Relevance of functional foods in the Mediterranean diet: the role of olive oil, berries and honey in the prevention of cancer and cardiovascular diseases

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ABSTRACT

The traditional Mediterranean diet (MedDiet) is a well-known dietary pattern associated with longevity and improvement of life quality as it reduces the risk of the most common chronic patholo- gies, such as cancer and cardiovascular diseases (CVDs), that represent the principal cause of deathworldwide. One of the most characteristic foods of MedDiet is olive oil, a very complex matrix, whichconstitutes the main source of fats and is used in the preparation of foods, both raw as an ingredientin recipes, and in cooking. Similarly, strawberries and raspberries are tasty and powerful foods whichare commonly consumed in the Mediterranean area in fresh and processed forms and have attractedthe scientific and consumer attention worldwide for their beneficial properties for human health.Besides olive oil and berries, honey has lately been introduced in the MedDiet thanks to its relevant nutritional, phytochemical and antioxidant profile. It is a sweet substance that has recently been clas-sified as a functional food. The aim of this review is to present and discuss the recent evidence,obtained from *in vitro*, *in vivo* and epidemiological studies, on the potential roles exerted by thesefoods in the prevention and progression of different types of cancer and CVDs

Introduction

Lifestyle and diet are crucial factors for promoting and maintaining good health during the entire life course and preventing several chronic diseases. The Mediterranean diet (MedDiet) is one of the healthiest dietary patterns in the world, associated with a decreased risk of many non-communicable diseases, such as cancer and cardiovascular diseases (CVDs) (Estruch et al., 2018; Giacosa et al., 2013), that represent the principal cause of death worldwide: according to the World Health Organization (WHO), approximately 8.8 and 17 million deceases occurred in 2015 for cancer and CVDs, respectively. MedDiet is the heritage of millennia of exchanges of foods, cultures and people within the Mediterranean area and is characterized by a high intake of cereals, vegetables, fruits, nuts, legumes, a low quantity of meat and meat products and a moderate amount of fish and seafood, as well as a modest consumption of alcohol (Bach-Faig, Fuentes-Bol, et al., 2011; Bach-Faig, Berry, et al. 2011; Robles-Almazan et al., 2018); thanks to its contribution to health and general well-being, MedDiet has been declared an Intangible Cultural Heritage of Humanity by UNESCO in 2010. Olive oil (OO), used for both dressing and cooking, is the most representative food of the MedDiet, with an unique composition of fatty acids, vitamins, minerals and polyphenols, whose consumption has been correlated to a decreased risk of several common pathologies, including cancers and CVDs (Barzanti et al., 1994; Bach-Faig, Fuentes-Bol, et al., 2011; Bach-Faig, Berry, et al., 2011; Robles-Almazan et al., 2018). Among fruits, strawberries and raspberries are the most consumed berries in the Mediterranean countries, thanks to their high nutritional and phytochemical contents, and are responsible for their preventive and therapeutic effects on human health (Luo et al., 2016; Mazzoni et al., 2016; Giampieri, Alvarez-Suarez, et al., 2017; Giampieri, Forbes-Hernandez, et al., 2017; Sette et al., 2017). Finally, honey has been recently classified as a functional food and introduced in the MedDiet because of its noticeable nutritional and phytochemical profile, responsible for its health benefits (Alvarez-Suarez, Giampieri, and Battino 2013).

This review aims to update and discuss the effects that OO, strawberry, raspberry and honey exert on cancer and CVDs prevention and managment, taking into account the *in vitro*, *in vivo* and epidemiological studies published in the last five years.

Olive oil

OO is a very complex matrix whose components can be divided into two fractions: (i) saponificable fraction (98–99% of the total weight of the oil), mainly represented by triacylglycerides (TGs), which contain mostly monounsaturated fatty acid (MUFA), particularly oleic acid and (ii) minor components (about 2% of the total oil weight), including more than 230 chemical compounds (primarily pigments, aliphatic and triterpenic alcohols, sterols, hydrocarbons, volatile and phenolic compounds) (Svegliati Baroni et al., 1999; Quiles et al., 2003; Quiles et al., 2004; Quiles et al., 2010; Servili et al., 2013). This food is an everyday part of MedDiet, with daily consumption averaging approximately two tablespoons (Bach-Faig, Fuentes-Bol, et al., 2011; Bach-Faig, Berry, et al., 2011).

OO and cancer

OO exerts several chemopreventive effects related to the initiation, promotion and progression of carcinogenesis (López-Miranda et al., 2010), thanks to the biological activities of its bioactive compounds, including squalene, oleanolic acid and polyphenols, which can reduce cellular oxidative stress and DNA damage from reactive oxygen metabolites and can modulate cellular processes and signaling pathways relevant to carcinogenesis (Fig. 1) (Warleta et al., 2010).

Many studies have been conducted in recent years to evaluate the cytotoxic and the potential chemotherapeutic effects of phenolic extracts from virgin olive oil (VOO) in different experimental models. Table 1 summarizes the experimental models, dosage and duration of treatment, as well as biological response for each described study.

Regarding *in vitro* studies, the effects of different VOO phenolic extracts (VOO-PE) have been tested on different colon or colorectal carcinoma cells (Alu'Datt et al., 2014; Hashim et al., 2014). Alu'Datt et al. (2014) reported that both free and lipid bound VOO-isolated phenolic extracts exerted antiproliferative activities against some colorectal cancer cell lines (CRC1 and CRC5), while Hashim et al. (2014) found that 24-h incubation did not inhibit cell migration but reduced cell spreading on fibronectin. Moreover, the expression of a range of α and β integrins was found to be negatively modulated by the treatment. Similar effects on human urinary bladder cancer cells (T24 and 5637) were reported by Coccia et al. (2016) who showed that extra virgin olive oil phenolic extract (EVOO-PE) inhibited cell proliferation and clonogenic ability in a dose-dependent manner. Cell cycle analysis after EVOO-PE treatment showed a marked growth arrest in the G2/M phase for both cell lines, which, in the case of T24, led to apoptosis induction. Finally, another EVOO-PE with a higher amount of phenolics (specifically secoiridoids comprising 83% of the total phenolic compounds) showed a significant decrease in cell viability on MCF-7 breast cancer cells in a dose- and time-dependent manner. 48 h-treatments with different concentrations of the phenolic extracts induced intracellular ROS generation and cell death (Reboredo-Rodr´ıguez et al., 2018). All these mechanisms (cell cycle arrest, increased ROS generation, and subsequent cell deaths) could also occur in other cancer cells explaining in part the previous findings (Alu'Datt et al., 2014).

The effect of OO on cancer has been also tested *in vivo*, using both carcinogen-induced and xenograft cancer models. Experimental models, dosage and duration of treatments

Figure 1. The main effects of olive oil in cancer and in cardiovascular disease. The figure summarizes the main effects of olive oil in cancer and in cardiovascular disease both *in vitro* and *in vivo* models. ROS: Reactive Oxygen Species; VCAM-1: vascular cell adhesion molecule 1; MDA: Malondialdehyde; TNF-*α*: Tumor necrosis factor alpha.

Table 1. Effects of VOO phenolic extracts on different types of cancer.

Experimental Model	Dosage and duration of the treatment	Biological response/involved pathway	Ref.
Human CRC cells (CRC1 & CRC5)	Free or lipid bound phenolic compounds at 30 °C (0 to 28.4 or to 12 lg, respectively) & 60 °C (0 to 14 or to 13.6 lg, respectively) (for 48 h).	-#Proliferation	Alu'Datt et al., 2014
Human colon adenocarcinoma (HT115) & fetal lung (MRC-5) cells	EVOO-PE (25 mg/mL for 24 h).	-#Invasion	Hashim et al., 2014
Human urinary bladder carcinoma cells (T24 & 5637)	EVOO-PE (0–100 mg/mL for 4 & 24 h & 14 d).	-#Proliferation & clonogenic ability -Arrest in the G2/M phase -"Apoptosis	Coccia et al., 2016
Human breast cancer cells (MCF-7)	EVOOPE (0–1 mg/mL for 24, 48 & 72 h).	-#Cell viability -"Cell death -"ROS generation	Reboredo-Rodr´ıguez et al., 2018

and main results of these studies here described have been summarized in Table 2.

For example, the anti-cancer effect of EVOO has been assessed in an athymic mouse model with xenograft colon tumors, showing that EVOO treatment significantly inhibited the growth of colon tumors compared to controls (Fezai et al., 2013). In a N-methyl nitrosourea-induced breast cancer rat model, animals fed with refined sunflower oil enriched to 50% oleic acid presented a reduction in tumor volume, those that consumed EVOO had a lower number of mitosis, while rats fed with refined sunflower oil showed a reduction in the number of tubules observed in tumor tissue (Ru´ız-Sanjuan et al., 2015). These results correlated with the differences in levels of DNA methylation and histone modification patterns found in mammary glands, and tumors present in them, from rats fed on EVOO- or corn oil-rich diets which suggested the presence of different epigenetic patterns (Rodr´ıguez-Miguel et al., 2015).

The effect of diets rich in EVOO on susceptibility to cancer induction by different carcinogens could be due to the activity of enzymes participating in the xenobiotic metabolism: for example, it has shown that in the liver of a 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced breast cancer model dietary fat (including EVOO) influenced reactive metabolite levels and subsequent DNA damage (Manzanares et al., 2014). The use of EVOO as predominant dietary fat could also have advantages since it would reduce intake of other dietary fat less healthy in relation to cancer. Compared with other diets including one based on OO, feeding on a diet high in saturated fats by using butter as fat source led to higher tumor volume in prepubertal mammary glands of the offspring after induction of cancer by a DMBA treatment (Govindarajah et al., 2016). Thus, the susceptibility of prepubertal mammary glands to DMBA-induced tumorigenesis can be modulated by dietary fat. In animals with a high intake of saturated fat, the increased susceptibility to DMBA-induced tumorigenesis involved aberrant gene expression and likely epigenetic dysregulation that affect rapid hormone signaling (Govindarajah et al., 2016). Similarly, high-corn oil and OO diets differentially influenced age-related changes in gene expression in a DMBA breast cancer model, suggesting that the different susceptibility to xenobiotic exposure depending on age may be modulated by dietary factors (Manzanares et al., 2015). In addition, the preventive effect of OO could be related to selective increase in CB1 expression in rat colon samples receiving dietary EVOO supplementation for 10 days (di Francesco et al., 2015), an effect also reported on an *in vitro* study (di Francesco et al., 2015).

The beneficial effects of EVOO against cancer could be due to the activities of different bioactive compounds present in this food, particularly in the phenolic fraction. Hashim et al. (2014) reported that a dosage of 25 mg per kg of body weight of EVOO-PE administered by gavage over 70 days decreased not only tumor volume but also the number of metastases in SCID Balb-c mice with a xenograft tumor implanted subcutaneously with HT115-Luc cells. VOO-PE would decrease cancer cell invasion and also inhibit metastasis, possibly through the modulation of integ- rin expression by some phenolic compounds of the extract. In addition, in a study that compared the effects of different oils on susceptibility to cancer, it was found that feeding on a high-fat diet in which fish oil was the only fat source slowed tumor growth and improved survival in mice injected with LAPC-4 human prostate cancer cells compared with those fed with OO, corn oil or animal fat (Lloyd et al., 2013). Since the fat source is OO, not EVOO or VOO, these results could emphasize the importance of EVOO phenolics in OO anticancer activities. However, other conditions such as fat amount in the diet or cancer type could also have an influence.

Dietary interventions on humans involving OO performed in the last five years are very few. Actually, only the DAMA (Diet, physical Activity and MAmmography) trial, a factorial randomized trial involving healthy nonsmoking postmenopausal women not using hormone replacement therapy and having mammographic breast density (MBD) higher than 50, has been included in this review. In this study, women were randomly assigned to 24-month interventions based on moderate-intensity physical activity and/or dietary modification focused on plant foods with a low glycemic load, low in saturated fats and alcohol, and rich in antioxidants and fiber, to test their effects on mammographic breast density that is an established risk factor for breast cancer. However, no differences across study arms in the baseline distribution of variables of interest related to diet and lifestyle were found (Masala et al., 2014).

In 2015 a systematic review, including either cohort or case-control studies, carried out a meta-analysis of an overall population of 1,784,404 subjects from 56 studies, confirming a prominent and consistent inverse association provided by adherence to MedDiet in relation to cancer mortality and the risk of several cancer types. The highest adherence score to MedDiet was significantly associated with a lower risk of

Table 2. *In vivo* effects of olive oil on different types of cancer.

