ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

REVIEW ARTICLE

Pharmacological Effects of Dexpanthenol

Solaiman Doba[1], Anna Buzlama[2], Alexander Kuznetsov[2]
[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Manarauniversity, Syria.
[2]Department of Pharmacology and Clinical Pharmacology,
Faculty of Pharmacy, Voronezh State University, Russia.
*Corresponding Author E-mail: **suliman.doba@manara.edu.sy, silversleman23@gmail.com, buzlama@pharm.vsu.ru, buzlamaa@yandex.ru**

ABSTRACT:
This article focuses on examining and combining published information regarding the latest pleiotropic pharmacological impacts of dexpanthenol.Particular attention in this article is paid to the pharmacological protective effects of dexpanthenol on the kidneys, liver, brain and nerves, gastrointestinal tract, and the cardiovascular and respiratory systems.In general, a substantial amount of experimental and clinical data has been accumulated, which allows us to conclude that further investigation into the pleiotropic effects of dexpanthenol holds promise. A wide range of target organs and tissues, coupled with its low toxicity, make dexpanthenol a promising ingredient for the development of new drugs.The most promising effects for further study are antioxidant, anti-inflammatory, gastroprotective, hepatoprotective, and neuroprotective effects. It is particularly crucial to investigate the efficacy of dexpanthenol through alternative methods of administration, in addition to the established external use and intraperitoneal route of administration used in preclinical studies. For instance, oral administration should be explored, encompassing a broad range of doses, including smaller ones.The development of various local dosage forms, such as gels, wound dressings, ophthalmic films, and others, as well as liquid forms like solutions and syrups, and solid forms like capsules with liquid contents, is significant. These developments have the potential to expand the clinical applications of dexpanthenol in various fields, including dermatology, gastroenterology, neurology, and general internal medicine.

KEYWORDS: Dexpanthenol, Pleiotropic effects, Pharmacological effects, Nephroprotective, Hepatoprotective, Neuroprotective, Gastroprotective, Cardioprotective, Pulmoprotectivedrugs.

INTRODUCTION:
Dexpanthenol is an amide of a monocarboxylic acid with hydroxy groups at specific positions and a 3-hydroxypropyl group attached to the carbomyl nitrogen[1,2]. Dexpanthenol functions as a provitamin B_5 and shares a resemblance to pantothenic acid. Pantothenic acid is a vital component of coenzyme A, which plays a crucial role in cellular metabolism as the coenzyme acetyl CoA. Pantothenic acid is crucial for the development and rejuvenation of the skin and mucous membranes[3].

Received on 04.12.2023 Modified on 16.03.2024
Accepted on 22.04.2024
Research J. Pharm. and Tech 2024; 17(7):3499-3504.
DOI: 10.52711/0974-360X.2024.00547

Dexpanthenol is considered non-toxic with an oral LD_{50} of 15g/kg in mice, but side effects and allergic reactions have been reported[4,5,6]. Although contact allergy to dexpanthenol is rare[7,8]. The authenticity of dexpanthenol is determined by IR spectroscopy, and quantitative determination is done chemically using perchloric acid. In this review we mentioned the newest well-studied pleiotropic effects of dexpanthenolon different body organs.

1. Wound healing effect of dexpanthenol:
The application of dexpanthenol on the skin to treat skin conditions is well-documented. Research has shown that using dexpanthenol topically can help accelerate the healing of minor wounds. Dexpanthenol initiates the activation of essential genes involved in the healing process, thereby expediting wound healing through the

facilitation of re-epithelialization and the restoration of the skin's barrier function[9]. The application of topical dexpanthenol serves as a moisturizing agent that improves skin hydration, diminishes water loss, and maintains the skin's suppleness and elasticity[10]. Dexpanthenol has been shown to promote the proliferation of fibroblasts, a crucial factor in the process of wound healing. Both in vitro and in vivo, the application of dexpanthenol has been associated with enhanced re-growth of epithelial cells, thereby expediting the overall wound healing process[11]. Moreover, there have been documented instances of expedited re-epithelialization in the context of wound healing, where the preservation of the epidermal barrier integrity is evaluated through the measurement of transepidermal water loss as as an indicator[12]. Furthermore, the application of a heparin-allantoin-dexpanthenol ointment has demonstrated the anti-inflammatory properties of dexpanthenol on UV-induced erythema in guinea pigs[13]. Dexpanthenol undergoes metabolic conversion within the body to yield pantothenic acid, where it functions as a constituent of coenzyme A. Coenzyme A is essential for facilitating the early steps of fatty acid and sphingolipid production, which are vital for preserving the structure of lipid bilayers in the stratum corneum and cellular membranes. The use of dexpanthenol has shown significant improvements in skin barrier repair, hydration of the stratum corneum, as well as a reduction in skin roughness and inflammation[14]. Due to extensive research on the wound-healing properties of dexpanthenol, it is evident that ointments and creams are the primary topical treatments used in dermatology. However, there is great potential in diversifying the range of local dosage forms for skin and mucous membrane application. This includes the development of hydrogels, patches, and wound coverings, which hold promise in enhancing the effectiveness of dexpanthenol.

