Nicotinamide: Mechanism of action and indications in dermatology

Pooja Bains, Manpreet Kaur, Jasleen Kaur, Saurabh Sharma

Introduction
Nicotinamide aka Vitamin B3 (niacinamide, nicotinic acid amide) is the pyridine 3 carboxylic acid amide form of niacin [Figure 1]. It is a water-soluble vitamin that is not stored in the body. The main source of vitamin in diet is in the form of nicotinamide, nicotinic acid, and tryptophan. The main source of niacin include meat, liver, green leafy vegetables, wheat, oat, palm kernel oil, legumes, yeast, mushrooms, nuts, milk, fish, tea, and coffee. The recommended daily dose of vitamin B3 in niacin equivalent is given in Table 1.

Metabolism of Nicotinamide
Nicotinamide is ingested in food as part of pyridine nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) in plant and animal tissues. After the co-enzymes have separated, nicotinamide is absorbed almost completely in the small intestine. After absorption, nicotinamide is stored as NAD in the liver and excretion occurs via kidneys. Tryptophan is converted to nicotinamide through kynurenine-anthranilate pathway in the liver. Tryptophan can thus satisfy the requirement for dietary nicotinic acid.

Biological Effects of Nicotinamide
Nicotinamide is mainly involved in the cellular energy metabolism, DNA repair, and in regulation of transcription process. The various biological effects along with the underlying mechanism of action are tabulated [Table 2].

Uses of Nicotinamide in Dermatological Disorders
Antiacne effect of nicotinamide
The anti-inflammatory and sebostatic role of nicotinamide plays a role in its use as an antiacne topical formulation. Propionobacterium acnes colonization induces IL-8 production in acne lesions.

Role of nicotinamide in atopic dermatitis
Nicotinamide containing moisturisers have been shown to be effective in treatment of atopic dermatitis. In atopic dermatitis, there is a decrease in ceramides, increase in transepidermal water loss (TEWL) and impaired skin barrier. An in vitro study showed that nicotinamide caused 2–3 fold increase in free fatty acids.

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and 1.5-fold increase in cholesterol. In atopic dermatitis, there is an upregulation of aquaporin 3 that encodes water permeable channels resulting in increased water loss, which is prevented by nicotinamide. In a study on 28 patients of atopic dermatitis, nicotinamide fared better than white petrolatum in decreasing TEWL. In a right left comparative study in 12 male patients with dry skin, nicotinamide 2% application twice weekly for four weeks reduced TEWL by 27% in comparison to vehicle and increased dry skin, nicotinamide 2% application twice weekly for four weeks reduced TEWL by 6–7% compared to placebo on the face and limbs.

**Antiageing effect of nicotinamide**
Nicotinamide increases collagen production in fibroblast cultures and reduces the increased dermal glycoaminoglycosides in photodamaged skin.

Nicotinamide also increases the production of the epidermal proteins keratin, filaggrin, and involucrin. The glycation between protein and sugar resulting in formation of cross linked products gives a yellow colour to the skin. As nicotinamide is a precursor of antioxidant NADPH, it has antiglycation effects, thus preventing sallowing of skin. In a double-blinded, split face, randomized controlled trial, 5% nicotinamide cream was compared to “vehicle only cosmetic” in 30 Japanese women on face for 8 weeks. There was a significant decrease in wrinkles and skin roughness with nicotinamide.

**Nicotinamide for skin lightening**
As nicotinamide inhibits melanosome transfer from melanocytes to keratinocytes, it is used as a lightening agent. A double-blinded, randomized controlled trial with 202 patients found that a topical formulation containing 2% N-acetyl glucosamine and 4% nicotinamide significantly reduced the detectable area of facial spots and the appearance of pigmentation compared to vehicle formulation.

