

Perspective

Antioxidant Properties of Bee Products Derived from Medicinal Plants as Beekeeping Sources

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Abstract: Plant species are fundamental source of nectar in beekeeping since bees access nectar and pollen from flowers. Consequently, bee products are strongly linked to the bee foraging flora source, and, depending on this, they acquire defined features, including their health and medicinal properties. Medicinal plants contribute greatly to increase the beneficial properties of bee products, such as honey, pollen, royal jelly, and propolis. Bee products represent a potential source of natural antioxidants that can counteract the effects of oxidative stress underlying the pathogenesis of many diseases. The antioxidant properties of bee products have been widely studied and there is an abundance of information available in the literature. Notwithstanding, the uniqueness of the presented perspective is to provide an updated overview of the antioxidant properties of bee products derived from medicinal plants as beekeeping sources. This topic is divided and discussed in the text in different sections as follows: (i) beekeeping and the impacts of environmental factors; (ii) an overview of the role of medicinal plants for bee products; (iii) definition and categorization of the main medicinal bee plants and related bee products; (iv) the study approach of the antioxidant properties; (v) the conventional and innovative assays used for the measurement of the antioxidant activity; and (vi) the antioxidant properties of bee products from medicinal plants.

Keywords: antioxidant properties; bee products; honey; propolis; plant sources; medicinal plants



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1. Introduction

Bee products represent a potential source of natural antioxidants, including phenolic acids, flavonoids, and terpenoids as well as numerous other phytochemicals, which are capable of counteracting the oxidative stress effects underlying the pathogenesis of many diseases [1]. The main action of the antioxidants is based on the capability to inhibit oxidation processes, thus reducing the production of free radicals, which result in triggering a chain reaction, which may cause harmful cellular alterations [2]. Reactive oxygen species (ROS) are produced by living organisms as a result of the normal cellular metabolism and environmental factors. The ROS are highly reactive molecules involved in many cellular signaling pathways, and can damage cell structures, such as carbohydrates, lipids, nucleic

antioxidant properties; (v) conventional and innovative assays used for the measurement of the antioxidant activity; and (vi) antioxidant properties of bee products from medicinal plants. To our knowledge, these features have not been studied together in previous perspectives in the literature.

2. Bee Products, Medicinal Plant, and Environment: An Overview

An overview of the linkage of beekeeping, bee products, medicinal plants, and environment is delineated in the following sub-sections by underlining the key role of medicinal plants for bee products. The following topics are explored: (i) beekeeping and the impacts of environmental factors; (ii) overview of the role of medicinal plants for bee products; and (iii) definition and categorization of the main medicinal bee plants and the related bee products. The sizable contribution of medicinal plants to health properties of bee products is notable.

2.1. Beekeeping and the Impacts of Environmental Factors

Bees are considered significant pollinators due to their effectiveness and wide diffusion worldwide. Bee pollination provides excellent value to crop quality and quantity, improving global economic and dietary outcomes [16].

Honeybees (*Apis mellifera*) are social species and represent one of the most important pollinators for agricultural systems [17,18]. Humans have managed honeybees for thousands of years, and developed bee breeding for all continents, mostly the United States and Europe [19,20].

Bees have been used to produce honey and play a mandatory role in pollination since the time of Ancient Egypt populations [21,22]. Many centuries later, in the seventeenth and eighteenth centuries, the improvement of beekeeping techniques made it possible to maintain large bee colonies giving rise to modern apiculture [23].

In the United States and Europe, Bruckner et al. [24] showed that beekeepers faced significant seasonal problems, namely high mortality occurred over the winter. In the United States, beekeepers contain 30% colony losses each winter. Other studies showed that seasonal floral resources, insecticide use, and the availability of natural environmental habitat are major drivers of bee health and abundance [25].

Honeybees are constituted by over 20,000 species and each colony contains thousands of individuals [26,27]. In Central Europe, the number of managed honeybee colonies have decreased since the 1960s [28,29].

This decrease in number could be attributed to bee activities, their survival and anthropic impact on the eco systems are closely connected; humans depend on bees for ecosystem services and the bees depend on the anthropic activities for their survival [30,31]. On the other hand, anthropic impact and environmental pollution are main issues regarding honeybee survival, and in this regard, it should be considered that the life of many plant species depends on bee pollination. The reduction of bee colonies poses a serious risk to many plant species survival, and can also be considered a biomarker for human health [32,33].

In an ecosystem global vision, recognizing several ecosystem services provided by bees is necessary, and so are the large variety of ecosystem services to humans, such as pollination, provision, regulation, and equilibrium [34]. If only one ecosystem service is considered, sharp declines in the provision of other ecosystem services may occur [35].

The honeybee is one of the most studied among all animals. This research has been almost entirely developed on the European honeybee *Apis mellifera*. According to the Food and Agriculture Organization (FAO) [36], only 11 new honeybee species have been recorded and identified in the past 15 years (Table 1).

Table 1. Eleven honeybees species as recorded worldwide [36–38].

