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Review Article

The role of nicotamide as chemoprophylaxis in basal cell carcinoma: A literature review

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Abstract Basal cell carcinoma is the most common nonmelanoma skin cancer. This carcinoma has slow progress, is locally invasive but rarely metastasizes. The incidence of basal cell carcinoma accounts for about 50% of all cancers in America, around 55% in Europe, and continues to increase by around 5% annually in the UK. Risk factors for basal cell carcinoma include exposure to ultraviolet light, skin phototype, gender, certain drugs, radiation therapy, family history of skin tumors, chronic arsenic exposure, immunosuppressive conditions, and other genetic syndromes. Recently, nicotinamide has become a topic of much discussion as a chemoprophylaxis against basal cell carcinoma, whereas nicotinamide (NAM; also known as niacinamide) is a water-soluble vitamin B3 (niacin) that exhibits minimal side effects and is reversible under routine use. Long-term protective effect with more than one mechanism of action. Biologically, NAM can affect the process of oxidation and reduction of co-enzymes that play a role in energy metabolism in DNA repair mechanisms. Nicotinamide can replenish ATP energy after damage to keratinocytes due to ultraviolet radiation and can increase the repair of skin cells after experiencing radiation. The efficacy of nicotinamide as a chemoprophylactic agent against nonmelanoma skin cancer, especially basal cell carcinoma, has been described in several studies. Oral administration of nicotinamide at a dose of 750-1500 mg per day results in an improvement in the condition of actinic keratosis which is a precancerous lesion, and reduces the incidence of basal cell carcinoma. Currently, the use of nicotinamide as a chemopreventive agent for basal cell carcinoma is recommended for administration twice daily 500 mg orally for at least 12 months in both immunocompetent patients and organ transplant recipients, although the recommended level of oral nicotinamide is still weak. However, taking into account the efficacy, level of safety, affordable price, and easy access on the market, nicotinamide can be used as a tertiary prevention of skin cancer, especially basal cell carcinoma.

Key words
Nicotamide; Chemoprophylaxis; Basal cell carcinoma; Human and health.

Introduction

Basal cell carcinoma is the most common nonmelanoma skin cancer. This carcinoma has slow progress, is locally invasive but rarely metastasizes. The incidence of basal cell carcinoma accounts for about 50% of all cancers in America, around 55% in Europe, and continues to increase by around 5% annually in the UK. Risk factors for basal cell carcinoma include exposure to ultraviolet (UV) light, skin phototype, gender, certain drugs, radiation therapy, family history of skin tumors, chronic arsenic exposure, immunosuppressive conditions, and other genetic syndromes. Basal cell carcinoma recurrence was found to be quite

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high, around 30-50% within 5 years, 10 times the risk in the general population.[1,2]
The high incidence and recurrence, the high cost of treatment required and the modifiable risk factors for basal cell carcinoma have made efforts to prevent this disease an important focus in the health sector, especially dermatology. Many efforts to prevent basal cell carcinoma have been carried out, including by reducing UV exposure, using sunscreen, recommending the use of hats and or long-sleeved clothing when doing outdoor activities, and using several chemoprophylactic agents. The involvement of chemoprophylaxis is widely discussed as a step in the management of basal cell carcinoma.[3]

Chemoprophylaxis is the administration of drugs to prevent the development of the disease. Chemoprophylaxis aims to inhibit the progression of a disease from premalignant to malignant or prevent recurrence in individuals who have been treated. Chemoprophylaxis has been shown to be effective in reducing the incidence of BCC in at-risk groups. Chemoprophylaxis can be derived from natural, biological and synthetic compounds. Chemoprophylactic agents can be drugs, vaccines, vitamins and minerals.[3,4]

