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Review Article

Gold Nanoparticles with Natural Ingredients as Anti-Aging: A Systematic Review

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ABSTRACT

Aging is a natural process characterized by physiological skin changes. It starts to appear when individuals are in their thirties, making it necessary to use anti-aging products with natural ingredients which are safe even though the penetration is relatively low into the skin. Natural ingredients that can be used are antioxidants that can inhibit aging and can act as bioreductants on gold nanoparticles. Gold nanoparticles can increase penetration into the target cells because of their small size with large surface area. This review article aimed to collect data relating to the development of gold nanoparticles with natural ingredients as anti-aging agents. This review searched through the PubMed and ScienceDirect databases with such keywords as aging, anti-aging, plant extract, antioxidants, and gold nanoparticles. The inclusion criteria were articles in English, available in a full-text version, and published in the last 10 years. Research on the use of natural ingredients as anti-aging agents found that natural ingredients perform better than chemical comparators. Gold nanoparticles are also reported to have been widely used in anti-aging products. Their activity is even better given the low IC_{50} value and a higher percentage of inhibition compared to those of the extracts without nanoparticle modification. It is reported that gold nanoparticles with natural ingredients as anti-aging agents have a better effect as opposed to purely natural ingredients.

INTRODUCTION

Wrinkles and black spots often appear as a sign of aging and are induced by both intrinsic and extrinsic factors (Tobin, 2017). Intrinsic aging of the skin occurs as a natural consequence of physiological and genetic changes in all of a person's tissues (Sanches Silveira and Myaki Pedroso, 2014). Extrinsic aging of the skin comes from ultraviolet (UV) light exposure (Rittie and Fisher, 2015; Koohgoli *et al.*, 2017). The oxidative metabolism in mitochondria accumulates reactive oxygen species (ROS) from UV irradiation and it makes the process of aging accelerated (Kammeyer and Luiten, 2015; Onyango *et al.*, 2016). An antioxidant is a chemical compound which can overcome ROS. Therefore, the activity of antioxidants is used in an anti-aging cosmetic product. Based on literature, the activity of such antioxidants as polyphenols, flavonoids, anthocyanins, and gallic acid can overcome ROS (Stojiljković, Pavlović and Arsić, 2014; Lee *et al.*, 2019). Anti-aging products from natural ingredient extracts have been developed, but the penetration into the skin is very low (Nowak *et al.*, 2021). One of the methods to overcome this is by using gold nanoparticles (Armendáriz-Barragán *et al.*, 2016).

Gold nanoparticles are inert, highly stable, biocompatible, and non-cytotoxic, and they can easily travel to the target cells due to their small size with large surface area, shape, and crystallinity (Yeh *et al.*, 2012; Verma *et al.*, 2014). Two basic approaches are commonly used in the particles using suitable equipment (Onaciu *et al.*, 2019; Slepička *et al.*, 2019). The nanoparticles synthesized might potentially be harmful to the environment and living organisms (Kim *et al.*, 2016). Toxicity testing also needs to be conducted to ensure that nanoparticles are safe considering that various factors such as size, dose, shape, and route of administration can affect the toxicity of nanoparticles (Adewale *et al.*, 2019; Fan *et al.*, 2020). Until now, research on the toxicity of nanoparticles is still limited, so it is highly recommended to conduct a thorough toxicity test during the nanoparticle manufacturing stage (Adewale *et al.*, 2019). Accordingly, it is necessary to develop a new method to overcome this problem. The green synthesis method is known to be more environmentally friendly and has a relatively low cost. The use of natural materials in this method can act as a reducing agent and stabilizer in the synthesis of gold nanoparticles. This material also has a lower toxicity effect so it is safer to use. The synthesis of gold nanoparticles from plant extract is a rather simple and easy process to produce nanoparticles on a large scale as opposed to the bacteria and fungi-mediated synthesis (Jha *et al.*, 2009; Malik *et al.*, 2014; Singh *et al.*, 2018).

Previous research into the anti-aging property of gold nanoparticles has been done on fibroblast cells and human skin explants, which have been shown to give protection to cells from cellular aging due to UVA irradiation by reducing the intracellular ROS production (Jun *et al.*, 2020). Existing review journals focus on the selection of excipients for nanocosmetic formulations, but until this review was written there had been no journal reviews related to natural compounds and/or nanogold with natural compounds as anti-aging agents. The review focuses on natural compounds reported as having an anti-aging activity and an application of gold nanoparticles of plant extracts as anti-aging agents which have proved to protect skin from UV irradiation in a reverse aging process in the literature before being applied on test objects. It provides a summary of research related to natural compounds that have been reported to have anti-aging activity and their differences when formulated into gold nanoparticles.

