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著者	Ariuntsetseg KHURELCHULUUN, Durga PAUDEL, Osamu UEHARA, Takahashi SHUHEI, Dedy ARIWANSA, Koki YOSHIDA, Tetsuro MORIKAWA, Fumiya HARADA, Jun SATO, Hiroko MIURA, Hiroki NAGAYASU, Yoshihiro ABIKO
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〔REVIEW〕

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Ariuntsetseg KHURELCHULUUN[1,2], Durga PAUDEL[3], Osamu UEHARA[4], Takahashi SHUHEI[1], Dedy ARIWANSA[1], Koki YOSHIDA[1], Tetsuro MORIKAWA[1], Fumiya HARADA[2], Jun SATO[1], Hiroko MIURA[4], Hiroki NAGAYASU[2], Yoshihiro ABIKO[1]

[1] Division of Oral Medicine and Pathology, Department of Human Biology and Pathophysiology, School of Dentistry, Health Sciences University of Hokkaido
[2] Division of Oral and Maxillofacial Surgery, Department of Human Biology and Pathophysiology, School of Dentistry, Health Sciences University of Hokkaido
[3] Advanced Research Promotion Center, Health Sciences University of Hokkaido
[4] Division of Disease Control and Molecular Epidemiology, Department of Oral Growth and Development, School of Dentistry, Health Sciences University of Hokkaido

Key words : bee pollen, anti−aging, bioactive compound

Abstract

Bee pollen has been used as a food and supplement for a long time. Bee pollen in diet can bring many beneficial effects on human health. Aging is an inevitable progress which leads to age−related degenerative diseases. Most of the age−related diseases are attributed to the accumulated oxidative stress in tissue over years. Natural products such as bee pollen are rich in antioxidant and anti−inflammatory activity contributing to anti−aging effect. Bee pollen contains abundant phenolic compounds, which are highly efficient antioxidants. Herein, we summarize the potential use of bee pollen as an anti−aging component.

Introduction

A variety of bee products have been used as food and medicine since ancient days. Products such as honey, propolis, bee pollen, royal jelly, beeswax, and venom have been studied for their beneficial effects on human health (Pasupuleti et al., 2017). Bee pollen abundant in proteins, amino acids, phenolic acids, and flavonoids (Campos et al., 2008), which have antioxidant, anti−inflammatory, antibacterial, and anticancer activities.

Aging is a complex process in humans and other living organisms. It is associated with physiological and functional decline, which leads to the development of age−related diseases such as arterial sclerosis, diabetes, cataract, Parkinson's disease, Alzheimer's disease, and others (Jaul and Barron, 2017). The acceleration of the aging process due to individual lifestyles may promote the development of age−related diseases (Rescigno et al., 2017). The accumulation of reactive oxygen species over a period of time is one of the most important factors for the acceleration of the aging process (Oliveira et al., 2010). The scavenging of the accumulated reactive oxygen species, which is an antioxidant activity, may serve as an anti−aging process (Wojdyło et al., 2018). Hence, owing to its antioxidant properties, bee pollen is proved to be beneficial as a potential natural anti−aging supplement.

Although a few studies have demonstrated the anti−aging effect of bee pollen *in vivo* and *in vitro*, a comprehensive review is lacking (Graikou et al., 2008 ; Liu and Li, 1990). The antioxidant property of bee pollen is due to the presence of its bioactive components, such as phenolics and flavonoids. The concentrations of these components in bee pollen vary among geographical regions (Kaškonienė et al., 2015).

The aim of this review is to summarize the potential use of bee pollen as an anti−aging component. Additionally, variations in the amounts of phenolics and flavonoids and the antioxidant properties of bee pollen are discussed.

Components of bee pollen

Bee pollen is produced by the stamen of the flower and collected by bees. The structure and ratio of the bioactive components in pollen differ among the various types of plants (Leja et al., 2007). The pollen grain consists of two layers, an outer shell, and the inner cytoplasm, which house a tube cell and a generative cell. The contents of the bioactive components in pollen can be affected by climate conditions, seasonal changes, or the use of pesticides.

