



# Pomegranate

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**N**ative to Iran and the Himalayas in northern India, the pomegranate (*Punica granatum*) has been cultivated throughout the Mediterranean, India, South-east Asia, and other parts of the world. For centuries, the fruit and seeds of the pomegranate have been used by various cultures in folk medicine and cosmetic applications, and can be found referenced in religious texts, art and mythology. As early as 1500 BC, pomegranate was used as a parasitic treatment. Today, it is used for a variety of ailments including hypertension, cardiovascular disease, end-stage renal disease, intestinal infestations, rheumatoid arthritis, cancer, influenza, diabetes, haemorrhoids, and dental plaque. More recently, pomegranate extracts have been promoted for their alleged anti-ageing properties.

**COMMON NAMES:** *Punica granatum*; pomegranate extract (PE), leaf extract (PLE), flower, fruit, leaf, or polyphenol extract; Fruit of the Dead, Granada (Spanish), Grenade (French), and more.

**PREPARATIONS:** Pomegranate products are available as capsules, softgels, tablets, extract, seed oil, juice, powder, and tea. They are also formulated into a range of cosmetic skin products including lipstick and lip balms; eye and face cream, oil, serum, foam, scrub, masque, powder, gel and foundation; shampoo and conditioner; deodorant; body scrub, lotion and oil; toothpaste; and soap.

**ACTIVE CONSTITUENTS:** Skin-promoting benefits of pomegranate are attributed to polyphenols such as hydrolysable ellagitannins (punicalagin), which are converted to ellagic acid. Ellagic acid is further processed by gut microflora to urolithins, of which urolithin A is most prominent. Pomegranate seed oil is a source of conjugated fatty acids of which punicalic acid is most common. Some capsules and softgels are standardised to contain 40% ellagic acid or 22% punicalic acid and 30% punicalagins; others may provide varying quantities of polyphenols or quantities of seed and fruit.

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## Summary message

There is promising scientific evidence to support oral and topical pomegranate extracts in maintaining or restoring protein integrity in the skin, thereby reducing skin damage and ageing from chronic UV exposure. Some evidence exists for enhanced mitochondrial and cellular health with urolithin A; however, few human studies have been done to date.

Pomegranate extracts are considered safe and well tolerated with diarrhoea as the most reported adverse effect. People with any allergies or sensitivities to pomegranate should not take supplements or use cosmetics with these ingredients. Supplementation should be discouraged in pregnancy and lactation due to limited evidence. Pomegranate may lower blood pressure, which could result in additive effects with antihypertensives and interfere with blood pressure control during surgery. It is advised pomegranate supplementation is stopped two weeks before surgery.

Herbal medicines are a popular health care choice, but few have been tested to contemporary standards. **POTION OR POISON?** summarises the evidence for the potential benefits and possible harms of well-known herbal medicines.

**MEDICAL CLAIMS:** Skin exposure to UV radiation is associated with the breakdown of collagen fibres resulting in rough, dry, wrinkled and pigmented skin. Processes responsible for epidermal hyperproliferation and accelerated collagen breakdown include an increase in reactive oxygen species (ROS), activation of metalloproteinases (MMP) and transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B). Oral and topical pomegranate preparations are claimed to offer photochemoprotection through their actions as potent antioxidants and anti-inflammatory agents, target pigmentation disorders as inhibitors of melanin, brighten and lighten uneven skin tone and promote anti-ageing activity.

**EVIDENCE:** Studies suggest that pomegranate extracts may protect human skin against the damaging effects of UVB radiation, thereby inhibiting photoaging. Antioxidants such as ellagic acid and hydrolysable tannins have shown to block infiltration of proinflammatory mediators causing up-regulation of collagen expression and down-regulation of matrix MMP-1. In a mouse model, topical ellagic acid was found to improve UVB-induced skin roughening and thickening by reducing the production of pro-inflammatory cytokines and blocking infiltration of inflammatory macrophages, preventing inflammatory responses and collagen destruction. Similarly, in human fibroblast cells, the photochemoprotective effects of pomegranate polyphenolics were attributed to a reduction in intracellular ROS generation and increased intracellular antioxidant capacity. Studies suggest that regulation of the NF- $\kappa$ B inflammatory cascade, gene expression, and transcription of proteins that increase DNA repair mechanisms and ameliorate or prevent UV-induced DNA damage could be mechanisms by which these compounds exert their effects. Punicalagins have also shown to reduce hyperpigmentation of the skin through *in vitro* inhibition of melanin and mushroom tyrosinase.

More recently, studies have looked at the potential for urolithin A to induce mitophagy, i.e. where cells eliminate damaged mitochondria, maintaining mitochondrial quality and delaying age-related disease. In rodents, urolithin A potentially induced mitophagy resulting in enhanced muscle strength and exercise capacity. A follow-up study in humans found that urolithin A induced a molecular

response resembling that which can be seen with a regular exercise regimen.

Overall, while these findings may provide evidence supporting the use of pomegranate polyphenolics in age-related conditions, it is important to recognise that these effects have been shown in largely in *in vitro* studies and animal models. Furthermore, a lack of characterisation and standardisation of pomegranate extracts in studies suggests that no conclusions can be made regarding the most effective formulations and concentrations for efficacy and safety in human subjects.

**ADVERSE EFFECTS:** When consumed orally and applied topically, pomegranate extracts and seed oils have been used safely and are generally well tolerated. Some reports of diarrhoea and other gastrointestinal side effects have occurred after oral intake as well as hypersensitivity reactions, with symptoms of itching, swelling, urticaria, angioedema and bronchospasm. Allergic reactions (dyspnoea and angioedema) may also occur with topical application. Pomegranate root, stems and peel are possibly unsafe when ingested orally in large quantities. While pomegranate juice is possibly safe in pregnancy and lactation, there is insufficient information about the safety of using other forms of pomegranate.

**DRUG INTERACTIONS:** Moderate caution is advised with ACE-inhibitors and antihypertensive drugs as pomegranate may lower blood pressure resulting in additive effects. Pomegranate may inhibit metabolism of rosuvastatin and warfarin. Inhibition of CYP3A4 and CYP2D6 enzymes may occur with pomegranate and caution is advised when taking supplements with medication metabolized by these enzymes; however, clinical significance of these interactions have not been shown in humans.

## Key references

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