

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 IC₅₀ 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; Slepíčka *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.

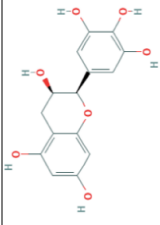
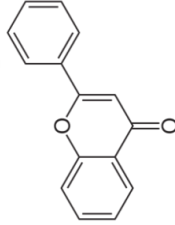
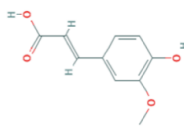
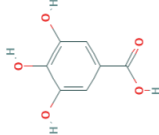
RESULTS AND DISCUSSION

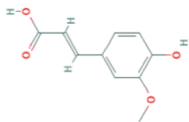
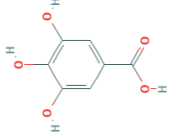
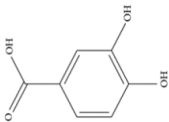
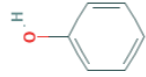
Natural Ingredients Used as Anti-Aging Agents

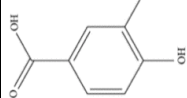
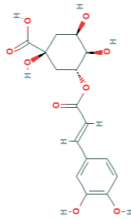
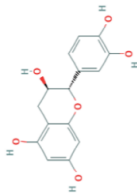
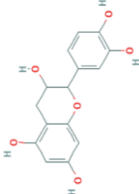
Natural ingredients are natural sources derived from plants containing active compounds which have an anti-aging activity obtained through the synthesis of collagen production. Anti-aging will reduce free radicals and modulate enzymes involved in the aging process. The biological activity of natural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

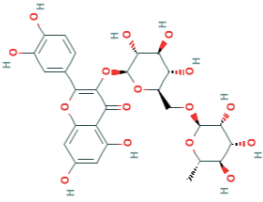
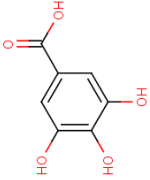
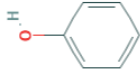
Antioxidants play a role in reducing the oxidative process and harmful effects of ROS in the human body (Gocer *et al.*, 2013; Cakmakci *et al.*, 2015). Some scientific studies have demonstrated that antioxidants are useful in the health sector with one of the benefits being the ability to delay the 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 IC₅₀, 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 IC₅₀ 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.

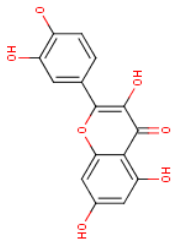
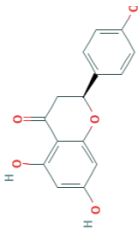
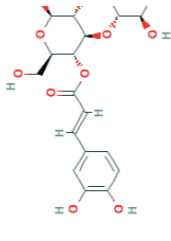
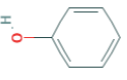
Table 1. Biological Activities of Natural Ingredients as Anti Aging Agents

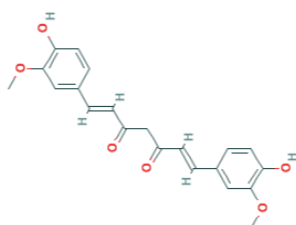
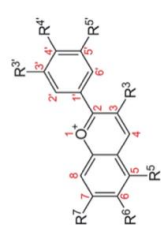
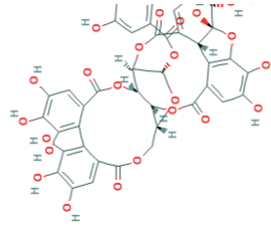
Natural Ingredients	Bioactive Compounds	Structure	Solvent	Mechanism	Aging Activity	Experiment/Dose		Ref
						Positive Control	In Vitro	
<i>Tamarindus indica</i>	Epigallocatechin		Ethanol	Inhibits collagenase activity	IC ₅₀ 1.44 ± 0.01 µg/mL	Vitamin C IC ₅₀ 3.40 ± 0.02 µg/mL	NHDF cell / 0.05; 0.01; 0.007 mg/mL	(Lourith <i>et al.</i> , 2017)
<i>Cecropia obtusa</i>	Flavonoids		Ethanol	Regulates IL-6 expression	IC ₅₀ 1.63 µg/mL	-	NHDF cell / 5 dan 20 µg/mL	(Alves <i>et al.</i> , 2019)
<i>Nephelium lappaceum</i>	Ferulic		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 <i>et al.</i> , 2017)
	Galic acid							