2. The nephroprotective effect of dexpanthenol:

The impact of dexpanthenol in protecting rats against gentamicin-induced nephrotoxicity was examined[15]. This research demonstrates that the administration of dexpanthenol can mitigate the nephrotoxic effects induced by gentamicin. The rats in the study were intraperitoneally injected with dexpanthenol at a dosage of 500mg/kg for a duration of 8 days. In the group treated with dexpanthenol, there were notable reductions in the levels of urea, creatinine, tumornecrosisfactor-alpha, total oxidant status, oxidative stress index, and malondialdehydein comparison to the group treated solely with gentamicin.Furthermore, the levels of catalase and glutathione peroxidase were notably increased in the gentamicin/dexpanthenol group. Histological analysis revealed pronounced tubular necrosis in the gentamicin group, whereas this condition was less severe in the dexpanthenol group[16]. In a separate investigation, researchers examined the potential protective impact of dexpanthenol against cisplatin-induced nephrotoxicity in rats[17]. The experimental group received a one-time administration of cisplatin, followed by a daily dosage of 500 mg/kg of dexpanthenol over a span of 10 days. Results indicated a reduction in levels of malondialdehyde, blood urea nitrogen, and creatinine, alongside an elevation in superoxide dismutase, catalase, glutathione peroxidase, and myeloperoxidase levels within the dexpanthenol-treated group. The group administered with dexpanthenol demonstrated reduced damage and inflammation in the renal tubules in contrast to the group treated with Cisplatin. The antioxidant and anti-inflammatory characteristics of dexpanthenol suggest its potential therapeutic efficacy in managing cisplatin-induced nephrotoxicity[18]. In another study, researchers examined the protective and healing properties of dexpanthenol in mitigating kidney injury caused by ischemia-reperfusion in rats. Dexpanthenol was delivered via intraperitoneal administration at a dosage of 500mg/kg prior to ischemia, during ischemia, and throughout the late reperfusion phase. The findings indicated that dexpanthenol effectively alleviated renal ischemia-reperfusion damage by diminishing significant tubular necrosis, glomerular impairment, and apoptosis as observed in histological assessments[19]. Experimental studies have shown that dexpanthenol possesses antioxidant properties and has the capacity to enhance renal function. The research utilized a dosage of 500 mg/kg delivered intraperitoneally, resulting in observed nephroprotective benefits. This data showed that dexpanthenol can play a promising role in the development of new nephroprotective drugs. In contrast, a dose of 500mg/kg appears to be a significant amount. Additionally, intraperitoneal administration is not a comfortable route for humans. Therefore, it is recommended to prepare dexpanthenol in a solution for injection and administer it through an alternative route, such as intravenous drip. This would make it technically feasible to administer the high dose.

3. The hepatoprotective effect of dexpanthenol:

The hepatoprotective effects of dexpanthenol in mitigating liver injuries induced by ischemia-reperfusion was examined *In vivo*. Results from this study demonstrated that pre-treatment with dexpanthenol successfully reduced oxidative stress and increased antioxidant levels in the rat model subjected to liver ischemia-reperfusion. The intraperitoneal administration of dexpanthenol at a dosage of 500mg/kg, administered 30 minutes prior to a 60-minute ischemic event followed by 60minutes of reperfusion, resulted in notable enhancements in overall glutathione levels and effectively mitigated the heightened myeloperoxidase