Bees are the most important pollinators for all plants/flowers (Hellerstein et al., 2017). During foraging, the pollen sticks onto the hairy bodies of the worker bees and is transferred to a pollen basket on the hind limbs where it is agglutinated with bee enzymes to form bee pollen. The bee pollen is carried to beehives where they are stored in niches of honeycombs as the main food for the bee colonies. Thus, the bee pollen should be collected before the worker bees enter the hive.

Various bee pollen products are available over–the–counter as supplements or food additives, and they are broadly divided into three major forms (Nuvoloni et al., 2020). The first is the raw bee pollen granules that are directly collected from the bee hive (Nogueira et al., 2012). The second type comprises granules that are mantled down to a powdered form, which can easily dissolve in liquids. The third type is the bee pollen extract, which has the highest nutritional value. The color of bee pollen varies from bright yellow to dark green or brown depending on its composition.

To date, over 200 chemical substances have been found in bee pollen. The main components include proteins and amino acids, reducing sugars, lipids, nucleic acids, and fiber (Campos et al., 2008 ; Almeida–Muradian et al., 2005). The minerals present include potassium, sodium, calcium, iron, zinc, and copper, and the vitamins include provitamin A (β–carotene), vitamin E (tocopherol), niacin, thiamine, biotin, folic acid, and enzymes. Bioactive substrates, such as phenolic compounds (phenolics, flavonoids, anthocyanins, phenylpropanoids), fatty acids (linoleic, γ–linoleic, and archaic acid), phospholipids, and phytosterols (Leja et al., 2007 ; Tomás–Lorente et al., 1992) contribute to the health effects of bee pollen.

Biological properties of bee pollen

Bee pollen has many biological activities, such as antioxidant, anti–inflammatory, anticancer, and antimicrobial activities. The antioxidant activities may be directly involved in the anti–aging process. The antioxidant activities of the components in bee pollen are shown in the section “Studies on the antioxidant activity of bee pollen”.

Bee pollen possesses anti–inflammatory effects similar to other apitherapeutic bee products such as propolis, bee venom, honey, and royal jelly (Kolayli et al., 2016). Phenolic compounds in bee pollen may exert anti–inflammatory activities by modulating the B cells, mast cells, macrophages, T cells, and neutrophils (Middleton & Kandaswami, 1992).

Important inflammatory cytokines, such as TNF–α, IL–1–β, and IL–6, might be inhibited by natural phenolic compounds via macrophage cell response (González et al., 2011 ; Yahfoufi et al., 2018). Quercetin is a phenolic component commonly found in bee pollen; it inhibits the activity of cyclooxygenase and lipoxygenase during the synthesis of prostaglandins from arachidonic acid. The inhibitory effect can halt the proinflammatory process and migration of immune cells, and reduce edema (Middleton E, 1998 ; M. Choi, 2007). Nonsteroidal anti–inflammatory drugs are known to have various side effects; hence, bee pollen may be considered as an alternative anti–inflammatory medication (Bindu et al., 2020).

Studies have shown that bee pollen can act against a variety of cancer cells. Quercetin, commonly found in bee pollen, demonstrated a significant inhibitory effect on the growth of ovarian cancer cells (Vafadar., et al 2020). Another pollen extract called cernitin was found to be effective for the treatment of benign prostatic hyperplasia (Yasumoto et al., 1995). The synergistic anti–tumor activities of bee pollen have been proven in breast cancer cells; bee pollen promoted cancer cell apoptosis and the inhibition of cancer cell growth in combination with cisplatin, suggesting that it might contribute to chemotherapy (Omar et al., 2016 ; Amalia et al., 2020). The activity of caspase–3, which is the main enzyme related to the induction of apoptosis, in HL–60/promyeloblast cells was increased following stimulation with bee pollen alone (Uçar et al., 2016). Furthermore, bee pollen alone might function as a potential anti–cancer agent. However, additional studies are required to determine the clinical potential of bee pollen as an anti–cancer agent.

