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Bee Pollen Flavonoids as a Therapeutic Agent in Allergic and Immunological Disorders

Masoomeh Jannesar[1,2], Maryam Sharif Shoushtari[1,3], Ahmad Majd[4], and Zahra Pourpak[1]

[1] Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Biology, Faculty of Sciences, Tehran University, Tehran, Iran
[3] Department of Biology, Faculty of Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran
[4] Department of Biology, Faculty of Sciences, North Tehran Branch, Islamic Azad University, Tehran, Iran

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ABSTRACT

Bee pollen grains, as the male reproductive part of seed-bearing plants contain considerable concentrations of various phytochemicals and nutrients. Since antiquity, people throughout the world used pollens to cure colds, flu, ulcers, premature aging, anemia and colitis. It is now well-documented that some bee pollen secondary metabolites (e.g. flavonoid) may have positive health effects. In recent years, the flavonoids have attracted much interest because of their wide range of biological properties and their beneficial effects on human health**.**

The current review, points out potential therapeutic effects of bee pollen flavonoids as one of the main bee pollen bioactive compounds in allergic and immunological diseases. Due to the fact that some types of flavonoid components in bee pollen have anti-allergic, anti-oxidant and anti-inflammatory properties, bee pollen flavonoids can be excellent candidates for future studies including phytotherapy, molecular pharmacology and substitutes for chemicals used in treating allergic and immunological disorders.

Keywords: Anti-allergic; Anti-inflammatory; Flavonoid; Pollen; Therapeutic applications

INTRODUCTION

Although pollen grains are known by their allergic effects, they are also used in folk medicine to alleviate symptoms of different diseases. Since ancient times people throughout the world have used pollens for their medical properties to alleviate symptoms or cure conditions such as common colds, flu, ulcers, premature aging, anemia and colitis.[1] Pollen products have long been used in medicine in the ancient world such as Egypt, Greece and China. The first references about its medicinal use were found in Islamic Spanish books. In the early 1200‘s Ibn el-Beithar described pollen grains as aphrodisiac, which is also beneficial for the stomach and, cures swellings produced by eating certain foods.[2]

Bee Pollens are rich in flavonoid and other healthy compounds. Flavonoids are known to possess several

Corresponding Author: Zahra Pourpak, MD, PhD; Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran. Tel: (+98 21) 6690 7415, E-mail: pourpakz@tums.ac.ir

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surprising health effects such as anti-allergic, anti-oxidant and anti-inflammatory properties.[3] It was demonstrated that polyphenolic compounds such as flavonoids, positively affect the human health due to their anti-oxidant activity.[4] Kawai et al reported that flavonoid and polyphenolic compounds possess anti-allergic activity that inhibits the release of histamine, production of IL-4, IL-13 and CD40 ligand expression by basophiles and mast cells. Studies on the relationship between the structure and activity of flavonoids and their related compounds indicated an inhibitory effect on IL-4 synthesis due to their specific structure.[5] Therefore, a correctly composed diet enriched in flavonoids may have preventive effect on development of a number of diseases. In the present study, we review the therapeutic effects of bee pollen flavonoids as a bioactive compound in allergic and other immunological disorders.

Bee Pollen Grains

Bee pollen is a mix of bee-collected floral pollen, which varies widely in composition depending on the botanical and geographical origins. These pollens are collected and stored at the hive entrance by the worker honey bees with nectar and salivary substances.[6] Worker bees collect pollen from flowers and carry it back to the hive packed in pellets on the pollen baskets on the rear legs. By leading field bees to enter the hive through small holes in a wire mesh or a punched plate, the pellets of bee pollen can be scraped from the legs and collected in a suitable tray. Bee pollen has great commercial interest owing to its high quality nutritional content such as vitamins, minerals, sterols, essential oils, amino acids, hormones, enzymes and significant quantities of natural antibiotics as well as being rich in carotenoids, flavonoids, polyphenols and other healthy compounds,[7-9] Therefore, using them in human diet can provide a well-being sensation and contributes to functional and harmonious balance of the human body.[10]

