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Review

Neuroprotective Properties and Molecular Mechanisms of Action of 4H-Pyran-Based Acids

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Abstract

The development of effective neuroprotective agents remains one of the most urgent and complex challenges in modern medical and biological research, given the increasing prevalence of neurodegenerative diseases and the limited efficacy of existing therapeutic options. In recent years, compounds belonging to the 4H-pyran chemical class have attracted significant attention due to their pronounced antioxidant, anti-inflammatory, and cytoprotective properties. These molecules exhibit structural versatility, enabling modulation of multiple molecular targets involved in neuronal survival, redox homeostasis, and mitochondrial function. This review provides a comprehensive analysis of the pharmacological activity and molecular mechanisms of action of five 4H-pyran-based compounds—maltol, kojic acid, chelidonic acid, comenic acid, and meconic acid. Special attention is paid to their effects on signaling pathways that play a central role in maintaining neuronal integrity and resistance to stress factors. In particular, the review examines how these compounds regulate key intracellular cascades such as nuclear factor erythroid 2–related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1)/antioxidant response element (ARE), Nrf2/PTEN-induced putative kinase 1 (PINK1)/Parkin, nuclear factor-kappa B (NF-κB), and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), which are critically involved in controlling oxidative stress, mitochondrial autophagy, inflammation, and neuronal plasticity. The integrated evaluation of these mechanisms demonstrates that 4H-pyran-based acids can act as multitarget neuroprotective agents capable of influencing both primary metabolic processes and secondary signaling responses to neurotoxic stimuli. Their pleiotropic action highlights the promise of these compounds as molecular scaffolds for the development of novel drugs aimed at preventing or delaying the progression of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Keywords: pyrans; maltol; kojic acid; chelidonic acid; comenic acid; meconic acid; NF-kappa B; transcription factor Nrf2; phosphatidylinositol 3-kinases; protein kinase B; metabolic networks and pathways

1. Introduction

Research into the pharmacological activity of known molecules and the synthesis of new compounds based on them, plays a key role in addressing various pathologies and health challenges. Compounds of the 4H-pyran series hold a special place among the studied substances. Their broad spectrum of biological activity makes them promising candidates for new drug development. Their potential mechanisms include direct interactions with enzymes and key regulators of cellular metabolism and the stress response.

This work aimed to review the current data on the pharmacological activity of selected 4H-pyran-based compounds, including maltol, kojic, chelidonic, comenic, and meconic acids, and their derivatives.

A literature search was conducted in the PubMed and ScienceDirect databases using the following keywords: 4H-pyran, maltol, kojic acid, chelidonic acid, comenic acid, meconic acid, neuroprotector, neurodegeneration, neuron, and brain. No restrictions were placed on the search depth.

The first part of the review provides a brief description of the therapeutic potential of these compounds, while the second part summarizes data on the most common molecular pathways mediating their biological activity. Fig. 1 shows the structural formulas of maltol, kojic, chelidonic, comenic, and meconic acids.

The activity of 4H-pyrans is due to the pyran ring (O atom, double bonds), but maximal biological efficacy is provided by substituents (–OH, C=O, –OR, etc.), which: direct the molecule to a specific biological target; determine the type of interaction (covalent/noncovalent); and regulate pharmacokinetic properties (absorption, distribution, metabolism). Chelating properties are associated with

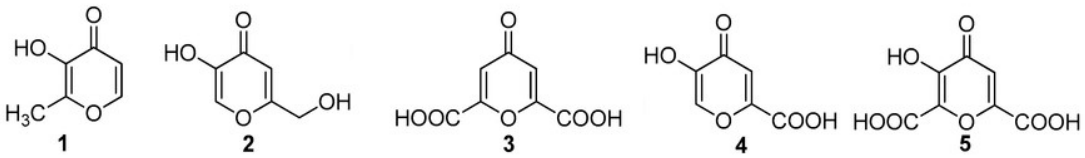

Fig. 1. Structural formulas of common 4H-pyrones. (1) Maltol. (2) Kojic acid. (3) Chelidonic acid. (4) Comenic acid. (5) Meconic acid.

adjacent –OH and C=O groups; alkylation and acetylation reactions are mediated by –OH groups; addition reactions are associated with the C=O group; the C=C double bond can participate in addition reactions (hydrogenation, halogenation) and oxidation; the γ-pyrone aromatic system participates in electrophilic substitution. The ring oxygen atom can coordinate with metals or become protonated in an acidic environment, affecting the reactivity of neighboring groups [1].

2. Maltol

Maltol (3-hydroxy-2-methylpyran-4-one; synonyms: 3-hydroxy-2-methyl-4-pyrone, 3-hydroxy-2-methyl-4H-pyran-4-one) has a molecular weight of 126.11 g/mol [2].

The neuroprotective effect of maltol has been studied in oxidative brain injury induced by kainic acid in mice. Administration of maltol (100 mg/kg) markedly alleviated neurobehavioral impairments and neuronal death in the hippocampus, leading to a reduction in animal mortality. In addition, pretreatment with maltol (100 mg/kg) restored glutathione levels, thiobarbituric acid-reactive substances, and glutathione peroxidase activity to control values. Based on these findings, maltol is suggested to be a functional agent capable of preventing oxidative brain damage in mice [2]. The results further indicate that projecting activity of maltol is realized with the participation of the nuclear factor erythroid 2–related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway in the brain by attenuating oxidative stress and apoptosis-mediated cell death. It may represent a promising therapeutic agent for the treatment and prevention of spinal cord injury, peripheral neuropathy, and functional disorders associated with brain aging. In a model of diabetic peripheral neuropathy (DPN), maltol significantly attenuated thermal and mechanical hyperalgesia, increased motor nerve conduction velocity (MNCV), enhanced Na^+/K^+-ATPase activity, and alleviated oxidative stress and apoptosis in diabetic rats. *In vitro*, maltol increased the viability of Schwann cells and inhibited apoptosis induced by hydrogen peroxide [3]. In another study on DPN, maltol improved peripheral nerve function by inhibiting Schwann cell apoptosis and upregulating membrane metalloendopeptidase [4]. Thus, maltol prevents the development of DPN and may serve as a novel alternative therapeutic approach for its treatment. In addition, maltol was shown to reduce behavioral dysfunction and neurological deficits induced by d-Gal (a model of brain aging) through activation of the Nrf2/HO-1 signaling pathway mediated by phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) in the mouse brain. As a result, there was a recovery in the Morris test, as well as levels of choline acetyltransferase and acetylcholinesterase in the hippocampus. Maltol also inhibited the development of oxidative stress in the brain by decreasing reactive oxygen species (ROS) and malondialdehyde (MDA) levels, while increasing catalase and superoxide dismutase (SOD) activity. Furthermore, elevated phosphorylation levels of PI3K, Akt, Nrf2, and HO-1 were detected [5]. In a spinal cord injury model, administration of maltol increased the expression of Nrf2 and downstream antioxidant proteins such as HO-1 and SOD2, resulting in a significant reduction in apoptosis in mice. A decrease in the expression of the pro-apoptotic protein Bax and an increase in the expression of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) were also observed in injured mice. Furthermore, maltol administration enhanced mitophagy through activation of the Nrf2/PINK1/Parkin signaling pathway in PC12 cells, thereby promoting the restoration of mitochondrial function [6]. Maltol has been shown to prevent chromatinolysis induced by oxygen-glucose deprivation in human neuroblastoma SH-SY5Y cells by inhibiting pyruvate depletion [7], as well as to suppress apoptosis induced by H_2O_2 [8]. The neuroprotective effect of maltol may be mediated through the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. Maltol also reduces H_2O_2-induced cytotoxicity in cultured embryonic rat neuroretinal progenitor cells, accompanied by decreased deoxyribonucleic acid (DNA) fragmentation. Western blot analysis revealed that maltol treatment reduces the phosphorylation of NF-κB, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) [9]. Similar results were obtained in a study on retinal ganglion cells. Maltol attenuated oxidative stress–induced injury in primary retinal ganglion cells of mice. It not only reduced apoptosis but also supported neurite outgrowth.

Moreover, maltol treatment decreased the level of the active phosphorylated form of NF-κB (p-NF-κB), which increases oxidative stress, restoring it to baseline values [10]. Thus, maltol may potentially serve as a novel neuroprotective therapeutic agent for oxidative stress–related ocular diseases, including glaucoma.

Maltol also exhibits hepatoprotective properties and shows potential for application in cases of acute chemically induced liver injury [11,12,13], as well as cardioprotective [14,15], chondroprotective [16,17], and nephroprotective activities [18].

Due to the unique electrochemical properties of metal ions, their use in modifying the properties of various pharmacologically active molecules—a modification that is impossible without their participation—is widely employed in drug development. The molecular geometry of metal complexes, which is unattainable for organic molecules, along with their ability to undergo ligand exchange and participate in unique catalytic reactions, makes this direction highly promising [19]. To date, metal complexes of 4H-pyran compounds occupy a place not only in experimental research but also in medical practice. In particular, iron maltolate has shown promise in the treatment of iron deficiency anemia (IDA), even in patients with intolerance to oral iron preparations [20]. Ferric trimaltol (iron(III) trimaltolate) has been approved for clinical use in IDA in many countries, including the USA and European Union member states. It has demonstrated efficacy and safety, with a superior therapeutic index compared to other iron preparations [21]. Moreover, in patients with inflammatory bowel disease, it is non-inferior in efficacy to intravenously administered preparations [22].

Gallium maltolate consists of a trivalent gallium cation (Ga^{3+}) coordinated with three maltolate ligands. Gallium maltolate exhibits anti-inflammatory [23,24], antiproliferative and antitumor effects [25,26,27,28], analgesic [24], anti-resorptive with respect to bone tissue [29] and antibacterial [30,31] effect. It possesses high bioavailability upon oral administration [32]. The bioavailability of gallium from oral administration of gallium maltolate in humans is approximately 25–57%, which is many times higher than that of gallium chloride (1–2%) [33].

Magnesium maltolate and magnesium ethyl maltolate are being considered as candidates for the therapy of hypomagnesemia—a pathology frequently observed in critically ill patients, in whom it can lead to severe, life-threatening complications [34]. A recent study has demonstrated the promise of using maltolate in complex with palladium for the development of anticancer agents [35]. Cobalt, copper, and zinc complexes with 1,10-phenanthroline (phen) and maltolate have demonstrated antiproliferative properties and potential for cancer therapy *in vitro* [36]. The antihyperglycemic effect of complexes of vanadium, molybdenum, and other metals with maltol has been established [37].

Aluminium maltolate is used as a toxicological agent in modeling neurodegenerative processes [38], and also in models investigating aluminum toxicity and protective agents against its effects [39,40,41,42]. However, in these studies, maltol is used as a delivery agent for aluminum.

Thus, complexes of various metals with maltol have demonstrated therapeutic potential across a wide range of pathological conditions, from hyperglycemia to anticancer activity. However, the neuroprotective activity of such complexes has scarcely been studied. Nevertheless, a case report [24] describes the successful use of gallium maltolate in the treatment of refractory postherpetic neuralgia. The patient applied gallium maltolate topically for five years without any adverse effects and with a significant improvement in quality of life. The discussion notes that gallium, being chemically similar to zinc, may inhibit the activity of matrix metalloproteinases (zinc-containing proteases), which are involved in the etiology of neuropathic pain.

The presented data indicate that maltol and its derivatives exhibit hepatoprotective, cardioprotective, nephroprotective, and neuroprotective effects. These properties are associated with their antioxidant, anti-inflammatory, and anti-apoptotic activities. Moreover, in modeling neurodegenerative processes, activation of molecular mechanisms mediated by Nrf2 and NF-κB has been observed.

3. Kojic Acid

Kojic acid (5-hydroxy-2-(hydroxymethyl)pyran-4-one; synonyms: 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one; 5-hydroxy-2-(hydroxymethyl)-4-pyrone) has a molecular weight of 142.11 g/mol [43].

Kojic acid is produced by various fungal species through aerobic fermentation and is mainly synthesized by fungi of the genera *Aspergillus* and *Penicillium* [44]. Its efficacy has been demonstrated in neuroprotection, as well as in hepato- and chondroprotection. Kojic acid significantly upregulates anabolic factor expression while suppressing catabolic and inflammatory factor expression *in vitro* in chondrocytes. Moreover, kojic acid markedly inhibited the activated NF-κB and PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathways and restored impaired autophagy [45]. Activation of the NF-κB pathway by kojic acid was also observed in human hepatoma (HepG2) cells after 24-hour exposure. In addition, kojic acid was shown to activate the MAPK signaling pathway and suppress inflammation [46].

