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niacin induced skin changes

# Aspirin in dermatology: Revisited

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## Abstract

Aspirin has been one of the oldest drugs in the field of medicine, with a wide range of applications. In dermatology, aspirin has shown benefit in a variety of disorders. Recently, reduction of melanoma risk with aspirin has been demonstrated. Although an analgesic to begin with, aspirin has come a long way; after cardiology, it is now found to be useful even in dermatology.

**Keywords:** Aspirin, dermatology, melanoma

## INTRODUCTION

Salicylates have been used as an analgesic since the time of Hippocrates.[1] However, it was only in the 1890s that aspirin was introduced as an anti-inflammatory agent,[2] and the role of aspirin as an antiplatelet agent was realized only 70 years later.[3] Of late, the beneficial properties of aspirin have been utilized in treating a number of dermatologic disorders. This review discusses the role of aspirin in dermatology.

## MECHANISM OF ACTION

Aspirin acts by irreversibly inhibiting both cyclooxygenase (COX) enzymes. Aspirin acetylates the serine 530 moiety of COX-1, and the serine 516 moiety of COX-2,[4,5] being 170 times more effective in inhibiting COX-1.[6] With the blockage of these enzymes there is a decreased production of prostaglandins and thromboxane-$A_2$, responsible for its anti-inflammatory and anti-platelet effects, respectively. Aspirin also inhibits the neutrophilic activation of platelets by utilizing nitric oxide and cGMP.[7]

## PHARMACOKINETICS

Taken orally aspirin is rapidly absorbed in the upper gastrointestinal tract.[8] The peak plasma level of aspirin is reached within 2 h of oral intake, following which it gradually declines. The plasma half-life of aspirin is 20 min.[9] Metabolism of aspirin occurs in the liver, with 75% of the drug getting metabolized to salicyluric acid, salicyl phenolic and acyl glucoronide, and gentesic acid.[10] The drug is excreted via the renal route. With increase in the urinary pH, elimination of aspirin is enhanced. The drug readily crosses the placenta and can be easily transferred via breast milk.

## APPLICATIONS IN DERMATOLOGY

In dermatology all indications of aspirin are off label.

### Necrobiosis lipoidica diabeticorum

Necrobiosis lipoidica diabeticorum (NLD) is an idiopathic dermatoses characterized by degenerative and granulomatous changes in the dermis.[11] The deposition of immune complexes in the walls of blood vessels, enhanced aggregation of platelets, and increased coagulation have been postulated as etiological factors for NLD development.[12] Aspirin has been found useful in NLD because of its antiplatelet property. By blocking aggregation of platelets, aspirin enhances cutaneous blood flow in NLD, and promotes ulcer healing.[13] An uncontrolled trial, with low doses of aspirin administered to seven NLD patients, showed considerable clinical improvement of lesions, in six out of seven patients.[14] Another uncontrolled trial using 80 mg of aspirin and 75 mg of dipyridamole, thrice daily in seven patients with ulcerative NLD heralded healing of ulcers in all patients over a 2 to 4 week period.[15] However studies by Beck *et al*.[16] and Statham *et al*.[17] did not agree with the therapeutic benefit of aspirin in NLD.

### Malignant atrophic papulosis

Malignant atrophic papulosis (MAP) is a rare thrombo-obliterative disorder characterized by porcelain white skin lesions with surrounding telangiectasia.[18] Increased platelet aggregation has been proposed as a causative factor in MAP. In this setting, low doses of aspirin ranging from 81 to 325 mg per day is administered.[19,20] However, the therapeutic role of aspirin for MAP is limited, with the disease having a fatal outcome.

### Erythromelalgia

Erythromelalgia is a clinical condition characterized by burning sensation and redness over the extremities.[21] Out of the three types of erythromelalgia, type I is associated with thrombocythemia, and occlusion of the vasculature of digital arteries and arterioles.[22] Aspirin's antiplatelet activity is responsible for the therapeutic benefit, seen in this condition. The dose of aspirin, ranges from 325 to 650 mg per day. The effect of a single 500 mg dose of aspirin lasts for 3 days. This long-lasting effect of aspirin can also be utilized as a diagnostic test for myeloproliferative disease-linked secondary erythromelalgia.[23,24,25] On the whole, however, it may be worthwhile using aspirin in all cases of erythromelalgia as considerable relief may be experienced after its usage.[26]

