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Review Article

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Dexpanthenol: New Insights on Wound Healing, a Review

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Abstract

Dexpanthenol, a vitamin from the B complex that is an alcoholic analogue of pantothenic acid (vitamin B5), is converted to pantothenic acid by certain enzymes and then circulated throughout the body as coenzyme-A. Pantothenic acid is rich in the liver, kidney, butter, almond and wheat bran. Dexpanthenol is administered topically as an ointment, emulsion, or solution at dosages of 2 to 5% to treat a variety of skin and mucosal conditions. Pantothenic acid is reported to act as anti-inflammatory, radical scavenger and assist in the wound healing. In this review, we shed some light on the dietary sources, medicinal significance, and wound healing applications of dexpanthenol.

KEYWORDS
Dexpanthenol, Dietary sources, Wound healing, Pantothenic acid.

INTRODUCTION

Dexpanthenol is an alcoholic analogue of pantothenic acid, a member of the B complex vitamins (vitamin B5), it is enzymatically oxidized to pantothenic acid, which is distributed into the tissues; mainly as coenzyme- A. Pantothenic acid is optically active, only the dextrorotatory isomer has biologic activity, dexpanthenol is freely soluble in water and alcohol, practically fat insoluble, and it is the most stable form of pantothenic acid in liquids (Fritz *et al*., 2020).

Dexpanthenol supports the body's natural response to injury by initiating the proliferation of cells involved in wound healing and re-epithelialization (Proksch *et al*., 2017). The addition of a medium containing 0.1% dexpanthenol to traumatized skin constructs lead to the regeneration of epidermal cells and the formation of new cellular layers within 1 week, as assessed histologically (Weber and Muller-Goymann, 2009).

In this review, we would like to throw the light on dexpanthenol dietary sources, medical importance, and its uses in the wound healing.

Dexpanthenol

Dexpanthenol is a B complex vitamin that is an alcoholic analogue of pantothenic acid (vitamin B5), it is oxidized by certain enzymes to pantothenic acid, which is subsequently transported throughout the body as coenzyme-A. Although all isomers of pantothenic acid are optically active, dextrorotatory isomer only is biologically active. Dexpanthenol is the most stable form of pantothenic acid in liquids, as it is dissolves easily in water and alcohol but essentially insoluble in lipids (Fritz *et al*., 2020).

Dexpanthenol is used as an adjuvant in the treatment of various skin and mucosal lesions when topically applied as an ointment, emulsion, or solution at doses of 2 to 5%. Topical formulations marketed in Europe typically have a 5% concentration, whereas US FDA-approved dexpanthenol preparations for topical treatment to reduce itching or promote healing of certain dermatoses have a 2% concentration. Dexpanthenol in addition to being used in topical preparations; can also be taken systemically; 250 to 500 mg of dexpanthenol has been given to adults (Fritz *et al*., 2020).

Dietary Sources and Intake of pantothenic acid

Peanut butter (5-8 mg/100 g), liver (5-7 mg/100 g), kidney (4-6 mg/100 g), peanuts (2-3 mg/100 g), almonds (2-3 mg/100 g), wheat bran (2-3 mg/100 g), cheese (1.5 mg/100 g) and lobster (1.5 mg/100 g) are all regarded great dietary sources of pantothenic acid. The majority of vitamin B5 present in foods is already integrated into Coenzyme-A (CoA) and as phosphopantetheine and is lost during refining, freezing, canning, and cooking, a modern processed food diet is likely to have lower levels of vitamin B5 than a whole foods diet (Ebner *et al*., 2002).

Bioavailability and Pharmacokinetics of pantothenic acid

The bioavailability of pantothenic acid is estimated to be between 40 and 63 percent based on existing evidence (Tarr *et al*., 1981). Following an oral intake, pantothenic acid appears to be rapidly absorbed, resulting in increased tissue levels of CoA and other pantothenic acid metabolites within six hours. The content of CoA and pantothenic acid in leukocytes and urine increases dramatically 6-24 hours after oral dosing. (Moiseenok *et al*.,

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1981).