The neuroprotective properties of kojic acid have been investigated in a mouse model of Alzheimer's disease (AD). Injection of amyloid-β ($A\beta_{1–42}$) (5 μL/5 min per mouse) in adult wild-type mice induced AD-like pathological changes in the hippocampus, characterized by increased oxidative stress and neuroinflammation, as well as impairments in memory and cognitive functions. Oral administration of kojic acid (50 mg/kg/day for 3 weeks) reversed AD pathology by downregulating the expression of Aβ and β-site amyloid precursor protein cleaving enzyme 1 (BACE-1). Kojic acid reduced oxidative stress by enhancing the expression of nuclear factor erythroid 2–related factor 2 (Nrf2) and heme oxygenase-1 (HO-1). Furthermore, kojic acid reduced lipid peroxidation (LP) and the generation of reactive oxygen species (ROS) in the brains of mice that were co-administered kojic acid with Aβ.

Administration of kojic acid also suppressed neuroinflammation by inhibiting Toll-like receptor 4 (TLR4), phosphorylated nuclear factor-κB, tumor necrosis factor-α (TNF-α), and interleukin-1β (TLR4, p-NF-κB, TNF-α and IL-1β). Furthermore, kojic acid enhanced synaptic markers (SNAP-23, SYN, and PSD-95) and improved memory performance in mice with AD-like pathology. *In vitro*, kojic acid treatment reduced Aβ expression, oxidative stress, and neuroinflammation in HT-22 mouse hippocampal cells [47].

Kojic acid can suppress neuroinflammation and oxidative stress in the cerebral cortex and hippocampus of mice by regulating the TLR4/NF-κB signaling pathway. Its administration prevented an increase in the expression of TLR4, phosphorylated NF-κB (p-NF-κB) and phosphorylated c-Jun N-terminal kinase (p-JNK) proteins in the mouse brain after intraperitoneal administration of lipopolysaccharides (LPS). Conversely, kojic acid treatment elevated the levels of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1), which were reduced by LPS exposure. Furthermore, it inhibited LPS-induced production of TNF-α and IL-1β in the mouse brain [48]. The kojic acid dimer (KAD) has demonstrated good safety in various cell types and exhibited important protective effects in SH-SY5Y cells. At concentrations below 50 μM, KAD outperformed vitamin C in free radical scavenging assays and prevented H_2O_2-induced ROS generation. KAD may enhance superoxide dismutase (SOD) activity, which could underlie its antioxidant mechanism. In addition, KAD moderately inhibited Aβ aggregation in the solution and selectively chelated Cu^{2+}, Zn^{2+}, Fe^{2+}, Fe^{3+}, and Al^{3+} ions, which are associated with the progression of Alzheimer's disease. Due to its favorable effects on oxidative stress, neuroprotection, Aβ aggregation inhibition, and metal ion accumulation, KAD shows strong potential as a multitarget therapeutic agent for Alzheimer's disease [49]. Intensive neuroinflammation is known to contribute to the development of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease [50,51]. A significant part of the protective activity of kojic acid and its derivatives is attributed to their anti-inflammatory effects. It has been established that kojic acid stimulates monocyte differentiation into macrophages and can act as an immunomodulator by increasing IL-6 levels [52]. It enhances several leukocytes functions and scavenges ROS that are excessively released from cells or generated in host tissues [53]. The kojic acid derivative (5-hydroxy-4-oxo-4H-pyran-2-yl)methyl 6-hydroxynaphthalene-2-carboxylate inhibits the production of inflammatory mediators in macrophages [54].

While kojic acid is widely used in various industries, such as pharmaceuticals, cosmetics, agriculture, and the food and chemical sectors, recent research has revealed its promising potential for application in neuroprotection [55].

4. Chelidonic Acid

Chelidonic acid (4-oxo-2,6-pyrandicarboxylic acid) has a molecular weight of 184.10 g/mol [56].

Chelidonic acid (ChA) is found in the rhizomes of *Chelidonium majus L.* [57]. Experimental studies on rats have demonstrated a positive effect of ChA on age-related neurodegenerative disorders and memory-related processes. In the brains of rats treated with ChA, improvements were observed in the overall antioxidant status as well as in the level of brain-derived neurotrophic factor (BDNF), which enhances neurogenesis in the nervous system and promotes synaptic functioning and cell survival [58].

Administration of ChA produced anti-inflammatory and antidepressant effects in mice. Treatment with ChA significantly reduced immobility time in the forced swimming test without altering locomotor activity in the open field test. ChA also increased the number of Nissl bodies in the hippocampus. ChA administration activated the expression of neurotrophic factors and the phosphorylation of extracellular signal-regulated protein kinase (ERK) in the hippocampus. Furthermore, ChA markedly increased hippocampal mRNA expression of estrogen receptor β. Levels of hippocampal IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) were effectively reduced following ChA administration. In addition, ChA significantly elevated serotonin, dopamine, and norepinephrine levels, as well as BDNF. These results suggest that ChA may serve as a novel therapeutic strategy for regulating inflammation-associated depression [59].

Chelidonic acid has also shown the ability to inhibit glutamate decarboxylase from rat brain. It has been found to compete with glutamate and inhibit glutamate-dependent apoenzyme formation [60]. Derivatives of ChA have been reported to inhibit BACE1 (β-site APP-cleaving enzyme 1), which is involved in the formation of amyloid precursor protein (APP). Although the membrane permeability of these compounds is similar to that of peptide compounds such as KMI, they are expected to be more bioavailable due to their enhanced enzymatic stability *in vivo* [61].

In a paclitaxel-induced neuropathy model, ChA normalized mechanical allodynia, hyperalgesia, and thermal hyperalgesia. Improvement in nerve conduction velocity and a reduction in oxidative stress were also observed. Levels of inflammatory markers (TNF-α, IL-6, and IL-1β), as well as nitric oxide and C-reactive protein, were significantly reduced. Histopathological examination revealed reduced neuronal damage, demyelination, and leukocyte infiltration. Moreover, levels of Nrf2 and pAMPK protein expression in the sciatic nerve were increased, whereas hypoxia-inducible factor 1-α (HIF-1α) expression was markedly decreased. Thus, ChA alleviates paclitaxel-induced neuropathic pain [62].

ChA also exhibits immunomodulatory [63,64], senolytic and senomorphic activities [65]; is used in anti-

cancer therapy [66]; possesses cardioprotective properties and osteogenic activity [67,68]. Like other 4H-pyrans, ChA is of interest as a ligand in metal–organic compounds for the delivery of essential elements to target organs [69].

5. Comenic Acid

Comenic Acid (5-hydroxy-4-oxo-2H-pyran-2-carboxylic acid; synonyms: 5-hydroxy-4-oxo-4H-pyran-2-carboxylic acid, 2-carboxy-5-hydroxy-4-pyrone) has a molecular weight of 156.09 g/mol [70].

For comenic acid, sedative effects [71] and analgesic effects [72] have been established. For potassium comenate, sedative effects have also been established [73].

Studies of the neuroprotective activity of comenic acid (CA) and its derivatives with alkali and alkaline earth metals (lithium, sodium, potassium, calcium, and magnesium comenates) have revealed the protective effects of these compounds under excitotoxic and oxidative stress *in vitro*, as well as under stress exposure *in vivo*. Comenic acid and all investigated comenates exhibit neuroprotective effects against glutamate-induced neurotoxicity in primary cultures of rat cerebellar neurons. The protective effect of the comenates significantly exceeds that of comenic acid, both in terms of the effective concentration range and the proportion of surviving neurons [74,75].

Comenic acid and its salts also demonstrated neurotrophic activity. They stimulated neurite outgrowth in spinal ganglia *in vitro* under both normal conditions and oxidative stress. The effectiveness of the comenates was higher and was observed over a broader concentration range [76,77]. CA and the comenates prevent the development of oxidative stress in brain tissue under experimental stress exposure: parameters of free radical oxidation, lipid peroxidation, and the activity of the glutathione antioxidant system (GSH, glutathione reductase, glutathione peroxidase), catalase, and superoxide dismutase remain at physiological levels. The antioxidant and stress-protective effects of the comenates are achieved at lower doses: for lithium and sodium comenates 1–2 mg/kg [74,77]; potassium comenate 2–8 mg/kg [78,79]; magnesium comenate 2–4 mg/kg [75]; whereas for comenic acid 4–8 mg/kg (at 2 mg/kg, complete normalization of oxidative processes was not observed) [79]. Calcium comenate is effective at doses of 1–4 mg/kg, but does not fully restore lipid peroxidation or superoxide dismutase activity at 4 mg/kg. Overall, the available data indicate that Comenic acid derivatives (lithium, sodium, potassium, calcium, and magnesium comenates) exert more pronounced neuroprotective effects in both cell cultures and animal models of stress and hypoxia.

These effects share both common mechanisms inherent to Comenic acid and specific mechanisms related to its derivatives. The presence of a hydroxyl group at position 5 and the pyran ring structure enables the Comenic acid residue to neutralize free radicals and suppress oxidative stress [80,81,82].

The neuroprotective activity of Comenic acid and its derivatives in neuronal cultures results from their antioxidant action under conditions of glutamate receptor overstimulation and stimulation of neurite growth in spinal ganglia under both normal and oxidative stress conditions. These findings are consistent with *in vivo* experiments demonstrating that Comenic acid and its derivatives prevent oxidative stress in the brain.

For lithium comenate, additional mechanisms are associated with the biological effects of lithium itself. Lithium plays a well-established role in maintaining cognitive function, and lithium deficiency has been linked to an increased risk of Alzheimer's disease [83,84,85,86]. By triggering multiple signaling cascades, lithium can enhance the cellular antioxidant defense [87]. Thus, the direct antioxidant action of lithium comenate may be complemented by the activation of intrinsic protective systems in cells and the organism as a whole. The pharmacological effects of lithium are mediated by the methylation of nuclear-binding proteins such as β-catenin, which is enhanced by the inhibition of glycogen synthase kinase-3β (GSK-3β) or inositol monophosphatase by lithium. Li^+ selectively inhibits GSK-3β and is not a general inhibitor of other protein kinases [88,89]. Moreover, Li^+ reduces GSK-3β transcription in various brain regions [90]. Increased GSK-3β activity is known to be one of the signaling pathways mediating oxidative neuronal damage [91,92]. GSK-3β negatively regulates the expression of nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 initiates a crucial endogenous antioxidant signaling pathway that is involved in regulating the expression of antioxidant genes [93]. The transcription factor β-catenin is a substrate of GSK-3β and a component of the Wnt pathway. Its cytoplasmic levels are negatively regulated by constitutively active GSK-3β. Inhibition of GSK-3β increases cytoplasmic β-catenin accumulation, facilitating its nuclear translocation and triggering the expression of genes encoding protective proteins such as BDNF, VEGF, Bcl-2, and HSP-70 [94]. Therefore, GSK-3β inhibition by lithium may be one of the mechanisms mediating the neuroprotective action of lithium comenate in both cell cultures and *in vivo*.

Lithium also enhances the activation of the transcription factor cyclic AMP response element-binding protein (CREB) [95]. Regulation of CREB activity is crucial for cellular viability, stress resistance, and numerous physiological functions [96]. CREB controls many central nervous system processes, including neurogenesis, neuronal survival, activation, and long-term memory [97]. Therefore, CREB activation by lithium may also mediate the neuroprotective and neurotrophic effects of lithium comenate.

The neuroprotective activity of comenic acid, as well as calcium and magnesium comenates, is associated with modulation of the transducer function of Na^+/K^+-ATPase. This enzyme modulates cell growth and plays an important role as a neuronal oxidative stress resistance factor [98].

Calcium and magnesium comenates represent chelate complexes of Comenic acid with Ca^{2+} and Mg^{2+} ions, respectively. As noted above, these complexes activate a specific molecular mechanism of membrane signaling that includes the α3-isoform of Na^+/K^+-ATPase as a signal transducer [99,100].

Active Na^+/K^+-ATPase prevents the accumulation of reactive oxygen species in neurons, thereby enhancing their resistance to oxidative stress [101]. The ability to regulate Na^+/K^+-ATPase transduction function may therefore contribute to the stimulation of neurite growth in spinal ganglia under normal and oxidative stress conditions, as well as to the overall protective effect during stress exposure.

Another mechanism for the neuroprotective action of magnesium comenate may involve the magnesium blockade of N-methyl-D-aspartate (NMDA) receptors. It is well-established that Mg^{2+} acts as a voltage-dependent blocker of glutamate NMDA receptors [101]. Through the blockade of NMDA receptors, magnesium sulfate attenuates glutamatergic signaling, thereby altering calcium influx and reducing excitotoxicity [102,103]. This mechanism may also operate in the case of magnesium comenate.

Comenic acid and its mono- and disodium salts exhibit antistress activity. They prevent alterations in long-term potentiation amplitude in the hippocampus, changes in free radical oxidation rates, and disturbances in glutathione metabolism [104].