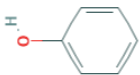
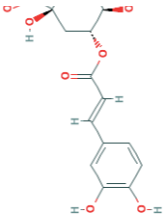
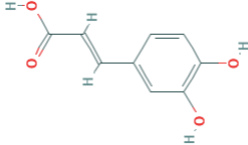
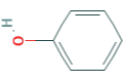
Natural Ingredients	Bioactive Compounds	Structure	Solvent	Mechanism	Aging Activity	Positive Control		Experiment/Dose		Ref
						Control		In Vitro	In Vivo	
<i>Litchi chinensis</i>	Ferulic		Ethanol	Inhibits collagenase activity	IC ₅₀ 2.29 ± 0.06 µg/mL	Vitamin C IC ₅₀ 3.40 ± 0.02 µg/mL	-	NHDF cell / 0.05; 0.01; 0.007 mg/mL	-	(Lourith <i>et al.</i> , 2017)
										
<i>Prunus domestica</i> 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 <i>et al.</i> , 2020)
<i>Cleistanthus nervosum</i>	Phenolic		Hot water, methanol, chloroform	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 <i>et al.</i> , 2015)

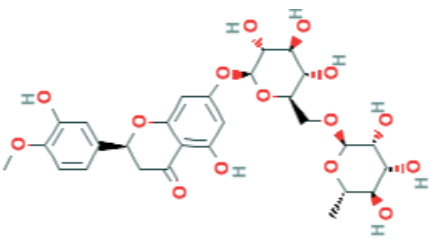
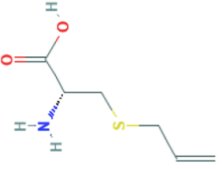
Natural Ingredients	Bioactive Compounds	Structure	Solvent	Mechanism	Aging Activity	Positive		Experiment/Dose		Ref
						Control	In Vitro	In Vivo		
	Protocatechuic acid									
	Chlorogenic acid									
<i>Nyssa fruticans wurmb</i>	Catechins		Ethanol	Inhibits the AP-1 pathway	IC ₅₀ 17.99 ± 1.63 & 10.78 ± 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 <i>et al.</i> , 2020)	
	Epicatechin									

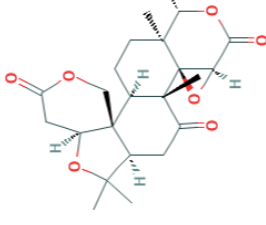
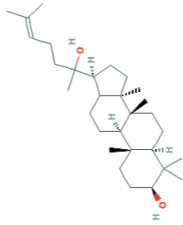
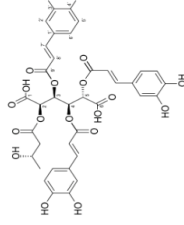
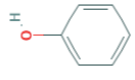
Natural Ingredients	Bioactive Compounds	Structure	Solvent	Mechanism	Aging Activity	Experiment/Dose		Ref
						Positive Control	In Vitro / In Vivo	
<i>Salvia officinalis</i>	Rutin		Petroleum ether, chloroform, methanol	Inhibits collagenase activity	IC ₅₀ 24.65 µg/mL	Ascorbic acid IC ₅₀ 20.10 µg/mL	- Female Swiss albino mice, weighing 15-25 g / 5% at 100 µg/cm ²	(Khare, Upmanyu and Jha, 2019)
<i>Alchemilla mollis</i>	Galic acid		Ethanol	Regulates IL-6 expression and TGF-β1 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)
<i>Prunella vulgaris</i> 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	Solvent	Mechanism	Aging Activity	Experiment/Dose		Ref
						Positive Control	In Vitro / In Vivo	
<i>Pterocarpus santalinus</i> L.	Quercetin		Ethanol	Inhibits the AP-1 pathway, regulates IL-6, and Nrf2, TGF- β activation	IC ₅₀ 46,55 μ g/mL	Arbutin	NHDF cell / 10 μ M	(Gao, Lin, Hwang, <i>et al.</i> , 2018)
	Naringenin							
<i>Orovanche cernua</i>	Acteoside		Ethanol	Regulates IL-6, and Nrf2, TGF- β activation	IC ₅₀ 56,28 μ g/mL	Arbutin	HDF cell / 100 μ g/mL	(Gao, Wang, Qu, <i>et al.</i> , 2018)
<i>Sambucus nigra</i> L.	Phenolic		Ethanol	Regulates IL-6, and Nrf2, TGF- β activation	IC ₅₀ 59,0 μ g/mL	Arbutin	HaCaT cell / 1; 10; 100 μ g/mL	(Lin <i>et al.</i> , 2019)