Pantothenic acid is absorbed in the small intestine of mice and it is sodium-dependent and saturable. Changing pantothenic acid intake in the diet – low, normal, or high levels – has no physiological influence on small intestine absorption (Stein *et al*., 1989).

After the absorption of pantothenic acid and its delivery into cells, a series of enzyme processes can convert it to CoA or ACP. Pantothenic acid appears to be concentrated in the liver, muscles, and blood in animals (Gurinovich and Moiseenok, 1987; Böhmer and Roth-Maier., 2007).

Saturable transport mechanisms appear to allow pantothenic acid to enter and exit the brain and cerebral spinal fluid in animal studies (Spector, 1986), lactating women's breast milk contains pantothenic acid. The amounts discovered correspond to the amount of pantothenic acid in the mother's diet the day before milk collection. (Johnston *et al*., 1981).

In humans, the amount of pantothenic acid measured in a 24/hour urine sample appears to correctly reflect consumption over the previous several days and blood pantothenic acid levels are less responsive to consumption than urine levels and are not regarded as a trustworthy indicator. In erythrocytes, pantothenic acid levels are linked to dietary intake and urine excretion (Eissenstat *et al*., 1986).

Absorption of pantothenic acid

Unlike pantothenic acid, dexpanthenol is readily absorbed through the skin and transformed to pantothenic acid. Experiments employing [3H]-labeled dexpanthenol showed that it was absorbed after topical application (Jakob *et al*., 1995). The pantothenic acid content in control rats ranged from 3 to 9 µg/g of fresh tissue; however, after a repeated treatment with 20 mg dexpanthenol, it rises to 40 µg/g of tissue.

The [3H]-labeled dexpanthenol absorption via skin was investigated in vivo using excised human skin. As a result, dexpanthenol can permeate the viable epidermis. In comparison to the ointment, dexpanthenol in olive oil was found to have lower absorption, underscoring the importance of the vehicle (Gregory and Kelly, 2011).

In a perfused skin udder model, the role of dexpanthenol's penetration capabilities in different vehicles was furtherly investigated. A water/oil vehicle had a substantially higher rate and extent of penetration than an oil/water formulation (Förster *et al*., 1999). After topical application of pantothenic acid to the hair, hair roots, nails, and skin epidermis and corium, a rise in pantothenic acid content was investigated. (Gregory and Kelly, 2011).

Deficiency of pantothenic acid

Under normal circumstances, deficiency of pantothenic acid does not appear to arise. This is likely due to pantothenic acid being found in sufficient amounts in a wide variety of foods to prevent deficiency, and other vitamin deficiencies being limiting factors in people who eat nutritionally poor diets (i.e., signs and symptoms of other nutrient deficiencies appear before pantothenic acid deficiency) (Rucker and Bauerly, 2007).

A progressive morphological and functional change to the adrenal glands has been observed in animal tests of pantothenic acid deprivation, the adrenal gland hypertrophies in early depletion (Gregory and Kelly, 2011). The adrenal cortex, in particular, enlarges, and ketosteroids from the zona reticularis and fasciculata are gradually depleted. Adrenal hypo function, or the inability to respond appropriately to stress, is the end result of insufficiency. The adrenals atrophy and morphological damage occurs in late-stage insufficiency. Improvement of reaction to stress can be achieved and morphological alterations to the adrenals can be reversed, if pantothenic acid is given early enough after deficit is created (i.e., before adrenal exhaustion), pantothenic acid is no longer efficient for these reasons if adrenal exhaustion has occurred (Gregory and Kelly, 2011).

Pantothenic acid lack causes testicular weight increase, sperm motility decrease, and lower the level of testosterone and corticosterone plasma in male rats (Yamamoto *et al*., 2009). Triglycerides level increase could be a mild shortage marker without being specific. A modest deficiency caused by a pantothenic acid deficient - meal (but not devoid of it) dramatically raised blood triglycerides level in rats (Wittwer *et al*., 1990).

