A critical appraisal of the efficacy of dietary supplements on skin ageing

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Abstract

The aim of this thesis is to provide a comprehensive and detailed understanding of an aspect of nutrition and dermatology. In particular, in investigating the evidence for the anti-ageing effects of oral supplements and topical applications on the skin by assessing the measurement parameters and methods used. The thesis broadly examines research related to the use of either topical or oral nutrient supplements for reducing skin aging. Chapter 2 focuses on a scoping review which assesses the literature base for human intervention trials that have examined the efficacy of dietary supplements by examining their effects on parameters of skin aging and the commonly used skin parameters, and reporting the equipment and methodologies used.

Human studies addressing skin anti-ageing effects of dietary supplements were systematically searched from February 2021 to April 2022 from four databases: CINAHL, Embase, PubMed, and Scopus. The scoping review protocol was submitted to the Open Science Framework with the DOI 10.17605/OSF.IO/7A8JB as a prospective registration. The Cochrane Risk of Bias (version 2) assessment tool was used to assess the quality of the randomised controlled trials (RCTs) included in the review. The selection criteria used resulted in 87 eligible studies of which, 30 human studies were suitable for detailed analysis which included 22 randomised controlled trials and, 10 intervention studies with two studies contributing to both. The majority of the studies yielded positive outcomes, with dietary supplements enhancing a wide range of skin parameters used to assess indications of ageing. However, 7 of the 22 RCTs examined had a high risk of bias, whereas 10 had a low risk of bias and 5 at some concern level. Moreover, 18 representative skin parameters were identified and reviewed, which are commonly used in the review studies which assessed either appearance, physical qualities, or biochemical parameters of the skin. The most widely measured skin parameters are skin wrinkles, hydration and elasticity with the corresponding measured methodologies or equipment are skin replica analysis, corneometer and cutometer. A meta-analysis was not possible since the included studies employed a range of dietary supplements and employed a diversity of different methodologies. To our knowledge, this is the first review that has classified and summarised the skin parameters, methods and equipment in skin ageing and food supplementation.

In conclusion, these results support the claims that topical applications can slow down the progress of skin ageing, but also, this is enhanced if combined with oral supplements. Based on the scoping review, the most effective oral supplements are those with combination formulations including micronutrients, macronutrients and anti-oxidants or plant extracts.

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Chapter 1

Introduction

1.1 Skin structure and function

For adult humans, the skin, has a range of 1.5-2.0 m^2 surface area and is the largest organ which functions as a physical barrier between the external and internal environment (Vollmer et al., 2018). Skin protects the human body from mechanical and chemical threats, potentially invading pathogens, ultraviolet radiation as well as maintaining hydration and regulating body temperature (Lopez-Ojeda et al., 2021). Skin is continuously in contact with the external surroundings especially the harmful effects of ultra-violet light so that the first signs of ageing are apparent on the skin (Pullar et al., 2017). Meanwhile, skin health and appearance have been suggested to manifest the overall inner-health status of the organism (Draelos, 2010) which can be affected by nutritional status with regards to both macronutrients and micronutrients (Pullar et al., 2017).

In addition, skin is a complex organ associating different types of tissues- epithelial, connective, vascular, muscular and nervous (Piccardi and Manissier, 2009), and is divided into three main layers- the epidermis, dermis and the hypodermis (**figure 1**). The outer epidermis contains only necrotic or dead cells in order to prevent water loss and acts as a barrier (Alberts et al., 2002). The epidermis layer is predominantly made of keratinocytes (80-95%) but also contains many different cells such as melanocytes, Langerhans cells and Merkel cells. Due to constant desquamation, the epidermis has a very high turnover rate which usually renews in around 28 days. It proceeds from the innermost layer to the outer surface: from the basal layer, spinous layer, granular layer to stratum corneum. After keratinocytes reach the stratum corneum, they attain their highest level of differentiation called coenocytes (dead cells) (Lorencini et al., 2014). However, this desquamation process will generally slow approximately 30-50% with ageing and the epidermis becomes thinner, keratinocyte vertical height falls, corneocyte surface area increases, keratinocyte adherence diminishes, and epidermal turnover rate typically slows. In short, the overall skin thickness decreases with age (Lorencini et al., 2014). The dermis resides in between the epidermis and hypodermis and includes a mass of sensory receptors, nerves, blood vessels and sweat glands to regulate the body temperature and melanin to limit the ultraviolet radiation. The deepest layer is the hypodermis. Its main function is to store fat which works as insulation and padding for the body (Kim and Dao, 2021; Yousef et al., 2021).

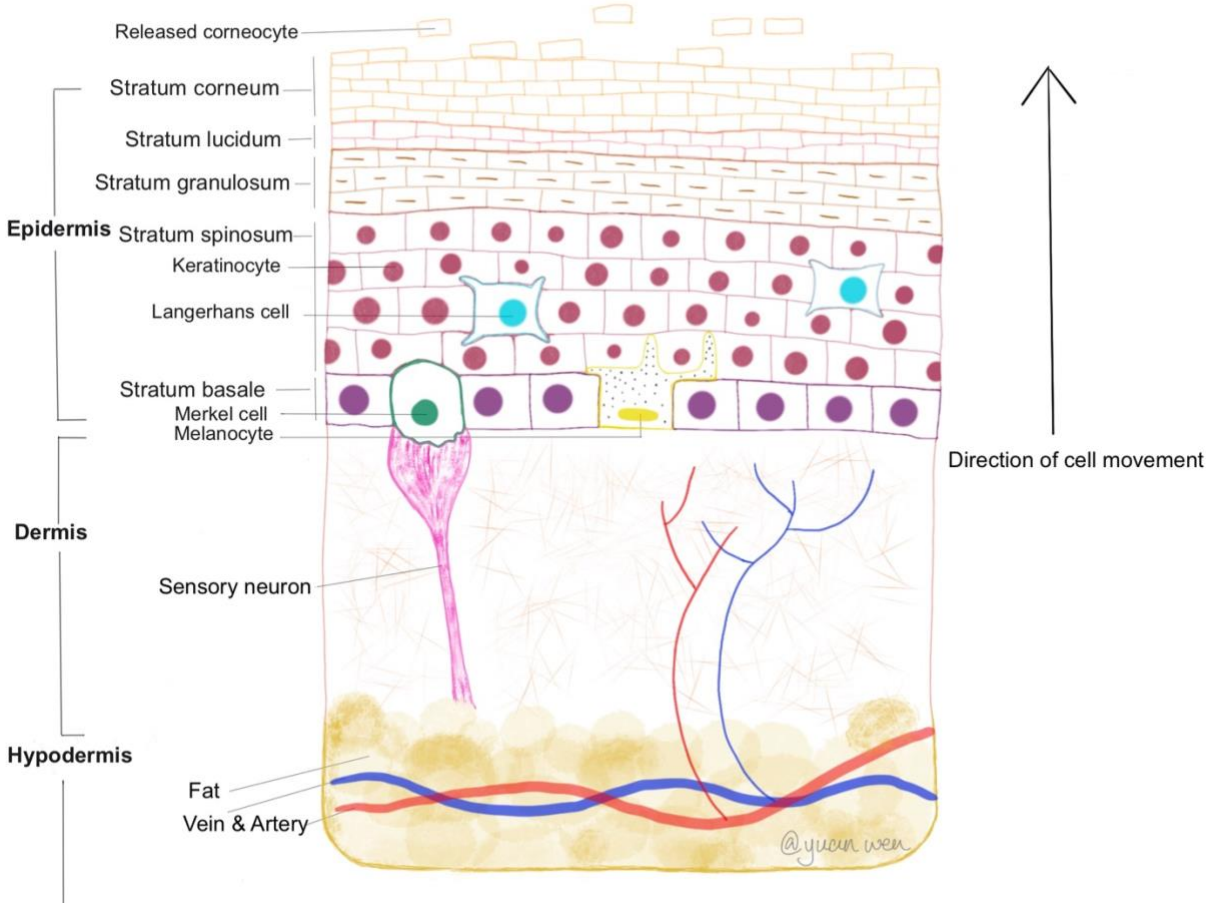

Figure 1. The human skin structure. There are 3 main layer of human skin. Epidermis, dermis and hypodermis. In addition, epidermis is consist of five principle layers, from the outermost layer stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum to the innermost layer stratum basale. The innermost layer, the stratum basale, includes stem cells to produce daughter cells which transit to the outermost layer and Merkel cells (detect touch sensation) are also scattered in. The stratum spinosum mainly contains keratinocytes which produce keratin fibres. Langerhans' cells (participate in immune responses) and melanocytes (produce pigment melanin), in a very less small amount, are inserted among these keratinocytes. In stratum granulosum, keratohyalin granules are flatter primarily existing as flatter and irregular shape in this layer. However, stratum lucidum usually contains 2-3 dead cell layers that found in a thick skin rather than a thin skin. The outermost layer is stratum corneum, the dead keratinocytes are released. [Source: the author, adapted from Tortora et al., (2001) and Lorencini et al., (2014)]

Moreover, the main components of skin, collagen (70-80%) and elastin (2-4%; a type of highly elastic protein makes up elastic fibre, are responsible to maintain skin structural integrity, elasticity and plumpness (Czekalla et al., 2017). Elastin is an extracellular matrix protein. Its cross-linked structure and extreme hydrophobicity let it become one of the most stable proteins in the human body. However, even a small amount of proteinase enzyme named elastase can degrade elastin (Mecham et al., 1997). It is fundamentally important to understand the structure, compositions and functions of skin before studying skin ageing.

1.2 Skin ageing

Skin ageing is a complex biological process and the mechanisms are not yet completely understood. However, there are two independent processes that make up skin ageing, intrinsic and extrinsic. Intrinsic skin ageing or chronological skin ageing is mainly affected by genetics, an inevitable process, which is the same process happening throughout the whole body and all internal organs (Papakonstantinou et al., 2012). Extrinsic skin ageing is caused by external factors and the environment, such as chronic exposure under ultraviolet radiation (referred to as photoageing), but also smoking, pollution, sleep deprivation and poor nutrition (Schagen et al., 2012).

Ultraviolet radiation is the main contributor to photoageing. Ultraviolet photons are endowed with wavelengths between 100-400 nm which can be separated into shortwave UVC (200–280 nm), midwave UVB (280–320 nm), and long-wave UVA (320– 400 nm) (Anna et al., 2007). UVA, UVB and UVC exposure can all result in skin damage. However, UVC is blocked by the atmosphere, and therefore not the key form of radiation inducing photoageing. UVB is nearly 99% absorbed by epidermis and affects epidermis causing sunburn. UVA penetrates deeper than UVB and can reach the dermis layer (**figure 2**) (Pérez-Sánchez et al., 2018). Moreover, UVA is more abundant in sunlight (95%UVA, 5%UVB), therefore UVA takes the major responsibility of causing photodamage (Pandel et al., 2013).

Unprotected or excessive exposure under sunlight, UVA damages DNA indirectly via producing reactive oxygen species such as superoxide radicals, hydrogen peroxide, singlet oxygen and hydroxyl radicals which promote the damage of biomolecules in the cell, in particular DNA damage such as generation of 8-hydroxy-2'-deoxyguanosine (8-oxo-dG) - a marker of DNA oxidative damage (Gonzalez et al., 2011). The UVA-induced reactive oxygen species also stimulate a great range of transcription factors in skin cells, for example, activator protein-1 (AP-1) which can raise the generation of matrix metalloproteinases that can degrade the skin collagen, elastin and other skin connective components causing structural changes in the skin, then, correlating with accelerated skin ageing (Pandel et al., 2013). Furthermore, Shuster (1975) stated that collagen density decreases around 1-2% per year with increase in age, which leads to damages in the dermis structural integrity contributing significantly to aged skin appearance. Also, elastin fibres gradually increase in length and relative surface area which means skin elasticity decreases continuously with age (Waller and Maibach, 2006). Therefore, to protect the skin from ultraviolet radiation can be an efficient way to slow down the process of extrinsic skin ageing.

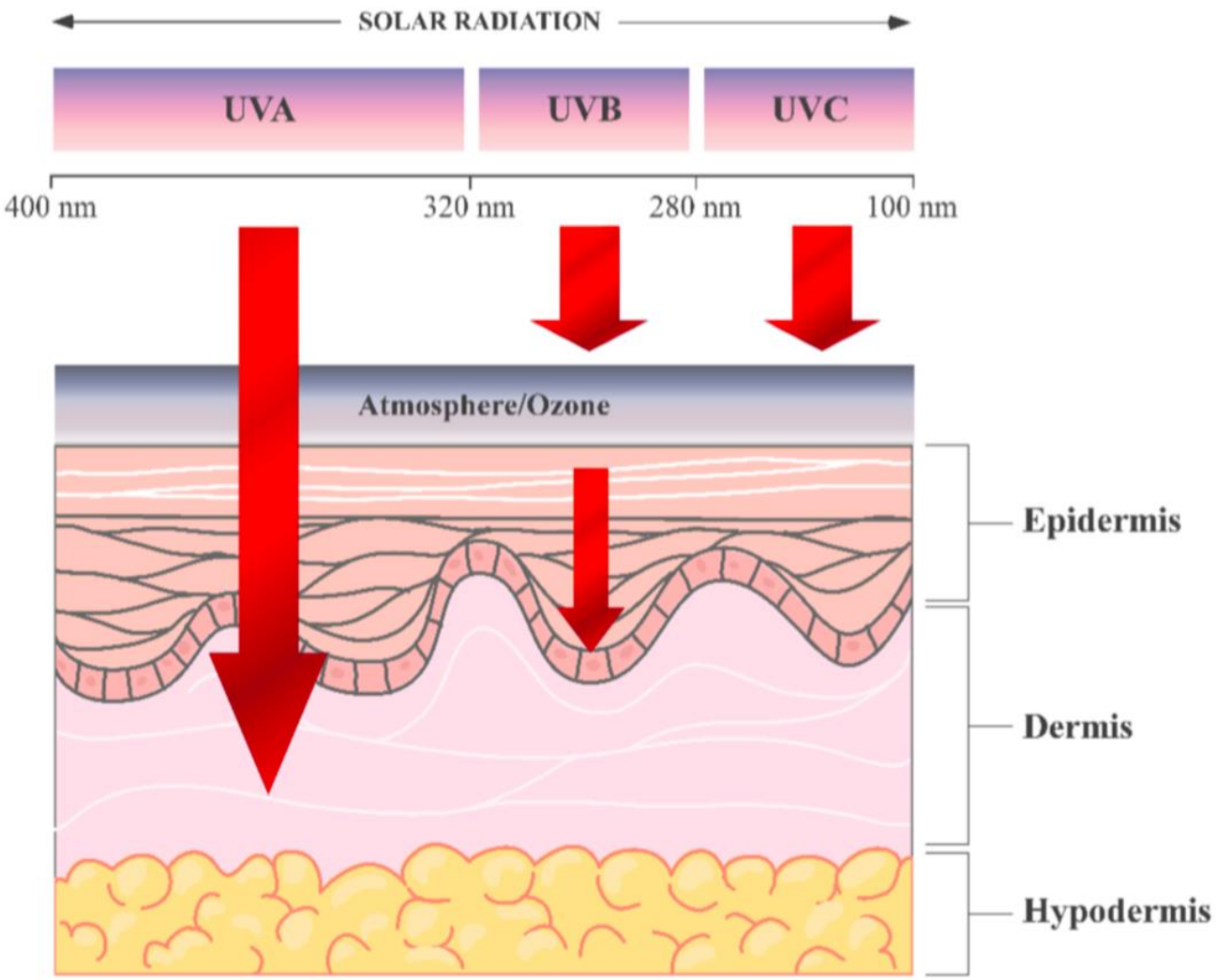

Figure 2. Ultraviolet radiation penetration into different skin layers. Ultraviolet A (UVA) is long-wave from 320 to 400nm. Ultraviolet B (UVB) is mid-wave from 280 to 320nm. Ultraviolet C (UVC) is short-wave from 200-280nm. UVA penetrates to reach dermis layer than UVB. [Source: Pérez-Sánchez et a., (2018)]

1.3 Skin parameters

The study of anti-aging skin begins with an understanding of skin parameters. A skin parameter is an observable and measurable characteristic of the skin. Human skin is a complex organ (Nguyen and Soulika, 2019). Many skin properties can be observed and measured in terms of the skin's appearance (Yousef et al., 2021), the skin's ability to react to the outside world (Nguyen and Soulika, 2019), and the skin's biochemical properties (Hussain et al., 2013), thus, the skin has many various parameters.

In addition, the number of skin parameters may continue to increase based on the development of technologies, the emergence of new advanced techniques and as new properties are discovered. At different times or in different fields, people will have some differences in the naming of certain skin parameters. And some skin parameters with similar names will also confuse the specific meaning of skin parameters. Therefore, it is necessary to clarify and classify skin parameters. The skin parameter reflects a certain characteristic of the skin, so the skin parameter referred to by the same skin characteristic, no matter what the name is, is actually the same parameter. For example, collagen structure or the quantity and quality of collagen, elastin and fibrillin measure the same content, whereas collagen structure is a more general term rather than the quantity and quality of collagen, elastin and fibrillin is more specific. Furthermore, a skin parameter can include some sub-parameters, such as the parameter of skin wrinkles, which actually has sub-parameters such as wrinkle depth, severity, volume, width, fine lines, deep lines, total wrinkles, total wrinkle score, skin relief, skin texture and skin smoothness. These sub-parameters are an individual characteristic of the skin, but together the sub-parameters can reflect the overall characteristics of the skin.

In Chapter 2, selected human studies were obtained by using the scoping review research method. Each of the selected human studies have measured at least one skin parameter, and have results on whether the skin parameter has been changed. Firstly, the skin parameters measured in each study have been counted (detail is displayed in **table 1**). After carefully identifying the skin parameters in these selected human studies, each different skin characteristic was counted as an independent skin parameter. Furthermore, one parameter in particular is known as the "subjective assessments". This parameter is the one measured by the subjective method such as self-assessment or/and expert assessment. This parameter is a collection of variable skin parameters. Generally, ‘subjective assessments’ contain skin appearance image parameters, but also can be a collection of parameters. Therefore, it is counted as a special type of skin parameter. Generalisation of parameters should be meaningful for both classification of skin parameters. The final results of this classification are illustrated in **table 2**.