Natural Ingredients	Bioactive Compounds	Structure	Solvent	Mechanism	Aging Activity	Experiment/Dose		Ref
						Positive Control	In Vitro / In Vivo	
<i>Curcuma heyneana</i>	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 <i>et al.</i> , 2020)
	Anthocyanidin							
<i>Rubus idaeus L.</i>	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 <i>et al.</i> , 2018)

Natural Ingredients	Bioactive Compounds	Structure	Solvent	Mechanism	Aging Activity	Experiment/Dose		Ref
						Positive Control	In Vitro / In Vivo	
<i>Cassia fistula</i>	Fenolic		Ethanol	Inhibits collagenase activity	IC ₅₀ 70 µg/mL	Vitamin E IC ₅₀ 72 µg/mL	HDF cell / 0-150 µg/mL	(Limtrakul <i>et al.</i> , 2016)
	Chlorogenic acid							
<i>Helianthus annuus L.</i>			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							
<i>Thunbergia laurifolia</i>	Fenolic		Ethanol	Inhibits collagenase activity	IC ₅₀ 89 ± 1 µg/cm ³	Ascorbic acid IC ₅₀ 4.4 ± 0.3 µg/cm ³	3T3 cell / -	(Chaiyana <i>et al.</i> , 2020)

Natural Ingredients	Bioactive Compounds	Structure	Solvent	Mechanism	Aging Activity	Positive Control		Experiment/Dose		Ref
								In Vitro	In Vivo	
<i>Citrus unshiu</i>	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 <i>et al.</i> , 2017)
<i>Allium stivum</i>	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	Solvent	Mechanism	Aging Activity	Experiment/Dose		Ref
						Positive Control	In Vitro / In Vivo	
<i>Lansium domesticum</i>	Limonoid		Hot water, methanol, chloroform	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 <i>et al.</i> , 2012)
<i>Panax ginseng</i>	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 <i>et al.</i> , 2021)
<i>Leontopodium vivale</i>	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 <i>et al.</i> , 2020)
<i>Gastrodia elata</i>	Phenolic		H ₂ O deionization	Inhibits the AP-1 pathway and Nrf2 activation	Percent inhibition 34.2%	Galic acid 89.5%	HDF cell / 0.2-2 mg/mL	(Song <i>et al.</i> , 2016)