Genus	Species of Honeybees
<i>Apis</i>	<i>Apis andreniformis</i>
	<i>Apis binghami</i>
	<i>Apis breviligula</i>
	<i>Apis cerana</i>
	<i>Apis dorsata</i>
	<i>Apis florea</i>
	<i>Apis koschevnikovi</i>
	<i>Apis laboriosa</i>
	<i>Apis mellifera</i>
	<i>Apis nigrocincta</i>
	<i>Apis nuluensis</i>

2.2. The Role of Medicinal Plants for Bee Products: An Overview

Plant species are fundamental in beekeeping as a source of nectar. The species visited by bees provide the honey with particular features: pleasant taste, typical color, and pharmaceutical beneficial properties. Honey is an exclusive vegetable product. About 80% of the world's population choose plant-based extracts for basic health care. The local population in many areas of the world uses medicinal plants holistically, and considers them an important source for the prevention and treatment of diseases, especially in low income countries where a conventional pharmacological approach may be difficult [39–42]. Honey is considered a therapeutic food, which possesses pharmacological activity [43].

The flora existing in the bees' environment is important for beekeeping since the bees collect nectar and pollen from flowers. The importance of flora in beekeeping has been observed by various authors around the world [44–46]. Plant species differ from place to place, in their flowering duration, due to climate, topography and agricultural practices. Knowing the type, density, and quality of bee flora are among the crucial factors for the success and productivity of beekeeping [47].

Forests, grasslands, agrophytocenoses (e.g., orchards, vineyards, flower crops), medicinal plant plantations, and aromatic herbs are frequently visited by bees to search for melliferous plants [48].

According to Bakour et al. [49], most beekeepers prefer plants characterized by several and numerous beneficial properties for the well-being of humans as antioxidant, anti-inflammatory, antifungal, antidiabetic, diuretic, having effects in the cure of different types of cancer, and also in the neurodegenerative, cardiovascular, and gastrointestinal tract diseases. The medicinal properties of bee products are also dependent on their botanical sources, as previously reported [50]; the several botanical origins provide bee products with numerous medicinal properties and products with therapeutic features for consumers.

Some of the most popular bee products for positive human health characteristics have been reported [51–53]:

1. Bee pollen: is a product rich in B vitamins, minerals, and unsaturated fatty acids. Many metabolic difficulties may be overcome with bee pollen supplementation and also it counteracts harmful bacteria.
2. Propolis: is effective against bacteria and purifies or disinfects. Its use is recommended for the treatment of colds, wounds, or ulcers, and diseases affecting the joints.
3. Bee bread: is a bee pollen-derived product, which acts as an activator of beneficial properties for blood circulation, is capable of healing and strengthening the immune and nervous system, and enriches polyunsaturated fatty acids intake.

The aforementioned products are strongly linked to the vegetable source from which the bees acquire their properties, including health and medicinal properties.

The importance of medicinal plants for beekeeping not only refers to the possibility of obtaining bee products from these species. In beekeeping, for some time, medicinal plant species have also been used as an alternative to pesticides [54–56]. According to

Khan et al. [57], many honey bee pathogens are contrasted with medicinal plants by beekeepers. Several medicinal plants are effective against fungi, mites as *Varroa* spp., and bacteria. Nguyen et al. [58] investigated physicochemical and viscoelastic properties of honey from medicinal plants, i.e., Tulsi, Alfalfa, and two varieties of Manuka honey derived from medicinal plants.

In the next section, bee products derived from medicinal plant sources are described and explored in detail.

2.3. Definition and Categorization of Main Medicinal Bee Plants and Related Bee Products

Many plants considered mainly as food or raw material sources have some special beneficial health effect [59–64]. Sage (*Salvia* spp.) leaves, for example, are the basis for an herbal tea, which can be used for medicinal purposes, but these are also used in food preparation as spices and seasonings (as an aromatic plant), while the essential oil is used in cosmetics (e.g., soaps, and toothpaste). In this sense, the term ‘medicinal’ is often understood in a wide sense, and includes several overlapping uses as herbal teas, spices, food, raw material, dietary supplements, and cosmetics containing extracts of derived compounds from plants [65].

The World Checklist of Useful Plant Species contains more than 40,000 taxon names from more than 400 families and 6000 genera with a documented human use [66]. Medicinal plants, both for human and veterinary use, account for 26,662 species, and this number constantly increases with research on uses in folk or traditional medicine systems and with the addition of new plant species. The exact number of species used as medicinal material in Europe is difficult to ascertain because of the limited amount of used material (which escape from trade catalogues), the origin from several (often undetermined) plant species and lack of documentation for local uses. About 2000 taxa commercially available are sources of medicinal and aromatic plant material, and two-third of them are represented by species native to Europe [65]. In particular, Germany (1500 taxa, 600 native), France (900 taxa, 450 native), and Spain (800, 600 native) are the leading countries in the trade of medicinal and aromatic plants in Europe.

The demand for wild-collected plants species is increasing worldwide, and has become a risk for the conservation and preservation of the natural resources [67]. Using data filtering from global checklists of medicinal plants, about 400 medicinal plant species native to Europe have been included in the European red list of medicinal plants [68]. For the species in which sufficient data are available, the 2.4% were assessed as threatened and the 4.5% near threatened, following International Union for Conservation of Nature (IUCN) Red List Categories. The highest number of species was found in the Mediterranean area and in mountain areas (e.g., Alps, Pyrenees, Massif Central, Balkan Peninsula), with a similar pattern for endemic plant species.

In the same study, the major threats have been identified as wild plant collection and loss of habitat (respectively, 26% and 30% of all species), connected to human impact, the so called anthropic effect (e.g., livestock farming, recreational activities, tourism, use of chemicals, pollution, and urban development).

