

## Review on Vinpocetine

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### Abstract

Vinpocetine is a synthetic ethyl ester of apovincamine. It is extracted from the periwinkle plant. Vincamine is extracted from either the seeds of *Voacanga-Africana* or the leaves. Vinpocetine is an herbal supplement used to treat various neurological disorders such as Alzheimer's and Parkinson's disease. Vinpocetine has also anti-inflammatory, analgesics, antioxidant property and treat various thinking and memory problem. The drug has neuroprotective property thus it is used for memory impairment. Vinpocetine drug dilates blood vessels and promotes cerebral blood flow. Pharmacodynamics, Pharmacokinetic and adverse effects were discussed.

**Keywords:** Vincamine, neuroprotective, memory enhancement and cerebral blood flow *Voacanga-Africana*

### Introduction

Vinpocetine was prepared under the trade name cavinton in 1978<sup>[1]</sup>, vinpocetine widely used in Germany, Russia, Japan, Hungar for the treatment of the cerebrovascular related disorder. Vinpocetine is a semi-synthetic derivative obtained from vincamine alkaloid. Vincamine present in the aerial part of the vinca minor and plant belongs to the Apocynaceae family. Vinpocetine is approved by the European and British pharmacopoeias. Vinpocetine as well as vincamine are used in Europe, Japan and Mexico as a pharmaceutical agent for the treatment of cerebrovascular and cognitive disorders.<sup>[2]</sup> Catecholamine levels were similarly increased 4-6 hours following the administration of vinpocetine. The authors also reported an inhibition of phosphodiesterase enzyme (PDE) suggesting a

possible mechanism by which cerebral ATP levels seemed to be increased after administration of the compound.<sup>[3]</sup>

Modern lifestyle has raised life hope but also increase chronic harm full disease, therefore, increasing chronic Pharmaceutical usage, it is also called some time nootropic agent meaning cognition enhancer.

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An analgesic role for vinpocetine show that it inhibits neuronal tetrodotoxin-resistant NAV1.18 with intraperitoneal (I.P) sodium channel current-induced calcium influx with (I.P) administration of vinpocetine reducing acetic acid visceral nociception, which is potentiated by muscarinic, adrenergic, opioid receptor and blocked dependent on adenosine receptor. Vinpocetine drugs also inhibit formalin-induced paw flinching and inhibition of c-fos expression in the ipsilateral dorsal horn, when intraperineurally administered. It blocks neuropathic pain through retrograde axoplasmic transport of nerve growth factor.<sup>[4]</sup> Although vinpocetine is not a microtubule inhibitor and its chemical structure shows no resemblance to that of vincristine, we found that at adequate concentration, vinpocetine inhibits retrograde axoplasmic transport of nerve growth factor (NGF), as shown by radiochemical studies.<sup>[5]</sup>

Vincamine is widely used as a neuroprotective agent for the prevention and treatment of central nervous system disorder of cerebrovascular origin.<sup>[6]</sup> In the U.S. vinpocetine supplements are marketed as sports supplements, brain enhancers, and weight loss supplements.<sup>[7, 8]</sup>

Vinpocetine is easily cross the blood-brain barrier (BBB), the therapeutic effect of vinpocetine high-capacity protect the neuronal cell from cytotoxic effects of inflammation oxidative stress and ion influx. Although vinpocetine inhibits phosphodiesterase-1 (PDE-1) enzyme and anti-inflammatory effect present to be PDE-1 independent.<sup>[9]</sup>

Vinpocetine regulates the level of circulating TLRs in Parkinson's disease patients. Toll-like receptors (TLRs) are a class of proteins that play a key role in the innate immune system. Recent studies have shown that blocking TLR2 can reduce nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells. Therefore, TLRs provide promising candidates for the development of PD therapies. The findings that vinpocetine causes dilation of isolated cerebral arteries and improves the global cerebral blood flow suggest that cerebral circulatory effects may contribute to its Cerebral protective activity.<sup>[10, 11]</sup>

Vinpocetine uses during pregnancy condition may harm the baby or result in miscarriage [12], the neuroprotective effects of vinpocetine related to blocking effects on the excitotoxicity effects of glutamate and aspartate, and partly related to phosphodiesterase enzyme inhibition increases cerebral blood flow and decrease platelet aggregation.<sup>[13, 14]</sup>

