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REVIEW

Royal jelly: a predictive, preventive and personalised strategy for novel treatment options in non-communicable diseases

Beatriz G. Baptista[1] · Ligia S. Lima[2] · Marcia Ribeiro[2] · Isadora K. Britto[2] · Livia Alvarenga[2,3] · Julie A. Kemp[3] · Ludmila FMF Cardozo[3] · Andresa A. Berretta[4] · Denise Mafra[1,2,3,5]

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Abstract

Royal jelly (RJ) is a bee product produced by young adult worker bees, composed of water, proteins, carbohydrates and lipids, rich in bioactive components with therapeutic properties, such as free fatty acids, mainly 10-hydroxy-trans-2-decenoic acid (10-H2DA) and 10-hydroxydecanoic acid (10-HDA), and major royal jelly proteins (MRJPs), as well as flavonoids, most flavones and flavonols, hormones, vitamins and minerals. In vitro, non-clinical and clinical studies have confirmed its vital role as an antioxidant and anti-inflammatory. This narrative review discusses the possible effects of royal jelly on preventing common complications of non-communicable diseases (NCDs), such as inflammation, oxidative stress and intestinal dysbiosis, from the viewpoint of predictive, preventive and personalised medicine (PPPM/3PM). It is concluded that RJ, predictively, can be used as a non-pharmacological therapy to prevent and mitigate complications related to NCDs, and the treatment must be personalised.

Keywords Royal jelly · Non-communicable disease · Oxidative stress · Inflammation · Dysbiosis · Predictive preventive personalised medicine (PPPM/3 PM)

Introduction

Non-communicable diseases (NCDs), specifically chronic kidney disease, cardiovascular diseases, diabetes, cancer and chronic respiratory diseases, are responsible for 17 million premature deaths yearly, causing nearly three-quarters of deaths worldwide [1]. By 2023, the NCD mortality rate would be 510.54 (per 100,000 population), whilst the global mean NCD deaths would be 75.26% of the total deaths [2].

✉ Denise Mafra
dm@id.uff.br

1 Graduate Program in Medical Sciences, Fluminense Federal University (UFF), Niterói, RJ, Brazil

2 Graduate Program in Biological Sciences – Physiology, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil

3 Graduate Program in Nutrition Sciences, Fluminense Federal University (UFF), Niterói, RJ, Brazil

4 Research, Development, and Innovation Department, Apis Flora Indl. Coml. Ltda, Ribeirão Preto, SP, Brazil

5 Unidade de Pesquisa Clínica, UPC, Rua Marquês de Paraná, 303/4 Andar, Niterói, RJ 24033-900, Brazil

NCDs are associated with some complications, such as inflammation, oxidative stress and gut dysbiosis [3]. Oxidative stress is mainly caused by a high production of reactive oxygen species (ROS) in the cells (most by macrophages) and low antioxidant levels. Oxidative stress is closely associated with inflammation since it can stimulate the expression of genes involved with nuclear transcription factors that can increase cytokine production [4].

Some unhealthy lifestyle is heavily linked to the causes and progression of NCDs, also known as lifestyle diseases. Prioritising a balanced diet, especially concerning a non-pharmacological treatment surrounding the "food as medicine" concept, is one of the steps to prevent and control NCDs, reducing the need for expensive therapies [1, 5]. Bioactive nutraceuticals found in foods could improve health in those diseases [6].

Royal jelly is a bee product used for feed of honeybee larvae. The worker bees are fed royal jelly until the third day of life, whilst the selected female that will become the queen bee is fed royal jelly throughout her life. The worker bees live around 40 days, whilst the queen bees are around 5–6 years old. The nutritional transformation of immature female larvae into a fertile queen bee is usually linked to the

benefits of royal jelly nutrients, including the longevity of the queen [7, 8].

Royal jelly (RJ), an acidic emulsion produced by young adult worker *Apis mellifera* bee specie, which comes from the secretion of bee hypopharyngeal and mandibular glands, has been studied as antimicrobial, anti-inflammatory, anticancer, bio-stimulating, antiaging, immuno-modulating and antioxidant besides several others [8, 9]. Due to the several biological effects already described, royal jelly can be used as a nutrient and as medicine (apitherapy), covering a great range of applications from sexual dysfunctions, fertility and menopause discomforts until longevity, including heart, blood circulation, nervous system, respiratory, dermatological and several other diseases [8]. These properties are due to their composition, based on amounts of major royal jelly proteins (MRJPs) and lipids, mainly the fatty acids 10-H2DA (10-hydroxt-trans-decenoic acid) and 10-HDA (10-hydroxydecanoic acid), besides peptides, amino acids, flavonoids, polyphenols, vitamins and minerals [7, 8, 10].

In vitro and in vivo studies have shown that RJ could modulate inflammation mechanisms by reducing nuclear factor-kB (NF-κB) and tumour necrosis factor (TNF-α) [11–14]. Moreover, royal jelly upregulates the Nrf2 expression, a master of antioxidants, mitigating inflammatory and oxidative burden [15–17].

Therefore, an integrative, personalised, evidence-based medical approach is essential for advancing health care. It is necessary to consider risk factors, promote prevention and adopt a collaborative approach between disciplines and health professionals. Advanced and innovative technologies are also encouraged to improve the health and well-being of patients [18].

In this context, this narrative review aims to provide an overview of the effects of royal jelly as a nutritional strategy for patients with NCDs, using the concept of "food as medicine" and its consideration in the context of predictive, preventive and personalised medicine (PPPM), helpful in preventing and treating diseases.

Royal jelly: origin and increasing value in pharmaco-business

Bee products have been used since the ancient world. The first use registered was when Greeks utilised a part of RJ to produce "ambrosia", giving immortality to the Olympus god [19, 20]. RJ's function in bee society was first discovered by Aristotle when he studied RJ's effects on the queen bee. In addition, RJ was used as a cosmetic by Cleopatra in ancient Egypt. In China, human medicine has used RJ for a long time for its health-protecting properties. The name of this substance came from a French scientist René Antoine de Réaumur (1683–1757), who correlated the queen bee food with its exceptional growth. Since the 60s, RJ properties have been investigated and used for human health [20].

No official data about RJ production exists, but the honey market is estimated at US$2.9 billion in 2020 in the USA. China is a big RJ producer and has grown considerably, from 200 tons per year in 1980 to 3500 tons per year in 2010 [21]. Other countries are responsible for RJ production, such as Korea, Taiwan, Japan, Mexico, Spain, Greece and France [10].

After fertilising flowers, the pollen digestion by bees results in the raw material for RJ production, which is secreted by *Apis mellifera* (3- to 12-day-old) worker (nurses) bees from hypopharyngeal and mandibular glands and used to feed the queen bee in larval, young and adult stages bee larvae, and also the worker bees until the 3 days of life. This feeding concept differentiates honeybee caste designation and honeybee larvae into queens due to the protein in royal jelly called royalactin [22].

Royal jelly composition

Considered a superfood, with a nutrient-dense natural item, it is heat and light susceptible, going through oxidation with air contact. RJ is known as "milky-white" because of its white or yellowish creamy substance. Its unique characteristics are its gelatinous-viscous sour and sweet taste and a slightly sour and pungent smell of phenol [23]. It is slightly acidic (pH 3.5–4.5), containing water (50–70%), carbohydrates (7–18%), proteins (9–18%) and lipids (4–8%). However, the most attractive attention of RJ is the exciting characteristic of fatty acid composition, with a rare and unusual structure. Around 90% of lipids are short chains of carboxylic acids—8 up to 12 (animal or plant materials usually contain 14–20 carbon atoms). This carboxylic acid is mainly the unsaturated hydroxyl fatty acid, 10-hydroxy-*trans*-2-decenoic acid (10-H2DA) (corresponds to around 50% of total FAs), often referred to as "royal jelly acid", followed by saturated hydroxyl fatty acid, 10-hydroxydecanoic acid (10-HDA), which has never been detected in another natural or bee product [7, 24]; together, 10-H2DA and 10-HDA sum around > 60–80% of total FAs, and a dicarboxylic fatty acid, sebacic acid (SEA), in small amount is also found in RJ (Fig. 1).

After ingestion, 10-HDA is metabolised into SEA, seen in urine samples and human plasma. However, when RJ is ingested without enzyme treatment (protease), the hydroxy fatty acids are not in the plasma [25].

Besides the fatty acids, some researchers attribute the protein fraction to the characteristic of the most important one in royal jelly since it is responsible for a specific physiological role in queen honeybee development and includes numerous essential amino acids. It presents a family of

