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Pharmaceutical Actives in Anti-Aging Creams: A Comprehensive Review of Ten Clinically Proven Therapeutic Agents

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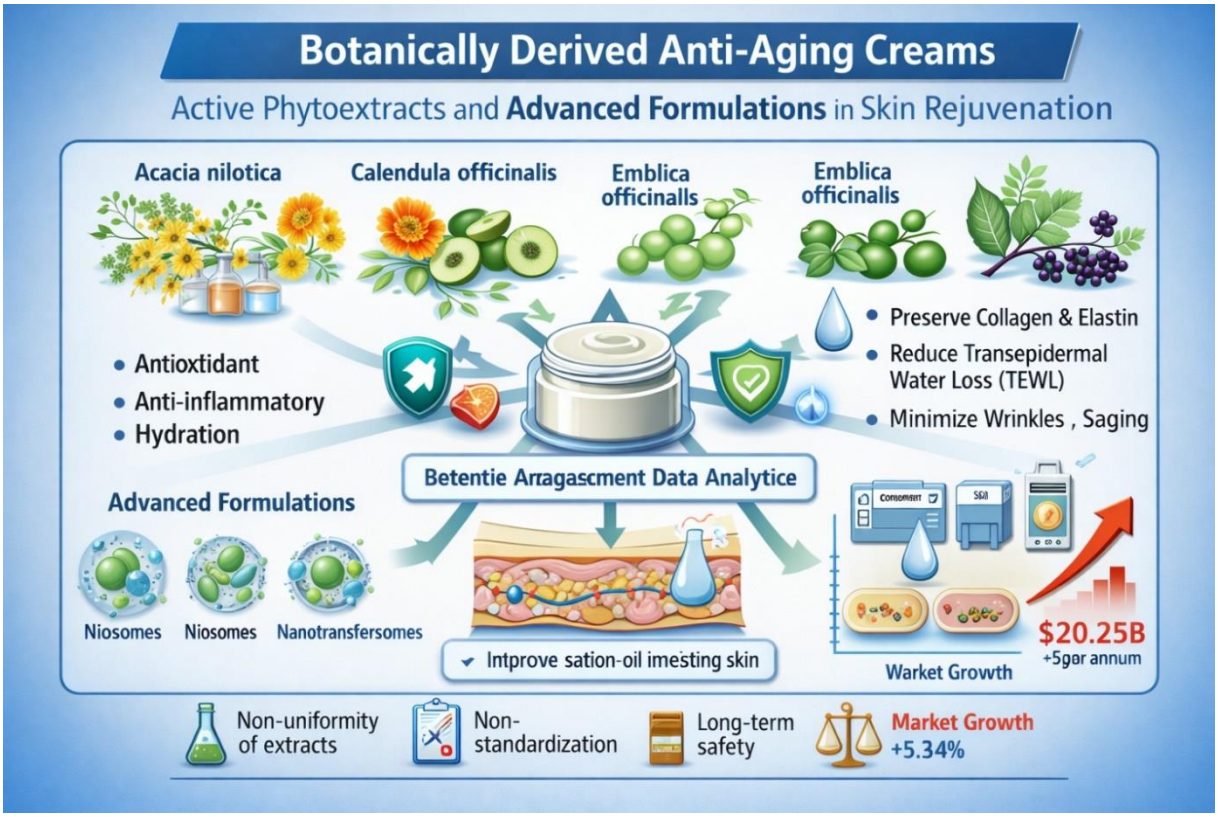
ABSTRACT