### Raynaud's phenomenon

Aspirin has been found useful in the management of Raynaud's phenomenon (RP) secondary to vaso-occlusive pathology. Low doses of aspirin between 75 and 81 mg has been employed for this indication.[27] Increase in the blood viscosity and platelet aggregation along with altered fibrinolysis have

been proposed as contributory mechanisms in RP involving the digital blood vessels.[28] Aspirin may therefore have a role in this setting, especially for patients with an acute ischemic crisis where aspirin is administered along with a short-acting calcium channel blocker-like nifedipine.[29] According to Akerkar and Bichile,[30] all patients with RP in a setting of scleroderma should receive a daily 150 mg of aspirin along with other medications for the same. Treatment may be given till the acute ischemic attack is tided or even for a long-term prophylaxis.

## Erythema nodosum

Erythema nodosum (EN) is a septal panniculitis characterized by tender erythematous nodules involving both the shins in a symmetrical distribution. Aspirin is used here as an adjunct to the specific treatment regimen. The anti-inflammatory property of aspirin is employed in this setting to enhance analgesia and quicken resolution of cutaneous lesions.[31] The dose of aspirin for EN is 325 mg given at a 6 hourly interval.[32]

## Vitiligo

Se Mn!

Vitiligo is an acquired idiopathic pigmentary disorder characterized by depletion of epidermal melanocytes. Recently, it has been suggested that oxidative stress in vitiligo, mediated by hydrogen peroxide ($H_2O_2$) may significantly contribute toward melanocyte apoptosis.[33,34,35] It has also been noted that, a decrease in the levels of systemic catalase, glutathione peroxidase, and manganese superoxide dismutase in vitiligo patients, further enhances oxidative stress.[36,37,38] Because of oxidative stress, the inducible inflammatory COX-2 mRNA is increasingly expressed, with release of numerous inflammatory mediators and cytokines, prompting melanocyte apoptosis.[39,40] Aspirin acts by inhibiting COX-2 irreversibly, reducing the oxidative stress, increasing the release of leukotriene C4, a potent melanocyte mitogen, and reducing leukotriene B4 release.[41] Apart from this aspirin also possesses antioxidant properties, reduces the activity of antimelanocyte antibodies and soluble interleukin-2 receptors (SIL-2R), therefore decreasing immune-mediated melanocyte damage.[42] Aspirin also significantly improves the oxidative status of peripheral blood mononuclear cells and epidermal melanocytes. The salicylic acid moiety of aspirin, by an unknown mechanism can itself trigger the de novo biosynthesis of reduced glutathione, a potent antioxidant. Furthermore aspirin on its own also, has free radical scavenging properties, which can inhibit DNA strand breakage and block lipid peroxidation of cell membranes.[43,44] Aspirin can go another step further by antagonising the effects produced by nuclear factor kappa-B and TNF-alfa, thus commemorating its role for unstable vitiligo and promoting a halt in disease progression.[45,46] Aspirin thus helps in changing an unstable active form of vitiligo to the stable form. Thus, aspirin may be beneficial in vitiligo only when the disease demonstrates signs of activity. Low doses of aspirin up to 300 mg per day is sufficient for this indication.[47] Duration for the same may need to be continued for a minimum period of 12 weeks, or till signs of disease activity are controlled. In childhood vitiligo too aspirin can be safely given during the active disease phase.[42]

## Kawasaki's disease

Kawasaki's disease (KD) is an acute vasculitis involving the small and medium-sized blood vessels, associated with a constellation of cutaneous and systemic features.[48,49] The antithrombotic property of aspirin has been utilized while treating KD.[50,51] Based on the acute, subacute, and chronic phases of the disease, there is variation in aspirin dosing. According to the American Heart Association, 80–100 mg/kg/day of aspirin is given during the acute phase of the disease.[52] and 3–5 mg/kg/day during the

subacute phase. In the chronic phase if coronary artery abnormalities are seen, then the same dose as the subacute phase is continued, till there is absence of coronary lesions on echocardiography.[53]

