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A Review on Natural Tyrosinase Inhibitors in Hyperpigmentation: Pomegranate Peel

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ABSTRACT
Hyperpigmentation is a dermatological phenomenon that causes excessive melanin production, leading to skin discoloration and darkening of skin. Skin hyperpigmentation is caused by several factors, including UV exposure, oxidative stress, and inflammatory responses that enhance melanin production. Skin pigmentation is mediated by melanocytes, situated in the epidermal basal layer which synthesize eumelanin and pheomelanin, responsible for dark and light skin tones. The melanogenesis pathway involves the three essential key enzymes: tyrosinase, TYRP1, and TYRP2. Tyrosinase is a copper-containing enzyme, that facilitates melanin biosynthesis and plays key roles in skin pigmentation, healing, protection from radiation, and immune function. Tyrosinase is a critical enzyme for melanin production, and its inhibition has become a key strategy for controlling melanin synthesis. Various synthetic agents are used as tyrosinase inhibitors, but they have been linked to various dermatological issues. Phenolic-rich pomegranate peel extract is evidenced as a safe herbal-derived material promising for skin hyperpigmentation treatment. With these, it also has Anti-neoplastic, Antioxidant, Anti-microbial, and Anti-diabetic activities. Its phenolic compounds can be obtained through various extraction technologies.

Keywords: Hyperpigmentation, Melanocytes, Pomegranate, Extraction, and Tyrosinase

Introduction

The kinetic ameliorate covering of the human body; skin behaves as the first line of defense of life by minimizing internal homeostasis with exterior environment. The skin then shields the internal organs and body system from rough conditions as it acts as a shield to microbes, chemicals, and ultraviolet radiation from sunlight and conserves water. Skin color, perhaps the most easily observed polytypic variation in humans, has likely been the topic of more research than any other aspect of human variation. The color of the skin is very important in the perception of beauty as beauty is only skin deep.

In humans, two forms of melanin pigmentation occur. The first of these is constitutive skin color, which refers to the amount of melanin pigmentation inherent in one's genes which is taken to be the skin color before the effects of the sun and other parameters have a chance to act. The other is facultative[inducible] skin color, the ratio of dark-brown eumelanin and red, yellow pheomelanin, and wherein the epidermal layers it is produced. The skin color other than melanin[brown] also depends on the blood flow [red oxygenated hemoglobin and blue reduced hemoglobin] and the content of β-karotin[yellow] or vitamin A fats[1].

Hyperpigmentation is usually a consequence of increased melanin, which can be localized in the epidermis or dermis, or both. Most commonly this occurs through an increased production of melanin by existing

melanocytes [melanotic hyperpigmentation]. Hyperpigmentation disorder of the skin is very frequent. Three of the typical are melasma, lentigines, and post-inflammatory hyperpigmentation. These include: The negative psychological implications can be quite massive. There are treatments available many of which are challenging and require long-term therapy.

There are two processes as to the development of increased pigmentation and both may occur in the epidermis only, dermis, or in both. As a rule, patient experiences the same outcomes as what they endure except when prescribed impacts their quality of life by hampering social interactions, employment or schooling, and esteem[2]. Besides that example, the brief differentiation of the most typical types of hyperpigmentation is differentiated as follows

Melasma

Melasma is a major acquired hyperpigmentation skin disease that develops as a slowly progressive, symmetrical figurate hypo melanosis of varying lighter shades of brown, Gray to dark brown.

Involve: This color variation depends upon which part of the skin is involved. When the lesion character is not clearly distinguishing epidermoid and dermo necrosis, a Wood's lamp may help illuminate the epidermal melasma, but not the dermal melasma. Melasma can be caused by photo exposure, pregnancy and hormones, oral contraceptives and hormone replacement therapy, family history, cosmetics, endocrine or liver conditions, and antiepileptic drugs. Nevertheless, most patients in men and up to one-third in women have idiopathic presentations, indicating that the root cause of the disorder is not well understood. Though the cause of melasma is still inconclusive, the current understanding is transmitted through a series of m DXA and genetic as well as environmental factors which cause the development of oxidative stress and raised vascularity that further enhances pigmentation. Melasma occurs in 1 % of the global population, while in skin-of-color populations these figures are expected at 50 %[3].