From ancient times, bee products have been used as a natural remedy for bacterial infections (Kurek–Górecka et al., 2020). The antimicrobial property of bee pollen might be related to the amylase enzymes produced by the salivary glands of bee (Campos et al., 2008). Amylases, which hydrolyze the polysaccharide backbone of extracellular polymeric substances, might contribute to the antimicrobial properties of bee pollen (Lahiri et al., 2021). Phenolic compounds such as quercetin, epicatechin, and tannic acid found in bee pollen inhibit β–lactamase activity and the formation of the bacterial biofilm (Mandal et al., 2017). Moreover, the phenolic compounds in bee pollen may be involved in antimicrobial activities. In our previous study, mice fed with a 5% bee pollen diet showed an increase in the abundance of beneficial bacteria such as Lactobacillus in the oral cavity and intestine; in addition, the growth of the periodontal pathogen *Porphyromonas gingivalis* was inhibited at a concentration of >2.5% (Khurelchuluun et al., 2021). Another study showed the diverse effects of bee pollen on various microorganisms, with *Candida albicans* being the most resistant and *Staphylococcus epidermidis* being the most sensitive (Soares de Arruda et al., 2021). These findings indicate that the antimicrobial activity of bee pollen might be dependent on the species of bacteria.

Function of natural foods as an anti–aging agent

Natural foods rich in bioactive components are known to have anti–aging activities. Bioactive components such as phenolic compounds, monounsaturated fat, and vitamins are the main antioxidants sources (Chrysohoou & Stefanadis, 2013). Curcumin, royal jelly, and blueberry are rich in bioactive components. Curcumin/turmeric is one of the main spices used in the Middle East. Diarylheptanoid, the main active ingredient in curcumin, is a strong antioxidant consisting of two aromatic rings. In animals, curcumin was found to extend the life span, protect against oxidative stress, and modulate the expression levels of several age–related genes (Lee et al., 2010). Royal jelly is another bee product and is similar to bee pollen. The anti–aging potential of royal jelly has been studied previously; a bee/queen bee fed with royal jelly was found to live 20 times longer than other bees (De Loof, 2011). Enhancement of the antioxidative capacity was suggested to extend the lifespan in various in *vivo* animal studies (Kunugi and Mohammed Ali, 2019). Blueberry has the most abundant antioxidant compounds among fruits. Some studies reported that the lifespan–prolonging activity of blueberry might involve the regulation of the related genes and the promotion of the Phase 2 defense enzymes superoxide dismutase (SOD) and catalase (CAT) (Peng et al., 2012 : Wojdyło et al., 2018). Certain environmental factors such as stress, UV exposure, pollution, and poor diet contribute to accelerated aging. Aging significantly decreases the quality of life and raises the risk of age–related diseases, such as neurodegenerative disease, cardiovascular disease, arthritis, hypertension, and diabetes (Jaul & Barron, 2017). Natural foods related to anti–aging have been successfully used to mitigate the harmful effects of environmental factors during aging.

The anti–aging potential of many foods is explained by their high content of phenolic compounds (Luceri et al., 2017). Phenolic compounds can be classified into two broad groups: phenolics and polyphenols/flavonoids. Phenolic compounds contain aromatic rings with a hydroxyl group in their molecular structure and are known as the secondary metabolites of plants. They possess the highest antioxidant potential among all the other natural substances (Safafar et al., 2015). The degree of antioxidant activity is related to the number of hydroxyl groups. The hydrogen atom from the hydroxyl group attaches to the active free radicals within the cell. Free radicals or ROS include highly active ions such as superoxide anion and hydroxyl radical, while the nonradical oxygen derivatives include singlet oxygen and stable hydrogen peroxide.

Excessive ROS can act as a secondary messenger in cellular signaling cascades and trigger prolonged DNA damage to the cell. Although ROS plays a key role in the normal biological developmental processes in cells, excessive ROS leads to the oxidative stress. Oxidative stress is a pathological condition caused due to an imbalance in the ROS and the antioxidant substances (Barnham et al., 2004).

Bee pollen is rich in phenolic and flavonoid components, which contribute to the antioxidant properties (Morais et al., 2011). These properties may be responsible for the anti–aging action of bee pollen.

