Scientific Bulletin. Series F. Biotechnologies, Vol. XXVIII, No. 2, 2024
ISSN 2285-1364, CD-ROM ISSN 2285-5521, ISSN Online 2285-1372, ISSN-L 2285-1364

THEORETICAL EXPLORING OF ANTIGENOTOXIC PLANT INGREDIENTS WITH ANTIAGING PROPERTIES

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Abstract

Aging could be considered a chronic disorder that comes with more devastating traits than we could imagine or see, both at cellular and molecular levels. The paper aimed to summarize the molecular mechanisms of ageing and to emphasize some plants which have antigenotoxic properties that can be linked to antiaging features. In cosmeceutical manufacturing, using natural and organic ingredients is the best way to maintain and offer skin rejuvenation qualities. Moreover, the synergy between plant phytochemicals can enhance the overall antiaging effect, addressing multiple aspects of skin aging simultaneously. There are tremendous antigenotoxic plants provided by nature, while few of them have antiaging features, such as: Trichilia emetica, Psoralea corylifolia, Ximenia americana, Schinziophyton rautanenii, and Hypericum perforatum. Thus, the review outlined their benefits in order to reveal their therapeutic potential in the cosmetic industry.

Key words*: aging and antigenotoxicity ingredients, Mafura butter, Ximenia oil, Manketti oil, vegan cosmeceuticals.*

INTRODUCTION

The whole human body bears the traces of time by natural aging. However, in two special ways, human skin suffers particularly aging trials over time: one by chronological or intrinsic/internal causes and another by extrinsic/external agents. The internal elements of skin aging are provoked by: (a) genomic unsteadiness; (b) cellular caducity and (c) decrease of telomers. The extrinsic aging is expedite continually exposing to environmental stresses and damages such as: (a) UV radiation; (b) pollution; (c) extreme temperature differences; (d) tobacco smoke and alcohol consumption.

Both of them have several serious consequences: (a) narrowing of both the epidermal and dermal layers by losing collagen and crashing of collagen fibrils; (b) increasing fragility; (c) undermining vascular support; (d) retarding injury healing and (e) augmenting vulnerability to cancer development, by appearing inflammatory environment. Hence, epidermal caducity exerts - beyond trivial cosmetic and aesthetic concern - an obvious bestowing to this ″chronic medical disorder″ named age-related skin issue(Quan, 2023).

Skin aging is a complex biological phenomenon that includes DNA, RNA, and protein damage, structural deterioration, and accumulation of reactive oxygen species at the cellular level. Going from basic molecular pathology and cell biology theory, which establish that there is an intrinsic connection between form and function, the skin morphology is the most important. For instance, diabetes patients' feet are suffered by thickening of the epidermis thus, increasing stiffness and being less able to distort, but more exposed to risk of cleaving and ulceration. (Lechner & al., 2019) In other words, changed form or structure of the cell leads to a modified function of it.

Mechanical skin traits, respectively adhesion strength of the dermo-epidermal junction could be improved by epidermal hydration (El Genedy-Kalyoncu et al., 2022). For centuries, human have used plant bioactive molecules to moisturize, smooth, and nourish their skin of

any age. Plant lipids are made up by 95% of mono and diglycerides and free saturated or unsaturated fatty acids and 5% of different substances in varying proportions: phosphorlipids, glycolipids, sphingolipids, waxes (saponifiable fraction) and hydrocarbons like squalene, pigments in the form of carotenoids and chlorophyll, vitamin E, phytosterols, polyphenols, and triterpene alcohols (non-saponifiable fraction). The latter one, triterpene esters are not only the principally reliable in anti-inflammatory, antitumor and antioxidant activities of plant lipids, but give them their unicity and specificity. On the other hand, essential oils are commonly volatile, concentrated, and vigorous, being claimed to have rejuvenated features and tremendous health benefits (Sarkar et al., 2017).

The goal of this theoretical investigation is to summarize the available molecular information about aging in humans and to emphasize the effects of selected plants against this unwanted ″chronical disease″ in order to propose a reliable cosmetic treatment.