Thus, the neuroprotective activity of Comenic acid and its comenates results from both common mechanisms inherent to the comenic acid structure and specific biological effects of the metals forming the comenate complexes.

6. Meconic Acid

Meconic acid (3-hydroxy-4-oxo-2,6-pyrandicarboxylic acid; synonyms: poppy acid, oxychelidonic acid) has a molecular weight of 200.10 g/mol [105].

Since the early 20th century, meconic acid has been used as an analytical marker for the detection of opium alkaloids in biological fluids [106,107]. However, studies devoted to the pharmacological activity of meconic acid are considerably fewer than those concerning other 4H-pyran derivatives discussed above.

From the perspective of neuroprotective activity, meconic acid is the least studied compound among the 4H-pyrans under consideration. Similar to comenic acid, meconic acid activates a subpopulation of opioid receptors that are negatively coupled to tetrodotoxin (TTX)-resistant (slow) sodium channels [108]. Meconic acid also exhibits antioxidant activity and protects cultured neurons against glutamate-induced excitotoxicity [108].

Regarding other pharmacological effects, it has been established that the monoethyl ester of meconic acid acts as an inhibitor of the active site of the ribonucleic acid (RNA)-dependent RNA polymerase NS5B of the hepatitis C virus [109].

According to a recent study, metabolites derived from algae (*Ulva lactuca*, *Sargassum cinereum*, and *Turbinaria decurrens*) show potential in inhibiting lung cancer progression, and meconic acid has been identified as a key factor in promoting cell survival [110].

7. General Mechanisms of Pharmacological Activity

Table 1 (Ref. [3,4,5,6,7,8,9,10,47,48,58,59,62,71,72,73,75,78,79,104,107,108,111,112,113,114,115,116,117]) summarizes the available data shedding light on the mechanisms of neuroprotective action of maltol, kojic acid, chelidonic acid, comenic acid, and meconic acid.

As can be seen from the table, the amount of available material for each of the five compounds varies considerably. Thus, nine publications examining the neuroprotective properties of maltol were identified, fourteen for comenic acid, two for kojic acid, three for chelidonic acid, and two for meconic acid. For maltol, suppression of oxidative stress and apoptosis has been demonstrated *in vitro* in various cellular models, as well as a reduction of oxidative stress *in vivo* in kainic acid-induced brain damage, experimental diabetic peripheral neuropathy, d-galactose-induced brain aging, and spinal cord injury. A decrease in apoptosis markers has also been noted in DPN and Spinal Cord Injury models. Also, a decrease in NF-κB phosphorylation was observed *in vitro* in retinal cell cultures (both primary murine cells and established cell lines) as well as in human neuroblastoma cells. This effect is attributed to the antioxidant activity of maltol, which suppresses the development of oxidative stress. As a result, the need for NF-κB activation is reduced. Conversely, in models of spinal cord injury and D-galactose–induced brain aging, activation of Nrf2—an important factor in cellular protection against oxidative damage—was observed..

For kojic acid, antioxidant and anti-inflammatory effects have been shown in a mouse model of Alzheimer's disease, as well as in LPS-induced neuroinflammation. For chelidonic acid, antioxidant and antiamnestic effects have been established in a rat model of experimental brain aging, along with anti-inflammatory and antidepressant effects, and an analgesic effect in paclitaxel-induced neuropathy.

For comenic acid, antioxidant effects have been established in experimental stress and hypoxia in rats, as well as a neuroprotective effect against glutamate excitotoxicity, and a neurotrophic effect in cultured chick embryo ganglia under oxidative stress. Neuroprotective action has also been shown in prenatal lead intoxication. Its sedative and analgesic effects, as well as an anxiolytic effect in a rat model of morphine withdrawal syndrome, have also been demonstrated. Regarding meconic acid, a neuroprotective effect against glutamate excitotoxicity *in vitro* has been established.

Table 1. Mechanisms of neuroprotective action of maltol, kojic acid, chelidonic acid, comenic acid, and meconic acid.

Effect	Mechanism (as hypothesized by authors)	*In vitro/in vivo*, dose/concentration of the neuroprotective agent	Exposure/Disease model	Efficacy indicator, effective doses/concentrations of the neuroprotective agent	Main direction of potential application
Maltol					
Neuroprotection under oxidative brain damage	Antioxidant activity	*in vivo* (mice) [111] 50 or 100 mg/kg orally, administered for 5 consecutive days in advance	Kainic acid-induced oxidative brain damage	Preservation of GSH level, glutathione peroxidase activity, thiobarbituric acid-reactive substances; reduction of neurobehavioral disorders and hippocampal neuron death; reduction of animal mortality. Effective dose: 100 mg/kg.	Pathologies associated with oxidative and excitotoxic brain damage (ischemia, strokes, chronic neurodegeneration)
Neuroprotection in diabetic peripheral neuropathy (DPN)	Antioxidant activity, stimulation of Na^+/K^+-ATPase activity, inhibition of apoptosis	*in vivo* (rat) [3] 50, 100, and 200 mg/kg orally for 12 weeks	DPN in streptozotocin-induced diabetic rats	Reduction of thermal and mechanical hyperalgesia; increase in MNCV; reduction of peripheral nerve damage (stimulation of Na^+/K^+-ATPase activity); reduction of oxidative stress (total antioxidant capacity, MDA, GSH, SOD) and apoptosis (caspase-3 activity, expressions of BAX, caspase-3, BAG4, Bcl-XL). Effective doses: 50–200 mg/kg, with a dose-dependent effect.	DPN
		in vitro (RSC96 cells) [3] 0.1 and 0.5 mM	OS (H_2O_2)	Reduction of oxidative stress (cell viability) and apoptosis (stimulation of Bcl-XL expression, reduction of BAX and caspase-3 expression). Effective concentrations: 0.1 and 0.5 mM, with a dose-dependent effect.	
Neuroprotection in DPN	PERK/eIF2α/CHOP Pathway and MME Upregulation	*in vivo* (rat) [4] 25 and 100 mg/kg orally for 12 weeks	DPN in streptozotocin-induced diabetic rats	Reduction of thermal and mechanical hyperalgesia; reduction of peripheral nerve damage (stimulation of Na^+/K^+-ATPase activity); dose-dependent increase in total antioxidant capacity, GSH and SOD levels, and decrease in serum MDA level; reduction of expression of glucose-regulated protein 78 (GRP78), C/EBP homologous protein (CHOP). Effective doses: 25 and 100 mg/kg, with a dose-dependent effect.	DPN
		in vitro (rat Schwann cells (RSC96)) [4] 1, 5, 10, 20, 40, and 80 μM	model using high concentration of glucose (HG) and palmitic acid (PA)	Increased viability upon incubation with HG and PA; increased expression of nerve growth factor and neuritin-1; suppression of apoptosis induced by HG/PA; attenuation of expression of ER stress-related proteins; MME Upregulation; reduction of DPN markers and apoptosis-related proteins; decreased expression of PERK and eIF2α; in the presence of PERK activator CCT020312, PERK expression remained unchanged, levels of phospho-PERK, CHOP, GRP78 increased. Effective concentrations: 5–20 μM, with a dose-dependent effect.	

Table 1. Continued.

Effect	Mechanism (as hypothesized by authors)	*In vitro/in vivo*, dose/concentration of the neuroprotective agent	Exposure/Disease model	Efficacy indicator, effective doses/concentrations of the neuroprotective agent	Main direction of potential application
Slows d-galactose-induced brain aging process	Activation of the Nrf2/HO-1 signaling pathway mediated by PI3K/Akt	*in vivo* (mice) [5] 50 and 100 mg/kg orally for 4 weeks	Brain aging model (d-Gal)	Restoration of parameters in the Morris water maze; restoration of choline acetyltransferase and acetylcholinesterase levels in the hippocampus; reduction of ROS and MDA levels and increase in catalase and SOD levels; increase in phosphorylation levels of PI3K, Akt, Nrf2, and HO-1. Effective doses: 50 and 100 mg/kg, with a dose-dependent effect.	Neuroprotection in brain aging, chronic neurodegeneration
Neuroprotection under oxidative stress in cell culture	NF-κB and mitogen-activated protein kinase signaling pathways	*in vitro* (R28 cells) [9] 0.1, 0.5, 1.0 and 1.5 mM	OS (H_2O_2)	Reduction of apoptosis, DNA fragmentation; reduction of NF-κB, ERK, and JNK phosphorylation. Effective concentrations: 0.5, 1.0, and 1.5 mM, with a dose-dependent effect.	Pathologies associated with oxidative brain damage
		in vitro (Human Neuroblastoma Cells (SH-SY5Y)) [8] No access to the full data.	OS (H_2O_2)	Reduction of apoptosis, DNA fragmentation, and $[Ca^{2+}]i$ concentration, NF-κB activation; maintenance of mitochondrial function.	
		in vitro (primary mouse retinal ganglion cells (RGCs)) [10] 0.001, 0.01, 0.5, 1 and 2 mM	OS (H_2O_2)	Reduction of apoptosis; maintenance of neurite outgrowth; reduction of NF-κB phosphorylation. Effective concentrations: 0.001, 0.01, 0.5, 1 and 2 mM, with a dose-dependent effect.	
Neuroprotection in spinal cord injury	Activation of mitophagy and suppression of oxidative stress via the Nrf2/PINK1/Parkin pathway	*in vivo* (mice) [6] 100 mg/kg orally for 2 weeks	Contusive Spinal Cord Injury	Activation of Nrf2 expression; Nrf2 translocation from the cytosol to the nucleus; blocking of OS signal and apoptosis-mediated neuronal death. Effective dose: 100 mg/kg.	Pathologies associated with oxidative brain damage; neuroprotection in spinal cord injury
		in vitro (PC12 cells) [6] 0.1, 0.5, 1, 2, 5 mM	OS (H_2O_2)	Enhancement of PINK1/Parkin-mediated mitophagy. Effective concentrations: 1, 2 and 5 mM, with a dose-dependent effect.	
Neuroprotection in oxygen glucose deprivation in cell culture	Prevention of chromatinolysis by inhibiting pyruvate depletion	*in vitro* (SH-SY5Y cells) [7] 0.5, 1, 2 and 4 mM	oxygen and glucose deprivation (OGD)	Inhibition of ROS accumulation; maintenance of cystine/glutamate antiporter level, catalase activity, xanthine oxidase, ATP, pyruvate, p-mTOR/mTOR ratio. Effective concentrations: 0.5 and 1 mM, with a dose-dependent effect.	Pathologies associated with oxidative and excitotoxic brain damage (ischemia, strokes)

Table 1. Continued.

Effect	Mechanism (as hypothesized by authors)	*In vitro/in vivo*, dose/concentration of the neuroprotective agent	Exposure/Disease model	Efficacy indicator, effective doses/concentrations of the neuroprotective agent	Main direction of potential application
Kojic acid					
Antioxidant and anti-inflammatory action	Antioxidant and anti-inflammatory action	*in vivo* (mice) [47] 50 mg/kg orally for 3 weeks	Aβ-Induced Mouse Model of Alzheimer's Disease	downregulating the expression of Aβ and BACE-1; enhancing the expression Nrf2 and HO-1; reduced lipid peroxidation (LP) and the generation of ROS; reduced level of TLR4, p-NF-κB, TNF-α and IL-1β. Effective dose: 50 mg/kg.	Chronic neurodegeneration (Alzheimer's disease)
Antioxidant and anti-inflammatory action	TLR4/NF-κB signaling pathway	*in vivo* (mice) [48] 50 mg/kg orally for 3 weeks	LPS-induced neuroinflammation	prevented an increase in the expression of TLR4, p-NF-κB and p-JNK; increases the level of Nrf2 and HO-1 expression; reduces the level of ROS and MDA; heal short-term memory loss; increased numbers of postsynaptic density protein 95 (PSD-95) and synaptosomal-associated protein 23 (SNAP-23) in the cerebral cortex and hippocampus. Effective dose: 50 mg/kg.	Pathologies associated with oxidative brain damage, neuroinflammation, vascular pathologies
Chelidonic acid					
Antioxidant and anti-amnestic action	Antioxidant action	*in vivo* (rat) [58] 2 mg/kg orally for 8 weeks	experimental aging (D-galactose)	Reduction of MDA level; increase in GSH level, total antioxidant status (TAS) and BDNF; normalized short- and long-term and spatial memory function. Effective dose: 2 mg/kg.	Neuroprotection in brain aging, chronic neurodegeneration
Anti-inflammatory and antidepressant action	anti-inflammatory action	*in vivo* (mice) [59] 0.02, 0.2 and 2 mg/kg orally for 2 weeks	"Forced swim" and "open field" tests	increase in the number of Nissl bodies in the hippocampus; reduced levels of hippocampal IL-1β, IL-6, TNF-α; increased the levels of serotonin, dopamine, norepinephrine; increased the BDNF expression, levels of pERK, levels of hippocampal ER-β. Effective doses: 0.2 mg/kg for serotonin; 2 mg/kg for dopamine and noradrenaline.	Depression
Analgesic action (attenuation of neuropathic pain)	Reduction of oxidative stress	*in vivo* (rat) [62] 10, 20, and 40 mg/kg orally for 3 weeks	paclitaxel-induced neuropathy	Reduced level of TNF-α, IL-6, and IL-1β, nitric oxide and C-reactive protein; increased level of Nrf2, pAMPK expression; reduced HIF-1α expression; improved nerve conduction velocity; normalization of mechanical allodynia, hyperalgesia, and thermal hyperalgesia. Effective doses: no information available.	Peripheral neuropathy
Comenic acid					
Neuroprotective activity	Antioxidant action	*in vitro* (primary culture of cerebellar neurons) [75] 0.01, 0.1 and 1 mM	glutamate excitotoxicity	increased neuronal survival. Effective concentrations: 0.01, 0.1 and 1 mM, with a dose-dependent effect.	Pathologies associated with excitotoxic brain damage (ischemia, strokes)

Table 1. Continued.