1.4 Skin ageing and nutrition

Moreover, nutrition is closely related to skin health and ageing (Liakou et al., 2015; Cao et al., 2020). Nutrition is described as a biological process in animals and plants that involves food consumption and subsequent absorption into tissues (Piccardi and Manissier, 2009). Food is a

complex combination of multiple ingredients, which can be divided into nutrients and non-nutrients. Nutrients are generally classified as macronutrients and micronutrients. Non-nutrients are those compounds that cannot be classified in macronutrients and micronutrients, such as fibre, polyphenols, probiotics and so on (Chen et al., 2018). Macronutrients include carbohydrates, proteins and fats and are all are a source of energy (Carreiro et al., 2016), and typically humans need in large quantities (Savarino et al., 2021). For example, the recommended dietary allowance of protein for adults is at 0.8g per kg of body weight. The carbohydrates recommended daily allowance is 130g per day for adults and kids (Ryan-Harshman and Aldoori, 2006). Micronutrients include vitamins and minerals that the human body only needs in small amounts (Chen et al., 2018),such as the recommended dietary allowance of vitamin A for adults is between 700 to 900μg and tolerable upper intake level is 3000μg/day (Institute of Medicine (US) Panel on Micronutrients, 2001). Micronutrients play an important role in metabolism and maintenance of tissue function (Shenkin, 2006). Lack of macronutrients and micronutrients will change skin structure (Hew et al., 2016). For example, the obvious skin changes of kwashiorkor, a severe form of protein malnutrition, is skin depigmentation and atrophy of hair follicles (McLaren, 1987). Therefore, balanced nutrition and a reasonable diet are important methods for maintaining skin health (Cosgrove et al., 2007) and may delay ageing (Cao et al., 2020). Existing studies investigating the effects of vitamins, trace minerals, fatty acids and plant extracts, which have been widely used in cosmetics as topically applied agents or as oral supplements (Schagen et al., 2012), have reported that have anti-ageing effects on skin and provide protection to skin against from ultraviolet radiation (Pérez-Sánchez et al., 2018).

1.5 Nutritional components

Nutritional components are analysed through a narrative review method. A narrative review generally does not have a preconceived research question or follow a specific search method, simply a topic of interest (Demiris et al., 2019). The purpose of a narrative review is to explain and synthesise the existing literature on a topic, and then providing a conclusion based on the evidence (Green et al., 2006). In this case, literature on nutrition and skin ageing has been summarised from Embase, Medline, PsycINFO and CINAHL, especially the anti-ageing effect of topical applications and oral supplements. These papers had been divided into three different groups following the standard nutritional classification, macronutrients (carbohydrates, fats

and proteins) , micronutrients (minerals and vitamins) and others (antioxidants, combinations, plant extracts and probiotics & prebiotics).

1.5.1 Macronutrients

1.5.1.1 Carbohydrates

In human diets, carbohydrates are one of three macronutrients. Carbohydrates are essential to the human body serving as a source of energy. There are four carbohydrate structures, monosaccharide, disaccharide, oligosaccharide and polysaccharide. The most simple forms are monosaccharides ($C_6H_{12}O_6$), such as glucose, galactose and fructose. Polysaccharides are polymers composed of long chains of monosaccharides (Holesh et al., 2022). Robert et al. (2004) used L-fucose and fucose-rich oligosaccharides (FROP-3) and fucose-rich polysaccharides (FROP-s) on skin explant cultures and fibroblast cell cultures alone or combined with vitamin A, C or E to study the effect of carbohydrates on the collagen biosynthesis and accumulation (deposition). FROP-s, from high molecular weight bacterial polysaccharide, are polymers made up by a trisaccharide containing galactose, acetyl galacturonic acid and fucose (Péterszegi et al., 2003). An endo-glycosidase preparation is used to partially degrade Fucogel to FROP-3. Unexpectedly, L-fucose significantly inhibited collagen accumulation and although FROP-3 was rich in fructose, FROP-3 did not show a significant inhibition of collagen accumulation. Both of L-fucose and FROP-s combined with vitamin A, C or E can modify collagen synthesis and accumulation by fibroblast in culture (Robert et al., 2004). It is important to consider the rate of collagen degradation while stimulating the collagen synthesis. Based on the Robert et al. (2004) study, the results showed that accurately regulating the nature and the proportion of the carbohydrates and vitamin components can achieve such an effect. In addition, glycosaminocans, a long linear polysaccharide contains repeating disaccharides units of an amino-sugar and an uronic acid, is one the most popular nutraceutical formulation ingredients. In this review, the results of effects of the oral glycosaminocans supplements on skin have been summed up from the five most relevant human studies by Pérez-Sánchez (2018) who reported that the overall skin appearance and skin condition were improved, periocular wrinkling was less, visual and tactile roughness was decreased and, mottled pigmentation was eliminated.

1.5.1.2 Fats

Many studies indicated that lipids could protect the skin from oxidative damage after exposure to UVR, by retaining the skin water content and reducing the symptoms of skin ageing. The effects of different sources of oil such as safflower seed oil cream, cultured coconut extract, flaxseed and borage oil supplement have been reported (De Spirt et al., 2008; S. Kim et al., 2017; Maraie et al., 2018). These oils have one thing in common: they all have a high proportion of unsaturated fatty acids (omega-3 and omega-6). Fish oil, for example, is one the most representative supplements rich in unsaturated fatty acids, especially omega-3 (De Spirt et al., 2008). Pilkington et al. (2011) and Pérez-Sánchez et al. (2018) stated that consuming fish oil reduced skin UVR-induced erythema and inflammation as well as providing the protection against photoaging. However, due to the limited amount of studies, no conclusive evidence showed that fish oil could reduce inflammation after exposure to UVR (Souyoul et al., 2018).

1.5.1.3 Proteins

The majority of studies used collagen hydrolysate or collagen peptide derived from fish to feed to animals or human participants. The participants were nearly all female subjects, but the study by Borumand and Sibilla (2014) used both genders. This is probably designed to assess the product consumer group because generally females are more likely to use supplements to maintain their appearance, especially for skin conditions. However, both females and males should be recruited in the human studies to ensure the effect is not different between genders. The main results indicated that collagen hydrolysate had a positive anti-ageing effect on these skin parameters. For example, skin elasticity and transepidermal water loss were significantly improved ($P < 0.001$) , periorbital wrinkles were significantly decreased ($P < 0.05$) (Koizumi et al., 2018), skin hydration and collagen density in the dermis were increased (Kimura et al., 2014; Asserin et al., 2015) and the content of haemoglobin (for investigating microvascular blood circulation in the dermis) was significantly increased ($P = 0.018$) (Schwartz S.R. and Park J., 2012).

1.5.2 Micronutrients

1.5.2.1 Minerals (Zinc, Selenium)

Zinc

Zinc with nearly 6% of the total concentration located in the skin plays an important role in cellular activity (as a cofactor in skin cell proliferation, wounding healing, and anti-inflammatory) and skin functions (such as morphogenesis, repair, and maintenance). Zinc itself is a common component used in sunscreen for exerting protective ability on UVR damage in keratinocytes and fibroblasts (Takino et al., 2012; Souyoul et al., 2018; Vollmer et al., 2018). Takino et al. (2012) used Zinc l-pyrrolidone carboxylate (Zinc PCA) to treat normal human dermal fibroblasts and found that Zinc PCA via controlling AP-1 activation to suppressed UVA-induced matrix metalloproteinases-1 formation as well as promoting collagen production in dermal fibroblasts.

Selenium

Selenium is an essential micronutrient needed for two types of enzymes called glutathione peroxidase and thioredoxin reductase to protect against oxidative stress in human. The intake of selenium could increase its activity level in the skin and showed a protective effect on UVB-induced erythema. Topical selenium can be delivered in the form of L-selenomethionine which has been reported to raise the MED in human study (Pinnell, 2003; Wang et al., 2010; Souyoul et al., 2018; Vollmer et al., 2018). Therefore, based on the above evidence, both zinc and selenium can be considered as a supportive topical anti-photoageing agents.

1.5.2.2 Vitamins

Vitamin C + Vitamin E

Vitamin C (or ascorbic acid) as an antioxidant, has been widely used in cosmetics and dermatology to treat and prevent signs of skin ageing, particularly in photoageing (Telang, 2013). Many studies and literature reviews have concluded that topical vitamin C and its derivatives can significantly improve skin conditions and skin appearance. In human studies, the participants with photodamaged/wrinkle skin conditions were selected and after vitamin C solution or cream treatments, the participants in all age categories indicated that collagen synthesis was significantly increased (Haftek et al., 2008; Crisan et al., 2015), skin wrinkles

(Fitzpatrick and Rostan, 2002; Ehrlich et al., 2006; Haftek et al., 2008), roughness were improved and skin hydration was raised (Fitzpatrick and Rostan, 2002; Haftek et al., 2008). Moreover, consuming vitamin C supplements with a chokeberry peel extract significantly increased the radical scavenging capacity of the skin by using the test radical TEMPO $(CH_2)_3(CMe_2)_2NO$ (Meinke et al., 2012). In a cell culture study, vitamin C and its derivatives increased the collagen expression in dermal fibroblast cells in a dose-dependent way (H.M. Kim et al., 2017), and was able to inhibit tyrosinase activity (Kwak et al., 2015) and also palmitate inhibited UVB-induced activation of epidermal growth factor receptor, extracellular regulated kinases 1 and 2, and p38 kinase (Meves et al., 2002). In addition, vitamin E is always combined to be used with vitamin C because the latter protects vitamin E from oxidation and they work synergistically. Consuming high doses of vitamin E and vitamin C can protect the human skin against UVR-induced erythema (Boelsma et al., 2001). The most active form of vitamin E is alpha-tocopherol which functions as a radical scavenger to protect cellular lipid membrane (Wang et al., 2010; Draelos, 2010). In animal studies, topical vitamin E has been documented to have photoprotective effects with the inhibition ability of melanogenesis and against tyrosinase and tyrosine (Pinnell, 2003). Therefore, there is good evidence to suggest that vitamin C and vitamin E have the photoprotective property based on both human studies and animal studies.

1.5.3 Others

1.5.3.1 Antioxidants

The group of antioxidants contains mainly two compound groups, polyphenols and carotenoids.

Polyphenols

Polyphenols are secondary plant metabolites with unique bioactive capabilities, with over 8,000 polyphenols discovered to date (Pandey and Rizvi, 2009). Polyphenols can be divided into 3 groups: phenolic acids (eg. caffeic acid, gallic acid), non-flavonoids (eg. resveratrol, tannic acid) and flavonoids (eg. flavone quercitin, catechins, EGCG, genistein) (Basheer and Kerem, 2015). Zhou et al. (2018) study showed that resveratrol can protect HaCaT cells from UVB-induced photoaging by upregulating HSP27 expression, increasing Bcl-2/Bax ratio, and inhibiting caspase-3 activity and p65 expression, which indictaes resveratrol can be used as a potential agent to protect the skin from photodamage. Meanwhile, in Subedi et al. (2017) , the authors also concluded that resveratrol has shown the ability to control matrix

metalloproteinases-1-mediated UVB-induced skin ageing, apoptosis-induced skin ageing, and inflammation mediated complications called inflammageing in dermal fibroblasts. For the human study conducted by Buonocor et al. (2012), 50 participants were given one capsule (133 mg resveratrol-procyanidin blend) per day for 60 days. After 60 days of intake of the capsule, the skin conditions (such as skin moisture, elasticity, roughness, wrinkles, age spots) of the participants were significantly improved as well as values for systemic oxidative stress ($p < 0.001$), plasmatic antioxidant capacity ($p < 0.001$), and skin antioxidant power ($p < 0.001$) had increased significantly Therefore, the investigators concluded oral resveratrol-procyanidin blends could be used as a supportive anti-ageing treatment for chronoageing or photoageing. However, the conclusive evidence of the anti-ageing effect of intake of oral resveratrol supplement alone is still lacking (Spiro and Lockyer, 2018).

Carotenoids

Carotenoids, 40-carbon isoprenoid molecules, are responsible for producing red/yellow/orange pigmentation for plants and can be found in various plants/microalgae/bacteria/fungi (Johnson, 2002; Langi et al., 2018). Most studies are confined to carotenoids because of their antioxidant activity. Beta-carotene, lycopene, lutein, astaxanthin (keto-carotenoid) and zeaxanthin (one of the most common carotenoid alcohols found in nature) (Johnson, 2002). Both Chalyk et al. (2017) and Ito et al. (2018) concluded that continuous astaxanthin supplement intake could improve human skin conditions and are protective against photoaging because of its strong antioxidant property. Moreover, Meinke et al.(2013) giving 24 healthy volunteers a dietary carotenoid complex capsule (containing lutein, beta-carotenoid, alpha-carotenoid, lycopene, zeaxanthin and crytoxanthin)/day for 8 weeks showed that consuming carotenoids increased radical scavenging activity of skin and decreased stress and induced radical formation. Later, in 2017, Meinke et al. stated that oral carotenoid supplements could also prevent the ageing-related collagen I degradation in the dermis and improve the extracellular matrix (Meinke et al., 2017). In addition, the combination of using zeaxanthin-based dietary supplements and topical serum showed that skin hydration and overall skin conditions were better, although oral intake of supplement alone was most effective in eliminating wrinkle count and severity (Schwartz S. et al., 2016). Furthermore, in most relevant literature reviews which have evaluated the anti-ageing effect of both oral and topical carotenoids concluded they are beneficial for skin health, especially for photoprotection but, carotenoids cannot replace sunscreen (Boelsma et al., 2001; Anunciato and da Rocha Filho, 2012; Pandel et al., 2013; Spiro and Lockyer, 2018; Pérez-Sánchez et al., 2018).

1.5.3.2 Combinations

The majority of combinations were derived from different types of antioxidants, or antioxidants with vitamins or minerals, or antioxidants with bioactive collagen. Generally, the overall facial appearance and conditions such as, skin elasticity, wrinkles, transepidermal water loss, skin erythema were significantly improved by consuming or applying the combinations. For example, in human studies, De Luca et al. (2016) used celergen supplement consisting of marine collagen peptides, grape-skin extract, coenzyme, luteolin, and selenium; and Costa et al. (2015) used an oral supplement containing marine protein, vitamin C, grape seed extract, zinc and tomato extract, both of the results indicated that skin physiology parameters were improved. In animal studies, Cho et al. (2007) fed the mixture of vitamin C, vitamin E, pycnogenol and evening primrose oil to female hairless mice; and Bhattacharyya et al. (2009) used a topical application of retinoic acid, glycolic acid, vitamin C, estrogen, and soy on female hairless mice. Either via an oral application or a topical application, the combinations of vitamins with antioxidants could improve skin histology (epidermal thickness, linear measurement, nuclear volume, morphometric observations). However, there is no research using both oral and topical application on human or animal so, it is worthy to investigate whether synergistic effects exist. It is also suggested that using combination compounds could be more effective to target different aspects of skin aging which can provide a comprehensive protection against photoageing.

1.5.3.3 Plant extracts

Different plant sources such as Hibiscus syriacus L., Koji, pycnogenol, rice bran were extracted to use topically or orally for reducing skin photoageing. In our narrative review, the plant extract has been mentioned in 15 original research papers and 12 literature reviews. The most mentioned was green tea extract. Green tea is extracted from the *Camellia sinensis L* plant leaves, particularly, rich in the active compound polyphenol catechins (such as (−)-epigallocatechin-3-gallate (EGCG), (−)-epicatechin-3-gallte (ECG), (−)-epigallocatechin (EGC), (−)-epicatechin (EC)) (Rutter et al., 2003; Lee et al., 2014). Multiple studies suggested that topically used green tea extract can act as a sunscreen to absorb UVR, scavenge ROS, repair DNA damage, reduce collage decomposition, inhibit collagenase activity, and regulate skin pigmentation due to its antioxidant activity (Wang et al., 2010; Barbosa and Kalaaji, 2014; Spiro and Lockyer, 2018). Thus, topical green tea extract can be a beneficial anti-ageing

skincare component. However, there was no human studies found in the four selected databases. So, it is suggested that more human research should be conducted.

1.5.3.4 Probiotics & prebiotics

Three double-blind, randomised, placebo-controlled human studies concluded that consuming probiotics and prebiotics can improve skin parameters such as transepidermal water loss, skin elasticity, wrinkles as well as UVB-induced erythema & pigmentation (Lee et al., 2015; Spiro and Lockyer, 2018; Kuwano et al., 2018). One animal study, by using the most common probiotics in humans galacto-oligosaccharide and in animals bifidobacterium longum supplementation to feed SKH-1 hairless mice also showed that the mice skin hydration was increased and transepidermal water loss was improved (Schagen et al., 2012; Hong et al., 2015). However, due to the limited studies, there is not a solid conclusion about probiotics and prebiotics to state they can improve skin conditions or protect skin from ageing. Moreover, there is not any research using probiotics or prebiotics for topical applications.

To summarise the above literature results, the most representative compounds analysed in each group are listed below.

Macronutrients:

- Carbohydrates- fucose and glycosaminocans
- Fats- omega 3 and omega 6
- Proteins- collagen hydrolysate

Micronutrients:

- Minerals- zinc and selenium
- Vitamins- C and E

Others:

- Antioxidants- polyphenols and carotenoids
- Combinations- antioxidants mixture, antioxidants and vitamins and minerals, antioxidants and bioactive collagen
- Plant Extracts- green tea extract
- Probiotics & Prebiotics- galacto-oligosaccharide and bifidobacterium longum

1.6 Research method

Literature reviews are an important part of the research literature. They play a critical role as a platform to summarize and synthesize knowledge, and identify the research gaps. There are many different kinds of review classification, for example, according to Samnani (2017), there are nine common basic types of review consisting of - literature review/narrative review/overview, scoping review, critical review, systematic review, meta-analysis, mapping review, qualitative systematic review, meta-synthesis, realist review, and review of reviews/umbrella reviews. Others, Grant and Booth (2009), have divided literature review into fourteen types. Each different type of literature reviews have their own different key features. Therefore, the researcher can choose the appropriate type of review for research purposes based on the strengths and weaknesses of the review.

In this study, a scoping review was chosen to be conducted after considering the different available types of literature reviews, as it is considered to be the appropriate approach to map a broad research question - in this case, the anti-ageing effect of nutrition on skin ageing by evaluating the commonly used skin parameters used, and reporting the equipment and methodologies. Scoping review, is a systematic review, which has not yet a common definition or firm procedure (Pham et al., 2014). The first paper to define the process about how to conduct a scoping review was Arksey and O' Malley in 2005. The paper suggested a five-stage procedure for scoping review: Stage 1: identifying the research question; Stage 2: identifying relevant studies; Stage 3: study selection; Stage 4: charting the data; Stage 5: collating, summarizing and reporting the results (Arksey and O'Malley, 2005).

The main aim of a scoping review is to 'map the literature on a particular topic or research area and provide an opportunity to identify key concepts' (Daudt et al., 2013), which matches with the purpose of this study. In addition, a scoping review is able to give an overview of the research field by examining the extent, range and the nature of research. It is efficient to quickly understand in a particular area; determine whether there is value to conduct a full systematic review, or a meta-analysis, and identify research gaps (Arksey and O'Malley, 2005; Levac et al., 2010). Therefore, a scoping review will be chosen in this study. The detailed process is displayed in chapter 2.

1.7 Overall aim and specific objectives

This study aimed to review the current nutritional and dermatological literature in order to summarise the evidence on the efficacy of tested active nutritional ingredients, both orally and topically from food supplements in relation to skin ageing. Primarily, the efficacy is assessed by examination of the skin parameters chosen and measurement methods i.e. experimental equipment to determine the effectiveness of food supplements on anti-ageing of skin.