Flavonoids

Flavonoids belong to the secondary metabolites of plants with different structures and low molecular weight, which play a vital role in photosynthesizing cells. They are also bioactive polyphenols and synthesized through the phenylpropanoid pathway, a major secondary pathway that exists in all higher plants.[11,12] The basic structure of bioflavonoids consists of three rings, including two benzene rings linked together through a third heterocyclic oxygen containing pyrane ring. Flavonoids differ in their arrangement of hydroxyl, methoxy and glycosidic side groups and in the conjunction between A and B rings.[11] Flavonoids have been divided into several sub-classes based on their C-ring structure (Figure 1). The presence of a double bond between C2 and C3 in the C ring in a flavonoid structure influences the flavonoid antioxidative properties. A carbonyl group at the C4 position enables the compounds to scavenge hydroxyl radicals.[13]

The original research on flavonoid apparently began in 1936, when Hungarian scientist Albert Szent-Gyorgi uncovered a synergy between pure vitamin C and flavonoids. It was also extracted from the peels of lemons and introduced as an unidentified cofactor called citrin, and later vitamin P.[14]

Graikou et al in 2011 indicated that the aqueous extract of Greek bee pollen material contains the flavonoids such as kaempferol, quercetin, isorhamnetin and herbacetin. Interestingly all isolated flavonoids were flavonols 3-glycosides, which are essential in constructing the pollen tube and finally fertilization process in several flowering plants.[16] Flavonoids are responsible for the color and the bitter taste of pollen.[17] Some studies reported the presence of flavonoids such as myricetin, luteolin, isorhamnetin, kaempferol, quercetin, selagin and catechin in bee pollen samples.[13,18] Table 1 lists the main identified flavonoid compounds of bee pollen.

Flavonoids are well-known by their immunomodulatory and anti-inflammatory activities. These effects of flavonoids are due to their inhibitory effect on the production of pro-inflammatory cytokine and their receptors.[19,20] Some flavonoids have antioxidant and radical scavenging properties.[21] Moreover, flavonoids affect many enzyme systems involved in allergic and inflammatory responses such as tyrosine and serine-threonine protein kinases, phospholipase A2, phospholipase C and lipoxygenase.[22] Most of these biological actions have been attributed to their intrinsic reduction capabilities of these compounds. They may also offer indirect protection by activating endogenous defensive systems and by modulating different physiological processes.[23]