#### Chemistry of vinpocetine

Ethyl-Apovincamine 22-oate (Ethyl-Apovincamate) is also known as vinpocetine,<sup>[15]</sup> Ethyl-

Apovincamate was first synthesized by Lo'rinicz et al. from alkaloid vincamine obtained from the leaves of Vinca.<sup>[16]</sup> The IUPAC Name of vinpocetine Eburnamenin-14-carboxylic acid ethyl ester and has molecular weight of 350.46g/mol, Formula: C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> (Fig. 1), it is marketed in Hungary, Japan and several other countries for the treatment of cerebral diseases originating from vascular or cerebral metabolic disturbances,<sup>[17]</sup> the drug improves the cerebral use of oxygen and protects the brain cells against ischemic anoxia.

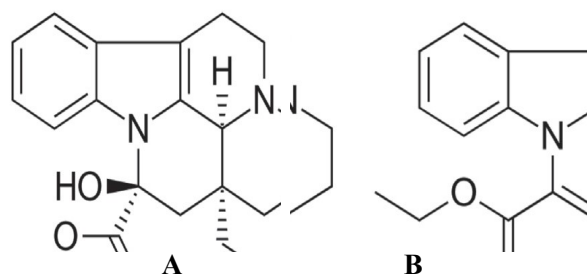


Fig. 1: A Vincamine B vinpocetine [18]

#### Marketed formulation of vinpocetin

There are the various formulation of vinpocetine was made various pharmaceutical company is given in the table, the recommended dose of vinpocetine is 15 to 30 mg in a day and sometimes increase the dose of vinpocetine to 40 Mg for special cases.

Table 1: Marketed formulation of vinpocetine

Brand Name	Pharmaceutical Company Name	Dosage Form
Neurovin	Micro Labs Limited	5,10 mg
Cogvin	Intas Pharmaceutical Limited	5 mg tablet
Vinpotin	MJ-Bio-Pharm Private limited	5mg/ tablet and

		5mg/ml injection
Vinpocetine	SRS Pharmaceutical	10,20,30 mg vial injection

**Mechanism of action**

Vinpocetine has many pharmacological and biochemical activity, including cerebral vasodilatation, enhancing the tolerance of cerebral tissue to hypoxia and ischemia insults, anticonvulsant property, inhibitory effects on (phosphodiesterase), improving hematological flow property and inhibitory thrombolytic aggregation.

The neuroprotective effect of vinpocetine promotes the selective inhibition of calcium calmodulin-dependent cGMP-PDE1, this inhibition may enhance intracellular cGMP level in vascular smooth muscle leading to reduced cerebrovascular resistance and increased cerebral blood flow This property is also responsible for neuroprotection.<sup>[19]</sup>It could be hypothesized that vinpocetine may be useful for the treatment of Rheumatoid Arthritis (RA) due to its well established anti-inflammatory effects. <sup>[20, 21]</sup> Furthermore, a recent study has revealed that vinpocetine also has an ant hyperglycemic effect, <sup>[22]</sup> vinpocetine has antioxidant activity, and it prevents reactive free radical generation which contributed to the reduction of high glucose-induced oxidative damage. <sup>[23]</sup>

**Pharmacology**

Vinpocetine has many pharmacological and biochemical action is given below.

**Inhibit the voltage-dependent sodium (Na<sup>+</sup>) channel-**Voltage-sensitive sodium channels (VSSC) play a fundamental role in the normal function of the CNS because they are responsible for the initiation and conduction of neuronal action potentials. Most of the energy demands coupled with the brainfunctional activity and used for ion transport and to restore the ionic gradients or degraded by excitation backto resting membrane potentials.<sup>[24]</sup>vinpocetine decreases DA and increased DOPAC in striatum isolated nerve endings, either under resting and under depolarized conditions.<sup>[25]</sup>

**Antioxidant effect of vinpocetine-**Oxygen-free radicals is a highly reactive chemical species generated in biologic systems during numerous

physiologic and pathophysiologic processes. In physiologic circumstances, they play a role in cellular metabolism and cellular-defense systems. On the other hand, a large amount of oxygen-free radicals is highly toxic for tissues and cells because they can oxidatively modify and damage a variety of biologic systems. <sup>[26]</sup>