Experimental Model, age	Treatments (dosage, frequency and duration)	Main results	Ref.
Female athymic nu/nu mice (6 weeks old) inoculated with HCT 116 tumors cells	EVOO (8 mL/kg, 3 d/week for 4 weeks)	-#Tumour growth	Fezai et al., 2013
Female virgin Wistar rats (149.4 ± 2.7 g) intraperitoneally injected with 3 doses of 50 mg/kg of N-methyl nitrosourea at 50, 80 & 110 d after birth	AIN-93 semipurified diets containing 4% of fat, constituted by EVOO, refined sunflower oil or refined sunflower oil enriched to 50% oleic acid	-#Tumour volume & their histopathological features	Ru´ız-Sanjuan et al., 2015
Female Sprague-Dawley rats (53 d old) with DMBA-induced breast cancer (a single dose of 5 mg by oral gavage)	Low-fat (3% corn oil), high corn-oil (20%) or a high EVOO diet (17% EVOOþ 3% corn oil) (from weaning onward)	DNA methylation & histone modification patterns in mammary gland (& tumor present in them) depend on diet consumed	Rodr´ıguez-Miguel et al., 2015
Female Sprague–Dawley (23 d old) with DMBA-induced breast cancer (a single dose of 10mg by oral gavage)	Low-fat (3% corn oil), high corn-oil (20%)or a high EVOO diet (17% EVOOþ 3% corn oil) (from weaning onward)	-"Coordinated Phase I and Phase II enzyme activity -#Reactive metabolites -#DNA damage	Manzanares et al., 2014
Female Sprague–Dawley (23 d old) with DMBA-induced breast cancer (a single dose of 10mg by oral gavage)	Low-fat (3% corn oil), high corn-oil (20%) or a high EVOO diet (17% EVOOþ 3% corn oil) (from weaning onward)	-#Phase I metabolism -"Phase II detoxification	Manzanares et al., 2015
VOO Phenolic Extracts			
Female SCID Balb-c mice (8–10 weeks old) implanted subcutaneously with HT115-Luc cells	EVOO-PE (25 mg/kg per d) pre implant (2 weeks), post implant (8 weeks) or pre and post implant (10 weeks)	-#Tumour volume -#Metastases number	Hashim et al., 2014
Other Minor Compounds			
Female Sprague–Dawley rats	Orally gavaged EVOO (250 1L/300 g, a single adminsitration after 9 d of water administration or a daily administration for 10 d)	-Modulation of DNA methylation of CB_1	di Francesco et al., 2015
Interventions in humans			
Healthy nonsmoking postmenopausal women not using hormone replacement therapy & having MBD >50% participating in The DAMA trial, N¼234	Moderate-intensity physical activity &/or dietary modification focused on plant foods with a low glycemic load, low in saturated fats & alcohol, and rich in antioxidants and fiber (24m)	No effect was observed	Masala et al., 2014

all cause cancer mortality, colorectal cancer, breast cancer, gastric cancer, prostate cancer, liver cancer, head and neck cancer, pancreatic cancer, and respiratory cancer. On the other hand, no significant association was observed for esophageal/ovarian/endometrial/and bladder cancer. Among cancer survivors, the association between the adherence to the highest MedDiet category and risk of cancer mortality, and cancer recurrence was not statistically significant (Schwingshackl and Hoffmann, 2015). Thus, preferring OO to other added lipids, particularly those rich in saturated fats, can decrease the risk of upper digestive and respiratory tract neoplasms, breast and, possibly, colorectal and other cancer sites.

Additional meta-analyses by cancer sites (breast, digestive and other) have also been performed. Concerning digestive system cancers, a Tunisian cross-sectional study found that the consumption of OO along with citrus oil was protective against gastric cancer. However, digestive cancers were associated with vegetables, fruits, fish, and coffee intake, but not with OO consumption (Baroudi et al., 2014). In contrast, a case-control study comparing colon and/or rectal cancer patients and healthy participants from Saudi Arabia reported that higher black tea and coffee intake would be associated with the risk of colon and/or rectal cancer, but not consumption of other foods (Azzeh et al., 2017). These results could indicate that not all cancers located in the digestive system are associated with OO intake and previous results are a consequence of considering many different cancers together in statistical analysis. Notwithstanding, lifestyle and dietary context in the different countries could also influence the results provided by these epidemiological studies.

OO intake association with incidence of breast cancer has also been studied. In the last five years, a number of epidemiological studies have been carried out, all in Mediterranean countries. Among them, a cross-sectional study based on a large sample (3,548) suggested that MBD, an important risk marker for breast cancer, is associated with OO consumption in Spanish peri- and postmenopausal women drawn from seven breast cancer screening programs. Importantly, other modifiable dietary factors, such as calorie intake, was also associated with this parameter (Garc´ıa-Arenzana et al., 2014). A more recent case-control study also reported that adherence to healthy dietary patterns characterized by a high consumption of OO together with other foods such as whole grains, fruits and vegetables, and fish seems to be favorable in decreasing breast cancer incidence among middle-aged women from Greece (Mourouti et al., 2015).

In addition, a more recent systematic review was carried out involving 11,161 breast cancer events from more than 150,000 females from 11 retrospective case-control studies and from five prospective cohort studies. A higher OO intake showed a protective effect against breast cancer, although it was not statistically significant among three of the cohort studies (Xin et al., 2015). Moreover, some subgroup analyses were performed highlighting that oils might impact on females with different strata of Body Mass Index (BMI). Despite the associations found for OO, these meta-

analyses suggested that a higher intake of vegetable oils, in general, is not associated with the lower risk of breast cancer. Still, recall bias and imbalance in study location and vegetable oils subtypes shouldn't be ignored.

All these results suggest that OO consumption is implicated in preventing certain cancers, with the most promising findings for breast and digestive tract cancers (Buckland and Gonzalez, 2015). However, these data come from observational studies and they are still not entirely consistent as they are mainly from case-control studies.

OO and CVD

Nowadays, it is considered that OO has an unequivocal cardio-protective role (Fig. 1) (Buckland et al., 2011). In the last five years, the effects of OO in reducing CVDs risk have been investigated mainly on animals (Table 3). For example, a study on male C57BL/6JOlaHsd mice fed with a café diet (rich in sugar and saturated fats) showed that the increase in high density lipoprotein (HDL)- and low density lipoprotein (LDL) levels induced by the café diet were prevented and the rise of plasma glucose concentrations were corrected by improving insulin sensitivity in animals simultaneously supplemented with oleuropein for 15 weeks, although body weight gain and increase of abdominal adipose tissue were not significantly influenced (Lepore et al., 2015). Concerning oxidative stress and inflammation, which are the two most known activities of OO phenolics, supplementation with 10% of EVOO attenuated increases in malondialdehyde (MDA) and tumor necrosis factor-*α* (TNF-*α*) levels in a diet-induced hypercholesterolemic rat model (Katsarou et al., 2016). Likewise, a diet with high quantities of EVOO, despite producing obesity and insulin resistance, decreased arterial lipoperoxidation compared to a diet rich in saturated fats (margarine) and showed a preserved endothelial response to carbachol. In addition, low levels of circulating cholesterol were found (Keita et al., 2013). Regarding unsaturated FAs, long-term feeding on a diet with VOO as unique dietary fat led to lower levels of oxidative damage markers (protein carbonyls, urinary F2-isoprostanes, thiobarbituric acid reactive substances) in different organs and blood compared with n-6 polyunsaturated fatty acid (PUFA)-rich diets from sunflower oil (Varela-Lopez et al., 2018; Varela-López et al., 2017; Bullon et al., 2013).

In addition to damage or dysfunction of endothelial or cardiac tissue, alterations in the liver or pancreas could also contribute to the increase of CVD risk since circulating risk markers or pathologies that augment the risk depend on a correct functioning of these organs. The "healthy" properties of OO might result useful in that sense. For instance, a VOO-rich diet has been shown to prevent the age-associated increase in the number of *β* cells in rat pancreas compared to a n-6 PUFA-rich diet based on sunflower oil, which led to increased insulin pancreatic contents and hyperleptinemia (Roche et al., 2014). Similarly, oleuropein supplementation prevented liver steatosis in male C57BL/6JOlaHsd mice fed with a café diet (Lepore et al., 2015).

Aging is associated with higher oxidative damage, as well as with pro-inflammatory states; thus, elevated age could be considered a risk factor for CVD. Similarly, some diets are

Table 3. *In vivo* effects of olive oil on cardiovascular health.

Experimental Model, age	Treatments (dosage, frequency and duration)	Main results	Ref.
Male C57BL/6JOlaHsd mice (19.4 ± 1.2 g) fed with a cafe diet (rich in sugar and saturated fats)	Oleuropein supplements (0.037 mmol/kg per d, for 15 week) or Ac-oleuropein supplements (0.025 mmol/kper d, for 15 week)	-#HDL-C and LDL-C levels -#Glucose concentrations -"Insulin sensitivity	Lepore et al., 2015
Wistar rats (190–210 g) with diet-induced hypercholesterolemia by feeding on a high-cholesterol diet (standard diet supplemented with 2 % cholesterol)	EVOO, sunflower oil, high-oleic sunflower oil, phenolics deprived-EVOO, sunflower oil enriched with the EVOO phenolics or high-oleic sunflower oil enriched with the EVOO phenolics supplements (10%, for 9 weeks)	-#MDA, TNF-α & aorta E-selectin levels. -#VCAM-1	Katsarou et al., 2016
Male albino Wistar rats (5–6 weeks old) fed on a high-cholesterol diet (standard diet supplemented with 2% cholesterol)	High-fat diets rich in EVOO (25% added to a standard diet for 20 weeks) or saturated (25% added to a standard diet for 20 weeks)	-#Arterial lipoperoxidation & circulating cholesterol levels -"Response to carbachol	Keita et al., 2013
Male Wistar rats (3 weeks)	Normolipid (AIN - 93) diets with VOO, sunflower or fish oil as unique dietary fat (4% Kcal, from weaning to 6/24 m)	-#Protein oxidative damage markers	Varela-Lopez et al., 2018
Male Wistar rats (3 weeks)	Normolipid (AIN - 93) diets with VOO, sunflower or fish oil as unique dietary fat (4% Kcal, from weaning to 6/24 m)	-#Urinay F2-isoprostanes	Varela-López et al., 2017
Male Wistar rats (3 weeks)	Normolipid (AIN - 93) diets with VOO, sunflower or fish oil as unique dietary fat (4% Kcal, from weaning to 6/24 m)	-"Apoptosis, autophagy, mitochondrial biogenesis and antioxidant defenses	Bullon et al., 2013
Male Wistar rats (3 weeks)	Normolipid (AIN - 93) diets with VOO, sunflower or fish oil as unique dietary fat (4% Kcal, from weaning to 6/24 m)	-#β cells in rat pancreas	Roche et al., 2014

considered less healthy such as saturated fatty acid (SFA)-rich diets. Although these have not been observed in specific risks for CVD, an elevated intake of VOO or a predominant use of it in the diet could prevent to a certain degree some oxidative damage accumulation when animals get old (Ochoa et al., 2011).

OO preventive effects against aging or inappropriate diets lead to molecular changes in rats. Compared with sunflower oil that is rich in n-6 PUFA, the use of OO as unique dietary fat source has been related with age-associated changes in different gene expressions. In gums, certain genes related to apoptosis, autophagy, mitochondrial biogenesis or antioxidant defenses have shown an increased expression in aged animals fed a VOO-rich diet compared with those receiving a sunflower oil-diet (Bullon et al., 2013). At liver level, microarray analysis has shown that genes deferentially expressed with age were largely involved in mitochondrial function and oxidative stress pathways, followed by cell cycle and telomere length control (Varela-Lopez et al., 2018). Since substitution of OO with sunflower oil in the same diet did not show such changes in gene expression, it was suggested that these fats could, to some extent, prevent the deleterious effects of aging through mechanisms induced after the over-expression of these genes.

Because some of the OO beneficial effects can be attributed to its minor components, phenols from EVOO has been used to create other functional foods, mainly other edible oils which have also been tested in animals. In a study investigating the effect of EVOO on a diet-induced hypercholesterolemic rat model (characterized by increased in serum total cholesterol, LDL and TGs), the use of other oils containing EVOO's phenol compounds namely sunflower or high-oleic sunflower oils attenuated the increases in MDA and TNF-α levels in the heart. Although, under these experimental conditions they did not affect glutathione and interleukin-6 (IL-6) levels, this would indicate that both antioxidant and anti-inflammatory activities were exerted by some of these phenolics (Katsarou et al., 2016). The absence of differences between enriched sunflower oil, EVOO and enriched high-oleic sunflower oil could be attributed to the duration of the intervention (9 weeks) since heterogeneity was found for heart fatty acid profile in all intervention groups.

Regarding human studies, the MedDiet rich in OO has been shown to reduce CVD incidence and improve cardiovascular risk factors, such as lipid profiles, blood pressure, postprandial hyperlipidemia, endothelial dysfunction, oxidative stress, and antithrombotic profiles.

A multicenter single-bind randomized control trial (RCT) has been performed in Spain on adults with cardiovascular risks providing interesting and very relevant results. Subjects were instructed to follow one of three different dietary patterns, a MedDiet enriched with EVOO (40% total fat), a MedDiet enriched with specific mixed nuts (walnuts, almonds, hazelnuts) (40% total fat) or a low-fat diet. In general, all interventions reduced blood pressure compared to baseline (Toledo et al., 2013). In addition, a MedDiet supplemented with EVOO reduced the incidence of CVD events (Martínez-González, Sánchez-Tainta, et al., 2014; Martínez-González, Toledo, et al., 2014; Estruch et al., 2013) compared to a low-fat diet, as well as of other pathological conditions such as diabetes and metabolic syndrome (MetS) (Martínez-González, Sánchez-Tainta, et al., 2014; Estruch et al., 2013). A similar finding was found for multiple CVD risk factors including blood pressure (Toledo et al., 2013; Doménech et al., 2014; Medina-Remón et al., 2015), insulin resistance (Martínez-González, Sánchez-Tainta, et al., 2014; Martínez-González, Castaner, et al. 2014, fasting blood glucose (Doménech et al., 2014; Babio et al., 2014) and total colesterol (Doménech et al., 2014) or body weight (Álvarez-Pérez et al., 2016; Babio et al., 2014; Estruch et al., 2016). MedDiet also showed beneficial effects on inflammation markers (Casas et al., 2016) and carotid atherosclerosis progression (Martínez-González, Sánchez-Tainta, et al., 2014). Other benefits have been reported, such as an increase in plasma total antioxidant capacity (TAC) after a year of MedDiet intervention that may be related to baseline levels of plasma non enzymatic antioxidant capacity (Zamora-Ros et al., 2013). These results correlated with the reported reduction of oxidative damage to lipids and DNA in MetS individuals (Mitjavila et al., 2013). The same was found for *in vivo* ox-LDL after EVOO-supplemented MedDiet (Fitó et al., 2014).

