

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

# Current Research in Pharmacology and Drug Discovery

journal homepage: [www.journals.elsevier.com/current-research-in-pharmacology-and-drug-discovery](http://www.journals.elsevier.com/current-research-in-pharmacology-and-drug-discovery)



## Promising effects of emoxypine and its succinate derivative in the management of various diseases-with insights on recent patent applications



Dhruv Sanjay Gupta, Siddhi Bagwe Parab, Ginpreet Kaur\*

Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, Shri Vile Parle Kelavani Mandal's Narsee Monjee Institute of Management Studies, Mumbai, 56, India

### ARTICLE INFO

#### Keywords:

Neuroinflammation  
Mitochondrial dysfunction  
Iron overload  
Mexidol  
Acute kidney injury  
Cerebroprotection

### ABSTRACT

Emoxypine and its succinate derivative share a common hydroxypyridine structure, which is similar to pyridoxine. These compounds have been utilized therapeutically and industrially, owing to the wide range of properties offered. This includes antihypoxic, neuroprotective and cardioprotective effects, along with pharmacokinetic benefits such as the ability to cross the blood brain barrier (BBB), owing to its relatively small size and low molecular weight. It was observed that emoxypine exhibited iron chelating property in vitro, indicating its usage as a promising therapeutic strategy in the management of neurodegenerative conditions such as Alzheimer's disease (AD), as well as hematologic disorders like thalassemia and hemochromatosis. In addition to this, it has been observed to exert a potent antioxidant effect, therefore, it may be considered for the amelioration of disorders resulting from free radical injury. Studies on its mechanism of action and implications on cellular and molecular levels would help to further the understanding of its benefits, as well as prospects for filing patents for novel applications. The primary focus of this review is to shed light on the broad spectrum of pharmacological properties offered by emoxypine and its succinate derivative, and to highlight the scope for an increased number of pre-clinical and clinical trials to assess its safety and efficacy. In addition to this, the highlights of this article include the recent patents filed and scope for novel applications of these agents.

### 1. Introduction

Emoxypine succinate is pyridoxine derivative (Manin et al., 2018), that finds its application most widely as an antioxidant ((Zor'kina et al., 1998a), followed by modulatory effect on receptors as a membranotropic agent (Rumyantseva et al., 2012). It has been observed to possess a wide range of therapeutic potentials, ranging from vascular effects such as anti-ischemic, cardioprotective and anti-atherogenic properties (Loznikova et al., 2014), to neurological effects like anti-convulsant, neuroprotective and nootropic effects (Volchegorskii et al., 2019a,b).

Its properties as a vascular agent have been extensively studied, demonstrating effects as a platelet aggregation inhibitor and retarder of blood clotting by activation of the prostaglandin-thromboxane system, or by modulating the activation and shape of the platelets (Loznikova et al., 2014; Krynytska et al., 2019). Smirnov and Kuzmin are credited as the originators of the drug, which is widely circulated in Russia under the brand name Mexidol and is being studied in other regions, on account of an increased interest in its properties. Owing to its Russian origin, approval was not obtained for its usage in the United States or Europe.

However, certain companies intend on engaging in screening of drugs such as emoxypine in globally accepted animal models for new diseases, filing new intellectual property rights and then progressing into an off level phase II trial in the country where approval is being sought (Smirnov, Kuz'min, and Kuznetsov, 2005).

Carrying out further research on the molecule and its derivatives would help to further our understanding of the spectrum of pharmacological actions, pharmacokinetic properties, and adverse effects, as well as possibilities for development of formulations using novel drug delivery systems, to overcome the barriers of traditional drug delivery. In addition to this, the broad range of effects of these agents could prove to be useful in combined administration with other drugs, mainly to exert a synergistic effect and to enhance the therapeutic potentials of these agents. This, in turn, may be employed for the management of a number of conditions, ranging from neurodegenerative, cardiovascular, ophthalmic and hematological complications (Voronina and Ivanova, 2019).

This review highlights the potential therapeutic properties of Emoxypine and the preclinical and clinical studies on the same. Also, the recent patent applications on the pharmacological properties of Emoxypine

\* Corresponding author.

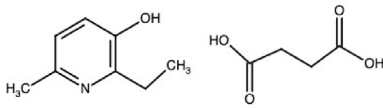
E-mail address: [ginpreet.aneja@gmail.com](mailto:ginpreet.aneja@gmail.com) (G. Kaur).

<https://doi.org/10.1016/j.crphar.2022.100121>

Received 24 March 2022; Received in revised form 25 July 2022; Accepted 26 July 2022

2590-2571/© 2022 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Table 1**  
General information on emoxypine succinate.

Structure	
Synonyms	Emoxypine succinate, Mexidol, Methylenehydropyridinol succinate, Mexiprim
IUPAC Name	Butanedioic acid, 2-ethyl-6-methylpyridin-3-ol
Molecular weight	255.26
Molecular formula	C <sub>12</sub> H <sub>17</sub> NO <sub>5</sub>
Elimination half-life	2–2.5 h
Melting point	170–172 °C

have been highlighted. The aim of this manuscript is to provide brief insight on the various pharmacological properties of Emoxypine and its molecular pathways, to boost the further research on this potential molecule.

## 2. Chemistry and SAR of emoxypine succinate

Emoxypine succinate (2-ethyl-6-methyl-3-hydroxypyridine) is a choline salt of succinic acid, derived from 3-hydroxypyridine and succinic acid (Table 1). (Voronina, 2012) Owing to its hydrophilic nature, 2-ethyl-6-methyl-1,3-hydroxypyridine has limited transport capacity to the nervous tissues and brain. Therefore, it is desirable to develop novel 3-hydroxypyridine derivatives, with increased lipophilicity, thereby increasing permeability across the blood brain barrier (BBB) (Biryukov, Dmitri Valerievich and POMYTKIN, Igor Anatolievich, n.d.). Experimental data shows that the 2-ethyl-6-methyl-3-hydroxypyridinium cation in emoxypine, in addition with the succinate ion (both of which are found in emoxypine succinate) exerts a combination effect. The succinate portion is responsible for a loss in the MAO-stimulating effect, while the 3-hydroxypyridine component brings about a marked reduction in the MAO-inhibiting activity (Volchegorskii et al., 2018). The presence of these moieties allows these agents to be considered as a highly promising therapeutic strategy in the management of metabolic diseases resulting from endothelial dysfunction. In addition to this, the membranotropic effects exerted by these molecules assist the maintenance of the viscosity of the lipid bilayer, thereby regulating key pharmacokinetic parameters (Burlakova et al., 1984). The succinate ion in the structure of emoxypine succinate shows an indirect prooxidant action. This activity is a result of the generation of hydrogen peroxide, which is the end-product of the mitochondrial oxidation of succinic acid, and is known to have a role in inducing free-radical oxidation (Shchulkin, 2018a). In terms of its chemical structure, emoxypine succinate is simultaneously a 3-hydroxypyridine and a succinic acid derivative (Volchegorskii et al., 2013).

## 3. Mechanism of action of emoxypine and its succinate derivative

Emoxypine succinate finds a wide application in the treatment of a variety of pathological conditions owing to its anti-inflammatory activity (Gubskii et al., 1999) and the ability to counteract stress-induced hypoxic conditions (Zor'kina et al., 1998a).

Experimental studies show the antinecrotic effects of Mexidol in skin ischemia. Administration of mexidol on an animal model of male albino rats (25 mg/kg, 3 days) showed a decrease in activity of the enzyme aspartate transaminase and creatine phosphokinase. Coupled with a decrease in cytolysis, the action of mexidol arrested the progression of skin necrosis. The target site for action of mexidol was observed to be the NADH-ubiquinone system (Galenko-Yaroshevskii et al., 2005).

Emoxypine succinate regulates the antioxidant defense system by increasing the activity of the enzyme catalase as well as glutathione peroxidase, resulting in the neutralization of hydrogen peroxide radicals. It shows a direct interaction with the lipophilic as well as water-soluble radicals present in the phospholipid membranes, and this activity may be employed in the protection of ischemic skin from secondary damage and the exertion of a dermatoprotective effect (Galenko-Yaroshevskii et al., 2005).

In addition to the anti-ischemic activity in the integumentary system, derivatives of emoxypine exert a wide range of pharmacological actions such as management of hypoxia (Luk'yanova et al., 1993), reduction of ATP loss in case of ischemia of the brain or myocardium and maintenance of oxidative phosphorylation (Luk'yanova et al., 1990; Ludmila D. Lukyanova and Kirova, 2015).

Administration of mexidol also decreased plasma ALT and AST levels significantly in the animal models being studied (Bushmina et al., 2018). Succinate containing derivatives of 3-hydroxypyridine, such as emoxypine succinate, are considered to be energetotropic substances (L. D. Lukyanova et al., 2009). The succinate component offers an energy-rich substrate, undergoing oxidation by the enzyme succinate dehydrogenase (SDH), present in the mitochondrial enzyme complex II (MEC II). In hypoxic or ischemic conditions, this oxidative process counteracts the reduction of mitochondrial enzyme complex I (MEC I), thereby maintaining the synthesis of ATP. In terms of mechanism of action, succinate derivatives are responsible for enhancing the flow of electrons between MEC I and MEC II, as well as directly interacting with the respiratory chain to raise the sensitivity of the process to malonate (Demchenko et al., 2008).