METHODS

Data Collection Strategy

The articles used in this review were published within the last 10 years. In this review, articles in PubMed and ScienceDirect databases were searched and collected with some keywords, including *aging*, *anti-aging*, *plant extract*, *antioxidant*, and *gold nanoparticle*. In the PubMed database, an advanced facility was used to combine the keywords in Boolean search strategies with "AND" and "OR". In the ScienceDirect database, articles were searched using filter article type narrowed to review articles and research articles.

Selection Criteria

The inclusion criteria of this review were English articles, full-text publications, and articles in the last 10 years. The discussion of the articles included *gold* nanoparticles, *plant* extract, and *anti-aging*. The exclusion criterion was studies conducted without the 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) methods.

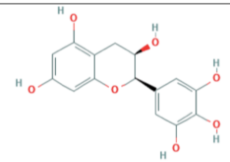
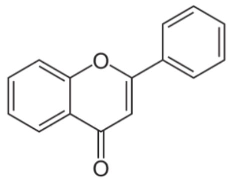
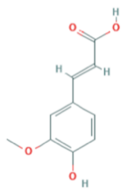
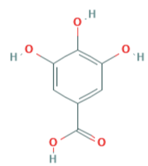
RESULTS AND DISCUSSION

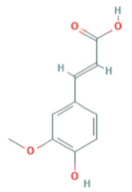
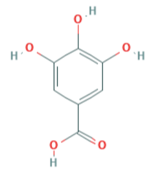
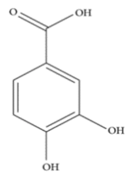
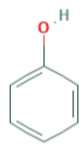
Natural Ingredients Used as Anti-Aging Agents

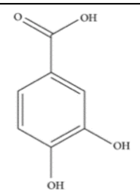
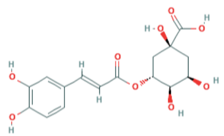
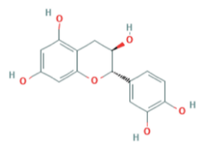
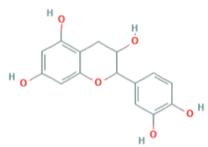
Natural ingredients are natural sources derived from plants containing active compounds which have an anti-aging activity obtained through the synthesis of collagen production. Anti-aging will reduce free radicals and modulate enzymes involved in the aging process. The biological activity of natural ingredients as anti-aging agents is summarized in Table 1.

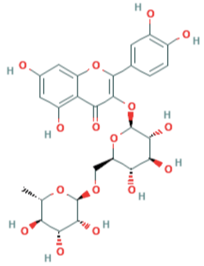
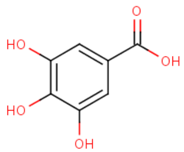
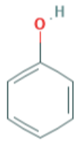
Antioxidants play a role in reducing the oxidative process and harmful effects of ROS in the human body (Gocer *et al.*, 2013; Cakmakci *et al.*, 2015). Some scientific studies have demonstrated that antioxidants are useful in the health sector with one of the benefits being the ability to delay the aging process (Sindhi *et al.*, 2013). Phenolic compounds can be classified as natural antioxidants (Shahidi and Ambigaipalan, 2015). Meanwhile, DPPH is often used to evaluate antioxidant activities and determine the antioxidant potential of phenolic compounds (Gulcin *et al.*, 2002; Gülçin *et al*, 2005; Roginsky and Lissi, 2005; Gulcin, 2020). In general, the result is reported in IC_{50}, which represents the amount of antioxidant required to reduce 50% of the free radicals, and in percent inhibition which describes the ability of antioxidants to inhibit free radical activities. The IC_{50} parameter is derived from biochemistry to characterize the ability of several substrates to inhibit enzyme activities. Meanwhile, the percent inhibition parameter is obtained from the difference in absorption between the control absorbance and the sample absorbance measured by UV-Vis parameters.

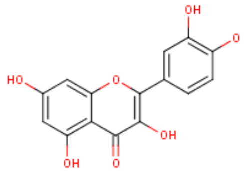
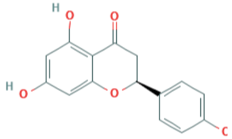
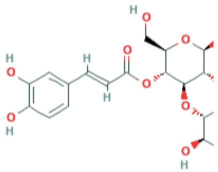
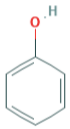
Table 1. Biological Activities of Natural Ingredients as Anti Aging Agents