Bee foraging activity on plants is dedicated to the search of nectar and honeydew as carbohydrate sources, pollen (as a protein source), and resins to produce propolis (for antimicrobial and defense purposes) [69]. Pollen is collected by the bees during their visits on the plant flowers and it is stored in pellets as a protein source into the hive. The botanical origin of both honey and pollen depends on the flora surrounding the area of foraging and influences physico-chemical, functional, and sensory properties of bee products [70–72].

More than half of the medicinal plant species of the European checklist might be considered as relevant nutrition sources for bees (Table 2).

Table 2. Main plant taxon (family, genus) of the European medicinal plant red list in relation to bee foraging sources. N = number of species belonging to the shown genus or group (W = attractive plants for wild bees). Plant data from Allen et al. [68], bee preferences for pollen and nectar from MLR, [73], MAA, [74].

Plant Family	N.	Nectar	N.	Pollen	Honeydew	N.	Wild Bees
AMARYLLIDACEAE	2	<i>Allium</i>	2	<i>Allium</i>		2	W
ANACARDIACEAE	1	<i>Cotinus</i>	1	<i>Pistacia</i>			
BETULACEAE			2	<i>Betula</i>	<i>Betula</i>		
BORAGINACEAE	3	<i>Borago</i> , <i>Symphytum</i> , <i>Pulmonaria</i>	3	<i>Borago</i> , <i>Symphytum</i> , <i>Pulmonaria</i>		3	W
CAPRIFOLIACEAE	4	<i>Valeriana</i> , <i>Viburnum</i> , <i>Sambucus</i>	4	<i>Valeriana</i> , <i>Viburnum</i> , <i>Sambucus</i>		2	W
ASTERACEAE	13	<i>Arctium</i> , <i>Aster</i> , <i>Cichorium</i> , <i>Taraxacum</i> , <i>Achillea</i> , <i>Inula</i> , <i>Matricaria</i> , <i>Silybum</i> , <i>Solidago</i> , <i>Tanacetum</i> , <i>Tussilago</i>	15	<i>Arctium</i> , <i>Aster</i> , <i>Cichorium</i> , <i>Taraxacum</i> , <i>Achillea</i> , <i>Inula</i> , <i>Matricaria</i> , <i>Silybum</i> , <i>Solidago</i> , <i>Tanacetum</i> , <i>Tussilago</i> , <i>Helichrysum</i>		8	W
CRUCIFERAE	1	<i>Brassica</i>	3	<i>Brassica</i> , <i>Capsella</i> , <i>Lepidium</i>		3	W
CUPRESSACEAE			4	<i>Juniperus</i>			
ERICACEAE	7	<i>Calluna</i> , <i>Erica</i> , <i>Vaccinium</i> , <i>Arbutus</i> , <i>Rhododendron</i>	6	<i>Calluna</i> , <i>Erica</i> , <i>Vaccinium</i> , <i>Rhododendron</i>		1	W
FAGACEAE	1	<i>Castanea</i>	4	<i>Castanea</i> , <i>Quercus</i>	<i>Castanea</i> , <i>Quercus</i>	3	W
IRIDACEAE	7	<i>Iris</i>				7	W
LAMIACEAE	34	<i>Hyssopus</i> , <i>Lavandula</i> , <i>Thymus</i> , <i>Glechoma</i> , <i>Nepeta</i> , <i>Origanum</i> , <i>Prunella</i> , <i>Rosmarinus</i> , <i>Salvia</i> , <i>Teucrium</i> , <i>Galeopsis</i> , <i>Lamium</i> , <i>Leonurus</i> , <i>Melissa</i> , <i>Satureja</i> , <i>Stachys</i> , <i>Mentha</i>	34	<i>Hyssopus</i> , <i>Lavandula</i> , <i>Thymus</i> , <i>Glechoma</i> , <i>Nepeta</i> , <i>Origanum</i> , <i>Prunella</i> , <i>Rosmarinus</i> , <i>Salvia</i> , <i>Teucrium</i> , <i>Galeopsis</i> , <i>Lamium</i> , <i>Leonurus</i> , <i>Melissa</i> , <i>Satureja</i> , <i>Stachys</i> , <i>Mentha</i> , <i>Clinopodium</i> , <i>Ballota</i>	<i>Thymus</i>	34	W
LEGUMINOSAE	7	<i>Melilotus</i> , <i>Trifolium</i> , <i>Medicago</i> , <i>Astragalus</i> , <i>Ononis</i> , <i>Pisum</i>	6	<i>Melilotus</i> , <i>Trifolium</i> , <i>Medicago</i> , <i>Ononis</i> , <i>Pisum</i>		7	W
MALVACEAE	3	<i>Malva</i> , <i>Althaea</i>	3	<i>Malva</i> , <i>Althaea</i>		1	W
OLEACEAE			3	<i>Fraxinus</i> , <i>Olea</i>	<i>Fraxinus</i>		
ORCHIDACEAE						30	W
PAEONIACEAE	3	<i>Paeonia</i>	3	<i>Paeonia</i>		3	W
PAPAVERACEAE			3	<i>Papaver</i> , <i>Chelidonium</i>			
PINACEAE			4	<i>Pinus</i> , <i>Abies</i> , <i>Larix</i>	<i>Pinus</i> , <i>Abies</i>		
PLANTAGINACEAE			6	<i>Plantago</i>		5	W
POLYGONACEAE	1	<i>Polygonum</i>	4	<i>Polygonum</i> , <i>Rumex</i>			
PRIMULACEAE	3	<i>Primula</i>	3	<i>Primula</i>		2	W
RANUNCULACEAE	7	<i>Aquilegia</i> , <i>Helleborus</i> , <i>Aconitum</i> , <i>Ficaria</i> , <i>Pulsatilla</i>	8	<i>Aquilegia</i> , <i>Helleborus</i> , <i>Aconitum</i> , <i>Ficaria</i> , <i>Pulsatilla</i> , <i>Hepatica</i>		2	W
ROSACEAE	15	<i>Malus</i> , <i>Prunus</i> , <i>Rubus</i> , <i>Agrimonia</i> , <i>Crataegus</i> , <i>Geum</i>	25	<i>Malus</i> , <i>Prunus</i> , <i>Rubus</i> , <i>Agrimonia</i> , <i>Crataegus</i> , <i>Geum</i> , <i>Rosa</i> , <i>Filipendula</i>		7	W
RUBIACEAE	3	<i>Galium</i>	3	<i>Galium</i>			
SALICACEAE	4	<i>Salix</i>	5	<i>Salix</i> , <i>Populus</i>	<i>Salix</i>	4	W
SCROPHULARIACEAE	5	<i>Digitalis</i> , <i>Veronica</i> , <i>Verbascum</i>	7	<i>Digitalis</i> , <i>Veronica</i> , <i>Verbascum</i>		7	W
TILIACEAE	3	<i>Tilia</i>	3	<i>Tilia</i>	<i>Tilia</i>	3	W
APIACEAE	5	<i>Foeniculum</i> , <i>Eryngium</i> , <i>Daucus</i> , <i>Angelica</i>	6	<i>Foeniculum</i> , <i>Eryngium</i> , <i>Daucus</i> , <i>Angelica</i> , <i>Carum</i>		5	W
VIOLACEAE	4	<i>Viola</i>	4	<i>Viola</i>		3	W