Specific objectives

Use the scoping review to assess the measurement techniques and skin parameters used to determine the efficacy of oral supplements for human skin ageing. Explain how to group skin parameters and explore the definition of the most measured skin parameters. Provide recommendation for key measurement methods and skin parameters for optimal assessment of supplement of supplement interventions. Summarise methodologies and experimental equipment used underpinning currently used skin parameter measurements.

Chapter 2

Dietary supplements and skin ageing: A scoping review

2.1 Introduction

Understanding the properties of skin and its associated changes during the normal ageing process has stimulated significant academic and commercial research interest. The largest voluminous and multifunctional organ of the human body, skin acts as a barrier to protect the body from the outer environment and is affected by both intrinsic and extrinsic factors (Zhang and Duan, 2018). While intrinsic ageing relates to genetics and the unavoidable passage of time, extrinsic ageing is a result of environmental factors including sun exposure, pollution, smoking (Vierkötter and Krutmann, 2012) and poor nutrition (Schagen et al., 2012). Therefore, the condition and appearance of the skin acts both as an indicator of age and health status (Draelos, 2010; Farage et al., 2013).

Although understanding the properties of skin and its relation to ageing is of research interest, the reduction or minimization of the effects of ageing on skin appearance is of tremendous interest to much of the public with significant commercial implications. The global skincare products market was worth $140 billion in 2020 and growing faster than any other segment of the cosmetics market (Research and Market, 2021). In addition to topical agents, dietary supplements are marketed for benefits in delaying skin ageing. Although some research has investigated the benefits of various nutraceutical preparations, including micro- and macronutrients such as carotenoids, vitamins, fatty acids and some proteins (Hew et al., 2016; Pullar et al., 2017), this has been dominated by work done in pre-clinical models, with only a limited number of high quality, randomized controlled trials done in humans (Cao et al., 2020). Like topical skincare products, the global market for dietary supplements is enormous (also valued at $140 billion in 2020) and predicted to continue to expand over the next 7 years (Research and Market, 2021).

Meanwhile, skin health and appearance is intimately associated with nutritional status with regards to both macronutrients (Hew et al., 2016) and micronutrients (Park, 2015). A lack of macronutrients and micronutrients will result in a manifest change skin structure (Hew et al., 2016). Therefore, balanced nutrition and an adequate diet are important for maintaining skin health (Cosgrove et al., 2007) and to mitigate the effects of ageing (Cao et al., 2020). However, if the daily diet is lacking sufficient nutrients, dietary supplements may be consumed to ameliorate the deficiencies (European Food Safety Authority, 2022). Existing studies

investigating the effects of vitamins, trace minerals, fatty acids and plant extracts, which have been widely used in cosmetics as topically applied agents or as oral supplementations (Schagen et al., 2012), have reported to have anti-ageing effects on the skin and provide protection against ultraviolet radiation (Pérez-Sánchez et al., 2018). For example, the earliest study by Darr (1992) stated that topical vitamin C can protect the skin from ultraviolet radiation which correlates with anti-ageing. Another example by Cosgrove (2007) indicated that higher vitamin C intakes were associated with less wrinkles and a younger skin age outlook.

Furthermore, in exploring the current literature on the effectiveness of dietary supplements on skin ageing, a key aspect is in identifying key skin parameters with the associating methods/equipment. The key parameters and measurement techniques are vital in demonstrating observable effects. These are primary outputs from the review herein. The purpose of this scoping review was to examine the evidence from published studies that can be used to determine the effectiveness of food supplements for anti-ageing of the skin by evaluating the measurement techniques and the skin parameters selected and to provide a guideline for dietary supplements and skin ageing field.

2.2 Methods

This scoping review was developed by using the five keys stages as defined by the O'Malley (2005) methodological framework. Stage 1: identifying the research questions; Stage 2: identifying relevant studies; Stage 3: study selection; Stage 4: charting the data; Stage 5: collating, summarising and reporting the results. A particular focus was made on the area of skin ageing and dietary supplements, specifically on skin parameters and their measured methods/equipment. In addition, the protocol was registered on Center for Open Science, it can be accessed via https://archive.org/details/osf-registrations-7a8jb-v1. The registration DOI is 10.17605/OSF.IO/7A8JB.

Search strategy

The following four databases Ovid database (Embase 1996-2020 week 46), EBSCOhost (CINAHL), PubMed and Scopus were searched on 02 February 2021 for studies about dietary supplements and skin ageing. Search terms for skin ageing included extrinsic skin ageing and photoageing of skin.

Published articles were limited from 2000 to the present date. Search terms for supplementations included oral, dietary, nutrient, and food supplement. Search terms for skin parameters included skin deterioration, skin wrinkle, cutaneous ptosis, cutaneous sagging, skin

sagging, skin ptosis, saggy skin or ptotic skin, droopy skin, skin permeability, skin tension, skin pigmentation, skin structure, skin thickness or epidermis thickness, epidermis or stratum corneum or skin surface and dermoepidermal junction. The complete search strategy is provided in appendix A.

Moreover, conference abstracts and non-academic publications were excluded in the first round. Titles and abstracts were screened for relevance based on inclusion and exclusion criteria. The inclusion criteria included randomised controlled trial, intervention trials in humans, published in peer review journals, with full-text articles published in English available.. Reviews, editorial content, conference abstracts, preclinical studies were excluded in addition to, non-English language and non-full text articles.

Study selection

Duplicates were removed using author, year and title. Full text of the remaining publications was obtained and assessed for eligibility using the pre-established inclusion and exclusion criteria. Publications that did not meet the inclusion criteria were systematically sorted into the corresponding reasons for exclusion. A PRISMA flow diagram was constructed in order to demonstrate the above study selection process and is provided in **figure 3**.

Data extraction and collating the results

Data from all publications meeting the eligibility criteria were extracted into a standardized excel spreadsheet, including: author, year, study design, ingredients, age range, sample size, study duration, dosage, outcome measures, key results and which skin parameters have been improved significant difference. The data was collated and is summarised in **table 1**. To assess the quality of the included studies, “Version 2 of the Cochrane risk-of-bias tool (RoB 2)”(Sterne et al., 2019) was used for the randomised controlled trials in **figure 4**. All data collected was verified by research supervision team members and checked for erroneous information.

2.3 Results

The search strategy yielded 87 potential articles from four selected databases. After the removal of duplicates, initial screening and review of eligibility, eventually, 30 articles were included and are summarised in the **table 1**. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram displaying the complete process is presented in **figure 3.** Three main themes were extracted from 30 articles: nutrition ingredients of the oral supplementations, skin parameters measured, as well as the associated methods & equipment.

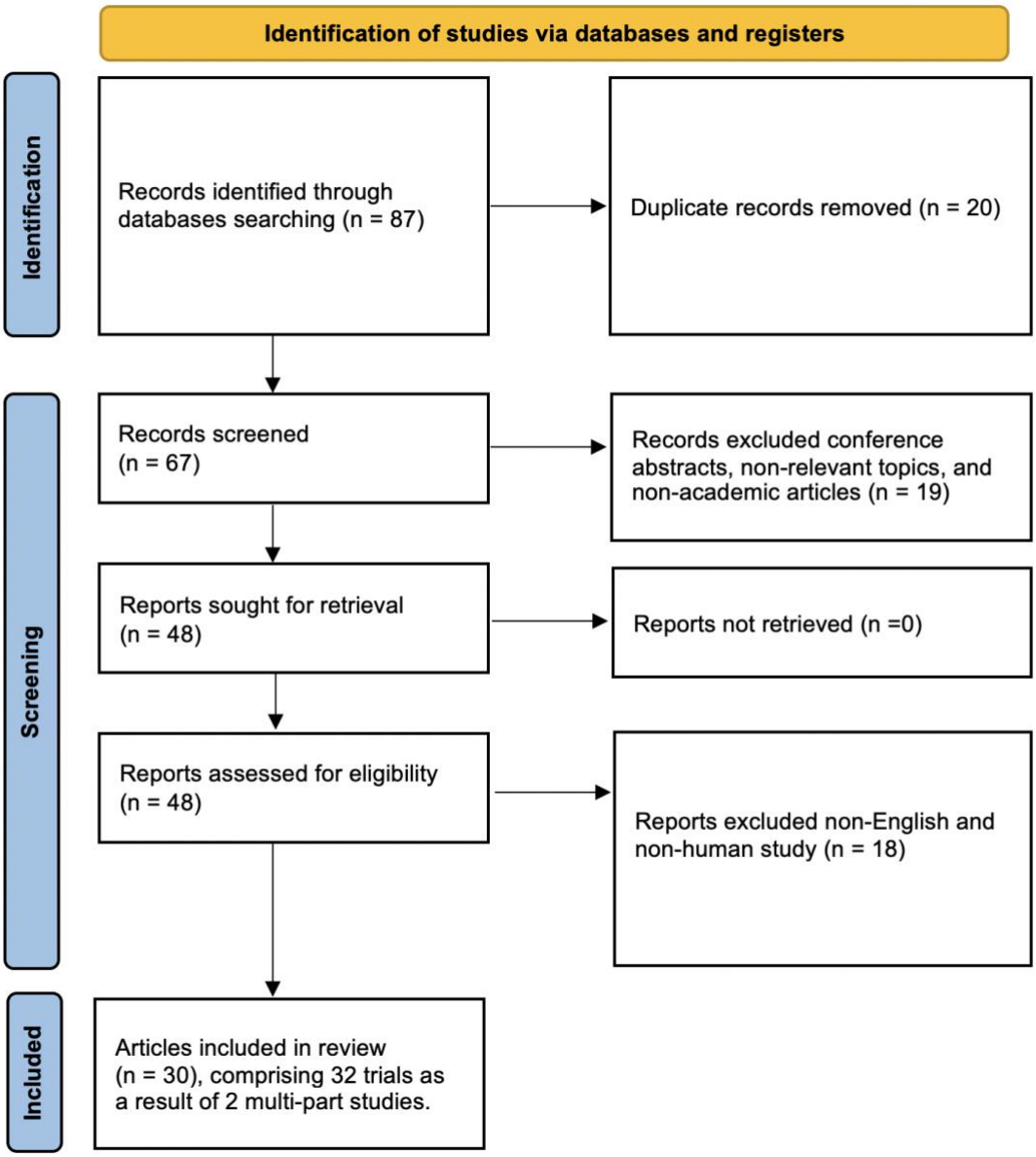

Figure 3. A PRISMA flow diagram

In these 30 articles, 22 articles included randomised, triple/double/single-blind, placebo-controlled trials and 10 articles were of the form triple/double/single-arm, open-label intervention trials. There were 2 articles involving two types of trials, such as Yoshikawa et al. (2014) and Tominaga et al. (2012). In addition, Schwartz et al. (2016) conducted a randomised, placebo-controlled trial, but it did not specify whether it was a double-blind study design or not. Moreover, the smallest sample size was 30 participants and the largest sample size was 159 participants included. The study duration of these 30 studies was at least 4 weeks which is comparable to the skin renew time of around 28 days.

Nutrition ingredients of food supplementation

The composition of the dietary supplements can be divided into 3 groups- macronutrients (including carbohydrate, protein and fat); micronutrients (including vitamins and minerals) and others (including plant extracts, animal tissue extracts, antioxidants and other ingredients). In the 30 human studies identified, only 2 studies tested the same and single ingredient (astaxanthin), the other 28 studies tested ingredients which were combination formulations. The most measured ingredient formulation used consisted of macronutrients + micronutrients + others; 30% (9/30). The second group comprised 23% (7/30) and used plant extract ingredients. All 30 studies reported that the dietary supplements tested were as finished manufactured products which contained multiple ingredients, therefore, the results of the studies were mainly to demonstrate the effect of a particular supplementation product on the skin rather than a specific single ingredient.

Skin parameters

In total, 49 skin parameters have been identified from the eligible articles considered. In order to display a clear overview of these skin parameters, they have been categorised into 3 groups due to their properties, namely appearance, physical and biochemical properties. These were then subdivided into 18 representational skin parameters. The three groups relate to either skin appearance, the physical properties of skin, or biochemical aspects. These parameters and the equipment used in their measurement are defined and summarised in **table 2**. Skin appearance image parameters represented a group that reflect skin appearance by the naked eye or by other instrumental techniques which analyse effects in the form of images. This group of parameters are also the most common parameters to be measured during the human studies. Skin physical properties group refers to the skin parameters specifically reflecting the physical properties of the skin, such as firmness, thickness, density and force-related elasticity of the skin. These physical properties are quantifiable and observables, also called physical quantity.

The skin biochemical group refer to parameters that reflect some of the biological cellular and chemical molecular properties of the skin. For example, serum, DNA, fibroblasts and so on. The feature of this group is to measure skin at the molecular and cellular level.

In addition, there were 3 skin parameters which were measured most frequently. First, wrinkles were by far the most measured skin appearance image parameter, with 73% (22/30) of the studies reviewed examining this property as an indicator of skin ageing. Second, hydration was examined with 60% (18/30) of studies reporting the water content in the stratum corneum layer. Third, elasticity was measured 50% (15/30). The least measured skin parameters were photodamage severity, pores, dermis echogenicity and the expression levels of key genes, which all only appeared once in the 30 studies.

Methodologies of skin parameter measurement

It has been found that 40 different methods or equipment were used to measure the 18 different skin parameters which may be divided into three groups, appearance, physical and biochemical and are summarised in **table 2**. The selected studies span a twenty-year period, therefore, both the earliest test methods and equipment (e.g. Corneometer CM 824, Cutometer SEM 575) as well as the latest test equipment (e.g. Corneometer CM 825, Cutometer MPA 580) can be seen from these 30 studies. Some devices only have a single function, but some can measure a range of skin parameters.

Risk of bias

The RoB 2 assessment tool was applied on 22 RCT studies in this scoping review (shown in **figure 4**). Ten studies were at low risk level overall. Seven studies were at high risk level and five studies were at some concern level. Reasons relating to high risk RoB were due to lack of sufficient information of conducting a randomisation process. RoB was relatively low for all included studies in bias in selection. It was considered RoB domain risk decreased from 2001 to 2020, possibly due to improving study quality.

687 **Table 1. Overview of studies published on nutritional oral supplements and skin ageing**

Author (Year)	Study design	Ingredients	Age range (years); gender; nationality/race; sample size	Study duration (dose/day or week or month)	Outcome measures	Key results
Randomised controlled trial (RCT) study						
Laing et al., (2020)	Randomised, double-blind, placebo-controlled trial	2.5g specific short-chain collagen oligopeptides, 666mg acerola fruit extract, 80mg vitamin C, 3mg zinc citrate, 2.3mg vitamin E, and 50 µg biotin	40-70; F; NI; 60	12 weeks (48unit/d)	Collagen structure*, SA (density*, softness*)	Collagen structure measured by VIVASCOPE VAS score 3.2 (Confidence Interval CI 95% 1.8, 4.5), unitless VAS (Visual Analog Scale) from -50 to 50), p=0.037 from baseline
Žmitek et al., (2020)	Randomised, double-blind, placebo-controlled trial	Active ingredients per 10 mL: hydrolysed fish collagen: 4000 mg, water-soluble CoQ10: 50 mg, vitamin C: 80 mg, vitamin A: 920 µg, biotin: 150 µg	40-65; F; Caucasian; 34	12 weeks (10 ml/d)	Density*, wrinkles*, smoothness*, hydration^, thickness^, TEWL^, viscoelasticity^	Density (dermis) measured by DermaLab SkinLab Combo 20 MHz Ultrasound probe, Score 5.8 (CI 95% 1.4, 10.2), unitless (score 0-100), p=0.005, 16.1% overall increase from baseline. Wrinkles, 19.4% overall decrease from placebo p=0.0001. Wrinkle area fraction using VisioFace CSI image from 0.103 ±0.016 vs 0.128 ±0.009. Smoothness measured by VisioFace image, placebo group −0.07 vs. test group 0.44, respectively; p<0.05

Draelos, (2019)	Randomised, double-blind, placebo-controlled trial	The morning formulation contained vitamin A (1,500 U), vitamin C (12mg), and vitamin E (9IU), Vitamin D (600 IU), other trace nutrients, including iodine for thyroid health (225mcg), the antioxidant ingredient selenium (24.75mcg), and magnesium (60mg) and zinc (3mg), flaxseed oil (1gm), l-cysteine (682 mg), tumeric extract (30 mg) and acetyl-l-carnitine and coenzyme Q10. The evening formulation contained flaxseed oil (933mg), l-cysteine (634mg), a variety of amino acids, such as lysine hydrochloride, l-glutamine, and l-arginine, alanine.	35-65; F; NI; 50	1 month (3 morning and 3 evening/d)	Firmness*, hydration*, dullness*, roughness*, overall skin appearance*, wrinkles*, SA (Wrinkles*, firmness*, healing ability*, hydration*, dullness*, roughness*, pigmentation*, overall appearance*)	Firmness 25% (p=0.035), hydration 41% (p<0.001), dullness -49% (p<0.001), roughness -50% (p<0.05) and overall skin appearance 32% (p=0.010); Unit (% change from baseline) Wrinkle (breadth) reduction (p=0.018) between placebo and test group by analyzing photographs with a scanning laser of silicone replicas.
Maia Campos et al., (2019)	Randomised, double-blind, placebo-controlled trial	Dose 10 g, hydrolyzed collagen (9 g) plus mix of vitamins A (600 µg), C (45 mg), E (10 mg), and zinc (7 mg).	40-50; F; NI; 60	90 days (10 g/d)	Hydration*, elasticity*, dermis echogenicity*	Hydration 70% (p<0.05) increase from baseline, unit (arbitrary units) Elasticity 0.58 (p<0.05) from baseline, unit (Ur/Ue = net elasticity = immediate recovery/elastic deformation) Dermis echogenicity (significant difference before and after treatment calculated by image analysis and related to the total number of pixels), unit (Echogenicity color scale: white>yellow>red>green>blue>black)
Schwartz S.R. et al., (2019)	Randomised, double-blind, placebo-controlled trial	Hydrolyzed-chicken sternal cartilage extract composed of hydrolyzed collagen type-II (HC-II), hyaluronic acid (HA), and chondroitin sulfate (CS)	39-59; F; Caucasian; 113	12 weeks (2 g/d)	Wrinkles*, elasticity*, collagen content*, dryness, erythema, TEWL^, melanin content and hemoglobin level^; SA (wrinkles*, texture^, smoothness^, color^)	Wrinkles: facial lines and wrinkles 6% (p=0.019) and crow's feet lines and wrinkles 10% (p=0.05), elasticity 125% (p=0.008), collagen content 12% (p<0.001); Unit (mean improvement %) from baseline