production in rat subjects. Furthermore, the administration of dexpanthenol led to a reduction in histological tissue damage in both the dexpanthenol and dexpanthenol combined with ischemia-reperfusion groups[20]. In a research study by Mukaddes Gurler et al., the protective potential of dexpanthenol against liver oxidative damage induced by methotrexate in rats was investigated. Dexpanthenol was delivered intraperitoneally at a dosage of 500mg/kg/day over a period of 24days. The findings indicated that dexpanthenol exhibited a mitigating effect on the hepatotoxicity induced by reactive oxygen species resulting from methotrexate exposure. The enhancement was noted in relation to the antioxidant/oxidant enzymes of liver tissue, liver function assessments, and histological alterations. Consequently, it was recommended that dexpanthenol could be utilized in conjunction with methotrexate therapy to mitigate liver toxicity[21]. Another researcher examined the protective effects of dexpanthenol at a dose of 500mg/kg intraperitoneally against acetaminophen-induced oxidative hepatorenal damage[22,23]. The study indicated that dexpanthenol led to a notable reduction in oxidant levels in the liver and kidney tissues, along with an elevation in antioxidant levels compared to the acetaminophen group. Additionally, findings from biochemical and histological evaluations demonstrated that dexpanthenol exhibited hepatoprotective effects similar to those of N-acetylcysteine[24]. Another research experiment was conducted to examine the impact of dexpanthenol on diabetic rats induced with streptozotocin. Streptozotocin is a commonly utilized agent for inducing diabetes in animal models[25]. Diabetes was experimentally induced through a single intraperitoneal dose of streptozotocin at a concentration of 50mg/kg. Following streptozotocin administration, one group was initiated on a daily intraperitoneal regimen of 300mg/kg of dexpanthenol for a duration of 6 weeks. The group subjected to dexpanthenol treatment demonstrated a partial restoration of normal hepatic parenchyma. The results of histochemical analyses demonstrated that the reduction in glycogen levels caused by diabetes was notably ameliorated through the administration of dexpanthenol. The supplementation of dexpanthenol in this group led to a decrease in the severity of degenerative changes. Levels of IL-1α and MCP-1 were comparable to those in the control group. These findings indicate that dexpanthenol exhibits efficacy in mitigating diabetic complications induced by streptozotocin and could offer therapeutic advantages for individuals with diabetes[26]. We can suggest that the administration of dexpanthenol may help prevent hepatotoxicity, inflammation, and necrosis. The development of new hepatoprotective drugs containing dexpanthenol in oral or injectable dosage forms should be considered relevant. The most promising application of dexpanthenol is specifically for drug-induced liver damage.

4. The neuroprotective and behavioral effects of dexpanthenol:

The neuroprotective effects of dexpanthenol were studied in rats with traumatic brain injury. Dexpanthenol was administered intraperitoneally at a dosage of 500 mg/kg. The group treated with dexpanthenol exhibited reduced neuronal damage in the cortices under microscopic observation following traumatic brain injury. Consequently, findings suggest that dexpanthenol mitigates oxidative damage, inhibits apoptosis through the activation of antioxidant mechanisms, and mitigates brain injury resulting from traumatic brain injury[27]. The behavioral effect of dexpanthenol in animals have not been adequately established. SalimİnanandYağmurAçikgöz conducted a study to investigate the anticonvulsant properties of dexpanthenol on seizures induced by Pentylenetetrazole, a GABA receptor antagonist commonly employed to induce chemically-induced seizures in research settings[28]. Of all the animal models used to study seizures and epilepsy, pentylenetetrazole-induced seizures are classified as a model representing generalized seizures, as opposed to partial or focal seizures. Additionally, the antidepressant-like effect was evaluated using the forced swim test. The forced swim test is a rodent behavioral test used for evaluation of antidepressant drugs, antidepressant efficacy of new compounds[29]. In their study, it was documented that the administration of dexpanthenol at a dosage of 500mg/kg via intraperitoneal injection resulted in notable antiepileptic and antidepressant properties, while not impacting motor function[30]. The findings of this study suggest that dexpanthenol demonstrates potential as a beneficial clinical intervention for managing pain and nerve injury. To induce a crush injury, the right sciatic nerve of all rats was clamped for a duration of one minute. In a specific experimental group, a dosage of 500mg/kg of dexpanthenol was administered intraperitoneally one day prior to the surgical procedure. This dosage was continued three times a week for a period of 28 days during the experiment. In another experimental group, rats received a dose of 10mg/kg of dexpanthenol to investigate the potential effects of dexpanthenol alone. The performance of the groups administered with dexpanthenol showed a notable increase during the rotarod test at both 30rpm and 40rpm. Subsequently, there was a significant rise in the number of rats capable of sustaining their position on the rod in these two groups during the acceleration test. Hot plate latency test results were also significantly higher in the dexpanthenol groups[31]. In this study, the comparative effectiveness of a low dose of 10mg/kg and a high dose of 500 mg/kg is of particular interest, which makes