SKIN AGING

Epidermal aging

Epidermal is composed of five sheets; basal, spinosum, granulosum, lucidum, and corneum. The basal sheet, also known as rete ridges or germinative area, is separated from the dermis by the basement membrane. The cells in this layer are cuboidal to columnar, mitotically active stem cells that constantly fabricate keratinocytes, but there are also melanocytes. (Yousef et al., 2024) Epithelial cells are fixed within basement mem-brane by multiprotein structures named hemidesmosomes, which are essential for final transformation of keratinocytes and their relocation through injury curing and carcinoma incursion (Walko et al., 2015).

Hence, in the rete ridges area there are interfollicular epidermis (IFE), melanocyte stem cells (McSCs) and hair follicle stem cells (HFSCs) that contribute permanently to the regenerating epithelium and are important in wound regeneration. Epiderma-dermal attachment requires type XVII collagen (COL17), a structural component of hemidesmosomes that have revealed more functions in homeostasis of the skin stem cells. COL17A1 encodes alpha chain of COL17, the protein produced by keratinocytes Thus, the decreasing of COL17A1 expression will affect adhesion of stem cells to the basement membrane, reducing keratinocytes and melanocytes turnover, leading to thinning epidermal layer and diminished hair follicle stem cells (HFSCs). All of them are the initial morphological traits of aging skin and, respectively, greying and losing hair. Moreover, a reduction in the expression of COL17A1 may also infirm the bond between the epidermis and dermis, conducting to other aging signs: skin fragility, blistering, retarding injuries healing, wrinkles emergence, and loosened skin (Quan, 2023).

In connection with narrowing of epidermal layer, Lintzeri et al. (2022) have published a systematic meta-analysis with epidermal thickness within 37 areas of human body. They have concluded that the epidermis is thinning by age with a mean of almost 20%. The most diminished part is cheek with 27.14%, while for lower leg is 14.10%, as is showed in Table 1.

Table 1. Diminishing of the epidermal thickness by age, adapted after (Linzeri & al., 2022)

No.	Skin area	Age	Thickness (μm)	Narrowing (μm)	Narrowing (%)	Epidermal reduction mean (%)
1.	forehead	23	83	20	24.10	**19.16**
		66	63			
2.	cheek	26	70	19	27.14	
		58	51			
3.	back	22	78	6	7.69	
		55	72			
4.	inner upper arm	23	89	12	13.48	
		63	77			
5.	volar forearm	27	81	17	20.99	
		60	64			
6.	dorsal forearm	24	79	11	13.92	
		60	68			
7.	abdomen	24	83	22	26.51	
		59	61			
8.	gluteal	29	88	17	19.32	
		59	71			

No.	Skin area	Age	Thickness (µm)	Narrowing (µm)	Narrowing (%)	Epidermal reduction mean (%)
9.	thigh	24	78	19	24.36	**19.16**
		59	59			
10.	lower leg	23	78	11	14.10	
		66	67			

Dermal aging

The dermis layer is composed by closely intertwined clusters of collagen wires forming an elaborate spatial array named extracellular matrix (ECM) where are dwelling dermal fibroblasts, that produce these collagen fibrils. Time leaves its marks in this environment as well, by showing adulteration in both collagen threads and fibroblasts, such as: disruption and disorder of collagen wires and its production. Still, in the same time an inflammatory medium appears, known as ″inflammaging″ (Quan, 2023).

All of these are triggers for similar chronic disease signs: heightened brittleness, deteriorated blood vessels, disrupted injury repairing and boosting tumor-like mutations. From molecular point of view there are four mainly incidents clearly reviewed by Quan et al., 2023:

(1) Metalloproteinases (MMPs) activity which causes collagen fragmentation. Human MMPs form a 20-member proteinase class that is involved in natural and pathological processes related to ECM degradation. MMPs are usually extremely present in tumor environment being implicated in metastasis by disrupting the balance between growth and antigrowth molecular signals and ECM degradation. In normal condition and young skin, MMP1 known as collagenase 1 and synthesized by dermal fibroblasts, is at the lowest level possible, by tearing the initial collagen threads. However, in aging skin, MMPs having an increased level are responsible for permanent disruption of dermal structural and mechanical part, encountering - beyond dermal thinning, uplifted fragility and retarding wound healing - jeopardy of carcinoma emergence.