Species belonging to the *Lamiaceae* (37 medicinal plant species), *Orchidaceae* (30), *Rosaceae* (26), and *Asteraceae* (16) plant families are the main species. *Lamiaceae* plant genera (e.g., *Lavandula*, *Thymus*, *Teucrium*, *Salvia*, *Stachys*) are visited by bees mainly as nectar sources, while *Rosaceae* (e.g., *Malus*, *Prunus*, *Rubus*, *Crataegus*) and *Asteraceae* (e.g., *Aster*, *Taraxacum*, *Tussilago*, *Tanacetum*, *Helichrysum*) are for both nectar and pollen foraging, although many plant species offer both nutrition resources to bees. On the opposite, genera of the *Orchidaceae* family (e.g., *Anacamptis*, *Dactylorhiza*, *Ophris*, *Orchis*) have a limited value for foraging, although these species attract wild bees (e.g., bumble bees of the genus *Bombus*) with their flowers [75]. Overall, many plants of these families have great relevance

for oligolectic wild bees, which are adapted to collect pollen only from a small number of plant species [76].

By extending the analysis from the European medicinal plant checklist to some mainly cultivated or non-native medicinal plant species (Table 3), several plant taxa are of importance as sugar or pollen resources for bees.

Table 3. Some examples of plant taxon (family, genus) of cultivated/non-native medicinal plants in Europe, in relation to bee foraging sources (nectar, pollen). Plant data from Wichtl [77], bee preferences for pollen and nectar from MLR, [73], MAA, [74].

Plant Family	Nectar and Pollen Sources
AMARYLLIDACEAE	<i>Allium, Galanthus</i>
BORAGINACEAE	<i>Echium, Lithospermum, Anchusa</i>
ASTERACEAE	<i>Carlina, Centaurea, Helianthus, Calendula, Eupatorium, Hieracium, Tanacetum, Artemisia, Bellis</i>
CRUCIFERAE	<i>Iberis, Isatis, Erysimum</i>
CUCURBITACEAE	<i>Cucurbita, Bryonia</i>
FABACEAE	<i>Anthyllis, Lotus, Hedysarum, Cytisus</i>
IRIDACEAE	<i>Crocus, Iris</i>
LAMIACEAE	<i>Lavandula, Teucrium, Mentha, Satureja</i>
MYRTACEAE	<i>Eucalyptus</i>
ONAGRACEAE	<i>Epilobium</i>
PLANTAGINACEAE	<i>Linaria, Plantago</i>
RANUNCULACEAE	<i>Helleborus, Nigella, Consolida</i>
RHAMNACEAE	<i>Rhamnus</i>
ROSACEAE	<i>Prunus, Geum</i>
RUTACEAE	<i>Citrus</i>
APIACEAE	<i>Coriandrum, Pimpinella, Levisticum</i>

Some examples include tree species of the families *Rutaceae* (e.g., *Citrus*), *Rosaceae* (e.g., *Prunus*), *Myrtaceae* (e.g., *Eucalyptus*), shrubs of *Fagaceae* (e.g., *Corylus*), *Eleagnaceae* (e.g., *Hippophae*), and herbaceous species *Asteraceae* (e.g., *Helianthus*), *Apiaceae* (e.g., *Coriandrum*, *Levisticum*, *Pimpinella*), which are planted for different purposes (fruit crop, timber, vegetable) or belong to an anthropic habitat. An example of an interesting new medicinal and melliferous plant, the *Perilla frutescens*, an annual herb originating from China, Japan, India, Thailand and Korea, and belonging to the mint family (*Lamiaceae*) also grows in Italy, and is described and discussed by Barbieri and Ferrazzi [78].