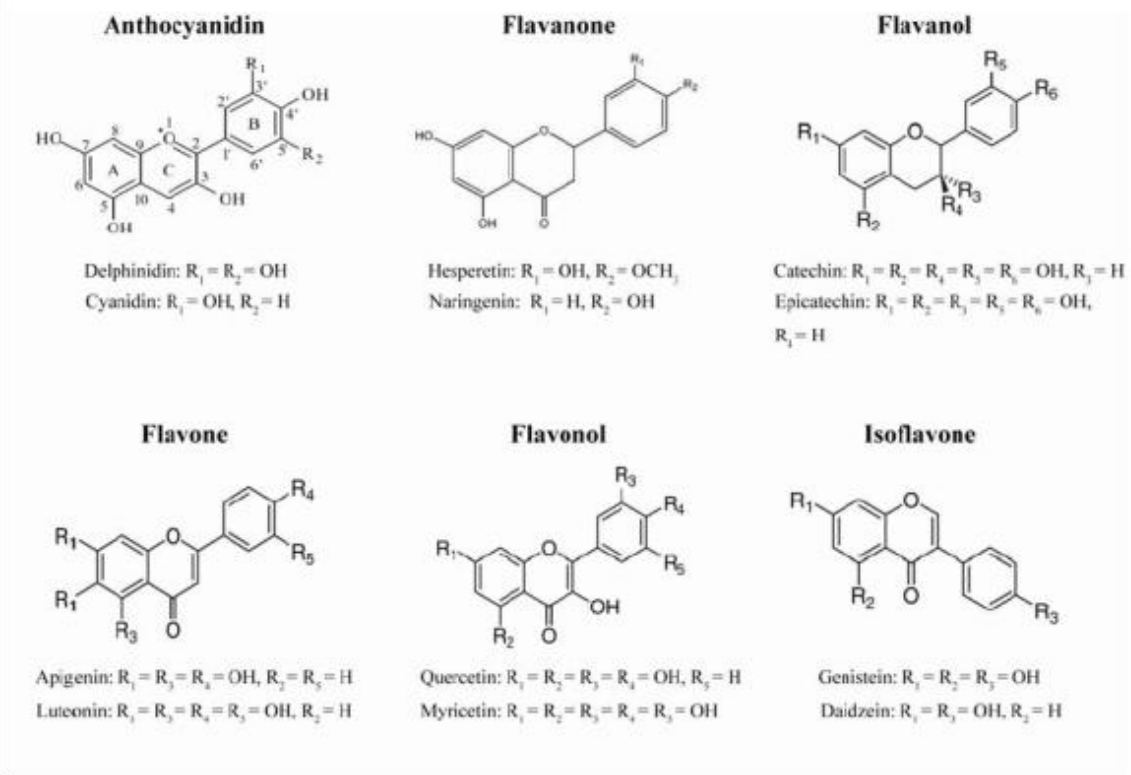

Figure1. Chemical structure of some important types of flavonoids (deduced from reference 15)

Table 1. Main identified flavonoid compounds of bee pollen

Flavones	Flavonols	Flavanones	Anthocyanidin	Flavanols	Isoflavones
Luteolin	Quercetin	Naringenin	Leucoanthocyanidin	Catechin	Genistein
Apigenin	Rutin	Pinocembrin			
Chrysin	Kaempherol				
Tricetin	Myricetin				
Selagin	Galangin				
Vitexin	Herbacetin				
	Isorhamnetin				

Allergic Effects of Pollen

Allergen

In the first half of the 20th century, many different allergen sources were identified. The major allergens purified since 1960 are proteins or glyco-proteins.[24] Further investigation revealed that allergens are mostly proteins with two characteristics inducing: 1) IgE-response in the sensitization phase, 2) triggering the clinical response on subsequent exposure.[25,26] However, some pollen allergens are resistant to heat that it made them not to be supposed as proteins.[27,28]

Busse et al demonstrated that pollen allergens can be carried by small particles. It was established that the size of these small particles ranged from some micrometers, i.e. 2-10 μm (paucimicronic) to less than 1 μm (submicronic).[29] The major pollen allergens were classified into 29 families of proteins that the most abundant of them includes expansins and profilins.[30]

An Overview of Pollen Allergy

Pollen allergy is a consequence of a specific reaction of the body's immune system to an allergen.

Antigen-presenting cells (APCs) initiate the immune response by delivering the environmental signals to other cells. T cells are activated by aeroallergens.[31] The T helper cell response is mainly the Th2 type, which is mostly associated with the allergic response. During sensitization to allergen, priming of allergen-specific CD4+ Th2 cells results in the production of Th2 cytokines.[32] Th2 cells in atopic disorders secrete a variety of cytokines, most notably IL-4, IL-5, and IL-13. IL-4 and IL-13 play a pivotal role in the production of IgE by B cells but importantly IL-4 induces IgE class switching. IL-5 induces terminal differentiation of activated B cells into antibody-forming cells, positively modulates IL-4-induced IgE synthesis and enhances proliferation and differentiation of eosinophil precursors into mature eosinophils.[33-36] Eosinophils are involved in proinflammatory mediators release, including granule-stored cationic proteins, newly synthesized eicosanoids, and cytokines.[37] IgE production by B cells leads to induction of mast cells and basophils degranulation, releasing vasoactive amines (principally histamine), lipid mediators (prostaglandins and cysteinyl leukotrienes), cytokines, and chemokines.[38] The immediate phase of allergic reaction is characterized by the existence of these factors. After the sensitization phase, allergic inflammation and reactions to allergen challenge are observed in the target organ, leading to development of allergic rhinoconjunctivitis, atopic dermatitis, asthma, and anaphylaxis.[39]