The data of the present study indicated that the skin of the body sites with darker pigment offered a more robust barrier and recovered more quickly towards baseline status after ischemic stress induced by tape stripping as compared to the skins of light-pigmented individuals. Such outcomes may have external ramifications in the topical or systemic administration of vehicle-borne therapeutic agents through the skin, the ability of skin of different colors to withstand environmental or work-related stresses, and changes in skin permeability through skin darkening or lightening[4].

Post-inflammatory Hyperpigmentation

PIH is an acquired hypo melanosis that takes place because of inflammation or any form of injury to the skin and it may affect any skin type, but it is more rampant in skin of color patients; this includes blacks, Hispanics-Latinos, Asians, Native Americans, Pacific Islanders, and Middle Eastern Origin Patients. More specifically, the skin of color patients, with Fitzpatrick skin phototype IV-VI, are susceptible to exhibiting marked psychosocial impact due to skin pigmentation changes because these changes are frequent and profound in such patients 1, dark-skinned individuals. However, there are many safe effective treatments for PIH in the skin of color including but not limited to topical depigmenting agents, chemical peels, and laser and light therapy.

A plethora of types of inflammatory dermatoses, or skin damage might result in alterations in skin color. The following diseases can cause changes in skin pigmentation: dermatophytosis or viral exanthems, insect bites or contact allergens, popular or squamous disease: psoriasis or lichen planus, medicament Osu's hypersensitivity reactions, chemical or thermal lesions, and cosmetic procedures. Nonetheless, acne

vulgaris, atopic dermatitis, and impetigo are among the common causes of PIH in skin color. In narrow Sense of PIH, the melanin is produced and transferred from epidermal melanocytes to neighboring keratinocytes. Regardless of the way this increase in the melanocyte's activity is achieved, we have elucidated that proteinoids cytokines chemokines, and other inflammatory mediators and reactive oxygen species generated during the inflammatory phase of wound healing are capable of stimulating melanocyte activity.

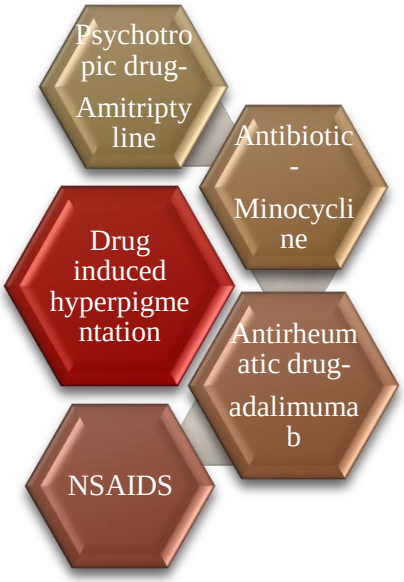
The treatment and prevention of Hyperpigmentation in case of Post Inflammatory Hyperpigmentation includes first-line therapy [Hydroquinone B4%, Sunscreen], Additional treatment needed after 8-12 weeks of therapy includes [Combinations therapy: HQ+ other depigmentation agents Chemical peeling- Glycolic acid, Salicylic acid, trichloroacetic acid, Jessner's solution, and laser/light therapy – Blue light photodynamic therapy, fractional, Photo thermolysis Nd: YAG laser First- line treatment for HQ allergy or prior long-term use Other depigmentation agents includes Tretinoin, Adapalene, Tazar. Further treatment is required after 8-12 weeks of therapy Chemexfoliation or laser/light therapy as described above first-line therapy includes [Combination therapy: HQ and other depigmentation agents Chemexfoliation – glycolic acid, salicylic acid, trichloroacetic acid, jessner's solution and laser/light therapy for HQ allergy or prior long term use other depigmentation agents including tretinoin, adapalene, tazarotene, mequinol, azelaic acid, and sunscreen. Further treatment is required after weeks of therapy Chemexfoliation or laser/light therapy as above[5].

Lentigo

Lentigines are clinically defined as several small round, brown, pigmented skin lesions, not exceeding 1 cm in diameter, without a raised border, and usually acquired genetically. What it does mean is that such a disease can be genetic or develop during childhood or adolescence. Lentigo[in the plural, lentigines] also cannot be defined as a hyperpigmentation brown macule that arises from an increased number of melanocytes[6]. Two types are recognized: Lentigo simplex lesions start in childhood and few, if any, while actinic or solar lentigines. Arise in middle age and are multiple in photo exposed area[7]. Up till now, no medical treatment has been known to treat the condition, as lentigines are benign skin changes that only present cosmetic concerns.