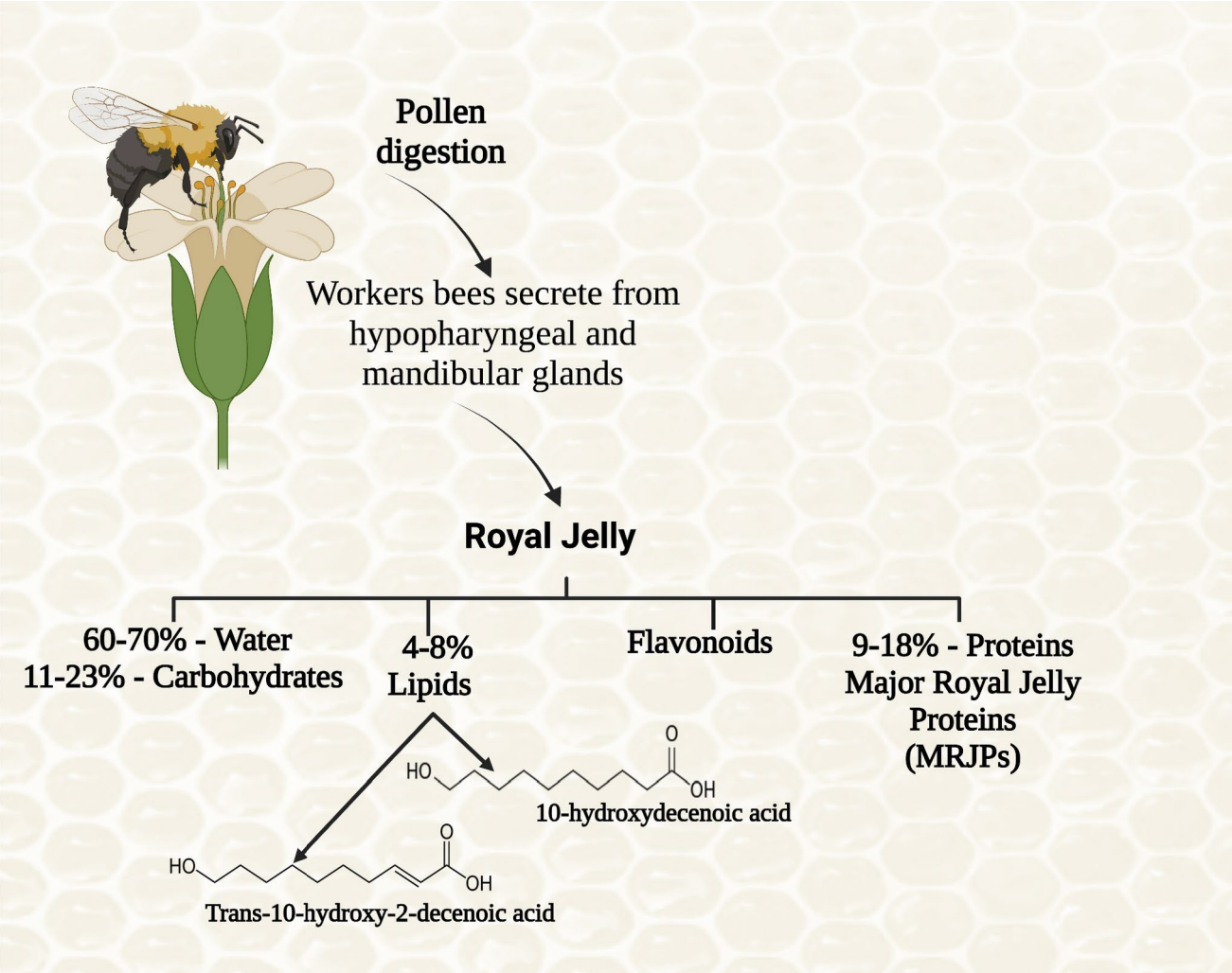

Fig. 1 Royal jelly composition. Created with BioRender.com

proteins called major royal jelly proteins (MRJPs), and several were already described as MRJP1, MRJP2 and so on [26].

Concerning micronutrients, it contains around 1.5% mineral salts (mainly copper, zinc, iron, calcium, manganese, potassium and sodium salts) and vitamins (B1, B2, B3, B5, B6, B7, B9, inositol and traces of vitamin C) [27, 28]. It is also relevant to keep in mind that in the fresh royal jelly, the hormones were also quantified: testosterone (0.20 ± 0.03), progesterone (4.61 ± 0.26), prolactin (70.8 ± 20.0) and estradiol (52.0 ± 6.0), in all cases, in nmoles/100 g [8].

Uthaibutra et al. (2014) estimated that RJ has gallic acid contents of 6.68 ± 0.60 mg gallic acid/g relative to total phenolic content [29]. However, it has already been clarified that harvest time is directly related to the content of phenolic compounds and flavonoids present in royal jelly. Therefore, the faster the harvest, the greater the antioxidant potential [30]. The main flavonoids found in royal jelly are hesperetin, isosakuranetin and naringenin from the flavanone group; acacetin, apigenin and their glycosides, chrysin and luteolin glycoside from the flavone group; isorhamnetin and kaempferol glycosides which are isoflavonols; and coumestrol, formononetin and genistein which are isoflavonoids [31, 32].

Carboxylic and phenolic groups form phenolic acids. The most commonly found in royal jelly are pinobanksin and organic acids and their esters, which comprise octanoic acids, 2-hexenedioic acid, dodecanoic acid, 1,2-benzenedicarboxylic acid and benzoic acid [33, 34].

Besides that, many aromatic components have also been found, such as pyrocatechol, hydroquinone, 2-methoxy-p-cresol, methyl salicylate, methyl benzoate, benzaldehyde, phenol, 2-methoxyphenol, toluene, benzoic acid, 4-hydroxyhydrocinnamic acid, 4-hydroxy-3-methoxyphenylethanol, p-coumaric acid, caffeic acid and nicotinic acid [35].

The presence of phenol groups provides the antiradical property [36]. Therefore, due to its biological properties, such as anti-inflammatory [37], antioxidant [38], cardioprotective [39], antimicrobial [40], antidiabetic [41], anticancer [42] and renoprotective actions [43], RJ has mainly been used in health foods, commercial medical products and cosmetics worldwide [44].

As previously informed, royal jelly is an unstable product. Besides the oxidation process that can suffer, it can also spoil or deteriorate and lose its commercial value if improper storage is used. The sensibility to temperature is the most important and impacting aspect. One alternative to a better and more convenient consumption of royal jelly is to transform it into a powder using freeze-drying or lyophilisation to avoid fast degradation. Some countries, such as Brazil and Japan, established minimal requirements of authenticity and quality for lyophilised royal jelly. In the case of Brazilian regulation, the maximum water content was established at 8%w/w. The minimum values of lipids, proteins and carbohydrates were defined as 3%w/w, 27%w/w and 27% w/w, and with the sum of 10-HDA, 10-H2DA and 10-HDAA minimum values of 5% w/w in the dry basis [45]. In the case of Japan, the standard was done based on Apilac product (the mixture of 6 parts of frozen RJ added to 1 part of dried glucose-lactose (1:1) with 50 mg/kg of L-ascorbic acid as an antioxidant being dried until 4% humidity) [8]. It must contain at least 4.0% and 8.0% of 10-H2DA (JP XVII). According to Ramadan and Al-Ghamdi [26], lyophilised royal jelly contains < 5% water, 27–41% protein, 22–31% carbohydrate and 15–30% fat. The quality and identity requirements must be followed to try to guarantee the effects of royal jelly. It is particularly interesting in the case of RJ in powder since it is usually the focus of adulteration that can substantially compromise the biological effects of this critical product [26].

Anti-inflammatory and antioxidant properties of RJ

The current literature points out that bee products, including honey, propolis, pollen and royal jelly, can mitigate the oxidative stress observed in various pathological conditions because they are sources of natural antioxidants [46]. Flavonoids and phenolic acids can scavenge ROS and prevent oxidative damage [47]. Some researchers demonstrated that three tyrosyl dipeptides (Lys-Tyr, Arg-Tyr and Tyr-Tyr) of RJ had high antioxidant activity in vitro model scavenging free radicals by a hydroxyl group [48].

In addition, the presence of hydroxydicarboxylic fatty acids, mainly 10-HDA described exclusively in royal jelly, also contributes to the antioxidant capacity of royal jelly [38]. Sugiyama et al. [7] attempted to explain the inhibitory antioxidant mechanism of 10-HDA by assessing its ability to inhibit nitric oxide (NO) production. For this, they encouraged the generation of NO in a RAW264 murine macrophage cell line from lipopolysaccharides (LPS), which can induce the production of interferon-β (IFN-β) and other factors involved with the induction of iNOS. Finally, it was confirmed that 10-HDA inhibited NO generation and attenuated the activation of the IFN-β-mediated nuclear factor NF-kB and the tumour necrosis factor α (TNF-α) [7].

From this, there is also an insight that, in addition to the antioxidant capacity of royal jelly, it is possible to observe an anti-inflammatory potential. According to Mihajlovic et al. [49], the hydroxydicarboxylic fatty acids present in royal jelly are the central modulators of the inflammatory cascade. These authors, when evaluating the effects of a dose of 500 µM of 10-HDA on dendritic cells derived from human monocytes (Mo-DCs) incited by LPS, observed that there was inhibition of the maturation of Mo-DCs and the production of the inflammatory cytokines IL-8, IL-12 and TNF-α [49].

Thus, it was elucidated that the anti-inflammatory potential of royal jelly revolves around the attenuation of the transcription of inflammatory cytokines from the modulation of the NF-kB signalling pathway.

In basal situations, NF-kB is coupled to its inhibitory protein IκB, which keeps it inactivated in the cytoplasm. After stimuli, such as induction by LPS, phosphorylation of IκB occurs, and consequent release of NF-kB to the nucleus, where the p65 subunit is phosphorylated, and activation of target genes for the transcription of pro-inflammatory factor occurs [50]. However, NF-kB activation can also occur through interferons, such as IFN-β, involving activation of the phosphatidylinositol 3-kinase (PI-3 K) and of the Akt, which, when active, induce NF-kB activation interferon-dependent, and when inactive suppress NF-kB activation [51]. As Sugiyama et al. [52] proposed, 10-H2DA, the primary fatty acid of RJ, would suppress the expression and transcription of IκB mRNA and inhibit the activation of PI-3 K/Akt, causing the inactivation of NF-kB mediated by IFN-β.

Corroborating this, it was also observed that RJ could exert anti-inflammatory activity by stimulating the NRF2 pathway, an endogenous defence transcription factor of the organism [16]. This mechanism is explained due to the ability of a fatty acid to increase the translocation of Nrf2 from the cytoplasm to the nucleus to bind to the element of antioxidant response (ARE), which consequently activates the transcription of genes encoding antioxidant enzymes, increasing the expression of these enzymes [53]. Aslan et al. (2023) confirmed in a study with albino Wistar rats for 8 weeks that 100 mg/kg of RJ effectively increases the expression of NRF2 and consequently was associated with increased levels of the antioxidant enzymes glutathione and catalase. These authors also observed that the intervention

with RJ reduced malondialdehyde levels, a lipid peroxidation parameter, and the NF-κB expression levels.