Effect	Mechanism (as hypothesized by authors)	*In vitro/in vivo*, dose/concentration of the neuroprotective agent	Exposure/Disease model	Efficacy indicator, effective doses/concentrations of the neuroprotective agent	Main direction of potential application
Stress-protective action	Antioxidant action	*in vivo* (rat) [78] 2, 4 and 8 mg/kg orally for 3 days during stress	immobilization-cold stress	Preservation in FRO and MDA levels. Effective doses: 2, 4, and 8 mg/kg, with a dose-dependent effect.	Pathologies associated with oxidative brain damage
	Antioxidant action	*in vivo* (rat) [104] 1 mg/kg orally for 4 days during stress.	immobilization-cold stress; surviving hippocampal slices	prevention of impairment of long-term potentiation parameters in the CA1 area of hippocampus under stress. Effective dose: 1 mg/kg.	
Protective action under hypoxia	Antioxidant action	*in vivo* (rat) [79] 4 mg/kg orally, administered for 3 consecutive days in advance	Normobaric Hypoxia with Hypercapnia	preservation of FRO, MDA, and catalase activity. Effective dose: 4 mg/kg.	
Neuroprotective action in prenatal lead intoxication	Antioxidant action	*in vivo* (rat) and *in vitro* (primary culture of cerebellar neurons) [112,113] 1 mg/kg throughout pregnancy (21 days) and for 7 days postpartum	Prenatal intoxication with lead acetate; glutamate excitotoxicity	Preservation of FRO level, MDA, GSH level, glutathione peroxidase, glutathione reductase activity if lead was administered prenatally in combination with comenic acid; Reduced survival of primary cerebellar neurons upon glutamate exposure *in vitro* under lead intoxication *in vivo*; Increased neuronal survival if lead was administered prenatally in combination with comenic acid. Effective dose: 1 mg/kg.	Brain protection in lead intoxication
Neurotrophic action under OS and in norm	Antioxidant action under OS, in norm—not studied	*in vitro* (chick embryo spinal ganglia) [114] 0.0001, 0.001, 0.01 and 0.1 mM	OS (H_2O_2)	Prevention of neurite outgrowth disruption after H_2O_2 exposure. Stimulation of neurite outgrowth under normal conditions. Effective concentration: 10 μM under OS; 0.0001 mM under normal conditions.	Pathologies associated with oxidative brain damage; pathologies requiring activation of regenerative processes
Neurotrophic action	Not discussed	*in vitro* (chick embryo dorsal root ganglia) [115] 10 nM	blood plasma from SMA-2 patients	eliminated the neuritic inhibitory effect of blood plasma from SMA-2 patients. Effective concentration: 10 nM.	Spinal muscular atrophy type 2
Neurotrophic action under normal conditions	Activation of the Na,K-ATPase/Src complex, then PKC, then ERK1/2	*in vitro* (chick embryo dorsal root ganglia) [73] 10 nM	PKA, PKC, p38 MAPK, and ERK1/2 inhibitors	PKC inhibitor and ERK1/2 inhibitor block the stimulating effect of comenic acid on neurite outgrowth. Effective concentration: 10 nM.	Pathologies requiring activation of regenerative processes

Table 1. Continued.

Effect	Mechanism (as hypothesized by authors)	*In vitro/in vivo*, dose/concentration of the neuroprotective agent	Exposure/Disease model	Efficacy indicator, effective doses/concentrations of the neuroprotective agent	Main direction of potential application
Decreasing voltage sensitivity of $Na_v1.8$ channels	opioid-like receptors/Na,K-ATPase/Src/$Na_v1.8$ channels	*in vitro* (rat dissociated sensory neurons) patch-clamp "whole-cell recording" [72] 100 nM	voltage sensitivity of $Na_v1.8$ channels, tetrodotoxin, PKC inhibitor	decreasing voltage sensitivity of $Na_v1.8$ channels regardless of PKC inhibitor. Effective concentration: 100 nM.	Analgesia
Decreased effective charge transfer in the activation gating system of TTX-resistant (slow) sodium channels	activates a subpopulation of opioid receptors that are negatively coupled to TTX-resistant (slow) sodium channels	*in vitro* (rat dorsal root ganglion cells) patch-clamp "whole-cell recording" [107] 1 mM	Slow sodium currents, tetrodotoxin	decreased effective charge transfer in the activation gating system of TTX-resistant (slow) sodium channels in a dose-dependent manner; nonspecific antagonist of opioid receptors naltrexone totally blocked the effects. Effective concentration: 1 mM.	
Sedative action	Mechanism not investigated	*in vivo* (rat) [71] 1, 10, 50 and 100 mg/kg	"Open field" test	Reduced motor activity. Effective doses: 50 and 100 mg/kg.	Mild forms of nervous tension and stress.
Decreased responsiveness of field CA1 hippocampal pyramidal neurons	inhibitory effect mediated by $GABA_A$-receptors	*in vitro* (rat) [116] 0.1, 0.01, 0.001 mM	surviving hippocampal slices	reversible decrease in the peak amplitude of focal response (popspike); noncompetitive $GABA_A$-antagonist picrotoxin prevented the effects of comenic acid. Effective concentration: 0.1 mM.	Pathologies associated with an imbalance between excitatory and inhibitory processes in the central nervous system
Anxiolytic effect	Interaction with opioid receptors	*in vivo* (rat) [117] 50 mg/kg intraperitoneally for 18 days	Morphine withdrawal syndrome	Normalization and stabilization of fear and anxiety levels in the "open field" and "elevated plus maze" tests. Effective dose: 50 mg/kg.	Treatment of morphine dependence
Meconic acid					
Neuroprotective activity	Antioxidant action	*in vitro* (primary culture of cerebellar neurons) [108] 0.001, 0.01, 0.1 and 1 mM	glutamate excitotoxicity	increased neuronal survival. Effective concentrations: 0.001, 0.01, 0.1, and 1 mM, with a dose-dependent effect.	Pathologies associated with excitotoxic brain damage (ischemia, strokes)
Decreased effective charge transfer in the activation gating system of TTX-resistant (slow) sodium channels	activates a subpopulation of opioid receptors that are negatively coupled to TTX-resistant (slow) sodium channels	*in vitro* (rat dorsal root ganglion cells) patch-clamp "whole-cell recording" [107] 1 mM	Slow sodium currents, tetrodotoxin	decreased effective charge transfer in the activation gating system of TTX-resistant (slow) sodium channels in a dose-dependent manner; nonspecific antagonist of opioid receptors naltrexone totally blocked the effects. Effective concentrations: 1 mM.	Analgesia

GSH, reduced glutathione; MNCV, motor nerve conduction velocity; MDA, malondialdehyde; SOD, superoxide dismutase; BAX, Bcl-2-associated X protein; BAG4, BAG cochaperone 4; Bcl-XL, B-cell lymphoma-extra large; OS, oxidative stress; PERK, protein kinase RNA-like ER kinase; eIF2α, eukaryotic translation initiation factor 2 subunit α; MME, Membrane metallo-endopeptidase; Nrf2, nuclear factor erythroid 2–related factor 2; HO-1, heme oxygenase-1; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; NF-κB, nuclear factor-kappa B; DNA, deoxyribonucleic acid; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; ATP, adenosine triphosphate; mTOR, mammalian Target of Rapamycin; Aβ, amyloid beta peptide; BACE-1, β-site amyloid precursor protein cleaving enzyme 1; TLR4, Toll-like receptor 4; p-NF-κB, phosphorylated NF-κB; TNF-α, tumor necrosis factor alpha; IL, interleukin; p-JNK, phosphorylated c-Jun N-terminal kinase; BDNF, brain-derived neurotrophic factor; ER-β, estrogen receptor β; pAMPK, phosphorylated adenosine monophosphate-activated protein kinase; HIF-1α, Hypoxia-inducible factor 1-α; FRO, free radical oxidation; SMA-2, spinal muscular atrophy type 2; PKC, protein kinase C; PKA, protein kinase A; TTX, tetrodotoxin; GABA, gamma-aminobutyric acid.

The mechanism underlying the sedative effect of comenic acid in the animal model has not been investigated. However, data obtained from surviving hippocampal slices suggest that its sedative action is related to an interaction with gamma-aminobutyric acid (GABA) receptors. Furthermore, for comenic and meconic acids, a reduction in the conductance of slow sodium channels has been shown, which is likely the mechanism of their analgesic action.

The available data on the mechanisms mediating the observed effects of these compounds will be discussed below.

7.1 Antioxidant Activity

As discussed above, the hydroxyl group at position 3 and the pyran ring are responsible for the antioxidant activity of the examined 4H-pyrans [80,81,82,118,119]. It is well known that the activation of oxidative processes accompanies virtually every external impact on the organism, as it represents part of the nonspecific adaptive response to any external stimulus, referred to as the general adaptation syndrome or stress [118]. Excessive activation of oxidation in the presence of insufficient antioxidant protection leads to the development of oxidative stress. This condition can accompany a wide range of pathologies, including neurodegeneration and neurological disorders [120,121], carcinogenesis [122,123,124], skin pathologies [125], and many others. Moreover, hyperproduction of ROS and reactive nitrogen species (RNS), oxidative stress, and impairment of antioxidant defense are among the key factors involved in the aging process [126,127]. Consequently, compounds exhibiting antioxidant activity are considered promising candidates for the therapy and prevention of these and other related pathologies [128,129]. Thus, the antioxidant activity demonstrated for maltol [130], komenic [78], kojic [118], chelidonic [58], and meconic acids represents an important property underlying their biological effects and pharmacological activity [108]. For instance, regulation of the inflammatory response maltol upon administration of lipopolysaccharide to mice is partly achieved through the suppression of ROS overproduction [131].

7.2 Nrf2/Keap1/ARE Pathway

The transcription factor Nrf2 regulates the expression of hundreds of genes involved in cellular defense against oxidative stress. In mammals, the nuclear factor erythroid 2–related factor 2 (Nrf2)–Kelch-like ECH-associated protein 1 (Keap1) system constitutes a major cellular defense mechanism that maintains homeostasis by counteracting oxidative stress [132,133,134]. The Nrf2/Keap1/antioxidant response element (ARE) pathway is therefore widely studied in the search for natural compounds capable of providing protection under pathological conditions [135].

The functional activity of Nrf2 is determined by its expression level and distribution between the cytoplasm and the nucleus (Fig. 2). Both parameters are controlled by the multifunctional regulator Keap1, which serves as a receptor for electrophilic compounds and as a substrate adaptor for the E3 ubiquitin ligase complex. Under physiological resting conditions, Nrf2 is sequestered in the cytoplasm by the Cullin-3-containing E3 ubiquitin ligase complex (Cul3–E3 ligase), which functions in association with RING-box protein 1 (RBX1). Through the mediation of Keap1, it is ubiquitinated and undergoes proteasomal degradation [132,136].

Exposure to various stressors is accompanied by hyperproduction of ROS—universal signaling molecules that trigger adaptive cellular responses [126,137]. Oxidative stress causes damage to macromolecules (lipids, proteins, and nucleic acids). Cysteine residues containing sulfhydryl (SH) groups, which play a critical role in regulating enzyme activity, are highly sensitive to pro-oxidant action. Accumulation of ROS in the cytoplasm modifies cysteine –SH groups within Keap1, disrupting its ability to retain Nrf2.

Furthermore, phosphorylation of Nrf2 by PKC, which is itself activated by oxidative stress [138], inhibits the interaction between Keap1 and Nrf2. Consequently, Keap1-dependent proteasomal degradation of Nrf2 is inhibited, leading to the release of Nrf2 into the cytoplasm. Along with continuous de novo synthesis, this results in cytoplasmic accumulation of Nrf2 and translocation into the nucleus [139].