**Role of nicotinamide in autoimmune skin disorders**
The proposed hypothesis behind use of nicotinamide in auto-immune vesiculobullous diseases is the anti-inflammatory effect of nicotinamide. It inhibits cytokines such as IL-1β, IL-6, IL-8, TNF. The most studied use of nicotinamide is in bullous pemphigoid. One case report suggests that nicotinamide monotherapy in dose of 1.5 g/day is an effective treatment in localized bullous pemphigoid.

A randomized, open-label clinical trial compared nicotinamide 500 mg thrice daily plus tetracycline 500 mg four times a day to prednisone 40 to 80 mg a day in 18 patients with bullous pemphigoid. In the nicotinamide and tetracycline group, 5 out of 12 patients had complete responses, compared with one of the 6 patients in the prednisone group. The results point towards a significant effect of nicotinamide and tetracycline therapy in comparison to prednisone in selected patients. There were decreased adverse effects in the nicotinamide and tetracycline group. In another double-blinded, controlled trial in eight pemphigus vulgaris patients, 60 lesions were randomized to either nicotinamide 4% gel or placebo gel for 30 days. It was seen that the mean epithelialisation index for the skin lesions that received nicotinamide was significantly higher. There are various case.

### Table 1: Recommended daily allowance of niacin for Indians

| Age       | Group category | Body weight (kg) | Niacin equivalent (mg/day) |
|-----------|----------------|-----------------|-----------------------------|
| Man       | Sedentary work | 60              | 16                          |
|           | Moderate work  | 18              |                             |
|           | Heavy work     | 21              |                             |
| Woman     | Sedentary work | 55              | 12                          |
|           | Moderate work  | 14              |                             |
|           | Heavy work     | 16              |                             |
|           | Pregnant woman | +2              |                             |
|           | Lactation 0-6 months | +4 |                             |
|           | Lactation 6-12 months | +3 |                             |
| Infants   | 0-6 months    | 5.4             | 710 µg/kg                   |
|           | 6-12 months   | 8.4             | 650 µg/kg                   |
| Children  | 1-3 years     | 12.9            | 8                           |
|           | 4-6 years     | 18.0            | 11                          |
|           | 7-9 years     | 25.1            | 13                          |
| Boys      | 10-12 years   | 34.3            | 15                          |
| Girls     | 10-12 years   | 35.0            | 13                          |
| Boys      | 13-15 years   | 47.6            | 16                          |
| Girls     | 13-15 years   | 46.6            | 14                          |
| Boys      | 16-17 years   | 55.4            | 17                          |
| Girls     | 16-17 years   | 52.1            | 14                          |

### Table 2: Various biological effects of nicotinamide

| Effects of nicotinamide | Mechanism of action |
|-------------------------|---------------------|
| Anti-inflammatory effects | Nicotinamide inhibits nuclear PARP-1 enzyme |
|                         | Nicotinamide inhibits the production of IL-12, TNF-α, IL-1 by controlling NFκB-mediated transcription. |
|                         | Nicotinamide suppresses cytokine-mediated induction of nitric oxide synthase. |
|                         | Nicotinamide inhibits leucocyte chemotaxis and the release of lysosomal enzymes. |
| Lightening effect       | Nicotinamide reversibly blocks the transfer of melanosomes from melanocytes into keratinocytes by inhibiting keratinocyte factors. |
| Anti-microbial effect    | Nicotinamide inhibits nuclear PARP enzyme, hence preventing the integration of proviral DNA. |
|                         | Nicotinamide inhibits Propionibacterium acnes and mycobacterium tuberculosis by acting on Sir2 enzymes (NAD-dependent deacetylases). |
| Barrier protective effect| Nicotinamide boosts ceramide synthesis by activating the mRNA expression of serine palmitoyl transferase, the key enzyme for sphingolipid synthesis. |
|                         | Nicotinamide stabilises mast cells by inhibiting cAMP phosphodiesterase. |
|                         | Nicotinamide inhibits nitric oxide synthase. |
|                         | Nicotinamide suppresses antigen-induced lymphocyte transformation. |

**NAD:** Nicotinamide adenine dinucleotide, PARP-1: Poly ADP ribose polymerase-1, IL-12: Interleukin-12, TNF-α: Tumor necrosis factor-α, PDE: Phosphodiesterase, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, cAMP: Cyclic adenosine monophosphate.
reports of successful use of nicotinamide and tetracyclines in other autoimmune blistering disorders including cicatricial pemphigoid, lichen planus pemphigoides, dermatitis herpetiformis, and immunoglobulin A bullous dermatosis. Nicotinamide can thus be used as a steroid sparing agent.

