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Dietary legumes, intestinal microbiota, inflammation and colorectal cancer

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ABSTRACT

Colorectal cancer is a worldwide disease with major clinical and economic impact, and its occurrence is determined by a variety of factors. In addition to its hereditary component, it is also known to be associated with various inflammatory processes, epigenetic alterations or modifications of the intestinal microbiota. The alimentary habits are crucial in the conformation of gut microbiota. The Mediterranean diet is widely recognized for its health benefits and has been associated with a lower risk of colon cancer. On the other hand, inflammation is a process commonly associated with cancer, and the intestinal microbiota interacts with the host to maintain normal function and health, particularly in processes of immunity and defense. Here, we are focusing in particular on two groups of substances (fibre, protein fractions) present in legumes whose mechanisms of action to prevent colon cancer or inflammation are likely to be mediated by the intestinal microbiota functional composition.

1. Introduction

According to the Global Cancer Observatory (GCO) (IARC, WHO, 2018), which reports on the incidence, mortality and prevalence of the main types of cancer for 184 countries of the world, colorectal cancer (CRC) was the second most common type of cancer in women (surpassed only by breast cancer) and in men (only surpassed by lung cancer) worldwide (Fig. 1A). In Mediterranean countries, values follow a similar trend although with substantially lower values generally including CRC (Fig. 1B). Prevalence values for CRC are second after breast cancer and third after breast and prostate cancers worldwide and in Mediterranean countries respectively (Fig. 1C & D). An increase in CRC incidence rates for both males and females had been documented from 1983–87 to 1998–2002 particularly in economically transitioning countries including Eastern European countries, most parts of Asia, and select countries of South America (Center, Jemal, & Ward, 2009). Given the magnitude of the problem, the competent authorities have developed a series of guidelines to ensure efficient early detection of the disease and appropriate monitoring of the people affected. The first edition of the 'European guidelines for quality assurance in CRC screening and diagnosis' was published in 2010 by the European Commission (Arpaia & Rudensky, 2014). Likewise, several American organizations came together to develop consensus guidelines for the detection of adenomatous polyps and CRC (Levin, Lieberman, McFarland, & Smith, 2008).

Scientific advances have made it possible to identify many of the factors associated with the promotion of CRC and have helped to show which of them can be modified to prevent the disease. In most cases, there is no single factor which determines the development of CRC. The age and male gender are important risk factors, but there are many other and varied factors such as a family history (with a heritable component of 35%, Lichtenstein, Holm, Verkasalo, & Iliadou, 2000), the presence of Inflammatory Bowel Disease (IBD), infectious or potentially infectious agents, and those associated with the diet like excessive alcohol consumption, high consumption of red and processed meat, obesity, etc. (Brenner, Kloor, & Pox, 2014). Legume consumption, the focus of the current review and one of the basic components of the Mediterranean diet, has been linked with a decreased risk of suffering 10 major chronic diseases including CRC (Kromhout, Spaaij, & de Goede, 2016; Song, Garrett, & Chan, 2015). In the current review, we are paying special attention to two groups of substances (fibre, protein fractions) present in legumes whose mechanisms of action to prevent

Abbreviations: BBI, Bowman-Birk protease inhibitors; COX-2, cyclooxygenase-2; CRC, colorectal cancer; DASH, dietary approaches to stop hypertension; DSS, dextran sodium sulfate; EGFR, epidermal growth factor receptor; GIT, gastrointestinal tract; HDACi, histone deacetylase enzymes; IBD, inflammatory bowel disease; IM, intestinal microbiota; iNOS, inductible nitric oxide synthase; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; NSP, non-starch polysaccharides; PRRs, pattern recognition receptors; PSE, pea (*Pisum sativum*) seed albumin extract; qPCR, real-time quantitative PCR. SCFA, short chain fatty acids; TLR, toll-like receptor; Treg, regulatory T cells