(2) Deterioration of the transforming growth factor-beta (TGF-β) signalling due to the dermal thinning and conducting to decreased collagen production. Being a multifunctional cytokine TGF-β is involved in various cellular activities, including the control of cell growth and differentiation and regulates production of collagen and elastin from ECM. Once dermal fibroblasts encounter disruption by dermal thinning, they present a malformation by diminishing the expression of the TGF-β Type II receptor (TβRII), which ends up damaging TGF-β signalling by inhibiting collagen production, increasing the activity of MMPs, and facilitating inflammaging emergence. Hence, the skin loses elasticity, firmness, resilience and expresses weakening, wrinkles, fine lines, appearance inflammations and all aging signs.

(3) The impact of elevated cysteine-rich protein 61 (CCN1/CYR61) on the aging process. CCN1 is one of the six proteins family which controls cell adhesion and cell migration - chemotaxis, the production of inflammatory mediators, cell-matrix interactions, the synthesis of ECM proteins, and wound responses. Its raised level in caducity skin brings elevated secretion of proteases, growth factors, chemokines and cytokines. Accordingly, as it was already observed in senescence, there are lofty expression of pro-inflammatory markers like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), Activator Protein 1 (AP-1), leading to a damaged and inflammatory microenvironment within dermis.

(4) Decline in autophagic activity. As in every cell, autophagy is an essential duty to maintaining homeostasis, especially in fibroblasts. In senescent dermal fibroblasts, undermined autophagy leads to the accumulation of lipofuscin, which causes age-related pigmentation irregularities (Quan, 2023).

Based on these molecular events, the aging effects could be viewed as mutagenic ones, hence ageing is not only a fancy beauty concept, even it could be considerate as a serious chronical disorder with similar tumors traits. While genotoxicity is a general term, which describes the capacity of noxious matter to induce DNA impairment, mutagenicity accurately does these DNA alterations in quantity and composition. Hence, genotoxic substances include mutagenic ones. In this context, any agent that reduce the DNA alterations can be is named antigenotoxic (Izquierdo-Vega et al., 2017).

There are tremendous antigenotoxic plants provided by nature but few of them have natural antiaging compounds that can reduce the DNA damages and stimulate the skin cell growth, including collagen production.

ANTIGENOTOXIC INGREDIENTS

Mafura butter

Trichilia emetica commonly known as the Natal mahogany is an evergreen tree belonging *Meliaceae* family and widely distributed growing naturally throughout sub-Saharan Africa from KwaZulu-Natal in the South, through Swaziland, Mpumalanga and Limpopo Provinces (South Africa), into Zimbabwe and northwards into Cameroon, Sudan and Uganda. *T. emetica* has multipurpose properties such as antibacterial, antiviral, antifungal, anti-inflammatory, antischistosomal, antiplasmodial, anticonvulsant, antioxidant, antitrypanosomal, antitussive, antimutagenic and hepatoprotective (Komane et al., 2011).

The main taxonomic markers of *Meliaceae* family are limonoids from *T. emetica.* The most important limonoids isolated from *T. emetica* are trichilin A, B, C, D, E, dregeana 4, trichilia substance Tr-B, nymania 1, rohituka 5 and seco-A protolimonoid, manifesting DNA damage repair, antifeedant qualities and obstructing insect extension. Interestingly, the extracts of *Trichilia emetica* with dichloromethane and methanol have displayed weak antimutagenic activities, unlike *Helichrysum* extracts, which have unveiled high antimutagenic properties compared to the positive control. However, an isolated sesqui-terpenoid from *Trichilia emetica*, named Kurubasch aldehyde - being tested on different cell lines - reduced the expansion of the breast tumor cells MCF-7 with IC50 = 78 μM and inhibited the augmentation of sarcoma cells S180 by being tested on murine cases with IC50 = 7.4 μM. Moreover, polysaccharides isolated from this plant were traditionally used in wound healing as they can stimulate the skin cells growth (Komane et al., 2011).