Particularly hyperpigmentation is a skin ailment that results in localized changes in color or pigmentation of the skin[8]. It may be due to a deposit of black iron [hemosiderosis], yellow pigment [carotenoderma], or other uncommon substances in the skin [dyschromia]. Hyperpigmentation is the darkening of the skin when melanocytes are promoted to produce more melanin by internal or external triggers including UV light, skin injury, infection, or inflammation[9]. Pigmentary disturbances are persistent and may have a significant negative impact on the person's quality of life, by producing considerable mental stress, reduced social participation, and diminished wellbeing[10,11]. German research revealed that individuals struggling with hyperpigmentation experienced social exclusion which leads to anxiety, impacts the quality of mental health and self-esteem[12]. Involvement of other factors including hormonal alterations[13], acne[14], and certain medical conditions such as malignancy[15], Addison's disease[16] and Acanthosis nigricans[17]can lead to hyperpigmentation. Skin and mucosal hyperpigmentation has been reported with the mentioned drugs; antibiotics[18], Antirheumatic drugs[19], NSAIDS[20], and psychotropic drugs[21].

Figure1: Drug induced Hyperpigmentation

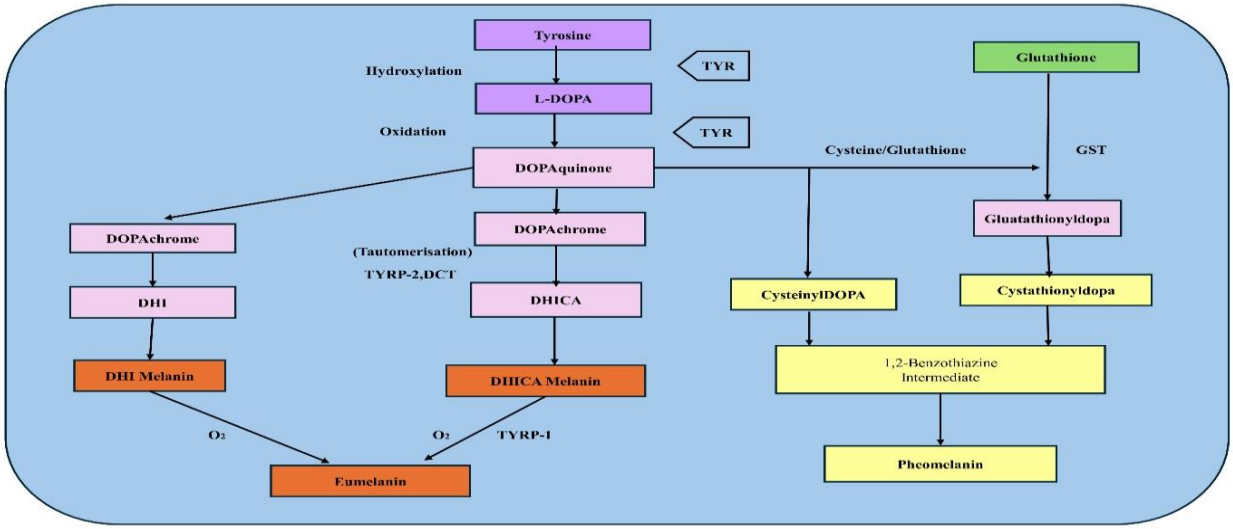


The normal pigmentation of skin and OM lesions is the visible manifestation of melanocytes biosynthetic aptitude with the synthesis of a brown-black pigment, melanin, in special organelles, melanosomes. Instead, melanogenesis is a complicated process that produces a chemical compound called melanin. It is a key biopolymer for skin protection against hazardous sun rays, toxic drugs, and chemicals. There are two types of melanin: eumelanin and pheomelanin. Tyrosinase is required sir synthesizing both the eumelanin that forms brown/black pigment, and pheomelanin that creates yellow/red pigment. Tissue pigmentation was caused by; Melanosomes in melanocytes, type of melanin within melanosomes, and transfer of melanosomes to keratinocytes[22,23].