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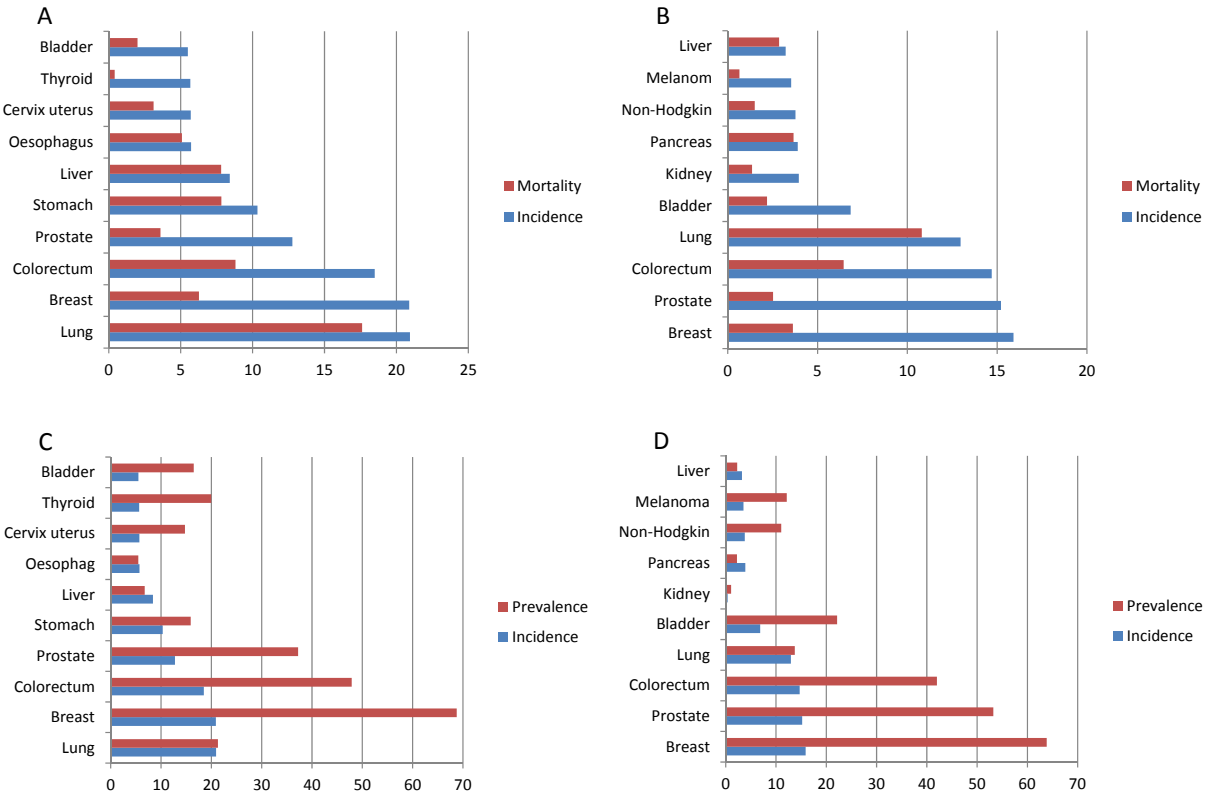

Fig. 1. Cancer incidence, mortality and prevalence values (number of cases per 100,000) worldwide (A,C) and in eight Mediterranean countries (Croatia, Cyprus, France, Greece, Italy, Malta, Slovenia and Spain) (B,D).

CRC or inflammation are likely to be mediated by the intestinal microbiota (IM) functional composition.