Regarding dietary interventions published in the last five years modifying only dietary fats, in general studies confirmed the activities and effects previously observed, but some interesting properties have started to be investigated. Compared with habitual diets, it has been reported that a 6-week nutritional intervention- as the only added fat, plus a daily dose of 50 mL- led to a significant reduction of total cholesterol, HDL, LDL and TGs and a significant increase of HDL levels in healthy elderly people (Oliveras-López et al., 2013). In turn, in healthy subjects who substituted a part of their habitual diets with 4.5% of energy from butter or refined OO during 5-weeks in a cross-over design, moderate intake of butter (and thus, SFA) increased total cholesterol and LDL more than OO intake and habitual diet did, although no differences were observed for TGs, hsCRP, insulin and glucose concentrations (Engel and Tholstrup, 2015). A school-based program located in rural areas, consisting of nutritional education (sessions held over 6 months) or nutritional education plus physical activity (60 minute sessions held twice a week), showed a positive effect on health-related parameters in children, including lower fat percentage, sum of skin folds and waist circumference, lower diastolic blood pressure and glycemia, improved proportion of macronutrients and dietary cholesterol and improved lipid profile when they substituted oil with EVOO (Muros et al., 2015). Changes in blood lipids were also observed at postprandial level even after a single intervention. However, in the context of a high protein meal, palmolein similarly to OO did not affect postprandial endothelial function in overweight/obese men (Stonehouse, Brinkworth, and Noakes 2015). Compared with saturated fats, VOO also would result beneficial in the context of a high-protein diet, according to a cross-over study in healthy Malaysian adults. A 5-week

treatment with high-protein diets with VOO representing two-thirds of 30% fat calories led to lower plasma leukotriene B4 *vs* coconut oil, thus leading to a lower pro- inflammatory state. However, no differences or changes were observed concerning thrombogenicity indices, cellular adhesion molecules (intercellular adhesion molecule (ICAM) and vascular cell adhesion molecules (VCAM)), thromb- oxane B2 (TXB2) and TXB2/prostacyclin (Prostaglandin F1α, PGF1α) ratios (Voon et al., 2015). In contrast, in another study performed on overweight and obese men, the use of OO supplements in combination with high-protein and high-fat meals during a week did not significantly affect postprandial endothelial function in comparison with palm olein (Stonehouse, Brinkworth, and Noakes 2015).

The beneficial effects of OO consumption on inflammation and endothelial function are supported by a metanalysis including results from 30 RCTs investigating the effects of OO on the main markers related to the inflammatory status and to the endothelial system. OO interventions resulted in a decrease in CRP and IL-6 when compared to controls, as well as in increased values of flow-mediated dilatation, confirming the positive effects of OO on CVDs (Schwingshackl, Christoph, and Hoffmann 2015).

Due to the effects attributed to phenolic compounds present in EVOO, different RCTs following a cross-over design have been carried comparing OO enriched with phenolic compounds with non-enriched OO (Biel et al., 2016; Oliveras-López et al., 2013; Silva et al., 2015; Pedret et al., 2015), or with OO with different amounts of phenolic com- pounds (Martín-Peláez et al., 2016; Farràs et al., 2015; Hernáez et al., 2015). For example, a systematic review of RCTs comparing high with low-phenolic OOs in either healthy participants or patients with CVDs summarized main differences between both products (Hohmann et al., 2015). Overall, there were medium effects for lowering sys- tolic blood pressure (and small effects for lowering ox-LDL): enriched EVOO produced small beneficial effects on systolic blood pressure and ox-LDL, but no effects were found for diastolic blood pressure, total colesterol, HDL, LDL and TGs, as well as MDA (Hohmann et al., 2015). Notwithstanding, the reduced number of studies (8 cross-over RCTs) and/or participants limited these conclusions.

An interesting systematic review of studies assessing the association between vegetable oil (including fried food) consumption and the risk of different diseases related to nutrition and/or diet (overweight/obesity or weight gain, type 2 diabetes mellitus or MetS and CVDs or hypertension) have provided additional advantages for OO use. Although authors concluded that the myth that fried food is generally associated with a higher risk of CVD is not supported by the available evidence, virgin olive oil significantly reduced the risk of CVD clinical events, based on the results of a large randomized trial that included, as part of the intervention, the recommendation to use high amounts of virgin olive oil, also for frying foods. Moreover, they suggested that high consumption of fried foods is probably related to a higher risk of weight gain, even if the type of oil may perhaps modify this association (Sayon-Orea, Carlos, and Mart´ınez-Gonzalez 2015). In addition, sex hormone-binding globulin (SHBG) serum levels were significantly higher in men using OO for cooking compared to subjects using sunflower oil. In the multiple regression analysis, MUFA were independently associated with SHBG levels and accounted for 20.4% of SHBG variance (Sáez-López et al., 2014).

An important feature of OO most recently reported, is that its intake can increase the bioavailability of other compounds with potential benefits on health. In particular, an increase was found in all lycopene isomers in subjects consuming 750 g of tomato juice containing a 10% of refined OO per 70 kg of body weight in a single ingestion reaching the maximum concentration after 24 h of consumption, compared with subjects taking the same amount of juice without oil. Importantly, this treatment also led to a postprandial decrease in LDL and total cholesterol after 6 h from ingestion that correlated with an increase of trans-lycopene and 5-cis-lycopene, respectively (Arranz et al., 2015). These results are very interesting since tomato sauces are usually cooked with the addition of oil. The potential of these findings have been explored by other studies showing that intake of tomato sauce with refined OO led to higher changes in plasma levels of IL-6 and VCAM-1, lymphocyte function-associated antigen-1 (LFA-1) from T-lymphocytes and CD36 from monocytes compared with raw tomatoes or non-enriched tomato sauce consumption in healthy subjects. In addition, changes were accompanied by increased plasma HDL and IL-10 concentrations, which occurred with all products (Valderas-Martinez et al., 2016). Besides the potential of combining OO with vegetable products containing healthy lipids for cardiovascular health, this finding also emphasizes the role of the lipid component of OO in this function.

Overall, epidemiological research confirmed the protective role of OO against CVD events and CVD mortality (Covas, Konstantinidou, and Fitó 2009; Ruiz-Canela and Martínez-González, 2011), but also against other health outcomes that increase cardiovascular risks, such as diabetes, metabolic syndrome (MetS) and obesity (Viscogliosi et al., 2013; Buckland, Bach, and Serra-Majem 2008; Pérez-Martínez et al., 2011). A meta-analysis based on the results from 11 prospective studies and a RCT found that individuals in the highest quartile of adherence to the MedDiet had lower incidence and mortality from CVDs compared to those least adherent (Grosso et al., 2017). Other meta-analysis using data from 841,211 subjects from 42 cohort studies attributed the protective effects of MedDiet likely to OO, fruits, vegetables and legumes. The results indicated an overall risk reduction of all-cause mortality, cardiovascular mortality, cardiovascular events and stroke when comparing the top versus bottom third of MUFA, OO, oleic acid and MUFA:SFA ratio intake which would all be associated with OO intake. In contrast, MUFA from mixed animal and vegetable sources *per se* did not yield any significant effects on these outcome parameters (Schwingshackl and Hoffmann, 2014).

Berries

Thanks to their nutritional and phytochemical composition, berries are the most commonly consumed fruits in the

MedDiet and often used as medicinal foods, as anti-inflammatory and anti-cancer agents, and even as cosmetics (Folmer et al., 2014; Pan, Huang, et al., 2018). Among the most important berries in commercial production and in scientific research there are members of the genus Rubus (raspberry) and Fragaria (strawberry), mainly evaluated for their potential against cancer and CVDs (Fig. 2).

Raspberry and cancer

The raspberry (Rubus sp., family: Rosaceae) has recently received much attention from both scientists and consumers for its beneficial health properties (Afrin et al., 2016); different *in vitro* and *in vivo* studies have been performed to deeply investigate its role in cancer prevention and treatment (Table 4).

For example, in rat oral fibroblasts black raspberry extract inhibited initiation of oral carcinogenesis induced by polycyclic aromatic hydrocarbons (Guttenplan et al., 2016), while in SCC-9 and SAS cells it counteracted cell migration and invasion, altering metastasis processes through the suppression of matrix metalloproteinase (MMP)-2 expression mediated by Focal adhesion kinase (FAK)/Scr/extracellular signal-regulated kinase (ERK) signaling pathway (Huang et al., 2017). Similarly, different raspberry extracts were effect- ive against human nasopharyngeal cancer models in which cell migration and invasion were counteracted by suppressing MMP-2 expression and the down-regulation of ERK1/2 pathway (Hsin et al., 2017). Moreover in a carcinogen-induced animal oral cancer model (Oghumu et al., 2017; Chen, Guttenplan, et al., 2018) and in patients with biopsy-confirmed oral squamous cell carcinomas (Knobloch et al., 2016), dietary administration of black raspberries inhibited oral carcinogenesis via the reduction of tumor incidence and the inhibition of pro-inflammatory and anti-apoptotic pathways, highlighting its efficacy in oral cancer chemoprevention. Interesting results were also obtained in Hamster cheek pouches, where a short or long-term topical administration of black raspberry suspension reduced the squamous cell carcinomas multiplicity, tumor incidence and proliferation rate in DMBA-treated hamsters, inhibiting the progression of premalignant oral lesions and modulating the biomarkers of cancer development in high at-risk mucosa (Warner et al., 2014). Similar data were obtained in subjects with confirmed premalignant oral epithelial lesions: also in this case the topical application of a black raspberry gel to oral lesions resulted in significant reductions in lesional sizes, histologic grades and loss of heterozygosity events (Mallery et al., 2014).

In N-nitrosomethylbenzylamine (NMBA)-induced esophageal carcinogenesis in rats, black raspberry powder, its anthocyanin-enriched fraction and one of its major metabolites, protocatechuic acid, inhibited tumorigenesis progression, by (i) preventing the aberrant DNA methylation (Huang et al., 2016), (ii) reducing the expression of genes associated with inflammation (Peiffer et al., 2014), (iii) altering cytokine expression and innate immune cell trafficking into tumor tissues (Peiffer et al., 2016), and (iv) reversing oxidative stress and suppressing the nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB)/ MAPK pathways (Shi et al., 2017).

Also in colon cancer raspberry extracts, their anthocyanin enriched-fraction and single bioactive compounds isolated from raspberry seeds showed beneficial effects, as demonstrated in HCT116, LoVo, HT-29 and CaCo-2 cell lines

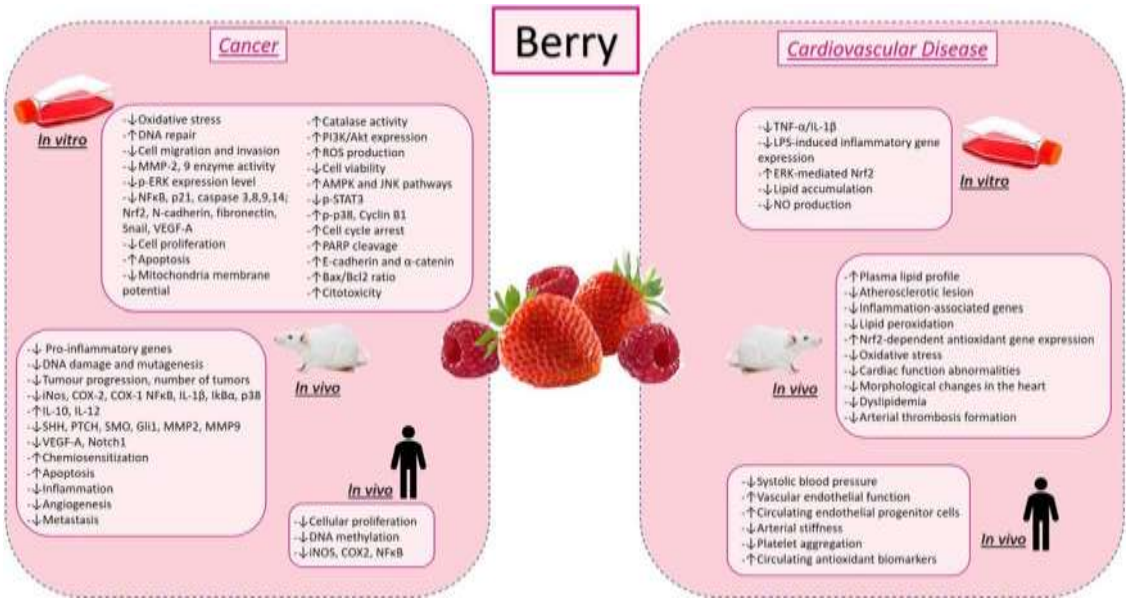

Figure 2. The main effects of berry in cancer and in cardiovascular disease. The figure summarizes the main effects of berry in cancer and in cardiovascular disease both *in vitro* and *in vivo* models. MMP-2: Matrix Metalloproteinase 2; MMP-9: Metalloproteinase 9; p-ERK: phosporilated-extracellular signal-regulated kinase; NF-*j*B: nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2: Nuclear factor (erythroid-derived 2)-like 2; N-cadherin: Neural cadherin; VEGF-A: Vascular endothelial growth factor A; PI3K: Phosphoinositide 3-Kinase; Akt: Protein Kinase B; ROS: Reactive Oxygen Species; AMPK: Adenosine Monophosphate-Activated Protein Kinase; JNK: Jun N-terminal Kinase; p-STAT3: phosporilated-Signal Transducer and Activator of Transcription 3; PARP: Poly ADP (Adenosine Diphosphate)-Ribose Polymerase; E-cadherin: Epithelial cadherin; Bax: Bcl2-Associated X Protein; Bcl2: B-cell lymphoma 2; iNOS: Inducible Nitric Oxide Synthase; COX-2: Cyclooxygenase-2; COX-1: Cyclooxygenase1; IL-1*b*: Interleukin 1 beta; IkB*a*: inhibitor of kappa B alpha; IL-10: Interleukin 10; IL-12: Interleukin 12; SHH: Sonic HedgeHog; PTCH: Patched; SMO: Smoothened; Gli1: Glioma-associated oncogene 1; TNF-*a*: Tumor necrosis factor alpha; LPS: Lipopolysaccharide; NO: Nitric Oxide.