Research on chemoprophylaxis against basal cell carcinoma has yielded several findings such as the use of retinoid drugs, non-steroidal anti-inflammatory drugs, photodynamic therapy, imiquimod, 5-fluorouracil, human papillomavirus vaccines, and nicotinamide which have yielded mixed results. Recently, nicotinamide has become a topic of much discussion as a chemoprophylaxis against basal cell carcinoma, whereas nicotinamide (NAM; also known as niacinamide) is a water-soluble vitamin B3 (niacin) that exhibits minimal side effects and is reversible under routine use. long-term and provide a protective effect with more than one mechanism of action. Biologically, NAM can affect the process of oxidation and reduction of co-enzymes that play a role in energy metabolism in DNA repair mechanisms. Nicotinamide can replenish ATP energy after damage to keratinocytes due to ultraviolet radiation and can increase the repair of skin cells after experiencing radiation.[3,5,6]

In 2015, a randomized control trial (Oral Nicotinamide to Reduce Actinic Cancer [ONTRAC]) conducted at the Royal Prince Alfred and Westmead Hospitals in Sydney, Australia found that within 1 year, the incidence of nonmelanoma skin cancer was reduced by 23% in the group receiving nicotinamide compared to the placebo group. In addition, there was a difference in outcomes in the form of a 20% reduction of nicotinamide and placebo users in using nicotinamide as chemoprophylaxis. In this research, it was also found that nicotinamide is safe, effective, easily accessible as chemoprophylaxis. Along with this research (Oral Nicotinamide to Reduce Actinic Cancer [ONTRAC]), knowledge in the scope of chemoprophylaxis has become wider and can be used as a strategy to reduce the high rate of basal cell carcinoma globally.[3-5,7,8]

Thus, the purpose of compiling this main reference is to present the theory and summarize the currently available scientific evidence regarding the role of nicotinamide as chemoprophylaxis in basal cell carcinoma.

Role of nicotinamide as chemoprophylaxis

Nicotinamide, as previously described, is the amide form of the vitamin B3 compound (niacin). NAM can come diet intake, rapidly absorbed in the gastrointestinal tract and methylated and oxidized and excreted by the kidneys.[3,9,10] In addition to the preformed niacin, the human body synthesizes NAM de novo by metabolizing tryptophan. NAM is the precursor

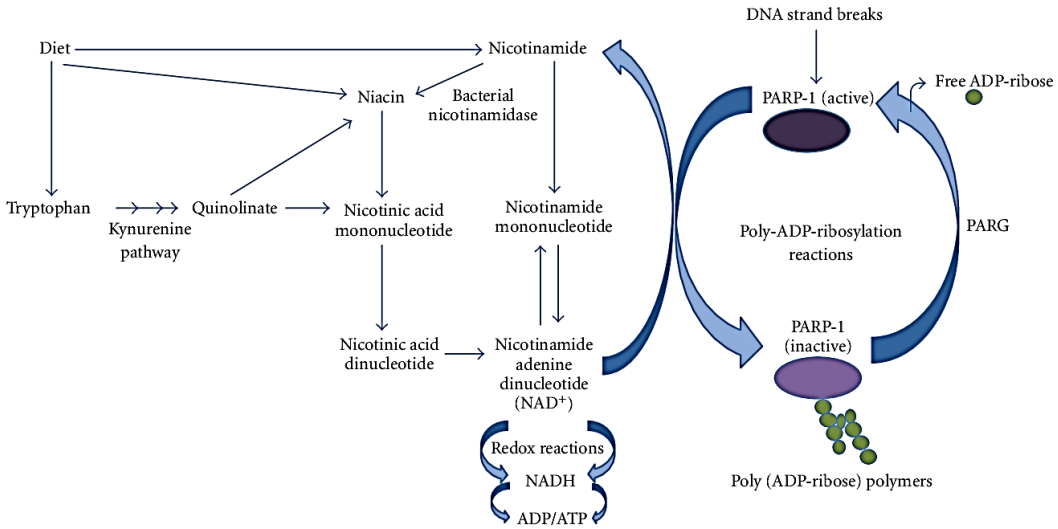

Figure 1. Simplified pathways for the metabolism of nicotinamide, niacin, NAD+, and PARP-1. Nicotinamide, niacin, and tryptophan obtained from food are precursors for the synthesis of NAD+, which plays an important role in ATP production and activation of PARP-1. Nicotinamide can be converted to niacin by nicotinamidese bacteria in the intestinal lumen. PARP-1 is activated by DNA strand breaking, cleaving NAD+ into nicotinamide and ADP-ribose. Poly(ADP-ribose) glycohydrolase (PARG) reactivates PARP-1 by removing the poly(ADP-ribose polymer), allowing continued utilization of NAD+.

