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REVIEW ON RECENT ADVANCES IN BOTANICALS IN ANTI-AGING FORMULATIONS

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Abstract:
Human skin, like all other organs, undergoes chronological aging. In addition, unlike other organs, skin is in direct contact with the environment and therefore undergoes aging as a consequence of environmental damage. The primary environmental factor that causes human skinaging is UV irradiation from the sun. Oxidative stress and low-grade chronic inflammation standout as key features of physiological skin ageing. Skin aging is a complex biological process influenced by a combination of endogenous or intrinsic and exogenous or extrinsic factors .Decreased levels of collagen is a primary cause for skin aging. Human skin, likeall other organs, undergoes chronological aging. In addition, unlike other organs, skin isin direct contact with the environment and therefore undergoes aging as a consequence of environmental damage.

KEYWORDS: Skin aging, Skin anti-aging, Plant extracts.

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INTRODUCTION:

Skin forms an important part of human innate immune system. Wrinkles, thinning and roughening of skin are some of the symptoms that affect the skin as it ages [1]Skin aging is mainly characterized by wrinkle formation, uneven pigmentation, darkening, thinning, sagging, and roughening of skin[2]. This could be caused either by intrinsic or extrinsic mechanisms Intrinsic skin aging is inevitable and occurs as age progresses [3,4].It mainly occurs due to cumulative effects of oxidative stress. Reactive oxygen species (ROS) (free radicals) are produced during normal cellular metabolism and are needed for normal biological functions. However, higher amounts of ROS such as hydrogen peroxide, superoxide, and peroxynitrite radicals cause oxidative stress, which damages DNA, RNA, lipids and proteins in skin, and cause skin cancer [5,6] · Extrinsic skin aging mainly occurs due to environmental factors such as UV irradiation, physical stress, nutritional deficiency, and alcohol consumption and thus can be controlled [7,8] .UV irradiation increases ROS production, accelerates aging process and telomere shortening. As both intrinsic and extrinsic mechanisms of skin aging are caused due to oxidative stress.Skin is a protective layer of the body of any animal including humans. As the age progresses, certain changes occur in the skin which are influenced by certain extrinsic and intrinsic factors. The changes in the skin are among the most visible signs of aging which include wrinkles, sagging skin, age spots and dryness, and also loss in the fat making the skin lose its natural smoothness. The skin is mainly composed of three layers, the outer part epidermis, middle part dermis, and the innermost subcutaneous layer. As a person ages, the epidermis slowly thins even though the number of cell layers remains same[10,11]. The inherent repairing ability of skin gradually reduces as a person ages which may be due to infections and pressure ulcers. In addition, the number of melanocytes decreases, aging skin becomes thinner, paler and clear withlarge pigment spots, age spots or liver spots. All these signs necessitates the need for the anti- aging treatment. As we age, our body produces less collagen and elastin which plumps our skin and makes it lose its elasticity respectively[12,13] By the use of anti-aging products or treatment, either the collagen production can be boosted, or its natural loss can be slowed down.Anti-aging treatments are also necessary to reduce fine lines, wrinkle, acne and it also helps in making the skin firm. Although sun-exposure is very essential for the synthesis of vitamin D, exposure to harmful UV rays results in premature aging, initiation of the reactive oxygen species generation, skin cancer, and degradation of extracellular matrix components[14] .

SKIN AGING AND ITS MECHANISM:

Skin aging is a complex biological process involving a blend of multiple components. Although the underlying mechanism of skin aging is not yet completely understood, multiple pathways were illustrated which were speculated to be responsible for skin aging namely changes in DNArepair and stability, mitochondrial function, cell cycle and apoptosis, ubiquitin-induced proteolysis, and cellular metabolism. The most vital factor responsible for skin aging may be a decline in the physiological hormone. UV radiations contribute about 80% in the skin disease development including skin aging and skin cancer. Thus UV radiation is a causative factor for skin aging. Repeated exposure to UV increases the degradation of collagen and alters the synthesis of new collagen accompanied by alterations in elastin fibers. The absence of both collagen and elastin in the skin leads to loss of its flexibility and strength. In addition, the skin also loses the ability to repair itself[15] .