Melanogenesis Pathway

It has been found that a variety of paracrine factors such as α-MSH, SCF, ET-1, NO, ACTH, PG, TD, and histamine in the melanocytes facilitates melanogenesis in individuals. All of these elements bring about melanogenesis because they stimulate proteins TYR, TYR-1, TYR-2, and MITF[24]. Melanogenesis is a biological synthesis of melanin pigment in melanocytes through a series of enzymatic as well as chemical-catalyzed oxidation reactions. Melanogenesis is regulated by the five signaling pathways that ultimately lead to the repression of microphthalmia-associated transcription factors. Also, many cytokines, engaged in the regulation of melanogenesis function in the role of development, proliferation, differentiation, and migration of melanocytes[25]. Formation of dopaquinone from tyrosine through oxidation, a critical rate-limiting step occurs next while subsequent reaction occurs without any oxidation. There is an auto-oxidation, which changes dopaquinone to dopa through dopachrome in the second step. Subsequently, dopa undergoes reoxidation to dopaquinone in the presence of tyrosinase and thereby completes the cycle. Further reaction transports dopachrome to dihydroxy indole as well as dihydroxy indole 2 carboxylic acid through which eumelanin formation occurs through an oxidative stage. In the presence of cysteine or glutathione, dopaquinone is transformed into cysteinyl dopa or glutathionyldopa, respectively. Then, what is called pheomelanin is made. Tyrosinase is a crucial component in melanogenesis. TYRP1 and TYRP2 proteins have additional functions[26].

Figure 2: Melanogenesis Pathway



[TYR: Tyrosinase; LDOPA: Levodopa; TYRP-1: Tyrosinase related protein-1; TYRP-2: Tyrosinase related protein-2; DHICA: 5,6-dihydroxyindole-2-carboxylic acid; DHI: 5,6-dihydroxyindole; GST: Glutathione S- transferase; DCT: dopachrome tautomerase]

Tyrosinase Inhibitors

Tyrosinase is known to be the rate-limiting enzyme in melanin biosynthesis, involved in determining the colour of mammalian skin and hairs[27,28]. Tyrosinase facilitates the conversion of L-tyrosinase to L-DOPA [monophenolase reaction] and L-DOPA to l- dopaquinone [diphenolase reaction][29]. Since tyrosinase is a key enzyme in synthesizing melanin through melanogenesis, it become successful target for melanogenesis inhibitors, that directly block the tyrosinase catalytic activity[30].

Table 1: – Tyrosinase inhibitors

Sr. Number	TYR Inhibitors	Source	References
1	Kojic Acid	Aspergillus, Penicillium	[31,32]
2	Aloesin	Aloe Plant	[33]
3	Ellagic Acid, Sinapic Acid	Pomegranate	[34]
4	Mulberry Extract	Mulberry plant	[35,36]
5	Arbutin	Bearberry, Pear, Blueberry	[36]
6	Glabridin	Glycyrrhiza	[37,38]
7	Ascorbic Acid	Citrus Fruit, Berries, Potato	[39]
8	Azelaic Acid	Potato	[40]

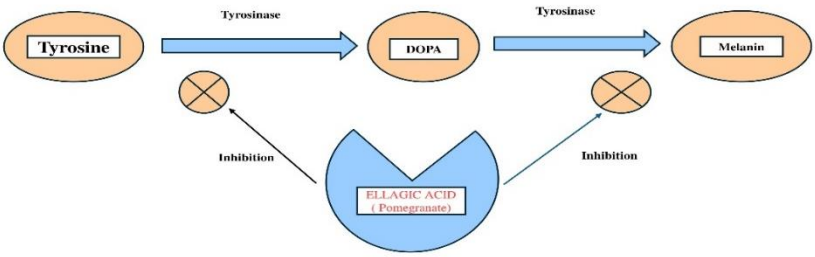
Pomegranate

Even though Hydroquinone, kojic acid, and arbutin are well-known synthetic tyrosinase inhibitors in skin-lightening products, it has been proven that they cause some dermatological problems such as skin

irritation, and acute dermatitis. Natural polyphenols and tannins isolated from plants are bioactive, potent replacements for synthetic molecules, for skin-lightening[41]. These results state pomegranate peel extract is a phenolic-rich herbal-derived material promising for skin hyperpigmentation treatment while safe[42].