Bakuchiol

Psoralea corylifolia (synonym *Cullen corylifolium*) is an herbaceous plant from the *Fabaceae* family that contains Bakuchiol (BAK) 1-(4-hydroxyphenyl)-3,7-dimethyl-3-vinyl-1,6-octadiene, a natural meroterpenoid. This terpenoid is present in the plant cold-pressed oil obtained from seeds in a percentage of 6.24%. BAK presents powerful biological features such as antiaging, anti-inflammatory, and antibacterial and can be a cosmetic ingredient as a natural alternative for retinoids without side effects or irritation. Because they contain a 4-hydroxystyryl moiety, both bakuchiol and resveratrol have analogous structural. Moreover, the pyrone, chromene, and quinazoline derivatives linked to the styryl moiety proved strong biological features useful in the cosmetic industry. Having a similar pharmacophore, the bakuchiol may express similar traits as resveratrol (Barna et al., 2023). BAK was found to have an effect comparable with retinol, proved by a randomized, double-blind trial performed in 2018 for 12 weeks. This clinical study with 44 volunteers demonstrated that BAK is comparable with retinol in its ability to improve photoaging effects while showing better skin tolerance. The researchers noted fewer wrinkles, increased skin firmness, and lower hyperpigmentation (Dhaliwal et al., 2018).

Bakuchiol inhibits oxidative stress by preventing mitochondrial lipid peroxidation and protecting other enzymes from oxidative stress. Being an electron-donating group, it is supposed to diminish its phenolic moiety's bond dissociation enthalpy, enhancing its antioxidant activity (Krishna et al., 2022). Moreover, BAK has been proved to inhibit the cell proliferation of prostate cancer cells (Miao et al., 2018).

Ximenia oil

Ximenia americana is a shrub or small tree up to 7 meters from the *Olacaceae* family, found in the tropics under popular name yellow plum. By aqueous decoction extraction, several phytochemicals were found, such as alkaloids, flavonoids, anthraquinones, cardiac glycosides, saponins, tannins, and terpenoids which exhibited high cytotoxicity against MCF-7, the breast tumor cell line (Sawadogo et al., 2012).

One lectin extracted from *X. americana* kernels that revealed antineoplastic activity is riproximin. (Horrix & al., 2010) Riproximin is a cytotoxic type II ribosome inactivating protein with high selectivity for colorectal and pancreatic tumor cell lines (Adwan et al., 2014).

In traditional medicine, the roots of *X. americana* are used to treat different skin problems, while the bark powder or decoction form can treat skin ulcers and burning. Moreover, the oil from seeds is marketed in cosmetics and useful for a variety of purposes: emollients, conditioners, skin softeners, body and hair oils, as well as ingredients in soaps, lipsticks, and lubricants. Xymelys 45 is a drug that protect ultrasensitive skin and contains bark extract from ximenia (Medeiros & Medeiros, 2018)

Manketti tree oil

Schinziophyton rautanenii named mongongo, is a large spreading tree species within *Euphorbiaceae* family, that grows in the semi-arid Kalahari region of southern Africa, reaching 15 m high.

It makes fruits with a sweet and edible pulp surrounded by a hard nut and holds 1 or 2 seeds or kernels. It is an essential food for elephants and mongongo nuts have been consumed by local communities for centuries. Local people from Zambia, Zimbabwe and elsewhere in southern Africa extract the oil from the kernels for cooking and cosmetics as a body rob (Chidumayo, 2016).