Upon binding to small Maf proteins (sMaf), Nrf2 activates the antioxidant response element (ARE) and enhances transcription of genes. These Nrf2-regulated genes provide defense against oxidative damage and include glutathione peroxidase 2 (GPx2), glutathione S-transferases, peroxiredoxin 1 (Prdx1), thioredoxin 1 (Txn1), sulfiredoxin (Srx1), glutamate-cysteine ligase, heme oxygenase 1 (HO-1), and NAD(P)H quinone dehydrogenase 1, among others [140].

Thus, the cellular response to an external stress stimulus involving the Nrf2/Keap1/ARE pathway can be divided into five consecutive stages (Fig. 3). At the first stage, there is an increased formation and intracellular accumulation of ROS. Hence, ROS disrupt the function of Keap1, leading to the accumulation of Nrf2 in the cytoplasm and its translocation into the nucleus. After binding to sMaf proteins, Nrf2 induces the expression of enzymes responsible for the antioxidant defense of the cell. Finally, the activity of these antioxidant enzymes results in a decrease in ROS levels, which eventually leads to a reduction in the concentration of free Nrf2.

As described above, the protective effects of maltol, which involve the Nrf2/Keap1/ARE pathway, have been demonstrated across various models, including: nanoplastic-induced toxicity [11], diabetic peripheral neuropathy [3], brain aging [5], and spinal cord injury [6]. Both the neuroprotective and antitumor effects of chelidonic acid are accompanied by increased Nrf2 expression [62,66]. Similarly, the senolytic and senomorphic activities

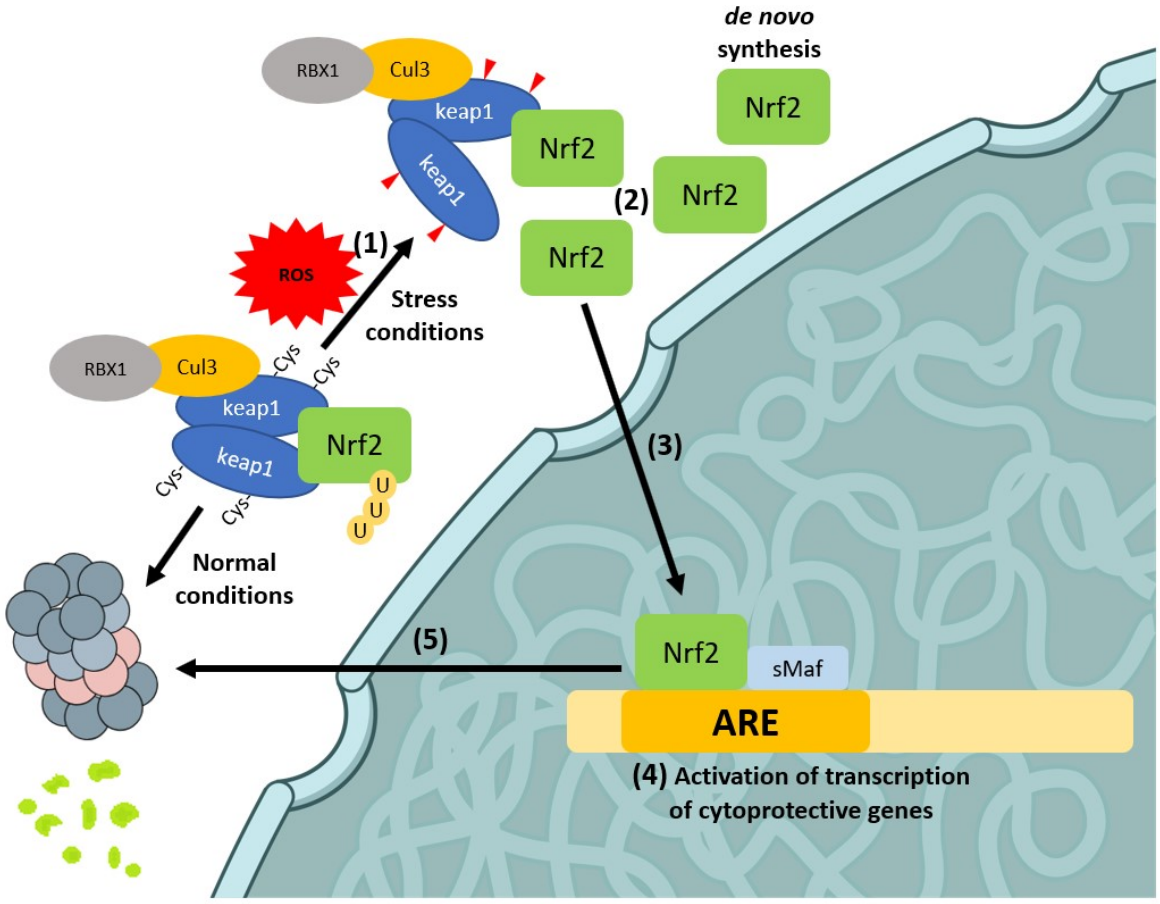

Fig. 2. Mechanism of Nrf2/Kelch-like ECH-associated protein 1 (Keap1)/ARE pathway activation under ROS overproduction. Under normal physiological conditions, Nrf2 is sequestered in the cytoplasm by the Cullin-3-containing E3 ubiquitin ligase complex (Cul3–E3 ligase), which operates in association with RING-box protein 1 (RBX1) and mediates ubiquitination through Keap1. Upon exposure to stress: (1) excessive production of ROS leads to the modification of cysteine (Cys)–SH groups within Keap1; (2) this modification, together with phosphorylation of Nrf2, promotes dissociation of Nrf2 from Keap1; (3) combined with continuous de novo synthesis, this results in cytoplasmic accumulation of Nrf2 and its subsequent translocation into the nucleus; (4) after binding to small Maf proteins (sMaf), Nrf2 activates the antioxidant response element (ARE) and enhances transcription of Nrf2-regulated genes; (5) after which it is degraded in the proteasome.

of chelidonic acid are associated with Nrf2 activation [65]. The neuroprotective effect of kojic acid has also been linked to Nrf2 induction [47,48]. For comenic and meconic acids, no studies have been found confirming their activation of the Nrf2 factor.

Direct interactions between 4H-pyrans and components of the Nrf2/Keap1/ARE pathway have not been confirmed. It is likely that their influence on Nrf2 is mediated by the reduction of ROS generation—that is, through their intrinsic antioxidant activity. Thus, their effect on the Nrf2/Keap1/ARE pathway is implemented at the first stage through a direct antioxidant action.

Regarding maltol, it has also been demonstrated to increase catalase activity (the fifth stage of the response) via direct interaction with the enzyme [141]. This effect may also contribute to ROS deactivation and modulation of the Nrf2/Keap1/ARE cascade. Nevertheless, a decrease in ROS levels would be expected to subsequently reduce the activity of the Nrf2/Keap1/ARE cascade. However, treatment with maltol, kojic, and chelidonic acid was observed to activate it. It is hypothesized that these compounds enhance the activity of the Nrf2/Keap1/ARE cascade by influencing multiple protein kinases involved in its nuclear translocation and stability [142,143]. Details on their potential interactions with proteins and enzymes are provided later. Further investigation is needed to elucidate the mechanisms by which 4H-pyrans modulate the Nrf2/Keap1/ARE cascade.

7.3 NF-κB Pathway

NF-κB represents a family of transcription factors that play crucial roles in numerous physiological and pathological processes. The NF-κB signaling cascade can be activated by various intracellular pathways triggered by inflam-

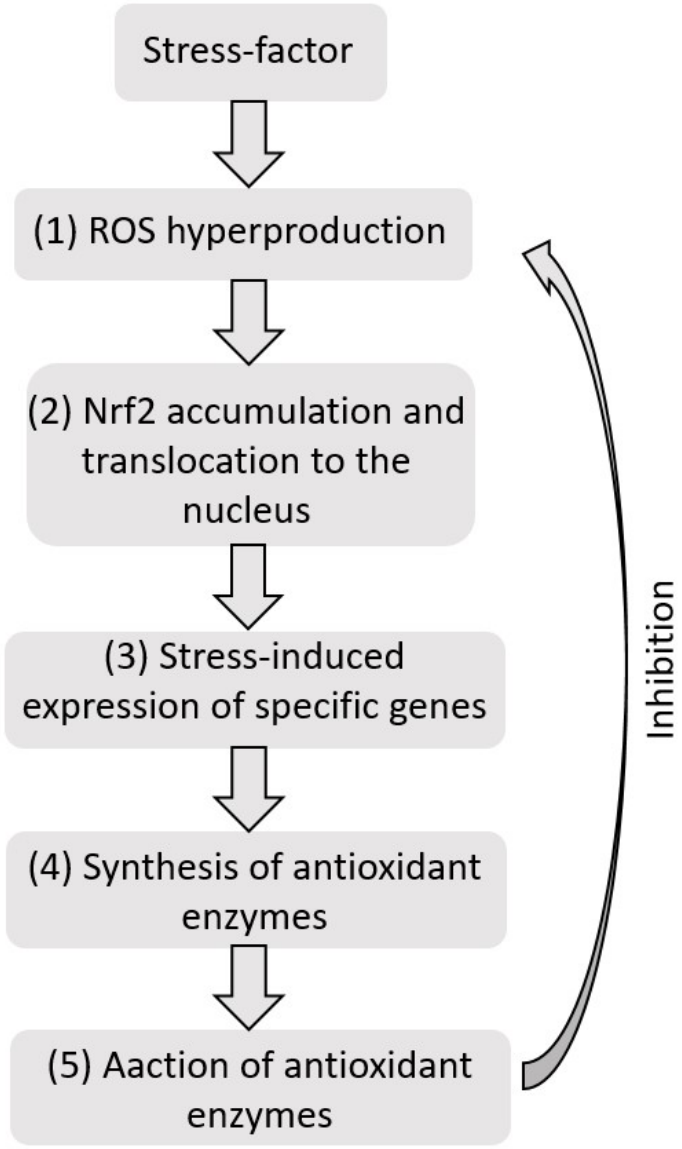

Fig. 3. Stages of the cellular stress response involving the Nrf2/Keap1/ARE pathway.

matory cytokines, lipid oxidation products, lipopolysaccharides, hypoxia, reactive oxygen species (ROS), and certain microorganisms [144].

The canonical NF-κB pathway is rapidly activated in response to a wide range of stress factors, leading to the expression of numerous proinflammatory mediators and molecules [145]. This, in turn, results in the development of inflammatory responses and the differentiation of immune cells. However, excessive activation of NF-κB contributes to chronic inflammation, oncogenesis, and autoimmune diseases [146].

The canonical activation pathway primarily depends on IκB, a specific inhibitor of NF-κB. In the resting state, NF-κB is bound to IκB and resides in the cytoplasm as an inactive complex. Upon stimulation, the IκB kinase complex is activated, leading to the degradation of IκB and the release of the NF-κB dimer. The liberated dimer then translocates into the nucleus and binds to specific DNA sequences. There, it regulates the transcription of target genes, resulting in the synthesis and release of inflammatory cytokines [147]. The noncanonical NF-κB pathway involves the p100/RelB transcription factor complex, which is activated only through specific members of the TNF receptor superfamily and induces a more specialized immune response.

The data presented above demonstrate that maltol, kojic, and chelidonic acids affect the NF-κB signaling pathway. Maltol suppressed NF-κB expression following exposure to CCl4 in the liver of mice [12] and under nephrotoxic effects on mice cisplatin [18]. Maltol reduced phosphorylation of NF-κB, IKKα/β, and IκBα in the liver during acetaminophen-induced toxicity [13]. A decrease in NF-κB phosphorylation in hydrogen peroxide-treated retinal neural cells [146] and macrophages [148], as well as the anti-

inflammatory effects of maltol in models of osteoarthritis in mice and postmenopausal osteoporosis were mediated by the NF-κB pathway [148,149,150].

Kojic acid has been shown potential for inhibition of NF-κB activity in human keratinocytes, a mechanism potentially underlying its anti-melanogenic effects [151,152,153]. Suppression of NF-κB pathway activity and reduction of inflammation were observed upon administration of kojic acid in chondrocytes [45].

In human corneal endothelial cells, kojic acid counteracted aging processes. Kojic acid enhances the proliferation of human corneal epithelial cells [154]. In human HepG2 cells, at kojic acid concentrations of 4.22 mM and 8.02 mM, an increase in p-Nrf2 and suppression of inflammation were observed. At a concentration of 12.67 mM, a decrease in p-Nrf2 was noted [46]. Thus, in different cellular models, NF-κB activity can either increase or decrease following kojic acid administration. On the other hand, a reduction in inflammation was observed in both cases. This bidirectional effect of kojic acid can likely be explained by differences in the treatments and cell types. Kojic acid also stimulates the differentiation of monocytes into macrophages [52]. An inhibitory effect on NF-κB has also been noted for its derivatives [55]. Chelidonic acid inhibited NF-κB in mast cell-mediated reactions [155,156].