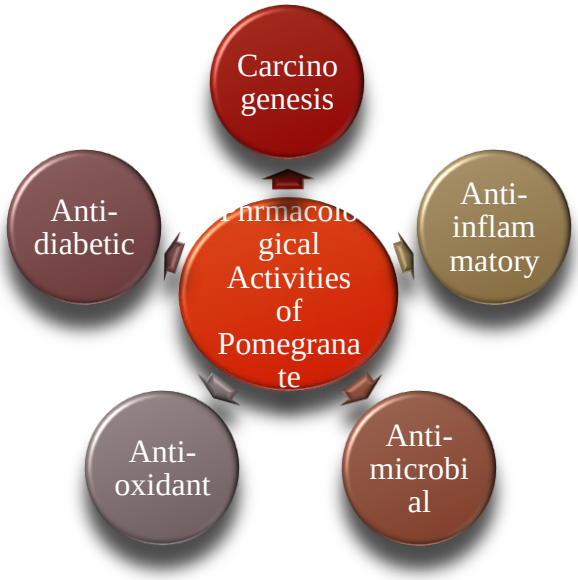
Pomegranate is from the family known as Punicaceae, from the Punica genus, and from the Granatum species. Pomegranate, A fruit with domestication, versatile plants can grow in large quantities in regions with low rainfall, drought, and on marginal soils[43]. Pomegranate is worldwide in south Europe, Pakistan, India, and West Asia. It occurs spontaneously in the northwest region in the western Himalayas [900-1800] and is cultivated throughout India for its fruit[44]. The pomegranate peel has many chemical constituents which are bioactive like Gallo tannins, ellagic acid, punicalins, punicalagins, and gallic acid. Etc The European authority has classified pomegranate as a safe food because pomegranate is proved to be a nutraceutical with many faces having multiple health benefits. Pomegranate peel contains a large number of bioactive substances including Gallo tannins, ellagic acid, etc [45,46]. Pomegranate phenolics have the potential for topical application as a natural skin depigmentation agents since they molecularly scavenge and inhibit tyrosinase and/or TRP-2r

Figure 3: Mechanism of Ellagic acid



Sinapic acid was presented as the major pomegranate peel phenolic, followed by gallic and ellagic acid, and 4 additional phenolics[47]. With hyperpigmentation, pomegranates have a wide range of pharmacological activities.

Figure 3: Pharmacological activities of Pomegranate



Anti-Inflammatory

In the state of acute inflammation, tissue is being protected against destructive processes, and in chronic inflammation diseases such as arthritis, bowel disease, and cancer can develop. Pomegranate averts inflammation through the action of these key enzymes of COX and LOX in the arachidonic acid cascade which hurts prostaglandin and leukotrienes syndrome[48]. Stomach anti-inflammatory effects of pomegranate are, however, largely researched on animals, while lab-based studies done in combating H. pylori bacteria are comparatively limited. In addition, there is limited evidence that pomegranate can significantly anti-pylori activity in vitro using metronidazole as the reference. Pomegranates possess antiulcerogenic activity in animals for using the juice of the peel and flower part of the fruits. Ellagic acid is the main constituent implicated here and other ellagitannins too have been accorded similar abilities. Further, extracts derived from the pomegranate possess notable anti-inflammatory properties in the gut[49].

Anti-Neoplastic

Oral cancer, which lies 11th by incident globally is notably associated with high metastatic rates. This turner is a highly aggressive and invasive disease. Traditional therapies encompass chemotherapy and radiotherapy, the side effects of which are damage to the neighbouring on–target tissues. The underlying polyphenolic content of pomegranate extracts turns out to be an effective supplementary treatment in preventing oral cancer. Pomegranate extracts exhibit anti-oral cancer properties through four key mechanisms: Cancer cell invasion and migration- decrease, apoptosis in oral cancer cells- stimulation, antioxidant gene expression- regulation, cancer cell proliferation- suppression[50].

Antioxidant

Many researchers have pointed out that oxidative stress can cause cancer and many other diseases. The juice and seed oil of pomegranate has a diverse blend of polyphenols, flavonoids, and anthocyanidin, which showed a high antioxidant effect. This antioxidant capacity reduces lipid peroxidation, supporting the anti-cardiovascular, anti-inflammatory, and other disease[51].

Anti-Microbial Activity

Punica granatum [pomegranate] shows extensive antimicrobial properties, the fruit juice, peel, arils, flowers, and bark of this plant show effectiveness against all groups of bacterial and viral pathogens making it a good candidate as a natural antimicrobial. Chemical leaven from pomegranate exhibits wide-spectrum antibiotics against various pathogens. Most of these extracts demonstrate varying antioxidant activities depending on their flavonoids and tannin content, with pomegranate peel extract giving the highest value. Active against some food spoilage organisms such as E.coli and Bacillus subtilis[52].