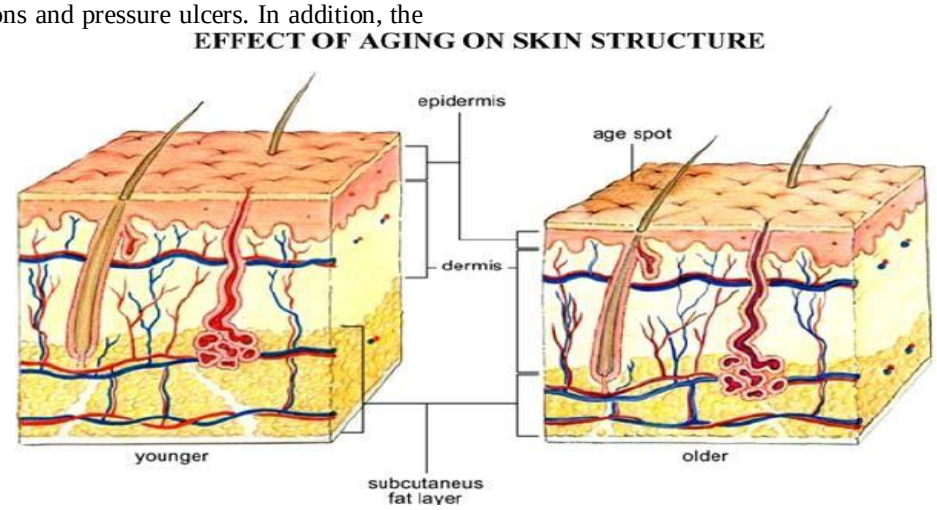

Figure 1: Differences in skin structure between normal and aged skin.

Factors responsible for skin aging:
Most of the changes occurring in the skin may be attributed to a mix of both, endogenous/intrinsic and exogenous/extrinsic factors. Intrinsic aging causes changes in the epithelial cell layer whereas extrinsic aging causes abnormal accumulation of elastic tissue in the dermis.

1]Intrinsic factors: In the process of intrinsic aging, these free radicals are formed by oxidative cellular metabolism. The free radicals produced in the process, are removed by anti- oxidative mechanisms, but as the age progresses, there is a decrease in the anti-oxidative mechanisms and eventually excessive free radicals in our body which leads to cellular aging.

Hormonal mechanisms: The skin aging takes place by certain modification in growth factors andhormonal activity. The decline in several hormones in our body such as estrogen, testosterone, dehydroepiandrosterone and its sulfate ester and also melatonin, insulin, cortisol, thyroxine, and growth hormone can deteriorate several skin functions. In postmenopausal women, there is a decline in the estrogen levels which results in several aging signs such as dryness, wrinkles, lossof elasticity, collagen breakdown and epidermal atrophy.

Mitochondrial DNA damage: Mitochondria consume oxygen and produce energy, and as a result, there is a continuous production of reactive oxygen species. These reactive oxygen speciescauses oxidative stress after exhaustion of cellular defense mechanisms and they also cause further mutation of mitochondrial DNA. These mitochondrial DNA cause high mutation rates because of inefficient recognition and repair mechanism. This damaged mitochondrial DNA produces less energy which affects the energy supply to the cells which in turn lead to cellular dysfunction. The damaged mitochondria undergo degeneration, rupture, leakage which are the prime reasons for aging.

Role of telomere: Telomere protects the chromosomes from degradation and also prevents cellular DNA damage. Due to shortening of the telomeres, the t-loop configuration is disrupted which initiates DNA damage response, apoptosis, senescence or cell cycle arrest. Hence the shortening of the telomeres is responsible for intrinsic aging and photoaging.