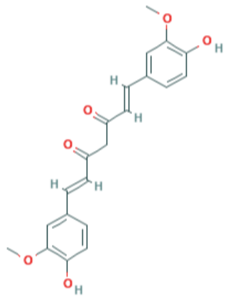
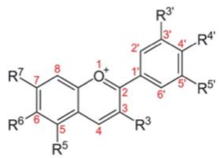
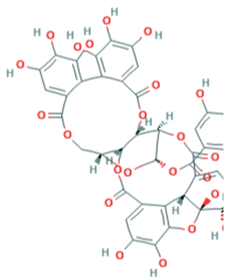
Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Tamarindus indica	Epigallocatechin		Ethanol	Inhibits collagenase activity	IC_{50} 1,44 ± 0.01 µg/mL	Vitamin C IC_{50} 3.40 ± 0.02 µg/mL	NHDF cell / 0.05; 0.01; 0007 mg/mL	-	(Lourith *et al.*, 2017)
Cecropia obtusa	Flavonoids		Ethanol	Regulates IL-6 expression	IC_{50} 1,63 µg/mL	-	NHDF cell / 5 dan 20 µg/mL	-	(Alves *et al.*, 2019)
Nephelium lappaceum	Ferulic Galic acid	 	Ethanol	Inhibits collagenase activity	IC_{50} 1.86 ± 0.06 µg/mL	Vitamin C IC_{50} 3.40 ± 0.02 µg/mL	NHDF cell / 0.05; 0.01; 0.007 mg/mL	-	(Lourith *et al.*, 2017)

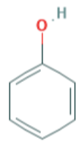
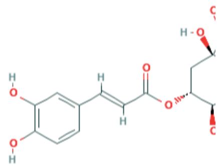
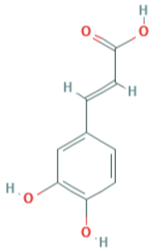
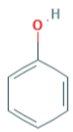
Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Litchi chinensis	Ferulic		Ethanol	Inhibits collagenase activity	IC_{50} 2,29 ± 0.06 µg/mL	Vitamin C IC_{50} 3,40 ± 0,02 µg/mL	NHDF cell / 0.05; 0.01; 0.007 mg/mL	-	(Lourith *et al.*, 2017)
	Galic acid								
Prunus domestica L.	Protocatechuic acid		N.a	Inhibits collagenase activity	IC_{50} 8,73 ± 0.47 µg/mL	Vitamin C Trolox (80%)	NHDF cell / 50 µg/mL	-	(Shin *et al.*, 2020)
Cleistocalyx nervosum	Fenolic		Hot water, methanol, chlorofor m	Inhibits collagenase activity	IC_{50} 0,01 ± 0.005 mg/mL	Ascorbic acid IC_{50} 0.04 ± 0.02 mg/mL	NHDF cell / 0.0001-1 mg/mL	-	(Manosroi *et al.*, 2015)

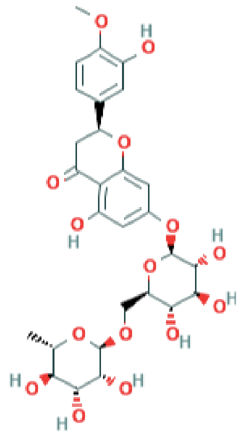
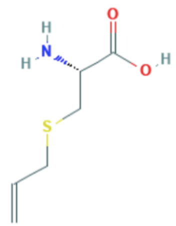
Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Nypa fruticans wurmb	Protocatechuic acid		Ethanol	Inhibits the AP-1 pathway	IC_{50} 17,99 ± 1.63 & 10.78 ± 0.63 µg/mL	Ascorbic acid IC_{50} 4.79 ± 0.52 µg/mL	HaCaT cell / 1; 3; 10; 30 µg/mL	Balb/c mice (20–22 g) aged 7 weeks / 150 µL	(Choi *et al.*, 2020)
	Chlorogenic acid								
	Catechins								
	Epicatechin								

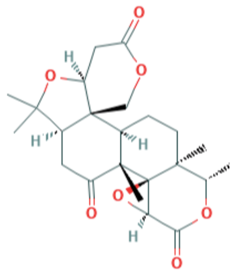
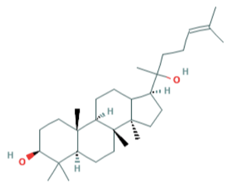
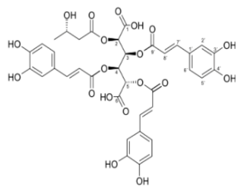
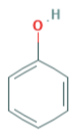
Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Salvia officinalis	Rutin		Petroleum ether, chlorofor m, methanol	Inhibits collagenase activity	IC_{50} 24.65 µg/mL	Ascorbic acid IC_{50} 20.10 µg/mL	-	Female Swiss albino mice, weighing 15-25 g / 5% at 100 µg/cm^2	(Khare, Upmanyu *and* Jha, 2019)
Alchemilla mollis	Galic acid		Ethanol	Regulates IL-6 expression and TGF-β, Nrf2 activation	IC_{50} 42,4 µg/mL	Vitamin C	NHDF cell / 1; 10; 100 µg/mL	Tikus jantan hairless HR-I umur 6 minggu / 0.1 dan 1%	(Hwang *et al.*, 2018)
Prunella vulgaris L.	Fenolic		Ethanol	Inhibits the AP-1 pathway	IC_{50} 46 µg/mL	Arbutin IC_{50} 93.64 µg/mL	NHDF cell / 1; 10; 100 µg/mL	-	(Zhang *et al.*, 2018)

Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Pterocarpus santalinus L.	Quercetin		Ethanol	Inhibits the AP-1 pathway, regulates IL-6, and Nrf2, TGF-β activation	IC_{50} 46,55 µg/mL	Arbutin	NHDF cell / 10 µM	-	(Gao, Lin, Hwang, *et al.*, 2018)
	Naringenin								
Orovanche cernua	Acteoside		Ethanol	Regulates IL-6, and Nrf2, TGF-β activation	IC_{50} 56,28 µg/mL	Arbutin	HDF cell / 100 µg/mL	-	(Gao, Wang, Qu, *et al.*, 2018)
Sambucus nigra L.	Fenolic		Ethanol	Regulates IL-6, and Nrf2, TGF-β activation	IC_{50} 59,0 µg/mL	Arbutin	HaCaT cell / 1; 10; 100 µg/mL	-	(Lin *et al.*, 2019)

Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Curcuma heyneana	CUR		Ethanol	Inhibits collagenase activity	IC_{50} 60,08 + 1.17 µg/mL	Trolox	-	Forty male rats (ICR), aged 3 months and weighing 150-200 g / -	(S. Shin *et al.*, 2020)
	Anthocyanidin								
Rubus idaeus L.	Ellagitannins		Ethanol	TGF-β activation and Inhibits the AP-1 pathway	IC_{50} 64.03 µg/mL	Ascorbic acid	NHDF cell / 1; 10; 100 µg/mL	-	(Gao *et al.*, 2018)

Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Cassia fistula	Fenolic		Ethanol	Inhibits collagenase activity	IC_{50} 70 µg/mL	Vitamin E IC_{50} 72 µg/mL	HDF cell / 0-150 µg/mL	-	(Limtrakul *et al.*, 2016)
Helianthus annuus L.	Chlorogenic acid		Ethanol	TGF-β activation and Inhibits the AP-1 pathway	IC_{50} 72.65 µg/mL	Arbutin	NHDF cell / 1; 10; 100 µg/mL	-	(Hwang *and* Gao, 2018)
	Caffeic acid								
Thunbergia laurifolia	Fenolic		Ethanol	Inhibits collagenase activity	IC_{50} 89 ± 1 µg/cm³	Ascorbic acid IC_{50} 4.4 ± 0.3 µg/cm³	3T3 cell / -	-	(Chaiyana *et al.*, 2020)

Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Citrus unshiu	Hesperidin		Ethanol	Regulates IL-6	IC_{50} 788,46 ± 0.45 μg/mL	-	HDF cell / 1; 2,5; 5; 10 μg/mL	Seven-week old female HR-1 hairless mice / 50, 100, 200 mg/kg	(Choi *et al.*, 2017)
Allium stivum	S-allyl cysteine		Ethanol	Regulates IL-6	IC_{50} 2.50 mg/mL	-	HaCaT cell / 50 dan 100 μg/mL	-	(Kim, 2016)

Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Lansium domesticum	Limonoid		Hot water, methanol, chlorofor m	Inhibits collagenase activity	IC_{50} 5,40 ± 1.23 mg/mL	Ascorbic acid IC_{50} 0.08 ± 0.02 mg/mL	NHDF cell / 0.001-10 mg/mL	-	(Manosroi *et al.*, 2012)
Panax ginseng	Ginsenosides		Methanol	Inhibits the AP-1 pathway and TGF-β activation	IC_{50} 6,96 ± 0.43 mg/g	Ascorbic acid	HDF cell / 12.5; 25; 50 µg/mL	-	(Heo *et al.*, 2021)
Leontopodium vivale	Leontopodic acid A 3,5-dicaffeoylquinic acid (LACCE)		Ethanol	Inhibits collagenase activity	Percent inhibition 20.4%	Vitamin C 14.05 %	Detroit 551 cell / 0.1; 0.5; 1%	-	(Cho *et al.*, 2020)
Gastrodia elata	Fenolic		H_2O deionizati on	Inhibits the AP-1 pathway and Nrf2 activation	Percent inhibition 34.2%	Galic acid 89.5%	HDF cell / 0.2-2 mg/mL	-	(Song *et al.*, 2016)

