Natural herb compounds for prevention of skin ageing

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Background of research

Skin ageing is a physiological process characterized by wrinkle formation, pigmentation, loss of elasticity, and impaired wound healing. It not only negatively affects individual appearance, but also impairs whole body health. It is proposed that skin ageing actively contributes to disrupted homeostasis in distal organs or tissues1. Also, Skin status reflects health conditions and physiological age of individuals2. Hence, anti-skin ageing strategies hold promise to improve both health and appearance of individuals. Considering the accelerated population ageing in China, there will be a huge demand for anti-skin ageing products.

Skin ageing is classified into two types: intrinsic skin ageing and extrinsic skin ageing. Intrinsic skin ageing is induced by physiological decline of cell function and disturbed tissue homeostasis. While extrinsic skin ageing is driven by exogenous stimuli including UV exposure, air pollution, and smoking.

Cellular senescence is the most important causal factor of both extrinsic and intrinsic skin ageing[3]. Cellular senescence is generally considered to be a state of irreversible cell cycle arrest and can be identified by a set of biomarkers including senescence-associated beta-galactosidase (SA-β-gal), expression of cell cycle inhibitors ($P16^{INK4A}$ and $P21^{CIP}$), enlarged morphology, senescence associated heterochromatin foci (SAHF), lipofuscin accumulation and senescence associated secretory phenotype (SASP)[4]. Skin is a regenerative tissue composed of various proliferating cells including hair follicle stem cells, melanocytes, keratinocytes, and fibroblasts. As organisms age, cellular senescence results in skin ageing[3].

Senescent cells are “zombie” cells. Although they do not proliferate anymore, they are metabolically active and hypersecretory. SASP is the most universal and important feature of cellular senescence. Generally, senescent cells secrete SASP components including inflammatory cytokines, extracellular matrix modifiers, growth factors, extracellular vesicles. With SASP, senescent cells actively participate in many biological processes including wound healing, fibrosis resolution, immune cell recruitment, and embryonic development[5-7].

Although SASP favors many biological processes in young individuals, as individuals age, accumulated senescent cells secret excessive amount of SASP factors that disrupt tissue homeostasis, lead to age-related disorders (ARDs) and ageing phenotype[8-10]. The chronic low-grade inflammation mediated by SASP is thought to be a major driver of organism ageing and the bridge between cellular senescence and organism ageing. Considering the importance of SASP in ageing, the SASP-mediated functional decline and ageing phenotype is also named inflamm-aging[11,12]. SASP is also a critical contributor to skin ageing. The structure of dermis layer is mostly sustained by collagen fiber and other extracellular matrix. Over 70% composition of collogen fiber is type 1 collagen. As people age, the content of type 1 collagen declines, which is associated with wrinkle formation and loss of elasticity. Matrix metalloproteinases (MMPs) secreted by senescent fibroblast cells can catalyze degradation of Type 1 collagen, resulting in fractured collagen fiber[3,13].

Considering the importance of SASP. Two therapeutic strategies targeting SASP have been developed: senolytics (drugs that selectively kill senescent cells) and senomorphics (drugs that block SASP secretion of senescent cells). Their effectiveness has been validated *in vitro* and *in vivo*[14]. Natural compounds are valuable resources of bioactive compounds. Some natural compounds including pro-cyanidin C, fisetin, curcumin, quercetin showed senolytic or senomorphic activities *in vitro* and *in vivo*[15,16]. The most well-known senomorphic compound is rapamycin that blocks SASP by specifically inhibiting mTORC[17]. Rapamycin has been demonstrated to improve the lifespan of mice[18]. In this study, we aim to define the senomorphic property of novel natural compounds and test if they can prevent skin ageing in mice. This research will provide reference to anti-ageing research and prompt anti-ageing skin care product development.