From these nuts, the comestible oil is expelled and holds beyond the linoleic, oleic, and linolenic acid, a special fatty acid, namely, alpha-eleostearic acid (α-ESA), with great value potential in both health and cosmetics (Cheikhyoussef et al., 2019). Natural phytochemicals, such as α-ESA provides excellent protection to the skin from damage caused by UV rays. Manketti oil contains high level of vitamin E and polyunsaturated fatty acids that are effective not only for moisturizing the skin but also for restructuring and rejuvenating the epidermis. Moreover, α-ESA can enter the central nervous system (CNS) through the brain-blood barrier, which is conducive to this axis of CNS pathology-CDGSH iron-sulfur domain 2 (CISD2) - nuclear factor κB (NFκB). This phytochemical is exerting neuro-modulatory effects on CISD2 elevation and can be considered to be applied in CNS injuries and diseases (Kung & Lin, 2021).

The melanoma cell line UACC-62 displayed sensitivity towards the aqueous bark and root extracts of *S. rautanenii*, especially the organic aqueous root extract that displayed the highest IC50 values of 315.5 µg/ml and 444.8 µg/ml against the human fetal lung fibroblast cell (Dushimemaria, 2014).

St. John's wort extract

Hypericum perforatum is the most popular medicinal herb from the family *Hypericaceae*. Even if it is a considered a noxious weed, *Hypericum perforatum* holds numerous biologically active components, such as naphthodianthrone derivatives (e.g., hypericin), phloroglucinol derivatives (e.g., hyperforin), flavonoids, procyanidins, tannins, essential oils, phenylpropanoids, xanthones, and other hydro soluble compounds. Hyperforin (HF) is one of the major constituents of St. John's wort, a substance that is collected in its leaves and flowers and composed of a phloroglucinol skeleton with lipophilic isoprene chains, being responsible for antimutagenic effect. HR was analyzed by Ames test using *Salmonella typhi-murium* (TA97, TA98, and TA100) bacterial strains as standard and showed the reduction of gene mutations. During the evaluation ″*in vitro* mammalian chromosome aberration test″, HF had anticlastogenic impact on both tumor cell line HepG2 and normal cell line VH10 (Imreova et al., 2017).

H. perforatum extract showed collagenase, elastase and hyaluronidase inhibitory activities and can be used together with *H. calycinum* extract as potential agents for anti-aging and skin-whitening purposes (ERSOY, 2019). Moreover, Wölfle et al. (2014) proved that hyperforin helps reduce transepidermal water loss by differentiating keratinocytes and protecting the skin barrier.

CONCLUSIONS

Aging is associated with the decline of cellular function and the accumulation of cellular damage. Therefore, exploring antigenotoxic plant ingredients with antiaging properties is valuable for protecting DNA, offering natural alternatives, promoting healthy cellular function, reducing oxidative stress and inflammation, preventing age-related diseases, and supporting sustainable practices. By identifying plant bioactive molecules with antigenotoxic properties, it can help find natural

ways to protect DNA and enhance its repair mechanisms, potentially slowing the aging process and reducing the risk of genetic mutations. Moreover, phytochemicals often work synergistically to enhance each other's effects and provide other benefits, such as antioxidant activity, anti-inflammatory effects, and promotion of collagen synthesis.

Exploring antigenotoxic plant ingredients with antiaging properties opens new ways for research and development in pharmaceuticals, cosmetics, and nutraceuticals. *Trichilia emetica, Psoralea corylifolia, Ximenia americana, Schinziophyton rautanenii,* and *Hypericum perforatum* are potential candidates with natural antiaging compounds that can reduce the DNA damages and stimulate the skin cell growth, including collagen production. Their exploration can lead to the discovery of novel compounds with unique mechanisms of action, fostering innovation and the development of next-generation products. Moreover, this research has the potential to improve human health, skincare, and the broader wellness industry by providing safer, more effective, and naturally derived solutions to combat aging.

REFERENCES

Adwan, H., Bayer, H., Pervaiz, A., Sagini, M., & Berger, M. R. (2014). Riproximin is a recently discovered type II ribosome inactivating protein with potential for treating cancer. *Biotechnology Advances*, *32*(6), 1077-1090.

Barna, A. S., Maxim, C., Trifan, A., Blaga, A. C., Cimpoesu, R., Turcov, D., & Suteu, D. (2023). Preliminary Approaches to Cosmeceuticals Emulsions Based on N-ProlylPalmitoyl Tripeptide-56 Acetat-Bakuchiol Complex Intended to Combat Skin Oxidative Stress. *International Journal of Molecular Sciences*, *24*(8), 7004.