In an experiment conducted by Motin et al., on an animal model using outbred albino rats, emoxypine succinate was found to stimulate the respiratory activity of the brain samples, at a concentration of 5 mM succinate. The central beneficial action of mexidol may be mediated by ion channels containing glutamate- and GABA-ergic components, predominantly via suppression of ion currents via the NMDA receptor complex (Motin et al., 2012).

Mexidol exerts its membrane protective action by decreasing the viscosity of cell membranes. It aids the enhancement of ligand-receptor interactions by inducing allosteric changes in receptor conformation (Rumyantseva et al., 2012). Mexidol has been shown to increase binding interaction at GABA-benzodiazepine receptor complex (Iasnetsov et al., 2012). As an anxiolytic agent, Mexidol exerts a GABA-modulating action and may be used in the treatment of acute strokes, in conjunction with traditional anxiolytics (Androfagina et al., 2015). Also, mexidol was found to be the most efficient in mitigating PTZ-induced seizures. Therefore, mexidol exhibits neuroprotective action by inhibiting the generation reactive oxygen species (ROS) and Nitric oxide (NO) formation (Bashkatova et al., 2003). The anti-aggregant action is precipitated by the ability to prevent thrombosis in the microcirculatory bed, and also by activating GABAergic vasodilation mechanisms (Mirzoian et al., 2014). Emoxypine exerts a protective action by inhibiting generation of free radicals and blocking markers of inflammation such as cytosine. When used in therapeutic concentrations, it suppressed the aggregation of platelets (Loznikova et al., 2014).

Emoxypine has been reported to have retinoprotective properties, owing to the suppression of the enzyme phosphodiesterase, which affects the levels of ADP and ATP due to variations in the amounts of cyclic nucleotides (Voronina, 2012). In the experimental animal models used (chick embryos and rabbits), emoxypine was seen to have an inhibitory effect on angiogenesis, even at low concentrations (Sologub et al., 1992). This makes it useful in the treatment and management of hemophthalmia.

A predominant causative factor for ophthalmic degenerative diseases like Cataract and Glaucoma is the expression of lipid peroxidation. (Babizhayev et al., 2009) Emoxypine exerts an antioxidant action, as well as causes a reduction of pupillary diameter and intraocular pressure. This may be attributed to the action on the cholinergic

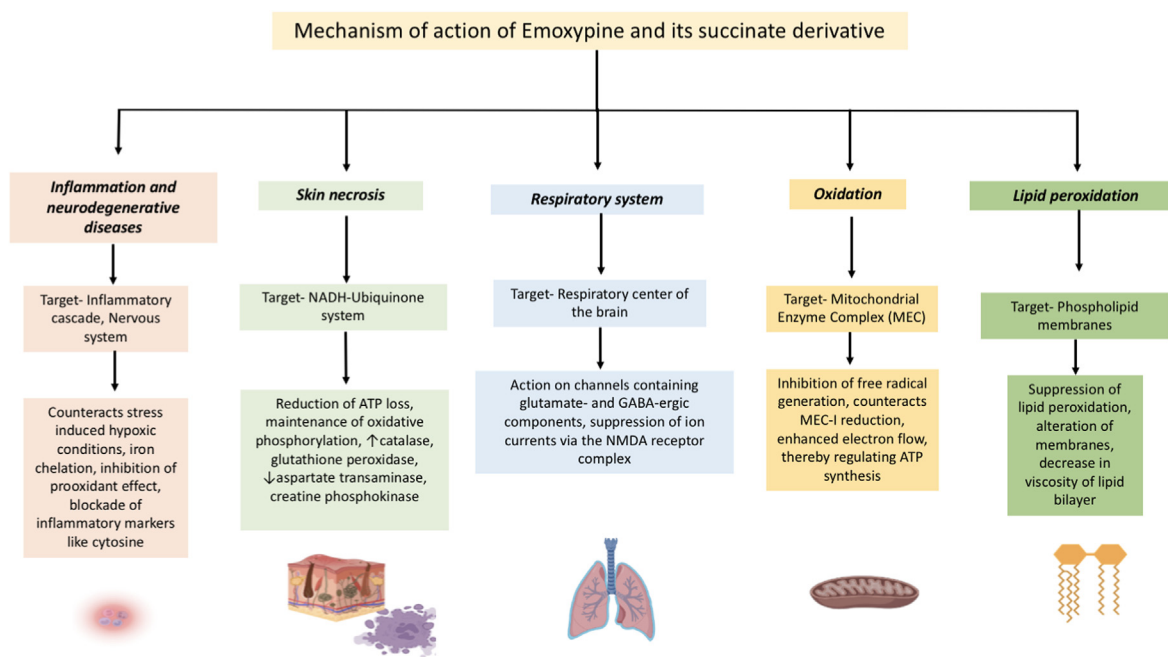


Fig. 1. An overview of the mechanism of action of Emoxypine and its succinate derivative.

**Table 2**

Pre-clinical studies of emoxypine and its succinate derivative.

Drug administered	Animal Specifications	Dose	Study duration	Study design	Results	Reference
Emoxypine	150 adult mongrel rats of both genders, weighing 180–240 g	6.25, 12.5 and 25 mg/kg	Open field test and forced swim test (25 min and 30 min after drug administration).	The duration of behavioural despair was assessed on the basis of the duration of immobility of the animals.	24% decrease in immobility while swimming, 53% decrease in orientational activity of rats.	<a href="#">Volchegorskii et al. (2019)</a>
Mexidol	310 adult mongrel rats of both genders, weighing 180–220 g	12.5, 25, 50 mg/kg)	17 days	Alloxan monohydrate induced model of Diabetes mellitus	1. Anxiolytic properties 2. Non-selective increase in movement into open arms of the Elevated Plus Maze 3. Mild tranquilising action	<a href="#">Volchegorskii et al. (2019)</a>
Mexidol solution	Rat liver	196 Mm Mexidol solution, diluted 25-fold	Experiments were performed in five repeat series.	Enzyme substrate reaction test on the rat liver homogenate	Anti-depressant and thymoanaleptic activity.	<a href="#">(Volchegorskii et al., 2018, 3)</a>
Mexidol	Non-linear albino rats (aged 4–6 months), albino mice (aged 2–3 months)	100 mg/kg i.p.	–	Acute Kidney Injury model for rat and mice	1. Significant improvement in the kidney injury. 2. Increased the chances of Survival	<a href="#">Shchudrova et al. (2018)</a>
Emoxypine	Isolated rat hearts	10 mg/kg, i.v.	Studied over 15 min	Intra-coronary administration of Emoxypine	1. Increase in collateral coronary blood flow without altering the systemic arterial blood pressure. 2. Decrease in perfusate outflow in rat hearts, indicating the coronary dilating action of emoxypine.	<a href="#">Gatsura and Smirnov (1993)</a>

structures of the sphincter muscles, or via alteration of the lipid membranes (Yanovskaya, Shtol'ko, and Burlakova, 1993).

Emoxypine and its succinate derivative have shown promising effects in the management of several neurodegenerative diseases (such as Alzheimer's, Parkinson's, and Multiple sclerosis), and the proposed mechanism of action was the inhibition of prooxidants in the mitochondria (Litvinenko et al., 2019). Additionally, the phosphorylated and unphosphorylated derivatives of Mexidol were seen to exert iron-chelating properties. This property may be used in the management of neurodegenerative disease conditions, as well as hematological disorders

characterized by an excessive iron build-up in the body (Imam et al., 2017). Fig. 1. Illustrates an overview of the mechanism of action of Emoxypine and its succinate derivative.

#### 4. Pharmacological actions of emoxypine and its succinate derivative

Emoxypine and its succinate derivative offer a wide range of pharmacological actions, which have been established based on results obtained from experimental studies. These agents have been employed in