Table 4. Effects of raspberry extracts on different cancer models.

Extracts/Fraction/Component	Experimental model	Dosage and duration of berry treatment	Biological response /involved pathway	Ref.
Black raspberry extract	MSK-Leuk1 human oral leukoplakia cancer cell line	0–50 mg/mL for 16 h	-#Oxidative stress	Guttenplan et al., 2016
	Rat oral fibroblast treated with DB[a,l]P to induce oral cancer	0–375 mg/mL for 24-72 h	-#DB[a,l]P-derived DNA adduct levels and mutagenesis -"DNA repair	
Rubus idaeus L. dried raspberry extracts	SCC-9 and SAS oral cancer cells	0–100 mg/m-L for 24 h	-#Cell migration and invasion -#MMP-2 enzyme activity, protein expression and mRNA levels -#FAK/src complex and ERK expression levels	Huang et al., 2017
Rubus idaeus L. raspberry extracts	HONE-1, NPC-39 and NPC-BM human nasopharyngeal carcinoma cell lines	0–100 mg/mL for 24 h	-#Cell migration and invasion -#MMP-2 enzyme activity, protein expression and mRNA levels -#p-ERK 1/2 expression levels.	Hsin et al.2017
Ellagic acid obtained from *Rubus occidentalis* "Jewel variety" black raspberries *Rubus occidentalis* "Jewel variety" black raspberry extracts	4NQO-treated F344 rats to induce oral cancer	0.4% of the diet for 6 weeks 5-10% of the diet for 6 weeks	-#Oral lesion incidence, multiplicity and cancer progression -#Pro-inflammatory Cxcl1, Mif, Nfe212, Il-1b, Nfkb1, Ptgs1, Pgs2, oral gene expression levels and COX-1 serum gene expression level -#Anti-apoptotic and cell cycle associated Aruka, Cyclin A1, Cyclin A2 oral gene expression levels -#Cellular proliferation in tongue lesions	Oghumu et al., 2017
Black raspberry powder	DB[a,l]PDE-treated B6C3F1 mice to induce oral cancer	5% of the diet for 7 or 40 weeks	-#DNA damage and mutagenesis, tumor incidence and malignant tumors	Chen, Guttenplan, et al., 2018
Black raspberry troches/lozenges	Male and female oral squamous cell carcinoma patients	4.3 g freeze-dried powder per day for 36 days	-#AURKA, BIRC5, EGFR, NFKB1 and PTGS2 pro-survival and pro-inflammatory genes expression	Knobloch et al., 2016
Freeze-dried *Rubus occidentalis* black raspberry powder	DMBA-treated hamster cheek pouches to induce oral cancer	10% of topical administration for 2 or 6 weeks	-"Rb1 expression -#cOral squamous cell carcinomas incidence, multiplicity, and oral dysplasia cell proliferation	Warner et al., 2014
Freeze dried black raspberry powder	Subject with confirmed premalignant oral epithelial lesions	10% of topical administration for 12 weeks	-#Lesional sizes, histologic grades and loss of heterozygosity events	Mallery et al., 2014
Black raspberry powder	NMBA–induced esophageal cancer in rats	5% of the diet for 35 weeks	-#Tumor progression -#cmRNA levels of DNMT1 and DNMT3B in esophagus -#cPromoter methylation of SFRP4 in esophagus	Huang et al., 2016
Rubus occidentalis freeze-dried black raspberry powder Anthocyanin-enriched fraction derived from black raspberries Protocatechuic acid, a major metabolite of black raspberry anthocyanin	NMBA–induced esophageal cancer in rats	6.1% of the diet for 15–25–35 weeks 1.6% of the diet for 15–25–35 weeks 0.05% of the diet for 15–25–35 weeks	-#Progression of preneoplastic lesions -#cNumber of tumors, total tumor volume -#csEH, COX-2, iNOS, NFkB and PTX3 esophageus expression levels	Peiffer et al., 2014
Rubus occidentalis freeze-dried black raspberry powder Anthocyanin-enriched fraction derived from black raspberries Protocatechuic acid, a major metabolite of black raspberry anthocyanin	NMBA–induced esophageal cancer in rats	6.1% of the diet for 15–25–35 weeks 3.8 mmol/g for 15–25–35 weeks 500 ppm	-#Number of tumors, total tumor volume -#cIL-1b expression level in the plasma and esophagus -"IL-10 and IL-12 expression levels in the plasma and esophagus -#cInfiltration of macrophages and neutrophils and microvessel density in the esophagus	Peiffer et al., 2016
Lyophilized black raspberries	NMBA-induced esophageal squamous cell carcinogenesis in F344 rats	5% of the diet for 35 weeks	-#Tumour incidence, multiplicity and volume -#cTissue oxidative stress, H_2O_2 and LPO, GSSG/GSH, $NADP^b$/NADPH -"GPx and SOD2 expression levels -#cNF-kB, p65, IkBa, IKKa/b expression levels -#p38, ERK and SAPK/JNK expression levels	Shi et al., 2017

Table 4. Continued.

Extracts/Fraction/Component	Experimental model	Dosage and duration of berry treatment	Biological response /involved pathway	Ref.
Ellagitannins, ellagic acid, urolithin A, urolithin	HT-29 human colon cancer cells	20 mg/mL for 24 or 48 h	-"Apoptosis and cell cycle arrest (G1 and G2/M phase) -"p21, caspase 3, 8 and 9 expression -"PARP cleavage -#cMitochondria membrane potential	Cho et al., 2015
Rubus strigosus raspberry methanolic extract	D/V-Src rar transformed colonic epithelial cells	0-100 mg/mL for 24 h	-#Cell proliferation	Wang, Zhu, and Marcone 2015
Rubus idaeus raspberry wine	CaCo-2 colon cancer cell lines	1–20% 72 h	-#Cell viability	Ljevar et al., 2016
Black raspberry anthocyanins extract	HCT116 and LoVo human colon cancer cells	25–50 mg/mL for 24, 48 h or 2 weeks	-#Cell viability, migration rate and colony formation capacity	Chen, Jiang, et al., 2018
Raspberry triterpenoid enriched fraction	H_2O_2 treated-HT29 human colon adenocarcinoma cells	100 nM for 24 h	-#DNA damage -"Nrf2 expression -#cNQO1 and HO-1 expressions	McDougall et al., 2017
Freeze-dried black raspberries	$Apc^{Min/þ}$ mouse as a model of colorectal cancer	5% of the diet for 8 weeks	-#Intestinal and colonic polyp number and size -#c"Colonic mucosa, liver and feces metabolites -#cLinolenate in colonic mucosa, putrescine and ODC expression in feces	Pan, Skaer, Wang, Zhu, and Marcone2015
Freeze-dried black raspberries	$Apc^{Min/þ}$ mouse as a model of colorectal cancer	5% of the diet for 8 weeks	-#Colonic polyp development and the cAMP-PKA-CREB-HDAC and Wnt pathways -"GR-1þ neutrophils and cytokine secretion in colonic LP -#cInfiltration of GR-1þ neutrophils and IL-1b expression in colon polyps	Pan et al., 2017
Black raspberry anthocyanins extract	AOM/DSS-treated C57BL/6J mice to induce colon carcinogenesis	5–10% freeze-dried powder in the diet for 12 weeks	-#Tumor multiplicity and pathogenic bacteria -#cDNMT31, DNMT3B, p-STAT3 colon expression levels -"Colon SFRP2 expression and mRNA levels	Chen, Jiang, et al., 2018
Freeze-dried black raspberries	Human colorectal cancer patients	60 g at day for 1–9 weeks	-"Urinary and plasma amino acid metabolism, urinary TCA cycle intermediate, urinary benzoate metabolites	Pan, Skaer, Stirdivant, et al., 2015
Freeze-dried black raspberry powder	Patients with familial adenomatous polyposis with at least 5, >2-mm rectal polyps on baseline endoscopy	20 g administered orally three times per day (60 g/d total), plus two rectal suppositories administered (containing 720-mg of powder) at bedtime for 9 months	-#Rectal polyps bunder -#cCellular proliferation, DNA methylation methyl transferase 1 protein expression, and p16 promoter methylation	Wang et al., 2014
Rubus coreanus Miquel raspberry ethanol extracts	PC-3 and DU 145 human prostate cancers cells	100–200 mg/mL for 8–72 h	-#Cell migration and invasion; -#cMMP-2, MMP-9 expression and activity -"TIMP-1 and TIMP-2 expression and activity -#cPI3K/Akt expression	Kim, Lee, and Kim 2014
Rubus idaeus L. raspberry extracts	A549 human lung adenocarcinoma cell lines	0–100 mg/mL for 24 h	-#Cell invasion and MMP-2 and u-PA activities -"E-cadherin and a-catenin epithelial marker expression levels -#cN-cadherin, fibronectin, snail-1, and vimentin esenchymal marker expression levels -#cp-FAK, p-paxillin and AP-1 expression levels	Hsieh et al., 2013
	BALB/c nude immunodeficient nude mice with subcutaneous implantation of A549 human lung adenocarcinoma cells	500 mg/kg BW per day for 40 days	-#Tumor volume and weight	
Ethyl acetate extract of *R. idaeus* raspberries	A549 human lung adenocarcinoma cell line	0-50 mg/mL for 0, 1, 6, 12, 24 or 48 h	-#Invasive, motility, spreading, and migratory potential -#cMMP-2 and u-PA proteinase and transcription activities -"E-cadherin, a-catenin expressions -#cSnail-1, N-cadherin, NF-jB and p-Akt expressions	Chu et al., 2014

	BALB/c nude mice with subcutaneous implantation of A549 lung adenocarcinoma cells	50 or 100 mg/kg BW per day for 41 days	-#Tumor volume, weight and proliferation	
Raspberry powder	Athymic nude mice with subcutaneous implantation of A549 lung adenocarcinoma cells	2.5% of the diet for 7 weeks	-#Tumor volume, weight and proliferation	Aqil et al., 2016
Total alkaloids fraction of *Rubus aleaefolius* raspberries	HepG2 hepatocellular carcinoma cells	0–1 mg/mL for 24 h	-#Cell survival and G1/S cell cycle progression -#cVEGF-A expression	Zhao et al., 2013
	BALB/c mice with subcutaneous injection of HepG2 hepatocellular carcinoma cells	3 g/kg BW per day for 21 days	-#pSTAT3 and PCNA gene expressions in tumor tissue -#cCyclinD1, cyclinE, CDK 4 and CDK2 gene expressions in tumor tissue -"p21 gene expression in tumor tissue	
Total alkaloids fraction of *Rubus aleaefolius* raspberries	HepG2 hepatocellular carcinoma cells	0–1 mg/mL for 24 h	-#Cell survival and G1/S cell cycle progression -#cVEGF-A expression	Zhao et al., 2014
Total alkaloids fraction of *Rubus aleaefolius* raspberries	HepG2 hepatocellular carcinoma cells	0.25–0.5 mg/mL for 48 h	-#Cell migration and invasion	Zhao, Liu, Wan, et al., 2015
	BALB/c mice with subcutaneous injection of HepG2 hepatocellular carcinoma cells	3 g/kg BW at day for 5 days weekly for 21 days	-#SHH, PTCH, SMO, Gli1, MMP2 and MMP9 1gene expression in tumor tissue -"TIMP-1 and TIMP-2 gene expression in tumor tissue	
Total alkaloids fraction of *Rubus aleaefolius* raspberries	BALB/c mice with subcutaneous injection of HepG2 hepatocellular carcinoma cells	3 g/kg BW per day days weekly for 21 days	-#VEGF-A and VEGF receptor-2 gene expressions and tumor angiogenesis in tumor tissues -#cNotch1, delta-like ligand 4 and jagged 1 gene expressions	Zhao, Lin, Cao, et al. 2015
Polysaccharides from fruit of of *Rubus chingii* raspberries	MCF-7breast cancer cells and Bel-7402 liver cancer cells	0.125–2 mg/mL for 48–72	-"Cytotoxicity	Zhang et al., 2015
Saponin from *Rubus parvifolius L.* raspberries	K562 human chronic myeloid leukemia cell	0–400 mg/mL for 6–24 h	-#Cell growth -"Apoptosis and cleavage of pro-apoptotic proteins -"AMPK and JNK pathways -#cp-STAT3 expression level	Ge et al., 2014
Rubus parvifolius L. medicinal serum obtained from healthy SD rats administered intragastrically with 9 g/kg of *Rubus parvifolius L.* raspberry extract	K562 human chronic myeloid leukemia cell	5–10-20% v/v for 72 h	-#Colony formation and cell proliferation	Zhang et al., 2014
Rubus parvifolius L. raspberry saponin fraction	K562 human chronic myeloid leukemia cell	10–150 mg/L for 72 h	-#Colony formation and cell proliferation	
Rubus parvifolius L. raspberry extract	BALB/c nude mice with subcutaneous injection of K562 human chronic myeloid leukemia cell	0.25–0.5–1 g per day for 5 days	-#Tumour weight and size	
Black raspberry ethanol extract	Myeloid-derived suppressor cells	100–200 mg/mL for 7 days	-#Cell expansion and suppressive capacity	Mace et al., 2014
Cyanidin-3-Rutinoside and Quercitin-3-Rutinoside isolated from black raspberries	Myeloid-derived suppressor cells	0–200 mM for 3 days	-#Cell expansion and IL-6-mediated STAT3 signaling	
Raspberry ketone	B16F10 melanoma cells	1–5 mM for 30 min or 24 h	-#Cell survival -"ROS production	Nagata et al., 2015
Raspberry pulp polysaccharides	C57BL/6 mice with subcutaneous injection of B16F10 mouse melanoma cells	100, 200, and 400 mg/kg BW per day for 2 weeks	-#Melanoma growth -"Body weight, spleen index, splenocytes proliferation -"ACP, ALP, LDH and SOD spleen activities -"Serum concentrations of TNF-a, IFN-c and IL-2 -"Tumor tissue necrosis and inflammatory cell infiltration -"Antitumor effect of docetaxel -#cDocetaxel-induced liver and kidney lesions	Yang, Xu, and Suo 2015
Urolithin A obtained from black raspberries	ECC-1, Ishikawa, and HEC1A endometrial cancer cell lines	10 lM and 10–50 lM 1–7 days and 48 h	-#Cell proliferation -#cCell cycle at the G2/M phase -"Cyclin-B1, cyclin-E2, p21, phospho-cdc2, and CDC25B gene expression -#cRa and GRIP1 gene expressions -"ERb, PGR, pS2, GREB1 gene expressions.	Zhang et al., 2016