Side Effects and Toxicity

In mice and rats, the acute oral LD50 for pantothenic acid is 10.000 mg/kg, with deadly dosages causing respiratory failure. In rats (doses up to 2,000 mg/kg), dogs (50 mg/kg), and monkeys (200-250 mg/kg), chronic administration for 6 months exhibited no toxic symptoms, weight loss, or histological abnormalities (Gregory and Kelly, 2011).

In rats, the lowest observed adverse effect level (LOAEL) was calcium pantothenate at 3% of the diet, with testes enlargement, diarrhea, and hair damage reported, together with the amount of weight gain and food intake. Calcium pantothenate no observed adverse effect level (NOAEL) was set at 1% of the diet (Shibata *et al*., 2005).

Previous pantothenic acid clinical studies were not designed to monitor and assess side effects, as a result, there is a scarcity of evidence on adverse effects in people. Temporary gastrointestinal disturbances (mild) such as nausea, heartburn and diarrhea are the side effects most commonly reported, adverse effects do not usually appear until the daily dose reaches 1 gram. (Gregory and Kelly, 2011).

A single case of eosinophilic pleuropericardial effusion (fluid accumulation around the heart and lungs) has been reported in a patient who received 300 mg/d of pantothenic acid and 10 mg/d of biotin for two months, after vitamins were stopped, the patient's condition has improved (Debourdeau *et al*., 2001). Occurrences of contact urticaria (Schalock *et al*., 2000) & dermatitis (Van Ketel, 1984) were reported in association with the use of dexpanthenol-containing hair treatments and conditioners.

Clinical Experience of dexpanthenol

Dexpanthenol has been used in the treatment of wounds and skin care, especially in Europe for decades (Tauschel and Rudolph, 1982). According to them (Eggensperger, 1994) dexpanthenol's favorable effects have been established in individuals who have had skin transplantation or scar treatment, as well as those who have been treated for burn injuries or various dermatoses. Epithelization stimulation, granulation, & itching relief were the most noticeable benefits of dexpanthenol formulations, were other effects, such as local blood flow decrease, have also been seen.

Dexpanthenol ointment has also been reported to be of great benefit in treatment of diaper dermatitis, this has been linked to an increase in epithelization in wound healing (Gurinovich and Moiseenok, 1987). The later could explain why leg ulcers or anal fissures could be treated using dexpanthenol. (Fritz *et al*., 2020).

Topical preparations containing dexpanthenol have been shown to have beneficial effects in the daily maintenance of scars,

burns, and skin transplantation. In clinical trials, topical long-term administration of formulations comprising heparin, allantoin collagen, and dexpanthenol improved scar quality following various skin lesions (Buttenmeyer, 1995).

Dexpanthenol is a component of topical treatments used to treat sports injuries and venous disorders. It is also used to increase the percutaneous absorption of other active substances (carrier-function) (Yamamoto *et al*., 2009). Clinical investigations using dexpanthenol-containing topical treatments in conjunction with heparin produced comparable positive outcomes (Kopp, 1985).

Dexpanthenol: A Vehicle for Translating New Insights into Practice Wound Management before Wound Closure, Protection from Infection

Cleaning and disinfection with an antiseptic is a crucial first step in the treatment of minor wounds where infection is a concern, it should be done as soon as possible after the injury and continued until the risk of infection has been decreased (Ubbink *et al*., 2015).

Antiseptics should only be used when a wound is at danger of becoming infected since some antiseptics can destroy healthy tissue, the use of a mild antiseptic at the proper concentration in combination with preparations containing chemicals that encourage epidermal keratinocyte proliferation may assist to counteract these effects and protect healthy tissue, dexpanthenol, a precursor and alcohol counterpart of D-pantothenic acid, can help restore the skin barrier, preventing disease-causing microbes from reaching the dermis and subcutaneous tissue (Atiyeh *et al*., 2009).