**Table 3**  
Clinical studies of Emoxypine succinate (Mexidol)-.

Drug administered	Subjects	Study duration	Study design	Results	Reference
Mexidol (500 mg/day, intravenously) followed by Mexidol forte (250 mg/3 times a day)	318 patients with chronic brain ischemia	Intravenous administration of Mexidol for 2 weeks, followed by oral administration of Mexidol Forte for 60 days	Multicentre, randomised, placebo-controlled trial	<ol style="list-style-type: none"> <li>1. Good safety profile for the usage of Mexidol</li> <li>2. Significant improvement of symptoms in comparison to the placebo group</li> <li>3. Improvement in the evaluation tests administered, such as CGI scale, Beck anxiety scale and Tinetti scale.</li> </ol>	(Finberg, 2014)
Mexidol (500 mg/day), administered intravenously followed by Mexidol forte (125 mg/3 times a day)	150 patients in acute and early stages of hemispheric ischemic stroke	10 days of intravenous administration, followed by 8 weeks of oral supplementation	Randomised, double-blind, multi-centre, placebo controlled trial	<ol style="list-style-type: none"> <li>1. Established efficacy in long-term therapy</li> <li>2. Reduction in depressive symptoms</li> <li>3. Improved cognitive functioning and mobility</li> <li>4. Prospects for usage in patients with diabetes mellitus in addition to ischemic stroke.</li> </ol>	Stakhovskaya et al. (2020)
Mexidol (500 mg, intravenously) followed by administration of Mexidol forte (250 mg, thrice a day)	50 patients with carotid IS	Intravenous administration of Mexidol for 14 days, followed by dosage of Mexidol forte for 60 days	Controlled clinical trial	<ol style="list-style-type: none"> <li>1. Improved memory</li> <li>2. Positive results for evaluating parameters such as NIHSS score and MOCA test</li> <li>3. Improved cognitive functioning</li> <li>4. Arrested progression of spatial impairment.</li> </ol>	Strelnikova et al. (2020)
Mexidol (500 mg/day, intravenously) for 2 weeks, followed by oral administration of Mexidol forte (250 mg/3 times a day)	60 patients with chronic cerebral ischemia	Intravenous administration of Mexidol for 14 days, followed by dosage of Mexidol forte for 60 days	Clinical trial	<ol style="list-style-type: none"> <li>1. Enhanced cognitive functioning</li> <li>2. Improved motor and emotional functioning</li> <li>3. Good patient adherence.</li> </ol>	Chukanova and Chukanova (2019)
Mexidol (500 mg/day, intravenously) for 2 weeks, followed by oral administration of Mexidol forte (250 mg/3 times a day)	56 patients with chronic cerebral ischemia, due to hypertensive and atherosclerotic complications	Intravenous administration of Mexidol for 14 days, followed by dosage of Mexidol forte for 60 days	Clinical trial	<ol style="list-style-type: none"> <li>1. Enhanced cognitive and motor functioning</li> <li>2. Reduction in symptoms</li> <li>3. Marked improvement of emotional functioning.</li> </ol>	Kutashov and Ulyanova (2019)
Mexidol (5 ml, intravenously) and Mexidol + Vinpocetine (5 ml of each, intravenously), diluted in 200 ml saline	90 patients with autonomic dysfunction	10 days	Clinical trial	<ol style="list-style-type: none"> <li>1. Exertion of a cerebroprotective activity</li> <li>2. Improved circulation</li> <li>3. Observation of a vegetostabilising effect</li> <li>4. Combinatorial therapy aided the exertion of a synergistic effect.</li> </ol>	Dyakonova and Makerova (2018)
Mexidol (125mg/3 times a day), p.o.	87 patients with chronic cerebral ischemia (CCI)	3 weeks	Randomised, controlled trial	<ol style="list-style-type: none"> <li>1. Reduced symptoms of asthenia</li> <li>2. Improvement of cognitive functioning</li> <li>3. Improved autonomic functioning.</li> </ol>	(PovarninaYu. et al., 2017)
Mexidol (100 mg) and Mexidol (300 mg)+ Picamilon (150 mg)	94 patients with primary open angle glaucoma	14–21 days	Randomised, controlled trial	<ol style="list-style-type: none"> <li>1. Enhanced velocity of blood flow to the retinal artery</li> <li>2. Improvement of visual acuity and other visual indices</li> <li>3. Exertion of a synergistic effect by combinatorial therapy.</li> </ol>	(Edmondson, 2014)
Mexidol (375 mg/day)	70 patients with panic disorder	2 weeks	Randomised, controlled trial	<ol style="list-style-type: none"> <li>1. Reduced frequency of episodes of anxiety and insomnia</li> <li>2. Improved autonomic functioning</li> <li>3. Enhancement of the overall quality of life of subjects.</li> </ol>	Kursakov and Remizevich (2013)
Mexidol (300 mg/day, intravenously)	103 patients with open angle glaucoma	2 weeks	Single-blind, placebo controlled, randomised trial	<ol style="list-style-type: none"> <li>1. Improvement of visual field and acuity</li> <li>2. Increased retinal photosensitivity</li> <li>3. Improved blood flow to the retina.</li> </ol>	(Volchegorskii et al., 2012)

Legend: CGI scale- Clinical global impression scale, 7-point scale used in pharmaceutical trials to determine the efficacy of treatment in psychiatric patients and to indicate improvement; Beck anxiety scale- 4-point scale used to assess the degree of physical and cognitive anxiety over the course of treatment, and the scores may be used to grade the severity of anxiety; Tinetti scale- 3-point scale used to assess mobility, by evaluating parameters such as gait, step continuity and walking time; NIHSS Score- National Institutes of health stroke scale, indicating the severity of a stroke based on sensory evaluation; MOCA test- Montreal Cognitive Assessment, used to assess cognitive functioning based on parameters such as attention span, memory and concentration.



the management of neurological conditions, owing to their potent antioxidant properties and advantages over conventionally used agents. In addition to this, they have been observed to exert protective effects on the renal and cardiovascular systems, as well as in the amelioration of disease conditions resulting from oxidative stress.

#### 4.1. Neurological actions

Oxidative stress has been linked with neurodegenerative disorders like Alzheimer's, Parkinson's and multiple sclerosis (Barnham et al., 2004). Terpene phenols, such as emoxypine, exert antioxidant properties and are hence neuroprotective (Shchulkin, 2018b). Emoxypine and its derivatives have shown promising results in pre-clinical and clinical trials, conducted to assess their efficacy in the management of a variety of neurological conditions, as outlined in Tables 2 and 3.

The antidepressant action of Emoxypine has been widely studied in animal models. In an experimental setup designed by Volchegorskii et al., the effect of the drug in the alleviation of immobility was examined. The onset of immobility was studied by subjecting the rats to forced swimming, and it was noticed that a single dose of 3-hydroxypyridine derivatives was responsible for a significant reduction in the immobility. In addition to this, emoxypine was responsible for a marked decrease in the period of behavioral distress. From the experimental evidence, it was concluded that emoxypine exerts a potent anti-depressant effect in the animal model studied. In place of emoxypine, using emoxypine succinate showed an even greater decrease in the immobility and behavioral distress period. On conducting an open-field test, it was observed that the succinate derivative exerted a lower sedative effect as compared to traditional anti-depressants (Volchegorskii et al., 2019a,b). In a pre-clinical study undertaken by Zamoshchina et al. to evaluate the effects of Mexidol on lactate levels in a rat model subjected to darkness and light, it was observed that the drug increased the activity and performance of the animals in environments such as forced swimming and monitoring of the physical activity of the rats under conditions of light exposure and deprivation. Mexidol prevented a sharp rise in the lactate levels following physical activity. The results obtained from a forced swimming test indicated an improvement in the physical performance and cognitive functioning of the test animals (Zamoshchina et al., 2018).

As for the mechanisms of action proposed for the thymoanaleptic effects of 3-hydroxypyridine derivatives, it was observed that these derivatives were able to stimulate the release of serotonin, followed by suppressing its uptake by synaptosomes present in the rat brain. This demonstrates a shared mechanism of action with traditional antidepressants as they both act as selective serotonin uptake inhibitors (SSRIs) (Volchegorskii et al., 2016). Other possible mechanisms of action may be the insulin-potentiating activity of drugs such as emoxypine succinate (permitting usage for the management of depression that may occur alongside Diabetes Mellitus), its anti-glucocorticoid activity and antagonism for NMDA receptors, hence preventing excessive stimulation (Volchegorskii et al., 2014).

The usage of emoxypine succinate has been proposed as an alternative approach for the treatment of anxious-depressive disorders (ADD) that may occur alongside diabetes mellitus (DM). Traditional approaches employed for the treatment of ADD have certain drawbacks, such as the decrease in thymoanaleptic activities of some selective serotonin reuptake inhibitors and varying effects of conventionally used antidepressants on carbohydrate metabolism. In addition to this, they may exert certain undesirable side effects, such as suppression of neurological and cognitive functioning due to their central myorelaxant action (Volchegorskii et al., 2019a,b). Studies have shown the insulin potentiating activities of 3-hydroxypyridine derivatives, alongside their antihypoxic actions, neuroprotective effects (Volchegorskii et al., 2014) and the ability to increase tolerance to glucose loading (Volchegorskii et al., 2019a,b). In a recent clinical trial conducted to assess the effects of Mexidol in the management of DM in conjunction with neurological complications, it was observed that the drug significantly improved cognitive functioning,

sleep patterns and led to an overall stabilization of biochemical parameters. According to research findings, Mexidol (75 days of therapy) can be used as an adjunctive medication for patients with diabetes. (Pugacheva, 2022).

In a study conducted by Deviatkina et al., pretreatment with emoxypine succinate before induction of conditions of immobilization stress showed positive effects in the regulation of glycolysis. Based on the monitoring of glucose levels in the brain and peripheral organs, it was observed that the administration of the drug facilitated the favoring of pyruvate, which is a more preferred substrate for the oxidation process (Deviatkina et al., 2004). In another study undertaken by Volchegorskii et al., derivatives of 3-hydroxypyridine, such as emoxypine and its succinate derivative, showed promising in vitro results, chiefly an improved glucose tolerance owing to the exertion of an antioxidant effect. The data obtained from this study indicates the potentials of these compounds in the management of conditions arising from an impaired glucose tolerance and sensitivity to insulin (Volchegorskii et al., 2011).

Monoamine oxidase (MAO) is a flavin-containing enzyme, with two known forms (MAO-A and MAO-B) (Youdim, 1971). MAO-A is chiefly responsible for the deamination of neurotransmitters such as serotonin and adrenaline, while MAO-B is responsible for the metabolism of monoamines (Finberg, 2014). Hydrogen peroxide, generated as a by-product of the reactions of MAO, results in the onset of oxidative stress on excessive production (Edmondson, 2014). This causes free-radical damage to lipids, proteins and nucleic acids (Leibovitz and Siegel, 1980). Emoxypine and its derivatives have been shown to exert potent MAO inhibiting activity in vitro, indicating its usage as a selective inhibitor of MAO. This points to the possibility of employing these compounds as a treatment strategy in the management of a variety of diseases resulting from oxidative stress induction, as previously discussed (TorshtinYu. et al., 2017).