Table 4. Continued.

Extracts/Fraction/Component	Experimental model	Dosage and duration of berry treatment	Biological response /involved pathway	Ref.
Rubus coreanus Miquel raspberry extract	NCI/ADR-RES doxorubicin-resistant human ovarian cancer cell line	0, 50, 100 and 200 lg/mL for 24 h	-#Cell viability - "Apoptosis, p-JNK and p-AKT expression	Kim et al., 2016
Raspberry extracts	A2780 human ovarian carcinoma cells	0–200 mg/mL for 24 h	-#Cell viability	Lee et al., 2016a
Sanguiin H-6, isolated from red raspberries	A2780 human ovarian carcinoma cells	0–40 mM for 24 h	-#Cell viability - "Apoptosis and PARP and caspase activation - "p-p38, p-ERK and truncated p15/BID activation	Lee et al., 2016b
Raspberry moisture	MCF-7 breast cancer cells	0.1-100 mg/mL for 24 h	-#Cell proliferation and viability	Wang et al., 2013
Rubus strigosus raspberry methanolic extract	MCF-7 breast cancer cells	0-100 mg/mL for 24 h	-#Cell proliferation and viability	Wang, Zhu, and Marcone 2015
Rubus idaeus raspberry wine	MCF-7 breast cancer cells	1-20% for 72 h	-#Cell proliferation and viability	Ljevar et al., 2016
Polysaccharides from fruit of *Rubus chingii* raspberries	MCF-7breast cancer cells	0.125-2 mg/mL for 48-72 h	- "Cytotoxicity	Zhang et al., 2015
Sanguiin H-6 extracted from *Rubus coreanus* raspberries	MCF-7 and MDA-MB-231 human breast carcinoma cell lines	0-100 mM for 24 h	-#Cell viability - "Apoptosis, cleavage of caspase-8,-3, and PARP, and Bax/Bcl-2 ratio	Park et al., 2017
Rubus ellipticus Himalayan yellow raspberry methanol, acid Methanol, acetonic, acid acetonic extracts	C33A human cervical cancer cells	0.667, 1.66, 3.33, 5.0 and 6.67 mg/ml for 24 h	-#Cell viability	Saini et al., 2014
Rubus idaeus raspberry wine	HeLa cervical cancer cell lines	1-20% for 72 h	-#Cell viability	Ljevar et al., 2016
Black raspberry extract	SW 954 vulvar squamous cell carcinoma cell line	0, 50, 100, 200, 400, and 800 lg/mL for 32 h	- "Caspase 14	Joehlin-Price et al., 2014
Enantiomeric phenylpropanoids isolated from red raspberries	H_2O_2-treated SH-SY5Y human neuroblastoma cells	25-50-100 lM for 48 h	- "Cell viability -#cApoptosis and ROS accumulation - "PARP and cleavage PARP expressions - "Catalase activity	Zhou et al., 2018

(Cho et al., 2015; Wang, Zhu, and Marcone 2015; Ljevar et al., 2016; Chen, Jiang, et al., 2018). In particular, a reduction in cell viability was observed, with a concomitant inhibition of migration, colony formation capacity and cell proliferation (Wang, Zhu, and Marcone 2015; Ljevar et al., 2016; Chen, Jiang, et al., 2018), mainly determined by the promotion of cell cycle arrest and apoptosis (Cho et al., 2015). Interestingly in H_2O_2-treated colon cancer cells, also raspberry triterpenoid enriched fraction exerted protective effects, reducing DNA damage and altering the expression of cytoprotective genes (McDougall et al., 2017). Black raspberries showed chemopreventive effects also *in vivo* in colorectal cancer mouse models (Pan, Skaer, Wang, Zhu, and Marcone 2015; Pan et al., 2017; Chen, Jiang, et al., 2018) and humans (Pan, Skaer, Stirdivant, et al., 2015), where dietary intervention modified the composition of gut microbiota and modulated multiple metabolic and energy pathways, affecting the host immune system and thereby enhancing the antitumor immune microenvironment. Finally, black raspberry consumption efficiently regressed rectal polyps in patients with familial adenomatous polyposis, as indicated by the reduction in rectal polyps bunder, cellular proliferation and DNA methylation (Wang et al., 2014).

The anti-metastatic potential of raspberry extract was also shown in prostate cancer cells by reducing MMP expression through the suppression of phosphoinositide 3-kinase (PI3K)/Akt phosphorylation and enhancing tissue inhibitors of metalloproteinases (TIMP) expressions and activities (Kim, Lee, and Kim 2014). In lung adenocarcinoma cells, raspberry extracts exerted anti-invasive/antitumor protective effects inhibiting the invasive, motility, spreading and migratory potential of highly metastatic cancer cells, also inducing the upregulation of epithelial markers and decreasing mesenchymal markers, that promote cell invasion and metastasis (Hsieh et al., 2013; Chu et al., 2014). These results were further confirmed in animal studies, where raspberry supplementation reduced mice tumor volume and weight (Hsieh et al., 2013; Chu et al., 2014; Aqil et al., 2016).

A number of articles have investigated how different raspberry fractions exhibit antitumor properties in hepatocellular carcinoma cells. *In vitro* results highlighted that raspberries reduced cell survival, migration and invasion by modulating anti-angiogenic mechanisms and inhibiting proliferation and cell cycle (Zhao et al., 2013; Zhao et al., 2014; Zhao, Liu, Wan, et al., 2015; Zhang et al., 2015). These results were further confirmed in studies performed on mice, suggesting raspberries as a potential source to develop antimetastatic drug in the treatment of hepatocellular carcinoma (Zhao et al., 2013; Zhao, Liu, Wan, et al., 2015; Zhao, Lin, Cao, et al., 2015).

Different raspberry fractions showed effective anti-proliferative properties against myeloid leukemia cells both *in vitro* and in mouse models, counteracting colony formation, cell proliferation and favoring apopstosis (Zhang et al., 2014; Ge et al., 2014) and reducing tumor weight and size (Zhang et al., 2014), respectively. Similar properties were further confirmed in a study performed by Mace et al. (2014), which investigated the ability of black raspberry extract to

limit the expansion of myeloid-derived suppressor cells and their suppressive capacity; results indicated that this extract and its physiologically-relevant metabolites contain phytochemicals that affect immune processes relevant to carcinogenesis and immunotherapy.

In B16F10 melanoma cells raspberry extracts increased ROS production and reduced cell viability (Nagata et al., 2015), showing interesting properties also *in vivo*, in a mouse model of malignant melanoma (Yang, Xu, and Suo 2015). In this case raspberry treatment alleviated liver and kidney lesions in tumor-bearing mice, enhancing the cellular immune response of the host organism (Yang, Xu, and Suo 2015).

In endometrial cancer cell lines urolithin A obtained from black raspberries was found particularly effective in suppressing cell proliferation in a time- and dose-dependent manner, arresting the G2/M phase of the cell cycle and modulating ER*α*-dependent gene expression, thereby inhibiting endometrial cancer proliferation (Zhang et al., 2016). Raspberry extracts promoted anticancer activities also in human ovarian carcinoma (Kim et al., 2016, Lee et al., 2016a; Lee et al., 2016b), breast (Wang et al., 2013; Zhang et al., 2015; Wang, Zhu, and Marcone 2015; Ljevar et al., 2016; Park et al., 2017) and cervical cancer cells (Saini et al., 2014; Ljevar et al., 2016) as demonstrated by the reduction in cell viability and promotion of apoptotic and cytotoxic processes. Interesting results were also obtained in vulvar squamous cell carcinoma cell line, where black raspberry extract treatment efficiently upregulated caspase-14 level, suggesting its possible use in topical treatment of vulvar lesions (Joehlin-Price et al., 2014). Finally, in H_2O_2-treated human neuroblastoma cells enantiomeric phenylpropanoids isolated from red raspberries selectively inhibited the apoptosis induction and ROS accumulation, highlighting the neuroprotective effects of these enantiomers (Zhou et al., 2018).

Raspberry and cardiovascular diseases

The anti-atherogenic effect of black and red- raspberries has been demonstrated in both *in vitro* and *in vivo* models. It has usually been related to their antioxidant and anti-inflammatory properties as highligthed by reduced LDL oxidation (Burton-Freeman, Sandhu, and Edirisinghe 2016), lipid peroxidation (Burton-Freeman, Sandhu, and Edirisinghe 2016), ROS generation (Kim et al., 2013), increased in antioxidant enzyme activities (Burton-Freeman, Sandhu, and Edirisinghe 2016), as well as reduced cytokine production (Kim et al., 2013; Medda et al., 2015; Burton-Freeman, Sandhu, and Edirisinghe 2016), NF-kB activity (Kim et al., 2013; Medda et al., 2015; Burton-Freeman, Sandhu, and Edirisinghe 2016), cyclooxygenase-2 (COX2) activity (Medda et al., 2015; Burton-Freeman, Sandhu, and Edirisinghe 2016) and prostaglandin E2 (PGE2) production, respectively (Table 5).

For example, in human esophageal microvascular endothelial cells, black raspberry extract (BRE) attenuated cell proliferation, migration and tube formation induced by vascular endothelial growth factor (VEGF) by reducing COX2 expression, PGE2 production, ICAM-1 and VCAM-1 expression. It also reduced NF-*j*B activation in TNF-*α* and

Table 5. Effects of raspberries on cardiovascular diseases.

Compounds	Model	Dosage and duration	Effects	Ref.
Black raspberry extract	Human esophageal microvascular endothelial cells (HEMEC)	100 mg/mL for 2 h	-#TNF-α/IL-1b ,"Activation of HEMEC	Medda et al., 2015
Unripe Rubus coreanus fruit extract	Immortalized murine macrophage RAW264.7 cells	500 lg/mL for 4 h and then stimulated with LPS (100 ng/mL)	-#LPS-induced inflammatory gene expression. -"ERK-mediated Nrf2 -"Phase 2 gene expression.	Kim et al., 2013
Unripe Rubus coreanus fruit extract	Male C57BL/6 J mice fed a high-fat diet (HFD)	1.67 g/kg of diet for 14 weeks	-"Plasma lipid profile. -#Atherosclerotic lesion development. -#Inflammation-associated gene expression -#Lipid peroxidation. -"Nrf2-dependent antioxidant gene expression	Kim et al., 2013
Dried unripe black raspberry powder	Patients with metabolic syndrome	750 mg/day for 12 weeks	-"Vascular endothelial function	Jeong et al., 2014
Dried unripe black raspberry powder	Pre-hypertensive patients	187.5 mg/d or 312.5 mg/d for 8 weeks	-#Systolic blood pressure	Jeong, Hong, et al., 2016
Dried unripe black raspberry powder	Patients with metabolic syndrome	750 mg/day for 12 weeks	-"Circulating endothelial progenitor cells -#Arterial stiffness	Jeong, Kim et al., 2016
Red raspberry extract	vascular smooth muscle cells	200 lg/mL	-#Ang II-induced senescence	Feresin et al., 2016
Freeze-dried red raspberries	obese diabetic (db/db) mice	0.8 g/d for 8 weeks	-#Inflammation -#Oxidative stress -#Cardiac function abnormalities -#Morphological changes in the heart	Noratto, Chew, and Ivano 2016
Raspberry ketone	Adult Wistar albino rats (180–200 g)	50, 100 or 200 mg/kg for 28 days	-#Oxidative stress -#Inflammation -#Dyslipidemia in ISO-intoxicated rats	Khan et al., 2018

IL-1β-activated cells (Medda et al., 2015). Likewise, in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages, pretreatment with BRE effectively attenuated LPS-mediated production of nitrite, nitric oxide (iNOS) protein expression levels and mRNA, as well as TNF-α and IL-1β mRNA levels. Moreover, it stimulated the activation of ERK, increased nuclear factor (erythroid-derived 2)-like 2 (Nrf2) protein levels and its translocation into the nucleus, and the transcriptional activity of the ARE promoter in a dose-dependent manner. It also suppressed LPS-induced ROS production, NF-kB activation and inflammatory genes expression (Kim et al., 2013).