Aging in the skin is an intricate process of both intrinsic and extrinsic compounds, which encompass genetic elements, hormonal shifts, and cell metabolism, and extrinsic influences in the form of ultraviolet radiation, pollution, and lifestyle choices with the resultant structural transformations including wrinkles, elasticity loss and the drop in hydration. The paper is a review in nature and explores the application of pharmacologically active compounds in anti-aging creams, and specific focus is given on phyto extracts of plants like Acacia nilotica, Calendula officinalis, Emblica officinalis and others that have proven to be potent as antioxidants, anti-inflammatory and also as a moisturizer. These plant compounds negate oxidative stress, maintain the integrity of collagen and elastin, and minimise transepidermal water loss (TEWL), thus slowing the appearance of aging.Among the main preparations that were discussed are water-in-oil emulsions, niosomes, and nanotransfersomes which increase the stability, bioavailability, and penetration of active phytoextracts into the dermis when compared to standard creams. Their effectiveness in ameliorating skin texture, skin elasticity and skin hydration as tested by gadgets such as corneometers and evaporimeters have been shown to work well in comparison with standard bases. Regardless of these advantages, several difficulties remain, such as non-uniformity in extract composition, non-standardization, and scarcity of large-scale trials, and the issue concerning safety in long-term application.The USD 20.25 billion in 2018 with 5.4 percentage per annum of growth rate, indicates the need to provide innovative, plant-based products that combine the traditional knowledge with modern dermatological developments across the global anti-aging market. The future perspectives propose stringent quality management, streamlined delivery channels, and thorough clinical trials to make phytoextracts-based creams a worthwhile alternative to the synthetic ingredients such as retinoids and hyaluronic acid. This combination makes medicinally active anti-aging creams a prospective frontier in skin care, which will raise skin health and vitality over time.

Keywords: Skin aging, anti-aging creams, phytoextracts, antioxidants, transepidermal water loss, botanical formulations, emulsions, niosomes, collagen preservation, skin hydration

Graphical Abstract:



1. OVERVIEW OF SKIN AGING AND ANTI-AGING MECHANISMS

Aging can be considered as the accumulation of alterations in cells and tissues resulting from a growing disorderliness of regulatory mechanisms that result in lower robustness of the organism to encountered stress and disease. The concept of increased disorder in aging is shown by the deterioration of the systematic neuroendocrine feedback control governing the secretion of luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), and growth hormone (GH) [1]. Aging-related changes also occur between and among cells via variations in the intercellular matrix, the intercellular exchange oftrophic factors, the release of inflammatory cytokine mediators, and the degree of infiltration by other associated cell types. In addition, the number and distribution of certain growth agents may affect wound healing.The deterioration of DNA repair mechanisms, along with the reduction of melanin, elevates the risk of photo-carcinogenesis and may lead to a decrease in enzymatically active melanocytes (10-20% every decade), hence enhancing sensitivity to UV radiation. However, it is not known why free radical damage does not adversely affect all of the body's cells (e.g., gonadal germ cells) [1].

Skin aging is a multifaceted biological phenomenon affected by a mix of endogenous or intrinsic variables (genetics, cellular metabolism, hormonal and metabolic processes) and exogenous or extrinsic factors (chronic light exposure, pollution, ionizing radiation, and chemical poisons). These elements collectively result in cumulative structural and physiological modifications, along with increasing abnormalities in each skin layer and changes in skin appearance, particularly in sun-exposed regions. Facial skin wrinkles serve as an indicator of intrinsic aging (Refer to wrinkle classification in Table 1). The primary perceived risk factors include poor dietary practices, stress, insufficient physical activity, dehydration, illness, and sleep patterns. The primary factor contributing to extrinsic aging is ultraviolet radiation (UVR).

Figure 1: Clinical appearance of extrinsic (a) and intrinsic (b) aging of skin.

Dermatologists addressing skin diseases related to aging should evaluate the impact of comorbidities, including prevalent metabolic disorders in the elderly, dietary deficits, corticosteroid usage, and cancer therapies [4]. Optimal skin condition can be preserved to a degree through alterations in controllable lifestyle factors, including smoking cessation and the application of sunscreen [5]. Human skin cells react to signals from specialized proteins or hormones known as growth factors. The growth differentiation factor GDF11, a member of the TGF-β family, is linked to the preservation of youthful characteristics in several human tissues and organs, and in the skin, it has been associated with the suppression of the inflammatory response. The synthesis of elastin and collagen dermal connective fibers diminishes, and with aging, the regenerative rates of glycosaminoglycans are postponed [6][7].