Therapeutic Effects of Bee Pollen in Allergic and Immunological Disorders

Anti-allergic Effects

Bee pollen can be used to cure allergy despite the fact that air born pollen is known to cause allergic reactions. Some studies indicated that bee pollen administration before IgE sensitization inhibited IgE-mediated mast cell activation in BALB/c mice. Also bee pollen significantly reduced serum IgE levels in ovalbumin-immunized mice by oraladministration.[40,41] Medeiros et al indicated that bee pollen phenolic extract (BPPE) could inhibit the production of the inflammatory mediators responsible for the edema formation or interfering with the mast cell degranulation in murine model of ovalbumin (OVA)-induced allergy. Their results also showed that BPPE inhibited both IgG_1 and IgE ovalbumin (OVA)-specific production and consequently mast cell inhibition. Finally, they concluded that these activities of BPPE are correlated to the immunomudulatory and anti-inflammatory properties of the flavonoid myricetin presence into the BPPE.[41] Elevated levels of IgE and IgG_1 antibodies are associated with allergies such as asthma. IgG_1 and IgE bind to FcεRIII and FcεRI respectively, on the surface of murine mast cells and activate these cells to release the inflammatory mediators including pro-inflammatory cytokines.[42] On the other hand, oral administration of luteolin, baicalein and quercetin have also been reported to have similar inhibitory effect on mast cell activation. These compounds also inhibited IgE-mediated histamine release and TNF-α and IL-6 production from bone marrow-derived mast cells (BMMCs) of mice.[43] Therefore, these studies indicated that both bee pollen and flavonoid compounds can inhibit immediate-type allergy reactions by inhibiting mast cell activation.

Flavonoid compounds such as myricetin, kaempferol, quercetin, and luteolin are able to inhibit the degranulation of mast cells and IgE-mediated allergies. Flavonoids suppress the intracellular calcium and also inhibiting the phosphorylation of the calcium-insensitive protein kinase Cθ in human mast cells.[44-46] Moreover, these compounds inhibit cyclic AMP phosphodiesterase and calcium dependent ATPase, which are responsible for histamine release from mast cells and basophils.[14]

To further elucidate the anti-allergic mechanisms of bee pollen, direct effect of bee pollen on mast cells was evaluated under in vitro condition. Ishikawa et al demonstrated that bee pollen significantly inhibited the *in vitro* mast cells degranulation and IgE binding to FcεRI on mast cells, when it was added to BMMCs of mice at the time of IgE sensitization.[40] Inhibition of IgE binding to mast cells also has been reported in BMMCs of mice treated with procyanidin-enriched extracts of apple.[47] Similar results were obtained from hydromethanolic extract of *Echium plantagineum* L. bee Pollen treatment in activated rat basophilic leukemic cells (RBL-2H3). *E. plantagineum* pollen extract inhibited β-hexosaminidase release in a dose-dependent manner and was effective in inhibiting basophils degranulation under an allergic stimulus. The tested *E. plantagineum* pollen extract contains derivatives of quercetin and kaempferol, which have

inhibitory effect on degranulation of mast-cells and basophils.[48] These results revealed that the anti-allergic properties of bee pollen and flavonoid compounds have similarities that include inhibition of mast cell activation both before and at the time of IgE sensitization. This effect is resulted from two mechanisms: one by which anti-allergic agents affect allergen-IgE complex formation and another through which they affect the binding of this complex to its receptor (Figure 2). Inhibition of FcεRI plays important roles, not only in the early phase, but also in the late phase of allergic reactions. These findings could highlight the role of some flavonoids such as quercetin, kaempferol, and myricetin as anti-allergic agent in bee pollen extract.