## Postherpetic neuralgia

Postherpetic neuralgia (PHN) refers to a chronic resistant pain that persists at the site of viral rash even after rash resolution. Aspirin, used topically has proven efficacious for this indication. King[54] demonstrated the analgesic activity of aspirin by crushing aspirin tablets in chloroform and applying it over the affected site. De Benedittis *et al*.[55,56] further proved the same response after using aspirin/diethyl ether mixture while treating PHN. Aspirin brings about pain relief in PHN by neuronal membrane stabilization, denervation hypersensitivity, and inhibition of prostaglandin synthesis.[57,58] Topical aspirin used for treating PHN is obtained by crushing aspirin tablets of strength 375 mg to a fine powder and dissolving it in solvents such as diethyl ether or chloroform to get a final concentration of 75 mg of aspirin per mL of solution. However, dispensing aspirin in these inflammable solvents has its own disadvantage and safer solvents for the same would definitely be a better alternative. One such solvent used for the same is, Vaseline intensive moisturizing lotion, which has shown to be effective with aspirin in managing PHN as demonstrated by Kassirer *et al*.[59] and Balakrishnan *et al*.[60] Here aspirin tablet of strength 375 mg is powdered and dissolved in 5 mL of the above-mentioned moisturizing lotion to get a solution containing 75 mg/mL of aspirin. This paste is then uniformly applied over the hyperesthetic skin. Applications are done every 8 h for a period of at least 3 weeks in order to experience pain relief.

## Mastocytosis

Mastocytosis is a rare disorder characterized by an abnormal population of mast cells in various organs of the body, namely, the skin, bone marrow, gastrointestinal tract, lymph nodes, spleen, and liver.[61] The role of aspirin in mastocytosis, is to alleviate the abnormal flushing seen during attacks. Aspirin acts by blocking the COX-2 enzyme, and reducing the elevated prostaglandin levels, associated with mastocytosis.[62,63] However caution is warranted while using aspirin because aspirin perse could even degranulate mast cells. Aspirin is therefore reserved for patients who have a vascular collapse that cannot be averted by the usage of H1 and H2 antagonists alone.[64] Treatment with aspirin should always be taken up in a hospital setting, starting with doses of aspirin ranging from 81 mg twice daily to 500 mg twice daily,[63] with prior administration of antihistaminics.[65] Aspirin is usually administered till the acute episode is brought under full control, with normalization of urinary 11-beta prostaglandin $F_2$ alfa levels.

## Niacin-induced cutaneous changes

Niacin has been found to be effective in the management of dyslipidemia. However facial flushing, associated with bothersome pruritus, may affect patient compliance. This complication of niacin is mediated by niacin G protein coupled receptor 109A expressed by Langerhans cells in the epidermis.[66,67] When these receptors are activated there is a release of arachidonic acid from the cellular stores of lipids via phospholipase A2.[68] Arachidonic acid is further sequentially metabolised by COX-1 and 2 to produce prostaglandins. Aspirin acts by blocking these cyclooxygenase enzymes, thus preventing prostaglandin release.[69,70,71] Studies done by Cefali *et al*.[72] and Whelam *et al*.[73] have demonstrated the benefit of aspirin in this condition. A double blinded placebo-controlled trial by Thakkar *et al*.[74] demonstrated similar efficacy of aspirin for niacinamide-induced flushing. Usually it is best to

! proposed mechanism of niacin flush!

administer aspirin 30 min prior to niacin intake. The daily dose commonly used is 325 mg.[75] Further aspirin usage here does not interfere with the therapeutic benefit of niacin in dyslipidemia.[76]

### Hughes' syndrome

Hughes' syndrome (HS) or antiphospholipid syndrome is a prothrombotic disorder manifesting with a constellation of cutaneous and systemic features. The most common complication occurring is recurrent abortion.[77] Low-dose aspirin employing 75–100 mg of the drug as a daily regimen has been found to be useful here.[78,79] Aspirin acts by decreasing platelet aggregation, thus preventing thrombosis in the uteroplacental circulation. Secondly, aspirin also reduces thromboxane to prostacyclin ratio and improves placental blood flow.[80] In this way, aspirin has shown to have a significant impact in reducing the rate of fetal resorption. Higher dosing has not shown any improvement in the thrombotic episodes in comparison to the low-dosing protocol.[81]

### Sunburn reaction

An acute cutaneous response secondary to excessive exposure to ultraviolet (UV) rays is referred to as a sunburn reaction. Once UVB is absorbed by the DNA in the skin, a chain of events follow, wherein numerous inflammatory mediators such as prostaglandins, lipoxygenase products, adhesion molecules, reactive oxygen radicals, and cytokines such as TNF-alfa are released into the local mileu.[82] Along with these, histamine and substance *P* released from mast cells also enhance the inflammatory response.[83,84] Aspirin acts by reducing the production of these mediators and decreasing the effects produced by these chemokines in the sunburn reaction.[85] Post–UV light exposure it has been seen that a single oral dose of aspirin is effective enough to delay the production of erythema.[86] A double blinded crossover study, with 3.6 g of aspirin administered to sunburn patients over 9 h in three divided doses, 30 min prior to UVB exposure, along with a control placebo group revealed a significant reduction of erythema in the aspirin-treated group 4–6 h post–sun exposure.[87] Synder and Eaglstein[88] demonstrated the benefit of intradermal aspirin injections in patients prone to sunburn. Edwards *et al*.[89] have also highlighted the efficacy of oral aspirin in sunburn reactions.