Studies on the antioxidant activity of bee pollen

We summarized the bee pollen studies in Table 1. Studies are performed total phenolic content, total flavonoid content with antioxidant activity of various bee pollen. The antioxidant activity in bee pollen has been evaluated by different methods, such as the 1,1–diphenyl–2–picryl–hydrazil (DPPH) assay, ABTS–radical scavenging capacity, and beta–carotene/linoleic bleaching test (Table 1). The wide vari-

Table 1. Summary of the studies on antioxidant activity of bee pollen

Authors	Region and Country	Content of phenolic compound(s)		Antioxidant activity [DPPH][TE/g]
		Total phenolic content [GAE/g]	Total flavonoid content [QE/g or RE/g]	
AbdElsalam (2018)	Egypt	0.8 – 2.3 mg	0.1 – 0.85 mg	63 – 90 RSA%
Anjos (2019)	Spring of 2017 in Castelo Branco, Portugal	35.05 mg	6.99 mg QE/g	2.62 mg/mL
Atsalakis (2017)	Greek endemic	15.2 – 60.2 mg	6.0 – 57.6 mg	0.7 – 44.6 RSA%
Bárbara (2015)	Bahia, Brazil (João Dourado)	40 ± 13 mg	1.0 ± 0.2 mg	–
Carpes (2013)	Brazil (Parana, Santa Catarina)	20.2 – 48.8 mg	6.6 – 28.4 mg	14.9 – 94.7 RSA%
Čeksterytė (2016)	Lithuania	3.5 − 23.3 mg	–	1.1 – 1.5 mg
De−Melo (2018) a	Brazilian regions	6.5–29.2 mg	0.3–17.5 mg	9.4–155 mmol
De−Melo (2018) b	Brazilian regions (Sao Paulo, Bahia)	13.31 mg	0.3 – 19.0 mg	10.0 – 110.8 mmol
Domenici (2015)	Italy (Tuscany)	13.5 – 24.7 mg	5.91 – 15.86 mg	37.95 – 94.45 RSA%
Duarte (2018)	Alagoas, Northeast region of Brazil	6.9 − 21 mg	0.3 − 17 QE/g	76.5 – 83.3 %
Fadzilah (2017)	Malaysia	33.5 – 135.9 mg	15.3 – 31.8 mg	0.86 – 3.24 mg/mL
Fatrcová. Š (2015)	Slovakia	0.69 – 0.80 mg	0.23 – 0.61 mg	48 − 50 RSA%
Freire (2012)	Canavieiras (northeastern Brazil)	41.5 – 213.2 mg	–	2.5 – 209 mg/mL
Jin (2018)	China	–	–	IC50 : 2.29−3.48 mg/mL
Karabagias (2018)	Greece	5 mg GAE/ml	–	68.7 – 88.26 RSA%
Kaškonienė (2014)	Latvia, Lithuania, China, Spain	14.2 – 26.8 mg	2.7 – 5.2 mg	0.9 – 8.4 mg
Ketkar (2014)	West Bengal, India	18.29 mg	12.23 mg	54.79 g/mL
Kostić (2019)	Serbia	2.91 – 3.82 mg	0.84 – 0.87 mg	–
LeBlanc (2009)	North of Tucson, USA	15.91–34.85 mg	2.66–5.48 mg	–
Mohdaly (2015)	Egypt	–	–	5 ug/ml conc : 15%
Morais (2011)	North and Centre regions of Portugal	10.50–16.80 mg	–	2.24 – 5.87 mg/mL
Pascoal (2014)	Portugal, Spain	18.5 – 32.1 mg	3.9 – 10.14 mg	0.35 − 3.70 mg/mg
Rocchetti (2019)	Italy	4.2 – 29.6 mg	–	11.9 – 134.7 mol
Sun (2017)	China	12.57 mg	22.89 mg	–
Ulusoy (2014)	Turkey	~ 74 mg	–	SC50 3.3 mg/ml
Vasconcelos (2017)	Brazil	5.85–46.25 mg	1.8 – 107.0 mg	42.35 – 78.58 RSA%
Zhang (2016)	China	–	604 mg RE/g	–
Zuluaga (2016)	Colombian central region	24.8 – 33.7 mg	552 – 778 µmol	100.6 – 126.5 µmol

[GAE : gallic acid equivalent ; QE : quercetin equivalent ; RE : rutin equivalent ; DPPH : 2,2−diphenyl−1−picrylhydrazyl ; RSA : radical scavenging activity ; TE/g : µmol Trolox equivalents per gr]

ation in the antioxidant activity and the concentrations of the phenolic and flavonoid components might be attributed to geographical variations and differences in the evaluation techniques. Nonetheless, bee pollen is reported to be rich in phenolic and flavonoid components, which contribute to its high antioxidant effect (Rzepecka−Stojko et al., 2015).