Anti-inflammatory Activity

Inflammation is a physiological response to the damage of tissue or cells, which is caused by physical or biological agents. Inflammation is directly related with many diseases, including cancer, allergies, arthritis, diabetes, cardiovascular diseases, etc. Bee pollen is characterized by a high anti-inflammatory activity. The significant positive correlation was found between contents of phenolic and flavonoid compounds and anti-inflammatory activity of bee pollen.[49,50]

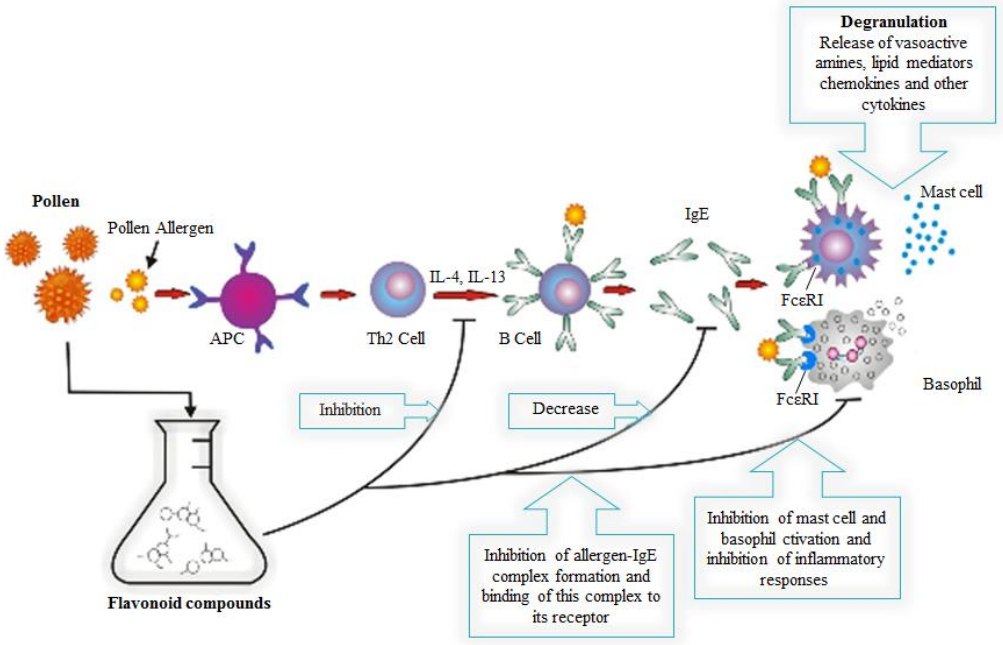

Figure 2. Two different effects of pollens on immune system: A) Immune responses to pollen allergens, Antigen-presenting cell (APC) presents protein allergens and delivers these signals to Th2 that leads to increase Th2 cytokines release, IgE production and finally mast cells and basophils activation that results in inflammatory responses; B) Some types of flavonoid compounds in bee pollen extract have anti-allergic effects through inhibition of IL-4, IL-13 and IgE production and inhibition of allergen-IgE complex formation and binding of this complex to its receptor. Consequently mast cell and basophil inhibition will occur.

An experimental research indicated that the ethanolic extract of *Cistus* bee pollen showed relatively strong inhibition of carrageenan-induced edema in rats. This extract inhibited the NO production and COX-2 activity. The production of prostaglandins such as PGE2 and PGI2 are facilitated through COX-2 activity in inflammatory response. Finally, it was concluded that isolated flavonoids from *Cistus* pollen such as quercetin, kaempferol and isorhamnetin may partly participate in some of the anti-inflammatory action of bee pollen.[51] Moita et al obtained similar results under *in vitro* condition. They demonstrated that *E.*

plantagineum pollen hydromethanolic extract had anti-inflammatory effects by reduction of NO and prostaglandin release in lipopolysaccharide (LPS)-induced macrophage. They indicated that the anti-inflammatory effects of bee pollen extract can be related to flavonoid compounds mainly quercetin and kaempferol.[52] From these studies it can be concluded that the mechanism of bee pollen anti-inflammatory effect is inhibiting the activity of cyclooxygenase and nitric oxide synthases. These enzymes play a role in turning arachidonic acid into prostaglandin and in production of NO from L-arginine, respectively.