### Livedoid vasculopathy

This is a disorder predominantly involving the lower limbs, and characterized by painful ulcers, associated with ivory white plaques surrounded by areas of hyperpigmentation and telengiectasias. There are a multitude of causative factors involved, out of which altered coagulation and increased platelet activation contribute significantly.[90] Owing to the thrombogenic mechanisms involved, therapy with anticoagulants has been found to be beneficial.[91,92] Aspirin at doses not higher than 325 mg per day is given to patients, as higher doses inhibit prostacycline formation, which may increase the thrombotic tendency.[93] Combination of aspirin with dipyrimadole is often helpful.[94] Another useful synergism is the concomitant use of aspirin and pentoxifylline for atrophie blanche, with a better outcome than using either of the drugs alone.[95] Duration of treatment depends on how the patient is responding to the therapy given. However, on an average, treatment usually goes on for around 2 months to a year.[94] Remission begins first by the reduction in pain followed by re-epithelialization of the ulcers over a period of several months.

### Lepra reactions

Aspirin given in doses of 600–1200 mg 4–6 times daily, has been found to be effective in mild type 1 lepra reactions. These reactions are clinically characterized by mild erythematous to oedematous plaques without any systemic disturbance or subjective or objective nerve involvement.[96] To start with, 600 mg of aspirin may be administered, up to 6 times per day and can be gradually tapered with reductions of 300–600 mg per week till the therapeutic outcome is achieved.[97]

### Pruritus associated with polycythemia vera

In the above indication too, aspirin has been found beneficial. Given in a dosing of 300 mg twice daily or 1 h prior to bathing, aspirin showed promise in this scenario. Aspirin acts by directly suppressing the prostaglandin metabolism within the mast cells and preventing its degranulation.[98]

### Pressure urticaria and Non-immunologic urticaria

Pressure urticaria has shown benefit with aspirin. With 3.9 g of aspirin administered to patients, in four divided doses for 3 days, a significant improvement in the painful pressure lesions have been noticed. However, no response is noted in the urticarial lesions following aspirin intake.[99] Nonimmunologic urticaria (NIU) has also shown improvement following administration of aspirin. Two doses of 1 g of aspirin administered a few hours prior to contactant exposure produces a favorable response in patients with NIU. However NIU associated with dimethyl sulfoxide exposure did not show any benefit with aspirin.[100]

### Relapsing polychondritis

There have been a few case reports of relapsing polychondritis responding favorably to aspirin therapy.[101,102]

### Systemic lupus erythematosus

In some cases of systemic lupus erythematosus (SLE) presenting with fever, cutaneous lesions, arthritis, and pyrexia, but without major organ involvement the beneficial role of aspirin at dosages of 3–6 g per day has been seen.[103] Aspirin's role in these patients is directed mainly toward alleviating the symptoms of pain associated with arthralgia and malaise and also in bringing the temperature down. Caution, however is mandated with the use of aspirin in these patients as they are at a greater risk for nonsteroidal anti-inflammatory drug (NSAID)-induced asceptic meningitis, hypertension, altered renal function, and deranged hepatic parameters after a long-term use of aspirin. Another subset of SLE patients requiring aspirin are those with positive antiphospholipid antibodies, who require long-term anticoagulation.[104,105]

### Kasabach Merritt's syndrome

Kasabach Merritt's syndrome (KMS) is considered to be a consumption coagulopathy associated with a vascular tumor that has a tendency to enlarge rapidly. Within the enlarging tumor, there is platelet sequestration, which is responsible for the thrombocytopenia associated with KMS.[106] Aspirin has been used as an additional therapy here, usually in combination with dipyridamole.[107] However, the role of aspirin in KMS is limited.[108,109]