Alzheimer's disease (AD) is a progressive neurological disorder, characterized by the prevalence of amyloid beta plaques and neurofibrillary (TAU) tangles in the cerebral cortex, resulting in the loss of neuronal connections. It occurs most commonly in individuals over 65 years of age (Matthews et al., 2019), and results in a gradual decline in cognitive and mental functioning in affected individuals. Recent advancements in research have found the deposition of amyloid plaques to be linked to excessive accumulation of iron (Smith et al., 1997). Notwithstanding the crucial role played by elemental iron in the regulation of homeostatic physiological processes like oxygen transportation, iron consumption beyond a threshold accelerates neurodegeneration via activation of inflammatory pathways (Tang et al., 2018). Emoxypine succinate, a potent antioxidant and iron chelator, has been proposed as a novel line of treatment for AD (Imam et al., 2017). Relevant data from in-vitro studies has supported its usage as an iron chelator. This characteristic enables the iron ion scavenging activity, thereby arresting the generation of superoxide radicals (Riabchenko et al., 2010).

Clinical studies have reported that the chronological administration of Mexidol (intravenous or intramuscular followed by oral drug delivery) is effective in the treatment of neurological disorders including neurodegenerative diseases, diabetic polyneuropathy, infectious neuropathies, endovascular surgery and spinal dystrophy. (Gromova et al., 2018).

In addition to this, the usage of Mexidol has also been proposed for the management of neurological disorders linked with addiction. It has been proposed as a treatment strategy for addiction linked with the abuse of alcohol and narcotic drugs, and further research must be undertaken to highlight its applications in the management of neurological and cognitive deficits associated with addictive disorders (Shamrey et al., 2020).

#### 4.2. Protective action on the renal system

Acute kidney injury (AKI) manifests itself as an independent cause of mortality (Rewa and Bagshaw, 2014), and may also be seen as a co-morbidity in several diseases (Pereira et al., 2012). In a study conducted by Shchudrova et al. to study the renoprotective effects of

Mexidol in conjunction with organospecific peptides, an animal model of non-linear white rats was used. AKI was induced by several methods, and it was observed that a therapy of Mexidol and peptides showed a survival rate of 100% in case of rhabdomyolysis-induced ischemia-perfusion AKI in the experimental group. This line of therapy also showed promising results in ethylene glycol-induced AKI over a short time duration. Among the compounds studied, it was observed that a combination of endothelial lipase blocking (EDL) peptides and mexidol had the highest success rate in preventing the death of the animals (Shchudrova et al., 2018).

The main mechanisms of pathogenesis of AKI include damage of proximal tubular cells, oxidative stress, apoptosis, and ischemia, to name a few. A combination therapy of organospecific peptides and Mexidol helps exert a cytoprotective effect, thereby countering these pathogenic mechanisms. A few possible explanations for the exertion of this activity include increased kidney resistance, inhibition of progression of the disease and protection of nephrons (Shchudrova et al., 2018).

#### 4.3. Effects on the cardiovascular system

With reference to the cardioprotective effects exerted, the efficacy of 3-hydroxypyridine derivatives was studied in rat models in a trial conducted by Gatsura et al. Emoxypine was seen to increase collateral coronary blood flow without significantly altering the systemic arterial blood pressure (Gatsura and Smirnov 1993). It was seen to have a greater dilatatory effect in comparison with other derivatives studied (Loznikova et al., 2014). In a separate study conducted by Konorev et al., emoxypine was seen to produce anti-anginal effects by initiating repair processes in the myocardial infarct zone (Konorev et al., 1990).

In a preclinical research conducted to assess the application of mexidol in the management of cardiotoxicity in case of acute pancreatitis using a model of adult mongrel dogs, it was observed that the drug boosted the antioxidant defense system, reduced lipid accumulation in the heart tissues and prevented the occurrence of cardiotoxicity (Polozova, 2018). Also, a preclinical study conducted by Konopljia et al. to monitor the effects of alcohol administration post occurrence of pancreatitis, thereby affecting the structure and functionality of erythrocytes. Mexidol administration helped in the stabilization of the erythrocytes and limited the damage to the cardiovascular system (Konopljia et al., 2017).

#### 4.4. Antioxidant and anti-hypoxic properties

Emoxypine succinate has been observed to control the expression of free radicals, alongside in vitro inhibition of prooxidative enzymes. In addition to a potent antioxidant effect, the presence of the succinic acid moiety supports enzymatic functioning in conditions of cell hypoxia, and increases the affinity of the molecule to receptors such as GPR91 as demonstrated in a trial conducted by Schulkin et al. (Shchulkin, 2018c). In order to further evaluate the antihypoxic effects of emoxypine succinate, a clinical trial conducted by Kulai and Kovalchuk assessed the effects of its concurrent administration with hyperbaric oxygen. Results showed a positive effect in the control of the acute phase of hypoxia, along with minimization of neurological implications of oxygen starvation (Kulai et al., 2018). The antioxidant effects of emoxypine succinate have also been employed in the designing of oral formulations and toothpastes, and its usage as the active ingredient has been observed to exert antioxidant effects in the oral cavity (Udyanskaya et al., 2020).

In a clinical trial conducted by Abramenko et al. to evaluate the efficacy of varying strengths of the compound administered by different routes (500 mg-intravenous/intramuscular injections and 250 mg-coated tablet doses), a marked improvement in cognitive and motor functioning of patients suffering from chronic cerebral ischemia was observed. In addition to this, a good patient compliance to the drug therapy was also observed (Abramenko and V, 2020). In a similar study, administration of similar dosing of emoxypine succinate over two months was associated with an improvement in indices used to evaluate ischaemic stroke, such as

the Rankin scale and Bartel Index (Loskutnikov et al., 2020). A pre-clinical study carried out by Kolesnikova et al. to evaluate the role of oxidative stress in reduced glucose uptake showed the protective effects of Mexidol in the management of oxidative stress, and regular therapy of this antioxidant was associated with improved glucose transportation (Kolesnikova et al., 2017).

In a separate study conducted by Lukyanova et al., emoxypine succinate was observed to exert an anti-ischemic action in the rat brain and ischemic myocardium by increasing the coupling of oxidative phosphorylation and mitochondrial respiration. This resulted in an increased synthesis of succinic acid, resulting in the activation of the succinate oxidase pathway in the event of hypoxic conditions. This shows the promising effects of the drug in the management of metabolic disorders linked with the onset of hypoxic conditions (L. D. Lukyanova et al., 2009). Intraperitoneal administration of Mexidol (100 mg/kg) for a week exerted an anti-ischemic effect in a rat model of ischemic stroke induced by transient occlusion of the middle cerebral artery. Thus, indicating the usage of this drug in the management of hypoxic conditions and cognitive deficits arising from neurological conditions (PovarninaYu. et al., 2017).

Emoxypine has also demonstrated certain benefits in the management of hypoxia, showing positive results in case of administration to hypoxia-sensitive rats. An increase in survival time was observed as a result of dosage, in a study conducted by Gatsura et al. (Gatsura and Smirnov 1993). With reference to high-stress conditions in animal models (such as sudden exposure to new environments, bright lights, or introduction of animals to open spaces), doses of emoxypine succinate between 50 and 100 mg/kg of body weight showed promising results in eliminating fear-like symptoms in the test animals (Zorkina et al., 1998b). As opposed to traditional anxiolytic medications, it possesses the advantage of not causing sedation or myorelaxation (Voronina et al., 2007). These results present the possibility of its usage for humans to produce similar effects in stress conditions.

In an *in-silico* research setup to assess the antioxidant potentials of Mexidol, it was observed that the drug initiated the chelation of copper ions, leading to the formation of Cu (II) complexes that were relatively more difficult to reduce than the element in its free form. Mexidol was observed to be mediated by suppressing the rate of reduction by ascorbic acid and oxygen, that function as the two main agents responsible for its reduction within biological systems. This supports its usage as an antioxidant agent, owing to its ability to scavenge hydroperoxyl radicals, thereby reducing oxidative stress (Hoa et al., 2022).

## 5. Contraindications and ADRs

Various clinical studies have been conducted to monitor the safety and efficacy levels of Mexidol (at a dosage of 500 mg, intravenously, for 14 days) and Mexidol Forte (250 mg, orally, 3 times a day for two months). Results from these trials have shown good patient adherence, observation of the desired clinical efficacy on completion of the dosage regime, and a low possibility of adverse drug reactions (ADRs) (Shchepankevich et al., 2021). In addition to this, a safety profile of concurrent intravenous and oral administration of Mexidol (in doses of 500 mg and 750 mg respectively) in the management of ischemic conditions has also been established. The results from the study indicate promising clinical efficacy and a well-established safety assurance of the combinatorial therapy (Kataeva et al., 2020). Stakhovskaya et al. studied the effects of Mexidol administration emphasizing more on the possibility of side effects. It was observed that there was no statistically significant difference (no adverse events reported) between the treated and the placebo control group, indicating low possibilities for the occurrence of side-effects (Stakhovskaya et al., 2020). However, as newer potentials of the molecule continue to emerge, there is a need to conduct a greater number of clinical trials, to monitor the long-term effects of drug administration, as well as studies conducted in conjunction with other agents to report contraindications, if any.