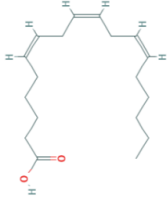
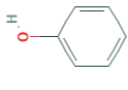
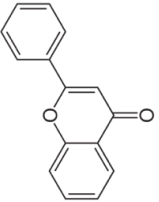
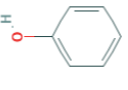
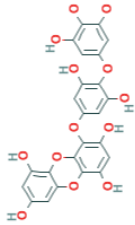
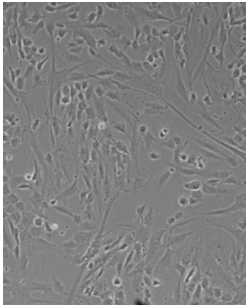
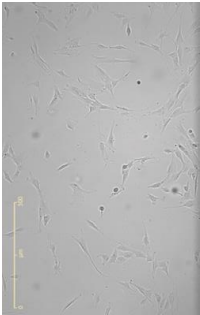
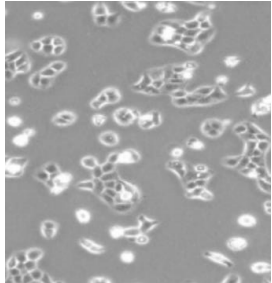
Natural Ingredients	Bioactive Compounds	Structure	Solvent	Mechanism	Aging Activity	Positive Control		Experiment/Dose		Ref
						Control		In Vitro	In Vivo	
<i>Borage officinalis</i> L.	Linolenic γ -acid		Ethanol	Inhibits the AP-1 pathway, regulates IL-6, and Nrf2, TGF β activation	Percent inhibition 49.8%	Arbutin		NHDF cell / 1-100 μ g/mL	Six-week-old male hairless mice (SKH: HR-1) (22-24 g) / 1%	(Seo <i>et al.</i> , 2018)
<i>Eucalyptus globulus</i>	Phenolic		Ethanol	TGF β activation and Inhibits the AP-1 pathway	Percent inhibition 65%	Arbutin		NHDF cell / 100 μ g/mL	Six-week-old female hairless mice (SKH:HR-1) (29-34 g) / 1 and 5%	(Park <i>et al.</i> , 2018)
<i>Hibiscus sabdariffa</i>	Flavonoids		Ethanol	Inhibits collagenase activity	Percent inhibition 77.7 $\pm$ 19.57%	Vitamin C	95.14 $\pm$ 0.07%	Hs68 cell / 0.1 and 1 mg/mL	-	(Li <i>et al.</i> , 2020)
<i>Camellia sinensis</i>	Phenolic		Distilled water	Nrf2 activation	Percent inhibition 79.85 $\pm$ 3.38%			HaCaT cell / 10; 30; 100 μ g/mL	-	(Zhao, Alam and Lee, 2018)
<i>Ecklonia stolonifera</i>	Phlorotannin		Ethanol	Inhibits the AP-1 pathway	Percent inhibition 80%	-		HDF cell / 25; 50; 100 μ g/mL	Zebra fish / 25; 50; 100 μ g/mL	(Kuda, 2016; Wang <i>et al.</i> , 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 <i>et al.</i> , 2020; Hwang <i>et al.</i> , 2018; Park <i>et al.</i> , 2018; Song <i>et al.</i> , 2016; Hänzelmann <i>et al.</i> , 2015; Vangipuram <i>et al.</i> , 2013; Auburger <i>et al.</i> , 2012)
Hs68		Human fibroblast	Spindle- shaped, cells are bipolar and refractile	N.a	(ATCC, 2021; Li <i>et al.</i> , 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)

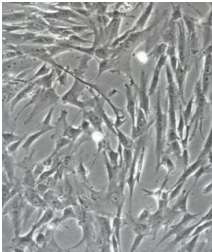
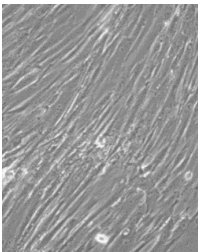
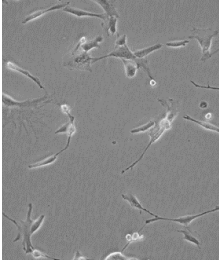
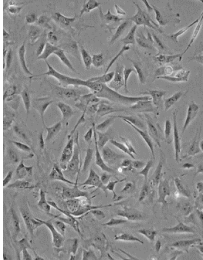
Cell Type	Image	Culture	Morphology	Advantages	Ref
Detroit 551		Human fibroblast	Spindle- shaped, cells are bipolar and refractile	N.a	(ATCC, 2021; Cho <i>et al.</i> , 2020)
					
3T3-L1		Mouse embryo	Spindle- shaped, cells are bipolar and refractile	N.a	(ATCC, 2021; Chaaryana <i>et al.</i> , 2020)
					

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

Natural Ingredients	Bioactive Compounds	Result	Toxicity	Ref
<i>Hubertia ambavilla</i>	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 <i>et al.</i> , 2020)
<i>Panax ginseng</i>	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 <i>et al.</i> , 2017)
<i>Ecklonia stolonifera</i>	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 <i>et al.</i> , 2020)

A lower IC₅₀ value and higher percent inhibition value indicate good antioxidant efficiency (Roginsky and Lissi, 2005; Cakmakci *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 IC₅₀ 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).