Other studies on royal jelly's antioxidant and anti-inflammatory capacity, in vitro and in vivo, are summarised in Table 1. Figure 2 illustrates the primary mechanisms that RJ promotes inflammation and oxidative stress reduction and increases antioxidant enzyme synthesis.

Beneficial effects of RJ on the multi-faceted mitochondrial functions

Mitochondrial function is vital to cellular health and functioning in the context of PPPM/3PM, since mitochondria are the organelles responsible for cellular energy production and play critical roles in regulating metabolism and cellular stress response. Mitochondrial dysfunction has been linked to various diseases, including metabolic disorders, neurodegenerative diseases, cancer and ageing. In this context, mitochondrial dysfunction can occur due to several factors, including genetic mutations, oxidative stress, mitochondrial DNA damage, nutritional deficiencies and exposure to toxins and drugs [54].

Mitochondrial dysfunction can lead to energy imbalance and ROS growth, triggering cell damage, decreased ATP production, resulting in lack of energy in cells and impaired metabolic functions, and metabolic disorders such as insulin resistance, dyslipidemia and accumulation of toxic substances [55].

Studies have shown that mitochondrial dysfunction plays a crucial role in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease because the accumulation of abnormal proteins in these diseases, such as beta-amyloid and alpha-synuclein, can lead to mitochondrial dysfunction, resulting in oxidative stress, impaired energy metabolism and cell death [56, 57].

Mitochondrial dysfunction has been implicated in the pathogenesis of type 2 diabetes. With reduced mitochondrial function and oxidative capacity, decreased ATP production and ROS accumulation occur, contributing to insulin resistance and impaired pancreatic beta cell function, leading to hyperglycemia and the development of type 2 diabetes [58].

Furthermore, mitochondrial dysfunction compromises the heart's contractile efficiency, increases the production of ROS and promotes cardiomyocyte apoptosis. These events contribute to the progression of cardiovascular diseases and worsen the prognosis of patients [59]. In ageing, the accumulation of mitochondrial DNA damage over time leads to reduced mitochondrial function, decreased ATP production and increased oxidative stress. These changes contribute to cellular ageing and are associated with the development of age-related diseases such as cancer, cardiovascular and neurodegenerative diseases [59].

The analysis of mitochondrial function includes mitochondrial DNA integrity, dynamics, oxidative stress and mitochondrial stress response capacity, which can provide a detailed view of mitochondrial health and can be used to identify early dysfunctions and monitor the effectiveness of personalised interventions [54].

Scientific studies have explored the possible effects of RJ on mitochondrial health, and some preliminary results are promising, showing improvement of mitochondrial biogenesis by AMPK activation [60]; antioxidant protection against oxidative stress due to the critical content of RJ antioxidant compounds, which help to neutralise ROS [16, 61]; and RJ may have a potentially protective effect against mitochondria-mediated apoptosis by modulating molecular mechanisms related to apoptosis, such as the Mfn2 protein and the Bax/Bcl2 ratio [62].

Whilst these preliminary studies are promising, it is essential to note that research on the effects of RJ on mitochondrial health is still in its early stages. More investigations, including human clinical studies, are needed to fully understand the mechanisms of action and determine the effectiveness of RJ in this context.

Royal jelly and its antidiabetic potential

Diabetes mellitus is an NCD and a global public health problem. Its prevalence increases each year dramatically, and between 2030 and 2040, about 439 and 642 million people will be diagnosed with diabetes mellitus [63]. In 2045, this number will increase to 700 million people [64]. Diabetes mellitus is characterised by glucose and insulin metabolism disturbances, generating chronic hyperglycemia [65, 66]. Chronic hyperglycemia increases oxidative stress and inflammation associated with macrovascular and microvascular complications, such as diabetic nephropathy, cardiovascular disease, renopathy and diabetic foot [67, 68].

Therapy strategies provide the patient with a better quality of life and control of the complications of diabetes, including insulin and oral hypoglycaemic agents [69]. Also, adjuvant nutritional strategies have been widely used, showing anti-inflammatory and antioxidant effects, such as cinnamon, curcumin, psyllium fibre and polyphenols [70–72].

In this sense, RJ has also been a target of experimental and clinical studies due to its antidiabetic potential. RJ is vital in scavenging free radicals and improving insulin resistance [9]. The antioxidant action may be related to three tyrosyl dipeptides in the RJ molecule, which have high antioxidant activity due to the hydroxyl group of their hydrogen atom [48]. Activation of detoxifying enzymes, such as glutathione-s-transferase and glutathione peroxide genes, has also been associated with RJ [33, 73].

Table 1 Studies involving the antioxidant and anti-inflammatory capacity of royal jelly

References	Sample	Intervention	Results
In vitro studies			
[179]	Human lung cancer cell lines (A549)	Treatment with 30 μM 10-HDA for 3, 6, 12, 24, and 36 h	↑ p-p38, p-JNK, and IκB expression ↓ p-ERK, p-STAT3, and NF-κB expression
[180]	Primary bone marrow cells (1 × 105 cells/cm^2)	Different doses of RJ (12.5–50 ng/mL) for 3 days	↓ NF-κB receptor activator
[181]	Microglial BV-2 and N9 cell lines	Different doses of 10-HDAA (1–4 mM) from RJ + LPS for 1 h	↓ iNOS, NO levels and levels of pro-inflammatory mediators ↓ NLRP3 inflammatory pathway, from P53 modulation
[53]	Human neuroblastoma SH-SY5Y cells	Treatment with 50 μM HPO-DAEE (4-hydroperoxy-2-decenoic acid ethyl ester, a synthesised RJ fatty acid derivative), for 4 h	↑ HO-1 by promoted phosphorylation of eIF2α ↑ Nuclear accumulation of Nrf2 and activated ARE
[123]	WiDR human adenocarcinoma cell (BCRC 60157)	Different doses of 10-HDA (0.1 to 5 mM) from RJ for 24 h	↓ IL-8, IL-1β, TNF-α and NF-κB ↑ IL-1Ra
[24]	Murine macrophage RAW 264.7 cells	Different doses of 10-H2DA, 10-HDAA and SEA, from RJ for 24 h	10-H2DA, 10-HDAA e SEA: ↓ IL-6, IL-10 and NO SEA: ↓ TNF-α
Animal studies			
[42]	60 male Wistar rats	(1) control group; (2) RJ (300 mg/kg); (3) Vit E (180 mg/kg); (4) 30 mg/kg of dimethylhydrazine (DMH); (5) RJ (300 mg/kg) + DMH; (6) Vit E (180 mg/kg) + DMH	DMH + RJ: ↓ hs-CRP, MDA levels ↑ CAT, SOD
[182]	42 adult albino rats	(1) DOX (3 mg/kg) for 6 weeks; (2) DOX + 500 mg/kg/d of honey orally; (3) DOX + 100 mg/kg/d of RJ; 4) DOX + 50 mg/kg/d of propolis; (5) DOX + oral honey, RJ and propolis for 21 days	DOX + RJ: ↓ MDA and TNF-α levels ↓ PARP-1 and Bcl-2 protein expression ↑ SOD and GPX levels ↑ Caspase-3
[183]	48 male BALB/c mice	8 groups: saline, 3 different doses of RJ (100, 150, and 200 mg/kg/d), nicotine (1.5 mg/kg), and 3 different groups of Nic + RJ (1.5 mg/kg of Nic + 100, 150, and 200 mg/kg of RJ)	After treatment with RJ regardless of dosage: ↑ Nfr2 and Bcl-2 gene expression ↓ MDA levels, NO, Caspase-3 and P53 gene expression
[184]	250 zebrafish—*Danio rerio*	5 different gelatine and casein-based diets were prepared containing RJ in the ratios of D1 (%0.00), D2 (%0.10), D3 (%0.40), D4 (%1.60) and D5 (%6.40), for 8 weeks	↑ mRNA levels and enzymatic activities of CAT, GR, SOD, GPx and GST
[15]	42 males Wistar albino rats	(1) Control; (2) RJ (100 mg/kg); (3) fluorine (F) (50 mg/kg); (4) fluorine (100 mg/kg); (5) F50 + RJ; (6) F100 + RJ for 8 weeks	↓ MDA levels, Bcl-2, Gsk-3 and NF-κB protein expression ↑ GSH, caspase-3, caspase-9, caspase-6, Bax, BDNF and Nrf2 protein levels
[134]	Healthy male BALB/c mice	4 groups: low-dose RJ (1000 mg/kg/d), medium-dose RJ (3000 mg/kg/d) and high-dose RJ (9000 mg/kg/d) and a control group for 30 days	↑ IL-10 and levels of antioxidant activities in the liver and kidney
[185]	36 male BALB/c mice	(1) normal saline; (2) RJ (100 mg/kg/d RJ; (3) testicular injury induced by nicotine (NIC) (0.50 mg/kg/d); (4) NIC (1 mg/kg/d); (5): NIC (0.50 mg/kg/d) + RJ; (6) NIC (1 mg/kg/d) + RJ for 35 days	↓ MDA levels, p53 and Caspase-3 m-RNA ↑ TAC and CAT

Table 1 (continued)

References	Sample	Intervention	Results
[186]	30 Wistar rats with exposing 40 Watt UV-B lamps for 2 h/day in 14 day	RJ cream application with doses of 2.5%, 5%, and 10%; negative control with vaseline; and normal control	The higher the RJ dose: ↑ Nrf2 levels ↓ NF-kB and TNF-α levels
[16]	28 Swiss male mice	(1) control group; (2) RJ (85 mg/kg); (3) CdCl2 (6.5 mg/kg); (4) RJ 1 h before $CdCl_2$ injection for 1 week	RJ pretreatment restored the oxidant/antioxidant balance: ↑ GSH content and the activities of GPx, GR, SOD, and CAT ↑ mRNA expression of GPx1, GR, SOD2, and CAT ↑ Nrf2 expression
Human studies			
[187]	20 high-level swimmers	400 mg of RJ and 60 mg of CoQ10 or placebo, once daily for 10 days	↓ Lipid peroxidation products (Diene conjugates and Schiff bases) ↓ Creatine kinase activity
[188]	72 overweight adults aged 25–50	RJ (333 mg of lyophilised organic—standardised to a minimum of 4% 10-HDA) or placebo for 8 weeks	↓ TC and hs-CRP ↑ Adiponectin, leptin and serum TAC
[189]	46 type 2 diabetic patients, aged 25–65	RJ (1000 mg) or placebo (glycerin) 3 ×/d for 8 weeks	↓ HOMA-IR ↑ TAC