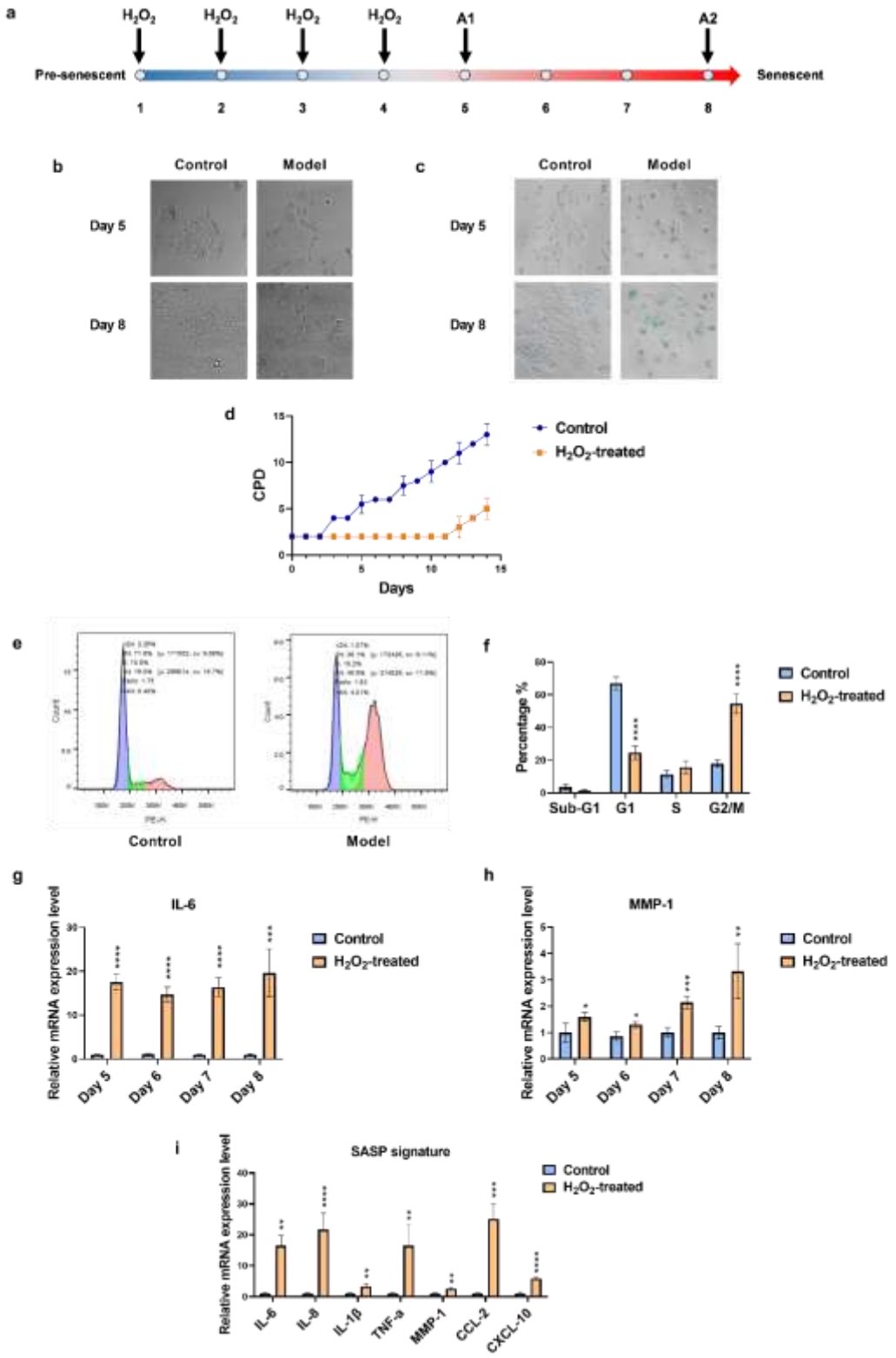

Figure 2. establishment of cellular senescence model. **a,** schematic design of in vitro model. **b,** morphological change. **c,** SA-β-gal. **d,** accumulated population doubling. **e,** cell cycle analysis. **f,** quantitative result of cell cycle analysis. **g,** IL-6 mRNA expression level from Day 5 to Day 8. **h,** MMP-1 mRNA expression level from Day 5 to Day 8. **i,** SASP signature on Day 8.