Table 4

Recent Patents of Emoxypine and its succinate derivative-.

Sr. No	Application year	Patent number	Title	Therapeutic application	Dosage	Inventors	References
1.	2019	RU2721289C1	Method for modelling haemorrhagic stroke in rats	Neuroprotective property, reduced mortality.	50 mg/kg, administered i.p. 1 h before surgery.	Nesterov Arkadij Vitalevich et al.	(Nesterov Arkadij Vitalevich, Kolesnichenko Pavel Dmitrievich, and Pokrovskij Mikhail Vladimirovich 2020)
2.	2019	RU2706692C1	New sulfur derivatives of 2-ethyl-6-methyl-hydroxypyridine	Protective antioxidant effect, preventing developing of hepatotoxicity in case of oxidative stress.	50 mg/kg in a HepG2 liver cell culture.	Borovikov Vitalij Eduardovich	<a href="#">Borovikov Vitalij Eduardovich (2019)</a>
3.	2019	RU2714193C1	Method of treating inflammatory or dystrophic eye diseases	Anti-inflammatory, anti-oedema, Tissue regeneration	50 mg	Bratko Vladimir Ivanovich et al.	(Bratko Vladimir Ivanovich, Arbeneva Natalya Sergeevna, and Kulakov Andrej Valerevich 2020)
4.	2019	WO2020191502A1	Use of emoxypine and derivatives thereof for treating kidney disorders and inflammatory bowel disease	Anti-hypoxic effects, Treatment or prophylaxis for kidney disorders and inflammatory bowel disease	160 mg/kg	Williams Mark	(Williams Mark)
5.	2019	RU2705040C1	Method for preventing the progression of primary open-angle glaucoma	Improvement in hydrodynamic indices of the eye, improvement in state of visual fields, decrease in Becker coefficient.	Emoxipine 1%, i.m.	Makogon Svetlana Ivanovna et al.	(Makogon Svetlana Ivanovna, Makogon Aleksandr Sergeevich, and Momot Andrej Pavlovich 2019)
6.	2018	RU2684783C1	Antioxidants composition suitable for oral administration in therapy of inflammatory process in lungs	Anti-inflammatory, antioxidant	5% solution of Mexidol, administered i.v.- twice a day	Mischenko Natalya Petrovna et al.	(Mishchenko Natalya Petrovna, Fedoreev Sergej Aleksandrovich, and Vasileva Elena Andreevna 2019)
7.	2018	RU2686462C1	Antioxidant anti-inflammatory preparation for animals	Decrease in serum C-reactive protein and erythrocyte sedimentation rate, decrease in WBC count. antioxidant action	Compositions with varying percentages of emoxypine succinate- 10 to 25%	Kireev Ivan Valentinovich et al.	(Kireev Ivan Valentinovich, Orobets Vladimir Aleksandrovich, and Denisenko Tatyana Sergeevna 2019)
8.	2018	RU2709614C1	Method of treating encephalopathy	Nootropic action, reduction of neurological deficits and improvement of cortico-subcortical connections.	2 ml of 5% Mexidol	Lure Arman Zhenisovich	<a href="#">Lure Arman Zhenisovich (2019)</a>
9.	2017	RU2677190C1	Method for treating pathology of total tear secretion in patients with rheumatoid arthritis	Restoration of normal tear production, prevention of dry eye syndrome.	1% solution of Emoxypine administered 3 times a day	Ponomareva Ekaterina Yurevna et al.	(Ponomareva Ekaterina Yurevna, Rudneva Larisa Fedorovna, and Ponomareva Mariya Nikolaevna, 2019)
10.	2017	RU2661861C1	Method for treatment of chronic mechanical trauma of the oral mucosa in patients suffering with insulin-dependent diabetes mellitus	Anti-inflammatory, antioxidant, inhibition of lipid peroxidation	5% solution of Mexidol applied to the area of injury (for 5 days, twice daily for 2 min)	Zharkova Inna Vasilevna et al.	(Zharkova Inna Vasilevna, Kabirova Milyausha Fauzievna, and Gerasimova Larisa Pavlovna 2018)
11.	2017	RU2662324C1	Agent with pancreas and hepatoprotective activity for parenteral administration	Reduced mortality in the animal model, hepatoprotective effect	100 mg/kg/day	Yasnetsov Vladimir Viktorovich et al.	(Yasnetsov Vladimir Viktorovich, Tsublova Elena Gennadevna, and Yasnetsov Viktor Vladimirovich 2018)
12.	2017	RU2670609C1	Intranasal pharmaceutical composition of 2-ethyl-6-methyl-3-oxypyridine	Neuroprotective action, increase in efficacy accompanied by reduction in the therapeutic dose.	0.2 mg/kg	Borovikov Vitalij Eduardovich et al.	<a href="#">Borovikov Vitalij Eduardovich and Pomytkin Igor Anatolevich (2018)</a>
13.	2013	WO201313778A1	Solid dosage form having neuroprotector, antiamesic, antioxidant, antihypoxic, and anti-schaemic activity	Neuroprotective, anti-amnesic, antioxidant, antihypoxic and anti-ischemic activity. May be used to treat acute cerebrovascular accidents, neurotic disorders, and withdrawal effects.	31g of Mexidol administered i.p. for seven days.	Chelyaeva Anastasia Gennadevna	(Chelyaeva Anastasia Gennadevna)

Legend: i.p.- Intraperitoneally, i.v.- Intravenous, i.m.- Intramuscular.

## 6. Recent patents on emoxypine and its succinate derivative

Numerous significant studies on the broad spectrum of pharmacological properties offered by emoxypine and its derivatives have carried out by researchers in Russia. Over time, studies have been conducted in other nations as well, to evaluate the therapeutic activities, efficacy, and safety profiling of these compounds. As a result, these compounds have been granted patents for inventions based on a variety of actions, including anti-amnesic, antioxidant, antihypoxic, anti-ischemic, antidepressant, anti-anxiety, and cerebroprotective properties. Table 4 summarizes a comprehensive list of current patents on emoxypine and its succinate salts from the year 2013–2019, their applications, inventors, and patent holders.

## 7. Challenges and future perspectives

Emoxypine, along with its various salt forms (with dicarboxylic acids such as succinic, maleic, malonic and adipic acids) offers a wide range of pharmacological and therapeutic benefits (Manin et al., 2018). Of these, the most widely used derivative, emoxypine succinate (Mexidol), has been extensively studied to assess its applications in the management of retinopathies, cardioprotective and neuroprotective effects, as well as anti-depressant and anxiolytic properties. Emoxypine was also observed to show limited effects as an anti-hypoxic, making it useful in the management of ischemic conditions and oxidative stress (Sinitiskii et al., 2021). Several pre-clinical and clinical studies have indicated its potentials as a novel agent for the alleviation and management of a wide spectrum of disease conditions.

A primary challenge with regards to the usage of emoxypine and its derivatives is the limited nature of studies conducted to establish the efficacy and safety of these compounds. This is mainly due to the sparse nature of studies conducted outside its country of origin, resulting in fewer experimental trials being undertaken in other countries. In the recent years, several patents have been filed for its usage in human and veterinary medicine. This drug finds its widest application in Russia and is included in the essential medicines list for the management of various conditions, primarily neurological. In terms of global approval, Algonon Pharmaceuticals, a clinical stage pharmaceutical development company, is seeking approval for emoxypine usage in Canada. While it is used in certain countries as a nootropic supplement owing to its antioxidant properties, it has not been approved for medical purposes (Algonon Pharmaceuticals 2019). Moving forward, an increased number of studies in accordance with regulatory guidelines would further the understanding of the properties of these molecules, as well as approaches that may be adopted to improve the delivery and safety profile of these agents.

Owing to its relatively small size and membrane modulating properties, emoxypine is gaining popularity as a primarily orally delivered drug molecule (Shchulkin, 2018a). This drug is most commonly administered in the form of tablets or injections (i.e., intravenous, or intramuscular administration). As the molecule is explored further, designing of nano formulations for improved bioavailability and drug delivery could be considered, to overcome drawbacks such as its nature and solubility profile. In addition to this, carrying out a greater number of studies would help in furthering the understanding of the interactions of emoxypine and its derivatives with other compounds, which would be beneficial in the understanding of drug-drug interactions, any possible adverse effects, and the possibilities of concurrent administration of these agents with other compounds (of synthetic as well as natural origin).

### CRedit authorship contribution statement

**Dhruv Sanjay Gupta:** Writing – original draft. **Siddhi Bagwe Parab:** Writing – original draft, Writing – review & editing. **Ginpreet Kaur:** Visualization, Writing – original draft, Supervision, Writing – review & editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Ginpreet Kaur reports financial support was provided by DEPARTMENT OF SCIENCE AND TECHNOLOGY, Science and Engineering Research Board, India.

## Acknowledgement

The authors acknowledge the financial support received by the core research grant of DST SERB, Government of India (CRG/2020/003316). The authors are also thankful to Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's NMIMS for providing the infrastructural facilities.