Abbreviatios: *RJ*, royal jelly; *10-HDA*, 10-hydroxy-2-decenoic acid; *10-HDAA*, 10-hydroxydecanoic acid; *TC*, total cholesterol; *hsCRP*, high-sensitivity C-reactive protein; *HOMA-IR*, homeostasis model assessment—insulin resistance; *TAC*, total antioxidant capacity; *CAT*, catalase; *MDA*, malondialdehyde; *GSH*, glutathione; *TXL*, taxol; *NO*, oxide nitric; *NF-Kb*, nuclear factor-Kb; *TNF-α*, tumour necrosis factor-α; *IL*, interleukin; *iNOS*, induced nitric oxide synthase; *NLRP3*, NOD-like receptor pyrin domain-containing-3; *10-H2DA*, trans-10-hydroxy-2-decenoic acid; *SEA*, sebacic acid; *GR*, glutathione reductase; *SOD*, superoxide dismutase; *GPx*, glutathione peroxidase; *GST*, glutathione S-transferase; *$CdCl_2$*, cadmium chloride; *eIF2α*, eukaryotic initiation factor 2α; *ARE*, antioxidant response element; *Nrf2*, NF-E2-related factor 2; *HO-1*, heme oxygenase-1

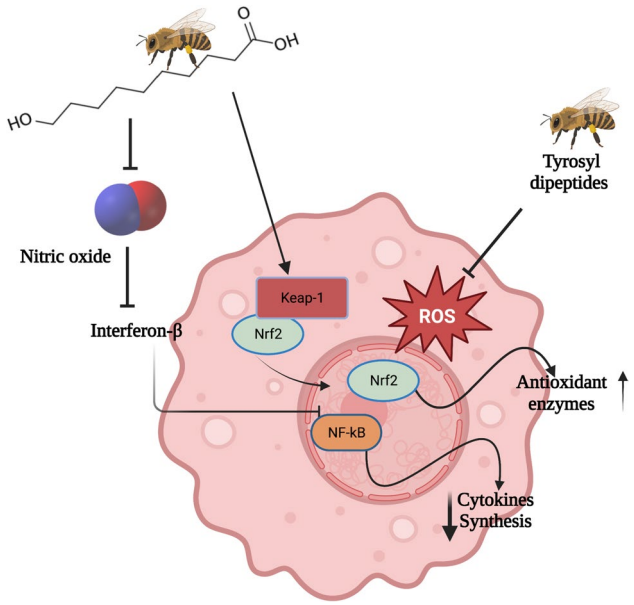

Fig. 2 The royal jelly mechanism mitigates inflammation and oxidative stress and increases antioxidant enzyme synthesis. Created with BioRender.com

In addition, RJ appears to increase glucose absorption by improving insulin signalling and activating the AMP-activated protein kinase (AMPK) pathway in the skeletal and hepatic muscle through increased adiponectin secretion, reducing gluconeogenesis and lipogenesis, leading to a decrease in glucose production and an improvement in the glycemic index [74, 75].

10-H2DA stimulates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/glycogen synthase kinase 3β (GSK3β) signalling pathway [76]. This pathway is critical in the metabolic control of glucose, with insulin activation leading to glycogen synthase activation and consequent reduction in blood glucose, showing a significant hypoglycemic action [76].

Furthermore, RJ is essential as an anti-hypercholesterolemic by decreasing very low-density lipoprotein (VLDL) and triglyceride plasma levels [77]. 10-H2DA can modulate apolipoprotein (Apo) A–I, and the Apo B/Apo A–I ratio, reducing the risk of cardiovascular disease in diabetic patients [41]. RJ seems to increase the mRNA and protein expression of thermogenic uncoupling protein 1 (UCP1), mitochondrial cytochrome c oxidase subunit IV (COX-IV) Nbat, promoting thermogenic effect, reducing body fat and improving the glucose homeostasis [78]. Table 2 shows the studies with RJ in diabetes.

Protective effects of RJ on cardiovascular diseases

Cardiovascular diseases (CVDs) persist as the leading cause of mortality worldwide. A dominant cause of CVD is atherosclerosis. CVDs are responsible for a reduced quality of life, despite the advances in managing CVD risk factors [79, 80]. Excessive ROS production is responsible for cardiovascular disorders, such as ischemia/reperfusion injury, cardiac hypertrophy, atherosclerosis, heart failure and myocardial infarction [81–83].

A multidisciplinary and personalised approach is essential for preventing CVDs such as ischemic stroke. Since the traditional approach to investigating these cases is not always sufficient to determine the root cause of the stroke, a more comprehensive assessment is necessary since traditional risk factors, such as high blood pressure, diabetes and dyslipidaemia, may not be sufficient to explain the stroke. Within this approach, the PPPM principles aim to identify risk factors and underlying causes through a detailed analysis of each stroke case, considering genetic factors, medical history and individual lifestyle. This allows for a more comprehensive understanding of stroke aetiology [84].

In this context, there is growing evidence linking healthy dietary habits with a reduced risk of developing or reversing the progression of CVD. These effects could be attributed to some foods, single nutrients or bioactive compounds [5, 85]. Royal jelly has beneficial effects in the prophylaxis and treatment of CVD risk factors, as seen in Table 3 [86].

It has been shown in the literature that RJ exhibited antihypertensive effects, but the exact mechanism has not been elucidated [87–90]. The antihypertensive effect of RJ may be linked to its capacity to increase NO production. Studies show that RJ has a muscarinic receptor agonist, potentially acetylcholine, which causes vasodilation via NO/cGMP (cyclic 3′,5′-guanosine monophosphate) pathway and through calcium channels [90, 91].

Experimental studies have shown that RJ can ameliorate dyslipidemia [92, 93]. However, the mechanisms by which RJ exerts its hypocholesterolemic effects are still under investigation. One possible mechanism is the large number of proteins in RJ, which may decrease plasma levels of cholesterol, LDL and small VLDL, reduce cholesterol biosynthesis enzyme, influence hepatic lipoprotein receptors that regulated VLDL uptake and suppress of hepatic sterol synthesis [94]. Royal jelly can up-regulate cholesterol 7-α-hydroxylase (CYP7A1), an enzyme associated with receptors that synthesise very low-density lipoproteins (LDL-c) [95]. A recent meta-analysis found that RJ reduces total cholesterol and increases HDL serum levels

Table 2 Summary of in vivo studies and clinical trials involving royal jelly supplementation and effects on diabetes mellitus

References	Sample	Intervention	Results
Animal studies			
[76]	STZ induced DM + HFD in mice	100 mg/kg of 10-H2DA for 4 weeks	↓ fasting blood glucose, ↑ insulin levels, ↑ area of pancreatic islets ↑ SOD, CAT and GPx activities ↓ lipid peroxidation; ↓ NF-κB nuclear translocation, ↓ IL-6 and TNF-α ↑ PI3K, AKT, and GSK3β protein levels
[77]	STZ induced DM in rats	2 g/daily of RJ by gavage for 28 days	↓ plasma VLDL and TG ↓ fasting blood glucose and HbA1c
[78]	Mice fed with HFD	HFD with 5% of RJ for 10 weeks	↓ fasting blood glucose and insulin ↓ HOMA-IR ↑ UCP1 mRNA and protein expression in BAT ↑ Cox-IV mRNA and protein expression in BAT
[74]	Obese/diabetic KK-Ay mice	10 mg/kg of RJ by gavage for 4 weeks	↑ *AdipoQ* and *AdipoR1* expression ↑ Pampk expression ↓ hyperglycaemia ↔ insulin resistance
[190]	STZ induced DM in rats	100 mg/kg of RJ administered orally	↓ serum levels of AST, ALT, ALP and fasting blood glucose ↑ CAT and FRAP ↓ MDA
Human studies			
[189]	46 T2D patients	1000 mg RJ 3×/d for 8 weeks	↓ HOMA-IR
[41]	50 T2D patients	1000 mg RJ 3×/d for 8 weeks	↓ fasting blood glucose
[73]	50 T2D female patients	1000 mg RJ / daily in soft gel or placebo	↓ fasting blood glucose and HbA1c ↑ insulin concentration ↑ erythrocyte superoxide dismutase and GPx ↓ MDA

Abbreviations: *STZ*, streptozotocin; *HFD*, high-fat diet; *T2D*, type 2 diabetes; *10H2DA*, 10-hydroxy-2-decenoic acid; *DM*, diabetes mellitus; *RJ*, royal jelly; *HbA1c*, glycated haemoglobin; *TG*, triglycerides; *VLDL*, very low-density lipoprotein cholesterol; *SOD*, superoxidase dismutase; *GPx*, glutathione peroxidase; *MDA*, malondialdehyde; *HOMA-IR*, homeostasis model assessment-insulin resistance; *BAT*, thermogenic capacities of brown; *UCP1*, thermogenic uncoupling protein 1; *COX-IV*, mitochondrial cytochrome c oxidase subunit IV; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *ALP*, alkaline phosphatase; *CAT*, catalase; *FRAP*, ferric reducing antioxidant power; *PI3K*, phosphoinositide 3-kinase; *AKT*, protein kinase B; *GSK3β*, glycogen synthase kinase 3 beta; *AdipoQ*, adiponectin gene; *AdipoR1*, adiponectin receptor-1 gene; *pAMPK*, phosphorylated AMP-activated protein kinase; *NF-κB*, nuclear factor kappa B; *IL*, interleukin; *TNF-α*, tumour necrosis factor-alpha

in studies with a long-term follow-up period. Otherwise, the same study indicates that triglycerides and LDL serum levels did not significantly ameliorate [96]. Also, RJ seems to block the reabsorption of bile acids, reducing cholesterol plasma levels [97].