2. Colorectal cancer (CRC) and inflammation

Inflammation is a process commonly associated with cancer as it involves the interaction of various immune and inflammatory cells, chemokines, cytokines and pro-inflammatory mediators which can lead to signals directed to the proliferation of tumor cell growth and invasion (Aggarwal, Shishodia, Sandur, Pandey, & Sethi, 2006; Aggarwal, Sung, & Gupta, 2014; Korniluk, Koper, Kemona, & Dymicka-Piekarska, 2017). The cancer-inflammation connection has two pathways: an extrinsic pathway, where inflammatory conditions facilitate the development of cancer (by releasing chemicals, for example), and an intrinsic pathway, where genetic alterations leading to cancer also stimulate the inflammatory process, thus contributing to the establishment of a microenvironment favorable to tumor development. For this reason, regardless of tumor origin, there are inflammatory cells in the vicinity of all tumors (Vendramini-Costa & Carvalho, 2012). In particular, patients with IBD (ulcerative colitis or Crohn's disease) have a higher risk of developing CRC, and the risk is higher if the inflammation becomes chronic (7 or more years). When chronic inflammation persists, an environment in which immune surveillance mechanisms fail is created. The inhibition of anti-tumor immune responses then leads to tumor development (Fantini & Pallone, 2008; Rizzo, Pallone, Monteleone, & Fantini, 2011). Other relevant factors are the extent and severity of colon inflammation, the co-existence with primary sclerosing cholangitis (bile duct inflammation/scarring) or colon cells of abnormal appearance (dysplasia), and family history (Mattar, Lough, Pishvaian, & Charabaty, 2011; Terzić, Grivennikov, Karin, & Karin, 2010). Among the many indications that confirm the link between inflammation and CRC is the observation that various anti-inflammatory therapies reduce or prevent CRC risk (Bastiaannet, Sampieri, Dekkers, & de Craen, 2012; Crawford, 2014). In consequence, the ultimate molecular mechanisms by which intestinal inflammation leads to cancer development are the focus of intense research. The studies conducted so far suggest mutations in tumor suppressor genes, induction of oxidative stress, nitric oxide (NO), inhibition of DNA repair enzymes and production of clastogens as possible links (Mandal, 2018; Shastri, Vemuri, Gueven, Shastri, & Eri, 2017; Vendramini-Costa & Carvalho, 2012). Non-steroidal anti-inflammatory drugs (NSAIDs) are currently the main anti-inflammatory agents with anti-tumorigenic properties, most likely due to their inhibition of cyclooxygenase-2 (COX-2), which has been shown to be of high activity in various types of tumors (Vendramini-Costa & Carvalho, 2012).

3. The implication of the intestinal microbiota (IM) in CRC

In addition to a number of beneficial roles, gut bacteria have been reported to be involved in various diseases, such as IBD, obesity, diabetes, carcinoma, HIV and autism (Sartor, 2008; Zhang, Li, Gan, & Zhou, 2015). The human gastrointestinal tract (GIT) is home to over 100 trillion microorganisms, which together make up what is called the IM. The size of this population far exceeds that of all other microbial communities associated with the body's surfaces, and was reported to be about 10 times greater than the total number of our somatic and germ cells (Bäckhed, Ley, Sonnenburg, Peterson, & Gordon, 2005), although the number of intestinal bacteria has been recently revised to be the same order as the number of human cells (Sender, Fuchs, & Milo, 2016). Microbial density reaches 10^4–10^7 cells per gram in the jejunum and ileum and 10^{11} per gram in the colon (Walker, Duncan, Louis, & Flint, 2014), and is dominated by five bacterial phyla (Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Verrucomicrobia) and one of archaea (Euryarchaeota). The IM interacts with the host to maintain normal function and health of the GIT and the whole organism. It plays a role in the processes of immunity and defense,

digestion and metabolism, inflammation and cell proliferation, and communicates not only with the intestinal epithelium but also with distant organs and body systems (Bajaj, Hylemon, & Younossi, 2012; Nicholson, Holmes, & Wilson, 2005; Tillisch, 2014). In turn, the genetic background of the host influences its microbiome functional composition (Knights, Lassen, & Xavier, 2013).