There is a close correlation between consumption of some flavonoids and reduction in the risk of inflammationrelated diseases.[53] Flavonoids such as quercetin and kaempferol that are the main flavonols of bee pollen,[13] have been documented as containing anti-oxidant[54] and anti-inflammatory properties.[53,55] Quercetin inhibits the activity of arachidonic acid metabolizing enzymes (phospholipase A2, cyclooxygenase and lipoxygenase) and inflammatory cytokines such as IL-8 implicated in the pathogenesis of chronic prostatitis/chronic pelvic pain syndrome (CPPS).[56] It has been reported that kaempferol has anti-inflammatory properties due to its potent effect in the inhibition of inflammatory cell function, the expression of pro-inflammatory cytokines and chemokines.[53]

Both bee pollen and flavonoids are recommended in acute and chronic inflammatory conditions because they have been proven to reduce the risk of inflammation related diseases.[50,53,57] The anti-inflammatory properties of bee pollens and flavonoids in inflammatory condition of prostate gland have been known for a long time. Moreover, this effect has been confirmed in clinical trials of patients with inflammatory conditions of prostate. Murakami et al indicated that supplementation with high dose of bee pollen ethanolic extract mainly composed of *Citrus* pollen for a period of 12 weeks, alleviated the symptoms of benign prostatic hyperplasia.[58] Moreover, It was demonstrated that both pollen extract (cernilton and quercetin) can improve the biochemical markers of inflammation and condition of patients with chronic prostatitis.[59,60] These data supported the hypothesis that some types of flavonoids such as quercetin, kaempferol and isorhamnetin are among the most effective compounds responsible for anti-inflammatory properties of bee pollen.

The anti-allergic and anti-inflammatory properties of bee pollens and their identified flavonoid contents have been proved by several studies, in animal models and *in vitro* conditions, as presented in Table 2.

Antioxidant and Radical Scavenging Activity

The excessive production of reactive oxygen species (ROS) can injure cellular biomolecules such as nucleic acids, proteins, carbohydrates, and lipids, which results in cellular and tissue damage through the inflammation.[61] Free radicals and oxidative stress are contributing to the development of different diseases and health conditions such as cancer, autoimmune disorders, inflammation, aging, cataract, diabetes mellitus, rheumatoid arthritis, stroke, liver disorders, renal failure, cardiovascular and neurodegenerative diseases.[62,63]

Intake of antioxidant may reduce the harmful effects of ROS and free radicals on the immune response, which result in better performance of the immune system. Dietary phytochemicals such as polyphenolic and flavonoid compounds with antioxidant effects improve the immune response in all taxa of vertebrates.[64]

The antioxidant activity of phenolic compounds depends on their chemical structure, which can be determined by the action of these molecules as a reducing agent.[65] Flavonoids, a subgroup of polyphenolic compounds are described as powerful antioxidant and free-radical scavengers. *In vitro* experiments demonstrated that the antioxidant activity of flavonoids are more than vitamins E and C.[66] The antioxidant activity of flavonoids are attributed to hydrogen-donating ability of them.[67]

Flavonoid compounds inhibit *in vitro* lipid peroxidation through scavenging the superoxide anion and hydroxyl radicals at an early stage. They terminate chain radical reaction by donating hydrogen ion to a peroxy radical. Subsequently, the radical form of falvonoids will react with free radicals to terminate the propagating chain.[68,69] Therefore, the ability to scavenge hydroxyl radical increases with the number of hydroxyl groups present in the B ring, especially at the positions 3′ and 4′. The presence of hydroxyl groups at the C5 and C7 positions in the A ring, C3′ and C4′ in the B ring, as well as C3 in the C ring enhances the inhibition of lipid peroxidation.[13,70]