Lastly, endothelin-1 is a vasoconstrictor peptide produced by endothelial cells and plays a vital role in regulating cardiovascular function, with conversion to a PPPM approach [98]. In this sense, in a study with hypertensive rats, treatment with a combination of propolis, royal jelly and bee venom at daily oral doses of 0.5, 1.0 and 2.0 mg/kg decreased serum levels of endothelin-1 and TNF-β NF-kB and biomarkers of oxidative stress, being considered a preventive factor and potential treatment for CVD [99].

Despite the cardioprotective potential of RJ, there is a lack of specific studies on how RJ can prevent the onset or progression of CVDs. The findings in the literature point to different protective effects of RJ on important risk factors for CVDs, which reinforces the importance of further studies to elucidate the mechanisms behind the already demonstrated effects and explore more that still need to be well established.

Can royal jelly be a promising strategy for treating chronic kidney disease patients?

Chronic kidney disease (CKD) is a significant global health burden and is increasing in prevalence [100]. The uremic phenotype is marked by elevated oxidative stress, persistent low-grade inflammation, gut dysbiosis and premature ageing, contributing to poor health status and premature mortality in CKD, where cardiovascular disease is the leading cause [100–102].

Table 3 Studies involving royal jelly and cardiovascular diseases

References	Sample	Intervention	Results
In vitro studies			
[90]	Isolated aortic rings from male Japanese white rabbits	Treatment with cumulative doses (0.01–10 mg/mL) of RJ	↑ vasorelaxation of the isolated aortic rings ↑ NO production ↓ NE-induced intracellular Ca^{2+} releases and high K^{+}-induced extracellular Ca^{2+} influx in denuded aortic rings
[91]	Thoracic aorta and superior mesenteric artery (contracted with phenylephrine) from male Wistar rats	Fresh RJ (0.0001–0.3 mg/mL), ACh (10^{-10} to 10^{-6} M) in the presence or absence of inhibitors L-NAME (10^{-4} M, 20 min) or atropine (10^{-5} M, 15 min)	↑ vasorelaxation in a concentration-dependent manner of isolated rat aortas and superior mesenteric arteries
[191]	Mouse (C57BL/6 strain) VSMC	MRJP1 group: *Mrjp1* gene was inserted into mouse VSMC and Control group	↓ Cell contraction, migration, and proliferation
[192]	Mice aortic VSMCs	Control, glycosylated MRJP1 (P +), deglycosylated MRJP1 (P), and glycans (L) All treatments were divided into subgroups: with or without AngII for 16 h	P +: ↓α-SMA *vs.* control, P and L; P + inhibited the migration of VSMCs
Animal studies			
[193]	32 Wistar rats	1) MRJ (15 mg/kg/d); 2) PRJ (15 mg/kg/d); 3) CRJ (15 mg/kg/d);4) captopril (50 mg/kg/d) 5) metabolic syndrome model—no treatment; 6) placebo (distilled water)	Continuous intake of RJ prevented elevation in BP values
[15]	42 rats	Control group; RJ group (100 mg of RJ/kg); F50 group (50 mg of fluoride/kg); F100 group (100 mg of fluoride/kg); F50 + RJ group (50 mg of fluoride/kg + 100 mg of RJ/kg); F100 + RJ group (100 mg of fluoride/kg + 100 mg of RJ/kg) for 8 weeks	In heart tissue: RJ in all groups: ↓ MDA; F50 + RJ and F100 + RJ groups: ↑ GSH level, CAT activity, caspase-3, caspase-9, caspase-6, Bax, BDNF and Nrf-2 proteins levels; ↓ Bcl-2, GSK-3 and NF-κB expression
[90]	Male SHR and WKY	WKY-control group; SHR-control group; SHR-RJ group: received 1 g/kg of RJ daily for 4 weeks	↓SBP and DBP in SHR; ↑NO levels in SHR
[91] *Experiment 1	10-week-old male Wistar rats	Control group and RJ group (100 mg/kg) for 6 days	↑ Tail blood flow and mass ↔ *velocity*, *SBP* or *HR*
[91] *Experiment 2	9-week-old male Wistar rats	Control group; L-NAME group (0.5 mg/mL); L-NAME + RJ (100 mg/kg)	RJ: ↔ Blood flow, mass, velocity, SBP and HR in L-NAME-treated rats
[39]	Healthy adult male Wistar rats	Control group; TXL group (7.5 mg/kg); T1 group (TXL—50 mg RJ/kg); T2 group (TXL + 100 mg RJ/kg); T3 group (TXL + 150 mg RJ/kg); T4 group: RJ (100 mg/kg) for 4 weeks	In heart tissue: ↓ MDA and NO levels; ↓CK-BM level and necrosis; In serum: ↑ total antioxidant capacity
Human studies			
[194]	88 healthy volunteers between 20 and 60 years	690 mg of RJ/day (equivalent to 2040 mg of fresh royal jelly) or placebo for 4 weeks	RJ group: ↑RH-PAT index
[195]	40 subjects w/ mild hypercholesterolemia	9 capsules (350 mg of RJ)/day or placebo for 3 months	RJ group: ↓ TC and LDL-c ↑DHEA-S

Table 3 (continued)

References	Sample	Intervention	Results
[196]	36 postmenopausal healthy women aged 53–66 years	150 mg of RJ/day for 3 months	↑ HDL-C ↓ LDL-C and TC
[94]	15 healthy adult volunteers	6 g RJ/day or placebo for 4 weeks	RJ group ↓ serum TC and ↓ serum LDL by lowering small VLDL levels

Abbreviatios: *α-SMA*, anti-α-smooth muscle actin; *BDNF*, brain-derived neurotrophic factor; *BW*, body weight; *CK-BM*, creatine kinase; *CRJ*, control royal jelly; *DBP*, diastolic blood pressure; *DHEA-S*, dehydroepiandrosterone sulphate; *FATP3*, fatty acid transport protein 3; *FGF21*, fibroblast growth factor 21; *HDL*, high-density lipoprotein; *HepG2*, cells of the human hepatoblastoma cell line; *HMG-CoA reductase*, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; *IVY*, Ile-Val-Tyr; *IY*, Ile-Tyr peptide; *LDL-c*, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor; *L-NAME*, L-NG-nitro arginine methyl ester; *MDA*, malondialdehyde; *MRJ*, mucuna royal jelly; *MRJP1*, major royal jelly protein 1; *NO*, nitric oxide; *Nrf-2*, nuclear factor erythroid 2-related factor 2; *PCT-RJ*, RJ hydrolyzed by peptide, chymotrypsin and trypsin; *PRJ*, pollen royal jelly; *ProRJ*, protease N treated royal jelly; *RJ*, royal jelly; *RH-PAT*, reactive hyperemia peripheral arterial tonometry; *SBP*, systolic blood pressure; *SHR*, spontaneously hypertensive rats; *SQLE*, squalene epoxidase; *SREBP-1*, sterol regulatory element binding protein 1; *TC*, total cholesterol; *VLDL*, very-low-density lipoprotein; *VSMCs*, vascular smooth muscle cells; *WKY*, Wistar Kyoto rats; *TXL*, paclitaxel—chemotherapeutic agent

Several factors, including excess ROS and a pro-inflammatory phenotype, explain chronic inflammation in CKD. The deregulation of pro-inflammatory and anti-inflammatory factors, such as those mediated by NF-kB and Nrf2, plays an essential role in the aggravation and progression of kidney damage [103, 104].

Accumulated evidence encourages using additional non-drug therapeutic strategies such as foods, nutrients and bioactive compounds with anti-inflammatory and antioxidant effects in managing the changes found in CKD [105–108].

Based on what has been exposed so far, RJ may be a promising strategy to be included as an adjuvant treatment for CKD. There are no published studies on patients with CKD. Only one clinical trial conducted by Ohba et al. [109] is in progress and will supplement 3600 mg/day of RJ in patients on haemodialysis for 24 months. Taking into account, animal studies with models related to kidney damage have demonstrated that RJ can improve markers of kidney function [43, 110] and alleviate oxidative stress and inflammation through upregulation of Nrf2 and downregulation of NF-kB [111], leading to increased antioxidant enzymes, reduction of lipid peroxidation [43] and production of inflammatory cytokines [112]. Thus, more studies, especially clinical trials, are needed to elucidate the possible effects of RJ on patients with CKD. Table 4 summarises the animal and one human study with models of kidney damage induced using RJ supplementation.

The role of royal jelly in cancer treatment

Significant changes in cancer treatment in terms of PPPM are occurring. In addition to conventional treatments for the disease, health care, in general, is part of this new perspective. During the development of the PPPM, new rapid, specific and sensitive methods are approached for early cancer detection, contributing to more efficient patient management. In addition, this management will contribute to patients' quality of life through the interaction of a multidisciplinary team [113].

In this sense, since the emergence and development of cancer are directly related to inflammation, using anti-inflammatory agents that can prevent its appearance and increase the effectiveness of cancer treatment is necessary [114, 115]. As in other products derived from beekeeping, the properties of RJ are due, amongst other factors, to the presence of phenolic structures capable of stabilising free radicals and reducing ROS and oxidative stress [46, 116].