Batiha, G. E. S., Shaheen, H. M., Elhawary, E. A., Mostafa, N. M., Eldahshan, O. A., & Sabatier, J. M. (2022). Phytochemical constituents, folk medicinal uses, and biological activities of genus angelica: a review. *Molecules*, *28*(1), 267.

Chaiyana, W., Punyoyai, C., Somwongin, S., Leelapornpisid, P., Ingkaninan, K., Waranuch, N., ... & Mueller, M. (2017). Inhibition of 5α-reductase, IL-6 secretion, and oxidation process of *Equisetum debile* Roxb. ex vaucher extract as functional food and nutraceuticals ingredients. *Nutrients*, *9*(10), 1105.

Cheikhyoussef, N., Kandawa-Schulz, M., Böck, R., & Cheikhyoussef, A. (2019). Mongongo/Manketti (*Schinziophyton rautanenii*) Oil. *Fruit Oils: Chemistry and Functionality*, 627-640.

Chidumayo, E. N. (2016). Distribution and abundance of a keystone tree, *Schinziophyton rautanenii*, and factors affecting its structure in Zambia, southern Africa. *Biodiversity and Conservation*, *25*, 711-724.

Czekalla, C., Schönborn, K. H., Lademann, J., & Meinke, M. C. (2019). Noninvasive determination of epidermal and stratum corneum thickness in vivo using two-photon microscopy and optical coherence tomography: impact of body area, age, and gender. *Skin pharmacology and physiology*, *32*(3), 142-150.

Dhaliwal, S., Rybak, I., Ellis, S. R., Notay, M., Trivedi, M., Burney, W., ... & Sivamani, R. K. (2019). Prospective, randomized, double-blind assessment of topical bakuchiol and retinol for facial photoageing. *British Journal of Dermatology*, *180*(2), 289-296.

Dushimemaria, F. (2014). *An Investigation into the Antineoplastic Properties of Schinziophyton rautanenii and Colophospermum mopane* (Doctoral dissertation).

El Genedy-Kalyoncu, M., Richter, C., Surber, C., Blume-Peytavi, U., & Kottner, J. (2022). The effect of a basic skin care product on the structural strength of the dermo-epidermal junction: an exploratory, randomised, controlled split-body trial. *International wound journal*, *19*(2), 426-435.

Ersoy, E., Ozkan, E. E., Boga, M., Yilmaz, M. A., & Mat, A. (2019). Anti-aging potential and anti-tyrosinase activity of three *Hypericum* species with focus on phytochemical composition by LC–MS/MS. *Industrial Crops and Products*, *141*, 111735.

Fernandes, G. D., Gómez-Coca, R. B., Pérez-Camino, M. D. C., Moreda, W., & Barrera-Arellano, D. (2017). Chemical characterization of major and minor compounds of nut oils: almond, hazelnut, and pecan nut. *Journal of Chemistry*, *2017*(1), 2609549.

Furlan, V., & Bren, U. (2023). Helichrysum italicum: From extraction, distillation, and encapsulation techniques to beneficial health effects. *Foods*, *12*(4), 802.

Gonçalves, S., & Gaivao, I. (2021). Natural ingredients common in the Trás-Os-Montes region (Portugal) for use in the cosmetic industry: a review about chemical composition and antigenotoxic properties. *Molecules*, *26*(17), 5255.

Horrix, C., Raviv, Z., Flescher, E., Voss, C., & Berger, M. R. (2011). Plant ribosome-inactivating proteins type II induce the unfolded protein response in human cancer cells. *Cellular and molecular life sciences*, *68*, 1269-1281.

https://en.wikipedia.org/wiki/Bakuchiol

https://en.wikipedia.org/wiki/Ximenia_americana#cite_note-:1-7

Imreova, P., Feruszova, J., Kyzek, S., Bodnarova, K., Zduriencikova, M., Kozics, K., ... & Chalupa, I. (2017). Hyperforin exhibits antigenotoxic activity on human and bacterial cells. *Molecules*, *22*(1), 167.