## References

- Abramenko, Yu, V., 2020. 'Results of the sequential use of mexidol and mexidol Forte 250 in patients with chronic cerebral ischemia'. *Zhurnal neurologii i psikiatrii im. S.S. Korsakova* 120 (3), 59. <https://doi.org/10.17116/jnevro202012003259>.
- Androfagina, O.V., Kuznetsova, T.V., Svetkina, A.A., 2015. 'Mexidol in the rehabilitation of patients in the acute ischemic stroke'. *Zhurnal neurologii i psikiatrii im. S.S. Korsakova* 77. <https://doi.org/10.17116/jnevro201511512277-79>.
- Babizhayev, Mark A., Ya, Aron, Bunin, 2009. 'Lipid peroxidation in open-angle glaucoma'. *Acta Ophthalmol.* 67 (4), 371–377. <https://doi.org/10.1111/j.1755-3768.1989.tb01617.x>.
- Barnham, Kevin J., Colin, L., Masters, Bush, Ashley I., 2004. 'Neurodegenerative diseases and oxidative stress'. *Nat. Rev. Drug Discov.* 3 (3), 205–214. <https://doi.org/10.1038/nrd1330>.
- Bashkatova, Valentina, Narkevich, Victor, Vitskova, Galina, Vanin, Anatoly, 2003. 'The influence of anticonvulsant and antioxidant drugs on nitric oxide level and lipid peroxidation in the rat brain during pentylenetetrazole-induced epileptiform model seizures'. *Prog. Neuro Psychopharmacol. Biol. Psychiatr.* 27 (3), 487–492. [https://doi.org/10.1016/S0278-5846\(03\)00037-X](https://doi.org/10.1016/S0278-5846(03)00037-X).
- Biryukov, Dmitri Valerievich and Pomytkin, Igor Anatolevich. n.d. SUBSTITUTED 3-HYDROXYPYRIDINES AND PHARMACEUTICAL COMPOSITIONS THEREOF. <https://patents.google.com/patent/WO2009078746A1/en>.
- Borovikov Vitalij Eduardovich, 2019. New sulfur derivatives of 2-ethyl-6-methyl-hydroxypyridine. RU-2706692-C1. <https://patentimages.storage.googleapis.com/c3/36/e7/322811fbcd4c51/RU2706692C1.pdf>.
- Borovikov Vitalij Eduardovich and Pomytkin Igor Anatolevich, 2018. Intranasal pharmaceutical composition of 2-ethyl-6-methyl-3-oxypyridine. RU-2670609-C1. <https://patentimages.storage.googleapis.com/d9/39/52/c4a9cd1d95555f/RU2670609C1.pdf>.
- Burlakova, E.B., Kairane, Ch B., Molochkina, E.M., Khokhlov, A.P., 1984. '[Changes in external membrane lipids of the mouse liver mitochondria and kinetic parameters of membrane-bound monoaminoxidase in vivo and in vitro]'. *Vopr. Med. Khim.* 30 (1), 66–72.
- Bushmina, Olga, Dolgareva, Svetlana, Konoplya, Alexander, Loktionov, Aleksey, 2018. 'Pharmacological correction of metabolic disorders in experimental acute pancreatitis on the background of chronic alcohol intoxication'. *Res. Results Pharmacol.* 4 (4), 9–19. <https://doi.org/10.3897/rpharmacology.4.31594>.
- Chukanova, E.I., Chukanova, A.S., 2019. Efficacy and safety of the drug mexidol FORTE 250 as part of sequential therapy in patients with chronic ischemia of the brain. *Zhurnal neurologii i psikiatrii im. S.S. Korsakova* 119 (9), 39. <https://doi.org/10.17116/jnevro201911909139>.
- Demchenko, E., Iu, N.V., Kulakova, T.A., Semiglazova, A.B., Golovacheva, E.V., Borodulina, Udut, V.V., 2008. '[Metabolic effects of mexidol in complex treatment of chronic brain ischemia]'. *Eksp. Klin. Farmakol.* 71 (6), 13–15.
- Deviatkina, T.A., Vazhnichaia, E.M., Lutsenko, R.V., 2004. '[The effect of mexidol on the process of glycolysis in rats under acute stress conditions]'. *Eksp. Klin. Farmakol.* 67 (4), 47–49. PMID: 15500047.
- Dyakonova, E.N., Makerova, V.V., 2018. Mono- and combination therapy with the mexidol in young patients with cerebral angiodystonia. *Zhurnal Neurologii i Psikiatrii Im. S.S. Korsakova* 118 (8), 52. <https://doi.org/10.17116/jnevro201811808152>.
- Edmondson, Dale, 2014. 'Hydrogen peroxide produced by mitochondrial monoamine oxidase catalysis: biological implications'. *Curr. Pharmaceut. Des.* 20 (2), 155–160. <https://doi.org/10.2174/13816128113190990406>.
- Finberg, John P.M., 2014. 'Update on the pharmacology of selective inhibitors of MAO-A and MAO-B: focus on modulation of CNS monoamine neurotransmitter release'. *Pharmacol. Ther.* 143 (2), 133–152. <https://doi.org/10.1016/j.pharmthera.2014.02.010>.
- Galenko-Yaroshevskii, V.P., Bagmetova, E.N., Fil'chukova, I.A., Sidel'nikov, A. Yu, Popkov, V.A., Gorelashvili, A.S., Antelava, N.A., Sukoyan, G.V., 2005. 'Antihypoxic and antinecrotic effect of mexidol in skin ischemia'. *Bull. Exp. Biol. Med.* 139 (2), 202–206. <https://doi.org/10.1007/s10517-005-0248-8>.
- Gatsura, V.V., Smirnov, L.D., 1993. 'Cardioprotective properties of some synthetic antioxidants'. *Pharmaceut. Chem. J.* 26 (11–12), 795–802. <https://doi.org/10.1007/BF00767648>.