Most of the studies in Tab. 1 focused on bee pollen are from Brazil and Spain, which are renowned for their bee pollen industries. Quercetin and following kaempferol, isorhamnetin, naringenin, rutin and cinnamic acid, caffeic acid, gallic acid, ferulic acid, luteolin, myricetin, catechin, and quinic acid were the most commonly found phenolic compounds in bee pollen. Quercetin, a strong antioxidant, is known to have a high effect on longevity and stress resistance in animal models (Pietsch et al., 2012).

Mechanism of antioxidant activity of bee pollen

The antioxidant activity of bee pollen involves the scavenging of excessive ROS. The phenolic compounds in bee pollen might be the main components responsible for its antioxidant activity (Leja et al., 2007). The commonly involved ROS pathways and the possible intervention by phenolic compounds in bee pollen are summarized in Figure 1.

The accumulation of excessive ROS can damage the cell via various pathways. The nuclear factor erythroid 2 (NFE2) −related factor 2 (Nrf2) is essential for signaling the production of drug−metabolizing enzymes. Nrf2 is connected to the endogenous inhibitor Kelch−like ECH associated protein 1 (KEAP1). ROS inhibits the ability of KEAP1 to attach to Nrf2, and the released Nrf2 connects to the antioxidant response element (ARE). Cytoprotective gene expression is

