for HepG2 and LS174T cancer cells. Additionally for further Pharmacodynamic study, markers of oxidative stress, markers of apoptosis, markers of mitochondrial function in HT-22 neurons were studied. Moreover, Tyrosine hydroxylase activity and markers of apoptosis (Caspase-3 activity) in N27 neurons were studied.3-Hydroxypterostilbene dose-dependently and significantly increased caspase-3 activity in

HT-22 neurons without affecting Oxidative stress markers and Mitochondrial function markers and 3-hydroxypterostilbene significantly inhibited Tyrosine hydroxylase activity and enhanced Caspase-3 activity significantly in N-27 neurons.

Conclusion:

Like Chemotherapeutics,3-hydroxypterostilbene induced neurotoxicity (hippocampal and dopaminergic) by enhancing apoptosis through caspase-3 activation and inhibited Tyrosine hydroxylase activity.

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