**Epilepsy-**Vinpocetine is a potent inhibitor of the epileptic cortical activity induced by the convulsing agents, pentylenetetrazole and 4-aminopyridine in the guinea pig in vivo, also we have shown that vinpocetine inhibits the release of several neurotransmitters triggered by the entrance of Nab,<sup>[27]</sup>vinpocetine and carbamazepine, valproic acid, whose mechanism of action mainly involves an increase in GABA nergic transmission was unable to decrease presynaptic ionic channels permeability in a broad range of concentrations.<sup>[28]</sup>The involvement of brain pre-synaptic Na<sup>+</sup>channels in the mechanism of action of vinpocetine and carbamazepine is supported by the sensitivity of the increase in the internal concentration of Na<sup>+</sup> induced by 4-AP and veratridine depolarization to those anticonvulsants in cerebral isolated nerve endings.<sup>[29]</sup>The effects of two classic antiepileptic drugs (carbamazepine and phenytoin) a potential antiepileptic (vinpocetine) and a monoamine oxidase inhibitor (clorgyline) on the simultaneous changes (detected by HPLC) on Glue, Asp, dopamine, and DOPAC inside and outside striatal isolated nerve endings were investigated.<sup>[30]</sup>

**Alzheimer's and Related Dementias-**Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with cognitive and behavioral dysfunction. It is the leading cause of dementia in the elderly, <sup>[31]</sup>since dementia and particularly senile dementia of the Alzheimer type are a major and ever-increasing problem there is a strong need for therapeutic intervention. The clinical diagnosis of dementia is very difficult (especially beginning of disease not only in general medical practices but also in the hospital which provides the full range of modern diagnosis facility therefore essential for dementia so that careful evaluation of the patient made to ensure the homogeneity of the syndrome under-investigated.<sup>[32]</sup> Vinpocetine is a PDE1 inhibitor so that play an essential role in Alzheimer's,<sup>[33]</sup>it is well known that acetylcholine deficiency plays

an important role in the etiology of Alzheimer's disease. To study the effect of vinpocetine on acetylcholine (ACh) metabolism and assess its possible use in the therapy of Alzheimer's disease we have applied a model in which in a one-trial step-through passive avoidance task the memory functions of mice were impaired by scopolamine, an anticholinergic agent.<sup>[34]</sup>

**Ageing Process**-Vinpocetine has been shown in animal studies to possess cerebral activating properties. In humans, reports indicate that vinpocetine improves cognitive processes and enhances recovery from cerebral ischemia. Thus both the preclinical and clinical pharmacologic profiles indicate that vinpocetine may be a useful therapeutic agent for treating diseases characterized by cerebral impairments and cognitive or attention deficits.<sup>[35]</sup>

**Vinpocetine protects liver against ischemia-reperfusion injury**-Hepatic ischemia-reperfusion (IR) injury is an important clinical problem that complicates liver surgery and transplantation. The pathophysiology underlying hepatic IR injury is complicated, involving oxidative stress as well as inflammatory and apoptotic mechanisms. The neuroprotective effect of vinpocetine has been reported concerning IR injury in hippocampal neuronal cells both *in vivo* and *in vitro*, its role in protecting against IR injury in the liver.<sup>[36]</sup>

**Vinpocetine Improves Neuronal Plasticity**-Vinpocetine is an alkaloid extracted from the periwinkle plant and was tested as a neuronal plasticity enhancer and marketed as a "memory-booster". Vinpocetine treatment was shown long-term improve spatial memory in animal models and enhance performance on cognitive tests in humans. The cognitive enhancement function of vinpocetine comes from its inhibition of PDE type 1, which leads to an increase in cAMP and cGMP levels. These cyclic nucleotides can turn activate a series of kinases that phosphorylate the transcription factors cAMP response element-binding protein (CREB) and serum response factor (SRF), leading to the expression of plasticity-related genes.<sup>[37]</sup>

**Anti-inflammatory activity**-Vinpocetine is an inhibitor of phosphodiesterase type-1 (PDE1), which can lead to increases in cAMP and cGMP, thus initiating plasticity-related gene expression. Vinpocetine has a high affinity for the 18-kDa