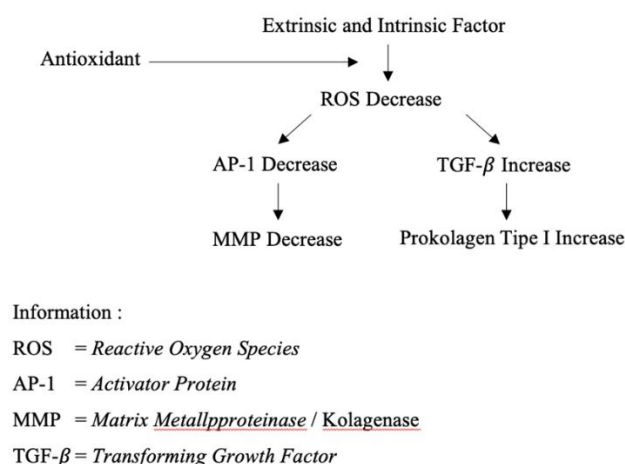


Figure 1. The mechanism of collagen production

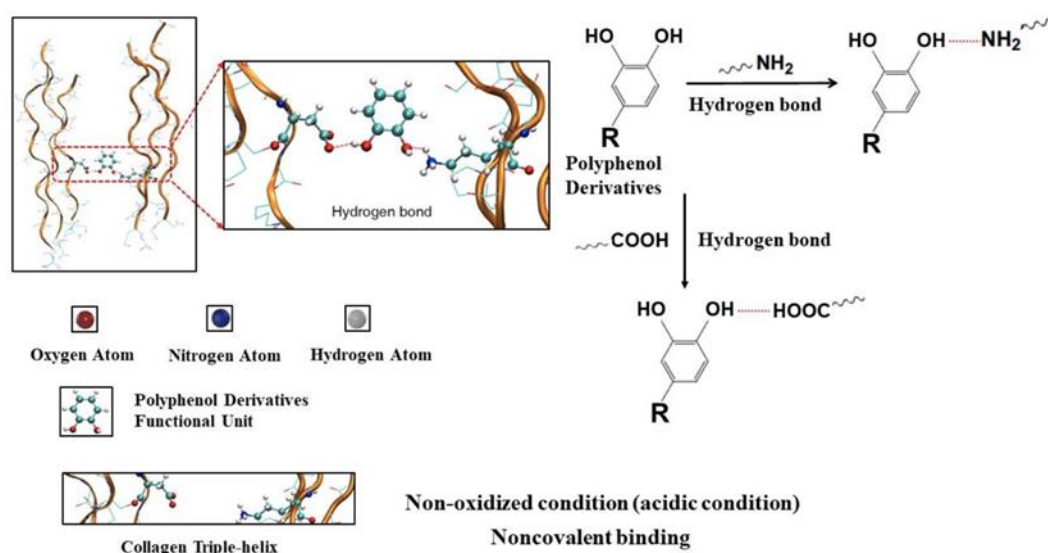


Figure 2. The mechanism of polyphenol (Wu *et al.*, 2019)

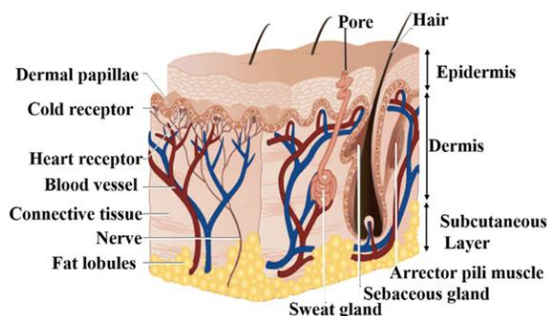


Figure 3. Skin Structure
(Nafisi and Maibach, 2018)

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; Anchin *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, TiO₂NPs, and ZnONPs have been widely developed in the field of dermatology. TiO₂NP 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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