further studies on the effects of dexpanthenol in small dose ranges promising. Due to the analysis of the data indicating potential neuroprotective, anticonvulsant, and antidepressant effects, as well as unclear and contradictory findings regarding its impact on muscle tone control, further research in this area is recommended. In any case, the specified list of pharmacological effects indicates the potential of using dexpanthenol as a nootropic and neurometabolic agent.

5. The gastrointestinal effect of dexpanthenol:

The efficacy of dexpanthenol in treating ulcers has been documented not in its isolated form but as part of a mixture. This study utilized an oral administration of dexpanthenol at a dosage of 6.88mg/kg. This research has indicated that a chitosan-based gel incorporating dexpanthenol exhibits notable gastroprotective properties in experimental models of NSAID-induced gastropathy, both in preventive and therapeutic regimens, as well as in stress-induced ulcer formation. It decreases the quantity and size of ulcerative lesions and mitigates the effects of organ-specific toxicity induced by NSAIDs. In this study, it was revealed that the gel diminishes the symptoms of organ-specific toxicity caused by diclofenac sodium. Additionally, it exhibits gastroprotective effects, anti-inflammatory, hepatoprotective, and hemostatic properties[32,33]. These results are consistent with literature data.The therapeutic potential of dexpanthenol was elucidated on the amelioration of colitis in rats. Colitis was provoked through the rectal administration of a single dose of 4% acetic acid into the colon for three consecutive days. 4% acetic acid solution led to the development of intense and profound colitis, accompanied by a notably elevated mortality rate[34]. In the experimental group, beginning on the fourth day, a single dose of dexpanthenol at a dosage of 500mg/kg was given intraperitoneally for three consecutive days. Total oxidant status and oxidative stress index levels in the dexpanthenol group were reduced compared to the acetic acid group. However, no significant increase in total antioxidant capacity levels was detected. The use of dexpanthenol resulted in positive changes in both biochemical and histopathological aspects, suggesting that dexpanthenol could potentially act as an antioxidant in treating colitis[35]. The anti-ulcer and anti-colitis activity of dexpanthenol was not clearly reported. The anti-ulcer effect of dexpanthenol itself was not studied, but rather a mixture containing dexpanthenol prepared in a chitosan-based gel. The anti-colitis effect was studied on a single model using a single dose and only one route of administration. However, further research in the area of gastroprotective activity is promising, considering the well-studied regenerative activity of dexpanthenol. This includes the potential development of oral dosage forms of dexpanthenol, such as liquid (solution, syrup) or solid (capsules with liquid contents), for the treatment of hyperacid gastritis, ulcerative diseases of the stomach and duodenum, as well as the treatment and prevention of NSAID gastropathy and stress ulcers.

6. The respiratory and cardiovascular protective effect of dexpanthenol:

A study documented a protective effect of pantothenic acid against bleomycin-induced pulmonary fibrosis in rats. For the experimental group, 500mg/kg of dexpanthenol was administered intraperitoneally 1 hour before the intratrachealbleomycin injection and continued for 14 days. It was shown that dexpanthenol significantly prevents bleomycin-induced lung fibrosis in rats[36]. Another research study examined the anti-inflammatory and anti-oxidative properties of dexpanthenol in vivo of acute lung injury induced by lipopolysaccharide. Lipopolysaccharide is known to trigger acute lung injury and alveolar hemorrhage through the cytokine storm[37]. Intraperitoneal administration of Dexpanthenol at a dosage of 500 mg/kg resulted in a notable decrease in pulmonary edema. Findings indicate that Dexpanthenol demonstrates a protective influence in this particular model by virtue of its anti-inflammatory and antioxidant properties[38]. Therefore, it can be inferred that the protective impact of dexpanthenol on the respiratory and cardiovascular systems primarily stems from its anti-inflammatory and antioxidant properties. However, further studies should be conducted to explore additional dosing options and routes of administration in order to gather more data for the development of new drugs containing dexpanthenol. It is also promising to study the direct anti-inflammatory effect of dexpanthenol on specific models of inflammation.