BRE supplementation also reduced atherosclerotic plaque formation and serum levels of TGs, total cholesterol, lipid peroxides, and inflammatory mediators (IL-1β, TNFα, iNOS) in mice fed with a high-fat diet (Kim et al., 2013). In this model, BRE treatment inhibited NF-kB by inducing Nrf2-dependent phase II gene expression (Kim et al., 2013). Furthermore, BRE administration improved vascular endothelial function in patients with metabolic syndrome during a 12-week follow-up. It reduced total cholesterol level and total cholesterol/HDL ratio, as well as IL-6, TNF-α, C-reactive protein, adiponectin, and VCAM-1 levels (Jeong et al., 2014; Jeong, Hong, et al., 2016). Similarly, Jeong, Kim, et al., (2016) demonstrated that BRE administration decreased the radial artery augmentation index while it significantly increased the circulating endothelial progenitor cells $CD34^{+}/CD133^{+}$, which has been inversely related to cardiovascular risk. In pre-hypertensive patients high-dose BRE treatment significantly reduced 24-h systolic blood pressure (SBP) and nighttime SBP during a 8-weeks follow-up. However, no significant changes were observed in serum levels of renin and angiotensin converting enzyme (Jeong, Hong, et al., 2016).

On the other hand, red raspberries (RB) mitigated angiotensin II (Ang II)-induced senescence in vascular smooth muscle cells, as evidenced by decreased number of cells positive for senescence associated β-galactosidase and down-regulation of p53 and p21 expression. It also attenuated Ang II-induced Akt and ERK1/2 phosphorylation, and at the same time up-regulated the expression of superoxide dismutase (SOD) and glutathione peroxidase 1 enzymes. In addition, RB treatment reduced the NADP/NADPH ratio but was not able to decrease Nox1 expression, indicating that RB attenuates Ang II-induced senescence by increasing the cellular antioxidant capacity response (Feresin et al., 2016).

In obese diabetic (db/db), heart proteomic analysis evidenced that RB consumption decreased the expression of proteins associated with cardiac remodeling (eg: the gap junction alpha-1 protein, the myosin regulatory light chain 2 and vimentin proteins), oxidative stress response (eg: the NADPH dehydrogenase, the glutathione S-transferase (GST) and the superfamily members GST-alpha 4) and inflammatory stress (eg: the heat shock protein 10 and the guanine nucleotide binding protein beta 2). Furthermore, it downregulated the expression of the natriuretic peptide precursor type A protein and the serine/threonine-protein phosphatase 2 (formerly 2A) protein, which have been associated with cardiovascular homeostasis and heart fibrosis, respectively. These results strongly suggest the RB-positive effects in preventing and/or delaying cardiac function abnormalities, oxidative stress, inflammation and morphological changes in the heart (Noratto, Chew, and Ivano 2016).

Also raspberry ketone (RBK) -a natural phenolic compound found in RB- presented cardioprotective effects against isoproterenol (ISO)-induced myocardial infarction in rats. Its oral administration inhibited the increased levels of LDL, TGs and malondialdehyde induced by ISO. It also counteracted the deleterious effect of ISO in the levels of gluthatione (GSH), SOD, and catalase enzymes (Khan et al., 2018).

Overall, the *in vitro* and *in vivo* data suggest that raspberries improve both emerging (oxidative stress, inflammation, and endothelial function) and traditional risk factors (lipid profile and blood pressure) of cardiovascular diseases.

Strawberries and cancer

In the last five years, many studies have highlighted the antiproliferative properties of strawberries in several cancer cell lines, animal models and humans (Afrin et al., 2016)(Table 6).

These anticancer effects have been related to the capacity of strawberry bioactive compounds in (i) reducing oxidative stress, (ii) suppressing inflammation; (iii) inhibiting cell proliferation by the induction of apoptosis and the arrest of cell cycle, (iv) protecting against DNA damage and (v) hindering angiogenesis (Afrin et al., 2016).

In different breast cancer cells, methanolic strawberry extract was shown to decrease, in a dose and time dependent manner, cellular proliferation, by promoting apoptosis, reducing the number of cells in S phase, inducing the accumulation of cells in G1 phase and modulating different genes involved in cellular migration, adhesion and invasion processes (Amatori et al., 2016; Somasagara et al., 2012). In addition, strawberry consumption significantly reduced both tumor weight and tumor volume in mice (Amatori et al., 2016) and extended animal lifespan (Somasagara et al., 2012). Similarly, strawberry metabolites induced cell death in HT-29 colon cancer cells by promoting apoptosis (López de Las Hazas et al., 2017), while in Crj:CD-1 mice strawberry phytochemicals reduced the expression of proteins that regulate inflammation, cell differentiation, proliferation and survival, inhibiting azoxymethane/dextran sodium sulfate-induced colon carcinogenesis (Shi et al., 2015). Similar results were found also on Fischer 344 rats (Fernández et al. 2018).

Strawberry extract and its anthocyanin-enriched fraction promoted anticancer activity also in B16-F10 melanoma cells (Forni et al. 2014), in A2780 ovarian cancer cells (Lee et al. 2016a), in HeLa cervical cancer cells (Spagnuolo et al. 2016) and in leiomyoma cells (Islam et al. 2017), as demonstrated by the reduction of cell proliferation, the enhancement of tissue transglutaminase activity, the impairment of metabolism and the induction of apoptosis and oxidative stress.

At the same time, in oral cancer, lyophilized strawberry inhibited DMBA-induced tumor in hamsters, reducing cancer multiplicity and incidence, volume and histologic grade

Table 6. Effects of strawberries on cancer.

Extracts	Model	Dosage and duration	Effects	Ref.
Strawberry extract	Breast cancer (T47D) cell line Swiss albino mice, injected with breast adenocarcinoma cells	(0.1, 0.2, 0.5 and 1 mg/ml) for 48 and 72 h 2 g/kg body weight for 45 days	-"Cytotoxicity -#Cells proliferation -"Apoptosis -#Tumor volume	Somasagara et al. 2012
Strawberry extract	Breast cancer (A17) cell line Swiss albino mice, injected with breast adenocarcinoma cells	(0.1, 0.2, 0.5 and 1 mg/ml) for 48 and 72 h 2 g/kg body weight for 45 days	-"Cytotoxicity -#Cell proliferation -"Apoptosis -#Tumor volume -#Cellular migration, adhesion and invasion	Amatori et al., 2016
Strawberry anthocyanins	HT-29 colon cancer cells	5, 50, and 100 lmol/L malvidinor pelargonidin-glucoside for 24 or 48 h	-"Cytotoxicity -"Apoptosis	López de Las Hazas et al., 2017
Lyophilized strawberries	Crj: CD-1 Mice injected with azoxymethane/dextran sodium sulfate	2.5%, 5% or 10% lyophilized strawberries for 20 weeks	-#Inflammation -#Nitrosative stress -#Cell proliferation	Shi et al., 2015
Strawberry anthocyanins	Rattus norvegicus F344 injected with azoxymethane/ dextran sodium sulfate	0.1% for 20 weeks	-#Tumor number -"Plasma antioxidant capacity	Fernández et al. 2018
Strawberry extract	B16-F10 murine melanoma cells	10 mM anthocyanin content for 24, 48 and 72 h	-#Cell proliferation -#Intracellular levels of polyamine -"Tissue transglutaminase -#Tumor progression and metabolism proteins	Forni et al. 2014
Strawberry extract	Human Ovarian Cancer A2780 Cells	0-200 mg/mL for 24 h	-"Cytotoxicity -#Cell proliferation	Lee et al. 2016a
Strawberry extract	Human Cervical Cancer HeLa Cells	0.001 and 1 mg/ml for 24 h	-"Cytotoxicity -#Cell proliferation -"Apoptosis	Spagnuolo et al. 2016
Strawberry extract	Leiomyoma cells	250 lg/ml for 48 h	-"Cytotoxicity -"Apoptosis -"Intracellular ROS -#Mitochondrial functionality -#Fibrotic proteins	Islam et al. 2017
Lyophilized strawberries	Hamster cheek pouch injected with dimethylbenz(a)anthracene	5% for 6, 18 or 24 weeks	-#Cell proliferation -#Angiogenesis -#Oncogenesis -#Arachidonic acid metabolism -#Formation of 8-hydroxydeoxyguanosine	Zhu et al 2015
Lyophilized strawberries	Hamster cheek pouch injected with dimethylbenz(a)anthracene	5% or 10% for 12 weeks	-#Tumor number -#Mild and severe dysplasia	Casto et al 2013
Strawberry Powder	Male Fisher-344 (F-344) rats injected with N-nitrosomethylbenzylamine	5% for 24 weeks	-#Tumor multiplicity -#Tumor burden -#Squamous epithelial cell proliferation	Pan et al., 2018
Lyophilized strawberries	Patients with Dysplastic Precancerous Lesions of the Esophagus	30 or 60 g/d for 6 months	-#Histologic grade of dysplastic premalignant lesion -#iNOS, COX2, NFkB, pS6, Ki-67	Chen et al 2012

of oral precancerous lesions, by the suppression of angiogenesis, oncogenic signaling and cell proliferation, and the reduction in 8-hydroxydeoxyguanosine formation and in arachidonic acid metabolism (Zhu et al 2015; Casto et al 2013). Recently, the chemoprotective effects of aspirin and strawberries against rat esophageal papilloma development have also been evaluated. Co-treatment with strawberries and aspirin significantly reduced both the tumor multiplicity and the total tumor burden in the esophagus as well as squamous epithelial cell proliferation; however, no differences were found for the expression of COX-1 and COX-2 or tumor incidence compared to the control group (Pan, Peiffer, et al., 2018).

Finally, the results from a randomized phase II trial highlighted that the consumption of freeze-dried strawberries significantly reduced the histologic grade of precancerous lesions in human patients with esophageal dysplasia, by downregulating genes involved in inflammation, gene transcription and cell proliferation, such as pS6, pNF*j*B-p65, iNOS, COX-2; in biopsy tissues of human esophagus, strawberry treatment significantly decreased the proliferation of cell proliferation (Chen et al 2012).

Strawberries and cardiovascular diseases

The cardio-protective effects of strawberries and/or their phenolic compounds have been recognized in recent years. Their capacity to prevent or delay the development of cardiovascular diseases has been associated with the diminution of oxidative stress and free radical generation, downregulation of foam cell formation, reduction of glucose absorption, dyslipidemia modulation, and attenuation of inflammatory gene expression via iNOS activity modulation (Forbes-Hernández et al., 2016; Afrin et al., 2016) (Table 7).

Data from *in vitro* experiments demonstrated that strawberry extract (SWE) treatment protected lipid bilayers against oxidative damage, decreased total cholesterol, LDL-cholesterol and inhibited the expression of the acetyl coenzyme A carboxylase and the 3-hydroxy-3-methylglu- taryl-CoA reductase, the major regulators of fatty acids and cholesterol synthesis, respectively. It also induced the LDL receptor expression and the levels of the peroxisome prolif- erator activated receptor gamma coactivator 1-alpha, which play an important role in the metabolic adaptations to energy expenditure (Forbes-Hernández et al., 2017). In LPS-stressed Raw 264.7 macrophages, strawberry leaf extract inhibited nitric oxide production but not iNOS protein expression, neither LPS-induced COX-2 immuno-reactivity, nor mRNA levels of IL-1*b*, indicating that its anti-inflammatory effect relies on direct nitric oxide scavenging capacity (Liberal et al., 2014).

In an *ex-vivo* model, Alarcón et al., (2015) confirmed that SWE inhibited platelet aggregation induced by ADP and arachidonic acid and decreased the levels of the atherosclerosis inflammatory mediators sCD40L, sP-selectin, RANTES, and IL-1*b*, which are determinant in both acute coronary syndromes and long-term atherosclerotic process. In addition, it significantly reduced thrombin induced sCD40L platelet release, confirming its significant protective effects on thromboembolic-related disorders. The same authors revealed that pretreatment with SWE prevented thrombus formation over 60 minutes after laser-injured thrombus formation in mouse mesenteric artery (Alarcón et al., 2015).

Other *in vivo* studies highlighted that SWE supplementation declined overall blood glucose concentrations, decreased circulating levels of VCAM-1 and C-reactive protein, reduced lipid peroxidation and decreased serum malondialdehyde, urinary isoprostane, and 8-hydroxy-2-deoxyguanosine levels, as summarized by Forbes-Hernández et al., (2016) and Afrin et al., (2016). Strawberry consumption also improved antioxidant status and antihemolytic defenses in healthy subjects (Afrin et al., 2016) and reduced SBP levels in type 2 diabetic patients (Amani et al., 2014).