In Figure 2, some medicinal plants growing in Italy are shown in relation to their foraging importance for bees (e.g., as sources of nectar, pollen, propolis or honeydew).

Apart from the nectar, bees also collect honeydew as a sugar source, if available in their foraging area. The main sources of honeydew are forests and conifer trees, which originate in the secretions from the living part of the plant (e.g., the leaves) or from sap-sucking insects [71]. In Europe, honeydew honey originates mainly from fir (*Abies alba*), spruce (*Picea abies*), and *Pinus* (e.g., *Pinus halepensis*, *P. brutia*) trees, but also from *Salicaceae* (*Salix*, *Populus*), *Fagaceae* (*Castanea*, *Quercus*), *Oleaceae* (*Fraxinus*, *Olea*), *Tiliaceae* (*Tilia*), *Betulaceae* (*Betula*) and *Sapindaceae* (*Aesculus*) [71]. Due to the variety of nectar and honeydew sources in natural or artificial habitats, a wide range of different types of honey can originate [79].

Various floral honeys are regarded as medicinal honeys with high polyphenol contents. Manuka dark-colored honey, for example, originates from *Leptospermum scoparium* and *L. polygalifolium*, shrubs native to Australia and New Zealand of the *Myrtaceae* family [80,81]. Another example are the honeys from *Acacia ehrenbergina* (*Fabaceae*) and *Ziziphus spinachristi* (*Rhamnaceae*), trees native to some areas of Africa and Asia, which show high phenolic contents [82]. Propolis originates from collected vegetable material by bees and is mixed with wax. Main sources for propolis production by bees are restricted to a small number of species, which are typical for specific geographic areas [79,83]. In Europe and North America, tree species of the genera *Populus* (e.g., *Populus tremula*, *P. nigra* in Europe, *P. deltoides* and *P. trichocarpa* in America) and *Betula*, are known as resin resources for

bees, while in tropical and subtropical areas, *Dalbergia* and *Acacia* (Fabaceae), *Macaranga* (Euphorbiaceae), *Mangifera* and *Rhus* (Anacardiaceae), and *Baccharis* (Asteraceae), are the main sources. In the Mediterranean areas, where *Populus* species might be less frequent, the source of resins for propolis are the *Cupressus sempervirens* and the *Juniperus phoenicea* [84].



Figure 2. Examples of medicinal plant sources for bees: (A) *Robinia pseudoacacia* (nectar), (B) *Tilia cordata* (nectar, pollen, honeydew), (C) *Rubus ulmifolius* (nectar), (D) *Eucalyptus camaldulensis* (nectar, pollen, honeydew), (E) *Populus nigra* (propolis), (F) *Pinus pinaster* shoot heavily infested by *Toumeyella parvicornis* (pine tortoise scale, honeydew).

3. Bee Products from Medicinal Plants: Antioxidant Properties Measurements

Natural products, including bee products, which often contain medicinal plants containing compounds, such as honeydew secretions of *Abies*, *Betula*, *Castanea*, *Fraxinus*, *Pinus*, *Quercus*, *Rosemary*, *Thymus*, *Tilia*, and other species, are particularly appreciated by consumers for therapeutic uses as an alternative to drugs [85]. Antioxidants are sourced from the plant species. Medicinal plants generally recognized as having potential beneficial value can therefore be utilized to obtain honey with greater bioactivity and bioavailability.

Nowadays, apitherapy has gained much attention from both consumers and researchers. In principle, apitherapy is a theory of alternative medicine that utilizes bee products, such as honey, pollen royal jelly, propolis, and bee venom, for medicinal purposes. However, it remains scarce and not exactly known whether treatments with bee products are safe and how the possible health risks of using such products can be minimized [85]. Proponents of apitherapy make claims for its health benefits, which in contrast, are unsupported by traditional medicine [50,86,87].

In this context, the antioxidant properties of bee products can be considered as an expression of the *melliferous* medicinal plants' therapeutic potential. Updates and considerations on the approach towards antioxidant properties have been mentioned; nonetheless, the conventional and innovative assays for the assessment of antioxidant properties and the remarkable antioxidant properties of bee products from medicinal plant cannot be neglected.

3.1. Study Approach of the Antioxidant Properties: Updates and Considerations

The combined action of bioactive compounds, nutrients, and nutraceuticals represents the first step to study antioxidant properties and can be regarded as an indicator of the "health properties" of the food matrices [88,89].

The diversity of the chemical structure of compounds, their possible interactions, and their different mechanisms of action and biological role, make difficult the assessment of a single, adequate, and reliable procedure for the determination of antioxidant properties. Antioxidant properties are an expression of the interactions between bioactive molecules and other components in terms of both the potential health benefits of food and can be viewed as a screening method for interpretation and supporting further research. Extraction, antioxidant capacity measurements, and expression of the results can be viewed as the three key steps in the evaluation of the antioxidant properties. A study by Durazzo et al. [90] reported as the main workflow in research approach of the antioxidant properties three main steps, namely: (i) the development of a system as model study of the compounds' interactions; (ii) the investigation of extractable and non-extractable compounds; (iii) the behavior study of bioactive compounds-rich extracts.