of nicotinamide adenine dinucleotide (NAD+), and production of adenosine triphosphate (ATP). NAM had important role in metabolism.[11-13]

NAM deficiency is a cause of pellagra, with specific clinical manifestations of diarrhea, dementia, and symmetrical photosensitive skin eruptions. Related to skin malignancy, NAM has a core role in fighting UV-induced carcinogenesis through the process of DNA repair, reducing UV-induced immunosuppression, and inflammation.[14,15]

Nicotinamide as DNA repair in basal cell carcinoma

UV exposure is one of the exogenous factors that can damage DNA breaks cross-links, and DNA mutations. Each cell has a different repair system that had consequence genomic instability. NAM had important role of NAM in cellular energy pathways. UV exposure is could poly-ADP-ribose-polymerase 1 (PARP-1), and block NAD+ production. Moreover, NAM regulates p53 and sirtuins.[16,17,19]

In vivo and in vitro studies document that since niacinamide restores intracellular NAD+ levels. Regarding sirtuins, the important role played by SIRT-1 is enzyme that depends on NAD+, which is able to suppress the action of p53. A recent study demonstrated a promising effect of NAM in inhibiting SIRT 1,3,4,19 in gene transcription.[3,19,20]

Nicotinamide reduce immunosuppresion of UV in basal cell carcinoma

Immunosuppression plays a central role in the process of skin carcinogenesis. Ultraviolet-B radiation interferes with the function of modulating the antigen-presenting cells (APC) immune system of the skin. Specifically, APCs respond to UV-induced DNA damage by producing interleukin (IL)-10, which downregulates the immune response. Unrepaired DNA damage is a major cause of UV immunosuppression, and previous studies demonstrated the possibility of stopping this phenomenon through DNA repair enzymes. The study found that giving topical nicotinamide to rats irradiated with UV light showed a decrease

in the percentage of skin cancer by up to 32.5%. Other human studies have also been conducted, with healthy subjects exposed to low doses of UV for three consecutive days. The results showed that subjects who were given oral nicotinamide had less delayed-type hypersensitivity responses than the placebo group.[3,20]

In addition, NAM also provided the same level of protection from UV from 500 to 1500 mg daily with spectrum UVB (310 nm) and UVA (370 nm) protection. In addition, UVA is also known to be very immunosuppressive and not able to be well inhibited by most sunscreens. In contrast to sunscreen, NAM does not alter sunburn susceptibility and immune response in unexposed areas; however, NAM acts by reducing the effects of immunosuppression, restoring adequate energy levels needed by cells to repair DNA damage and preventing over-activation of PARP.[20,21]

Nicotinamide as anti-inflammation in basal cell carcinoma

Exposure to ultraviolet light causes different processes in human skin that can trigger skin carcinogenesis, including inflammation. Many studies show that UVB radiation increases the level of skin inflammation through PARP-1 activation. PARP-1 regulates the function of nuclear factor kappa B and can therefore enhance the transcription of inflammatory cytokines and inflammatory mediators. Because one of the properties of NAM includes PARP-1 inhibition, Monfrecola (2013) investigated the role of nicotinamide in reducing inflammation in UVB-irradiated keratinocyte colonies. This study noted a significant reduction of IL-6, IL-10, MCP-1, and TNF-a mRNA levels, confirming the anti-inflammatory effect of NAM. The anti-inflammatory results provided by NAM include the inhibition of neutrophil recruitment: blocking the action of IL-8, promotes angiogenesis, and melanoma cell migration toward endothelial cells.[20-22]

Nicotinamide also plays a role in restoring disturbed skin barriers. Nicotinamide 2% cream applied twice daily for 8 weeks has been shown to reduce trans-epidermal water loss (TEWL) and is more effective than petrolatum. An in vitro molecular study showed that NAM suggested as an adjunctive treatment in chronic skin diseases such as atopic dermatitis, acne vulgaris, and rosacea.[20,21]