Bee pollen has high content of flavonoids.[21] The flavonoids of pollen extract, play an important role in the antioxidant and radical scavenging properties of

Table 2. A summary of anti-allergic and anti-inflammatory effects of bee pollen or main pollen type present in bee pollen samples and their flavonoid contents

Bee pollen	Family	Therapeutic effect	Identified flavonoids	Study model	Mechanism of action	Reference
Echium	*Boraginaceae*	Anti-inflammatory	Quercetin, Kaempferol	Macrophage RAW 264.7 cell	Reduction of NO and prostaglandin release in LPS-induced macrophage	52
Cistus	*Cistaceae*	Anti-inflammatory	Quercetin, Kaempferol, Isorhamnetin,	Male Wistar rats, RAW 264.7 cell	Inhibition of NO production and COX-2 activity	51
Echium	*Boraginaceae*	Anti-allergic	Quercetin, Kaempferol	Rat basophil cell line RBL-2H3	Inhibition of basophils degranulation, Inhibition of allergen-IgE complex formation, Inhibition of binding of allergen-IgE complex to basophil FcεRI	48
Bee * pollen		Anti-inflammatory			Inhibition of hyaluronidase activity	56
Bee pollen		Anti-allergic, Anti-inflammatory	Myricetin, Quercetin ,Tricetin, Luteolin	Male or female BALB/c mice, Wistar rats	Inhibition of IgG1 and IgE production, Inhibition of mast cell activation , inhibition of inflammatory mediators production	41
Bee pollen		Anti-allergic		BALB/c mice	Inhibition of mast cell activation, inhibition of TNF-α production, Inhibited of IgE binding to mast cells	40

* More than one main pollen type present in bee pollen sample

pollen.[16] It was demonstrated that, radical scavenging activity of bee pollen extract correlate with their total amount of phenolic and flavonoid compounds.[71,72] Moita et al reported that hydromethanolic extract of *E. plantagineum* pollen, which isrichin flavonoids mainly quercetin and kaempferol has antioxidant activity against NO and O_2 in a concentration-dependent manner.[52] Moreover, experimental studies indicated that *Cystus incanus* L. bee pollen as a food supplement, modulated antioxidant enzymes in the mice liver, brain, and lysate of erythrocytes; reduced hepatic lipid peroxidation and also showed anti-oxidant properties.[73]

In addition to flavonoids, it is possible that several compounds such as polyphenols, proteins and vitamins

contribute to antioxidant and radical scavenging activity of bee pollen. However, in the living systems, phenolic compounds such as flavonoids play an important role as dietary antioxidants for prevention of oxidative damage.[74]

The anti-oxidant and radical scavenging activity of bee pollens and their flavonoid contents, which have been proved by several studies, are presented in Table 3.

Bee Pollen Intake

Bee pollen has been used in folk medicine for centuries against various diseases. Bee pollens based on botanical and geographic origins have various bioactive compounds and thus have different types of therapeutic properties. The lay public probably uses bee pollen without regardingits contents and more often than is prescribed in clinical practice.

Recommended doses of bee pollen intake are based on those most commonly used in available trials or in historical practice. In the case of natural products it is often not clear what the optimal doses are to balance efficacy and safety. However, doses can be determined based on folkloric, traditional, or anecdotal use. In adults (age ≥ 18) an initial theoretical recommended dose is 1/8 to 1/4 teaspoon, once per day. The dosage may be gradually increased to 1–2 teaspoons one to three times per day. In pediatric (age < 18) available evidence for determining of bee pollen dosage is insufficient.[77] Therefore, it seems very difficult to determine the effective dose of bee pollen intake and bee pollen combination for each disorder so further *in vivo* experiments and clinical trials are needed to determine the doses and compositions of bee pollen for consumption in each disease.