Anti-Diabetic

Type two diabetes mellitus is a disease, that is associated with insulin deficiency and perpetual hyperglycemia and is closely associated with obesity. Screpado et al., Fourati et al., and Mayasankaravalli et al., established that concerns such as unhealthy diet and obesity are associated with diabetes. The current study showed the antidiabetic potential of pomegranate peel extract that can prevent hyperglycemia and oxidative stress. Its antioxidant also increases metabolic rates. Ge et al depicted that pomegranate flower extract has anti-diabetic beneficial effects in Glycogenic and Glycosidase enzyme activity and

postprandial hyperglycemia in type 2 diabetes mellitus patients. In another study on methanolic leaf extracts in diabetic rats, it was discovered that the methanolic extract of plant leaf contains antioxidant compounds that have anti-diabetic properties because of their impact in correcting metabolic derangement and restring normal glucose homeostasis[53].

Extraction of Pomegranate peel

Pomegranate is among the most healthy fruits in the world and is loaded with the phenolic compound[54]. Several extraction techniques are used to recover bioactive compounds from pomegranate peels. Methanol or methanol-organic solvent blend is commonly used to extract pomegranate peel polyphenols by traditional technique. Methanol extraction is more efficient than water under normal atmospheric pressure, but water has a lower extraction efficiency. Pressurized water extraction technology enhances the solvent characteristics of water.

Traditional methods/Conventional

Decoction

The decoction is one of the traditional methods. Pomegranate peel decoction was prepared by mixing milled dried materials with 40 mL of Milli Q water in a beaker. The suspension was heated and boiled for 10 minutes, then filtered using a Buchner funnel with Whatman n 1 paper. The filtered mixtures were centrifuged at a relative centrifugation force of 2016 for 10 min. The resulting extract, labelled AK_D and WO_D was stored at -20º C for further analysis[55].

Percolation

The extraction process involves percolating 100g of air-dried pomegranate peel powder with 70% methanol at room temperature for 24 hours. Following extraction, the methanol was removed under reduced pressure [with a bath temperature of 50ºC] and the resulting concentrate was dried in a vacuum evaporator. The residual extract was then dissolved in distilled water[56].

Maceration

Pomegranate fruits were processed by removing the peel manually cutting it into 1 cm2 pieces and separating them for ethanolic and aqueous extraction. For the ethanolic extraction, 10g of peel was mixed with 100 mL of ethanol-water solution [7:3] and macerated in darkness for 10 days at 25ºC. The obtained extracts were filtered, and ethanol was evaporated at 63 rpm and 45 ºC. The dry sample then underwent hydrolysis with 4M HCL until reaching pH 2. The resulting dispersions were freeze-dried. In contrast, aqueous extraction involved mixing 1g of dried and crushed pomegranate peel with 40 of distilled water, heating in a water bath at 100º C for 30 minutes, filtering, and freeze-drying[57].

Traditional extraction methods have drawbacks including long processing times, costly solvents, and thermal degradation of sensitive compounds.

Non- conventional method

Ultrasound-assisted extraction

Pomegranate peel powder was milled and sieved to 425 microns. UAE was performed on 10g of POP mixed with 40 mL distilled water [1:4w/v]. Post-UAE, the mixture was agitated in darkness for 48 hours. The extract was filtered, concentrated using vacuum rotary evaporation, and freeze-dried[58]. Ultrasound-assisted extraction is more efficient in comparison to traditional extraction. Faster extraction time, Easier

processing, solvent and energy saving, and higher yield are advantages of UAE over the conventional methods[59].

Conclusion

Hyperpigmentation, a common dermatological disorder, significantly impacts quality of life. Causing psychological distress and social stigma. Pomegranate peel extract, rich in phenolic compounds, offers a promising natural alternative for hyperpigmentation treatment, inhibiting tyrosinase and TYRP-2, with anti-inflammatory, antioxidant, anti-neoplastic, anti-microbial, and anti-diabetic properties. Future research should be focused on clinical trials to establish efficacy and safety, standardization of extraction methods, investigation of synergic effects, elucidation of molecular mechanism, and development of topical and oral formulations for preventive and therapeutic applications, potentially unlocking novel solutions for hyperpigmentation and other dermatological disorders, such as acne, psoriasis, and vitiligo, promoting healthier, more radiant skin.

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