On the other hand, the microbiota inhabiting the GIT can be differentiated into two major group: that closely associated with the mucosa and that forming part of the intestinal content. This is relevant because while mucosal microorganisms would be crucial for immunological priming, those mainly involved in nutrient digestion and metabolic exchange with the host are more abundant in the lumen (Van den Abbeele, Van de Wiele, Verstraete, & Possemiers, 2011). It has been accordingly proposed that the intestinal lumen microbiota potentially influences CRC risk via co-metabolism or metabolic exchange with the host, while mucosa-associated microbiota potentially affects CRC risk primarily through direct interaction with the host (Chen, Liu, Ling, Tong, & Xiang, 2012). It is also known that mucosa-associated IM composition differs from that in the feces (Eckburg, Bik, Bernstein, & Purdom, 2005), which is likely to be closer in composition to that in the lumen.

The IM is a rich source of molecules able to cause inflammation in peripheral tissues of the body, such as lipopolysaccharide and peptidoglycan (Sartor, 2008). Lipopolysaccharide molecules bind to Toll-like receptor 4 (TLR4) and to peptidoglycan type NOD receptors, which activate pro-inflammatory signaling cascades (Tremaroli & Bäckhed, 2012). Toll-like receptors (TLRs) are proteins members of the pattern recognition receptors (PRRs) family of the immune system (Dolasia, Bisht, Pradhan, Udgata, & Mukhopadhyay, 2017). Their regulation in the epithelial cells of the large intestine seems to be related to the composition of the IM and the presence or not of pathogenic microorganisms, with increased expression of TLR2 and TLR5 in specific pathogen-free mice (Lundin, Bok, Aronsson, & Björkholm, 2008). Overexpression of TLR4 seems to be a critical factor in inflammation-associated colorectal neoplasia through a mechanism associated with increased production of COX-2 enzyme and the regulation of epidermal growth factor receptor (EGFR) phosphorylation (Fukata, Chen, Vamadevan, & Cohen, 2007; Fukata, Shang, Santaolalla, & Sotolongo, 2011). It has also been observed that REP sequences (remarkably conserved extragenic palindromic nucleotide sequences) repeated throughout the bacterial genome (Stern, Ames, Smith, Robinson, & Higgins, 1984) from genomes of Gram-negative bacterial pathogens are able to stimulate the Innate Immune System through the TLR9 receptor, detecting a strong induction of production of IFN-α in splenocytes from mice (Magnusson, Tobes, Sancho, & Pareja, 2007). Since it has been described that REP sequences are species specific (Tobes & Ramos, 2005) and their distribution in the genome differs between strains of the same species (Aranda-Olmedo, Tobes, Manzanera, Ramos, & Marqués, 2002), different bacteria could be expected to interfere differently in the immune response of the host. In general, all these results suggest that the stimulation of the immune system caused by microbiota associated-inflammation could be regulated by regulating the expression and/or the functionality of TLRs. As TLRs regulation is linked to the IM composition, which in turn is mainly influenced by the diet, TLRs activity, and consequently immunity/inflammation, may be modulated by appropriate dietary interventions.

A recent review (Dahmus, Kotler, Kastenberg, & Kistler, 2018) has examined the current research evaluating multiple proposed pathogenic microorganisms including sulfidogenic bacteria such as *Bilophila wadsworthia*, as well as *Streptococcus bovis, Helicobacter pylori, Bacteroides fragilis,* and *Clostridium septicum*. However, only a few microorganisms have been identified as carcinogens by the International Agency for Research on Cancer (IARC) (Plummer, de Martel, Vignat, & Ferlay, 2016). Within the GIT, some virulence factors stemming from certain bacteria of the IM may be responsible for the initiation and promotion of CRC by creating a pro-inflammatory environment that favors the penetration of other species of bacteria in the epithelium (Kostic, Chun, Robertson, & Glickman, 2013; Rubinstein, Wang, Liu, & Hao, 2013). The intestinal tissue has thereby its barrier function impaired, facilitating the translocation of bacteria and the induction of cytokines which maintain an inflammatory environment in the tumor (Jobin, 2012). Intestinal bacteria thus regulate the inflammatory response in the tumor microenvironment (Iida, Dzutsev, Stewart, & Smith, 2013), and CRC may be caused by certain microbes that progress within the inflammatory environment (Arthur, Perez-Chanonam, Mühlbauer, & Tomkovich, 2012). In the opposite direction, the altered host immune signaling could promote the extension of cancer promoting bacteria in the IM in an inflammatory process.