Table 3. A summary of anti-oxidant and radical scavenging activity of bee pollen or main pollen type present in bee pollen sample and their flavonoid contents

Bee pollen Genus)(	Family	Therapeutic effect	Flavonoids content	Reference
Cistus	*Cistaceae*	Anti-oxidant	Quercetin, Kaempferol, Isorhamnetin,	51
Prosopis	*Fabaceae*	Anti-oxidant	Naringenin, Quercetin	75
Cystus	*Cistaceae*	Anti-oxidant	Pinocembrin, Quercetin, Kaempferol, Galangin, Isorhamnetin, Chrysin	73
Yucca	*Agavaceae*	Anti-oxidant	Naringenin, Quercetin	75
Ambrosia	Asteraceae	Anti-oxidant	Quercetin, Kaempferol and Isorhamnetin	76
Echium	*Boraginaceae*	Anti-oxidant	Quercetin, Kaempferol	52
Zea	*Poaceae*	Radical scavenging	Apigenin	72

Side Effects of Bee Pollen

Although bee pollen appears to be safe and there are recommendations for using bee pollen for allergic, immunological and other disorders and healthy compounds of it has been emphasized, it is very important to consult a physician before using any natural product for health condition. Some pollens have toxic substances such as mannose sugars, various alkaloids, heavy metals, pesticides, herbicides, mycotoxins, bacteria, antibiotics and polyphenolic compounds.[3,78] Some studies reported that allergic reactions including anaphylaxis have been recognized after intake of bee pollen.[79,80] Greyman et al have suggested that although bee pollen allergy is relatively rare, warnings regarding potential adverse reactions in sensitive individuals are urgently needed to protect the public from this hazard; therefore, it is better that bee pollen are used with caution in atopic individuals.[77,81] It

is suggested that patients with existing liver disease, hematological disorders, honey intolerance and allergic or hypersensitive to bee pollen and other bee products avoid bee pollen intake.[77] Further experimental and clinical studies concerning bee pollen extract activity and bioavailability are necessary before using it as a phytomedicine in allergic diseases. Identification and purification of bioactive compounds from bee pollen extracts for therapeutic use can prevent the possible harmful effects of direct intake of bee pollen or its extract. Therefore, bee pollen for phytotherapy should be taken under medical supervision.

CONCLUSION

Various herbal medicines have been used for centuries in treatment of different diseases. Phytotherapy has some advantages e.g. unique mechanisms of action, typically low side-effect profiles, low cost and a high level of acceptance by patients.[49] Thus, the idea of developing better drugs has encouraged researchers to find strategies to treat allergies[82] and other disorders by bee pollens or their bioactive compounds.

Although pollen grains are known by their allergic effects, they are used in folk medicine to alleviate symptom of some diseases such as allergies themselves.[41] Several studies indicated that bee pollen extract have anti-allergic,[41] immunomodulatory,[83] anti-oxidant.[18] radical scavenging[16] and anti-inflammatory[52] properties. These medicinal effects of bee pollens are partially mediated by some types of flavonoids. Several studies showed that some flavonols such as quercetin, kaempferol, myricetin and isorhamnetin have an important role in anti-allergic and anti-inflammatory properties of bee pollens.[41,48,51,52] Due to the fact that the structure of many flavonoids can be used as templates in the production of new medicines,[84] bee pollens with high contents of flavonoids are excellent candidates for future pharmacological, immunological and molecular studies.

Differences in the botanical origin, geographical location and the growing stage of plant samples affect the bee pollen composition and consequently the types and levels of bee pollen flavonoids.[85] Further comparative studies are recommended focusing on types, levels and medicinal properties of bee pollen flavonoids that originate from different plants collected from various geographical areas and at different growing stages.

Given that in most studies about the therapeutic effect of flavonoids, these compounds were examined separately, further experimental or clinical studies are recommended in the future for evaluating the therapeutic effects of different combination of flavonoids and their interaction with each other. Moreover, comparison between therapeutic effects of natural and synthetic flavonoids is recommended. These researches can contribute to production of more effective drugs and also will be useful for identification of bioactive compounds and their mechanism of action in bee pollens.

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