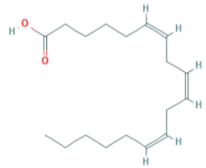
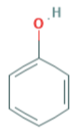
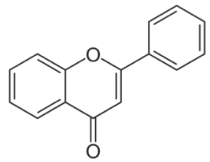
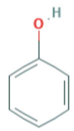
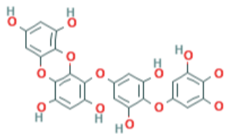
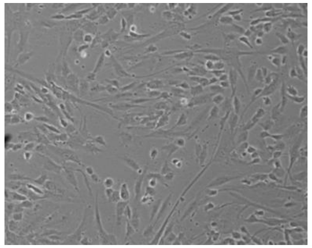
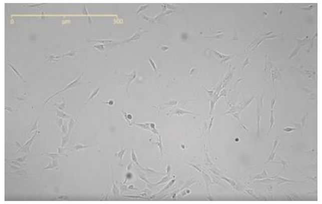
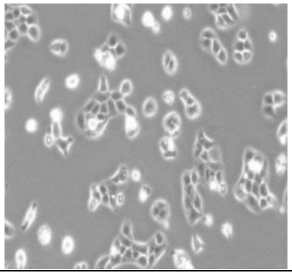
Natural Ingredients	Bioactive Compounds	Structure	Solven	Mechanism	Aging Activity	Positive Control	Experiment/Dose		Ref
							In Vitro	*In Vivo*	
Borage officinalis L.	Linolenic γ-acid		Ethanol	Inhibits the AP-1 pathway, regulates IL-6, and Nrf2, TGF-β activation	Percent inhibition 49.8%	Arbutin	NHDF cell / 1-100 µg/mL	Six-week-old male hairless mice (SKH: HR-1) (22-24 g) / 1%	(Seo *et al*., 2018)
Eucalyptus globulus	Fenolic		Ethanol	TGF-β activation and Inhibits the AP-1 pathway	Percent inhibition 65%	Arbutin	NHDF cell / 100 µg/mL	Six-week-old female hairless mice (SKH:HR-1) (29–34 g) / 1 and 5%	(Park *et al*., 2018)
Hibiscus sabdariffa	Flavonoids		Ethanol	Inhibits collagenase activity	Percent inhibition 77.7 ± 19.57%	Vitamin C 95.14 ± 0.07%	Hs68 cell / 0.1 and 1 mg/mL	-	(Li *et al*., 2020)
Camellia sinensis	Fenolic		Distilled water	Nrf2 activation	Percent inhibition 79.85 ± 3.38%		HaCaT cell / 10; 30; 100 µg/mL	-	(Zhao, Alam *and* Lee, 2018)
Ecklonia stolonifera	Phlorotannin		Ethanol	Inhibits the AP-1 pathway	Percent inhibition 80%	-	HDF cell / 25; 50; 100 µg/mL	Zebra fish / 25; 50; 100 µg/mL	(Kuda, 2016; Wang *et al*., 2020)

Table 2. Cell Types in Collagenase Activity Testing

Cell Type	Image	Culture	Morphology	Advantages	Ref
NHDF		Human fibroblast	Spindle- shaped, cells are bipolar and refractile	Relatively easy to obtain, can be easily propagated for long periods of time without genetic manipulation, only stored in liquid nitrogen for years, consist of mitotic, can retain genetic stability for 15–20 passages, and cost-effective experimental model	(ATCC, 2021; Shin *et al.*, 2020; Hwang *et al.*, 2018; Park *et al.*, 2018; Song *et al.*, 2016; Hänzelmann *et al.*, 2015; Vangipuram *et al.*, 2013; Auburger *et al.*, 2012)
Hs68		Human fibroblast	Spindle- shaped, cells are bipolar and refractile	N.a	(ATCC, 2021; Li *et al.*, 2020)
HaCaT		Human fibroblast	Cobblestone appearance, cells are rounded, not flat	Dense and easily differentiated cells	(ATCC, 2021; Christopher Gabbott and Tao Sun, 2018; Kim, 2016; Wilson, 2013)