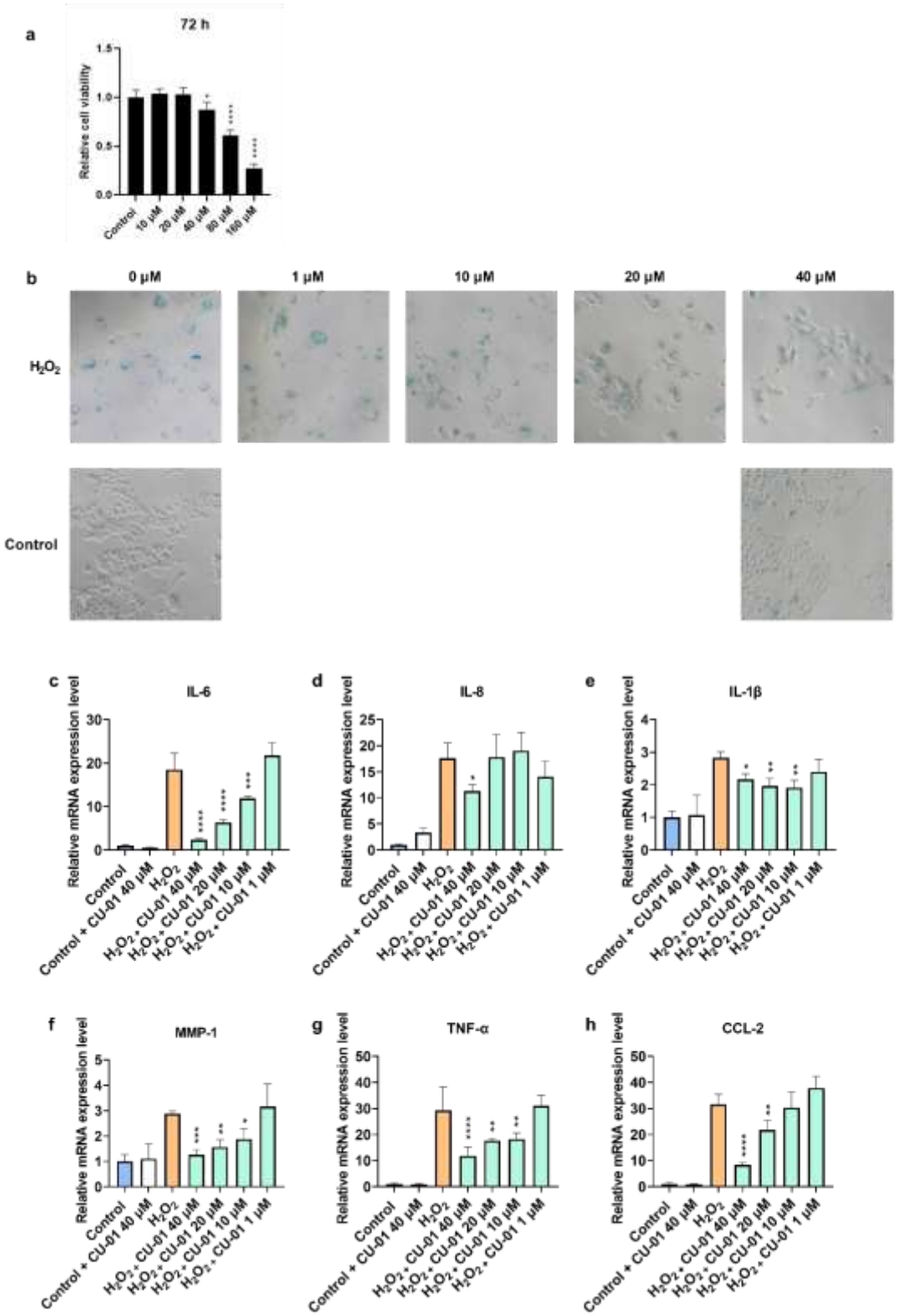

Figure 3. senomorphic effect of CU-01. **a,** chemical structure of CU-01. **b,** cytotoxicity of CU-01 for 72 h. **c,** SA-β-gal on Day 8 upon treatment of CU-01. **d-i,** expression levels of SASP components on Day 8 upon treatment of CU-01.

References

1 Franco, A. C., Aveleira, C. & Cavadas, C. Skin senescence: mechanisms and impact on whole-body aging. *Trends Mol Med* **28**, 97-109 (2022).

2 Gunn, D. A. *et al.* Facial appearance reflects human familial longevity and cardiovascular disease risk in healthy individuals. *J Gerontol A Biol Sci Med Sci* **68**, 145-152 (2013).

3 Low, E. *et al.* How good is the evidence that cellular senescence causes skin ageing? *Ageing Res Rev* **71**, 101456 (2021).
4 Hernandez-Segura, A., Nehme, J. & Demaria, M. Hallmarks of Cellular Senescence. *Trends Cell Biol* **28**, 436-453 (2018).
5 Ritschka, B. *et al.* The senescence-associated secretory phenotype induces cellular plasticity and tissue regeneration. *Genes Dev* **31**, 172-183 (2017).
6 Dugan, B., Conway, J. & Duggal, N. A. Inflammaging as a target for healthy ageing. *Age Ageing* **52** (2023).
7 Di Micco, R. *et al.* Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol* **22**, 75-95 (2021).
8 Rea, I. M. *et al.* Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. *Front Immunol* **9**, 586 (2018).
9 Lee, H. J., Yoon, Y. S. & Lee, S. J. Molecular Mechanisms of Cellular Senescence in Neurodegenerative Diseases. *J Mol Biol* **435**, 168114 (2023).
10 Kritsilis, M. *et al.* Ageing, Cellular Senescence and Neurodegenerative Disease. *Int J Mol Sci* **19** (2018).
11 Ferrucci, L. & Fabbri, E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* **15**, 505-522 (2018).
12 Li, X. *et al.* Inflammation and aging: signaling pathways and intervention therapies. *Signal Transduct Target Ther* **8**, 239 (2023).
13 Kammeyer, A. & Luiten, R. M. Oxidation events and skin aging. *Ageing Res Rev* **21**, 16-29 (2015).
14 Zhang, L., Pitcher, L. E., Prahalad, V., Niedernhofer, L. J. & Robbins, P. D. Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. *FEBS J* **290**, 1362-1383 (2023).
15 Luis, C. *et al.* Nutritional senolytics and senomorphics: Implications to immune cells metabolism and aging - from theory to practice. *Front Nutr* **9**, 958563 (2022).
16 Benhamu, B. *et al.* New Trends in Aging Drug Discovery. *Biomedicines* **10** (2022).
17 Herranz, N. *et al.* mTOR regulates MAPKAPK2 translation to control the senescence-associated secretory phenotype. *Nat Cell Biol* **17**, 1205-1217 (2015).
18 Harrison, D. E. *et al.* Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* **460**, 392-395 (2009).