López-Romero, D., Izquierdo-Vega, J. A., Morales-González, J. A., Madrigal-Bujaidar, E., Chamorro-Cevallos, G., Sánchez-Gutiérrez, M., ... & Madrigal-Santillán, E. (2018). Evidence of some natural

products with antigenotoxic effects. Part 2: plants, vegetables, and natural resin. *Nutrients*, *10*(12), 1954.

Komane, B. M., Olivier, E. I., & Viljoen, A. M. (2011). Trichilia emetica (Meliaceae) - A review of traditional uses, biological activities and phytochemistry. *Phytochemistry Letters*, *4*(1), 1-9..

Kramberger, K., Kenig, S., Jenko Pražnikar, Z., Kočevar Glavač, N., & Barlič-Maganja, D. (2021). A review and evaluation of the data supporting internal use of *Helichrysum italicum*. *Plants*, *10*(8), 1738.

Krishna, T. A., Edachery, B., & Athalathil, S. (2022). Bakuchiol–a natural meroterpenoid: structure, isolation, synthesis and functionalization approaches. *RSC advances*, *12*(14), 8815-8832.

Kung, W. M., & Lin, M. S. (2021). Beneficial impacts of alpha-eleostearic acid from wild bitter melon and curcumin on promotion of CDGSH iron-sulfur domain 2: Therapeutic roles in cns injuries and diseases. *International Journal of Molecular Sciences*, *22*(7), 3289.

Lechner, A., Akdeniz, M., Tomova-Simitchieva, T., Bobbert, T., Moga, A., Lachmann, N., ... & Kottner, J. (2019). Comparing skin characteristics and molecular markers of xerotic foot skin between diabetic and non-diabetic subjects: An exploratory study. *Journal of tissue viability*, *28*(4), 200-209.

Lintzeri, D. A., Karimian, N., Blume-Peytavi, U., & Kottner, J. (2022). Epidermal thickness in healthy humans: a systematic review and meta-analysis. *Journal of the European Academy of Dermatology and Venereology*, *36*(8), 1191-1200.

Medeiros, A. C. D., & de Medeiros, F. D. (2018). Ximenia americana L. *Medicinal and Aromatic Plants of South America: Brazil*, 477-486.

Petrisor, G., Motelica, L., Craciun, L. N., Oprea, O. C., Ficai, D., & Ficai, A. (2022). *Melissa officinalis*: Composition, pharmacological effects and derived release systems - A review. *International Journal of Molecular Sciences*, *23*(7), 3591.

Quan, T. (2023). Human skin aging and the anti-aging properties of retinol. *Biomolecules*, *13*(11), 1614.

Sarkar, R., Podder, I., Gokhale, N., Jagadeesan, S., & Garg, V. K. (2017). Use of vegetable oils in dermatology: an overview. *International journal of dermatology*, *56*(11), 1080-1086.

Sawadogo, W. R., Schumacher, M., Teiten, M. H., Dicato, M., & Diederich, M. (2012). Traditional West African pharmacopeia, plants and derived compounds for cancer therapy. *Biochemical pharmacology*, *84*(10), 1225-1240.

Ulrich-Merzenich, G., Welslau, L., Aziz-Kalbhenn, H., Kelber, O., & Shcherbakova, A. (2019). Synergy quantifications to identify individual contributions of combination partners to the overall activity - The example of STW 5. *Phytomedicine*, *60*, 153013.

Walko, G., Castañón, M. J., & Wiche, G. (2015). Molecular architecture and function of the hemidesmosome. *Cell and tissue research*, *360*, 529-544.

Wölfle, U., Seelinger, G., & Schempp, C. M. (2014). Topical application of St. John's wort (*Hypericum perforatum*). *Planta medica*, *80*(02/03), 109-120.

Yousef, H., Alhajj, M., & Sharma, S. (2017). Anatomy, skin (integument), epidermis *StatPearls Publishing; Treasure Island (FL), June 8, 2024*.