- Gromova, O.A., Torshin, I. Yu, Stakhovskaya, L.V., Pepelyaev, E.G., Semenov, V.A., Nazarenko, A.G., 2018. 'Experience with mexidol in neurological practice'. *Zhurnal Nevrologii i psikiatrii im. S.S. Korsakova* 118 (10), 97. <https://doi.org/10.17116/jnevro201811810197>.
- Gubskii, Iu I., Goriushko, A.G., Vistunova, I.E., Kurapova, T.N., Sachenko, L.G., Danilenko, V.F., 1999. '[Antiradical and antioxidant properties of nonsteroidal anti-inflammatory agents—derivatives of pyridinecarboxylic acid]'. *Ukrains'kyi Biokhimichnyi Zh.* 71 (5), 85–89.
- Hoa, Nguyen Thi, Van Bay, Mai, Mechler, Adam, Vo, Quan V., 2022. 'Theoretical insights into the antiradical activity and copper-catalysed oxidative damage of mexidol in the physiological environment'. *Royal Soc. Open Sci.* 9 (1), 211239. <https://doi.org/10.1098/rsos.211239>.
- Iasnetsov, V.V., Prosvirova, E.P., Tsublova, E.G., Vik, V., Iasnetsov, Motin, V.G., Karsanova, S.K., 2012. '[Comparative studies of antihypoxic, neuroprotective and analgesic action of succinate-containing drugs]'. *Aviakosmicheskaja Ekologicheskaja Meditsina Aerosp. Environ. Med.* 46 (6), 41–45.
- Imam, Mustapha, Zhang, Shenshen, Ma, Jifei, Wang, Hao, Wang, Fudi, 2017. 'Antioxidants mediate both iron homeostasis and oxidative stress'. *Nutrients* 9 (7), 671. <https://doi.org/10.3390/nu9070671>.
- Kataeva, N.G., Zamoshchina, T.A., Svetlik, M.V., 2020. 'Effectiveness and safety of mexidol Forte 250 in the sequential therapy in patients with chronic ischemia'. *Zhurnal Nevrologii i psikiatrii im. S.S. Korsakova* 120 (11), 59. <https://doi.org/10.17116/jnevro202012011159>.
- Kolesnikova, L.I., Kolesnikov, S.I., Korytov, L.I., Suslikova, M.I., Darenskaya, M.A., Grebenkina, L.A., Kolesnikova, L.R., 2017. 'Oxidative stress as a mechanism of reduced glucose absorption under conditions of immobilization stress'. *Bull. Exp. Biol. Med.* 164 (2), 132–135. <https://doi.org/10.1007/s10517-017-3941-5>.
- Konopljia, A.I., Litvinova, E.S., Sunyaykina, O.A., Bushmina, O.N., Harchenko, A.V., Konopljia, A.A., 2017. 'Disorders in structural-functional properties of erythrocytes in experimental acute destructive pancreatitis of alcohol etiology and their correction'. *Biomed. Khim.* 63 (6), 527–532. <https://doi.org/10.18097/PBMC20176306527>.
- Konorev, E.A., Iu Polumiskov, V., Avilova, O.A., Golikova, A.P., 1990. '[Emoxipin in reperfusion of ischemic myocardium in dogs: effects on infarct size and plasma creatine kinase activity]'. *Biulleten Eksp. Biol. Meditsiny* 110 (9), 252–254.
- Krynyska, Inna, Marushchak, Mariya, Holovatiuk, Liudmyla, Shkrobot, Leonid, Sokhor, Natalia, Stepas, Julia, 2019. 'Features of leukocytes' apoptosis and emoxypine succinate efficacy in case of combined trauma of the chest and both thighs in rats'. *Bangladesh J. Med. Sci.* 18 (2), 244–251. <https://doi.org/10.3329/bjms.v18i2.40693>.
- Kulai, N.S., Yu, E., Kovalchuk, 2018. 'Assessment of the efficacy of mexidol in the combination with hyperbaric oxygen in acute ischemic stroke'. *Zhurnal Nevrologii i psikiatrii im. S.S. Korsakova* 118 (3), 69. <https://doi.org/10.17116/jnevro20181183269-72>.
- Kursakov, E.S., Remizevich, R.S., 2013. 'The effect of mexidol in the combination with antidepressants on sleep disturbance in young patients with panic disorder'. *Zhurnal Nevrologii i Psikiatrii Imeni S.S. Korsakova* 113 (2), 33–38.
- Kutashov, V.A., Ulyanova, O.V., , and, 2019. 'The study of the efficacy and safety of Mexidol and Mexidol Forte 250 in patients with chronic cerebral ischemia'. *Zhurnal Nevrologii i Psikiatrii Imeni S.S. Korsakova* 119 (12), 89–92. <https://doi.org/10.17116/jnevro201911912289>.
- Leibovitz, B.E., Siegel, B.V., 1980. 'Aspects of free radical reactions in biological systems: aging'. *J. Gerontol.* 35 (1), 45–56. <https://doi.org/10.1093/geronj/35.1.45>.
- Litvinenko, I.V., Krasakov, I.V., Bisaga, G.N., Skulyabin, D.I., Poltavsky, I.D., 2019. 'Current concepts in the pathogenesis of neurodegenerative diseases and treatment strategies'. *Neurosci. Behav. Physiol.* 49 (4), 399–405. <https://doi.org/10.1007/s11055-019-00746-8>.
- Loskutnikov, M.A., Domashenko, M.A., Vakin, T.M., Trushina, I.A., Konstantinov, V.I., Proskuryakova, O.S., Shchukina, E.P., 2020. 'The trial of the efficacy and safety of sequential therapy with mexidol Forte 250 in acute and early recovery stages of hemispheric ischemic stroke'. *Zhurnal Nevrologii i psikiatrii im. S.S. Korsakova* 120 (10), 22. <https://doi.org/10.17116/jnevro202012010122>.
- Loznikova, S.G., Sukhodola, A.A., Shcharbina, N. Yu, Shcharbin, D.G., 2014. 'The effects of magnesium, acetylsalicylic acid, and emoxypine on platelet aggregation'. *Biophysics* 59 (6), 900–903. <https://doi.org/10.1134/S0006350914060098>.
- Lukyanova, Ludmila D., Kirova, Yulia I., 2015. 'Mitochondria-Controlled signaling mechanisms of brain protection in hypoxia'. *Frontiers in neuroscience* 9 (october). <https://doi.org/10.3389/fnins.2015.00320>.
- Lukyanova, L.D., Germanova, E.L., Tsybina, T.A., Chernobaeva, G.N., 2009. 'Energetic effect of succinate-containing derivatives of 3-hydroxypyridine'. *Bull. Exp. Biol. Med.* 148 (4), 587–591. <https://doi.org/10.1007/s10517-010-0771-0>.
- Luk'yanova, L.D., Romanova, V.E., Chernobaeva, G.N., Lukinykh, N.V., Smirnov, L.D., 1990. 'Features of the antihypoxic action of mexidol associated with its specific effect on energy metabolism'. *Pharmaceut. Chem. J.* 24 (8), 532–535. <https://doi.org/10.1007/BF00766466>.
- Luk'yanova, L.D., Atabaeva, R.E., Yu, S., Shepeleva, 1993. 'Antihypoxic effects of some 3-hydroxypyridine derivatives in isolated rat myocardium'. *Bull. Exp. Biol. Med.* 115 (4), 384–386. <https://doi.org/10.1007/BF00850908>.
- Lure Arman Zhenisovich, 2019. Method of treating encephalopathy. RU2709614C1. <http://patentimages.storage.googleapis.com/aa/06/d1/62e7938191b619/RU2709614C1.pdf>.
- Manin, Alex N., Voronin, Alexander P., Drozd, Ksenia V., Churakov, Andrei V., Perlovich, German L., 2018. 'Pharmaceutical salts of emoxypine with dicarboxylic acids'. *Acta Crystallogr. C Struct. Chem.* 74 (7), 797–806. <https://doi.org/10.1107/S2053229618007386>.
- Matthews, Kevin A., Xu, Wei, Gaglioti, Anne H., Holt, James B., Croft, Janet B., Mack, Dominic, McGuire, Lisa C., 2019. 'Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 Years'. *Alzheimer's Dementia* 15 (1), 17–24. <https://doi.org/10.1016/j.jalz.2018.06.3063>.
- Mirzoian, R.S., Gan'shina, T.S., Khaïlov, N.A., Gnezdilova, A.V., Maslennikov, D.V., Kurdiymov, I.N., Lebedeva, M.A., Gorbunov, A.A., 2014. '[Cerebrovascular pharmacology of separate and combined vascular pathology of brain and heart]'. *Eksp. Klin. Farmakol.* 77 (3), 3–8.
- Motin, V.G., Iasnetsov, V.V., Zabozaev, A.A., Karsanova, S.K., Iasnetsov, V.V., 2012. '[Electrophysiological study of the mechanism of mexidol action]'. *Eksp. Klin. Farmakol.* 75 (1), 3–7.
- Pereira, Mariana B., Dirce, M.T., Zanetta, Regina, C.R.M., Abdulkader, 2012. In: Emmanuel, A. (Ed.), 'The Real Importance of Pre-existing Comorbidities on Long-Term Mortality after Acute Kidney Injury', vol. 7. Burdmann. PLoS ONE, e47746. <https://doi.org/10.1371/journal.pone.0047746>, 10.
- Pharmaceuticals, Algenon, August 2019. 'Algenon pharmaceuticals announces emoxypine (NP-178), a top selling drug in Russia, as its lead drug for inflammatory bowel disease'. Newswire distribution network. Algenon Pharmaceuticals Announces Emoxypine (NP-178), a Top Selling Drug in Russia, as Its Lead Drug for Inflammatory Bowel Disease (blog), 2. <https://www.globenewswire.com/news-release/2019/08/02/1896228/0/en/Algenon-Pharmaceuticals-Announces-Emoxypine-NP-178-a-Top-Selling-Drug-in-Russia-as-its-Lead-Drug-for-Inflammatory-Bowel-Disease.html>.
- Polozova, E.I., 2018. 'Preventive therapy with mexidol in toxic damage to the heart'. *Khirurgiya. Zhurnal Im. N.I. Pirogova* 4 (71). <https://doi.org/10.17116/hirurgia2018471-76>.
- Povarnina, P., Yu, Volkova, A.A., Gudasheva, T.A., Seredenin, S.B., 2017. 'Comparison of the pharmacological effects of dimeric dipeptide nerve growth factor mimetic GK-2 and mexidol on the model of ischemic stroke in rats'. *Bull. Exp. Biol. Med.* 164 (2), 173–176. <https://doi.org/10.1007/s10517-017-3951-3>.
- Pugacheva, E.L., 2022. 'Efficacy of mexidol in patients with type 2 diabetes mellitus with neurological complications'. *Zhurnal Nevrologii i psikiatrii im. S.S. Korsakova* 122 (5), 84. <https://doi.org/10.17116/jnevro202212205184>.
- Rewa, Oleksa, Bagshaw, Sean M., 2014. 'Acute kidney injury—epidemiology, outcomes and economics'. *Nat. Rev. Nephrol.* 10 (4), 193–207. <https://doi.org/10.1038/nrneph.2013.282>.
- Riabchenko, N.I., Riabchenko, V.I., Ivannik, B.P., Dzikovskaia, L.A., Sin'kova, R.V., Grosheva, I.P., Degtiareva, E.S., Ivanova, T.I., 2010. '[Antioxidant and prooxidant properties of the ascorbic acid, dihydroquercetin and mexidol in the radical reactions induced by the ionizing radiation and chemical reagents]'. *Radiatsionnaya Biol. Radioecologia* 50 (2), 186–194.
- Rumyantseva, S.A., Fedin, A.I., Sokhova, O.N., 2012. 'Antioxidant treatment of ischemic brain lesions'. *Neurosci. Behav. Physiol.* 42 (8), 842–845. <https://doi.org/10.1007/s11055-012-9646-3>.
- Shamrey, V.K., Kurasov, E.S., Nechiporenko, V.V., Kolchev, A.I., Tsygan, N.V., 2020. 'Possibilities of using mexidol in the complex therapy of mental disorders'. *Zhurnal Nevrologii i psikiatrii im. S.S. Korsakova* 120 (5), 160. <https://doi.org/10.17116/jnevro2020120051160>.
- Shchepankevich, L.A., Nikolaev, YuA., Taneeva, E.V., Pervuninskaya, M.A., Shchepankevich, M.S., 2021. 'The efficacy and safety study of mexidol and mexidol FORTE 250 in patients with chronic cerebral ischemia'. *Zhurnal Nevrologii i psikiatrii im. S.S. Korsakova* 121 (10), 32. <https://doi.org/10.17116/jnevro202112110132>.
- Shchudrova, T.S., Zamorskii, I.I., Korotun, O.P., 2018. 'Evaluation of A renoprotective potential of organospecific peptides under the conditions of acute kidney injury of different etiology'. *J. Educ. Health Sport* 31 (8), 221–227. <https://doi.org/10.5281/ZENODO.1188278>, 1.
- Shchulkin, A.V., 2018a. 'A modern concept of antihypoxic and antioxidant effects of mexidol'. *Zhurnal Nevrologii i psikiatrii im. S.S. Korsakova* 118 (12), 87. <https://doi.org/10.17116/jnevro201811812287>.
- Shchulkin, A.V., 2018b. 'A modern concept of antihypoxic and antioxidant effects of mexidol'. *Zhurnal Nevrologii i psikiatrii im. S.S. Korsakova* 118 (12), 87. <https://doi.org/10.17116/jnevro201811812287>.
- Shchulkin, A.V., 2018c. '[A modern concept of antihypoxic and antioxidant effects of mexidol]'. *Zhurnal Nevrologii i psikiatrii Imeni S.S. Korsakova* 118 (12. Vyp. 2), 87–93. <https://doi.org/10.17116/jnevro201811812287>.
- Sinitskii, A.I., Kochkina, O.T., Grobovoi, S.I., 2021. 'Influence of 2-ethyl-6-methyl-3-hydroxypyridine on the functional state of rat liver mitochondria. In: Vitro'. *Pharmaceutical Chemistry Journal*, vol. 55, pp. 6–10. <https://doi.org/10.1007/s11094-021-02362-8>, 1.
- Smirnov, L.D., Kuz'min, V.I., Yu, V., Kuznetsov, 2005. 'Synthesis of 3-hydroxy-6-methyl-3-hydroxy-2-(2-Phenylethyl)Pyridines and their sulfur-containing amino and hydroxymethyl derivatives'. *Chem. Heterocycl. Compd.* 41 (8), 1013–1018. <https://doi.org/10.1007/s10593-005-0270-9>.
- Smith, M.A., Harris, P.L.R., Sayre, L.M., Perry, G., 1997. 'Iron accumulation in alzheimer disease is a source of redox-generated free radicals'. *Proc. Natl. Acad. Sci. USA* 94 (18), 9866–9868. <https://doi.org/10.1073/pnas.94.18.9866>.
- Sologub, A.A., Akberova, S.I., Ziangirova, G.G., 1992. 'Emoxipine as an inhibitor of angiogenesis. Biulleten Eksp. Biol. Meditsiny 114 (12), 620–622.
- Stakhovskaya, L.V., Mkhitaranyan, E.A., Tkacheva, O.N., Ostroumova, T.M., Ostroumova, O.D., 2020. In: Korsakova, S.S. (Ed.), 'Efficacy and Safety of Mexidol across Age Groups in the Acute and Early Recovery Stages of Hemispheric Ischemic Stroke (Results of Additional Sub-analysis of a Randomized Double Blind Multicenter Placebo-Controlled Study, vol. 120. Parallel Groups Trial EPICA)'. *Zhurnal Nevrologii i Psikiatrii Im*, p. 49. <https://doi.org/10.17116/jnevro202012008249>, 8.
- Strelnikova, I.A., Svetkina, A.A., Androfagina, O.V., 2020. 'The efficacy and safety of mexidol Forte 250 as part of long-term sequential therapy in patients with carotid