In the brain (both cerebral cortex and hippocampus) of mice exposed to LPS, kojic acid reduced markers of oxidative stress, TNF-α, and IL-1β. A decrease in the expression of the phosphorylated form of NF-κB was also observed. These results suggest that kojic acid may suppress LPS-induced neuroinflammation and oxidative stress by regulating the NF-κB signaling pathway [48]. In the Aβ-Induced Mouse Model of Alzheimer's Disease, kojic acid reduced p-NF-κB, markers of inflammation, and oxidative stress. Moreover, kojic acid enhanced synaptic markers and improved memory functions [47]. Thus, the cytoprotective and immunomodulatory pharmacological effects of maltol, kojic acid, and chelidonic acid are also mediated through the NF-κB signaling cascade. Currently, no studies have been identified that confirm the involvement of this pathway in the pharmacological effects of comenic and meconic acids. Nevertheless, given their structural similarity and fundamental antioxidant activity, a role for the NF-κB cascade in their action cannot be ruled out, due to the close interconnections between all the regulatory cascades under consideration.

7.4 PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTOR pathway is a highly conserved central signaling cascade found in all eukaryotic cells. It functions to promote cell survival, growth, and proliferation in response to extracellular signals [157]. This cascade can be activated by various molecules, including insulin, glucose, and numerous growth factors and cytokines. Typically, these molecules activate receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCRs), which in turn recruit and activate PI3K to generate phospholipid second messengers. These lipid signals then trigger the activation of downstream kinases, including Akt and mammalian target of rapamycin complex 1 (mTORC1) [158].

The anti-apoptotic effects of many pharmacologically active molecules are mediated through PI3K/Akt activation [159,160]. Activation of the PI3K/Akt/mTOR pathway has been observed upon maltol exposure in cardiomyocytes. In cultured H9C2 cells, maltol increased the expression level of PI3K/Akt upon exposure to cisplatin. Inhibition of PI3K/Akt with LY294002 and HY-10249A reduced the efficacy of maltol [15]. Additionally, maltol restored the cisplatin-induced decrease in PI3K/Akt and mTOR levels by increasing AMPK expression in cisplatin-treated HEK293 cells [18]. In the brain of d-Gal-treated mice, maltol minimized oxidative stress by increasing the phosphorylation levels of PI3K, Akt, Nrf2, and HO-1. That is, maltol activated the Nrf2/HO-1 signaling pathway via PI3K/Akt [5]. A similar pattern was observed in the liver of mice during acetaminophen-induced intoxication. The addition of maltol increased the level of phosphorylated NF-κB, IKKα/β, IκBα, PI3K, and Akt phosphorylation in a dose-dependent manner [13].

A concomitant decrease in various apoptotic markers was reported.

According to molecular docking studies, the maltol molecule interacts with PI3K through alkyl, hydrogen, T-shaped Pi-Pi, and pi-alkyl interactions [161]. It is presumed that activation of the PI3K/Akt pathway by maltol in hepatocytes and chelidonic acid in fibroblasts is mediated via AMPK activation. Through this mechanism, maltol and chelidonic acid may also inhibit the activity of p53, a regulator of the anti-apoptotic protein Bcl-2 [18,65]. Considering that p53 is involved in cellular stress response and interacts with other regulatory pathways, the ability to suppress its positive regulation underscores the therapeutic potential of maltol and chelidonic acid.

More than 150 proteins have been identified as participants in the PI3K/Akt/mTOR cascade. This pathway performs numerous functions in both normal and pathological processes, which complicates the verification of its specific effects [158]. It is suggested that the protective action of kojic acid in osteoarthritis is mediated by inhibition of the PI3K/Akt/mTOR pathway, thereby maintaining a normal level of autophagy [45].

7.5 Nrf2/PINK1/Parkin Pathway

Mitochondria are key cellular organelles responsible for the synthesis of ATP (adenosine-5′-triphosphate) during oxidative phosphorylation. They regulate energy homeostasis, cellular signaling, and apoptosis. In neurons, the high demand for ATP is driven by the need for: the formation of synaptic vesicles; ensuring axonal transport; maintaining ion gradients; preserving the mitochondrial mem-

brane potential [162]. Due to these features, the nervous system is particularly vulnerable to mitochondrial dysfunction [163]. The state of mitochondria significantly influences neuronal activity, as well as brain development and neuroplasticity, through metabolic processes, calcium level regulation, apoptosis, autophagy, and mitochondrial dynamics. Furthermore, mitochondria play an important role in cell differentiation, neurite outgrowth, changes in dendritic structure, and the process of neurotransmitter release and reuptake [164].

Characteristic manifestations of mitochondrial dysfunction observed during aging include: a decrease in adenosine triphosphate (ATP) synthesis, leading to reduced cellular energy supply; the occurrence of mutations in mitochondrial DNA (mtDNA), which disrupts normal mitochondrial function; increased formation of ROS in mitochondria, contributing to the development of oxidative stress; a decline in the activity of antioxidant enzymes, which normally protect cells from damage caused by free radicals; excessive release of pro-apoptotic factors, increasing the likelihood of triggering the programmed cell death (apoptosis) pathway; oxidative damage to various cellular components, including: lipids (disruption of cell membrane integrity), nucleic acids (damage to RNA, DNA, mtDNA), and proteins (denaturation and loss of functional properties) [165,166,167]. Collectively, these changes lead to impaired cellular and tissue function, which is one of the key factors in organismal aging.

It is known that the activation of free radical processes is part of the body's nonspecific response to any external influence, termed the general adaptation syndrome or stress [88]. As noted above, a wide spectrum of nervous system pathologies, ranging from stress of various origins to chronic neurodegeneration, are accompanied by increased ROS production. Cellular antioxidants and free radical-scavenging enzymes eliminate the bulk of the ROS generated. Nevertheless, a small fraction of ROS evades this detoxification system and can damage mitochondrial DNA (mtDNA), proteins, and lipids. Accumulating mutational changes intensify over time, provoking specific defects in respiratory chain complexes and hyperproduction of ROS. This ultimately triggers mitochondrial dysfunction. Most often, its cause is a combination of abnormalities disrupting the expression of genes and proteins associated with mitophagy and mitochondrial dynamics in neurodegenerative pathologies [164].

Neurodegeneration is characterized by disruption of mitochondrial structure, alterations in cristae size, and a decline in both the quality and quantity of mitochondria, leading to an ATP deficit. Impairments in the functional activity of mitochondria may serve as a key regulator of the aging process [166].

Autophagy is a natural cellular process for the utilization and recycling of a cell's internal components. During autophagy, the cell identifies damaged or unnecessary structures (proteins, protein complexes, organelles); isolates them within a special membranous structure called an autophagosome; fuses the autophagosome with a lysosome; degrades the contents via the lysosome into basic "building blocks"; and reuses the resulting molecules for the synthesis of new structures and for energy production [168].

Mitophagy is the process of selective removal of damaged or aged mitochondria through autophagic mechanisms. It is essential for maintaining mitochondrial function and intracellular homeostasis [131,132]. It is a prerequisite for the formation of new, healthy mitochondria through biogenesis [169]. Induction of mitophagy is considered a promising therapeutic target for neuroprotection in aging and age-related diseases [164]. The Nrf2/PINK1/Parkin regulatory cascade ensures the functioning of autophagy and mitophagy processes, leading to the degradation of damaged mitochondria and proteins.

It is suggested that the protective activity of maltol in spinal cord injury may be associated with activation of the Nrf2/PINK1/Parkin pathway, which supports mitophagy [6]. Another study, that investigated the protective effect of maltol on nanoplastics-induced liver injury/investigating the protective effect of maltol on liver damage induced by nanoplastics, reported that maltol maintained the expression of LC3II/I, a key autophagy marker, as well as the p62 protein, while also activating the Nrf2/HO-1 pathway [11].

The p62 protein is primarily localized between adjacent mitochondria and, in PINK1/Parkin-induced mitophagy, facilitates the accumulation of damaged mitochondria. The absence or inhibition of this protein prevents the elimination of dysfunctional mitochondria [132]. In addition to antioxidant defense, activation of the Nrf2 signaling pathway regulates mitochondrial membrane potential, antioxidant protection, biogenesis, and structural integrity [170,171].

Currently, PINK1/Parkin is recognized as the classical mitochondrial autophagy pathway: in dysfunctional mitochondria, the membrane potential decreases, PINK1 accumulates in the outer mitochondrial membrane, and promotes activation and translocation of Parkin [6]. Experimental studies have demonstrated the involvement of Nrf2 in mitophagy via upregulation of *PINK1* and *p62* gene expression [172,173]. The light chain 3 II (LC3-II) protein promotes autophagosome membrane elongation, leading to sequestration of damaged material (proteins or organelles) [174].

Thus, current data suggest that maltol supports impaired mitophagy through activation of the Nrf2/PINK1/Parkin pathway and by maintaining LC3II/I expression induced by the transcription factor FOXO3 [175]. The latter is activated by ROS overproduction and may represent a link to the ROS/FOXO3 signaling pathway (Fig. 4) [176].

Furthermore, maltol has been shown to enhance AMPK expression in a mouse model of cisplatin-induced

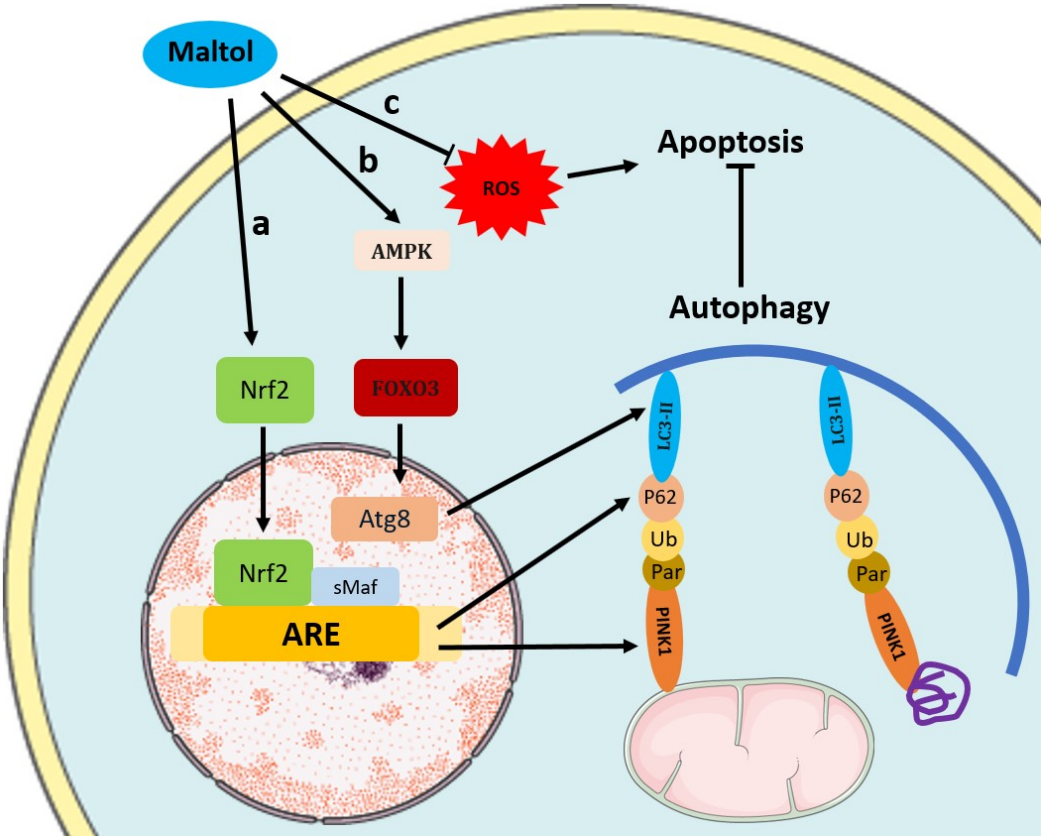

Fig. 4. Potential pathways of maltol action on apoptosis via ROS inhibition and maintenance of ubiquitin-dependent autophagy through Nrf2 and AMPK. A decrease in the membrane potential of a damaged mitochondrion leads to its depolarization. As a result, (1) PINK1 accumulates on the outer mitochondrial membrane (under normal conditions, it is continuously translocated to the inner membrane and subsequently degraded); (2) This triggers a mechanism involving phosphorylation of Parkin (Par) and its substrate ubiquitin (Ub); (3) subsequently, with the involvement of the linker protein p62, which can specifically bind ubiquitinated cargo to autophagosomes, an interaction with microtubule-associated protein 1 light chain 3 II (LC3-II) occurs; (4) this is followed by the sequestration of the material targeted for removal (proteins, organelles) within the autophagosomal membrane. It is hypothesized that maltol may: (a) through activation of Nrf2, influence the formation of p62 and PINK1, thereby stimulating mitophagy; (b) through activation of AMPK, enhance FOXO3 expression, with FOXO3 binding to the Atg3 gene promoter and increasing the amount of Atg3 protein in the cell, where Atg3 is involved in the formation of LC3-II for autophagosome membrane formation; (c) by virtue of its antioxidant activity, inhibit apoptotic processes. FOXO3, forkhead box O3.

nephrotoxicity [18]. AMPK activation in turn can increase FOXO3 expression [177]. Therefore, this represents another potential mechanism by which maltol may support disrupted mito- and autophagy.