Protection from Free Radicals

The body must be able to tolerate free radicals while also shielding itself from their damaging effects in order to combat infection. Dexpanthenol can help with this by lowering the generation of reactive oxygen species (ROS) and reducing tissue damage. Both panthenol and pantothenic acid suppressed nicotinamide adenine dinucleotide phosphate-dependent ROS generation in human skin cells in an in vitro study (Wiederholt *et al*., 2009).

D and L are the two enantiomers of panthenol. Only D-panthenol (dexpanthenol) is biologically active, but both forms moisturize the skin (Jens *et al*., 2020). After panthenol or pantothenic acid therapy, the cytoprotective, anti-inflammatory protein Hemeoxygenase-1 (HO1) (a product of HMOX-1) was upregulated, and a functional experiment revealed a reduction in the generation of reactive oxygen species (ROS) (Wiederholt *et al*., 2009).

Modulation of Inflammation

Compounds that assist the body's own modulatory activities are useful in wound-healing preparations because inflammation must be carefully managed throughout the wound-healing process. Dexpanthenol has the ability to change the expression of both pro- and anti-inflammatory genes, allowing it to promote the body's normal reaction to inflammation after an injury.

Treatment with dexpanthenol, or calcium pantothenate, upregulates the expression of genes that act across the three phases of wound healing, including the pro-inflammatory cytokines IL-6 (Heise *et al*., 2012) and IL-1 (Marquardt *et al*., 2015), as well as HO-1 (Wiederholt *et al*., 2009; Marquardt *et al*., 2015)

The increase of IL-6 in dexpanthenol-treated human skin biopsies underscores the vital role of IL-6 in wound healing (Lin *et al*., 2003; Heise *et al*., 2012). Increased expression of the matrix metalloproteinase-3 (MMP3) gene is also of interest in the context of the overlap of the inflammatory and proliferative stages of wound healing, because the MMP3 protein is involved in re-epithelialization and fibroblast recruitment, wound contraction/angiogenesis, and the downregulation of inflammatory mediators in macrophages (Pastar *et al*., 2014; Krishnaswamy *et al*., 2017). MMP3 levels drop after skin injury (Schmitt *et al*., 2018), but this effect can be mitigated by using a dexpanthenol-containing ointment, which has been demonstrated to work in vitro (Marquardt *et al*., 2015).

Support of Cell Proliferation

Dexpanthenol aids the body's natural response to injury by triggering the proliferation of wound-healing and re-epithelialization cells (Proksch *et al*., 2017). The addition of a medium containing 0.1 percent dexpanthenol to traumatized skin constructs resulted in epidermal cell regeneration and the creation of new cellular layers within one week, as determined by histological examination (Weber and Muller-Goymann, 2009).

In the medium only control, a further decline in the structure of the multi-layer equivalent was observed, indicating that, in an artificial skin construct model, dexpanthenol can support the proliferation stage of wound healing (Weber and Muller-Goymann, 2009). In another study (Schmitt *et al*., 2019) standardized lesions were induced with a non-sequential fractional ultra-pulsed CO2 laser in a full-thickness in vitro model of the non-keratinized mucous membrane.

Dexpanthenol and other proliferation-enhancing ingredients were eliminated from the culture media, in contrast to previous experiments, in order to clearly identify the effect of the dexpanthenol-containing topical ointment, the wound closure was improved in the dexpanthenol-treated group compared to the untreated controls, as measured histologically , the Genes linked with wound healing, such as C-X-C motif chemokine ligand 10 (CXCL10), mucin protein family genes, and a retinoid acid receptor responsive gene, were shown to be over 1.5-fold increase in microarray and quantitative real-time polymerase chain reaction (qRT-PCR) study (Schmitt *et al*., 2019).

In comparison to a control medium, culturing human keratinocytes in a pantothenic-deficient medium inhibited their proliferation and lowered the production of keratinocyte growth factor mRNA (Kobayashi *et al*., 2011). This shows that pantothenic acid may help keratinocytes proliferate by promoting the generation of keratinocyte growth factor. (Kobayashi *et al*, 2011).