Czajka A. et al., (2018)	Randomised, double-blind, placebo-controlled trial	Hydrolyzed collagen (from fish), glucosamine HCI, L-carnitine black pepper and dried maca extracts, hyaluronic acid, zinc, copper, vitamin c, vitamin b3, vitamin b6, biotin, vitamin d, vitamin b12, chondroitin sulphate, N-acetylglucosamine, water, citric acid, malic acid, stevia (natural sweetener), flavoring (apple and mango)	21-70; F&M; mainly Caucasian; 120	90 days (one bottle/d)	Elasticity*. positive changes in the skin architecture, with a reduction in solar elastosis and improvement in collagen fiber organization	Elasticity from baseline (7.9 ± 0.2) to day 90 (9.8 ± 0.2), unit (Young's modulus), p<0.0001, 40% overall increase
Bertuccelli G. et al., (2016)	Randomised, double-blind, placebo-controlled trial	Fermented papaya preparation (FPP) per 100 g is as follows: 90.7 g carbohydrates, 17 µg vitamin B6, 2 µg folic acid, 2.5 mg calcium, 16.9 mg potassium, 240 µg niacin, 4.6 mg magnesium, 14 µg copper, 75 µg zinc, 16 mg arginine, 6 mg lysine, 5 mg hystidine, 11 mg phenylalanine, 9 mg tyrosine, 18 mg leucine, 9 mg isoleucine, 5 mg methionine, 13 mg valine, 11 mg glycine, 8 mg proline, 37 mg gluthamic acid, 11 mg serine, 8 mg treonine, 27 mg aspartic acid, and 2 mg triptophane	40-65; ; F&M; Caucasian; 60	90 days (twice 4.5 g/d)	Evenness*, hydration*, elasticity (R6)*, roughness^, wrinkles^, spots^; the expression levels of key genes (AQP3*, CyPA*, CD147*, progerin^), redox balance and NO (MDA*, SOD*, NO*)	Evenness 3.1 (p<0.05) from baseline, unit VAS (Visual Analog Scale) Hydration ~95% increase (p<0.04) from baseline, unit (arbitrary units) Elasticity (R6) 0.9 (p<0.01) from baseline, unit (Uv/Ue) = ratio of viscoelasticity over skin extensibility The expression levels of key genes, after 90 days of treatment vs. baseline values: AQP3 2.8, (p<0.05) and CyPA 1.6 (p<0.05) and CD147 1.6 (p<0.05); unit (unit of 2^Ct[-actin]-Ct[gene of interest]); MDA 1.6 (p<0.05), unit (nmol/mg protein); SOD 600 (p<0.05), unit (cpm/mg protein); NO concentration 4.1 (p<0.05), unit (Mm)
Lademann J. et al., (2016)	Randomised, double-blind, placebo-controlled trial	Tablets including active ingredients vitamin E acetate, plant-derived vitamin C acetate, plant extracts (green tea, green coffee, pongamia, pinnata seed and an- gelica) and 0.2% of the carotenoids β-carotene and lycopene at the same concentrations.	20-73; F; NI; 75	2 months (1 tablet twice/d)	Thickness*, hydration^, elasticity^, wrinkles^	Thickness 91% (p<0.01) from baseline, unit (epidermal thickness µm)
Schwartz S. et al., (2016)	Randomised, placebo-controlled trial	Zeaxanthin, sea buckthorn fruit oil, wheat ceramides, alpha lipoic acid, green tea, red clover leaf, gotu kola seed, maritime pine bark, vitamins C, E, D3	35-65; F; Caucasian or Hispanic; 31	12 weeks (no mention)	Wrinkles*, hydration^, color^	Wrinkles (emerging lines) at week 12, Group 1 vs placebo (p=0.026), Mean difference ± SD from baseline (-5.80 ± 4.44) by using clarity image analysis

Jenkins et al., (2014)	Randomised, double-blind, placebo-controlled trial	Total isoflavone (expressed as aglycone), lycopene, vitamin C, vitamin E, omega-3 EFA's (23% EPA:16% DHA)	48-71; F; NI; 159	14 weeks [one dose of study treatment (both drink and capsule)/d]	Wrinkles*, firmness^, elasticity^, TEWL^, hydration^, tone^, histological biopsy analyses (collagen and elastin) ^	Wrinkles 1. Mean Replica R3z (mean of 3 samples) between baseline and test values. Test group 1 High dose, score -2 (p=0.045), Test group 2 Low dose, score -1 (p=0.081), unit (change in R3z at week 15). PRIMOS image analysis of silicone replicas. 2. The mean treatment effect on R3z value. High dose -score 6 (p< 0.05), Low dose -7.8 (p< 0.05) 3. Regression fits of baseline against endpoint R3z, Test 1 group (p=0.057), Test 2 group (p=0.01), (gradients evaluated)
Proksch et al., (2014)	Randomised, double-blind, placebo-controlled trial	The specific bioactive collagen peptide (BCP) VERISOL® composed of different specific collagen peptides	45-65; F; NI; 140	8 weeks (2.5 g/d)	Wrinkles*, procollagen I*, elastin*, fibrillin^	Wrinkles, 4 weeks -7.2% (p< 0.05), 8 weeks -20.1% (p< 0.01), both values vs. baseline, overall 49.9% reduce Procollagen I, 8 weeks 65% (p< 0.001) vs. baseline Elastin, 8 weeks, 18% (p<0.01) vs. baseline
Yoshikawa et al., (2014)[1]	Randomised, open-label, placebo-controlled trial (part 3)	Porcine placental extract (PPE)	50-60; F; Japanese; 44	12 weeks (three 350 mg/d)	Wrinkle widths below the eye*	Wrinkle widths below the eye, from 58 decrease to 37, unit (mean μm), p<0.05 vs control group at 24 weeks and p<0.01 vs baseline
Fanian F. et al., (2013)	Randomised, double-blind, placebo-controlled trial	Bio marine collagen (CartideaTM), grape seed extract (95% proanthocyanidins), pine bark extract (95% proanthocyanidins), green tea extract, lycopene extract 5%, blackcurrant seed oil, alpha lipoic acid, coenzyme Q10, betacarotene, vitamin D3 (as D3 IU), vitamin e (natural source), vitamin C, thiamin (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), vitamin B6, folacin (folic acid), vitamin B12, biotin, pantothenic acid, magnesium, iron, zinc, copper, manganese, selenium (yeast-free), chromium, iodine (from purified sea kelp extract), silicon, L-cystine	35-55; F; Caucasian; 80	4 months (2 tables/d)	Viscoelasticity*, thickness*, density*, photographic evaluation^, wrinkles^, roughness^, SA^	Viscoelasticity, -13% (p<0.05) reduction in resonance running time at 45° from T0 to T5.5 (baseline and 6 weeks after termination of treatment) in active group. Measured by Reviscometer RVM600 acoustic velocity meter resonance. Thickness and density (at forearm area), generally (p<0.05) vs baseline. Thickness was calculated from a region of interest determined directly on the image. Density was calculated as the mean region of interest luminance.

Babizhayev M.A. et al., (2012)	Randomised, double-blind, placebo-controlled trial	N-acetylcysteine (600mg), L-hisidine (300mg), Carnosine (210mg), Vitamin E (150IU), D-pantethine (90mg), L-methione (75mg), Zinc picolinate (15mg)	17-80; F; Caucasian; 42	4 months (3 months with supplement (take 1 capsule on every second day) +1-month supplement-free)	Skin surface evaluation (surface*, entropy^, contrast*, circular roughness*)	Surface, -16% ($p \leq 0.05$) at the first 3 months vs. baseline; final data was 87% ($p \leq 0.05$) vs. baseline; Contrast, -23% ($p \leq 0.01$) at the first 3 months vs. baseline; final data was 82% ($p \leq 0.05$) vs. baseline; Circular roughness, -18% ($p \leq 0.01$) after 4 months vs baseline. Units: Surface values are expressed in surface units; Contrast parameter values are expressed in contrast units; Circular roughness Rz values are expressed in roughness units. All above are calculated by Visioscan VC 98 software.
Oyama A et al., (2012)	Randomised, double-blind, placebo-controlled trial	A standardized natural S-equol-containing material, named SE5-OH. SE5-OH contains approximately 0.65% S-equol, 0.024% daidzein, 0.022% genistein, and 0.030% glycitein	45-65; F; Japanese; 101	12 weeks (10 mg S-equol twice/d—EQL10 group), or 30 mg S-equol twice/d---EQL30 group)	Wrinkles*, hydration^, TEWL^, elasticity^	Wrinkle area from baseline vs. at 4, 8, 12 weeks of treatment, in placebo and EQL 10 group, the percent change in wrinkle area increased with time (placebo: 10.5% ± 5.5%, 17.3% ± 6.0%, and 20.2% ± 5.1%; EQL10: 1.5% ± 3.5%, 7.1% ± 4.5%, and 8.9% ± 4.3%), whereas EQL 30 did not change. In the EQL30 group, the wrinkle area was significantly smaller than that in the placebo group at week 12, and the wrinkle areas in both the EQL10 and EQL30 groups were significantly smaller throughout the treatment period compared with that in the placebo group ($p=0.029$ and $p=0.004$, respectively). Maximal largest wrinkle depth from baseline vs. at 4, 8, 12 weeks of treatment, in the placebo group, the maximal largest wrinkle depth increased with time (5.5% ± 2.6%, 3.7% ± 2.7%, and 6.5% ± 2.8%), whereas that in the EQL10 group did not change and that in the EQL30 group decreased (-5.9% ± 2.0%, -4.0% ± 2.4%, and -4.5% ± 2.6%). Statistically significant differences were observed in the EQL30 group at weeks 4 ($p=0.002$) and 12 ($p=0.015$) and for the change over time ($p=0.001$) compared with the placebo group. Both parameters exhibited a dose-dependent improvement ($p=0.001$ and $p=0.017$, respectively).

Tominaga et al., (2012)[1]	Randomised, double-blind, placebo-controlled trial (study 2)	Astaxanthin	20-60; M; Japanese; 36	6 weeks (6 mg/d)	Wrinkles*, elasticity*, TEWL*, hydration^, sebum^	At week 6 vs. baseline values: Wrinkles, area ratio of all wrinkles 1 ($p<0.05$) and volume ratio of all wrinkles 1 ($p<0.05$); Elasticity 1 ($p<0.05$); TEWL 0.9 ($p<0.01$). Unit, change rate (post/pre)
Cho S et al., (2009)	Randomised, double-blind, placebo-controlled trial	KTNG0345 in each capsule consisted of 45.3% (by weight) of Korean red ginseng extract powder and 54.6% of the powdered extracts of two herbs, Torilus fructus and Corni fructus. KTNG0345 (ginsenoside-Rb1, torilin, and loganin) were 10.85 mg/g, 0.12 mg/g, and 3.33 mg/g, respectively.	over 40; F; NI; 82	24 weeks (3 g/d)	Wrinkles*, elasticity^, hydration^, erythema^, pigmentation^, thickness^	Wrinkles: At 12 weeks, treatment group vs. placebo group, 14.7% ($p=0.004$) and 19.0% ($p=0.010$) in improvement in depth of roughness (R1) and arithmetic average roughness (R5), respectively. At 24 weeks, treatment group vs. placebo group, 14.1% ($p=0.027$) and 23.5% ($p=0.007$) in R1 and R5, respectively.
Skovgaard et al., (2006)	Randomised, double-blind, placebo-controlled trial	Dietary supplement (Imedeen Prime Renewalt) contained soy extract, fish protein polysaccharides, extracts from white tea, grape seed and tomato, vitamins C and E, zinc and chamomile extract.	45-65; F; Caucasian and Hispanic; 80	6 months (2 Imedeen Prime Renewalt twice/d)	Wrinkles*, pigmentation*, laxity*, sagging*, dark circles*, density*, overall appearance*, density*, roughness^, teleangiectasia^	Clinical grading: Active vs. placebo group, after 6 months treatment, $p<0.05$. For parameters: forehead, periocular and perioral wrinkles, mottled pigmentation, laxity, sagging, under eye dark circles and overall appearance. Ultrasound measurements: Active vs. placebo group, after 6 months treatment, $p<0.0001$.

Beguin, (2005)	Randomised, double-blind, placebo-controlled trial	One capsule of the supplement contained 220 mg marine protein, 308 mg marine lipids, of which 180 mg is polyunsaturated fatty acids of omega-3 type, 8 mg natural tocopherols, 18 mg plant flavonoids, and 6 mg natural carotenes.	35-54; F; Caucasian; 38	4 months (3 months with supplement (1 capsule/d) +1-month supplement-free)	Wrinkles*, color*, oily skin appearance*, overall appearance*, thickness*, density*, skin surface evaluation*	Photographs at baseline vs. 3 months in active group: Wrinkles 63%, color 47%, oily skin appearance 63%, overall appearance 68%, which all present by photo, unit %, ($p<0.05$) Baseline vs. 3 months treatment (in active group): 1. Thickness, forearm 20% ($p<0.0001$) & hand 15% ($p<0.0001$) 2. Density, forearm 48% ($p<0.0001$) & hand 78% ($p<0.0001$) 3. Skin surface evaluation: Surface, forearm -14% ($p< 0.05$) & hand -11% ($p<0.001$); Entropy, forearm 2.2% ($p<0.05$) & hand 0.8% ($p<0.01$); Contrast, forearm -19% ($p<0.01$) & hand -16% ($p<0.01$); Circular roughness, forearm -13% ($p< 0.01$) & hand -14% ($p<0.01$).
Distante et al., (2002)	Randomised, double-blind, placebo-controlled trial	A capsule containing 250 mg of marine fish cartilage associated with an antioxidant mix (gingko biloba, flavonoids, centella asiatica)	35-60; F; NI; 30	8 weeks (3 capsules/d)	Thickness*, viscoelasticity*, wrinkles*, color(brightness)*, color(pigmentation)*, hydration*, distensibility^, elasticity^	The results showed statistically significant changes in the active-treated group in comparison to the placebo: 1. Thickness (dermal) (after treatment, from 1.13 to 1.23 mm; $p<0.0001$, unit mm) 2. Wrinkles, microrelief improvement of 9.5% ($p<0.02$) and waviness 13.5% ($p<0.002$), unit (relative change in roughness) 3. Colour (after treatment, overall was brighter and less pigmented) - Colour (brightness) from 64.39 to 65.1 ($p<0.006$),unit (brightness) -Colour (pigmentation) from 15.25 decrease to 14.4 ($p<0.002$), unit (pigmentation) 4. Viscoelasticity (after treatment, from 0.70 to 0.97%, $p<0.02$, unit %) 5. Hydration (after treatment, from 63 to 66, $p<0.01$, unit hydration)
Murad and Tabibian, (2001)	Randomised, single-blind, placebo-controlled trial	N-acetyl D-glucosamine, glucosamine sulfate, L-proline, L-lysine, manganese, copper, zinc, quercetin, and grape seed extract.	39-56; F; NI; 53	5 weeks (2 tables in morning and 2 tables in evening/d)	Wrinkles*, hydration^	Total % difference (treated vs. control) at final baseline: Number of wrinkles -34% ($p< 0.01$), unit %; Number of fine lines -34% ($p< 0.05$), unit %

Rigano et al., (2001)	Randomised, double-blind, placebo-controlled trial	A capsule containing 250 mg of marine fish cartilage associated with an antioxidant mix (gingko biloba, flavonoids, centella asiatica)	35-69; F; NI; 30	8 weeks (3 capsules/d)	Dryness*, tone*, wrinkles*, spots^	In active group, dryness from 4 to 2 ($p<0.003$), tone from 5.9 to 6.2 ($p<0.02$), wrinkles from 5.5 to 4.5 ($p<0.002$) vs. from baseline. Unit: the scoring system was based on a scale ranging from 0 to 9 according to the following ranks: 0=no signs, 1-3=smooth, 4-6=moderate, 7-9=severe.
Intervention study						
Aguirre et al., (2017)	Single-arm, open-label trial (study 1) Single-arm, open-label trial (study 2)	Ovoderm (Eggnovo, Spain), the major components (collagen and hyaluronic acid)	Study 1: 30 to over 60; F&M; Caucasian; 18 Study 2: 38-60; NI; Caucasian; 7	Study 1: 50 days (300 mg/d) Study 2: 5 weeks (300 mg/d)	Study 1: SA (softness, hydration, brightness, smoothness) -the most positive parameters Study 2: Elasticity*, hydration^, pigmentation^	Study 2: Week 5 of treatment vs. baseline, elasticity 12% ($p=0.0136$)
Chalyk et al., (2017)	Single-arm, open-label trial	Astaxanthin	over 40; F&M; Caucasian; 31	4 weeks (4 mg/d)	Oxidative stress^, RSSC (lipid droplet size*, corneocyte desquamation*, microbial presence*, lipid crystals^)	RSSC analysis after 29 days treatment (day 29 vs. baseline): 1. Lipid droplet size ($p=0.0214$) but only among obese participants (body mass index >30 kg/m2). 2. Corneocyte desquamation ($p=0.0075$) 3. Microbial presence ($p=0.0367$)
Göllner et al., (2017)	Single-arm, open-label trial	Oral HA preparation diluted in a cascade-fermented organic whole food concentrate supplemented with biotin, vitamin C, copper, and zinc (Regulatpro Hyaluron)	45-60; F; NI; 20	40 days (20 ml/d)	Hydration*, elasticity*, roughness*, wrinkles*	Hydration Baseline was 39.32±5.17, after 20 days was 47.79±8.19, after 40 days was 48.87±8.41, (repeated-measures ANOVA, $p<0.001$). This corresponds to an increase in skin hydration by 21.63% at the first assessment at 20 days and by 24.43% after 40 days. Maximum increase was 37.18%. Elasticity Baseline was 0.616±0.056, after 20 days was 0.668±0.057, after 40 days was 0.697±0.051 (repeated-measures ANOVA, $p<0.001$). This corresponds to an overall increase of 8.58% at day 20 in comparison with the start of the study. After 40 days of intake, an increase by 13.25% was noticed. The maximum gain of elasticity was 26.16%.