Amongst phenolics, flavonoids play an essential role in cancer prevention. They can act by stimulating the action of antioxidant enzymes that protect cells from damage, such as superoxide dismutase (SODs), catalase (CAT), cyclooxygenase-2 (COX-2) and glutathione (GSH), in

Table 4 Summary of in vivo studies involving royal jelly supplementation and renal effects

References	Sample	Intervention	Results
In vivo			
[61]	Fluoride-induced nephrotoxicity in rats	RJ (100 mg/kg) + fluorine (100 or 50 mg/kg) for 8 weeks	↓ MDA in renal tissue ↑ CAT activity and GSH in renal tissue ↑ caspase-3, caspase-6, caspase-9 and Bcl-2 proteins
[43]	Moxifloxacin-induced renal and hepatic injury in rats	RJ (100 mg/kg/d) or ECH (40 mg/kg/d) or RJ + ECH for 30 days	RJ group: ↓ creatinine, urea, K^+, and Ca^{2+} ↑ GSH and ↓ MDA in renal tissue ↓ renal tissue KIM-1 contents Attenuated MOX-induced histopathological changes and reduced caspase-3 in renal tissue
[197]	Silver nanoparticles-induced liver and kidney inflammation in rats	Groups: 30 mg/kg of nano-silver + 100 mg/kg of RJ; 100 mg/kg of RJ alone; control group; 30 mg/kg of nano-silver for 28 days	RJ alone: ↓ kidney IL-6 when compared to control group RJ and nano-silver groups: ↓ kidney IL-1β and IL-33 levels NS + RJ group: ↑ IL-33 and IL-1 β levels in kidney tissue compared to nano-silver group
[110]	Diclofenac-induced hepato-renal damage and gastrointestinal ulcerations in rats	Diclofenac (50 mg/kg/d) for 7 days + RJ (150 or 300 mg/kg/d) for 30 days	RJ (150 and 300 mg/kg): ↓ blood urea and creatinine ↑ PGE2 and ↓ MPO in renal tissue
[111]	Cadmium-induced nephrotoxicity in male mice	85 mg/kg RJ 2 h prior to i.p. injection of 6.5 mg/kg $CdCl_2$ daily for 7 days	↓ Cadmium, urea, creatinine and uric acid levels ↓ kidney weight ↓ Lipid peroxidation, NO ↑ Glutathione levels ↑ Nrf2, HO-1, and NQO1 protein expressions and ↓ NF-κB protein expression ↓ Bax and caspase-3 expressions ↓ kidney levels of TNF-α and IL-1β
[198]	Renal ischemia/reperfusion –induced in rats	300 mg/kg of RJ before bilateral renal ischemia for 30 min followed by 24 h of reperfusion for 15 days	↓ blood urea nitrogen, creatinine ↓ kidney malondialdehyde, ↓ glomerular diameter, leukocyte infiltration, levels of TNF-α, adhesion molecule-1 expression, and NO
[43]	Cisplatin-induced nephrotoxicity in rats	100 mg/kg of RJ or 20 mg/kg of bee honey orally 1 h before intraperitoneal cisplatin (2 ×/week) for 10 weeks	↓ urea, creatinine and uric acid in the RJ group
[112]	Ethylene glycol induced renal urolithiasis and inflammation in rats	100 mg/kg of RJ by oral gavage for 4 weeks	↓ IL–1 and IL-18 in renal tissue
Clinical trial			
[199]	Cisplatin-induced nephrotoxicity in patients with cancer	2 capsules of RJ or bee honey (80 g) daily 3 days before the onset of cisplatin chemotherapy and continued during the regimen of the 2 cycles (21 days each) ± 50 days	RJ group: ↔ urea and creatinine serum levels

Abbreviatios: *RJ*, royal jelly; *NO*, nitric oxide; *MPO*, myeloperoxidase; *PGE2*, prostaglandin-E2; *ECH*, Echinacea; *MDA*, malondialdehyde; *KIM-1*, kidney injury molecule-1

addition to stimulating anti-inflammatory pathways such as that of NRF2 [75, 117]. This further highlights the vital role of an adequate and balanced diet in preventing and treating cancer.

It is also necessary to draw attention to the essential role of the immune system as a natural mechanism to fight cancer. In addition to acting to protect the body through the action of natural killer cells, preventing cancer from installing, when a cell becomes cancerous, there is recognition of the antigens/membrane proteins of this cell by the immune system, which starts to attack, blocking its action and promoting its lysis [118–120]. Despite its essential role, the immune system often fails to act as it should, given the location, progression and characteristics of the disease [119, 120].

One of the mechanisms by which RJ can mitigate cancer is also through modulation of the immune system [121]. The RJ 10-HDA compound can inhibit the cellular activation of NF-κB and inflammatory cytokines, such as TNFα, IL-1β and IL-8, and even increase IL-1Ra, an interleukin 1 antagonist, with a dose–response effect [121–123]. Interleukin-1 receptor (IL-1R) is expressed in several types of cells and acts as a receptor/ligand for IL-1α and IL-1 β, both with inflammatory potential. This receptor plays a vital role in the emergence of some types of cancer since, with the binding of interleukin 1, it regulates cell signalling pathways such as NF-kB and MAP kinase, which are pro-proliferative and pro-tumorigenic [124, 125].

Some scientific findings have also discussed the role of hormonal modulation in the onset of cancer. In this context, oestrogen, for example, plays an essential role in the emergence of breast cancer since binding to receptors on these cells stimulates its development [126, 127]. In addition to endogenous factors, environmental/synthetic compounds may also play a role. Bisphenol A (BPA), a compound used in the manufacture of polycarbonate, is found in most plastic products [128, 129] and has recently gained prominence. In addition to other risks, studies point to a probable relationship between BPA consumption and the onset of cancer, especially oestrogen-dependent ones such as breast cancer, since it is an endocrine disruptor [128, 129].

BPA can accelerate cell ageing by decreasing telomerase activity, generating telomere shortening with the upregulation of telomerase reverse transcriptase. Furthermore, BPA binds to oestrogen receptors, increasing the risk of cell proliferation of cancerous cell lines that are hormone-dependent [128, 129].

It is suggested that RJ can interrupt the damage caused by BPA in breast cancer cells, inhibiting their proliferative activity. In these cases, it can suppress the binding between oestrogen and cancer cells and thus interfere with cell signalling that stimulates cell lineage proliferation (MCF-7) [122, 130, 131]. Despite this, there is still a need for more robust studies that prove this theory, as well as the dose and time that would be ideal.

RJ can also mitigate the levels of prostaglandin E (PGE-2), which, in addition to being a carcinogenesis stimulator, is also an apoptosis inhibitor, modulating the cellular response [132–134]. Also, RJ can increase macrophage colony-stimulating factor (M-CSF) levels, suppress TNF-α production dose-dependently and influence the picture of anorexia and fatigue in cancer, minimising involuntary weight loss, common in these patients [135].

In addition to potentially mitigating the development of some types of cancer and possible symptoms, as previously mentioned, RJ has also been able to reduce mucositis. Mucositis can be defined as an inflammation of the epithelium, which arises as a result of chemotherapy and radiotherapy treatments or a combination of both and manifests itself as an increased sensitivity in areas of the gastrointestinal mucosa, which in more severe cases leads to wounds and prevents the feeding [136, 137]. Given the high burden of drug therapy that cancer patients undergo, associating non-pharmacological adjuvant treatments such as RJ can be interesting.

In addition to its anti-inflammatory potential, RJ plays an important role in preventing the progression of mucositis due to its antimicrobial and bactericidal capacity, which prevents pathogenic bacteria from adhering to the site and worsening inflammation [123, 138, 139]. It was observed that the healing of wounds resulting from mucositis was facilitated using RJ [136, 139–141]. Such effects seem to be primarily related to the ability to reduce inflammation and modulation of the immune system through the reduction of activated macrophages [136, 139–141]. Its antioxidant and anti-inflammatory capacity neutralise free radicals and decrease the production of pro-inflammatory cytokines, promoting wound healing [138, 139].

Studies are still needed to clarify better the different mechanisms of action of royal jelly on mucositis and robust data on its effectiveness in prophylaxis and treatment. Furthermore, it is essential to remember the allergenic potential of RJ, which should always be considered when recommending its use.

Table 5 presents the studies that evaluated the effects of RJ on cancer. Although its mechanisms of action have not yet been fully elucidated, RJ can be a promising adjuvant agent in cancer treatment. More studies are needed to evaluate the dose × response.

New promising therapeutic avenues of royal jelly in neurological diseases

Positive results have been found against neurodegenerative diseases, cognitive performance, increased life expectancy and improvement of specific behaviours after RJ consumption [142].

Table 5 Studies involving royal jelly and its effects on cancer

References	Sample	Intervention	Results
In vitro studies			
[123]	WiDR human adenocarcinoma cell (BCRC 60157)	Control group and cells treated with 10-HDA (0.1, 0.5, 1, 2, 3, and 5 mM) for 24 h	10-HDA (3 mM):↓ IL-8, IL-1β, TNF-α, NF-κB Dose response 10-HDA ↑ IL-1Ra ↓ *Staphylococcus aureus*, *Streptococcus alactolyticus* (+), *Staphylococcus intermedius* B(+), *Staphylococcus xylosus* (+), *Pseudomonas aeruginosa* (−), *Salmonella choleraesuis* (−), *Vibrio parahaemolyticus* (−), *Escherichia coli* (hemolytic)
[200]	Human colorectal adenocarcinoma cells (CaCo2)	Cells treated with 10-HDA and human HuIFN-αN3	RJ antiproliferative activity of 2.0 HuIFN-αN3 antiproliferative activity of 2.5 10-HDA antiproliferative activity of 1.5 RJ + HuIFN-αN3 (2:1) antiproliferative activity of 3.8 ↓ GSH ↑MDA
Animal studies			
[201]	56 female Swiss albino mice induced with the animal model of EST	Mice: control; normal saline; CP (50 mg/kg); Non-EST mice: RJ (200 or 400 mg/kg); EST mice: RJ (200 or 400 mg/kg) for 2 weeks	Both doses of RJ (200 and 400 mg): ↓ Tumour size and markers (AFP and CEA) ↓ LPO and NO, ↓ TNF-α, ↓ Bcl ↑ GPx, CAT, SOD ↑ Caspase-3, Bax genes
[42]	60 rats and HT-29 cells	Control group (saline); DMH (30 mg/kg); Vitamin E (180 mg/kg); DMH + RJ (300 mg/kg); DMH + vitamin E (180 mg/kg)	RJ Group ↓ PCNA, ↓ PDGF, ↓ CEA ↓ Congestion, necrosis, inflammation and cell proliferation
Human Studies			
[14]	Patients with metastatic renal cell carcinoma 33 patients, aged 54–79	Capsules containing 900 mg of RJ or placebo, 3 ×/d for 3 months	↓ Tumour size ↓ TNF-α e TGF-β ↓ Anorexia and fadiga
[135]	Patients with renal cell carcinoma treated with TKIs	Capsules with 800 mg of RJ 3 times/d or placebo for 3 months	Week 2 to 4: ↑ TGF-β, ↑ M-CSF ↓ TNF-α ↔ after 12 weeks
[140]	103 patients undergoing radiotherapy and chemotherapy	1 g of RJ divided in 2 times/d as long as the symptoms persist or standard treatment	↓ Healing time in all grades of mucositis