Kojic acid demonstrated the ability to induce the expression of LC3-II/I and beclin-1, as well as Atg3, other key positive regulators of autophagy, thereby restoring impaired autophagic function [45]. Moreover, 3-MA, a specific autophagy inhibitor, significantly suppressed the anti-inflammatory and chondroprotective effects of kojic acid in a mouse model of osteoarthritis. Thus, the chondroprotective activity of kojic acid is at least partly mediated by normalization of autophagy.

It should be noted that the mechanisms of mitophagy impairment are quite diverse and can vary significantly depending on the specific organ and pathology. The development of effective strategies aimed at correcting mitophagy defects requires a detailed study and identification of the causes of its dysfunction [169]. For maltol, the stimulation of participants and regulators of the Nrf2/PINK1/Parkin cascade has been demonstrated in spinal cord injury in mice [6], a mouse model of cisplatin-induced nephrotoxicity [18], and in nanoplastics-induced liver injury in mice [11]. Thus, it appears that the protective activity of maltol may be realized through the maintenance of auto- and mitophagy in various pathologies, including pathologies of the nervous system.

Chelidonic acid has been shown to activate AMPK as well [65]. Although its effect on autophagy has not been demonstrated, this possibility cannot be excluded in view of its ability to modulate AMPK activity.

7.6 Interconnection of Regulatory Cascades and Pharmacological Activity of 4H-Pyrans

The Nrf2/Keap1/ARE, Nrf2/PINK1/Parkin, NF-κB, and PI3K/Akt/mTOR pathways regulate the physiological homeostasis of the cellular redox state, stress responses, and inflammation. The molecular mechanisms underlying this regulation are still being elucidated. It is currently believed that Nrf2 plays a crucial role in counteracting the inflammatory response mediated by NF-κB in various experimental models [136]. Activation of Nrf2 in response to injury, intoxication, inflammation, and other stress factors occurs via ROS overproduction and primarily leads to the activation of the cellular antioxidant defense system.

NF-κB induction occurs through inflammatory cytokines, lipid oxidation products, and lipopolysaccharides, suggesting that the signaling cascades of Nrf2 and NF-κB function as a balanced regulatory mechanism, mutually modulating each other's activity [144].

All the discussed signaling and regulatory cascades are closely interconnected and interregulated. In particular, it has been established that the mutual influence of NF-κB and Nrf2 is a complex crosstalk mechanism. These signaling cascades ensure a balance between the inflammatory response and the antioxidant response. The mutual regulation of these cascades occurs at different levels. ROS activate both pathways, but Nrf2 reduces the activity of NF-κB by mitigating oxidative stress, while NF-κB can influence Nrf2 expression. As mentioned above, activated Nrf2 triggers the synthesis of numerous antioxidant enzymes (GPx2, GST, Prdx1, Txn1, Srx1, HO-1, NQO), which leads to a decrease in ROS levels and suppression of ROS-dependent NF-κB activation. Nrf2 also modulates the activity of NF-κB through IκB kinase (IKK). IKK consists of three subunits: IKKα (catalytic); IKKβ (catalytic, the primary kinase in the canonical pathway); and IKKγ (regulatory subunit, also known as NEMO—NF-κB Essential Modulator). In cells, the Keap1 protein constantly suppresses Nrf2, acting as a sensor of intracellular homeostasis. Upon Nrf2 activation, the Nrf2-Keap1 complex dissociates, increasing the concentration of free Keap1 in the cytoplasm. Keap1 interacts with IKKβ, blocking the phosphorylation of the NF-κB inhibitory complex and preventing the nuclear translocation of p65, thereby suppressing signaling through NF-κB [178,179]. Furthermore, Keap1 is capable of directly binding to the p65 subunit of NF-κB [180]. Another point of intersection between the Nrf2 and NF-κB regulatory cascades is the CREB-binding protein (CBP). CBP is a transcriptional co-activator capable of binding to both Nrf2 and the p65 subunit of NF-κB [181]. Thus, Nrf2 can regulate NF-κB signaling by competing with it for CBP protein.

The PI3K/Akt signaling cascade also interacts with the NF-κB pathway. PI3K/Akt-mediated phosphorylation and activation of the RelA/p65 subunit of NF-κB has been demonstrated [181]. This pathway was engaged by maltol in the brain of d-Gal-treated mice [5] and in the liver of mice following paracetamol exposure [13] (see above).

Thus, regulatory cascades exist in a state of continuous dynamic interaction and mutual regulation, not only under normal conditions but also in pathologies. As is known, neurodegenerative processes, both acute and chronic, are associated not only with oxidative stress but also with the activation of inflammatory processes [182,183]. Under conditions of severe ischemia, when significant and irreversible brain damage occurs, NF-κB contributes to neuronal death. This happens through the activation of inflammatory pathways that lead to damage to cellular structures. At the same time, NF-κB may be involved in the mechanism of preconditioning during transient (short-term) or sublethal (non-lethal) ischemia. It is hypothesized that in these cases, NF-κB is partially activated but does not reach full activation. Thus, depending on the degree and duration of the ischemic insult, NF-κB can either promote the development of neuronal death or participate in mechanisms of brain protection [184]. Inhibition of NF-κB is a current strategy to counteract neuroinflammation and neurodegeneration in the brains of individuals with Alzheimer's disease [185].

In this context, maltol has been shown to suppress the NF-κB pathway through the activation of Nrf2 in a mouse model of experimental osteoarthritis [151]. In cell cultures of R28 cells [9], Human Neuroblastoma Cells (SH-SY5Y) [8], and Primary mouse RGCs [10], the neuroprotective effect of maltol was accompanied by the prevention of NF-κB activation. Similarly, the neuroprotective effect of kojic acid in LPS-induced neuroinflammation was also accompanied by the prevention of NF-κB activation [48].

The tumor suppressor p53 regulates apoptosis, cell cycle arrest, senescence, autophagy, DNA repair, and angiogenesis, while NF-κB enhances resistance to programmed cell death and is considered a major regulator of cancer development and maintenance. NF-κB modulates p53 activity, and p53, in turn, influences NF-κB [186].

The cascades regulated by Nrf2 intersect with the p53 pathway in oncopathologies, and Nrf2 may contribute to cancer cell resistance to chemotherapy [187]. It has been demonstrated that the studied 4H-pyran compounds (maltol, chelidonic, and kojic acids) alter the expression and levels of apoptosis regulators such as Bax, caspase-3, and the anti-apoptotic factor Bcl-2 [6,13,15,18,65,188]. These effects are often accompanied by simultaneous modulation of components of the aforementioned regulatory cascades, including MAPK [9,46,48].

Such cross-regulation among Nrf2, NF-κB, PI3K, MAPK, and other signaling factors highlights the remarkable variability of cellular response mechanisms and pathways through which biologically active compounds exert cytoprotective effects, particularly their antitumor activities. Therefore, the pharmacological mechanisms of these compounds may be more specific and not limited to those discussed in the present work. Specifically, this pertains to the neuroprotective effect of maltol in DPN. The au-

thors showed that maltol attenuated the phosphorylation of protein kinase RNA-like ER kinase (PERK) andeukaryotic translation initiation factor 2 subunit α (eIF2α) in rats, suggesting that maltol inhibits ER stress-induced apoptosis by reducing the expression of PERK and eIF2α. This hypothesis was confirmed in experiments on RSC96 cells, where the levels of phospho-eIF2α, eIF2α, phospho-PERK, and PERK were determined in RSC96 cells in the presence of the PERK activator CCT020312 [4]. This also applies to the anti-inflammatory effects of maltol in acetaminophen-induced hepatotoxicity in mice [13], osteoarthritis (a study on mice and human chondrocytes) [149], and intervertebral disc degeneration (a study on mice and culture of rat NPC lines) [161], as well as to kojic acid in an osteoarthritis model in mice and mouse chondrocytes [45]. The same principle extends to maltol and comenic acid metal complexes, in which part of the protective activity is likely attributed to the intrinsic biological activity of the metal ion.

7.7 Direct Interaction With Participants of Regulatory Cascades

As mentioned previously, no direct molecular interactions have been identified to date between the 4H-pyran compounds in question and the immediate components of the Nrf2/Keap1/ARE, NF-κB, and PI3K/Akt/mTOR cascades. Although, as reported above, maltol can potentially activate PI3K [162]. Nevertheless, evidence exists for their interaction with other proteins and enzymes.

It was shown that incubation of hepatocytes with maltol increased catalase activity by 11% [141]. The observed protective effects of maltol under oxidative stress conditions are attributed to the increased catalase activity, which accelerates H_2O_2 decomposition, reducing its concentration and preventing cellular damage. It has been established that maltol forms a complex with catalase, causing conformational changes in the enzyme molecule—loosening of its structural framework, an increase in α-helices, and a slight reduction in β-sheets. Maltol binds to catalase mainly through hydrogen bonds with amino acid residues ARG111, ARG71, and SER113. The binding sites are located near the heme ring of the enzyme's active center; however, maltol does not interact with residues directly responsible for enzymatic activity [141].

It is plausible that the physiological activity of maltol is also mediated by interactions with other proteins and enzymes. For instance, previous studies have shown that maltol binds to bovine serum albumin (BSA) primarily through hydrophobic interactions. A single class of binding sites for maltol has been identified within BSA, with the compound located in subdomain IIA (site I). Similar to its interaction with catalase, maltol binding to BSA induces changes in the secondary structure of the protein [189].

Thus, the confirmed interaction of maltol with catalase, resulting in altered enzymatic activity [141], its binding to BSA [189], and the potential interaction of chelidonic acid with proteins p21, p16, and p53 involved in aging-related signaling and maintenance of cellular homeostasis collectively support the possibility of broader protein interactions [65]. These findings justify further research into the molecular mechanisms underlying the biological activity of 4H-pyran compounds.

7.8 Interaction With Opioid-Like Receptors and GABA Receptors

As mentioned earlier, the molecules of comenic and meconic acids are capable of binding to opioid-like receptors, which underlies their analgesic activity [72,99,100,107]. In addition, the analgesic drug Anoceptin®, based on comenic acid, has successfully completed Phase I clinical trials [190]. The mechanism of analgesic action has been established and described in the literature. It involves interaction with the opioid-like receptor, leading to modulation of the Na,K-ATPase/Src complex. As a result, two signaling cascades are activated.

Signal transduction along the neuronal membrane to the $Na_V1.8$ channel reduces its potential sensitivity, thereby producing an analgesic effect. The second cascade involves transmission of the signal first to PKC and subsequently to ERK1/2, which in turn promotes the activation of trophic processes. ERK1/2 affects transcription factors, coactivators, and corepressors of gene expression through direct interactions [191]. Moreover, ERK1/2 acts upstream of Nrf2 and regulates Nrf2-dependent gene expression, thereby contributing to the protection of cells from oxidative damage [192].

Such activity has been demonstrated for comenic acid and its metal complexes, as well as for meconic acid. To date, it has also been shown that the activity of the $Na_V1.8$ channel is modulated by 5-methoxy-gamma-pyrone-2-carboxylic acid. Further studies in this area are expected to facilitate the development of new, effective, and safe analgesic agents [99].

The mechanism of the [effect/results] observed in the study [117]. The mechanism of the anxiolytic effect of comenic acid in morphine withdrawal syndrome observed in the study has not been investigated. It is known that during withdrawal syndrome, inhibition of GABA release occurs [193]. At the same time, there is data on the interaction of comenic acid with GABA receptors [116]. Thus, it is logical to expect that the anxiolytic effect of comenic acid is related not only to its interaction with opioid receptors but also with GABA receptors. Testing this hypothesis requires further investigation.