2]Extrinsic factors:
Smoking: Smoking damages the collagen and elastic fibers in the dermiswhich makes the skin more slack, hardened and less elastic.Nicotine, carbon monoxide and othertoxic substances produced during smoking result in vasoconstrictive and hypoxic effects on the skin. These contribute to premature skin aging.
Ultraviolet (UV) radiations: About 80% of the facial aging is attributed to sun exposure. Photo damaged skin contributes for loss of skin elasticity, skin roughness and dryness, irregular pigmentation and deep wrinkling. *Life style*: It also has a major impact on aging. Lack of exercise, alcohol consumption, unhealthy diet, pollution, stress contributes to aging. Certain lifestyle factors cause an increase or decrease in the rate of telomere shortening[15].

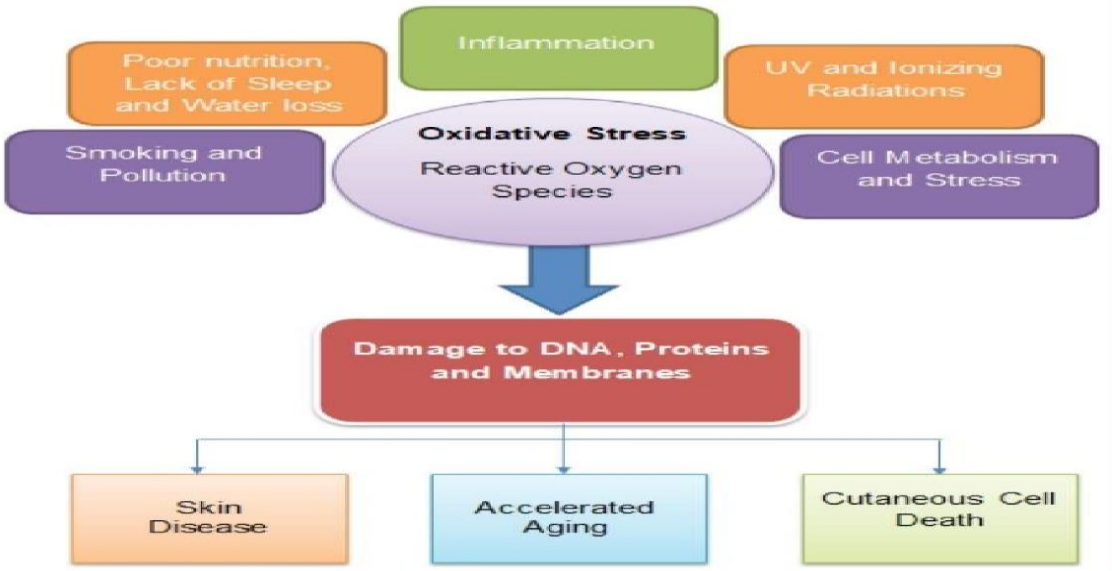

Figure 2 : The different causes of aging are depicted

Strategies for anti-aging:

The proportion of the aged population is gradually on the rise owing to developments in healthcare and improvement in lifestyle, particularly in developed countries. With aging, some of the body functions get affected leading to a variety of diseases like a chronic coronary disease,hypertension, and diabetes. Increased production of oxygen-derived free radicals plays a vital role in the aging process. Aging is a process that affects all cells, tissues, organs, diminishing homeostasis and increasing organism vulnerability. Premature photo aged skin leads to the thickened epidermis, deep wrinkles, discoloration, roughness, and dullness. Further loss of skin elasticity leads to a phenomenon called sagging.This in turn, leads to less effective desquamation and slower wound healing in older people. It is a fact that skin beauty is perceived as an important indicator signifying the overall well-beingof an individual.

Anti-aging diagnostic medicine:

Figure 3. Various approaches for healthy life extension and anti-aging. Aging is difficult to judge in terms of appearance before all age-related diseases or pre-diseases become apparent. Therefore, it focuses on preventing thedeterioration of health through periodic and systematic health checkups. In addition, since it is possible to induce an increase in function before complications and organ damage occur, through various approaches to anti-aging diagnostic medicine, it is the most effective method in the pre- or early stages of the disease[17].

Skin anti-aging botanicals:

In 2011, 63.8% of anti-aging products contained botanical preparations while in 2018, 73.8% of products contained these ingredients. This corresponds to a 16% increase in a seven-year period, which is consistent with market growth trends[18].