Nowadays, the distinction between extractable and non-extractable antioxidants has been recognized as a fundamental aspect in the definition of the healthy properties in terms of the prevention of diseases [91,92]. In particular, the distinction between extractable and non-extractable antioxidants has achieved a shared consensus in the scientific community.

Indeed, new research directions point to the exploitation of new and unconventional sources for antioxidants and to the identification of new possible applications.

This research on the antioxidant properties should be based on an integrated and multidisciplinary approach, resulting from a combination of studies in several areas, such as nutrition, food chemistry, phytochemistry, and medicine. Innovative design of study research includes green procedures and sustainable technologies, and the joined up use of statistical methods, such as chemometrics.

An overall challenge is the development of dedicated databases for the antioxidant properties and the inclusion into harmonized databases; these are studies currently being carried out.

The inclusion of extractable and non-extractable compounds in current comprehensive and harmonized databases have been developed in the eBASIS BioActive Substances in Food Information System [93–95]. The development of search protocols and data collection systems have allowed to obtain new quality evaluated data on extractable and non-extractable antioxidants, used for the expansion eBASIS, leading thus, to a valuable unique data resource [96]. A total of 437 datapoints on the composition of extractable and/or non-extractable compounds were added into the database. This update of eBASIS can be viewed as the first examples of building a database dedicated to antioxidant properties. This eBASIS' expansion provides a new and unique tool for dietitians, nutritionists, and researchers for a great range of uses, e.g., dietary assessment, epidemiological studies, and exposure studies [96].

In this context, the study of Pellegrini et al. [97], by summarizing 25 years of investigations on antioxidants research in foods and biological fluids, remarked how the availability of well-constructed Total Antioxidant Capacity databases deserves attention and must be considered. Moreover, the same authors highlighted how the appropriate use of Total Antioxidant Capacity measurement both in food and in vivo can still support interpretation of complex phenomena and can be viewed as a useful tool, for instance, for the sample screening when making a quick decision toward in-depth research investigations [97].

3.2. Antioxidant Properties Assessment: An Overview of Conventional and Innovative Assays

A variety of assays aimed at evaluating the dietary antioxidant properties have been proposed, although a reliable and commonly accepted assay has not been so far identified [98]. Overall, the methods available can be grouped into three major classes, namely in vitro, cellular, and in vivo assays. In vitro chemical assays are the most frequently used, because these are cheap and have high-throughput, but their prediction ability has been questioned in recent years [99,100]. Cell-based assays are considered a middle ground between the in vitro and in vivo tests (the latter posing ethical issues, high cost, and limited throughput) [101]. However, cellular antioxidant assays still suffer from poor standardization (e.g., differences in cell line, radical generators, fluorescent probes, etc.), making the reported results difficult to be compared across the available studies [102]. Moreover, some authors claimed that cell culturing itself may induce oxidative stress as a consequence of culture conditions, hence inducing cell acclimation and, thus, overestimating the antioxidants efficacy [103].

In this complex framework, in vitro tests still represent the most frequently used antioxidant assay methods in food science. Among others, they include the DPPH (α, α -diphenyl- β -picrylhydrazyl), the ABTS (2,2'-azinobis(3-ethylbenzothiazolin-6-sulphonate), FRAP (ferric reducing antioxidant power), the CUPRAC (cupric-ion reducing antioxidant capacity), and ORAC (oxygen radical absorbance capacity) assays, [98,104–106]. The measurement of the ability of a food or a food component to scavenge specific free radicals or to reduce a target molecule are the base for all the above mentioned methods. Differences in their principles, mechanisms, experimental conditions, and in how their end points are measured occur, and for this reason the use of several methods to estimate and/or determine the antioxidant properties is suggested. Procedures and applications for these assays should be considered for standardization [107]. Moreover, one of the main concerns on the above mentioned assays is that these are not carried out under physiological conditions, and thus, their ability to predict in vivo effects has been questioned. Notwithstanding, most of the scientific literature on bee product antioxidant capacity is referred to in vitro tests, as with other foods, with the exception of a recent paper that investigated the cellular antioxidant capacity of different Moroccan Zantaz honey samples [108].

In general, in vitro assays account for different antioxidant mechanisms that include hydrogen atom transfer (HAT), and single electron transfer (SET) rather than chelation of transition metal ions. ORAC is probably the most representative HAT-based assay, while DPPH, CUPRAC, ABTS and FRAP are SET-based methods. However, the ability to chelate Cu^{2+} and Fe^{2+} , a key initiation step in the oxidation processes, has also been considered in the context of the foods antioxidant properties [109].

Regarding the antioxidant properties of bee products, as with any other food, the limitations in these assays must be considered. Moreover, it must also be considered that in many situations, both HAT and SET occur simultaneously in vivo, and that antioxidant compounds may also act indirectly, via the regulation of antioxidant enzymes.