						Roughness Baseline was 151.48±17.92, after 20 days decreased to 132.34±18.47, after 40 days decreased to 125.94±19.18 (repeated-measures ANOVA and post hoc comparisons, p<0.001 for each comparison). Skin roughness decreased from baseline to the assessment after 20 days by 12.67% and after40daysby16.9% The maximum decrease seen in this trial was 30.40%. Wrinkles (depth) Baseline was 450.28±209.12, after 20 days of intake, significantly decreased to 394.02±191.74 and after 40 days further significant decreased to 331.35±142.18 (repeated-measures ANOVA, p=0.02 and post hoc comparisons with baseline, p=0.002 at day 20 and p=0.048 at day 40). This corresponds to a reduction of wrinkle depth by 12.5% after 20 days and by 26.36% after 40 days. The maximum reduction of wrinkle depths was 37.57%.
Dumoulin et al., (2016)	Single-arm, open-label trial	Daily dose of 150 mg of an antioxidant-rich formulation containing superoxide dismutase-rich melon concentrate, grape seed extract rich in monomers of flavanols, vitamin C, and zinc	40-70; F; NI; 35	8 weeks (150 mg/d)	Color*, luminosity*, brightness*, dark circles*, redness*, spots*, firmness*, elasticity*, transparency^, heterogeneity^	T0 vs. T8 (baseline vs. week 8): Color, red pink -34.8% and olive -21.6% (both p<0.0001); Luminosity 25.9% (p<0.0001); Brightness -12.3% (p<0.05) (have significant difference, but in negative way) Dark circles, relief -11.7% (p<0.01) & color -19.2% (p<0.0001); Redness -19.3% (p<0.0001); Spots -20.7% (p<0.0001) Firmness was classified as Absent–Light firmness or Moderate–Important firmness. A chi-square analysis revealed a significant change from the Absent–Light category to the Moderate–Important category of firmness after the supplementation (chi-square =4.121; p<0.05). Elasticity (Ur/Ue) was measured by cutometer, increased 8.53% (p<0.05) from baseline.
Puglia C. et al., (2014)	Single-arm, open-label trial	Red orange extract contains anthocyanins (cyanidin-3-O-gluco- side) 2.8–3.2% w/w, hydroxycinnamic acids (caffeic, cumaric, ferulic, sinapic acid) 1.8–2.2% w/w, flavone	For erythema, 26-47; NI; Caucasian; 20	For erythema, 15 days (100 mg/d)	Erythema*, melanin content^	Erythema was decreased from 1.4 to 0.98 from subjects before and after red orange extract supplementation, unit area under curve (AUC) value, ; p<0.05; Around 40% a mean reduction.

		glycosides (narirutin, hesperidin) 8.5–9.5% w/w, and ascorbic acid 5.5–6.5% w/w.	For melanin content, NI; NI; 45-70; 25	For melanin content, 5 weeks (100 mg/d)		
Yoshikawa et al., (2014)[2]	Triple-arm, open-label trial (part 1) Single-arm, open-label trial (part 2)	Porcine placental extract (PPE)	Part 1: 40-60; F; Japanese; 123 Part 2:40-60; F; Japanese; 47	Part 1. 12 weeks (three 350 mg/d) and 12 weeks (six 350 mg/d) Part 2. 24 weeks (three 350 mg/d)	Wrinkle widths below the eye*	Wrinkle widths below the eye, Part 1. Three cap/day was from 70 to 38 ($p<0.05$) vs. no treatment group; Six cap/day was from 70 to 15, ($p<0.01$) vs. no treatment group; three cap/day vs. six cap/day was $p<0.05$. Unit was (mean μm). Part 2. At 12 weeks 47 ($p<0.05$) vs. baseline, at 24 weeks 26 ($p<0.01$) vs. baseline; unit (mean μm).
Furumura et al., (2012)	Randomised, open-label, parallel trial	French maritime pine bark extract (PBE)	Below 60; F; NI; 101	High dose (100 mg/d); Low dose (40 mg/d) 12-24 weeks	Melanin pigmentation in age spots*, corneocyte size*, skin color^	Melanin pigmentation in age spots, 1. High-dose trial, a significant decrease at weeks 4 (was 1.6) and 12 (was 1.4); Unit (melanin index scores); both p values were $p<0.05$ vs baseline, n=24 2. At week 24 vs baseline, Group 1 (n=38) (from 2.6 to 1.5) and Group 2 (n=39) (from 2 to 1.3), both p values were $p<0.05$ Corneocyte size was from 700 decreased to 600, unit (the mean surface size of the corneocytes μm^2), $p<0.05$ vs. baseline, around 14% decrease (improvement).
Schwartz S.R. and Park J., (2012)	Single-arm, open-label trial	Each capsule contained 500 mg of BCC, providing a naturally occurring composition of hydrolyzed collagen (300 mg), depolymerized chondroitin sulfate (100 mg), and HA (50 mg).	35-59; F; Caucasian & African American & Hispanic; 26	12 weeks (1g/d)	Dryness*, wrinkles*, hemoglobin level*, collagen content^, melanin level^	At week 12 vs. week 0 (baseline), dryness (-76%, $p=0.002$) and global lines/wrinkles (-13.2%, $p=0.028$) as both measured by visual/tactile score and calculated unit was % change. At week 12 vs. week 0 (baseline), hemoglobin level (15%, $p=0.008$), measured by Cosmetrics™ SIAscope and calculated unit was % change.

Tominaga et al., (2012)[2]	Single-arm, open-label trial (study 1)	Astaxanthin	20-55; F; Japanese; 30	8 weeks (6 mg/d)	Wrinkles*, elasticity*, age spot*, skin texture*, hydration^	Wrinkles, unit (μm): 1. Deepest wrinkle (at week 8 vs. week 0 (as baseline), p<0.01) 2. Mean depth of the deepest wrinkle (week 4 & week 8 vs. baseline, p<0.01) 3. Maximum width of the deepest wrinkle (at week 8 vs. baseline, p<0.01) 4. Mean depth of all wrinkles (at week 4 & week 8 vs. baseline, p<0.05) Elasticity (of crow's feet area), at week 4 vs. baseline, p<0.05; week 8 vs. baseline, p<0.01; unit (skin elasticity %). Age spot (area of cheek), at week 8 vs. baseline, p<0.01, unit (area of age spot mm^2). Skin texture: 1. Mean depth of texture, at week 4 vs. baseline, p<0.01, week 8 vs. baseline, p<0.05; unit (mean depth μm) 2. Total area of the corneocytem, at week 8 vs. baseline, p<0.05, unit (size of total area μm^2).
Yang B. et al., (2009)	Double arm, open-label trial	Sea buckthorn oil	50-70; F; Caucasian; 60	3 months (4 capsules 0.5 g/d)	Hydration*, elasticity (overall elasticity*, maximal deformation^), luminosity^, roughness^, thickness^	Hydration, unit (corneometric unit) 1 month of treatment of capsule vs. baseline, was from 40 to 52, p<0.001, 33.6% increased. 3 months of treatment of capsule vs. baseline, was from 40 to 59, p<0.001, 48.6% increased. Overall elasticity, unit (overall elasticity) 1 month of treatment of capsule vs. baseline, was from 0.42 to 0.49, p<0.001, 18.6% increased. 3 months of treatment of capsule vs. baseline, was from 0.42 to 0.54, p<0.001, 21.9% increased.

Unitless Visual Analog Scale VAS from -50 to 50, TEWL=Transepidermal water loss, RSSC=Residual skin surface components, R6=Ratio of viscoelasticity over skin extensibility (Uv/Ue), SA=Subjective assessment, *=Significant difference, ^=No significant difference, Female=F, Male=M, NI=No information, Confidence intervals=CI; Ur/Ue (net elasticity)= immediate recovery/elastic deformation

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Parameters	Descriptions	Methods	References
Skin appearance image parameters (7): color, photodamage severity, pores, residual skin surface components (RSSC), roughness, skin surface evaluation, wrinkle.			
Color	There are 4 pigments which contribute to skin color: melanin, carotene, oxygenated hemoglobin, and reduced hemoglobin. Moreover, the particle size, shape, and location of melanin contribute most significantly (Everett et al., 2012). Definitions include pigmentation, mottled hyperpigmentation, teleangiectasia, under eye dark circles, erythema, brown spot intensity, dermal hemoglobin level, luminosity, radiance, discoloration and skin pigmentation homogeneity. Pigmentation is most often measured.	1. Camera + photo evaluation 2. Chromameter C200/ C300/ C400 3. Colorimeter 4. UV-irradiation device (ultraviolet lamp) 5. DermaSpectrometer (Cortex technology) 6. Multi-dermascope MDS 800 7. Clarity 2D Research Systems 8. Visia-CR imaging system 9. Cosmetrics SIAscope	Schwartz S.R. et al., (2019); Aguirre et al., (2017); Bertuccelli G. et al., (2016); Hyun-Sun Yoon et al., (2016); Schwartz S. et al., (2016); Puglia C. et al., (2014); Jenkins et al., (2014); Furumura et al., (2012); Schwartz S.R. and Park J., (2012); Cho S et al., (2009); Yang B. et al., (2009); Skovgaard et al., (2006); Beguin, (2005); Distante et al., (2002)
Photodamage severity	Photodamage/ageing (dermatoheliosis) results from prolonged or excessive UV exposure causing changes in the structure, function, and appearance(Samuel et al., 2015). Usually, scales are used for determination of severity of the photodamage (Yu and Baron, 2013).	1. Camera + photo evaluation	Fanian F. et al., (2013)
Pores	Topographic feature of skin surfaces composed of tiny ostia (pilosebaceous follicles, eccrine sweat glands). Categories 'visible skin pores' (0.1–0.6 mm^2), 'enlarged skin pores' (0.3–0.6 mm^2), and 'blackhead embedded skin pores'. (Flament et al., 2015; Sang Ju Lee et al., 2016).	1. Clarity 2D Research Systems 2. VisioFace digital photography imaging system + VisioFace CSI software	Maia Campos et al., (2019)
Residual skin surface components (RSSC)	Derived from lipid droplet size measurement, lipid crystal count, desquamated corneocytes, and evaluation of bacterial presence (Chalyk et al., 2017). Also, corneocyte size, sebum oil and oily skin appearance also assessed.	1. Microscopy 2. Digital image analysis 3. SEBU sheet 4. Camera + photo evaluation	Chalyk et al., (2017); Furumura et al., (2012); Tominaga et al., (2012); Beguin, (2005)
Roughness	Skin surface topography (Korn et al., 2016).	1. PRIMOS compact 2. Visia-CR imaging system 3. Skin replica analysis 4. Visioscan VC 98 system + a b/w CCD camera	Göllner et al., (2017); Bertuccelli G. et al., (2016); Fanian F. et al., (2013); Yang B. et al., (2009)
Skin surface evaluation	Surface evaluation of living skin (SELS) obtained by the camera, digitalised, and further processed to yield four surface parameters. *Surface/Smoothness*: the average width and depth of the wrinkles. Closer to 1, smoother the skin (Khazaka G., 2000; Beguin, 2005). *Entropy/Scaling*: the hydrate level of stratum corneum. A highly hydrated skin gets a higher entropy value (Beguin, 2005; Theek et al., 2020). *Contrast/Roughness:* calculates the ration of dark pixels. A good skin condition shows low contrast values (Beguin, 2005; Ali et al., 2013).	1. Visioscan VC 98 system + a b/w CCD camer 2. Camera + photo evaluation	Babizhayev M.A. et al., (2012); Skovgaard et al., (2006); Beguin, (2005)

	Circular roughness (Rz)/Wrinkling: a key parameter for identify skin surface including wrinkles and is calculated from the proportion of horizontal and vertical wrinkles (Khazaka G., 2000; Beguin, 2005; Ali et al., 2013).		
Wrinkle	Skin wrinkle parameters, depth, severity, volume, width, fine and deep lines, total wrinkles/score, total, skin relief, texture and smoothness. Regions measured include forehead, periocular, perioral and nasolabial folds. Periorbital (crow's feet) wrinkle most often measured.	1. VisioFace digital photography imaging system + VisioFace CSI software 2. PRIMOS compact 3. Skin-Visiometer SV 600 4. Skin replica analysis 5. Camera + photo evaluation 6. A DUBplus 20 Ultrasound unit 7. SDSNA 8. Facial Stage 9. Visia - CR imaging system 10. Clarity 2D Research Systems 11. DermaVision software 12. Visioscan VC 98 system + a b/w CCD camera	Zmitek et al., (2020); Draelos Z.D., (2019); Maia Campos et al., (2019); Schwartz S.R. et al., (2019); Czajka A. et al., (2018); Göllner et al., (2017); Bertuccelli G. et al., (2016); Hyun-Sun Yoon et al., (2016); Lademann J. et al., (2016); Schwartz S. et al., (2016); Jenkins et al., (2014); Proksch et al., (2014); Yoshikawa et al., (2014); Fanian F. et al., (2013); Oyama A et al., (2012); Tominaga et al., (2012); Cho S et al., (2009); Skovgaard et al., (2006); Beguin, (2005); Distante et al., (2002); Murad and Tabibian, (2001); Rigano et al., (2001)
Skin physical properties parameters (8): density, dermis echogenicity, elasticity, firmness, TEWL, hydration, thickness, viscoelasticity.			
Density	Dermis density, related to the amount of properly structured dermal proteins, e.g., collagen and elastin (Beguin, 2005; Skovgaard et al., 2006; Žmitek et al., 2020).	1. DermaLab series, skinlab combo 2. A DUBplus 20 Uutrasound unit 3. Dermcup 4. Dermascan C	Zmitek et al., (2020); Fanian F. et al., (2013); Skovgaard et al., (2006); Beguin, (2005)
Dermis echogenicity	High-frequency ultrasound imaging can be used to identify the dermis (Milner et al., 1997). Skin echogenicity measured as a ratio between the upper and lower dermis may be used to objectively estimate photoageing (Gniadecka, 2001).	1. Dermascan C	Maia Campos et al., (2019)
Elasticity	Deformation and recovery potential (Everett and Sommers, 2013).	1. DermaLab series, skinlab combo 2. Cutometer MPA 580 / SEM 575 3. Multi-dermascope MDS 800	Maia Campos et al., (2019); Schwartz S.R. et al., (2019); Czajka A. et al., (2018); Aguirre et al., (2017); Göllner et al., (2017); Bertuccelli G. et al., (2016); Dumoulin et al., (2016); Hyun-Sun Yoon et al., (2016); Lademann J. et al., (2016); Jenkins et al., (2014); Oyama A et al., (2012); Cho S et al., (2009); Yang B. et al., (2009); Skovgaard et al., (2006); Distante et al., (2002)
Firmness	Skin firmness were measured by cutometer which reported using the R0 (Uf) parameter. R0 represents the passive behaviour of the skin to force. As the skin becomes firmer, the value decreases (Schwartz S.R. et al., 2019).	1. DermaLab series, skinlab combo 2. Cutometer MPA 580 / SEM 575	Schwartz S.R. et al., (2019); Jenkins et al., (2014)

TEWL	Surface evaporation (Campbell and Lichtensteiger, 2004) flux ($g \cdot m^{-2} \cdot h^{-1}$) vapour density measurement (Alexander et al., 2018). Estimates ability to maintain moisture indicator of skin's water-barrier function (Hester et al., 2004; Wallen-Russell, 2019).	1. DermaLab series, skinlab combo 2. Tewameter TM 210 3. VapoMeter	Zmitek et al., (2020); Schwartz S.R. et al., (2019); Hyun-Sun Yoon et al., (2016); Jenkins et al., (2014); Oyama A et al., (2012)
Hydration	Hydration is the water content measured by change in capacitance due to water content within the stratum corneum (Agache et al., 2001).	1. DermaLab series, skinlab combo 2. Corneometer CM 824/ 825 3. Multi-dermascope MDS 800 4. Skicon-200EX 5. NOVA dermal phase meter 9003 6. Moisture Meter SC	Zmitek et al., (2020); Draelos Z.D., (2019); Maia Campos et al., (2019); Schwartz S.R. et al., (2019); Aguirre et al., (2017); Göllner et al., (2017); Bertuccelli G. et al., (2016); Hyun-Sun Yoon et al., (2016); Lademann J. et al., (2016); Schwartz S. et al., (2016); Jenkins et al., (2014); Oyama A et al., (2012); Schwartz S.R. and Park J., (2012); Cho S et al., (2009); Yang B. et al., (2009); Skovgaard et al., (2006); Distante et al., (2002); Murad and Tabibian, (2001)
Thickness	There are 3 skin thickness parameters: Dermis thickness, epidermal thickness, epidermal and dermal thickness. The most measured are epidermal and dermal thickness, and epidermal thickness.	1. DermaLab series, skinlab combo 2. BMI plus software (an image analysis) 3. A DUBplus 20 Ultrasound unit 4. Dermcup 5. Dermascan A/ C/ V3	Zmitek et al., (2020); Lademann J. et al., (2016); Fanian F. et al., (2013); Cho S et al., (2009); Yang B. et al., (2009); Skovgaard et al., (2006); Beguin, (2005); Distante et al., (2002)
Viscoelasticity	Skin viscoelasticity (compares to elastic property) incorporates viscous effects of fluids. This property provides protection for skin structure without breaking (Seehra and Silver, 2006; Clancy et al., 2010; Everett and Sommers, 2013).	1. DermaLab series, skinlab combo 2. Cutometer MPA 580 / SEM 575 3. Reviscometer RVM 600	Zmitek et al., (2020); Schwartz S.R. et al., (2019); Fanian F. et al., (2013); Distante et al., (2002)
Skin biochemical parameters (3): the quantity and quality of collagen, elastin and fibrillin, oxidative stress, the expression levels of key genes.			
Collagen, elastin and fibrillin (quantity and quality)	Collagen is the most abundant component of the extracellular matrix maintains the skin structure (Bolke et al., 2019). Elastic fibers comprising fibrillin microfibrils and elastin contributes to the viscoelasticity of the skin (Eckersley et al., 2018; Schwartz S.R. et al., 2019).	1. Confocal laser scanning microscopy (VIVASCOPE) 2. Histological biopsy analyses 3. Cosmetrics SIAscope 4. In vitro enzyme immunoassay kits	Laing et al., (2020); Schwartz S.R. et al., (2019); Jenkins et al., (2014); Proksch et al., (2014); Schwartz S.R. and Park J., (2012)
Oxidative stress	Induced by excessive oxidants above antioxidant defence capacity (Kruk and Duchnik, 2014). These measurements have been used for redox balance and NO concentration, determination of lipid peroxidation, superoxide dismutase activity measurement and in vivo NO assessment to reflect oxidative stress.	1. Thiobarbituric acid reactive substances assay 2. Biochemical assessments	Chalyk et al., (2017); Bertuccelli G. et al., (2016)

The expression levels of key genes	Learn about the state of skin by testing your genes such as AQP3, CyPA, CD147 (Bertuccelli G. et al., 2016).	1. Reverse transcription-polymerase chain reaction (RT-PCR)	Bertuccelli G. et al., (2016)
Subjective assessments (method): Self-assessment or/and expert assessment. This is an assembly of skin parameters.			
Subjective assessments	Self-assessment or/and expert assessment, for examples, questionnaires, grading (ordinal visual grading, C.L.B.T scale and imperfections scale and visual analog scale).	Self-assessment or/and expert assessment	Laing et al., (2020); Draelos Z.D., (2019); Schwartz S.R. et al., (2019); Czajka A. et al., (2018); Aguirre et al., (2017); Göllner et al., (2017); Bertuccelli G. et al., (2016); Dumoulin et al., (2016); Fanian F. et al., (2013); Furumura et al., (2012); Schwartz S.R. and Park J., (2012); Cho S et al., (2009); Skovgaard et al., (2006); Distante et al., (2002); Rigano et al., (2001)