Translocator protein (TSPO) which is a biomarker of activated microglia and inhibits microglial proliferation through the NF  $\kappa$ B/activator protein-1 (AP-1) pathway. It also suppresses the release of inflammatory factors. Vinpocetine suppressed the release of pro-inflammatory molecules by inhibiting the inhibitor of the IKK/NF- $\kappa$ B pathway after TNF-stimulation [38]. Progression of the inflammation after ischemia-reperfusion injury, inflammatory cytokines activates nuclear transcription factor (NF-B) through toll-like receptor 4 (TLR4). NF-B signal transduction pathways promote target gene activation and induce neuronal apoptosis and even necrosis ultimately aggravating the cerebral disease however it remains unclear whether vinpocetine also suppresses mucus overproduction.<sup>[39, 40]</sup>

**Vinpocetine inhibits the hearing loss induced by PTZ and Amikacin****PTZ (Pentylentetrazole)**-The auditory thresholds for 8 and 4 kHz tone frequencies were tested in all animals before the injection of PTZ and then 30 and 50 min after the injection of PTZ in the animals pre-injected with the vehicle or in the animals pre-injected with vinpocetine. PTZ in the animals pre-injected with the vehicle at the two-tone frequencies tested is lost in the animals pre-injected with vinpocetine. Vinpocetine alone (i.e. before the injection of PTZ) does not change the BAEP threshold.<sup>[41, 42]</sup>

**Amikacin**-Amikacin administered for 5 days at a dose of 450mg/kg/day markedly increased the auditory threshold for 4 and 8 kHz tone frequencies in guinea pigs. This threshold increase was established at day 40 and lasted for more than 5 months, suggesting that the Amikacin regimen used caused a permanent (or at least long-lived) hearing loss in the animals. The animals also receiving vinpocetine, in contrast, maintained their auditory threshold values before treatment until the end of the experiment.<sup>[43]</sup>

**Effect of Vinpocetine on Lipid Peroxidation**-Atherosclerosis is the major trigger of myocardial infarction and strokes the leading causes of morbidity and mortality in developed countries. Cholesterol deposition in the artery wall plays a critical role in atherosclerosis. The extent of lipid peroxidation was determined by measuring thiobarbituric acid reactive substances (TBARS) expressed as malondialdehyde (MDA) using the thiobarbituric acid assay (TBA). The amount of

TBARS formed was calculated using a molar coefficient of  $1.56 \times 10^5 \text{ mol}^{-1} \text{ cm}^{-1}$  and expressed as mole MDA/mg protein. The oxygen consumption was measured using a Clark-type electrode in a closed glass chamber equipped with magnetic stirring thermostatic at 30°C reactions were started by the addition of ascorbate-iron. The changes in O<sub>2</sub> tensions were recorded in a potentiometric chart recorder and the oxygen consumption calculated assuming an oxygen concentration of 230 nmol O<sub>2</sub>/ml. Vinpocetine and Trolox were introduced in the incubation medium before the addition of ascorbate-iron. Blank experiments, in the absence of synaptosomes were performed to evaluate the oxygen consumption rate induced by ascorbate/Fe<sup>2+</sup> itself.<sup>[44]</sup>

**Tinnitus/ Meniere's disease/ Visual Impairment-** Tinnitus are the phantom perception of sound in the absence of overt acoustic stimulation. It is well known that chronic tinnitus is difficult to treat though lots of modalities are used for treatment. Current possibilities for chronic tinnitus treatment vary from neuroprotective substances, calcium-channel blockers, corticosteroids glutamate agonists, and thrombolytic drugs to intravenous or Intraperitoneal lidocaine application vinpocetine (Cavinton) Pentoxifylline (Agapurin, Trental), or Piracetam infusions. Vinpocetine Benzodiazepines also may provide relief, especially for patients with concurrent depression. In one study 76% of patients taking alprazolam had a reduction in the loudness of their tinnitus, whereas only 5% of the placebo group showed benefits also been starting to be useful in treating Meniere's disease and in vision impairment.<sup>[45, 46]</sup>