Results of evidence-based use of nicotinamide in basal cell carcinoma

Nicotinamide is associated with a significant reduction of BCC compared with controls in several clinical trials, although the strength of the evidence is low and requires further research. Nicotinamide works by preventing ATP depletion and UV radiation-induced blockade of glycolysis increasing cellular energy and optimizing DNA repair. Nicotinamide also reduces levels of UV-induced immunosuppression, which is triggered by DNA damage.[3,18]

Table 1; Studies regarding the role of nicotinamide as chemoprophylaxis for nonmelanoma skin cancer

The ONTRAC study was conducted to assess the incidence of new nonmelanoma skin cancer in the group given nicotinamide 500 mg twice daily compared to the placebo group. The average number of nonmelanoma skin cancers was 1.8 in the nicotinamide group and 2.4 in the placebo group. During the active treatment period, the NAM group had skin cancers, notably the relative differences were 25%, 27%, 18%, and 29%, at 3, 6, 9, and 12 months.[1,9,23]

Table 1 Studies regarding the role of nicotinamide as chemoprophylaxis for nonmelanoma skin cancer.

No	*Author, Year*	*Research*	*Study Design*	*Intervention*	*Conclusion*
1	Chen *et al*. 2015 [18]	A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention	Randomized controlled trial	Oral nicotinamide 500 mg twice daily and placebo, given for 12 months, evaluated every 3 months	Oral nicotinamide is found to be safe and effective in reducing the incidence of new nonmelanoma skin cancer and actinic keratosis in high-risk patients.
2	Mainville *et al*. 2022 [24]	Effect of Nicotinamide in Skin Cancer and Actinic Keratoses Chemoprophylaxis, and Adverse Effects Related to Nicotinamide: A Systematic Review and Meta-Analysis	Systematic review and meta analysis	-	Nicotinamide 500 mg orally twice daily should be considered for skin cancer chemoprophylaxis for at least 12 months in healthy people or organ transplant recipients (GRADE: weak recommendation; moderate evidence base), as BCC chemoprophylaxis (GRADE: weak recommendation; evidence base low) and KSS chemoprophylaxis (GRADE: weak recommendation; moderate evidence base)
3	Moloney *et al*. 2010 [26]	Randomized, double-blinded, placebo controlled study to assess the effect of topical 1% nicotinamide on actinic keratoses	Randomized controlled trial	Topical 1% nicotinamide twice daily vs. placebo, given for 6 months, evaluated every 3 months	Nicotinamide can accelerate the resolution of actinic keratosis, and reduce the incidence of non-melanoma skin cancer by reducing the impact of UV-induced immunosuppression.
4	Drago *et al*. 2017 [27]	Prevention of nonmelanoma skin cancers with nicotinamide in transplant recipients: a case control study	Case control	Oral nicotinamide 250 mg 3x daily (case) and no treatment (control), administered for 6 months	Administration of nicotinamide increases total remission of actinic keratosis and continuously reduces the incidence of nonmelanoma skin cancer.

This study by Chen and colleagues evaluated the efficacy of oral nicotinamide as a chemopreventive agent in nonmelanoma skin cancer, as a treatment, as well as assessing the safety and side effects of oral nicotinamide. The mean number of basal cell carcinomas was 1.3 in the NAM group and 1.9 in the placebo group, illustrating that the findings of BCC cases in the NAM group were 20% lower than in the placebo group. The chemoprotective effect of NAM appears to disappear after 6 months after completion of therapy.[3,18,24]

Nicotinamide was found to be relatively more effective in reducing the risk of superficial BCC compared to other BCC subtypes. Available data show no reduction in the incidence of BCC subtypes that are more aggressive (micronodular BCC, infiltrative BCC, and morphoic BCC) after nicotinamide administration, although supporting data are still very limited.[18,24,25]

Nicotinamide is considered potentially superior to current non-chemoprophylaxis and other chemoprophylaxis prevention. Studies in high-risk groups show that the use of sunscreen is effective in reducing actinic keratosis rates and the incidence of skin cancer, however, even in high-risk groups who do not use sunscreen, nicotinamide administration still shows satisfactory results. The use of sunscreen in combination with nicotinamide produces a greater immunoprotective effect.[26,27]