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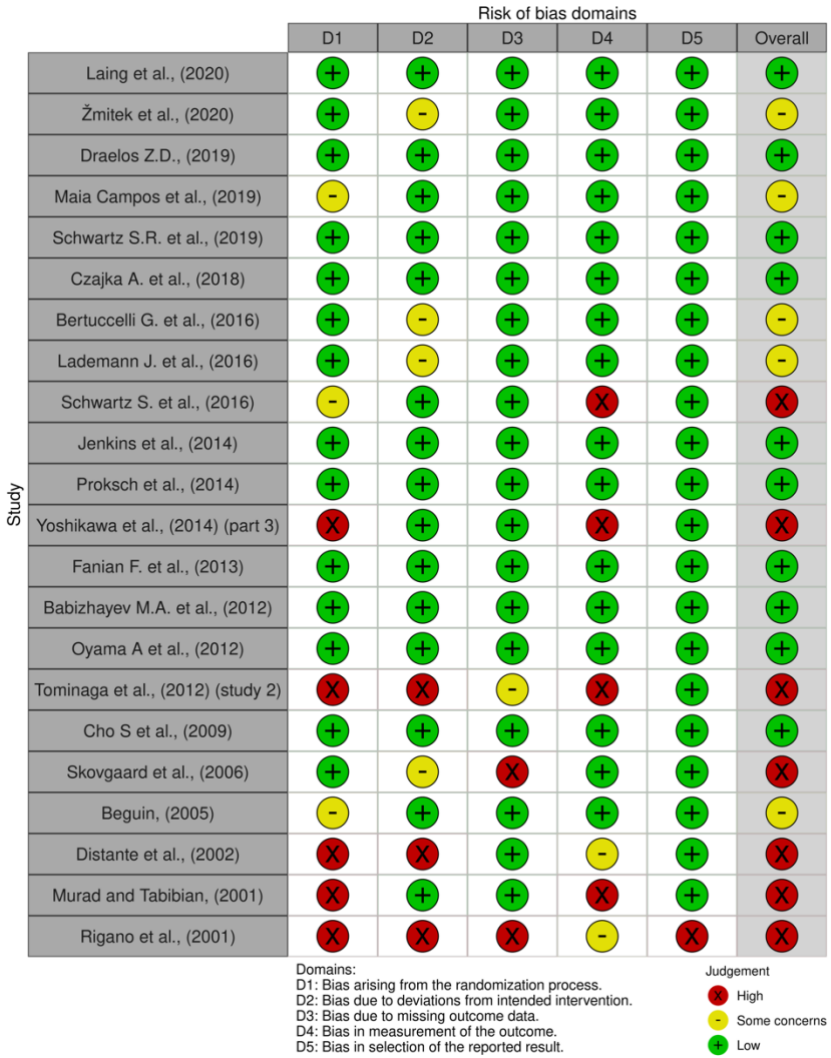
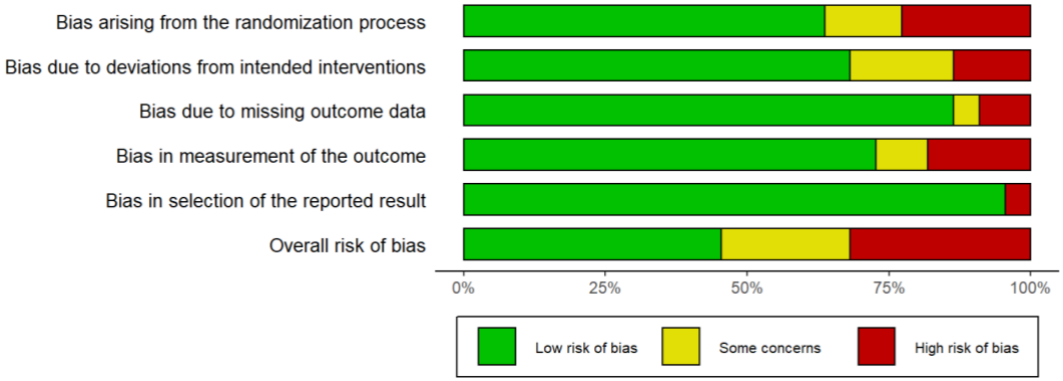
Figure 4. A risk of bias RoB 2 graph of all included RCT studies (left); An overview displayed as percentages graph of each risk of bias items of all included RCT studies (right)





2.4 Discussion

The main findings of this scoping review are three-fold, nutritional (ingredients), skin parameters and measurement/methods. No convincing evidence was considered to show a specific supplementation or single/multiple ingredient retarded skin ageing. Despite studies reporting positive results in anti-ageing effects, reproducibility has not been demonstrated. Only Rigano (2001) vs Distante (2002) and Chalyk (2017) vs Tominaga (2012) had both used the same ingredient in their studies, but the criteria of particpant's age/sample size/study duration/skin parameters were not consistent. Many different skin parameters have been used across the studies with no clear application of definitions. The 49 skin parameters have been merged to 18 most representative and non-repetitive skin parameters and been classified into 3 large groups based on the key properties. Changes in skin age included skin outlook, structure, biochemistry, metabolism functions. The measurement/methods have also been also summarised and catalogised according to the skin parameters (outcomes). In addition, the most important point for this scoping review was each skin parameter had been clearly described and methods have been summarised in the **table 2**, which greatly facilitates the work of subsequent researchers in finding and comparing different formulations using these skin parameters and effects.

First, there was no conclusive evidence for reducing skin ageing by the intake of supplementation, but the most effective combination was found from the 30 studies which was macronutrients + micronutrients + others (here, 'others' represented different antioxidants or plant extracts) formulation. Next, 18 skin parameters were divided into 3 main groups, namely, skin appearance image parameters, skin physical property parameters and skin biochemical parameters. The skin parameters were divided based on their individual property and description. For example, in skin appearance image group, 7 skin parameters were included, color, photodamage severity, pores, residual skin surface components (RSSC), roughness, skin surface evaluation and wrinkle. And in the color group, a number of sub-skin parameters were presented such as pigmentation, erythema, brown spot intensity, dermal hemoglobin and so on. Skin color was defined as "the perceived skin pigmentation resulting from the selective absorption and scattering of light from the dermis of the body" (Piérard, 1998). Meanwhile, melanin, carotene, oxygenated hemoglobin, and reduced hemoglobin contribute to skin color (Everett et al., 2012). Therefore, these sub-skin parameters were grouped into color skin parameter, the rest may be deduced by analogy. In addition, according to the above results,

wrinkles, elasticity and hydration were the most measured skin parameters. Firstly, wrinkles were measured about 73% of 30 studies in this review. The reason could be it can represent the recovery ability of skin which decreased progressively with age (Hatzis, 2004). Also, wrinkles was one of the most skin ageing phenotypes and is used as a skin ageing indicator (Wong and Chew, 2021). Secondly, half of the included studies measured elasticity as loss of elasticity can cause skin sagging (Ganceviciene et al., 2012) which is another common clinical feature of skin ageing (Imokawa and Ishida, 2015; Vashi et al., 2016). In addition, although more than half of the studies in the review chose hydration to test, it had only very low correlation with skin ageing (Luebberding et al., 2013). Although the dryness of skin can be directly detected by the eye, measuring hydration is to quantify the amount of water in the stratum corneum (Mojumdar et al., 2017). However, to determine if the skin is ageing or damaged, the transepidermal water loss (TEWL) is a more appropriate parameter to be measured due to the correlation between TEWL and the function of skin barrier. Generally, an increased TEWL is associated with increased damaged skin, which means anti-ageing strategies can be adjusted by observing the process of TWEL changes, and also measuring the effectiveness of the product on the skin (Draelos, 2015). To conclude, one single skin parameter cannot reflect the extent of skin ageing or the efficacy of the product. The better solution should be selecting several different skin parameters from different groups is more appropriate and provides a less-biased approach.

Furthermore, accurate measurement to quantify skin ageing features (represented by each individual skin parameter) is a prerequisite for investigating the efficacy of food supplementation. The methods were grouped in 3 large groups based on the results, which was the same as the classification of skin parameters. The most widely used group of methods was skin appearance image because of ease of use, non-invasive and rapid access of results. For example, to be specific, the most frequently used method and equipment to measure wrinkles was skin replica analysis plus camera + photo evaluation. Skin replication is a non-invasive, objective technique that measures micro-topographical features of the skin through the use of silicone replicas (Grove et al., 1991; Fischer et al., 1999; Yin et al., 2001) and is one of the most frequently used methods to produce precise reproductions of the skin surface (Pirisinu and Mazzarello, 2016). This method is easy to replicate, fast, accurate and does not cause damage to the skin. Also, camera + photo evaluation approach uses a camera such as Nikon, Canon to take photographs of the skin, usually the facial skin, before and after treatment in order to compare it with the baseline images through artificial intelligence software or manual analysis (Rigano et al., 2001; Beguin, 2005). Alongside this, equipment and methodology

underpinning most commonly measured skin parameters are discussed in detail in chapter 3. As technology advances, camera technology and computational power are increasingly able to capture, measure and analyse information that cannot be directly observed by the naked eye, providing objective and quantitative information for the research in dermatology. Undoubtedly, this will change the state of the current research in food supplementation and skin ageing and will greatly simplify the way where research is conducted and more people can easily participate in experiments. While the focus of this review is on a summary of measurements and equipment, it must be emphasised that where possible, a three-pronged approach, i.e. expert graders' evaluations, participants' self-assessment and instrumental measurements, is recommended to obtain more accurate and comprehensive data to assess the efficacy of various food supplements on skin anti-ageing.

To our knowledge, this is the first review that has classified and summarised the skin parameters, methods and equipment in skin ageing and food supplementation. There were 30 eligible human studies including 22 RCTs with 10 at low risk bias level. Among these low-risk-bias-level human RCTs, 4 RCTs can be taken as very good examples, such as Cho S et al. (2009), Oyama A et al. (2012), Jenkins et al. (2014) and Schwartz S.R. et al. (2019). These studies utilised strict protocols to minimise bias, ensure adequate randomisation and in obtaining sufficient and representative samples. For example, Jenkins et al. (2014) conducted a double-blind RCT in accordance with the standards of good clinical practice established internationally. The products were coded and randomly assigned at the source, and the subjects, researchers, and statistician were kept in the dark about the coding until the study and preliminary data analysis were finished. Jenkins et al. (2014) also got the largest sample size (n=159) among selected RCTs. The age of these female participants were between 48-71 years, suggesting that participants should probably be in the menopausal stage to avoid fluctuations in hormone levels affecting skin condition during menstruation. Measured skin parameters were chosen from three different skin parameters groups and with different assessment methods to prevent bias, for instance, wrinkles were measured by using PRIMOS analysis of silflo replicas + camera photo analysis, skin firmness and elasticity were determined using Courage & Khazaka Cutometera CM825; barrier function and skin hydration (Dermalaba TEWL); skin colour (Konica Minolta Chromameter CR300) and collagen & elastin (histological biopsy analyses). The blood samples had also been taken to analyse vitamin and carotenoid levels. Another RCT is Oyama A et al. (2012), this study had sufficient sample size size with required power (n=101) and specifically mentioned menopaused Japanese participants in the study. These participants were randomly assigned to 3 groups, control and

two levels of dose (10 mg and 30 mg). Also, Cho S et al. (2009) conducted a study of long duration, 6 months, with a sample size (n=82) and multiple skin parameters measured. As above, Schwartz S.R. et al. (2019), had a good sample size (113 Caucasian female participle), 3 months study duration and multiple measured skin parameters.

In general, from the papers reviewed, multiple compounds were used in the tested formulations. This makes the identification of the biological activity of the combination and, of specific single components problematic, particularly if synergistic effects exist between the compounds. For example, in Jenkins et al. (2014), five separate compounds isoflavone, lycopene, vitamin C, vitamin E and omega-3 were utilised. Isoflavone is a phenolic compound belongs to the polyphenol group (Gómez-Zorita et al., 2020; Yamagata and Yamori, 2021). Lycopene is a non-provitamin A carotenoid and belongs to a pigment family called carotenoids (Story et al., 2010). Polyphenols and carotenoids are promising compounds in anti-ageing research mainly due to their antioxidant capabilities (Schagen et al., 2012; Meinke et al., 2013), which have the ability to scavenge free radicals (Romera-Castillo and Jaffé, 2015). It was found that different types of polyphenols have a positive effect on the anti-ageing of the skin, such as equol which improved skin conditions (skin roughness, texture, smoothness, firmness and elasticity these parameters), and can significantly increase the length of telomeres in humans (Magnet et al., 2017) which means a more healthier status (Terry et al., 2008). In the Chen (2017) animal study, they observed that EGCG can be absorbed via the skin. The overall skin conditions and skin structure were improved after EGCG treatment. Even though polyphenol is extracted from different plants, it has a beneficial anti-ageing effect on the skin. For example, cocoa flavanols are extracted from raw cocoa. According to Hyun-Sun Yoon (2016) , regular consumption of cocoa favanol supplements has been found to improve facial wrinkles and elasticity and slow down the progression of skin ageing. Although, in this study, the result showed that cocoa favanol supplements did not improve significant differences in skin hydration and barrier integrity. Another example, polyphenols including four different fractions extracted from grape pomace, most of these fractions demonstrated an inhibitory effect on collagenase and elastase activity as well as showing a dose-dependent inhibitory activity (Wittenauer et al., 2015). However, the anti-ageing benefits of polyphenols may be influenced by their molecular properties, food matrix, bioavailability and, this is not always determined by total intake/consumption (Menaa et al., 2014). Therefore, this is only a small step in determining the doses and concentrations effective in skin anti-ageing and more investigations should be done in terms of food matrices, bioavailability, absorption rates, and delivery systems.

Carotenoids, are widely dispersed fat-soluble plant pigments that give fruits and vegetables colours such as red, yellow and orange (Khoo et al., 2011). Due to carotenoids' chemical structure, they can be classified into two groups, carotenes (which do not contain oxygen, and are hydrocarbons, such as α-carotene, β-carotene, and lycopene) and xanthophylls (which contain oxygen as a functional group, such as β-cryptoxanthin, lutein, zeaxanthin, astaxanthin, fucoxanthin, and peridini) (Cazzaniga et al., 2016; Maoka, 2020). Carotenoids have a C40 polyisoprenoid structure with a set of conjugated double bonds in the center. These double bonds are responsible for light absorption in the blue portion of the visible spectrum (Bartley and Scolnik, 1995; Balić and Mokos, 2019). As previously mentioned, the main cause of skin ageing is UV light. Due to their double-bonded chemical structure, carotenoids can absorb light directly, thus achieving a photoprotective effect and improving the signs of skin ageing (Balić and Mokos, 2019). Ito (2018) conducted a randomised, double-blind, placebo-controlled trial with 4 mg astaxanthin supplement which showed minimal erythemal dose (MED) level increase and skin moisture decrease. Minimal erythemal dose (MED) is defined as the lowest dose UV radiation that might elicit sunburn or redness due to capillary engorgement within a few hours following the exposure (Heckman et al., 2013) and it is a critical parameter in skin photosensitivity research (Valbuena et al., 2020). MED level increase means the photosensitivity of skin has been increased. In other words, carotenoid supplements provide a photoprotection on the skin and thereby slowing down the process of skin ageing. Also, according to the results of the study by Menike (2013), it was also observed that carotenoid supplements boost the skin's radical scavenging ability and offers considerable protection against stress-induced radical production. Darvin's study (2011) furthermore demonstrated that a combination of oral supplement and topical application of carotenoids might give superior skin protection than either alone. Thus, carotenoids, due to their chemical structure and properties, have shown a great potential for skin anti-ageing research.

In addition, the major strength of this review is providing clear lists of the studies undertaken and so future research may select the skin parameters and methods/equipment when they conducting experiments and which then be compared with previous results. Besides, there are few research gaps. For the nutrition area, it is not possible to compare the anti-ageing efficacy of food supplementation on skin as there is not yet a clear standard. For the dermatological area, the definition of skin parameters, equipment and methods are not unified. Although it was found that both oral or/and topical agents have more or less positive anti-ageing effects on the skin and improve most skin parameters, there is no quantitative or proportional application of oral or topical agents, in other words, there is no standard for the

concentration and dosage. High concentrations do not mean better results and sometimes high concentrations can have negative effects on the human body. For example, if the concentration of topical salicylic acid (a plant extract) is higher than 2%, this could cause skin peeling and dryness (Liu et al., 2020). Also, too high concentrations can also lead to safety issues, such as skin discomfort or long-term effects on organs which can lead to lesions. For example, long-term intake of high doses of vitamin C could increase the risk of kidney stones (Lykkesfeldt et al., 2014) and digestive distress (Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds, 2000), because vitamin C can swap functions and behave as a tissue-damaging pro-oxidant rather than an antioxidant (Poljšak and Ionescu, 2009). But using too low a concentration has no visible effect and is only a psychological support. Therefore, finding the suitable concentration or dosage to apply or take orally is a key factor in establishing an effective anti-ageing treatment for the skin. According to our findings from the existing literature, vitamin C has a significant and effective anti-ageing effect on the skin by increasing collagen synthesis, stabilizing collagen fibers and reducing collagen breakdown, especially working synergistically with vitamin E on topical application (Al-Niaimi and Chiang, 2017). Therefore, the absence of a uniform standard makes it difficult to compare differences in test results and thus to determine the effectiveness of dietary supplements.

Meanwhile, the reliability of the experimental data also depends on the selection of the participants' health conditions, skin conditions and age. In the review, it was found that some studies selected post-menopausal women rather than non-menopausal women and over-representation of female participants in this research field, which limits comparisons of the efficacy of dietary supplements. Besides, this review also includes a RoB assessment to assess the quality of each included studies. However, this review also has its limitations. Only English language studies were included. And searching were conducted in four databases with time constraints, so potentially, not all relevant studies were included. There was insufficient data to conduct a meta-analysis due to the lack of consistency in treatments, parameter selection and measurement methodologies. Furthermore, the key words picked to search in these four databases was primarily based on measurement techniques and skin parameters rather than specific supplements or materials. Consequently, some single compound studies were not detected by the search strategy.

In conclusion, to establish a common definition of skin parameters and classification of methods is an important step toward enhancing the future research quality and efficiency, which would provide a common framework and guidelines.

Chapter 3

Equipment and methodologies of commonly measured skin parameters

Based on the results of scoping review in Chapter 2, the top three most measured skin parameters were wrinkle, hydration and elasticity.