Tabl 1: Pleiotropic effects of dexpanthenol:

Organ	Effect	Dose	In vivo model
Skin	Wound healing, anti-inflammatory effect[9-14], topical administration	5%	Lesions (superficial wounds) of the skin and mucous membranes
Kidneys	Nephroprotective effect[16-19], intraperitoneal administration	500 mg/kg, 8 days	Gentamicin-induced nephrotoxicity
		500 mg/kg, 10 days	Cisplatin-induced nephrotoxicity
		500 mg/kg, before, during ischemia and late reperfusion	Ischemia-reperfusion
Liver	Hepatoprotective,antioxidant,anti-inflammatory effect[20-26],intraperitoneal administration	500 mg/kgfor 30 min before 60 min of ischemia, followed by 60 min of reperfusion	Ischemia-reperfusion-induced liver injury

		500 mg/kg/day, 24 days	Methotrexate-induced liver oxidative toxicity
		500 mg/kg	Acetaminophen-induced oxidative hepatorenal damage
		300 mg/kg/day, 6 weeks	Streptozotocine-induced diabetic
Brain/ Nerves	Neuroprotective effect[27-31], Intraperitoneal administration	500 mg/kg	Induced traumatic brain injury
		500 mg/kg	Sciatic nerve injury
	Antiepileptic,antidepressant-like effects[30], intraperitoneal administration	500 mg/kg	Antiepileptic: convulsions caused by pentylenetetrazole;antidepressants:forced swim test
Gastrointestinal tract	Gastroprotective, hepatoprotective,anti-inflammatory,hemostatic properties[32,33], oral administration	6,88 mg/kg	NSAIDs, stress, and ethanol induced stomach ulcer
	Anti-colitis effect[35], intraperitoneal administration	500 mg/kg/day, 3 days	Acetic acid-induced colitis
Respiratory and Cardiovascular system	Respiratory protective effect[36,38], intraperitoneal administration	500 mg/kg, 1 hour before of bleomycin, 14 days	Bleomycin-induced pulmonary fibrosis
		500 mg/kg	Lipopolysaccharide-induced acute lung injury

CONCLUSION:

The pleiotropic effects of dexpanthenol include its protective effects on the kidneys, liver, brain and nerves, gastrointestinal tract, and the cardiovascular and respiratory systems (table. 1). The precise mechanism underlying the pleiotropic effects of dexpanthenol has not been fully elucidated. However, it is established that the application of antioxidants can mitigate the detrimental impacts of free radicals in the context of inflammation[39]. Dexpanthenol acts as an antioxidant by elevating the concentrations of reduced glutathione, coenzyme A, and promoting ATP synthesis. These mechanisms play a vital role in protecting cells against oxidative stress, thereby influencing the reduction of inflammatory reactions and accelerating the healing process. These results are believed to be a result of the synergistic impact of its antioxidant and anti-apoptotic characteristics. Research has firmly established that dexpanthenol demonstrates significant capabilities in scavenging free radicals and providing antioxidant benefits in both in vivo and in vitro investigations[37, 38]. In most of the studies reviewed, it can be concluded that dexpanthenol has beneficial effects on the tissue level due to its anti-inflammatory properties and protective effects against oxygen free radicals, as indicated by biochemical and histopathological results.

A substantial body of experimental and clinical evidence has been gathered, supporting the potential for additional research on the multifaceted impacts of dexpanthenol. Given its broad spectrum of target organs and tissues, as well as its minimal toxicity profile, dexpanthenol emerges as a favorable candidate for the formulation of novel pharmaceuticals. Particularly noteworthy are its antioxidant, anti-inflammatory, gastroprotective, hepatoprotective, and neuroprotective properties, which warrant further investigation. It is imperative to explore the effectiveness of dexpanthenol using alternative modes of delivery, in conjunction with the conventional methods of topical application and intraperitoneal administration employed in preclinical research. For example, it is important to investigate the oral delivery method across a wide spectrum of dosages, including lower amounts. The creation of diverse localized dosage formats such as gels, wound coverings, ophthalmic films, and similar products, as well as liquid formulations such as solutions and syrups, and solid formulations like capsules containing liquid components, holds considerable importance[40- 43]. These developments have the potential to broaden the clinical applications of dexpanthenol in fields such as dermatology, gastroenterology, neurology, and general internal medicine.

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