Furthermore, in vitro skin models have revealed that calcium pantothenate promotes the proliferation and migration of human dermal fibroblasts, dexpanthenol has also been shown to improve wound healing in human dermal fibroblast investigations by activating proliferation, enhancing migration, and boosting intracellular protein synthesis (Wiederholt *et al*., 2009).

Dermal fibroblasts and keratinocytes proliferate during wound healing, responding to the inflammatory process and maintaining the skin barrier's integrity (Wojtowicz *et al*., 2014).

When comparing a dexpanthenol-containing ointment to petroleum jelly on days 1, 2, and 5, the diameter of laser-generated lesions was measured and visual evaluation of their appearance revealed considerably enhanced re-epithelization and appearance with the dexpanthenol-containing ointment (Heise *et al*., 2019).

However, because this trial was not blinded, more clinical research is needed to back up the findings in vitro. The use of dexpanthenol mouthwash or gel three times per day had no in-

fluence on the dimensional change of denture-induced lesions, according to a third trial (Bural *et al*., 2018). Despite the fact that the formulations used in this study were not intended for use in the mouth, the availability of conflicting clinical data is highlighted.

Dexpanthenol-containing preparations may hasten wound healing and shorten the time to wound closure, which is significant for minimizing trans epidermal water loss (TEWL) and reducing infection risk (Proksch *et al*., 2017).

Proactive scar management after wound closure

Following wound closure, occlusive silicone-based scar management solutions are advised; these products offer hydration and prevent excessive collagen deposition by lowering inflammation (Monstrey *et al*., 2014).

The efficacy of a silicone-based panthenol-containing product combined with the use of a massage ball in enhancing the look of hypertrophic scars was investigated in a single-group, single-center, open-label pilot trial, after 8 weeks of treatment, subjective and objective evaluations of hypertrophic scar healing revealed an improvement in scar appearance and skin moisture, as well as a decrease in discomfort and TEWL (Stettler *et al*., 2016).

However, the role of panthenol in scar treatment in this study is difficult to differentiate. To allow TEWL to rebound to the levels seen before to skin injury, a silicone-based anti-scar treatment should be used for up to a year after wound closure (Suetake *et al*., 1996; Monstrey *et al*., 2014). Reactive treatment of fully grown hypertrophic scars or keloids is preferred to this proactive method to scar care (Wolfram *et al*., 2009).

Throughout the three phases of wound healing, dexpanthenol promotes lamellar lipid mobility and enhances fluidity in the lipid bilayers of the skin, which may help hydrate a fresh scar (Proksch *et al*., 2017). Dexpanthenol treatment boosted the molecular mobility of a variety of stratum corneum lipids and protein segments, allowing the stratum corneum to adopt moist skin qualities even in dehydrated conditions, according to an experimental investigation with excised pig skin (Bjork Lund *et al*., 2016).

Dexpanthenol is interacts with lipid segments of extracellular lamellae and protein residues in corneocytes in the stratum corneum, compensating for decreased hydration by maintaining (or enhancing) molecular fluidity (Bjork Lund *et al*., 2016). The efficacy of two topical preparations of dexpanthenol on epidermal barrier function was evaluated in a randomized, double-blind, placebo-controlled research (Gehring and Gloor, 2000). The hydration of the stratum corneum was greatly enhanced after 7 days of dexpanthenol therapy, and the TEWL was significantly reduced (Gehring and Gloor, 2000).

TEWL is a sign of skin barrier disturbance, which represents a superficial wound (Kelleher *et al*., 2015). This research backs up dexpanthenol's beneficial effects on epithelial wound healing and points to increased epidermal hyper proliferation and differentiation, as well as increased epidermal lipid production, both of which are required for wound healing.

Other methods, including as pressure garments, topical corticosteroid injections, radiation, excision, and laser therapy, may be required for the care of hypertrophic scars, even though they are not required for mild wounds (Wolfram *et al*., 2009).

CONCLUSION

Dexpanthenol is regarded as an ideal medication that support wound healing and endorse scar formation after wound closure via its enhancement ability for cell proliferation with proper antioxidant properties.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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