3.3. Antioxidant Properties of Bee Products Relates to Foraging on Medicinal Plants

The link between bee foraging on medicinal plants and antioxidant properties of bee products has received increasing attention. Nicewicz et al. [110] compared the antioxidant capacity of honey from urban areas vs. rural apiary, reporting that all antioxidant parameters were significantly higher in honey from rural than in urban areas. Such differences

were not ascribed to the effect of the floral composition of honey, being rather due to the location of the honeybee colonies. In recent years, while wild pollinators are declining in many landscapes, urban areas provide high plant diversity and foraging sources for bees. Therefore, a growing interest for beekeeping in cities is observed, but the quality and safety of honey produced in urban areas impacts on the consumers' concerns. Therefore, further research in this direction is needed [75].

The following sub-sections discuss the relationship between floral diversity and bioactivity of bee products, with a specific focus on each product.

3.3.1. Honey

Honey (or honeybee honey) is a sugary foodstuff prepared by honeybees. Bees produce honey from the sugary secretions of plants (floral nectar) or from secretions of other insects of the *Aphids* family (honeydew) through their enzymatic activities and other biochemical processes, such as regurgitation and water evaporation. Honeybees store honey in wax structures called honeycombs, whereas stingless bees store honey in pots made of wax and resin [111]. Many centuries ago, in different civilizations, honey was used by ancient Greeks and Egyptians, and in Indian and Chinese traditional medicine both orally and topically to treat various illnesses. Traditional medicine reports uses towards stomach disorders, ulcers, skin wounds, and skin burns [112]. Several honey products have gained medical status and have been approved by the United States Food and Drug Administration (FDA) for their use in the treatment of wounds and burns [113]. It has been reported that honey has antioxidant, antibacterial, and antibiotic properties. The existence of numerous phytochemicals in different types of honey originating from plants known for their medicinal properties, such as *Thymus*, *Abies*, *Pinus*, *Castanea*, and *Rosemary* botanical species supports its antioxidant activity [114–118].

In more detail, Gheldof et al. [118] reported that buckwheat (*Fagopyrum esculentum*) honey increased human's serum antioxidant activity. Anand et al. [119] characterized the physico-chemical and antioxidant properties of *Agastache* honey produced from *Agastache rugosa* in comparison with commercial honeys sold in the Australia market. Their results confirmed that *Agastache* honey had a superior antioxidant capacity [119]. More recently, Adgaba et al. [120] studied, among others, the antioxidant and anti-microbial properties of some Ethiopian monofloral honeys, reporting average total antioxidant values of $320.3 \pm 15.1 \mu\text{M Fe(II)}/100 \text{ g}$ with a range of 225.4–465.7 $\mu\text{M Fe(II)}/100 \text{ g}$. The same study reported relatively higher values (421.5 ± 23.4 and $465.7 \pm 21.8 \mu\text{M Fe(II)}/100 \text{ g}$) for *Croton macrostachyus* and *Vernonia amygalina* honeys, respectively. Nonetheless, in a review article focusing, among others, on the antioxidant properties of monofloral honeys, several honey types produced in different countries, such as acacia (*Acacia* sp.), astragalus (*Astragalus microcephalus* Willd), linden (*Tilia* sp.), willow (*Salix* sp.), and others, were reported to provide antioxidant capacity using multiple antioxidant assays, such as ABTS, DPPH, FRAP, ORAC, and TEAC (Trolox equivalent antioxidant capacity) [121].

The antioxidant activity of the studied honeys was affected by the botanical source and the geographical origin [121].

3.3.2. Bee Pollen and Its Derivatives

Bee pollen is among the honeybee products that contain nourishing nutrients, which can provide energy to humans. The health-enhancing value of bee pollen is owed to plant secondary metabolites, such as tocopherols, niacin, thiamine, biotin and folic acid, polyphenols, carotenoids, phytosterols, enzymes and other co-enzymes [85,122]. However, the studies highlighting the antioxidant, anti-inflammatory, anticarcinogenic antibacterial, antifungicidal, hepatoprotective, anti-atherosclerotic, immune enhancing properties need to be more extensive, concerning mainly the application of cohort clinical trials. The basic hurdle in the use of bee pollen as functional component is probably related to the broad species/specific variation in its composition [122]. Such variations may differently contribute to the properties of bee-pollen and biological activity, and thus, may affect

its therapeutic effects (positively or negatively). Notwithstanding, bee pollen has been recommended as a valuable dietary supplement [85]. Pollen antioxidant activity has been related to a wide range of botanical species, such as *Papaver rhoes*, *Chamomila recutita*, *Sinapis arvensis*, *Cistus* sp., *Trifolium* sp., *Dorycnium* sp., *Cichorium* sp., *Convolvulus* sp., *Cirsium* sp., *Malva sylvestris*, *Fumana* sp., *Eucalyptus camaldulensis*, *Anemone* sp., *Ononis* sp., *Asphodelus* sp., and *Quercus ilex* [122].

Moving toward bee pollen-derived products, bee bread has a similar composition to bee pollen, but with marked quantitative differences mainly related to the fermentation process, which it undergoes. For instance, bee bread delivers higher amino acids, sugar, lactic acid, and vitamin content compared to bee pollen [123,124]. In a recent study, bee bread from different regions in Greece, containing *Castanea sativa*, *Cistus* sp., *Hedera helix*, *Borago* sp., and other pollen grains belonging to the *Brassicaceae* family, showed both antibacterial and antioxidant activity [125].