The definition of wrinkle has not been clearly stated. Only few papers have described wrinkles as a skin parameter. Firstly, Manriquez et al. (2014) refer to 'wrinkles are visible creases or folds in the skin' and defined fine wrinkles with width and depth less than 1 mm, wrinkles equal or more than 1 mm are deep wrinkles. Then, in the Sandulescu et al. (2019) article, it is stated that there is no a clear definition for wrinkles as 'facial folds and creases are established descriptive anatomical terms for structures of which the morphological characteristics and origins are not clearly defined' and 'wrinkles this term is used to describe redundant skin excess that forms undulating skin relief due to aging'. Meanwhile, Huang et al. (2019) explain that 'wrinkles are uneven concave-convex folds, ridges or creases in skin'. However, to summarise all of the above definitions or descriptions, our study defined skin wrinkle as the morphology of striped texture on the surface of the skin. Furthermore, the parameter 'wrinkles' contains a number of sub-parameters, such as depth, severity, volume, width, fine lines, deep lines, total wrinkles, total wrinkle score, skin relief, skin texture and skin smoothness. Some of these sub-parameters of wrinkles are easily understood in a literal sense such as depth, severity, volume, width, fine lines, deep lines, total wrinkles, skin texture, skin relief and skin smoothness. Some sub-parameters such as total wrinkle score, require further definition and interpretation. For example, total wrinkle score is a parameter used to assess wrinkles by looking at the area of wrinkles and having the expert or device calculate a score for the number or severity of wrinkles.

Furthermore, referring to table 2, there are 12 methods and equipment collected from 30 studies that can be used to measure wrinkles. As previously mentioned, skin replica analysis plus camera + photo evaluation is a repeatable, objective measurement for assessing skin surface topography (Grove et al., 1991). This technique has been widely used, with only few weaknesses, to measure surface skin wrinkles. However, the weaknesses of this technique are the replica material required to cover the measured area which is not easy to apply. The size of the measured area is also limited by the equipment utilised. Also, using this method needs a high resolution equipment and stable environmental condition to obtain clear images, 3-dimensional image analysis equipment (PRIOR) or expensive high resolution 2-dimensional image analysis equipment (skin microscopy) (Wu and Tanaka, 2021). Except skin replica

analysis plus camera + photo evaluation this method, there are many other methods or equipment that can measure wrinkles, but these are not widely used, such as Skin-Visiometer SV 600, Visia-CR imaging system, and Visioscan VC 98 system + a b/w CCD camera (appendix B).

Hydration has been grouped into biochemical skin parameters as its definition is 'the water content of the epidermis and the dermis' (Moortgat et al., 2020). This paper argues that hydration can be defined as a property of the skin associated with moisture. However, in a textbook on scar management, hydration was grouped into physiological scar parameters (Moortgat et al., 2020). Hydration usually indicates water content in the stratum corneum layer and acts as a factor indirectly reflecting skin barrier health (Berardesca and Maibach, 1990; Hester et al., 2004; Mojumdar et al., 2017). The hydration in the stratum corneum layer is also essential for proper stratum corneum maturation and skin desquamation (Verdier-Sévrain and Bonté, 2007). In recent years, many methods and devices are available for measuring hydration, but the mainstream is still using electrical probe-based instruments (Qassem and Kyriacou, 2019). There were 6 devices and methods collected as shown in **table 2**, but the most commonly used is the skin capacitance method, the equipment named Corneometer and MoistureMeter. These use the distribution of water in the stratum corneum layer and measure the electrical properties of the skin (Birlea et al., 2014). The Corneometer principle is based on the capacitance of an electrode depends on the permittivity of the dielectric medium placed between it and the electrode being charged (Gidado et al., 2022). Corneometer, developed in 1980, includes 2 electrodes with different electrical charges that form an electromagnetic field which can measure the first 10-20 μm of the stratum corneum and has been widely applied in cosmetics and dermatological studies (Birlea et al., 2014; Constantin et al., 2014). Corneometer is stated as a gold standard device to measure skin hydration in the stratum corneum layer. Such worldwide acceptance is attributable to its great repeatability, simplicity of use, speed of measurement, and cost-effectiveness (O'goshi and Serup, 2005). However, corneometer is not very accurate and sensitive at high hydration levels of the skin condition (Clarys et al., 2012). This suggests that using only capacitance-based methods may not be adequate to produce accurate data for skin that is highly hydrated. For the different types of the skin, combining use with other instruments that use different principles to get a range of results may provide more accurate results, such as optical based equipment (Raman spectroscopy), skin impedance based equipment (Novameter) (Gidado et al., 2022).

In addition, not mentioned in the selected 30 studies, there is an innovative device called SkinChip using silicon image sensor technology created by L'Oreal which can provide detailed

and rapid hydration analysis of human skin (L'Oréal, 2002; Verdier-Sévrain and Bonté, 2007; Qassem and Kyriacou, 2019). The principle is based on image-micro-sensing which is able to provide in vivo mapping of skin surface capacitance and a non-optical image of stratum corneum hydration (Piérard, 2005). A more complete analysis and quantification of skin surface hydration data will be obtained if using a Corneometer and Skinchip together in one experiment (Batisse et al., 2006; Lévêque et al., 2006; Qassem and Kyriacou, 2019).

Skin elasticity is defined as "a physical property of the skin that enables it to change and recover shape when stretched or deformed" (Clancy et al., 2010; Everett and Sommers, 2013). In the selected studies, there were 15 studies which tested elasticity by using DermaLab series, skinlab combo, Cutometer MPA 580 / SEM 575 and Multi-dermascope MDS 800. Among these devices, the Cutometer is the most frequently used. The Cutometer MPA 580 / SEM 575 has been used 13 times in these 15 studies, the other two devices were only used once. Cutometer MPA 580 or called Cutometer dual MPA 580 is the newest version of the Cutometer SEM 575. In the 15 studies, Cutometer MPA 580 has been used 6 times, Cutometer SEM 575 has been used 6 times, one study has not mentioned which version it used but only mentioned Cutometer. The Cutometer MPA 580 is displayed in **figure 5.** The measurement principal of Cutometer MPA 580 is based on a suction measurement method.

The principal of Cutometer is, negative pressure generated by the probe sucks the measured skin area into the aperture of the probe. There is a non-contact optical measuring system inside the probe to measure the skin travel distance. The process is defined as, "The resistance of the skin to being sucked into the aperture is determined by the firmness of the skin. The elasticity is the ability of the skin to return to its previous position". The mechanism is shown on **figure 6.** The results are displayed as a curve with a series parameters such as R-parameters, F-parameters and Q-parameters (Courage & Khazaka, 2021). The detail of these parameters is illustrated in **table 3**. Moreover, Cutometer has not only been used in studying skin ageing, but also widely applied in skin suction examinations of different areas like systemic sclerosis (Dobrev, 1999) and scar assessment (Jaspers and Moortgat, 2020). According to the parameters in **table 3**, Cutometer can provide data on skin firmness, elasticity and viscoelasticity simultaneously, which facilitates researchers to quantify the physical properties of the skin, such as quantifying changes in elasticity with age (Bonaparte et al., 2013). Also, various body locations are measured safely via using the Cutometer (Draaijers et al., 2004). Although Cutometer offers a number of advantages, the biggest limitation is the force and angle applied by operators via the probe and therefore on the skin which may different by each user's operating technique contributing as a variable. Because the outcome measures of skin elasticity

may change appreciably by external moderate-to-heavy contact force applied to the probe on the skin. The higher the contact force, the greater the initial elevation level, and the larger the response (Bonaparte et al., 2013; Müller et al., 2018).

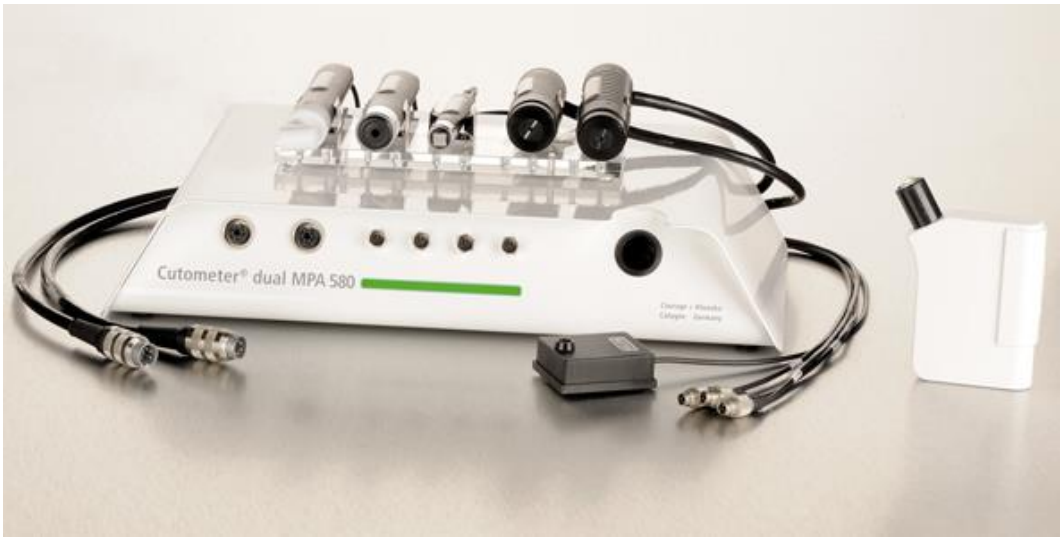


Figure 5. Cutometer Dual MPA 580 (Courage & Khazaka, 2021)

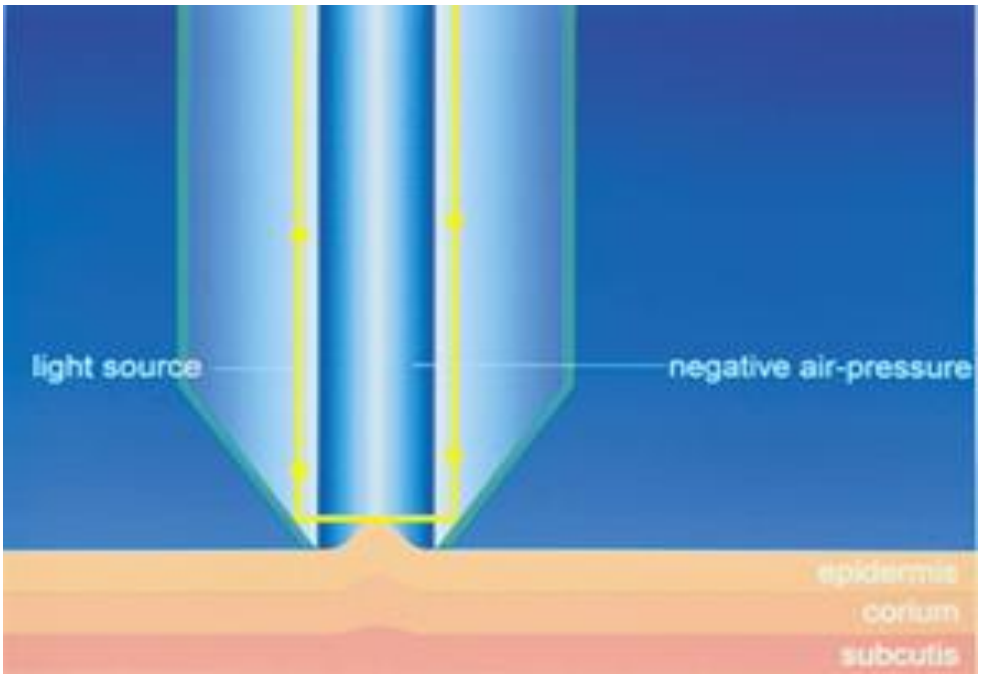


Figure 6. The measurement principle of Cutometer Dual MPA 580 (Courage & Khazaka, 2021)

Table 3. The interpretation of R, F and Q parameters- reproduced from Courage and Khazaka (Courage & Khazaka, 2021)

R-PARAMETERS
➢ R0: The passive behaviour of the skin to force
➢ R1: The ability of the skin to return to its original state
➢ R2: Gross elasticity, the closer to 1 (100%) the more elastic
➢ R3: Maximum amplitude of last and first curves compared to give 'tiring effects' of skin
➢ R4: Minimum amplitude of the last and first curves compare to give 'tiring effects' of skin
➢ R5: Net elasticity, the closer to 1 (100%) the more elastic the skin
➢ R6: Portion of viscoelasticity on the elastic part of the curve (the smaller the value the higher the elasticity)
➢ R7: Portion of elasticity compare to complete curve, closer to 1 (100%) the more elastic
➢ R8: Ability of the skin to return to normal state
➢ R9: Tiring effects of the skin after repeated sucking, the smaller R9 the smaller the effect

F-PARAMETERS
➢ F1: Elasticity, the closer to 0 the more elastic (based on area of curve)
➢ F2: Area above the upper envelope curve
➢ F3: Area within the envelope curve
➢ F4: Firmness, the smaller F4 the greater the ability to resist suction

Q-PARAMETERS
➢ Q0: Maximum recovery area, decreases with increasing firmness of the skin
➢ Q1: Elastic recovery, higher with great firmness
➢ Q2: Viscous recovery
➢ Q3: Viscoelastic recovery (overall elasticity), higher with more skin firmness

Chapter 4

Conclusion

To conclude, chapter 1 provided a background relative information to nutrition and skin ageing field. The core of this study was the scoping review provided in chapter 2. The full searching process is included in appendix A. Chapter 3 was a supplement to the results from the scoping review in chapter 2. Providing detail about the definition of skin parameters and how they were classified, as well as three most commonly measured skin parameters and the equipment and methods used. A table of methods and their descriptions is provided in appendix B.

In chapter 2, a scoping review was conducted by following O'Malley (2005) methodological framework. Thirty human studies were selected from a total of 87 papers extracted from four databases (CINAHL, Embase, PubMed and Scopus). In these 30 studies, 22 of them were randomised, double-blind, placebo-controlled trials. The RoB 2 assessment tool was used to assess the quality of the included RCTs, 22 RCTs reviewed, 7 trials showed high and 5 trials showed some risk of bias. Moreover, dietary supplements improved a wide range of skin parameters used to evaluate indications of ageing in the majority of these 30 studies. The most effective formulation was micronutrients + macronutrients + others (antioxidants or plant extract or animal tissue extracts). Besides, there were 49 skin parameters identified from the eligible articles considered. These skin parameters have been analysed, and merged to 18 representational skin parameters. Then, these 18 representational skin parameters were classified and summarised into three groups, skin appearance image, skin physical property parameters and skin biochemical parameters. The most measured skin parameters in this area were wrinkles, hydration and elasticity with corresponding measurement methodologies or equipment being skin replica analysis, corneometer and cutometer. The skin parameters are measured using 40 different methods or equipment which have been divided into 3 groups based on the measured skin parameter properties.

In summary, it is suggested the ideal study should be designed as a randomized, double-blind, placebo-controlled trial, with measured multiple skin parameters from three different skin parameter groups such as wrinkles and residual skin surface components (skin appearance image parameters group), hydration, TEWL, elasticity and viscoelasticity (skin physical properties parameters group), oxidative stress and key genes expression level (skin biochemical parameters group). In order to prevent biases and dependence on the different types of skin, different measurement equipment and techniques should be chosen based on the principles of equipment and the situations of study. Combined use of equipment can avoid biases caused by

the use of a single equipment. Similarly, measurement of multiple skin parameters can more accurately describe the conditions of the skin. This way allows a more repeatable and robust approach to assess the efficacy of supplements.

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Appendix A
The detail of search strategy in four databases

Appendix A. The detail of search strategy in four databases

CINAHL	title (TI) or abstract (AB) or extract subject heading (MH)		
	Search terms	**Details**	**Results**
1	skin aging	TI skin aging OR AB skin aging OR MH skin aging	2816
2	extrinsic skin aging	TI extrinsic skin aging OR AB extrinsic skin aging OR MH extrinsic skin aging	22
3	photoaging of skin	TI photoaging of skin OR AB photoaging of skin OR MH photoaging of skin	186
4	1 or 2 or 3		2877
5	skin deterioration	skin deterioration	58
6	skin wrinkl*	skin wrinkl*	294
7	cutaneous ptosis or cutaneous sagging	cutaneous ptosis or cutaneous sagging	3
8	skin sagging or skin ptosis or saggy skin or ptotic skin	skin sagging or skin ptosis or saggy skin or ptotic skin	48
9	droop* skin	droop* skin	3
10	skin permeability	skin permeability	66
11	skin tension	skin tension	139
12	skin pigmentation	skin pigmentation	1362
13	skin structure	skin structure	749
14	skin thickness or epidermis thickness	skin thickness or epidermis thickness	2115
15	epidermis or stratum corneum or skin surface	epidermis or stratum corneum or skin surface	3652
16	dermoepidermal junction	dermoepidermal junction	55
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16		8034
18	"oral supplement*"	TI "oral supplement*" OR AB "oral supplement*" OR MH "oral supplement*"	779
19	"diet* supplement*"	TI "diet* supplement*" OR AB "diet* supplement*" OR MH "diet* supplement*"	46902
20	"nutrit* supplement*"	TI "nutrit* supplement*" OR AB "nutrit* supplement*" OR MH "nutrit* supplement*"	3191
21	"supplementary diet*"	TI "supplementary diet*" OR AB "supplementary diet*" OR MH "supplementary diet*"	10
22	"food supplement*"	TI "food supplement*" OR AB "food supplement*" OR MH "food supplement*"	501
23	18 or 19 or 20 or 21 or 22		48825
24	4 and 17 and 23		23

Embase	title (ti) or abstract (ab) or keyword (kw) or all fields (af)		
	Search terms	**Details**	**Results**
1	skin ag?ing or ag?ing skin	(skin ag?ing or ag?ing skin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	4478
2	extrinsic skin ag?ing	extrinsic skin ag?ing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	140
3	photoag?ing of skin	photoag?ing of skin.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	360
4	1 or 2 or 3		4775
5	skin deterioration	skin deterioration.af.	40
6	skin wrinkl*	skin wrinkl*.af.	528
7	cutaneous ptosis or cutaneous sagging	(cutaneous ptosis or cutaneous sagging).af.	4
8	skin sagging or skin ptosis or saggy skin or ptotic skin	(skin sagging or skin ptosis or saggy skin or ptotic skin).af.	74
9	droop* skin	droop* skin.af.	1
10	skin permeability	skin permeability.af.	5633
11	skin tension	skin tension.af.	676
12	skin pigmentation	skin pigmentation.af.	12901
13	skin structure	skin structure.af.	4295
14	skin thickness or epidermis thickness	(skin thickness or epidermis thickness).af.	2278
15	epidermis or stratum corneum or skin surface	(epidermis or stratum corneum or skin surface).af.	74536
16	dermoepidermal junction	dermoepidermal junction.af.	2755
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16		97008
18	oral supplement*	"oral supplement*".ab,kw,ti.	4075
19	diet* supplement*	"diet* supplement*".ab,kw,ti.	34059
20	nutrit* supplement*	"nutrit* supplement*".ab,kw,ti.	10167
21	supplementary diet*	"supplementary diet*".ab,kw,ti.	144
22	food supplement*	"food supplement*".ab,kw,ti.	2796
23	18 or 19 or 20 or 21 or 22		49666
24	4 and 17 and 23		27