For chelidonic and kojic acids, however, no evidence of interaction with the opioid-like receptor has been found. Minor structural differences between these molecules appear to significantly affect receptor affinity. According to the authors, the inability of chelidonic and kojic acids to bind to the receptor is determined by their inability to interact with certain inorganic cations. This may result from the

absence of specific functional groups: the hydroxyl group in chelidonic acid (preventing Ca chelation) and the carboxyl group in kojic acid (preventing salt formation at physiological pH) [24].

Nevertheless, a recent study demonstrated that chelidonic acid significantly improved conduction velocity in motor and sensory nerves and attenuated neuropathic pain [62], indicating that this issue requires further investigation.

The analgesic activity of gallium maltolate, mentioned earlier, is most likely associated with its anti-inflammatory properties [194]. No data have yet been reported regarding analgesic activity or interaction of maltol with opioid-like receptors.

8. Limitations of Current Data and Future Perspectives

8.1 Blood-Brain Barrier

When developing drugs with neuroprotective activity, it is necessary to consider the difficulty of delivering the therapeutic agent to the brain, due to the presence of the blood-brain barrier (BBB). The primary task of the BBB is to protect the brain: it regulates the transport of substances, thereby maintaining a stable environment without which the normal functioning of the nervous system is impossible. On the other hand, the BBB can prevent the penetration of drugs into the brain, hindering the manifestation of their neuroprotective activity [195]. Due to the structure of the BBB, only small lipophilic molecules are able to penetrate it [196]. However, most lipophilic drugs capable of penetrating the BBB are prone to efflux from the cell due to the function of the BBB [197]. No pharmacokinetic studies have been found that determine the ability of the compounds under consideration to cross the blood-brain barrier and distribute within the brain. No publications have been found that address the distribution of these compounds in the body, their metabolism, or their elimination rate. The relatively small molecular sizes of these compounds suggest the possibility of BBB penetration. Indirect evidence for the ability to cross the BBB can be inferred from the sedative effect of comenic acid [71]. Nevertheless, this issue requires further investigation.

An inability to cross the BBB would necessitate the development of a method to deliver these compounds to the brain. In particular, nanoscale drug delivery systems are showing promising clinical results: they facilitate drug transport into the brain and optimize their pharmacokinetic profiles. However, further research is required to translate these approaches into clinical practice in humans [197,198]. Intranasal administration offers a non-invasive and patient-friendly method to bypass the BBB and reach the CNS. The advantages of intranasal administration include rapid absorption, immediate onset of action, absence of first-pass hepatic metabolism, and high patient comfort [199]. In article [200] successful delivery of neurotrophic factors carried by extracellular vesicles was achieved via intranasal administration for the treatment of ischemic stroke in mice. In the study [201] successful delivery of nanoparticles for targeted therapy of ischemic stroke was achieved via the nasal route. Progress in the field of drug delivery to the brain is reviewed in reviews [198,199,202] and others.

8.2 Limitations of the Models

The use of rodents (rats and mice) is the “gold standard” in preclinical research; however, there is a significant gap between successful results in animals and failures in human clinical trials.

The main limitations of these models in the context of neuroprotection include: biological and anatomical differences, methodological discrepancies, genetic homogeneity, and others. Biological and anatomical differences stem from the fact that the ratio of white to gray matter differs between rodents and humans. In humans, white matter (myelinated fibers) constitutes about 50% of the brain, whereas in rodents it is only about 10%. Many neuroprotective agents protect neurons (gray matter) but are ineffective at protecting axons, which is critical for humans. The rodent brain lacks convolutions (it is lissencephalic), while the human brain is gyrencephalic. This affects pressure distribution during injury and the characteristics of blood supply. Furthermore, the response of microglia and astrocytes to damage proceeds differently in mice. Neuroinflammation—a key target of neuroprotection—has different timescales and mediators across species.

Methodological discrepancies arise because most studies are conducted on young, healthy animals. However, neurodegeneration is primarily a problem of the aging brain. The aging brain possesses different regenerative mechanisms and levels of oxidative stress. Additionally, rodents and humans differ, for example, in the growth of the infarct zone [203]. The issue of genetic homogeneity is related to the fact that the use of inbred strains allows for reproducible results but does not account for the genetic diversity of the human population. Even the influence of the circadian rhythm on neuroprotection must be considered in translational research on stroke and central nervous system diseases [204].

Overcoming these limitations requires testing neuroprotectants in multiple animal species. Gyrencephalic primates or cats are desirable as a second species following rodent tests; however, cost, availability, and ethical acceptability may pose challenges. It is necessary to include groups of aged animals and animals with conditions like hypertension. The minimum effective dose and the maximum tolerated dose must be determined. It is also essential to verify that the drug reaches the target organ within these dose ranges. Both histological and behavioral outcomes should be assessed, with behavioral evaluations conducted over the long term. Key physiological parameters must be monitored regularly. Finally, positive results obtained in one laboratory need to be replicated in at least one independent laboratory before proceeding to clinical trials [205].

As discussed above (Table 1), the neuroprotective activity of the compounds under consideration has been investigated *in vitro* in various cellular models, as well as *in vivo* in rodents. However, for each neurodegeneration model, there is only one, or at most two, studies in animal models. The neuroprotective effect of maltol in experimental DPN has been studied in two works. For comenic acid, there are several studies examining its antioxidant effect under general stress exposure and hypoxia, but no studies exist on its selective effect on the brain. Only two studies have been performed on aging models (maltol and chelidonic acid) and one on an Alzheimer's disease model (kojic acid). The sedative effect of comenic acid has been investigated in a single model. For meconic acid, no animal studies were found—only *in vitro* work confirming a mechanism similar to that of comenic acid.

Thus, the currently available data on the neuroprotective properties of the compounds under consideration are, overall, at an early stage of preclinical research. To better understand their therapeutic potential, further studies are necessary, not only in rodents but also in other models more closely related to humans. Furthermore, the existing data do not allow for an assessment of the range of effective concentrations, nor the doses at which these are achieved. The importance of this point can be illustrated by study [47], in which HepG2 cells showed an increase in p-Nrf2 at kojic acid concentrations of 4.22 mM and 8.02 mM, whereas a decrease in p-Nrf2 was observed at a concentration of 12.67 mM.

8.3 Mechanisms of Neuroprotective Activity

The antioxidant effect of these compounds is well-documented in experiments with cell cultures and in animal models. The mechanism of direct antioxidant activity is generally understood. However, considering the established ability of maltol to activate catalase, it is logical to continue research in this direction. The possibility of influencing the activity of other antioxidant enzymes by maltol and other compounds could be explored.

It remains unclear how the activation of the Nrf2/Keap1/ARE cascade, the transcription factors NF-κB, the PI3K/Akt/mTOR cascade, and the Nrf2/PINK1/Parkin cascade occurs. Direct interaction has not been established for the compounds under consideration. The mechanism of the anxiolytic effect of comenic acid requires elucidation. Currently, the triggering of a particular molecular cascade has been documented, but it is not clear what serves as the trigger for this activation. It should be noted that molecular cascades have functional peculiarities in different cell types. Therefore, results obtained for one cell type may not be reproducible in others. The importance of addressing this issue is illustrated, for example, by the bidirectional effect of kojic acid. In chondrocytes [45] and melanocytes [151], its application was observed to suppress NF-κB activation, whereas in hepatoma cells, activation of NF-κB was noted [46]. Considering the involvement of the discussed molecular cascades in a wide range of pathologies, selecting the pathology optimal for therapeutic efficacy seems important.

Pb^{2+} ions reduce the activity of PKC and NF-κB *in vitro* [206]. NF-κB and Nrf2 are involved in the response to stress [207,208]. Therefore, it is logical to investigate the involvement of these pathways in the stress-protective activity of comenic acid and its neuroprotective effect in lead intoxication.

Addressing these questions should appropriately begin with Structure–Activity Relationship (SAR) analysis and molecular docking to identify the most probable molecular interactions and binding sites. For example, for maltol, an interaction with PI3K is suggested based on docking results [161]. Subsequent *in vitro* and *in vivo* experiments will need to confirm or refute these findings. The development of modern high-throughput technologies, which enable the quantitative analysis of thousands of proteins and metabolites in biological fluids, offers the prospect of progress in solving this task [209]. Furthermore, live-cell imaging with fluorescent labels [210], single-cell and spatial transcriptomics analysis should help resolve the issue of differences in the response of different cell types [211,212].

9. Conclusions

4H-pyran derivatives exhibit a broad spectrum of pharmacological activity. They have demonstrated hepatoprotective, nephroprotective, cardioprotective, chondroprotective, and neuroprotective effects, as well as the ability to inhibit tumor cell growth. Due to the structural similarity of these compounds, many of their biological effects are analogous. Recently, the greatest research interest has been directed toward the protective effects of maltol, comenic acid, and chelidonic acid in pathologies of the nervous system. These compounds have been tested and have shown good results in oxidative brain damage, DPN, brain aging models, and paclitaxel-induced neuropathy, as well as in more numerous cell culture studies. On the other hand, the greatest progress towards clinical application has been noted for comenic acid. It has been reported that the analgesic drug Anoceptin®, based on this compound, has completed the first phase of clinical trials. The anti-inflammatory and wound-healing properties of comenic acid are utilized in medicine in the preparations "Baliz-2" and "Baliz" suppositories. For the other compounds considered, no reports of clinical trials regarding neuroprotective activity were found. Meconic acid currently remains the least studied; only *in vitro* studies have been conducted for it.

All the 4H-pyran compounds examined possess significant potential for the development of new, effective, and specific pharmaceutical agents, including those with neuroprotective activity. However, despite the documented involvement of the Nrf2/Keap1/ARE, NF-κB, PI3K/Akt/mTOR, and Nrf2/PINK1/Parkin cascades in the

observed neuroprotective effects of maltol, chelidonic acid, and kojic acid, the specific molecular interactions responsible for engaging these pathways have not been identified. Although for comenic acid, the mechanisms of its analgesic and neurite-stimulating actions have been elucidated.

Furthermore, the pharmacokinetics of these compounds regarding their ability to cross the blood-brain barrier has not been investigated. The issues of optimal therapeutic concentrations and the most effective doses also need to be addressed.

To date, studies have been conducted on rodents. To confirm the obtained data, research on other models closer to humans, particularly primates, should be undertaken. This will provide a better understanding of the therapeutic potential of each compound for specific pathologies.

SAR analysis, molecular docking, live-cell imaging with fluorescent labels, single-cell and spatial transcriptomics analysis, as well as other modern techniques, should help resolve these questions.

Abbreviations

DPN, diabetic peripheral neuropathy; MNCV, motor nerve conduction velocity; ROS, reactive oxygen species; SOD, superoxide dismutase; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; HO-1, heme oxygenase-1; Bcl-2, B-cell lymphoma 2; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; AD, Alzheimer's disease; Nrf2, Nuclear factor erythroid 2-related factor 2; LP, lipid peroxidation; TLR4, Toll-like receptor 4; p-NF-κB, phosphorylated NF-κB; LPS, lipopolysaccharides; p-JNK, phosphorylated c-Jun N-terminal kinase; KAD, kojic acid dimer; TNF-α, tumor necrosis factor-α; CA, comenic Acid; ChA, Chelidonic acid; BDNF, brain-derived neurotrophic factor; IL, interleukin; RNA, ribonucleic acid; CHOP, C/EBP homologous protein; GRP78, glucose-regulated protein 78; HG, high concentration of glucose; PA, palmitic acid; MME, Membrane metallo-endopeptidase; eIF2α, eukaryotic translation initiation factor 2 subunit α; ER-β, estrogen receptor β; HIF-1α, Hypoxia-inducible factor 1-α; SMA-2, spinal muscular atrophy type 2; TTX, tetrodotoxin; GABA, gamma-aminobutyric acid; APP, amyloid precursor protein; IKK, IκB kinase; GSK-3β, glycogen synthase kinase-3β; CREB, response element-binding protein; NMDA, N-methyl-D-aspartate; Keap1, Kelch-like ECH-associated protein 1; RBX1, RING-box protein 1; sMaf, small Maf proteins; ARE, antioxidant response element; GPx2, glutathione peroxidase 2; PERK, protein kinase RNA-like endoplasmic reticulum kinase; Prdx1, peroxiredoxin 1; Txn1, thioredoxin 1; Srx1, sulfiredoxin; DNA, deoxyribonucleic acid; Cul3–E3 ligase, Cullin-3-containing E3 ubiquitin ligase complex; GPCRs, G protein-coupled receptors; RTKs, receptor tyrosine kinases; CBP, CREB-binding protein; mTORC1, mammalian Target of Rapamycin Complex 1.

Author Contributions

AK: conceptualization and writing original draft. SK: conceptualization and writing original draft. RK: writing—review & editing and search references. OkL: search references. AD: search references and writing—review & editing. OlL: visualization and writing—review & editing. JLHC: writing original draft and search references. SD: writing—review & editing and search references. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

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