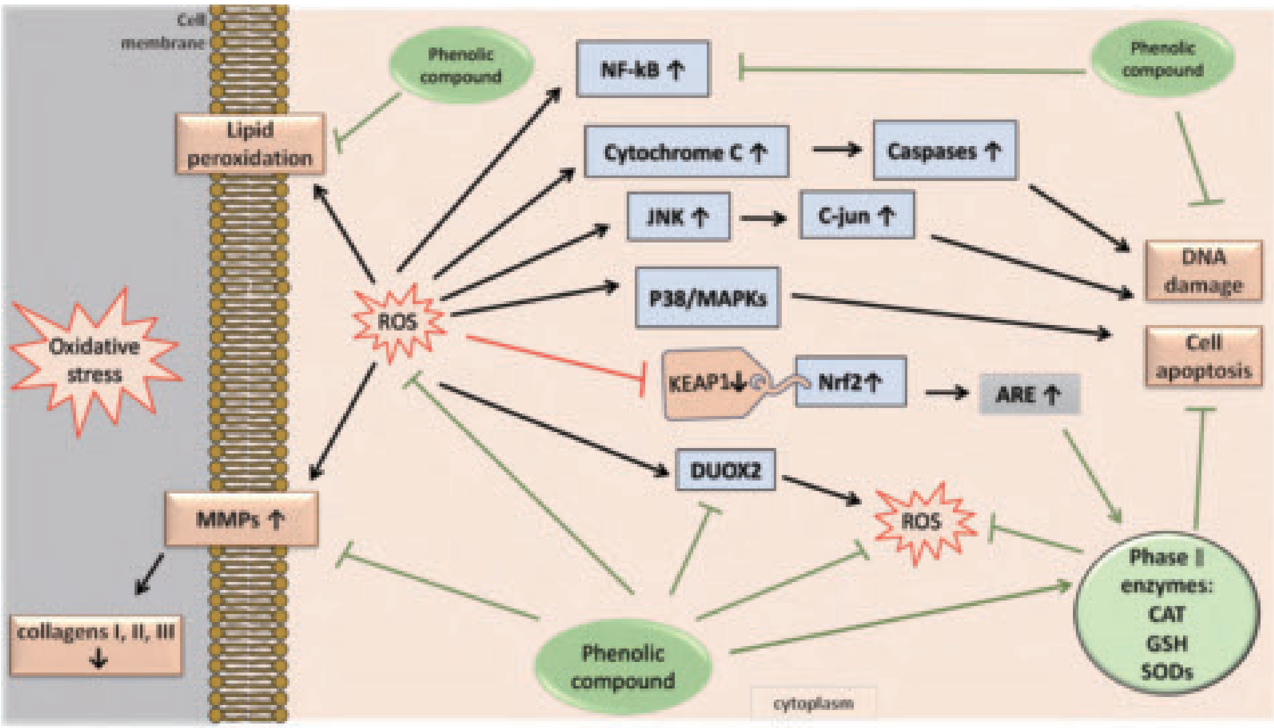

Figure 1. Excessive ROS pathways in oxidative stress. High amount of ROS in cells leads to cell senescence, DNA damage, cell apoptosis and cell death. Phenolic compounds in natural foods work as an antioxidant agent and halt the oxidative damages within the cell.

regulated by Nrf2–ARE binding, which codes the cellular antioxidant and anti–inflammatory cytokine defenses. Although the ROS–Nrf2 pathway is a normal biological defense system, a high amount of ROS can activate tyrosine kinases and lead to the failure of the Nrf2–Keap1 complex (Sajadimajd and Khazaei, 2018). Quercetin has been shown to enhance the Nrf2–ARE binding activity ; Nrf2 protein is stabilized by the deceleration of the ubiquitination and proteasomal turnover, whereas Keap1 protein is reduced by the formation of a modified Keap1 protein in exposure of quercetin (Tanigawa et al., 2007). Phenolic compounds can induce Phase 2 enzymes such as CAT, SODs, and glutathione (GSH), these work as an endogenous antioxidant (Petri et al., 2012).

NF–kB (nuclear factor kappa–light–chain–enhancer of activated B cells) is a transcriptional factor that targets genes, particularly those involved in the antioxidant response, such as the ferritin heavy chain and SOD2. Another NF–κB target gene that contributes to both survival and innate immune functions is the HIF–1α gene, which encodes the oxygen–regulated subunit of the hypoxia–responsive transcription factor–1. Phenolic compounds can inhibit the NF–kB pathway to impart the antioxidant property (Pham et al., 2004).

Cytochrome C is a designated scavenger of ROS and is released from the mitochondrial membrane of the cell. Excessive ROS induces activation of caspase 3 and caspase–3–like proteases caused by the release of cytochrome C (Higuchi et al., 1998). The C–Jun NH (2)–terminal kinase (JNK) signaling pathway is one of the mitogen–activated protein kinase (MAPK) signaling pathways, which regulates certain cellular processes such as cell proliferation, embryonic development, and apoptosis. Over–activation of JNK/c–Jun signals induced by excessive ROS can lead to cell death (Singh et al., 2009). The inhibition of these pathways by phenolic compounds can result in antioxidative effects. P38/MAPK is the highly conserved enzyme responsive to oxidative stress. It can regulate the production of proinflammatory mediators (such as IL–1β, TNF–α, and IL–6), and is involved in cell differentiation, apoptosis, and autophagy processes. The ROS–induced p38/MAPK pathway induces the exhaustion of the cell population and limits cell proliferation (Ito et al., 2006). Phenolic compounds inhibit the p38/MAPK pathway (Xia et al., 2018). Furthermore, *p*–coumaric acid, one of the phenolic acids in bee pollen, enhances the ability of the cell to resist the SKN–1–mediated oxidative stress and regulates the activity of the MAPK pathway (Yue et al., 2019).

Matrix metalloproteinases (MMPs) are a group of enzymes responsible for the degradation of proteins and collagens in the extracellular matrix. MMPs play a major role during all stages of the tissue healing process by modifying the structural tissues and supporting cell growth. ROS is known to trigger the MMPs via the NF–kB pathway. Elevated MMPs are often observed in cancer cells and contribute to their growth and invasion (Morgia et al., 2005). The phenolic component, including polyphenols, phenolic acids, and monophenols act against tumor growth and invasion by reducing the MMP content (Weng and Yen, 2012).

Conclusion

Bee pollen has antioxidant properties, which can prove useful during the anti–aging process. This review demonstrates the potential use of bee pollen as a natural supplement that might aid in the prevention of pathological aging in humans.

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