Some specific cancers have been linked to bacterial or viral infection (Selgrad & Muller-Schilling, 2018). As for CRC, it has not yet been related with any particular germ, but there is increasing evidence that the IM is associated with the development and progression of CRC (Irrazábal, Belcheva, Girardin, Martin, & Philpott, 2014; Marchesi, Dutilh, Hall, & Peters, 2011) through the metabolites generated (Louis, Hold, & Flint, 2014). A number of mechanisms have been proposed (Nistal, Fernández-Fernández, Vivas, & Olcoz, 2015): (i) the induction of chronic inflammation; (ii) genotoxins biosynthesis could act either directly, by damaging DNA, or indirectly by interfering for example with cell cycle regulation; and (iii) accumulation of toxic metabolites or activation of certain dietary pro-carcinogenic components. A number of examples of bacteria/bacterial groups for which some information exists on their implication in CRC are collected in Table 2.

Although the exact composition of the IM and its potential role in the development and progression of CRC is still largely unknown, the microbial structures of CRC patients and healthy individuals have been shown to differ significantly (Gao, Guo, Gao, Zhu, & Qin, 2015; Pennisi, 2013). Even more, the mucosa-associated microbiota was found to differ structurally between cancerous tissue and para-cancerous regions (i.e., in “normal” mucosa of diseased individuals) (Chen et al., 2012). As for particular groups, Gao et al. (2015) reported that *Firmicutes* and *Fusobacteria* were over-represented whereas *Proteobacteria* was under-represented in CRC patients. Also, *Lactococcus* and *Fusobacterium* exhibited a relatively higher abundance while *Pseudomonas* and *Escherichia-Shigella* were reduced in cancerous tissues compared to adjacent non-cancerous tissues. However, Shen, Rawls, Randall, and Burcal (2010) found higher bacterial diversity and richness in colonic polyps when compared with control patients, with higher abundance of mucosal Proteobacteria and lower abundance of Bacteroidetes. Therefore, although CRCs have an increased enrichment of opportunistic pathogens and polymicrobial Gram-negative anaerobic bacteria, it is not yet clear whether these opportunistic pathogens merely benefit from the CRC microenvironment or influence disease progression. For the same reason, the potential usefulness of pre- and probiotics to prevent CRC remains controversial, since the number of clinical trials in humans involving the use of probiotics for prevention or treatment of CRC is scarce and study results obtained are very heterogeneous and not consistent (Tsai et al., 2019). Nevertheless, in animal (rodent) studies a clear reduction in aberrant crypt foci is mostly observed with prebiotic and synbiotic preparations (probiotics plus prebiotics) even though the effect of probiotics alone is not as clear (Azcárate-Peril, Sikes, & Bruno-Bárcena, 2011). However, the rapid evolution of “omics” technologies is beginning to provide the information needed to generate disease-oriented, next generation probiotics able to modulate the IM by introducing a carefully selected blend of beneficial organisms capable of survival, persistence, and delivery of a wide range of bioactive compounds.