- stroke. *Zhurnal Nevrologii i Psikiatrii Im. S.S. Korsakova* 120 (3), 54. <https://doi.org/10.17116/jnevro202012003254>.
- Tang, Mingzhu, Chen, Zhe, Wu, Di, Chen, Linxi, 2018. 'Ferritinophagy/Ferroptosis: iron-related newcomers in human diseases'. *J. Cell. Physiol.* 233 (12), 9179–9190. <https://doi.org/10.1002/jcp.26954>.
- Torshin, I., Yu, Gromova, O.A., Sardaryan, I.S., Fedotova, L.E., 2017. 'A comparative chemoreactome analysis of mexidol'. *Zhurnal nevrologii i psikiatrii im. S.S. Korsakova* 117 (1. Vyp. 2), 75. <https://doi.org/10.17116/jnevro20171171275-84>.
- Udyanskaya, I.L., Slonskaya, T.K., Yankova, V.G., Romanchenko, I.A., Chernykh, A.A., Lodina, A.A., 2020. 'Toothpastes of the «mexidol dent» line — parapharmaceuticals with stable Antioxidative activity'. *Stomatologiya (Mosc.)* 99 (2), 45. <https://doi.org/10.17116/stomat20209902145>.
- Volchegorskii, I.A., Rassokhina, L.M., Miroshnichenko, I. Yu, Mester, K.M., Novoselov, P.N., Astakhova, T.V., 2011. 'Effect of pro- and antioxidants on insulin sensitivity and glucose tolerance'. *Bull. Exp. Biol. Med.* 150 (3), 327–332. <https://doi.org/10.1007/s10517-011-1134-1>.
- Volchegorskii, I.A., Pravdin, E.V., Uzlova, T.V., 2013. '[Effect of 3-oxypyridine and succinic acid derivatives on endometrial leucocyte infiltration and lipid peroxidation in recrudescence of inflammatory diseases of the uterus and its appendages]'. *Eksp. Klin. Farmakol.* 76 (3), 13–18.
- Volchegorskii, I.A., Iu Miroshnichenko, I., Rassokhina, L.M., Faizullin, R.M., 2014. '[Insulin potentiating and antidepressant effects of 3-oxypyridine and succinic acid derivatives]'. *Eksp. Klin. Farmakol.* 77 (5), 6–9.
- Volchegorskii, I.A., Miroshnichenko, I. Yu, Rassokhina, L.M., Malkin, M.P., Faizullin, R.M., Pryakhina, K.E., Kalugina, A.V., 2016. 'The antidepressant actions of 3-hydroxypyridine and succinic acid derivatives in experimental studies'. *Neurosci. Behav. Physiol.* 46 (6), 677–681. <https://doi.org/10.1007/s11055-016-0296-8>.
- Volchegorskii, I.A., Sinitskii, A.I., Miroshnichenko, I. Yu, Rassokhina, L.M., 2018. 'Effects of 3-hydroxypyridine and succinic acid derivatives on monoamine oxidase activity. In: *Vitro*'. *Pharmaceutical Chemistry Journal*, vol. 52, pp. 26–29. <https://doi.org/10.1007/s11094-018-1760-2>, 1.
- Volchegorskii, I.A., Miroshnichenko, I. Yu, Rassokhina, L.M., 2019a. 'Acute antidepressant effects of derivatives of 3-hydroxypyridine and succinic acid in experiments on rats'. *Neurosci. Behav. Physiol.* 49 (4), 495–501. <https://doi.org/10.1007/s11055-019-00761-9>.
- Volchegorskii, I.A., Miroshnichenko, I. Yu, Rassokhina, L.M., Faizullin, R.M., Pryakhina, K.E., 2019b. 'Anxiolytic and antidepressant actions of emoxypine, reamberin, and mexidol in experimental diabetes mellitus'. *Neurosci. Behav. Physiol.* 49 (1), 136–141. <https://doi.org/10.1007/s11055-018-0706-1>.
- Voronina, T.A., 2012. '[Mexidol: the spectrum of pharmacological effects]'. *Zhurnal Nevrologii i Psikiatrii Imeni S.S. Korsakova* 112 (12), 86–90.
- Voronina, T.A., Ivanova, E.A., 2019. 'Combined administration of mexidol with known medicines'. *Zhurnal nevrologii i psikiatrii im. S.S. Korsakova* 119 (4), 115. <https://doi.org/10.17116/jnevro2019119041115>.
- Voronina, T.A., Iasnetsov, V.V., Smirnov, L.D., Molodavkin, G.M., Iasnetsov, V.V., Larentsova, L.I., Shashkov, V.S., 2007. '[Mexidol effects in extreme conditions (experiments with animals)]'. *Aviakosmicheskaya Ekologicheskaya Meditsina Aerosp. Environ. Med.* 41 (1), 42–47.
- Yanovskaya, N.P., Shtol'ko, V.N., Burlakova, E.B., 1993. 'Effect of low-dose emoxypine and pyridoxine hydrochloride on human Cataract and glaucoma'. *Bull. Exp. Biol. Med.* 115 (5), 517–520. <https://doi.org/10.1007/BF00784176>.
- Youdim, M.B.H., 1971. 'Rat liver mitochondrial monoamine oxidase, a flavin-containing enzyme'. *Biochem. J.* 121 (1). <https://doi.org/10.1042/bj1210020Pa>, 20P–20P.
- Zamoshchina, T.A., Gostyukhina, A.A., Zaitsev, K.V., Svetlik, M.V., Zhukova, O.B., 2018. 'Effect of mexidol on physical working capacity and level of lactate in the blood of rats in conditions of light deprivation'. *Zhurnal nevrologii i psikiatrii im. S.S. Korsakova* 118 (11), 82. <https://doi.org/10.17116/jnevro201811811182>.
- Zor'kina, A.V., Ya, V., Kostin, Inchina, V.I., Sernov, L.N., Smirnov, L.D., 1998a. 'Antioxidant and hypolipidemic properties of mexidol and emoxypine during prolonged immobilization stress'. *Pharmaceut. Chem. J.* 32 (5), 231–233. <https://doi.org/10.1007/BF02471877>.
- Zor'kina, A.V., Ya, V., Kostin, Inchina, V.I., Sernov, L.N., Smirnov, L.D., 1998b. 'Antioxidant and hypolipidemic properties of mexidol and emoxypine during prolonged immobilization stress'. *Pharmaceut. Chem. J.* 32 (5), 231–233. <https://doi.org/10.1007/BF02471877>.