The number of botanical species used in anti-aging cosmetic products per year was slightly higherin 2011, with 106 different species versus 96 in 2018. However, 177 products were analyzed in 2011 comparing with 103 products in 2018, which could have influenced this finding.

Botanicals Anti-Aging Mechanisms:

After analyzing the literature regarding each botanical preparation, the ingredients whose anti- aging mechanisms are documented in the scientific literature were categorized and quantified.

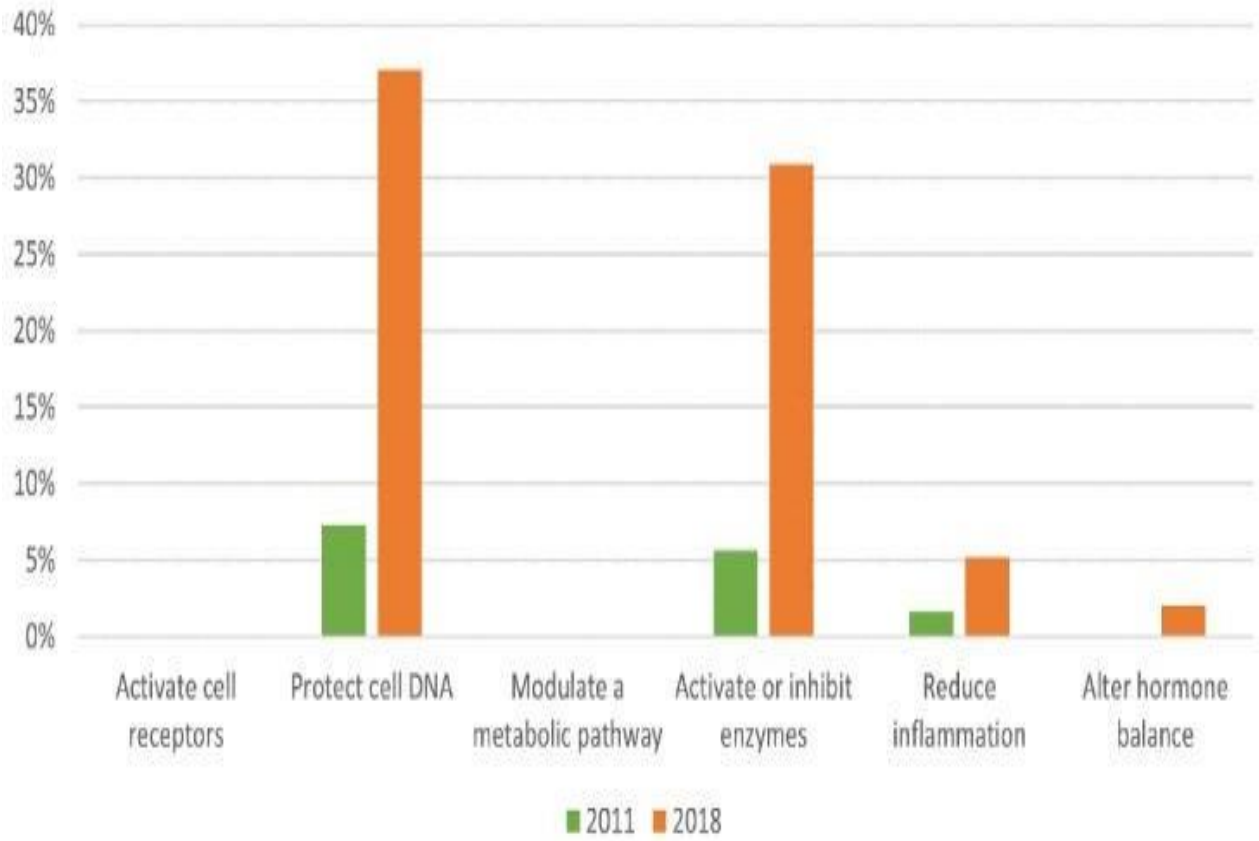

Figure 4: Relative amount of botanical ingredients classified by anti-aging mechanism.