Table 1: Comparison of Intrinsic Aging and Photoaging [8][9]

Feature	Intrinsic aging	Photoaging
Clinical appearance	Fine wrinkles, some deepening of skin surface markings, some loss of elasticity, redundant skin; Skin is smooth, unblemished, but shows saggy appearance	Nodular, leathery surface sallow complexion, yellowish mottled pigmentation, coarse wrinkles, severe loss of elasticity, reddened appearance with initially light wrinkles, which later deepen, thus showing loss of collagen fibers
Epidermis	Thin and viable; Thinner than normal with lower cell growth, minor abnormalities in keratinocyte regularity; Normal stratum corneum; There is loss of rete pegs here as well	Marked acanthosis, cellular atypia; Thick skin, with acanthosis followed by atrophy of the cells; High basal keratinocyte irregularity; Stratum corneum appears compact; There is loss of rete pegs here as well
Elastic tissue	Increased, but almost normal	Tremendous increase, degenerates into amorphous mass
Reticular dermis	Thinner, fibroblasts decreased, inactive mast cells decreased, no inflammation; Elastin fibers appear irregular in their arrangement, whereas collagen fibers begin to lower in number and thickness	Thickened, elastosis, fibroblasts increased, hyperactive mast cells; Excessive production of elastin fibers in an improper orientation, collagen fibres appear to thicken and then wear out soon; Appearance of grenzzone
Collagen	Bundles thick, disoriented	Marked decrease of bundles and fibers
Glycosaminoglycans	Slightly decreased	Markedly increased
Papillary dermis	No grenz zone	Solar elastosis with grenz zone,
Microvasculature	Moderate loss	Great loss, abnormal and telangiectatic

2. PHARMACEUTICAL MEDICINES USED IN ANTI-AGING CREAMS

Skin care products may exist in solid, semisolid, or liquid forms. Semisolid formulations comprise creams, ointments, and pastes. Cream is an emulsion of oil and water formulated for dermal applications. Emulsions are a kind of dispersion systems consisting of two insoluble, thermodynamically stable phases: the continuous phase and the scattered phase [11]. An emulsion is classified as water-in-oil when the dispersed phase is oil, and conversely, as oil-in-water when the dispersed phase is water. This category of emulsion is referred to as a simple emulsion. A simple emulsion that is further dispersed in the dispersed phase media is referred to as a multiple emulsion. Emulsions can be classified into many categories, including macroemulsions and microemulsions,

based on the size of the dispersed phase globules [12].

Skin care products can be found in solid, semisolid, or liquid forms. Semisolid formulations include creams, ointments, and pastes. Cream is an emulsion of oil and water designed for topical use. Emulsions are dispersion systems comprising two insoluble, thermodynamically stable phases: the continuous phase and the dispersed phase. An emulsion is designated as water-in-oil when the dispersed phase consists of oil, and as oil-in-water when the dispersed phase comprises water. This type of emulsion is designated as a simple emulsion. A basic emulsion that is additionally dispersed inside the dispersed phase medium is termed a multiple emulsion. Emulsions can be categorized into many types, such as macroemulsions and microemulsions, according on the size of the dispersed phase globules [12].