### Malignant melanoma

The use of aspirin has been associated with marked reduction in melanoma risk. Studies have demonstrated a dose-dependent reduction in the proliferation of B16 murine melanoma cells and SK-28 human melanoma cells following aspirin intake.[110] Other mechanisms involved include oxidation of aspirin by tyrosinases present in the melanoma cells and depletion of intracellular glutathione with eventual formation of reactive oxygen species, all of which exert a toxic effect on the mitochondria of the melanoma cells, thus stopping its proliferation.[111,112] Aspirin also inhibits COX-2, which is increasingly expressed in the melanoma cells, and halts advancement of the tumor.[113,114] Further contributory effects include suppression of nuclear factor kappa-B and antiapoptotic transcription factor, which puts a stop to melanoma progression.[44,115,116,117] Proven studies[118,119,120] in this regard have been summarized in Table 1.

## CONTRAINDICATIONS

Aspirin is contraindicated in patients who are allergic to NSAIDs and also in patients with asthma, allergic rhinitis, nasal polyps, and peptic ulcer disease. Another contraindication for aspirin usage, are children and young teenagers with viral infections because of the risk of precipitating Reye's syndrome. It should be avoided during pregnancy especially in the third trimester because it could lead to closure of the ductus arteriosus in the fetus. Nursing mothers should also avoid aspirin as it is secreted in breast milk.[9]

## ADVERSE EFFECTS

The commonest side effect, even with low doses of aspirin is peptic ulcer disease. Other toxicities include angioedema, urticaria, asthma exacerbation, and rhinitis.[32] Rarer adverse effects are prolongation of prothrombin time, thrombocytopenia, tinnitus, and interstitial nephritis. Chronic usage of aspirin for cutaneous disorders and malignant melanoma, has not been associated with major side effects apart from gastrointestinal bleeding, which too has been reported in 2% of subjects. Overall, aspirin has a well-tolerable safety profile.

## CONCLUSION

Aspirin although an old and inexpensive drug, has shown promise for a variety of dermatologic disorders. With its role in reduction of melanoma risk aspirin has also found to have a place in oncology. With further advances in the field of molecular pharmacology, in the near future more newer indications could be discovered for aspirin, one of the oldest drugs in the field of medicine.

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## Figures and Tables

### Table 1

Summary of studies proving the role of aspirin in malignant melanoma

| Study | Study subjects | Control subjects | Gender of subjects | Drugs used | Conclusion |
|---|---|---|---|---|---|
| Joosse *et al.*[118] (case control study) | 1318 | 6786 | Male and female | Aspirin and other NSAIDs | Reduction in melanoma risk in females with a consistent low dose of aspirin |
| Curiel-Lewandrowski *et al.*[119] (case control study) | 400 | 600 | Male and female | Aspirin and other NSAIDs | Reduction in melanoma risk in both genders following long-term aspirin usage |
| Gamba *et al.*[120] (observational study) | 59,806 | Nil | Female | Aspirin | 21% Reduction in melanoma risk with aspirin usage and 30% reduction in melanoma risk if aspirin use exceeded 5 years |

### Table 2

Level of evidence for the use of aspirin in various dermatoses mentioned in the review

| Cutaneous condition | Level of evidence for aspirin use |
|---|---|
| Necrobiosis Lipoidica Diabeticorum | C |
| Malignant atrophic papulosis | E |
| Erythromelalgia | D |
| Raynaud's phenomenon | D |
| Erythema Nodosum | E |
| Vitiligo | C |
| Kawasaki's disease | B |
| Postherpetic Neuralgia | C |
| Mastocytosis | D |
| Niacin induced cutaneous changes | C |
| Hughs' Syndrome | C |
| Sunburn reaction | C |
| Livedoid vasculopathy | C |
| Lepra reactions | B |
| Pruritus associated with polycythaemia vera | E |
| Pressure urticaria and Non-immunologic urticaria | E |
| Relapsing polychondritis | E |
| Systemic Lupus Erythematosus | C |
| Kasabach Merritt Syndrome | E |
| Malignant melanoma | B |

A: Double blind study: At least one prospective randomized double blind controlled trial without major design flaws, B: Clinical trial with 20 or more subjects: Prospective clinical trials with 20 or more subjects, trials lacking adequate controls or another key facet design, which would normally be considered desirable, C: Clinical trial with less than 20 subjects: Small trials with less than 20 subjects with significant design limitations, very large number of case reports (at least 20 such in literature), D: Series of five or less subjects: Series of patients reported to respond with at least five reports of the same in literature, E: Anecdotal case reports

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