**Anticarcinogenic and photoprotective effect of nicotinamide**

The enzyme PARP-1, which is inhibited by nicotinamide, is involved in cell senescence, ageing, and cancer. The excessive activation of PARP-1 by UV rays result in depletion of cellular NAD, which further cause glycolytic failure leading to cell necrosis. Nicotinamide replenishes cellular energy as it is a precursor of NAD and NADP. Secondly, it prevents overactivation of PARP-1 by negative feedback, thus preventing cell senescence. Besides, nicotinamide protects against UVA and UVB induced immunosuppression. In a phase 3 clinical trial, the administration of nicotinamide 500 mg twice daily led to a statistically significant reduction in the number of cases of non melanoma skin cancers and actinic keratosis though the effect disappeared 6 months after stopping nicotinamide. This is an area of further research but nicotinamide might prove beneficial in prevention of skin cancers.

**Treatment of pellagra**

Nicotinamide has been named PP factor or Vitamin PP due to its role in treating pellagra and was first used clinically in 1937. Pellagra is characterized by triad of diarrhea, dermatitis, and dementia. Pellagra is caused because of cellular deficiency of niacin, resulting from an inadequate dietary supply of niacin and tryptophan mostly seen in chronic alcoholics, and in patients with gastrointestinal diseases or severe psychiatric disturbances. Rare causes are functioning carcinoid tumors and Hartnup disease, therapy with isoniazid, 6-mercaptopurine, or 5-fluorouracil. The cutaneous changes include erythema and scaling on sun exposed areas with a “butterfly” eruption on face and a well-margined eruption on the front of the neck (“Casal’s necklace”). Oral nicotinamide is given initially as 100–300 mg daily in 3–4 doses until improvement in acute symptoms, then slowly tapered to 50 mg BD or TDS. Oral nicotinamide is preferred over niacin/nicotinic acid as it does not precipitate flushing, itching and burning commonly seen with ingestion of niacin in large doses.

**Nicotinamide as anti-psoriatic agent**

Nicotinamide has a potential role in the treatment of psoriasis because of its anti-inflammatory effect, inhibition of the expression of ICAM-1 and MHC-II, and production of IL-12, TNF-α, and IL-1. The nicotinamide-methotrexate combination may prove to be superior to methotrexate alone in the treatment of psoriasis. In a randomized controlled trial, the combination of topical calcipotriene and nicotinamide was more effective than either of the two as monotherapy as a steroid sparing topical treatment. The addition of nicotinamide as an adjuvant to calcipotriene can enhance the efficacy of calcipotriene when used for topical psoriasis treatment.

**Adverse Effects and Safety Profile**

Nicotinamide is a safe and inexpensive compound with negligible side effects. It is well tolerated even in doses of 1 g/day to 3 g/day. There are no reports of teratogenicity with nicotinamide. Minor side effects include nausea, vomiting, headache, fatigue. It does not cause vasodilatory side effects like flushing, alteration in blood pressure, body temperature or pulse as seen with niacin. In topical formulation, it does not cause skin irritation, photosensitization in concentrations of 0.0001% to 4%.

**Conclusion**

The existing clinical data and literature on nicotinamide suggests that it is an inexpensive, safe drug with beneficial effects as an adjunct in many dermatological diseases because of its anti-inflammatory, anti-oxidant, barrier repair and protective effects. It can be used both as a topical and oral drug without any major adverse effects.

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**Conflicts of interest**

There are no conflicts of interest.

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