Abbreviatios: *RJ*, royal jelly; *PCNA*, proliferating cell nuclear antigen; *PDGF*, platelet-derived growth fator; *CEA*, carcinoembryonic antigen; *DMH*, dimethylhydrazine; *EST*, Ehrlich solid tumours; *TKIs*, tyrosine kinase inhibitors; *M-CSF*, macrophage colony stimulating factor; *HuIFN-αN3*, human interferon-alpha; *CaCo2*, human colorectal adenocarcinoma cells; *10-HAD*, 10-hydroxy-2-decenoic acid; *HuIFN-αN3*, interferon-alpha; *AP*, antiproliferative effect

Some components can be pointed out as responsible for the results of studies that relate RJ to neuronal capacity. 10-H2DA can stimulate the differentiation of neuronal stem cells [143], probably due to its similarity with the omega 3, docosahexaenoic acid, which acts in the neurogenesis of glial cells [144, 145]; further studies are needed to confirm this hypothesis.

It is also important to note that vitamins and minerals account for up to 3% of the composition of RJ [146]. Amongst them, those of the B complex, particularly pantothenic acid (B5), are highlighted and related to neuronal function [146, 147]. The protective effects of this group of vitamins are due to their antioxidant capacity that neutralises free radicals. They also act as cofactors in the synthesis reactions of some neurotransmitters and ATP when they form the acetyl-coenzyme A (acetyl-CoA) molecule, which is significant in cellular respiration [148–150]. Complex B also reduces homocysteine, which, when elevated, is related to adverse neuronal outcomes, improving cognitive function [147].

Acetylcholine (ACH) is a neurotransmitter derived from the reaction of choline with acetyl-CoA in nerve endings in the central and peripheral nervous system [151, 152]. This neurotransmitter is also found in the composition of RJ (1 mg/g). It has been linked to preventing neurodegenerative disorders and diseases and improving memory and cognitive

functioning [146, 153]. Cholinergic neurons are susceptible to coenzyme A, and its increase by external sources such as RJ helps maintain their optimal levels [151, 152].

Deficiency of B vitamins and neurotransmitters such as acetylcholine has been observed in some diseases of a neurodegenerative nature, such as Alzheimer's disease (AD), dementia with Lewy bodies and Parkinson's [148, 154, 155]. One of the possible treatments for AD involves increasing the availability of acetylcholine in the brain [156].

RJ contains nucleotides, DNA and RNA-forming subunits, such as adenosine and guanidine, and is a phosphate source that gives rise to ADP and ATP molecules, which are fundamental in energy metabolism [147, 157]. Adenosine N1-oxide, the active component present in royal jelly, can be 20× more active than adenosine monophosphate (AMP) and demonstrates, in addition to neurogenic effects, an affinity for the CNS, stimulating neurite growth and inducing differentiation of PC12 cells in neurons with a role in the sympathetic nervous system (SNS). The activity of adenosine N1-oxide is achieved through A2A adenosine receptors present in the brain, regulating apoptosis [146, 147]. There was also an improvement in neuronal function and regeneration of essential cells in the process of cognition and memory, present in the hippocampus, an action similar to that of the nerve growth factor (NFG), a signalling protein that stimulates the development of neurons [46, 146, 147, 158]. RJ may even reduce apoptosis in the hippocampus of mice by reducing caspase-3 activation, inhibiting JNK phosphorylation and negatively regulating the bax/bcl2 ratio and pro-apoptotic pathway, and further increasing the cAMP/PKA/CREB/BDNF pathway, generating better memory [159].

The ingestion of RJ by the queen bees causes an endocrine stimulus to the development of their ovaries, which allows that unlike the sterile workers, the queen bees are fertile and perpetuate the species [146, 160]. RJ, based on its lipid compounds, mimics the activity of oestrogen, improving the blood–brain barrier and binding to nuclear and membrane receptors compatible with it in the brain, such as ERα and ERβ, which are mainly expressed in the hypothalamus, amygdala, hippocampus and cortex [149, 161, 162].

More results from studies performed in rats and humans regarding the neuroprotective effect of RJ can be found in Table 6.

Royal jelly could be an ally to re-establish the balance of the gut microbiota

The gut microbiota is a complex microbial community of microorganisms that coexist in the host organism [163]. The most abundant bacterial domain has around 1000 to 1200 intestinal bacteria species [164, 165]. Approximately 90% of the human gut microbiota comprises the phyla *Firmicutes* and *Bacteroidetes*, whilst the rest comprises *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia* and others [166]. Genetic variations in gut microbiota composition may occur because of several factors, including sex, age, medication, socioeconomic disparities, diet and diseases [167–171]. Indeed, this compositional variation can affect host-microbe interactions influencing health and disease [134].

Gut microbiota imbalance and toxins dysbiosis-derived have been associated with several NCDs, and nutritional strategies are the first driver to modulate the gut microbiota [172].

RJ has an antibacterial property and can be a new strategy to be included in the list of treatments such as pre, pro and symbiotics. In 2003, Eshraghi and Seifollahi demonstrated that RJ inhibited the growth of more than 30 bacterial species in vitro [173]. Moreover, an animal model study observed that a moderate dose of RJ (3 g/kg/day) for 30 days decreased the abundance of the phylum *Proteobacteria* and increased the abundance of the genera *Lachnospiraceae_*NK4A136_group and *Bacteroides* in healthy mice [134]. Corroborating, it was reported that 2.0 g/kg of RJ in dextran sulphate sodium (DSS)–induced colitis for 31 days decreased intestinal permeability due to increased expression of tight-junction proteins. Moreover, RJ increased the expression of MUC2, a protein related to the mucin layer. The authors suggested that these results might occur because RJ decreases the relative abundance of *Proteobacteria*, improving the mucosal barrier. Besides, RJ upregulated the beneficial genus *Muribaculum* [174]. Recently, Wang et al. [175] found that major royal jelly proteins (MRJPs) affect the gut microbiota composition of mice. The MRJP enriched the diversity of the gut microbiota in mice. Moreover, they observed mice fed with a high dose of MRJP 0.5 g/kg/day for 30 days presented a significantly higher abundance of the phylum *Bacteroidetes*, which they suggested to be involved with the improvement of the immunity [175].

Although there is evidence regarding the beneficial effects of RJ on gut microbiota modulation, all studies are in animal models. Given the potential role of RJ in the gut microbiota composition, it could be an ally to re-establish the balance of the gut microbiome composition and improve the host's health. More studies are needed to enhance the knowledge about the effect of RJ on gut microbiota.

Perspectives and preliminary conclusions

Predictive medicine

Predictive medicine seeks to identify risks for developing NCDs, such as cardiovascular disease, chronic kidney diseases, diabetes and cancer. Chronic inflammation and oxidative stress are biological processes that lead to the

Table 6 Studies involving the neuroprotective properties of royal jelly

References	Sample	Intervention	Results
In vitro studies			
[202]	Human neuroblastoma SH-SY5Y cells (ATCC® CRL-2266™)	H2O2- and glutamate-damaged cells: treated or pretreated with RJH (200 µg protein/mL)	↓ cell death from the H2O2- and glutamate-induced cell damage
[203]	Mouse neuroblastoma N2a cells and N2a/APP695	Cells were treated with RJP fractions	RJPs (3 and 9 µg/mL): ↓ the Aβ1-40 and Aβ1-42 levels, ↓ BACE1 mRNA expression
Animal studies			
[204]	Adult male Wistar rats	Non-stress group; control stress group (saline); stress group with EE; stress group with RJ; stress group with EE + RJ for 14 days	RJ: ↓ corticosterone levels ↑ BDNF levels in the hippocampus and PFC in stressed rats RJ prevented the detrimental effects of stress on anxiety-like behaviours and memory processes
[202]	Adult male Wistar rats	(1) Control; (2) donepezil (1 mg/kg); groups 3–5: RJH (10, 50, to 100 mg/kg/d) for 2 weeks through the experimental period and 2 weeks after inducing MCAO	RJH: ↓ Escape latency ↓ escape latency in 14 days after MCAO ↑ working memory ↓ AChE activity in the hippocampus after rtMCAO
[205]	Male Wistar rats	(1) Control; (2) STZ (icv); (3) Ringer's solution (icv) + RJ (og); (4) STZ (icv) + RJ (og). From day 7 after the surgery until day 21: treatment with RJ or distilled water	RJ: ↑ beneficial effects in animals injured by STZ, ↑ retention time for working spatial memory ↑ proliferation of new neurons in the hippocampus ↓ neurodegeneration and oxidative stress level
[16]	Adult male Swiss mice	(1) Control; (2) CdCl2 (6.5 mg/kg); (3) CdCl2 (85 mg); (4) 85 mg RJ/kg 2 h before IP-injection with 6.5 mg/kg CdCl2 for 7 1 week	RJ: was able to mitigate CdCl2-increased Cd concentration in cortical tissue Pre-treatment with RJ: ↓ LPO, NO, iNOS TNF-α and IL-1β; levels; Ameliorated Cd-induced oxidative damage in cortical tissue; ↑ GSH-Px, GSH-R, SOD and CAT activity; ↑ Nrf2 expression; ↑ mRNA Bcl-2; ↓ mRNA expression levels of Bax and caspase-3 ↓ cortical Cd-produced damage
[206]	Female WHBE rabbits	Sham group; HCD group; OVX + HCD group; OVX + HCD + RJ group (400 mg RJ/kg/d) for 12 weeks	RJ: ↑ behavioural deficits of OVX cholesterol-fed rabbits and brain structure ↓ blood lipids, Aβ, AchE and MDA levels, Evans blue in brain ↓ BACE1, and RAGE mRNA expression ↑ LRP-1 expression, activities of ChAT and SOD ↑ HRV and BRS in OVX cholesterol-fed rabbits
[159]	APP/PS1 transgenic mice with a C57BL/6 background and age-matched C57BL/6 mice	4 groups with IGAS treatments: (1) Wt group: saline; (2) Tg group: APP/PS1 transgenic mice that received saline; (3) TgRJ group: APP/PSI Tg mice that received RJ (300 mg/kg/d); (4)WtRJ group: Wt mice received RJ. 3 months of intervention	RJ: ↓ caspase-3 activation; Inhibited JNK phosphorylation and negatively regulated the bax/bcl2 ratio and pro-apoptotic pathway ↑ cAMP/PKA/CREB/BDNF pathway, generating better memory and learning results in mice that consumed RJ