**Vinpocetine effect on Parkinson's disease-** Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease that is characterized by the irreversible loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The most general clinical sign of PD is tremor; it is present in 80-92% of patients. Rigidity is a common symptom not only for PD. However, it can be noticed in 67-99% of patients with this disease.<sup>[47]</sup> It is widely used as a neuroprotective agent that improves blood circulation, oxygen uptake and glucose utilization by the brain. Vinpocetine has been used in brain disorders and treatment of the signs of aging it can help improve

cognitive function and short-term memory in both animals and humans.<sup>[48]</sup> In the brain from patients with PD an increased number of major histocompatibility complex (MHC) class II antigen [human leukocyte antigen-DR (HLA-DR)]-positive activated microglia which suggests an inflammatory process to occur in the brain in PD patients and the origin of cytokines most probably to be activated microglia.<sup>[49]</sup>

**Cardio protective activity of vinpocetine-** Cardiovascular diseases (CVD) is a common problem which is manifested by myocardial infarction due to deficient oxygen supply to cardiac muscles. Despite having a considerable amount of drugs available a search for better, safer, efficient and cost-effective drugs is always there. This study is a move in this direction. We have chosen vinpocetine a PDE1 inhibitor to assess its cardio protective role in this drug acute myocardial infarction (AMI) which is one of the most common diseases in recent years, has been affected by several adverse living conditions of advancing technology. Myocardial infarction occurs as a result of a sudden interruption of blood flow with thrombotic occlusion of the previously narrowed coronary artery due to atherosclerosis. Vinpocetine has been documented that it has powerful antioxidant, anti-inflammatory and free radical scavenger effects. Consequently, it is possible to say that vinpocetine has a positive effect on cardiac function.<sup>[50, 51]</sup>

#### **Pharmacokinetic of Vinpocetine**

In human studies vinpocetine is absorbed from the small intestine and its active metabolites apovincaminic acid absorbed from the stomach. The pharmacokinetics of vinpocetine and its main metabolite apovincaminic acid were studied in the aged. Vinpocetine was eliminated with a mean half-life of  $2.12 \pm 0.51$  h. Protein binding is about 86.6-±99.99%. The rate of vinpocetine absorption from the gastrointestinal tract is Rapid and peak plasma level is reached at about 1 hour after oral administration irrespective of dose food intake. Vinpocetine is more soluble in gastric pH (1.2) and intestinal PH (6.8). The vinpocetine is 1-2 hours and after 8-hour vinpocetine is eliminated from the body.<sup>[52-53]</sup>

#### **Adverse Effects**

Adverse effects of vinpocetine include flushing, nausea, dizziness, dry mouth, transient hypo- and

hypertension, headaches, heartburn and decreased blood pressure.<sup>[54,55]</sup> FDA stated 2019 warning that vinpocetine may cause a miscarriage or harm fetal development.<sup>[56]</sup> Vinpocetine has been implicated in one case in the induction of agranulocytosis serious condition in which granulocytes are markedly decreased. Some people have anecdotally noted that their continued use of vinpocetine reduces immune function. Commission E warned that vinpocetine-reduced immune function could cause apoptosis (cellular death) in the long term. Vinpocetine is dry mouth, transient hypotension, transient tachycardia, pressure-type headache and facial flushing. Slight reductions in both systolic and diastolic blood pressure with prolonged use of vinpocetine have been reported, as well as slight reductions in blood glucose.<sup>[57]</sup>

### Conclusion

Vinpocetine first introduced to the market in under the trade name cavinton in 1978 (chemical works of Gedeon Richter Ltd, Budapest, Hungary) is a widely used compound in the treatment of cerebrovascular disorders. Vinpocetine smart drugs and smart nutrients with a wide variety of effects. And uses various treatments such as cerebrovascular disorder neurodegenerative disorder such as Parkinson's Alzheimer's disease, ototoxicity, analgesic and anti-inflammatory activity, cardioprotective activity hepatoprotective activity. Tinnitus Meniere's disease Visual Impairment, antioxidant activity, epilepsy activity, in the United States America vinpocetinesupplements are marketed as sports supplements, brain enhancers, and weight loss supplements. Vinpocetine has very few side effects and it has good pharmacokinetic and pharmacodynamics activity it is the best nutrients or drug for age-related memory impairment.

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