Overall, there was an increase in the use of botanicals with proven anti-aging action from 2011 to 2018. It is noticeable that the most used categories are the same in both years. Botanicals with DNA-protecting action were used more frequently, followed by enzyme-inhibiting ingredients and those with inflammation-reducing action. It is also worth mentioning the emergence of ingredients that alter hormone balance.

Stability studies

The formulations are sealed in vials (10 mL capacity) after flushing with nitrogen and stored at 4 and 25°C for different periods of time (10, 20, and 30 days). The stability of the formulations is assessed by monitoring the residual drug content, size, and morphology of the vesicles, withrespect to time[20] .

MATERIALS AND METHOD:

Data Collection:

Data were collected from anti-aging cosmetic products from multination brands marketed in pharmacies and parapharmacies in Portugal.

Anti-aging cosmetics were included in the study if they exhibited in the label one of the followingwords: anti-wrinkle(s); anti-age/anti-aging; wrinkles repair; regenerator; aging; firming. All the information available in the product's label was collected, along with the information available on the manufacturers' websites. The data collection started in 2011 and was updated with products launched in 2018 or whose composition has been renewed that year, in order to avoid duplicate product analysis and to reflect the market trends. Cosmetics for application on the face, neck, and eye contour were included, comprising more than 40 multinational brands. Followingthese criteria, 280 products were selected, namely 177 and 103 respectively in 2011 and 2018[21].

1.Coffea Arabica extract :

Polyphenols such as chlorogenic acid, proanthocyanidins, quinic acid, and ferulic acid, which possess antioxidant properties are highly present in Coffea arabica. Coffea Arabica extract decrease levels of MMP-1 and IL-1b and downregulated MMPs gene expression and upregulatedthe gene of expressions for collagen structural proteins[21] .

Figure 5-Coffea Arabica Extract

2.Calendula officinalis extract:

Calendula officinalis includes terpenoids, carotenoids, and flavonoids. Calendula officinalis flower extract displayed can delay skin aging through its ability to motivate skin tightness, skin elasticity, and increasing the skin hydration by reducing transepidermal water loss (TEWL), which is vital for preventing skin aging[22] .

3.Hippophae rhamnoides extract:

Hippophae rhamnoides includes antioxidants such as -carotene, vitamin C, and vitamin E. Hippophae rhamnoides extract stimulate dermal fibroblasts that is important for producing collagen necessary the skin water holding capability, it also has the tendency to decrease the trans epidermal water loss (TEWL)[23] .

4.Moringa oleifera:

The hydro alcoholic extract of Moringa oleifera leaves decreased the undesirable skin sebum concentrations and reduced skin trans epidermal water loss leading to increased skin hydration.

Moringa oleifera extract was also effective against skin wrinkles, and scariness. Moringa oleifera extract acquires its antiaging properties because of the presence of phenolic compounds which can scavenge thereactive oxygen species[24] .

Figure 6-Moringa Oleifera

5.Pomegranate:

The high antioxidant content of Punica granatum (pomegranate) makes it a motivating constituent in cosmetics. Pomegranate contains a variety of active components such as, tannins, piperidine alkaloids, niacin, and anthocyanins. In vitro, pomegranate extract shields human fibroblasts from UV-induced cell damage, owing to the deactivation of NF-kB, inhibition of proapoptotic caspace-3, and augmented

DNA repair.18 Topically, pomegranate extract reduces COX-2 in porcine skin, causing a significant anti-inflammatory properties[21].

6.Soy extract:
Soy, derived from Glycine maxi, contains anti-aging isoflavones, including equol, glycitein, anddaidzein. Glycitein exhibits antioxidant effects. Glycitein displayed an increased cell proliferation in dermal fibroblasts. Glycitein improved production of collagen and decreased MMP-1.20 Daidzein, has established skin-lightening, anti-wrinkle, and skinhydrating properties.Endogenous antioxidants are enhanced by diadzein. In addition, diadzein has decreased the proliferation of keratinocytes.

The soy-derived equol improved collagen and elastin and diminished MMPs in cell culture.Soy isoflavones repressed UV-induced keratinocyte death and lessened epidermal thickness, and trans epidermal water loss (TEWL) in UV-exposed mouse skin[27] .