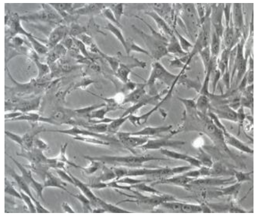
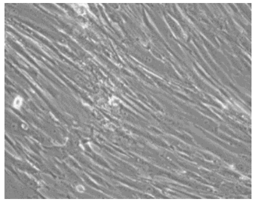
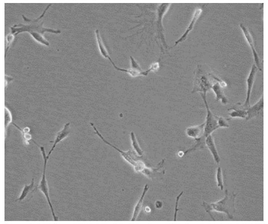
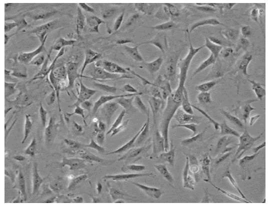
Cell Type	Image	Culture	Morphology	Advantages	Ref
Detroit 551	 	Human fibroblast	Spindle- shaped, cells are bipolar and refractile	N.a	(ATCC, 2021; Cho *et al.*, 2020)
3T3-L1	 	Mouse embryo	Spindle- shaped, cells are bipolar and refractile	N.a	(ATCC, 2021; Chaiyana *et al.*, 2020)

Table 3. Application of Gold Nanoparticles with Natural Ingredients as Anti-aging

Natural Ingredients	Bioactive Compounds	Result	Toxicity	Ref
Hubertia ambavilla	Flavonoid	The IC_{50} value for antioxidant activity of GAuNP was found to be 9.25 g/mL	There was no change in cell morphology and a decrease in NR uptake in the dose range of 0.32-1000 g/mL. This indicates that there is no toxicity	(Ben Haddada *et al.*, 2020)
Panax ginseng	Ginsenosides	The IC_{50} value for antioxidant activity of GBAuNP was found to be 1,96 µg/mL	There was no change in cell morphology in the dose range 1-100 g/mL. This indicates the absence of toxicity	(Jiménez Pérez *et al.*, 2017)
Ecklonia stolonifera	Phlorotannin	ES-GNPs inhibiting the SA-β-galactosidase activity, reducing intracellular ROS production, lysosome content, and inhibiting G1 arrest and senescence related proteins	Does not show any toxicity up to a dose of 200 g/mL	(Jun *et al.*, 2020)

A lower IC_{50} value and higher percent inhibition value indicate good antioxidant efficiency (Roginsky and Lissi, 2005; Cakmakcı *et al.*, 2019; Oztaskin *et al.*, 2019; Eruygur *et al.*, 2019).

Based on Table 1, the natural extract that has the most active antioxidant activity with a lower IC_{50} in stimulating collagen production as an anti-aging agent is *Tamarindus indica*. Meanwhile, the extract of natural ingredients with the most active percent inhibition of free radical activity to stimulate collagen production as an anti-aging is *Leontopodium vivale*. The positive control used as a comparison to determine collagenase activity is vitamin C. The mechanism of collagen production is summarized in Figure 1.

Most of the compounds reported having anti-aging activities are polyphenols. Polyphenols can precipitate the proline-rich protein through covalent and hydrogen bonding. Collagen with high proline has a high affinity toward polyphenols. It has been reported that polyphenols enhance the activity of proline hydroxylase, and therefore it can improve the biosynthesis process of collagen (Castellan *et al.*, 2010; Shavandi *et al.*, 2018).

Polyphenols can act as antioxidants in their reduced form or prooxidants in the oxidized form (Tuominen, 2013). In this review, the antioxidant activity of polyphenols works in an oxidized form through the formation of reactive phenoxyl radicals. The two hydrogen bonds have a function to control and inhibit collagenase activities (Velmurugan *et al.*, 2014). The mechanism of polyphenol is summarized in Figure 2.

The experiment to determine collagenase activities can be conducted through *in vitro* and *in vivo* assays. *In vitro* assay is generally performed on fibroblast cells. Fibroblasts are a heterologous cell type that contributes to the imbalance between the extracellular matrix (ECM) protein synthesis and degradation (Foote *et al.*, 2019). These cells are usually obtained from human or animal skin cell cultures. The types of cells used to determine collagenase activities are summarized in Table 2.

Based on Table 2, each cell type has different characteristics adapted to the needs of the study. However, in this review article, most of the tests were done using the results of fibroblast cell culture, including NHDF cells, HaCaT cells, and Detroit 551 cells. The results of fibroblast cell culture were able to show changes in the molecular mechanisms of skin aging. In aged skin, fibroblast attachment is impaired due to progressive ECM degradation, resulting in fibroblast size reduction, decreased elongation, and collapsed morphology (Varani *et al.*, 2006; Fisher, Varani and Voorhees, 2008; Fisher *et al.*, 2009; Quan *et al.*, 2013; Fisher *et al.*, 2016; Shin *et al.*, 2019).