PubMed			
	Search terms	**Details**	**Results**
1	skin aging	"skin aging"[MeSH Terms]	8392
2	extrinsic skin aging	("extrinsic"[All Fields] OR "extrinsically"[All Fields] OR "extrinsics"[All Fields]) AND "skin aging"[MeSH Terms]	262
3	skin aging	"skin aging"[Title/Abstract]	2042
4	extrinsic skin aging	"extrinsic skin aging"[Title/Abstract]	59
5	#1 or #2 or #3 or #4		9411
6	"skin deterioration"	"skin deterioration"[All Fields]	30
7	"skin wrinkl*"	"skin wrinkl*"[All Fields]	406
8	"cutaneous ptosis"	"cutaneous ptosis"[All Fields]	4
9	"skin sagging"	"skin sagging"[All Fields]	32
10	"skin ptosis"	"skin ptosis"[All Fields]	8
11	"ptotic skin"	"ptotic skin"[All Fields]	5
12	"skin permeability"	"skin permeability"[All Fields]	1199
13	"skin tension"	"skin tension"[All Fields]	362
14	"skin pigmentation"	"skin pigmentation"[All Fields]	9476
15	"skin structure"	"skin structure"[All Fields]	1873
16	"skin thickness"	"skin thickness"[All Fields]	1863
17	"epidermis thickness"	"epidermis thickness"[All Fields]	108
18	"epidermis"	"epidermis"[All Fields]	52260
19	"stratum corneum"	"stratum corneum"[All Fields]	9543
20	"skin surface"	"skin surface"[All Fields]	7397
21	"dermoepidermal junction"	"dermoepidermal junction"[All Fields]	558
22	#6 or #7 or #8 or #9 or #10 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21		77661
23	"oral supplement*"	"oral supplement*"[Title/Abstract]	3073
24	"diet* supplement*"	"diet* supplement*"[Title/Abstract]	8054
25	"supplementary diet*"	"supplementary diet*"[Title/Abstract]	157
26	"food supplement*"	"food supplement*"[Title/Abstract]	4224
27	#23 or #24 or #25 or #26		15414
28	#5 and #22 and #27		19

Scopus	title (TITLE) or abstract (ABS) or keyword (KEY)		
	Search terms	**Details**	**Results**
1	"skin ag?ing" or "ag?ing skin"	ALL ("skin ag?ing" OR "ag?ing skin")	5901
2	"extrinsic skin ag?ing"	ALL ("extrinsic skin ag?ing")	125
3	"photoag?ing of skin"	ALL ("photoag?ing of skin")	5
4	#1 or #2 or #3		5903
5	"skin deterioration"	ALL ("skin deterioration")	77
6	"skin wrinkl*"	ALL ("skin wrinkl*")	2675
7	"cutaneous ptosis" OR "cutaneous sagging"	ALL ("cutaneous ptosis" OR "cutaneous sagging")	12
8	"skin sagging" OR "skin ptosis" OR "saggy skin" OR "ptoti	ALL ("skin sagging" OR "skin ptosis" OR "saggy skin" OR "ptotic skin")	77
9	"droop? skin"	ALL ("droop? skin")	1
10	"skin permeability"	ALL ("skin permeability")	13301
11	"skin tension"	ALL ("skin tension")	1531
12	"skin pigmentation"	ALL ("skin pigmentation")	26365
13	"skin structure"	ALL ("skin structure")	14532
14	"skin thickness" OR "epidermis thickness"	ALL ("skin thickness" OR "epidermis thickness")	11373
15	"epidermis" OR "stratum corneum" OR "skin surface"	ALL ("epidermis" OR "stratum corneum" OR "skin surface")	236111
16	"dermoepidermal junction"	ALL ("dermoepidermal junction")	2862
17	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16		287993
18	"oral supplement!"	TITLE-ABS-KEY ("oral supplement!")	1058
19	"diet! supplement!"	TITLE-ABS-KEY ("diet! supplement!")	771
20	"nutri! supplement!"	TITLE-ABS-KEY ("nutri! supplement!")	1
21	"supplementary diet!"	TITLE-ABS-KEY ("supplementary diet!")	241
22	"food supplement!"	TITLE-ABS-KEY ("food supplement!")	6591
23	#18 or #19 or #20 or #21 or #22		8618
24	#4 and #17 and #23		18

Appendix B
Methods and their descriptions

Appendix B. Methods and their descriptions

Methods	Descriptions	Measured skin parameters	References
1. A DUBplus 20 Ultrasound unit	Ultrasound measurements	Wrinkle, density, epidermal and dermal thickness	Skovgaard et al., (2006)
2. Biochemical assessments	Dermal redox balance and nitrogen oxide (NO) assessment; Determination of lipid peroxidation was determined by measuring the malondialdehyde (MDA) content in tissue homogenates; Superoxide dismutase (SOD) activity measurement; In vivo NO assessment.	the antioxidant capacity of the skin	Bertuccelli G. et al., (2016)
3. BMI plus software	An image analysis program	Thickness	Cho S et al., (2009)
4. Camera	Photo evaluation	Wrinkles, fine lines, skin color, oily skin appearance, overall skin appearance, pigmentation (the melanin index of the age spot)	Czajka A. et al., (2018) Furumura et al., (2012) Jenkins et al., (2014) Beguin, (2005) Rigano et al., (2001)
5. Chromameter	There are different versions of chromameters, such as C200, C300 and C400 etc. For example, the Chroma Meter C400 is a handheld, portable measurement tool that is used to assess the color of items, especially those with smoother surfaces and less color fluctuation. This high-accuracy, dependable colorimeter lets users manage the color quality, consistency, and appearance of their samples in a more efficient, simplified process both internally and throughout the supply chain using standard or customised assessment formulae. It reliably recognises color features in items, determines color contrasts across objects, and gives pass/fail evaluations to decide if the sample fits the required criteria quickly. The CR-400 is therefore excellent for color inspections of food, construction materials, plastics, and dermatological applications in quality control, quality assurance, and research and development (Konica Minolta Sensing Americas, 2020).	Color, luminosity	Schwartz S.R. et al., (2019) Jenkins et al., (2014) Yang B. et al., (2009) Distante et al., (2002)

6. Clarity 2D Research Systems	Clarity 2D Research Systems is a skin analysis device that uses cutting-edge technology to offer state-of-the-art 2D measurement. Acne, wrinkles, sub-surface pigmentation, skin type, radiance, enlarged pores, texture, under eye bags, lash health, and lip wrinkles are all included in the comprehensive and in-depth measuring characteristics (BrighTex Bio-Photonics, 2021).	Pigmentation, radiance, redness, wrinkles, skin texture, pores, acne and lips	Schwartz S.R. et al., (2019) Schwartz S. et al., (2016)
7. Colorimeter	Colorimeter can be used to measure UV-induced erythema and pigmentation, the severity of illnesses, and the success of treatment methods in a quantitative manner.The Minolta Chroma Meter CR-200 colorimeter is a portable device with a flexible hand-held probe that may be readily relocated. The diameter of the measured region is 8mm. This colorimeter uses reflected light to measure five different color systems. The Commission International de l'Eclairage's L*a*b* system was used to assess skin color, which is represented in 3 dimensions: The L* value (luminance) gives the relative lightness ranging from total black (L*=0) to total white (L*=100); the a* value represents the balance between red (positive value) and green (negative value); and the b* value represents the balance between yellow (positive value) and blue (negative value). Before each measurement, the equipment was calibrated using a calibration plate (CR-A43) (Park et al., 1999).	Color	Furumura et al., (2012)
8. Confocal laser scanning microscopy (VIVASCOPE)	Photography+expert grader on a visual analog scale (VAS) from -50 (= left image better) to +50 (= right image better)	Collagen structure	Laing et al., (2020)
9. Corneometer CM 824	The Corneometer CM 825 is the most widely used device for determining the degree of moisture on the skin's surface, particularly the stratum corneum. The measurement is based on a dielectric medium's capacitance measurement. All computer-driven MPA devices (MPA 2, MPA 6, MPA 10, and Cutometer® dual MPA 580) may use the Corneometer® CM 825 probe. Corneometer CM 824 is the old version of CM 825 (Courage & Khazaka, 1980).	Hydration	Draelos Z.D., (2019) Maia Campos et al., (2019) Göllner et al., (2016) Hyun-Sun Yoon et al., (2016) Lademann J. et al., (2016) Cho S et al., (2009) Yang B. et al., (2009) Distante et al., (2002) Murad and Tabibian, (2001)
10. Cosmetrics SIAscope	a Cosmetrics SIAscope, its ability to accurately identify melanin, hemoglobin, and collagen was found to be extremely high; and sensitivity and specificity to detect melanoma (Moncrieff et al., 2002)(Emery et al., 2010).	Epidermal melanin, dermal hemoglobin, and collagen (concentration/content/level)	Schwartz S.R. et al., (2019) Schwartz S.R. and Park J., (2012)
11. Cutometer MPA 580 (newest version) Cutometer SEM 575 (old version)	The Cutometer uses negative pressure to assess the elasticity of the top skin layer, mechanically deforming the skin. .The measuring principle is based on the suction method. (Courage & Khazaka, 2021)	Elasticity, viscoelasticity	Maia Campos et al., (2019) Schwartz S.R. et al., (2019) Göllner et al., (2017) Bertuccelli G. et al., (2016) Dumoulin et al., (2016) Hyun-Sun Yoon et al., (2016)

			Lademann J. et al., (2016) Jenkins et al., (2014) Oyama A at al., (2012) Cho S et al., (2009) Yang B. et al., (2009) Skovgaard et al., (2006) Distante et al., (2002)
12. Dermascan A	a 20-MHz ultrasounds device (Cortex Technology, Denmark)	Thickness (dermal)	Distante et al., (2002)
Dermascan C	A 20 mHz resolution B scanner set on medium focus (Dermascan®C, Cortex Technology ApS, Hadsund, Denmark) was used to provide cross-sectional pictures of the skin down to a depth of about 20 mm.	Ultrasound measurements (50-MHz system DermaScan v3 (Cortex Technology, Denmark)	Maia Campos et al., (2019) Yang B. et al., (2009) Beguin, (2005)
Dermascan V3	Ultrasound measurements (50- MHz system DermaScan v3 (Cortex Technology, Denmark)	Epidermal thickness	Lademann J et al., (2016)
13. DermaSpectrometer (Cortex technology)	The light emitting diodes in this device emit light at two distinct wavelengths: 568 nm (green) and 655 nm (blue) (red). The light reflected by the skin is measured using a photodetector. The metre on this device is based on the same optical concept as Diffey and colleagues'. For haemoglobin and melanin, it measures the absorbed and reflected light at wavelengths in the green and red, respectively. The intensity of the absorbed and reflected light at 568 and 655 nm, respectively, is used to calculate a melanin index and an erythema index. The measurement area for the skin is 6 mm in diameter (surface 0.28 cm2). Simply by weight, the probe is placed on the skin surface (3.46 cm2) (640 g). The application pressure on the skin is 158 g/cm2. A black and white calibration plate is used to calibrate the device. Measurements are taken in a discrete manner (Clarys et al., 2000; Clarys et al., 2012).	Erythema, pigmentation	Cho S et al., (2009)
14. DermaVision software	DermaVision which is a clinical version of the polarization color imaging system, was developed for routine clinical applications in dermatology (Kang et al., 2007).	Skin texture	Czajka A. et al., (2018)
15. Dermcup	An ultrasonic wave (frequency 20 MHz) was applied via an echographic device	Thickness, density	Fanian F et al., (2013)
16. DermaLab series, skinlab combo (20MHz ultrasound probe, elasticity probe, hydration probe, TEWL probe)	A multi-parameter skin analysis system	Density, firmness, hydration, TEWL, thickness, viscoelasticity	Zmitek et al., (2020) Czajka A. et al., (2018) Jenkins et al., (2014)
17. Digital image analysis	Image analysis is the extraction of meaningful information from images; mainly from digital images by means of digital image processing techniques (Solomon and Breckon, 2011).	Corneocyte size	Furumura et al., (2012)

18. Facial stage	A cutting-edge full-face camera collects digital photos in multi-spectral illumination, including genuine white light and blue light, to capture and show information on and under the skin's surface layers.	Wrinkle	Tominaga et al., (2012)
19. Histological biopsy analysis	The study of the microscopic anatomy of tissues in plants and animals is known as histological analysis. As a result, histological analysis necessitates the use of specialist equipment to prepare tissues for examination and magnify features so that they may be seen (Crowder and Dominguez, 2014).	Collagen and elastin (quantity and quality)	Jenkins et al., (2016)
20. In vitro enzyme immunoassay kits	In vitro enzyme immunoassay kits were used for the quantitative analysis of human procollagen type I, human elastin and human fibrillin-1 in the suction blister fluids (Proksch et al., 2014).	procollagen I, elastin and fibrillin (quantity)	Proksch et al., (2014)
21. Microscopy	Morphological analysis of residual skin surface components samples.	Residual skin surface components	Chalyk et al., (2017)
22. Moisture Meter SC	MoistureMeter is a novel capacitive device for measuring the hydration of stratum corneum (Alanen et al., 2004)	Hydration	Schwartz S.R. et al., (2019) Schwartz S. et al., (2016)
23. Multi-dermascope MDS 800	The multifunctional skin analyzer MSD 800 which allows measurement of skin parameters using different probes	Hydration, pigmentation, elasticity	Aguirre et al., (2017)
24. NOVA dermal phase meter 9003	The DPM 9003™ is a portable, multifunctional electronic laboratory instrument that measures skin impedance It is intended to provide a non-invasive, objective, and repeatable technique of measuring biophysical parameters and relative skin moisture (Nova Technology corporation, 2021).	Hydration	Bertuccelli G. et al., (2016) Schwartz S.R. and Park J., (2012) Skovgaard et al., (2006)
25. PRIMOS compact	PRIMOS compact is an optical 3-dimensional in vivo skin measuring system based on the stripe projection technique.	Roughness, wrinkle depth, wrinkle volume	Göllner et al., (2017) Lademann J. et al., (2016) Proksch et al., (2014)
26. Reverse transcription-polymerase chain reaction (RT-PCR)	Reverse transcription-polymerase chain reaction (RT-PCR) is a sensitive in vitro method and has a crucial role in medical science and biomaterial fields (Omidi et al., 2017).	the expression levels of key genes	Bertuccelli G. et al., (2016)
27. Reviscometer RVM 600	The Reviscometer® RVM600 that measures resonance running time (RRT) has been shown to be inversely related to the skin stiffness (Paye et al., 2007).	Viscoelasticity	Fanian F et al., (2013)
28. SDSNA	a convenient tool for evaluating skin wrinkle widths.	Wrinkle widths below the eye	Yoshikawa et al., (2014)
29. SEBU sheet	Unable to find anything	Sebum oil	Tominaga et al., (2012)
30. Skicon-200EX	The Skicon-200EX (IBS Japan) determined the hydration level of the stratum corneum by measuring electrical conductance (Clarys et al., 2012).	Hydration	Oyama A at al., (2012)

31. Skin replica analysis	The shadow produced by the relief of the wrinkle replica when light from the projecting device was illuminated was isolated. The percentage of the wrinkle area was calculated as the shadow percentage, and the maximal largest wrinkle depth was calculated as the largest area of shadow in the analysis area (10×10 mm) (Grove et al., 1991; Yin et al., 2001; Pirisinu and Mazzarello, 2016).	Wrinkle, roughness	Draelos Z.D., (2019) Hyun-Sun Yoon et al., (2016) Jenkins et al., (2014) Oyama A at al., (2012) Cho S et al., (2009) Yang B. et al., (2009) Distante et al., (2002) Murad and Tabibian, (2001)
32. Skin-Visiometer SV 600	The visiometer is a computerized instrument that uses the transmission of light to produce a microrelief of skin from a blue-colored replica. It determined 5 roughness variables: skin roughness (Rt), maximum roughness (Rm), average roughness (Rz), smoothness depth (Rp), and arithmetic average roughness (Ra). Visiometer R values decrease as the wrinkles diminish in depth (improve).	Wrinkles	Hyun-Sun Yoon et al., (2016) Cho S et al., (2009)
33. Tewameter	Tewameter TM210: quantitative measurements of TEWL	TEWL	Hyun-Sun Yoon et al., (2016) Oyama A at al., (2012)
34. Thiobarbituric acid reactive substances assay	To assess the degree of oxidative stress in the plasma sample	Oxidative stress	Chalyk et al., (2017)
35. UV-irradiation device TL20W/12RS UV lamps (Philips); UVM-57 ultraviolet lamp + a lamp simulating sunlight (Helios Italquartz srl, Milan, Italia)	A UV-irradiation device that used TL20W/12RS UV lamps (Philips) with an emission spectrum between 275 and 380 nm (peak: 310–315 nm) served as the UV source. Twelve 1×1–cm squares of skin on the buttock were irradiated in 10-mJ/cm2 increments of UV doses, and the MED was determined 24 h later. The MED was defined as the minimal UV dose that caused recognizable erythema on all 4 edges of the square	MED, erythema, pigmentation	Hyun-Sun Yoon et al., (2016) Puglia C. et al., (2014)
36. VapoMeter	VapoMeter is for measuring TEWL and evaporation rates. The VapoMeter is completely wireless and portable, and its measurements are unaffected by its orientation. The measurements take only a few seconds, and the findings are reliable and reproducible at both high and low evaporation levels. Franz cell adapters are available for in-vitro research in a variety of sizes (Delfin Technologies, 2021).	TEWL	Schwartz S.R. et al., (2019)
37. Visia-CR imaging system	Facial imaging system for clinical research with fast capture times and lighting modes designed to enhance the visualization of skin features, VISIA-CR is the standard in repeatable clinical imaging (Canfield, 2021).	Roughness, wrinkle (depth), brown spot intensity	Bertuccelli G. et al., (2016)
38. VisioFace digital photography imaging system + VisioFace CSI software	Photography+software analysis logarithms that automatically identified and quantified wrinkles.	Wrinkle area fraction (wrinkle area divided by the assessment area) of periorbital wrinkles; pores	Zmitek et al., (2020) Maia Campos et al., (2019)

39. Visioscan VC98 system + a b/w CCD camera	The Visioscan® VC 98 USB is a high-resolution UVA-light video camera for studying the skin surface directly. The photos are quite amazing in terms of displaying the structure of the skin as well as the amount of dryness. A high-resolution b/w video sensor and a ring-shaped UV-filter are included in the camera. A source of light that illuminates the skin uniformly (Courage & Khazaka, 2021)	Skin surface evaluation (surface, entropy, contrast, circular roughness)	Fanian F. et. al., (2013) Babizhayey M.A. et al., (2012) Beguin, (2005)
40. Subjective assessment	Expert evaluation and/or Self-assessment questionnaire		Laing et al., (2020) Zmitek et al., (2020) Draelos Z.D., (2019) Schwartz S.R. et al., (2019) Czajka A. et al., (2018) Aguirre et al., (2017) Bertuccelli G. et al., (2016) Dumoulin et al., (2016) Fanian F. et. al., (2013) Furumura et al., (2012) Schwartz S.R. and Park J., (2012) Cho S et al., (2009) Skovgaard et al., (2006) Distante et al., (2002) Rigano et al., (2001)

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