7.Salvia officinalis:
Salvia officinalis contains rutin, a polyphenolic bioflavonoid, which is important for skin nourishment.Rutin has the ability to deactivate free radicals which aid in vitamin C regenerationrestoring its antioxidant potential.24 Vitamin C plays an important role in collagen secretion, thiscould certainly stimulate the health of human skin. The antiwrinkle effect of Salvia officinalis was investigated by using a UV-induced photoaging model. Salvia officinalis extract had revealed antioxidant activity by DPPH radical scavenging assay[28].

8.Protocatechuic acid: Protocatechuic acid (PCA), is widely found in plants and fruits, including plums (Prunus domestica L.), and rosemary (Rosmarinus officinalis L.).PCA has an inflammatory antioxidant and effect.26 Protocatechuic acid has the capability to scavenge free radicals (DPPH, ABTS. Uisng human dermal fibroblasts, PCA induced the synthesis of type I collagen, and prevented MMP-1 production from the UVA-exposed human dermal fibroblast. Treatment with a lotion containing 0.02% PCA for 8 weeks considerably reduced the percentageof all skin wrinkle considerations. Accordingly, PCA shows anti-wrinkle potentials[29] .

9.Coenzyme:
Q10 Coenzyme Q10 is a free radical scavenger; it is capable of vitamin E regeneration.

It reduces MMP production and hastens the restoration of ATP levels after UV- irradiation in human fibroblasts in fibroblasts. It enhances the production of both collagen and elastin.30 Coenzyme Q10 reduces micro-relief lines and wrinkles. In a high dose, coenzyme Q10 displayed further enhancement of wrinkles in the upper radial lip lines, nasolabial folds, and corner of the mouth lines[30] .

10.Aloe barbadensisleaf extract :

Aloe barbadensis contains triterpenoids (lupeol, βsitosterol) that exert a protective effect. A 10%cream of A. barbadensisleaf extract was investigated to determine its efficacy on epidermal hydration and the degree of skin elasticity. Consequently, this study has exhibited that the A. barbadensis cream increases skin firmness, improves its moisture content, and enhances

its elasticity[31] .

Figure 7- . Aloe barbadensisleaf extract

11.Saffron extract and avocado oil :
Avocado oil contains phytosterols that are considered as skin rejuvenators. Crocin is a carotenoid present in Avocado oil (Persea Americana) that scavenges free radicals, so it can play a major role in preventing skin wrinkle.An anti-wrinkle cream that are composed of saffron[32]


Figure 8 - Saffron and avocado oil extract

13. Grape peel extract:
Resveratrol present in grape is able to reduce the intracellular concentrations of reactive oxygenspecies (ROS).36 Using grape peel extract or resveratrol increased the antioxidant enzymes in the skin and prevented metalloproteinases. The grape peel extract (GPE) had a protective effecton formation of wrinkles that are exposed to UVB. Thus, grape peel extract, containing a considerable amount of resveratrol, can be utilized for the production of beauty products[33] .

14.Melatonin:

Melatonin protects keratinocytes from UVB-induced oxidative damage.Melatonin protects against wrinkle formation, and transdermal water loss. It has inhibited dermal collagen degradation in UVB irradiated hairless mice. Melatonin prevented the production of cyclooxygenase (COX-2), phosphoextracellular signal-regulated kinase-1 (p-ERK) which are responsible for inflammatory reactions in UVB exposed HaCaT keratinocytes[34].

15.Sanguisorba officinalis extract:
A skin cream prepared with ziyuglycoside I isolated from Sanguisorba officinalis prevented thesecretion of interleukin (IL)-1β, matrix metalloproteinase (MMP)-2, MMP-9, in the mice. Additionally, the skin cream inhibits the formation of wrinkles and breakdown of collagen in UVB-induced hairless mice. Subsequently, the skin cream prepared with ziyuglycoside.

It may be a photoprotective compound for skincare[35].