Testing of collagenase activity can also be conducted by *in vivo* assay. The object used in this test is mice (HR-I/ICR). Human and mouse skin cells have similarities in the dermis and epidermis layers, thus enabling them to provide results that are insignificantly different. Research that has been done generally uses male and female mice. Both of them have a difference in, for instance, mice dermis which is thicker and 40% firmer in male subjects compared to in females. The epidermis on the other hand is thicker in females than in males. Mice are the most commonly used animal model since they are easy to handle and maintain, reproduce rapidly, and are economically accessible. They can be standardized by age, sex, history, and genetic predisposition, and they allow the use of a relatively high number of animals for statistical validation (Wong *et al.*, 2011; Abdullahi, Amini-Nik and Jeschke, 2014; Gerber *et al.*, 2014; Zomer, 2018).

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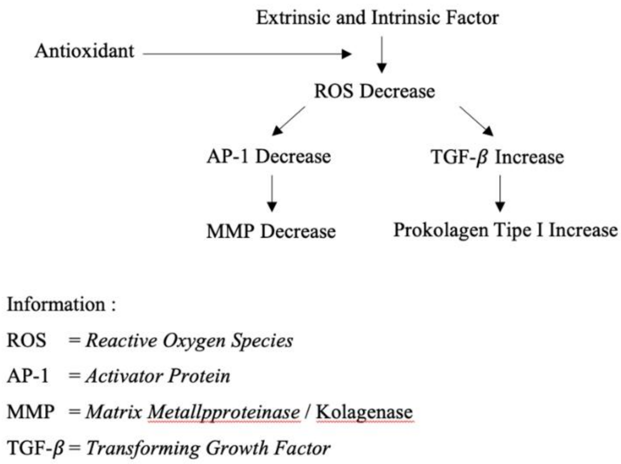

Figure 1. The mechanism of collagen production

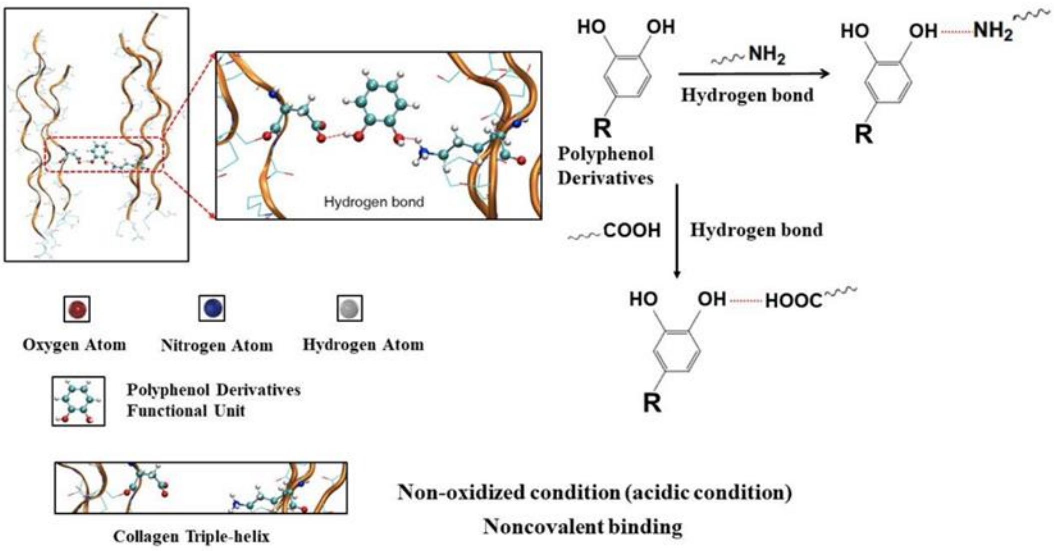

Figure 2. The mechanism of polyphenol (Wu *et al.*, 2019)

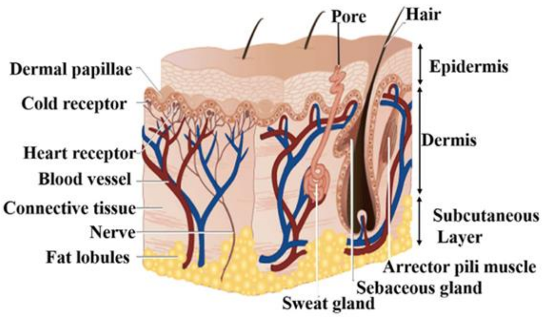

Figure 3. Skin Structure
(Nafisi and Maibach, 2018)