In adults with abdominal adiposity and elevated serum lipids, strawberry intervention for 12 weeks increased plasma antioxidant capacity, serum catalase activity and whole blood glutathione content in a dose-dependent manner (Basu et al., 2016).

Honey

Honey is a sweet edible substance, produced by honey-bees from the nectar of plant blossoms or aphid honeydew. Nowadays, it is classified as a functional food because of its content in antioxidants, which contribute to the prevention of certain diseases (Alvarez-Suarez, Giampieri, and Battino 2013; Alvarez-Suarez et al., 2012; Alvarez-Suarez et al., 2016; Afrin, Giampieri, Gasparrini, Forbes-Hernández, Cianciosi, Reboredo-

Table 7. Effects of strawberries on cardiovascular diseases.

Compounds	Model	Dosage and duration	Effects	Ref.
Strawberry methanolic extract	HepG2	10, 50, 100 lg/mL for 24 h	-#Lipid accumulation	Forbes-Hernández et al., 2017
Fragaria vesca leaves hydroalcoholic extract	Raw 264.7 macrophages	160 lg/mL for 1 h prior to stimulation with LPS(1 lg/mL)	-#NO production	Liberal et al., 2014
Strawberry aqueous extract	Human platelet suspensions from young healthy volunteers	0.1, 0.5, and 1 mg/mL	-#Platelet aggregation	Alarcón et al., 2015
Strawberry aqueous extract	C57BL/6 mice	200 mg/kg intraperitoneally injection	-#Arterial thrombosis formation	Alarcón et al., 2015
Freeze-dried strawberry beverages (mixture of strawberries varieties)	Adults with abdominal adiposity and elevated serum lipids	low dose strawberry (25 g/day FDS), high dose strawberry (50g/d FDS) for 12 weeks	-"Circulating antioxidant biomarkers	Basu et al., 2016
Freeze-dried strawberry powder	Type 2 diabetic patients.	25 g/day for 6 weeks	-#SBP levels	Amani et al., 2014

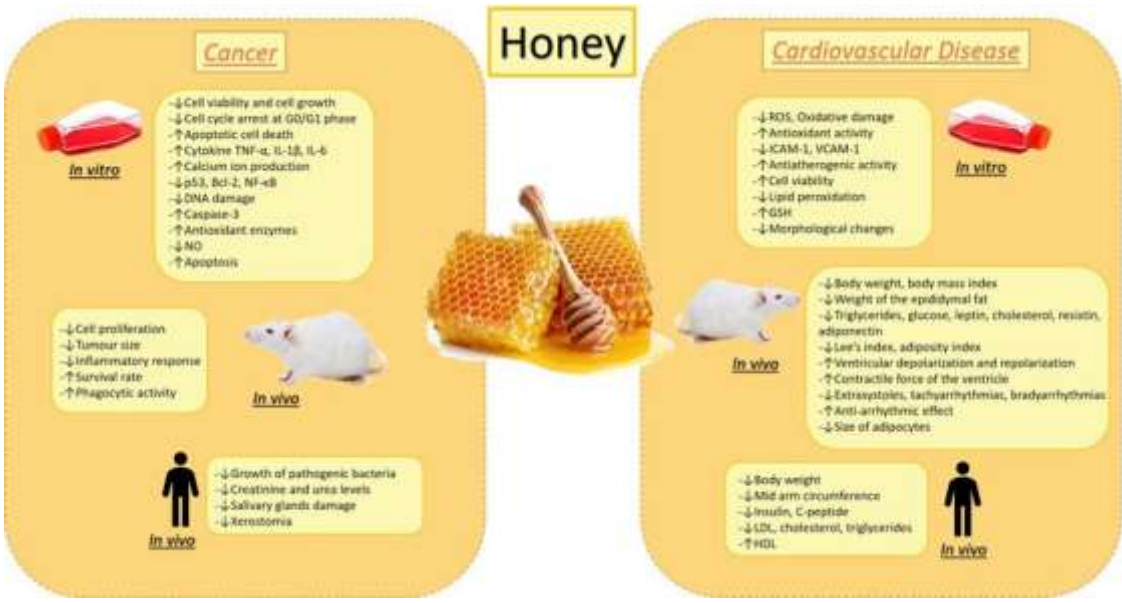

Figure 3. The main effects of honey in cancer and in cardiovascular disease. The figure summarizes the main effects of honey in cancer and in cardiovascular disease both *in vitro* and *in vivo* models. TNF-*a*: Tumor necrosis factor alpha; IL-1*b*: Interleukin 1 beta; IL-6: Interleukin 6; Bcl2: B-cell lymphoma 2; NF-*j*B: nuclear factor kappa-light-chain-enhancer of activated B cells; NO: Nitric Oxide; ROS: Reactive Oxygen Species; ICAM-1: Intercellular Adhesion Molecule 1; VCAM-1: vascular cell adhesion molecule 1; GSH: Glutathione.

Rodriguez, Amici, et al., 2018; Afrin, Giampieri, Gasparrini, Forbes-Hernández, Cianciosi, Reboredo-Rodriguez, Manna, et al., 2018; Badolato et al., 2017; Alvarez-Suarez et al., 2018) and to the increased interest of this foodstuff worldwide. Unlike olive oil and berries, honeys have been newly introduced in the Mediterranean diet thanks to the variety of phenolic compounds, such as diverse flavonoids, ugenol, ferulic acid, caffeic acid and so on, the antioxidant capacity (Alvarez-Suarez, Giampieri, and Battino 2013; Badolato et al., 2017) and different types of sugar, proteins, free amino acid, organic acid, essential minerals, water, enzymes and vitamins (da Silva et al., 2016) (Table S1).

The special climate and geographical characters of the Mediterranean areas make the compounds of honey distinctive (Badolato et al., 2017). According to former research performed on Rosemary, Heather and Heterofloral honey from Spain, Acacia and Strawberry-tree honey from Italy, Coriander and Crude honey from Egypt and Thyme honey from Greece, honey can downregulate or modulate several physiological pathways to exert anti-cancer and cardiovascular effects (Alvarez-Suarez, Giampieri, and Battino 2013; Badolato et al., 2017). Only few studies have addressed the preventive effects of honey, typical of the Mediterranean area, on cancer and cardiovascular diseases (Fig. 3).

Honey and cancer

The anti-proliferative effects of honey has been proven in several experimental models (Table 8).

For example, Acacia honey exerted cytotoxic activities in melanoma (A375 and B16-F1) (Pichichero et al., 2010), breast (MCF-7) (Salleh, Eshak, and Ismail 2017) and lung (NCI-H460) (Aliyu et al., 2013) cancer cells. This honey suppressed, in a dose and time dependent way, cancer progression by arresting the cell cycle at G0/G1 phase (Pichichero et al., 2010; Aliyu et al., 2013), elevating cytokine (TNF-*a* and IL-1*b*) and calcium production and finally activating apoptosis by decreasing p53 and Bcl-2 levels (Aliyu et al., 2013). In *in vitro* colon cancer model, Strawberry tree honey induced cell death in a dose and time dependent way, by increasing ROS generation due to its high content of polyphenols and antioxidant capacity; results also showed that the same concentration was less toxic on non-cancer cells (Afrin et al., 2017). Moreover, three different commercial Polyfloral, Rosemary and Healther honeys from Madrid (Spain) activated apoptosis independently by ROS, promoting leukemia cells death (Morales and Haza, 2013) and induced defensive effects against DNA damage exerted by dietary mutagen in hepatoma cancer cells (Haza and Morales, 2013). Both studies highlighted that the floral origin and the polyphenolic compounds were strongly related with disease-preventive effects (Morales and Haza, 2013; Haza and Morales, 2013).

Honey from Egypt acted as a therapeutic agent in hepatocellular carcinoma (Hassan et al., 2012; El-kott et al., 2012) and Ehrlich ascites tumor (EAT) (Gabry and Othman, 2008) both in *in vitro* and *in vivo* models. In HepG2 liver cancer cells, honey treatment significantly decreased cell viability by activating apoptosis through increasing caspase-3 levels; additionally, the status of total antioxidant enzyme was improved while the levels of nitric oxide were reduced (Hassan et al., 2012). Furthermore, the addition of adiponectin hormone to Crude honey protected the over growth of HepG2 cells induced by honey treatment. This combination exerted chemopreventive effects by reducing cell growth and differentiation via decreasing alkaline phosphatase activity and moderately activated apoptosis by downregulating Bcl2 levels (Hanaa and Shaymaa, 2011). Moreover, Crude honey protected the cisplatin chemotherapy induced nephrotoxicity in cancer patients by decreasing kidney parameters,

Table 8. Effects of honey on different types of cancer.

Honey types	Experimental model	Dosage and duration of honey treatment	Biological response / involved pathway	Ref.
Acacia honey	A375 and B16-F1 melanoma cancer cells	0.01–0.2 g/mL for 24, 48 or 72h according to different assays	-#Cell viability -"Cell cycle arrest at G0/G1 phase	Pichichero et al., 2010
	MCF-7 breast cancer cells	3.125–100 % v/v for 24, 48 or 72h according to different assays	-#Cell viability -"Apoptotic cell death	Salleh, Eshak, and Ismail 2017
	NCI-H460 lung cancer cells	0.5–8 % v/v for 48h	-#Cell viability -"Cell cycle arrest at G0/G1 phase -"Cytokine TNF-a and IL-1b -"Calcium ion production -#p53 and Bcl-2	Aliyu et al., 2013
Strawberry tree honey	HCT-116 and LoVo colon cancer cells	3–20 mg/mL for 24, 48 and 72h	-#Cell viability -"ROS generation	Afrin et al., 2017
Polyfloral, Rosemary and Healther honey	HL-60 leukemia cells	1–125 mg/mL for 24, 48 or 72h according to different assays	-#Cell viability -"Apoptosis	Morales and Haza, 2013
	HepG2 hepatic cancer cells	0.1–100 mg/mL for 24h	-#DNA damage	Haza and Morales, 2013
Egyptian honey	HepG2 hepatic cancer cells	5–20 % for 6, 24, 48 or 72h according to different assays	-#Cell viability -"Caspase-3 -"Antioxidant enzyme -#Nitric oxide	Hassan et al., 2012
	Acute lymphoblastic leukemia patients with oral mucaitis (n ¼ 90)	0.5 g/Kg for 3 times in a day for 10 days or until healing	-"Healing properties	Abdulrhman et al., 2012
	Acute lymphoblastic leukemia patients with febrile neutropenia (n ¼ 32)	2.5 g/Kg for 2 times in a week for first 12 weeks	-#Febrile neutropenia -"Hemoglobin levels	Abdulrhman et al., 2016
	Head and neck cancer patients with oral and oropharyngeal mucaitis (n ¼ 40)	20 ml of honey for 15 minutes before, 15 minutes after and 6 hours after radiation therapy for whole the period of rediotherapy	-#Mucaitis -#Growth of pathogenic bacteria	Rashad et al., 2009
Crude honey	HepG2 hepatic cancer cells	100 mg/mL with adiponectin hormone for 24 h	-#Cell growth and differentiation -#Alkaline phosphatase activity -#Bcl-2	Hanaa and Shaymaa, 2011
	Cancer patients with nephrotoxicity (n¼ 32)	80 g daily for 3 days before the chemotherapy and continued whole the period of the cycle	-#Creatinine and urea levels	Osama et al., 2017
Bee honey	Ehrlich ascites tumor cells and xenograft mice model	– 1, 10 and 100 mg/mL for over night -10, 100 or 1000 mg/100g of body weight daily for 4 weeks	-#Cell proliferation -#Tumor size -"Peritoneal macrophages, T and B cells function -total lipid and protein, as well as liver and kidney enzyme activities	Gabry and Othman, 2008
	Diethylnitrosamine induced hepatocarcinogenesis rat model	2 g/rat/day for 6 months	-"Body weight -#Tumor volume and inflammatory response -Normalized p53 and PCNA markers	El-kott et al., 2012
Coriander honey	Ehrlich ascites tumor bearing xenograft mouse model	500 mg/Kg/mouse daily for 21days	-#Tumor size -"Survival rate -"Immunoglobulin M, G and A levels -"Phagocytic activity -#Lymphocyte transformation and hypersensitivity	Hegazi et al., 2015
Greek honey extract	Prostate (PC-3), breast (MCF-7) and endometrial (Ishikawa) cancer cells	0.2–125 mg/mL for 48h	-#Cell viability -#Oestrogenic effects	Tsiapara et al., 2009
	Prostate (PC-3) and breast (MCF-7) cancer cells	20–500 mg/mL for 48h	-#Cell viability	Spilioti et al., 2014
Thyme honey-derived monoterpene	PC-3 prostate cancer cells	100 mM for 24, 48 and 72h	-"Apoptotic cell death -#IL-6 and NF-rB	Kassi et al., 2014
Thyme honey	Thyroid cancer patients with salivary glands damage (n¼ 120)	Four Thyme honey mouthwashes in 1h after the candy sucking and within 12h after the radiation for 4 days	-#Salivary glands damage	Charalambous, Frangos, and Talias 2014
	Head and neck cancer patients with xerostomia (n¼ 72)	Thyme honey mouthwashes 3 times per day	-#Xerostomia	Charalambous et al., 2017
Anatolian honey	MCF7, SKBR3, and MDAMB-231 breast cancer cells	1, 2.5, 5, 7.5 and 10 mg/mL for 24, 48 and 72h	-#Cell proliferation -"Apoptotic effects	Seyhan et al., 2017

creatinine and urea levels, compared to control group (Osama et al., 2017). Bee honey and Coriander honey form Egypt decreased EAT cell proliferation and viability, as well as tumor size, increasing the life span of EAT xenograft mice model (Gabry and Othman, 2008; Hegazi et al., 2015). The preventive effects were exerted by improving immune system through (i) activating peritoneal macrophages in addition to T and B cell function (Gabry and Othman, 2008), (ii) increasing immunoglobulin M, G and A levels and phagocytic activity, iii) reducing lymphocyte transformation and hypersensitivity skin test (Hegazi et al., 2015), and lastly iv) maintaining total lipids and proteins, as well as liver and kidney enzyme activities (Gabry and Othman, 2008). Additionally, Bee honey acted as a defending agent in diethylnitrosamine (DEN) induced hepatocarcinogenesis rat model by improving body weight, decreasing tumor volume and inflammatory responses; in particular, honey supplementation induced the normal levels of p53 and proliferative (PCNA) markers in liver tissue compared to DEN treated rats (El-kott et al., 2012).