3.3.3. Propolis

Propolis, commonly known as the “bee glue” is a resinous mixture that honeybees produce by mixing their saliva, which contains enzymes and beeswax, with exudate gathered from different plant materials such as leaf and flower buds, stems, and bark cracks of numerous tree species. The word propolis originates from the two Greek words “pro” and “polis”, which mean “defense” and “city” or “community,” respectively [50]. Propolis is typically composed of 50–60% of resins and balms (including phenolic compounds), 30–40% of wax and fatty acids, 5–10% of essential oils, 5% of pollen, and approximately 5% of other components, including amino acids, micronutrients, and vitamins (thiamin, riboflavin, pyridoxine, vitamins C, and E). More than 300 compounds belonging to polyphenols, terpenoids, steroids, sugars, amino acids, and others have been identified in propolis [126].

The antioxidant activity of propolis has been determined by the use of in vitro methods, such as DPPH, ABTS+, FRAP, and ORAC [50]. Interestingly, the antioxidant activity of propolis extracts was comparable to the synthetic antioxidant butylated hydroxytoluene (BHT) or to ascorbic acid. Moreover, studies regarding the antioxidant properties of propolis, have also been carried out on cell cultures and animals. Clinical trials investigating the antioxidant effect of propolis reported a positive modulation of cardiovascular disease markers, a mitigation of chemotherapy side effects, as well as neuroprotective effects [127–129].

Similar to other bee products, plant sources are related to the profile of bioactive compounds and antioxidant properties of propolis [130,131]. More specifically, in regions with a large diversity of trees, bees may also gather resin from flowers in the genera *Clusia* (*Clusia* L.) and *Dalechampia* (*Dalechampia* L.), which are the major plant genera that produce floral resins to attract pollinators [132]. *Clusia* resin contains polyprenylated benzophenones [133,134]. In some areas of Chile and Brazil, propolis contains viscidone, a terpene from *Baccharis* (*Baccharis* L.) shrubs, and prenylated acids, such as 4-hydroxy-3,5-diprenyl cinnamic acid [135,136].

3.3.4. Royal Jelly

Royal jelly is a mixture of secretions from the mandibular and hypopharyngeal glands of bees of the *Apis mellifera* species, representing the major food source for the queen honeybee [50]. Concerning its composition, royal jelly is an emulsion of proteins, sugars, and lipids in water. Moreover, it contains approximately 1.5% (*w/w*) of minerals (mainly copper, zinc, iron, calcium, manganese, potassium, and sodium) and considerable amounts of flavonoids, polyphenols, and vitamins (biotin, folic acid, inositol, niacin, pantothenic acid, riboflavin, thiamine, and vitamin E). Among the flavonoids, the flavanones (hesperetin, isosakuranetin, and naringenin), flavones (acacetin, apigenin, and its glucoside, chrysin, and luteolin glucoside), flavonols (isorhamnetin and kaempferol glucosides), and isoflavonoids (coumestrol, formononetin, and genistein) are the most abundant [137].

The antioxidant activity of royal jelly, in terms of DPPH, hydroxyl and superoxide radical scavenging, has been reported in the literature [138,139]. In this regard, both in vitro and in vivo tests have been conducted, whereas less information has been reported from clinical trials. In a recent study carried out by Pourmoradian et al. [140], the positive impact of royal jelly consumption on the parameters associated with diabetes and oxidative stress in people affected by Type 2 diabetes mellitus has been postulated. On the other hand, studies on rats and rabbits reported that royal jelly intake can be associated with antioxidant and neuroprotective effects [141,142]. This is consistent with the antioxidant activity of monophosphate nucleotides and peptides isolated from royal jelly [143].

More generally, the antioxidant activity of royal jelly may be differentiated compared to honey, bee pollen and propolis. However, the specific contribution of the botanical species available for foraging on the actual functional properties of royal jelly is still poor.

4. Conclusions and Future Directions

It is clear that medicinal plants can contribute to the antioxidant activity of bee products along with the honeybee contribution as a living organism; the antioxidant properties can be regarded as an indicator of the *melliferous* medicinal plant's potential. In this context, more research should be focused on bee products obtained from the broad range of medicinal plants and on the identification of the possible relationships between the bioactive components, which are present in plant parts and their nectars as well as the bee products.

At the same time, research and clinical trials should be conducted on humans to assess the relationship between the consumption of bee products and the aiding or treatment in health disorders. In this way, the potential use of bee products in phytomedicine (as an alternative to drugs) could be better substantiated by the scientific evidence. The complementary use of the nanotechnologies [144,145] opens new directions and new frontiers. For instance, Neupane et al. [146], by developing Himalayan honey-loaded iron oxide nanoparticles, showed that the biological activity of Himalayan honey was enhanced significantly after loading into iron oxide nanoparticles. Sarhan and Azzazy [147] developed biocompatible, antimicrobial crosslinked honey/polyvinyl alcohol/chitosan nanofibers, which hold potential as an effective wound dressing source. These aspects are relevant and trigger an additional interest for research to obtain a greater bioavailability and efficacy of bee products in the field of health, including anti-COVID-19 possible beneficial effects [148–151], also increasing the interest in studies that are carried out to assess the safety aspects of nanoformulations, which are indeed new frontiers to explore.

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