Table 2: Phytoextracts loaded to creams with antioxidant features studied in human

S.NO	Botanical Name	Antioxidants†	Nature of cream	References
1.	*Acacia nilotica*	Phlobatannin, pyrocatechol, (+)-catechin, protocatechuic acid, (−)-epigallocatechin-7-gallate, and (−)-epigallocatechin-5, 7-digallate	Simple W/O cream††	[14]
2.	*Benincasa hispida*	Caffeic acid	Simple W/O cream††	[15]
3.	*Calendula officinalis*	Isorhamnetin, quercetin, myricetin, and kaempferol	Simple W/O cream††	[16]
4.	*Castanea sativa*	Catechin and myricetin derivatives	Simple W/O cream††	[17]
5.	*Capparis decidua*	Isoginkgetin and ginkgetin	Simple W/O cream††	[18]
6.	*Emblica officinalis* Gaertn	Emblicanin A, emblicanin B, punigluconin, and pedunculagin	Simple W/O cream††	[19]
7.	*Oryza sativa*	Gallicacid, pyrogallol, apigenin, and rutin	Niosomes loaded cream	[20]
8.	*Punica granatum*	Ellagic acid	Nanotransfersomes loaded cream	[21]
9.	*Silybum marianum*	Silymarin (silybin, silydianin, and silychristin)	W/O emulsion cream	[22]
10.	*Trigonella foenum-graecum*	Kaempferol derivatives such as 3-O- -D-glucosyl(1 2) - -D-galactoside	Simple W/O cream††	[23]

3. BIOLOGICAL ACTIVITIES AND MECHANISMS OF ACTION OF SELECTED MEDICINES

Skin care products are available in solid, semisolid, or liquid forms. Semisolid formulations encompass creams, ointments, and pastes. Cream is an emulsion of oil and water intended for external application. Emulsions are dispersion systems consisting of two insoluble, thermodynamically stable phases: the continuous phase and the dispersed phase. An emulsion is classified as water-in-oil when the dispersed phase is oil, and as oil-in-water when the dispersed phase is water. This emulsion is classified as a simple emulsion. A fundamental emulsion that is further dispersed within the dispersed phase medium is referred to as

a multiple emulsion. Emulsions can be classified into various forms, including macroemulsions and microemulsions, based on the size of the dispersed phase globules [12].

The water-in-oil cream containing floral extract of Calendula officinalis shown the ability to enhance skin tightness and improve elasticity, thereby delaying the aging process. This formulation increases skin moisture, as indicated by decreased TEWL values, which is essential for regular skin metabolism and avoids premature aging [27]. Castanea sativa (Fagaceae) comprises catechin, myricetin 3-O-glucoside, quercetin 3-O-rutinoside, quercetin 3-O-glucoside, kaempferol 3-O-rutinoside, and kaempferol 3-O-glucoside. The surfactant-free cream derived from the ethanolic extract of Castanea sativa leaves has demonstrated a moisturizing effect on human skin via regulating transepithelial water loss. Capparis decidua is a member of the Capparidaceae family. This plant contains abundant active substances such as isothiocyanate glucoside, glucocapparin, stachydrine, n-triacontane, β-carotene, and β-sitosterol.

Emblica officinalis Gaertn (Euphorbiaceae), commonly referred to as Amla, contains several strong antioxidants, such as gallotannins, including emblicanin A, emblicanin B, punigluconin, and pedunculagin. This plant is found in China, India, and Indonesia. Every component of this plant, from root to fruit, possesses therapeutic efficacy for many health issues; for instance, its fruit is beneficial in treating diarrhea and jaundice.

Oryza sativa (Poaceae) contains potent antioxidants such as ferulic acid, gamma-oryzanol, and phytic acid. The extract of Oryza sativa grains was incorporated into niosomes, which were subsequently utilized to make a water-in-oil cream. This cream was determined to be effective in diminishing transepidermal water loss, as evidenced by measurements taken using a Corneometer and Evaporimeter. This formulation can be utilized as an anti-aging treatment, as transepidermal water loss significantly contributes to the aging process by improving skin hydration. The cream's characteristic may be attributed to the potent antioxidants found in Oryza sativa extract [33].