The study conducted by Moloney (2010) included 30 research subjects with at least four non-hyperkeratotic actinic keratosis (AK) lesions who were given two different treatments, 1% nicotinamide application and placebo, which were applied twice daily. Study subjects were evaluated at 0, 3, and 6 months for the number and location of AK lesions. The results of the study found BCC (1 case in the nicotinamide group, 3 cases in the placebo group) and SCC (3 cases in the placebo group) after 6 months. The number of AK lesions was also significantly reduced in the nicotinamide group (21.8+10% at 3 months and 24.6+15.4% at 6 months) compared to baseline.[18,26]

Nicotinamide can accelerate the natural resolution of AK by suppressing UV-induced

immunosuppression. Research shows that the use of 1% topical nicotinamide provides an immunoprotective effect similar to that of 5% nicotinamide, although it does not rule out that the use of higher concentrations or different formulations can increase its efficacy.

The case control study conducted by Drago (2017) obtained similar results to previous studies. Oral administration of nicotinamide 250 mg 3 times a day for 6 months showed improvement in AK cases to complete remission (44%) and reduced the incidence of non-melanoma skin cancer compared to the control group.[27]

Recently, a systematic review and meta-analysis was conducted by Mainville *et al.* (2022) regarding the effects of nicotinamide as chemoprophylaxis in skin cancer and actinic keratosis. Mainville found that nicotinamide was associated with a significantly reduced incidence of basal cell carcinoma compared with the control group (rate ratio 0.46 (95% CI, 0.22–0.95; I2=53%; 552 patients; 5 clinical trials), despite the strength of the evidence. was declared low due to the inconsistency of the available clinical trials.[24,25]

Nicotinamide can be used both in groups of organ transplant recipients who are immunocompromised and in those who are immunocompetent. This study also emphasizes the consideration of the use of nicotinamide as a chemopreventive agent for BCC which until now has not been the main indication for the use of nicotinamide.[24] Recommendations published in the Journal of the American Academy of Dermatology (JAAD) from 2018 to 2020 support the use of oral nicotinamide 500 mg twice daily in patients with suspected nonmelanoma skin cancer.[24-27]

Regarding the safety of using nicotinamide, Chen *et al*. have conducted studies which show that nicotinamide has a favorable safety profile. Nicotinamide has been used for many years at pharmacological doses (up to 3 grams daily) with minimal side effects. In contrast to niacin (nicotinic acid), nicotinamide does not cause vasodilation side effects such as flushing, itching, hypotension, and headaches. The use of high doses of nicotinamide (>3g/day) can cause reversible hepatotoxicity after discontinuation of the drug. Besides this, the use of nicotinamide is declared safe and well tolerated. The safety of using nicotinamide in groups with co-morbidities such as kidney failure needs further investigation.[18,24-27]

Conclusion

The efficacy of nicotinamide as a chemoprophylactic agent against nonmelanoma skin cancer, especially basal cell carcinoma, has been described in several studies. Oral administration of nicotinamide at a dose of 750-1500 mg per day results in an improvement in the condition of actinic keratosis which is a precancerous lesion, and reduces the incidence of basal cell carcinoma.

However, topical administration of nicotinamide was found to have no significant protective effect when compared to placebo as chemoprophylaxis, so further research is still needed. Based on previous research, the side effects of giving nicotinamide are not many. However, gastrointestinal complaints such as diarrhea were found in two clinical trials which were improved by reducing or stopping the dose of nicotinamide. Hepatotoxicity can also occur with high doses of nicotinamide (>3000 mg/day).

Currently, the use of nicotinamide as a chemopreventive agent for basal cell carcinoma is recommended for administration twice daily

500 mg orally for at least 12 months in both immunocompetent patients and organ transplant recipients, although the recommended level of oral nicotinamide is still weak. However, taking into account the efficacy, level of safety, affordable price, and easy access on the market, nicotinamide can be used as a tertiary prevention of skin cancer, especially basal cell carcinoma.

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