Egyptian honey also protected the chemotherapy persuaded adverse effects in grade 2–4 acute lymphoblastic leukemia (Abdulrhman et al., 2012; Abdulrhman et al., 2016) and head and neck cancer (Rashad et al., 2009). In chemotherapy induced oral and oropharyngeal mucositis patients, honey intervention induced faster healing activities by acting as a topical prophylaxis against some pathogenic bacteria (Abdulrhman et al., 2012; Rashad et al., 2009). Similarly, in acute lymphoblastic leukemia patients, honey supplemented groups showed significantly decreased febrile neutropenia (side effects of chemotherapy) and improved hemoglobin levels compared to control groups (Abdulrhman et al., 2016).

The anti-cancer potential of Greek honey (Thyme, Pine and Fir) extracts has been evaluated in prostate (PC-3), breast (MCF-7) and endometrial (Ishikawa) cancer cells (Tsiapara et al., 2009; Spilioti et al., 2014). All the extracts significantly suppressed the viability of cancer cells (Tsiapara et al., 2009; Spilioti et al., 2014), while Thyme honey prevented MCF-7 cancer cells progression by decreasing estrogenic effects (Tsiapara et al., 2009). Furthermore, Thyme honey-derived monoterpene induced apoptotic PC-3 cell death, in part by decreasing the secretion of IL-6 and NF-rB (Kassi et al., 2014). In randomized controlled trial, Thyme honey mouthwashes exerted safety and effectiveness for the management of radiation induced salivary gland damage in thyroid cancer patients (Charalambous, Frangos, and Talias 2014) and xerostomia in head and neck cancer patients (Charalambous et al., 2017)

Finally, Anatolian honey with diverse botanical origin such as pine, chestnut and cedar exerted more anti-proliferative and apoptotic effects on a panel of breast cancer cells (MCF7, SKBR3, and MDAMB-231) in dose and time manner, while multifloral honey was less effective (Seyhan et al., 2017).

Honey and cardiovascular diseases

The beneficial effects of honey in reducing CVDs risk have been investigated mainly on animals (Table 9).

For example, Clover honey exerted anti-inflammatory activity in rodent macrophages and human neutrophils through the suppression of ROS generated by bovine thrombin (BTh), suggesting a protective effect of this honey against the possible onset of cardiovascular problems related to the inflammatory state (Ahmad, Khan, and Mesaik 2009). In male Sprague-Dawley rats a Clover honey-based diet was effective in reducing body weight, epididymal fat, serum triglycerides and leptin levels compared to rats fed with sucrose. These results showed that the substitution of sucrose with honey in a high carbohydrate diet can lead to benefits in decreasing physical and biochemical parameters closely linked to the risk of incurring diseases such as type 2 diabetes mellitus, hypertension, atherosclerosis or coronary heart disease (Nemoseck et al., 2011). The beneficial effect of Clover honey in patients affected with type 1 diabetes mellitus, a risk factor for the early onset of cardiovascular disease, has been also demonstrated: compared to the baseline measurement, a reduction in anthropometric and biochemical parameters (body weight, triglycerides, cholesterol, LDL) was evidenced after 12 weeks of honey administration; similar results were shown at the end-point time (Abdulrhman et al., 2013).

The effect of Acacia honey on factors and parameters closely linked to obesity has been recently investigated (Samat et al., 2017). Obese Sprague-Dawley rats fed with Acacia honey for 4 weeks presented lower levels of serum glucose, triglyceride and cholesterol levels as well as leptin and resistin levels, compared to those who received Oristat, without compromising liver functions. Honey consumption induced also a reduction in body weight gain, BMI, adiposity index and the Lee's index (cardiac risk Index) (Samat et al., 2017).

The antioxidant effect of Pine honey from Greece has been demonstrated on the *in vitro* oxidation of human serum lipoproteins and isolated plasma LDL: honey treatment significantly delayed the oxidation of both types of lipoproteins, protecting them from oxidative damage (Makedou et al., 2012). In addition to the antioxidant capacity exerted by the high amount of total phenolic compounds, the antiatherogenic potential of extract of different types of Greek honey (Thyme, Fir, Pine, Citrus and wild) has been also demonstrated on endothelial cells. Honey treatment reduced the expression of some proteins involved in the atherogenic process, such as ICAM-1 and VCAM-1, markers of coronary risk, closely linked to the process of atherosclerotic plaque formation (Spilioti et al., 2014).

In 12 healthy subjects the effect of Basswood honey on serum glucose, insulin and C-peptide levels was evaluated. Subjects who received Basswood honey had lower serum insulin and C-peptide levels, compared to individuals who received a water solution with the same amounts of glucose and fructose of honey. These results suggest that honey contains some substances capable of exerting this effect, probably modulating the absorption and metabolism of glucose and/or fructose. For this reason honey could have an antidiabetic effect and consequently counteract this factor that

Table 9. Effects of different types of honey on cardiovascular diseases.

Honey types	Experimental model	Dosage and duration of honey treatment	Biological response / involved pathway	Ref.
Clover honey	Human neutrophils and rodent macrophages	0.4–15 mg/ml for 30 min, before and after stimulation with BTh	-#ROS	Ahmad, Khan, and Mesaik 2009
	Sprague-Dawley rats	11.41 Kj/g for 33 days	-#Body weight -#Weight of the epididymal fat -#Triglycerides -#Leptin	Nemoseck et al., 2011
	Patients with type 1 diabetes mellitus (DM) (*n* ¼ 20)	0.5 mL/kg body weight/day for 12 week	-#Body weight -#Mid arm circumference -#Triceps skin fold thickness -#Subscapular skin fold thickness -#Triglycerides -#Cholesterol -#LDL -"HDL	Abdulrhman et al., 2013
Acacia honey	Sprague-Dawley Obese rats	n.d.	-#Glucose -#Triglycerides -#Cholesterol -#Leptin -#Resistin -"Adiponectin -#Body weight -#Body Mass Index -#Lee's index -#Adiposity index	Samat et al., 2017
Pine honey	Human serum lipoproteins and low density lipoproteins (LDL)	100, 200 and 400 mg/mL for human serum lipoproteins; 10, 20 and 40 mg/mL for LDL	-"Antioxidant activity -#Oxidative damage	Makedou et al., 2012
Thyme, Fir, Pine, Citrus and wild honey	endothelial cells	20, 200 and 500 mg/mL for 18-24h	-#ICAM-1 -#VCAM-1 -"Antiatherogenic activity	Spilioti et al., 2014
Basswood honey	Healthy subjects (n ¼ 20)	221.3 g (75 g of glucose)	-#Insulin -#C-peptide	Mc Gunstedt et al., 2008
Wild honey from Egypt	Isolated toad hearts from *Buforegularis*	0.5 g/mL for 30 min	-Negative chronotropism and dromotropism -Positive ionotropism - Ventricular depolarization and repolarization -"Contractile force of the ventricle -Physiolological and direct activity on the myocardium	Rakha, Hussein, and Nabil 2003
	Isolated toad hearts from *Buforegularis*	0.5 g/mLfirst pretreated with epinephrine (adrenaline)	-#Extrasystoles -#Tachyarrhythmias -#Bradyarrhythmias -Anti-arrhythmic effect	Hussein, Miran, and Nabil 2003
	Sprague-Dawley albino rats	5 g/kg body weightbefore and after the injection with epinephrine	-#Extrasystoles -#Tachyarrhythmias -#Bradyarrhythmias -Cardioprotectiveeffect -Therapeutic effect against cardiac disorderscaused by a hyperadrenergic activity	Rakha, Nabil, and Hussein 2008
Italian multifloral honey	Endothelial cells (EA.hy926)	Honey solution (1% w/v in PBS) overnight before and after exposition to CuOOH	-#Damage at the membrane and at the intracellular level -#Free radical species -#Progression of the oxidative cascade -"Cell viability -#Lipid peroxidation -"GSH	Beretta, Orioli, and Facino 2007
Multifloral natural honey	Wistar rats	20% honey in diet/day for 8 weeks	-#Morphological changes -#Blood pressure -#Size of adipocytes (compared to sucrose supplemented group)	Romero-Silva et al., 2011
	Diabetic type 2 patients (*n*¼ 48)	(First 2 weeks, 1 g/kg/day; second 2 weeks, 1.5 g/kg/day; third 2 weeks, 2 g/kg/day; and last 2 weeks, 2.5 g/kg/day) for 8 weeks	-#Body weight -#LDL -#Cholesterol -#Triglycerides -"HDL	Bahrami et al., 2009

predisposes to the onset of heart disease (Menstedt et al., 2008).

Wild honey from Egypt had a direct effect on the electrical activity of the heart: after atropine and nicotine or verapamil administration, perfused honey played a pronounced effect on the activity of the heart muscle in isolated toad hearts (*Buforegularis*), as demonstrated by the negative chronotropism and dromotropism and the positive ionotropism, increasing the ventricular depolarization and consequently the contractile force of the ventricle; these effects were due mainly to the high concentration of potassium and calcium present in these types of honey. In addition, an increase in the ventricular repolarization tension was also noted, confirming a real physiological and direct activity of honey on the myocardium (Rakha, Hussein, and Nabil 2003). Similarly, the application of wild honey from Egypt was almost able to eliminate all the effects due to perfusion of epinephrine (extrasystoles, tachyarrhythmias, bradyarrhythmias) on isolated toad hearts (*Buforegularis*), suggesting an anti-arrhythmic effect of wild honey (Hussein, Miran, and Nabil 2003). These results were confirmed in a subsequent *in vivo* work, where wild honey from Egypt administered intraperitoneally before or after epinephrine injection protected adult male Sprague-Dawley albino rats (*Rattus rattus*) from the onset of cardiac disorders, improving electrocardiographic parameters, highlighting a cardioprotective and therapeutic effect against cardiac disorders caused by hyperadrenergic activity (Rakha, Nabil, and Hussein 2008).

The antioxidant effects and the radical scavenging activity of multifloral honey from Italy have been demonstrated on endothelial cells (EA.hy926) subjected to oxidative stress induced by Cumen hydroperoxide (CuOOH). Honey was able to reverse damage progression both at membrane and intracellular levels, inhibiting free radical species and the progression of the oxidative cascade, increasing cell viability compared to untreated cells. In addition, when cells were preincubated with honey and then stressed with CuOOH, a protective effect was also evidenced: cells pretreated with honey showed a lower susceptibility to lipid peroxidation, fewer morphological changes, a rise in GSH levels and an increase in cell viability compared to the control. These results lead to the assertion that honey had a preventive and protective role against oxidation and inflammation of endothelial cells present for example in the arterial wall, preventing and counteracting the atherogenic action (Beretta, Orioli, and Facino 2007).

The effect of three different types of diet (hypercaloric diet with addition of sucrose, hypercaloric with addition of honey and standard diet) on blood pressure and adipocyte size was evaluated in Wistar Rats. The arterial blood pressure was significantly higher in the sucrose supplemented group, while there were no differences between the rats that received honey and those who followed a standard diet. There was also an increase in the size of adipose cells present in the intra-abdominal fat both in with hypercaloric diet with sucrose supplement, and in that with honey; in the latter, however, the increase was much lower. For this reason honey can exert a protective effect against hypertension in an hypercaloric diet and can decrease alterations of the metabolism associated with a carbohydrate-rich diet, counteracting the factors closely related to the onset of cardiovascular diseases (Romero-Silva et al., 2011). Finally, in patients with type 2 diabetes, a multifloral honey showed a beneficial effect by reducing body weight and the serum levels of LDL, cholesterol and triglycerides and increasing HDL levels compared to the control group (Bahrami et al., 2009).

Conclusion

In this review, we highlighted the beneficial roles of these foods and of their bioactive compounds, which exert positive effects on the onset and progression of cancer and CVDs. Several *in vitro* and *in vivo* studies have indeed demonstrated that these foods play key roles in cancer prevention by inactivating carcinogens, decreasing cell proliferation, inducing cell cycle arrest and apoptosis, and inhibiting angiogenesis in many types of tumors. In the same way, they exert cardioprotective effects by decreasing oxidative stress and inflammation, modulating carbohydrate digestion through the reduction of glucose absorption, improving blood lipid levels, augmenting the resistance of LDL to oxidation, normalizing endothelial function, vascular elastic properties of the arterial tree, blood pressure and platelet functions.

All these protective effects are due not only to the antioxidant properties exerted by these food matrices but also to the capacity of their bioactive compounds in modulating several genes involved in cellular antioxidant defenses, inflammation, metabolism, survival and proliferation.

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