Table 6 (continued)

References	Sample	Intervention	Results
[207]	Male Sprague–Dawley rat pups	Group I: 0.4 mL distilled water; Group II: RJ (300 mg/kg); Group III: CLO (0.4 ml/kg); Group IV: tartrazine (500 mg/kg); Group V: RJ (300 mg/kg) + tartrazine (500 mg/kg); Group VI: CLO (0.4 ml/kg) + tartrazine (500 mg/kg)	RJ in the group V: ↑ GABA, CAT, SOD and GSH levels in brain tissue; ↓ MDA in brain tissue; ↓ cells w/ pyknotic nuclei and less ssDNA positive cells in the cerebral cortex when compared with the group IV
Human studies			
[208]	42 healthy postmenopausal women	Enzyme-treated RJ: 800 mg of protease-digested lyophilised powder of RJ daily and placebo for12 weeks	Improve the anxiety score and backache and low back pain score

Abbreviatios: *Aβ*, amyloid-beta; *Aβ1-40*, beta-amyloid 40; *Aβ1-42*, beta-amyloid 42; *AChE*, acetylcholinesterase; *AMP*, adenosine monophosphate; *APP*, amyloid precursor protein; *BACE1*, beta-site APP cleaving enzyme 1; *Bax*, Bcl-2-like protein 4; *BBB*, blood–brain barrier; *Bcl-2*, B-cell lymphoma 2; *BDNF*, brain-derived neurotrophic factor; *BRS*, baroreflex sensitivity; *BW*, body weight; *CAT*, catalase; *Cd*, cadmium; *CdCl2*, cadmium chloride; *ChAT*, choline acetyltransferase; *CLO*, cod liver oil; *CNPase*, *2′,3′*-cyclic nucleotide 3′-phosphodiesterase; *CREB*, cAMP-response element-binding protein; *CTR*, control; *EE*, environmental enrichment; *ERK1/2*, extracellular signal-regulated protein kinase; *GABA*, gamma amino butyric acid; *GDNF*, glial cell line-derived neurotrophic factor; *GFAP*, glial fibrillary acidic protein; *GSH*, glutathione; *GSH*, glutathione peroxidase; *GSH-R*, glutathione reductase; *HCD*, high cholesterol diet; *HDEA*, 10-hydroxy-trans-2-decenoic acid; *HRV*, heart rate variability; *icv*, injected intracerebroventricularly; *IGAS*, intragastric; *IP*, intraperitoneal; *LDL*, low-density lipoprotein; *LPO*, lipid peroxidation; *LRP-1*, LDL receptor-related protein 1; *MCAO*, middle cerebral artery occlusion; *MDA*, malonaldehyde; *N2a/APP695*, N2a cells stably expressing human APP genes; *NO*, nitric oxide; *Non-ST*, non-stress; *Nrf2*, nuclear factor erythroid 2-related factor 2; *NSCs*, neural stem/progenitor cells; *og*, oral gavage; *OVX*, ovariectomy; *PFC*, prefrontal cortex; *PERJ*, PBS-extract of RJ; *PG*, propylene glycol; *RAGE*, receptor for advanced glycation end products; *RJ*, royal jelly; *RJH*, royal jelly hydrolysate; *RJPs*, royal jelly peptides; *Rt.MCAO*, occlusion of the right middle cerebral artery; *SOD*, superoxide dismutase; *ssDNA*, single-stranded DNA; *SOD*, superoxide dismutase; *STZ*, streptozotocin; *ST*, stress groups; *Tg*, transgenic; *TNF-α*, tumour necrosis factor-α; *Tuj1*, neuron-specific class III β-tubulin; *IL-1β*, interleukin-1β; *VaD*, vascular dementia; *WHBE*, white hair and black eyes; *Wt*, wild-type

development of these diseases and play a key role in modulating these processes [176]. Healthy foods, such as fruits, vegetables, legumes, nuts and seeds, can reduce chronic inflammation and oxidative stress, and RJ is presented here as one of these foods that can be part of a healthy diet. A particular value of RJ in reducing complications in patients with chronic non-communicable diseases can be considered in the framework of predictive, preventive and personalised medicine (PPPM). Furthermore, personalised nutrition can be a powerful tool in predictive medicine.

Preventive medicine

There is evidence that RJ can be an excellent option to mitigate inflammation, increasing the expression of Nrf2 and antioxidants and reducing the NF-kB and synthesis of cytokines in patients with non-communicable diseases. Figure 3 summarises the benefits of royal jelly for NCDs such as cancer, neurological disease, CVD, diabetes and CKD, including gut dysbiosis. Nutritional interventions can cover terms of individualization for the best possible care for the individual in ethical terms of medicine, which is a right of any patient in health care [177, 178]. However, despite many studies, we still need more data to determine a prescription's exact dose. Nevertheless, if nature shows that it is suitable for a queen's honeybees, why wouldn't it be good for the simple human being?

Future of personalised medicine

There is a growing interest in a healthy lifestyle, and a significantly improved health economy can bring benefits of the proposed PPPM paradigm shift; also, close collaboration between all stakeholders is essential for implementing the concepts in daily practice [84].

In this sense, personalised and individualised nutrition can be used to prevent or treat disease-related complications. Nutritional treatment should be approached according to the characteristics of the disease, being beneficial for the patient in terms of quality of life, prognosis and reduction of mortality. RJ is a bee product rich in bioactive compounds, specific fatty acids and proteins with therapeutic properties, playing a vital role as an antioxidant and anti-inflammatory. Thus, RJ can be used as a non-pharmacological therapy in nutritional treatment to mitigate NCD complications, such as diabetes, cancer and cardiovascular and chronic kidney diseases. In the future, it is believed that the use of RJ can be part of personalised nutrition to improve the immunological health of patients. In this context, PPPM can help identify the problem and find a solution to mitigate complications related to inflammation and oxidative stress present in NCDs through the concept of "food as medicine" [105].

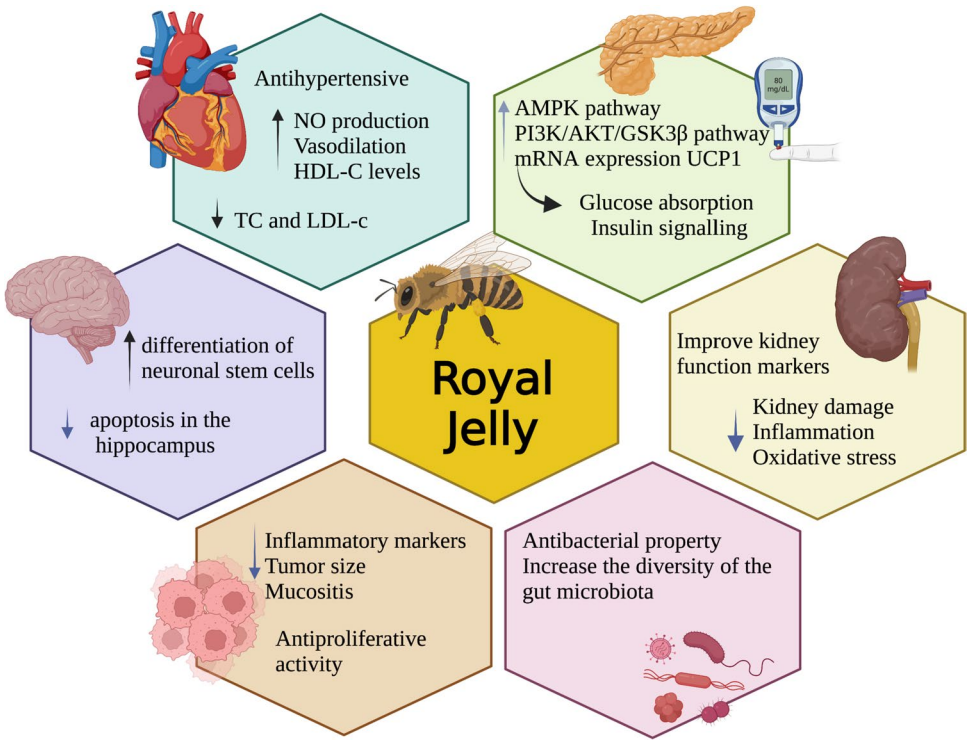

Fig. 3 Effects of royal jelly for NCDs such as cancer, neurological disease, CVD, diabetes and CKD, including gut dysbiosis. Created with BioRender.com

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