The researchers utilized nanotransfersomes containing ethanolic extract of Punica granatum (Punicaceae) seeds to manufacture an innovative cream alongside the production of a traditional cream. The efficacy of various formulations in anti-aging effects was ranked as follows: nanotransfersomal cream > conventional cream > blank nanotransfersomal cream > base cream [34]. Application of a water-in-oil emulsion cream containing ethanolic extract of Silybum marianum (Asteraceae) seeds over eight months resulted in decreased transepithelial water loss, leading to enhanced moisture levels in human skin [35]. Trigonella foenum-graecum is a member of the Fabaceae family. This medicinal plant contains many active substances such as polyphenols, galactomannans, flavonoids, protodioscin, trigoneoside, diosgenin, and yamogenin. Galactomannan enhances skin moisture [36].

4. SAFETY, FORMULATION CHALLENGES, AND FUTURE DIRECTIONS

In 2018, the global market for anti-aging products was valued at USD 20.25 billion. The projected yearly growth rate is calculated at 5.4%. The rising proportion of the global senior demographic, coupled with technological advancements in the cosmetic sector, are pivotal factors propelling the expansion of the anti-aging products market[37]. Anti-wrinkle solutions are becoming increasingly significant due to improved formulas designed to mitigate the aging process. The most favored active ingredients are retinoids, hyaluronic acid, and alpha hydroxy acids, whereas serums and creams are currently regarded as the most appealing product types/formulations by customers[38].

yaluronic acid (HA) and its derivatives are extensively utilized in cosmetic formulations due to the recognition that the natural concentration of hyaluronan in the dermis declines with age. Incorporating HA into skincare products can aid in preserving skin hydration, reducing fine wrinkles, and improving skin texture and elasticity. Hyaluronic acid exhibits multiple actions that give it superior to other cosmetic chemicals, facilitating skin regeneration, hydration, and anti-aging benefits. The biological activity and dermal absorption of hyaluronic acid (HA) are contingent upon its molecular weight, exhibiting diverse advantageous effects on the skin. Cosmetics available in the market incorporate hyaluronic acid or its derivatives alongside other active ingredients, including as peptides, probiotics, proteins, amino acids, vitamins, and plant extracts. These auxiliary actives augment the quality and performance of the cosmetic composition, offering additional benefits [41]

Figure 2: Improvements in skin condition [42]

5. CONCLUSION

Skin aging is a natural and gradual phenomenon affected by internal variables including heredity and hormonal fluctuations, alongside environmental influences such as ultraviolet exposure, pollution, lifestyle choices, and regular skincare practices. This review emphasizes the significance of pharmacologically active components in anti-aging creams, specifically concentrating on botanical extracts and their biological functions. The analyzed phytoextracts exhibit potent antioxidant, anti-inflammatory, moisturizing, and skin-protective attributes, which are essential for mitigating oxidative stress, enhancing skin hydration, and maintaining collagen and elastin integrity. These measures collectively contribute to postponing observable manifestations of aging, including wrinkles, dryness, and diminished suppleness.

Recent advancements in formulation technologies, such as emulsions, niosomes, and nanovesicular delivery systems, have markedly enhanced the stability and transdermal absorption of active substances. These improvements improve the efficacy of anti-aging creams by facilitating superior distribution of bioactive substances to deeper layers of the skin. In contrast to pharmaceutical creams that include specific and powerful active ingredients, phytoextract-based formulations provide a milder, multi-targeted strategy and are typically more appropriate for prolonged usage owing to their advantageous safety profile.

Nonetheless, obstacles such as inconsistencies in plant extract composition, absence of uniform standardization, and insufficient large-scale clinical data persist. Mitigating these constraints via enhanced quality control, standardized extraction techniques, and rigorously structured clinical trials would bolster the scientific validity of phytoextract-derived anti-aging therapies. Medicinally active anti-aging creams signify a promising and advancing domain of skincare research, integrating ancient botanical wisdom with contemporary dermatological and formulation technology to promote healthy and youthful skin.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this article. The authors alone are responsible for the content and writing of this manuscript.

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