Meanwhile, the fish model is suitable for studies of aging because they have a number of biomarkers, such as lipofuscin, SA-β-gal, and permeability on Smurf dye, which have been validated to be associated with aging (Kishi *et al.*, 2003; Kishi, 2004; Kishi *et al.*, 2008; Martins *et al.*, 2018). Studies demonstrate that a decline in physiological conditions reflects an aging process (Keller and Murtha, 2004; Gilbert, Zerulla and Tierney, 2014). In addition, the entire genome has been translated using technology in the form of effector nuclease (TALEN) for manipulating and editing the fish genome (Taylor *et al.*, 2001; Mitani *et al.*, 2006; Kawakami, 2007; Kwan *et al.*, 2007; Takeda, 2008; Bedell *et al.*, 2012; Huang *et al.*, 2013; Zu *et al.*, 2013; Auer and Del Bene, 2014). Finally, several genetic mutants or transgenic models displaying accelerated aging phenotypes have been created (Kishi *et al.*, 2008; Koshimizu *et al.*, 2011; Anchelin *et al.*, 2013; Liang *et al.*, 2019). All of these traits make the zebrafish possible to use in the study of the biological functions of specific aging-associated genes in greater details. A freshwater vertebrate with a complement of genes is very similar to mammals, has rapid development of embryos, is transparent thereby allowing visual inspection of internal organs, is easy to breed with a large number of embryos and larvae, has easy manipulation of gene expression with a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) tool, and has a facile and cost-efficient system for large-scale screening (Auer and Del Bene, 2014; Li and Uitto, 2014)

Development of Gold Nanoparticles with Natural Ingredients

Gold nanoparticles (AuNPs) have been widely developed in the industrial field. However, the application of AuNPs as anti-aging agents remains limited. There are only three research articles that discuss the development of natural extract AuNPs as anti-aging agents which are summarized in Table 3. The characteristic earmarked for AuNPs is their size range of 1–100 nm (Kumar and Liang, 2011; Sharma *et al.*, 2019; Singh, Kumar and Das, 2019). Nanoparticles by virtue of their small particle size are more effective than bulk pigments in absorbing and scattering UV light (Morabito *et al.*, 2011). The particle size of AuNPs has been demonstrated to play an important role in toxicity and distribution assessments (Iswarya *et al.*, 2016; Li *et al.*, 2018). Particles with a smaller size can cause greater toxicity (Lopez-Chaves *et al.*, 2018; Khan and Saeed, 2019).

AgNPs, TiO_2NPs, and ZnONPs have been widely developed in the field of dermatology. TiO_2NP and ZnONPs are only detected on the outermost layer of the stratum corneum (Iavicoli, Leso and Bergamaschi, 2012; Raju *et al.*, 2018), while AuNPs have a better penetration depth into the dermis layer (Nafisi and Maibach, 2018). Stratum corneum is the main skin layer into which nanoparticles should penetrate (Filipe *et al.*, 2009; Liu *et al.*, 2012). AgNPs are toxic to numerous organisms, mammalian cells, and humans (Das *et al.*, 2018). The cytotoxicity of AgNPs is associated with the relaxed oxidation of Ag^+ ions, which is toxic to cells, leading to toxicity and harm to DNA (Gliga *et al.*, 2014; Yaqoob *et al.*, 2020). Based on research by Jiang *et al.*, nanorods with a size of 10 nm show greater toxicity compared to other forms because they are able to cluster inside the cells, leading to cell death (Connor *et al.*, 2005; Jiang *et al.*, 2010; Woźniak *et al.*, 2017).

Based on Table 3, the gold nanoparticles of *Panax ginseng* extract (GBAuNPs) (1.96 g/mL) have a better antioxidant activity when compared to *Panax ginseng* (6.96±0.43 mg/g). In addition, the gold nanoparticles of *Ecklonia stolonifera* extract (ES-GNPs) show no toxicity up to a dose range of 200 g/mL when compared to *Ecklonia stolonifera* which is only limited to a dose range of 100 g/mL. GBAuNPs and ES-GNPs show better effectiveness when compared to purely natural ingredients that have not been modified with gold nanoparticles. While research on *Hubertia ambavilla* as an anti-aging agent has never been done before, there is only research on gold nanoparticles of *Hubertia ambavilla* extract (GAuNPs) to date. In addition, the three studies indicate no toxicity as evidenced by the absence of changes in cell morphology and a decrease in NR uptake. The Neutral Red Uptake (NRU) phototoxicity test is used to identify the phototoxic potential of a test chemical activated by exposure to a light (OECD, 2019). These results indicate that natural extract AuNPs are promising for application in anti-aging products.

CONCLUSION

The effectiveness of anti-aging can be identified by a large number of collagens in the cells. It is proven by the inhibition of collagenase activity and increasing synthesis of collagen production, either *in vivo* or *in vitro* methods. Anti-aging agents from plant extracts developed with gold nanoparticles can penetrate the skin better than natural ingredients. Therefore, the use of natural compounds in the form of nanogold is highly recommended for the development of anti-aging cosmetics.

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