16.Sibseonsan extract:
The antioxidant, anti-inflammation, skin wrinkle inhibition effects of Sibseonsan was determinedin vitro using murine macrophage and melanocyte cell lines. Sibseonsan act as a free radical scavenger.
There is a progressive production of elastase and collagenase upon treatment of B16/F10 cells with Sibseonsan[36].

17.Green tea extract :
Green tea is composed of several active components as epigallocatechin gallate, epigallocatechin, and epicatechin gallate. Green tea in a 0.5% possess a noncytotoxic concentration and demonstrated its several activities against skin aging, like suppression of melanin production through its ability for inhibition of tyrosinase activities. Green tea extract is a potent antioxidant, and it has a matrix metalloproteinase-2 inhibition activity. The results of this study demonstratesthat green tea is useful as an skin anti-aging agent in cosmetic products[37].

18.Saffron extract :

Curcuma manga (White saffron) contains several bioactive compounds, some of which are curcuminoids. The antiaging properties of C. mangga extract (CME) in oxidative stress-inducedhuman BJ fibroblasts were studied with an emphasis on collagen protection against pro- inflammatory mediators MMP1, MMP3, and MMP13.

The results demonstrated that treatment using CME (25 μg/mL) could protect the collagen contents in H2O2-treated fibroblasts, whereas the negative control has the lowest collagen contents[38].

Figure 10 – Saffron Extract

19.(3,5)-Dicaffeoyl-epi-quinic Acid :

Caffeoylquinic acid has been reported to display antioxidant effects. The antiphotoaging effect of 3,5-dicaffeoyl-epi-qinic acid DEQA on MMPs and type I procollagen in UVA-irradiated human dermal fibroblasts (HDFs) has been examined. collagen production in UVA-deteriorated HDFs. Moreover, treatment of UVA-irradiated HDFs with DEQA inhibited MMP-1, MMP-3, and MMP-9 expression.

Furthermore, DEQA alleviates the UVAmediated suppression of collagen expression. Thus, DEQA is a probable cosmetic agent for the treatment of skin photoaging[39].

20.Licorice root :

Glycyrrhiza glabra (Licorice) contains glycyrrhizin that shows anti-inflammatory properties. Certain phenolic components like glycyrrhizin, chalcone, and glabridin are also important for theantiinflammatory activity of licorice. Glabridin has many advantages in cosmeceutical products. Topically, it has an antioxidant, skin-whitening agent and antiinflammatory properties. Licorice extracts have tyrosinase and elastase inhibitory activity which shows the anti-aging properties of the studied root extracts[40].

Figure 11- Licorice root

Evidence for Botanicals Anti-Aging Efficacy:

The botanical preparations that showed anti-aging activity in clinical trials were grouped according to their mechanisms of action, as described by Hyland Cronin and Zoe Draelos.This classification system categorizes the anti-aging ingredients according to eight distinct mechanisms of action: “modify the skin barrier” (e.g., smooth skin scale, exfoliate skin scale), “enhance intercellular lipids” (e.g., cholesterol, triglycerides, essential fatty acids, ceramides, natural moisturizing factor), “activate cell receptors” (e.g., retinoids), “protect cell DNA” (e.g., antioxidants, sunscreens), “modulate a metabolic pathway” (e.g., peptides), “activate or inhibit enzymes” (e.g., skin-lightening agents), “reduce inflammation” (e.g., botanic antioxidants, plantsterols), or “alter hormone balance” (soy phytoestrogens). Botanicals that were found to solely modify the skin barrier and/or enhance intercellular lipids were not considered as anti-aging active ingredients[41].\

CONCLUSION:

These botanical preparations stand out for their content in compounds with interest for anti- aging cosmetics, and their efficacy has been shown both in vitro and in vivo. It is noteworthy that all these preparations contain polyphenols, mostly flavonoids, but also stilbenes. The skin anti-photoaging aging properties of botanical extracts with their various skin protecting mechanisms have been elucidated. Additional randomized, placebo-controlled, double-blind studies are required to approve many of the claims made about these plant extracts. vitamin Dis expected to be a main anti-aging medicine in the near future due to its numerous positive effects in elderly population.

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