The overall composition and diversity of the IM is probably relevant in CRC development. Chen et al. (2012), by using pyrosequencing-based analysis of the 16S-rRNA genes found that the overall microbial structures of cancerous tissue and noncancerous tissue were similar; however, the tumor microbiota exhibited lower diversity. The structures of the intestinal lumen microbiota and mucosa-adherent

microbiota were also different in CRC patients compared to matched microbiota in healthy individuals. Huipeng, Lifeng, Chuang, Jiaying, and Yuankun (2014) found that the diversity and abundance of the IM in the descending, transverse and ascending colon were more abundant in healthy *vs* patients with CRC, with bacteria of the type *Bacteroides* as predominant. Interestingly, these findings have also been found in patients and experimental animals with precancerous lesions (adenomatous polyps) (Noor, Ridgway, Scovell, & Kemsley, 2010; Wei, Dong, Wang, & Zhang, 2010). Sobhani, Tap, Roudot-Thoraval, and Roperch (2011) found that the IM of patients with CRC had more *Bacteroides/Prevotella* as compared with normal controls. Also, Mai, Maccrary, Sinha, and Glei (2009) found a different IM composition between Native Americans and Afro-Americans, being *Bacteroides* spp more abundant in the former. There are therefore a number of studies which focus on the role of gender *Bacteroides* (*B. fragilis*, common and polymorphic *Bacteroides*) in CRC (Chu, Esworthy, Chu, & Longmate, 2004; Hooper, Wong, & Thelin, 2001; Moghimi-Dehkordi & Safaee, 2012).

4. Dietary habits that modulate factors associated with CRC

According to the World Cancer Research Fund (2007), all factors taken into account, cancer is mostly a preventable disease, and cancers of some sites, notably of the colon, are generally agreed to be greatly or mostly affected by food and nutrition. On a global scale, it is estimated that over 3 to 4 million cases of cancer can be prevented every year by appropriate food and nutrition, regular physical activity, and avoidance of obesity (Anand, Kunnumakkara, Sundaram, & Harikumar, 2008; Wiseman, 2008). Many hypotheses have been developed to explain the relationship between diet and CRC risk. These hypotheses tend to be based on the concept of high-risk diets, which may either contain high levels of carcinogens or lack one or more anticarcinogenic protective factors (Sugimura, 2000).

However, the issue of the relationship between dietary components and CRC risk is very complex and multifactorial. Diet plays a dominant role in shaping the structure of the IM by influencing both its composition and functionality (Candela, Biagi, Maccaferri, Turroni, & Brigidi, 2012), and changes in the biodiversity and composition of the IM have far-reaching consequences on the health and development of the host. Cultural factors have a great influence in the type of diet consumed by a population. Western diets are typically high in fat and animal protein, while the Eastern diets are high in fiber. As a result, the IM appears with different population profiles in individuals with different eating habits. The impact of diet on the composition of the IM has been demonstrated for example by comparative studies in children. Thus, African children consuming a traditional rural diet (low in fat and animal protein and rich in starch, fiber, and plant polysaccharides), showed a significant enrichment in Bacteroidetes and a reduction in Firmicutes and *Enterobacteriaceae* (*Shigella* spp and *Escherichia* spp) with respect to European children (De Filippo, Cavalieri, Di Paola, & Ramazzotti, 2010). Also, Firmicutes were more represented and microbiota turned out to be more diverse in Bangladeshi than in USA children (Lin, Bik, Costello, & Dethlefsen, 2013).

The complex interactions between components of the diet and the microbiome have further consequences on the immune function of the host and on the origin and development of disease (Maslowski & Mackay, 2011). In this context, further studies in different countries with different dietary habits which influence the type and composition of the IM are at present of utmost importance. A lot of attention has been paid to dietary compounds able to modulate intestinal parameters including those related with the IM. Dietary fibre is arguably the most studied food component regarding the relationship between IM composition and gastrointestinal inflammatory processes (Ananthakrishnan, Khalili, Konijeti, & Higuchi, 2013). One reason for this is probably because it is broadly accepted that dietary recommendations to increase fibre consumption (up to at least 25 g/d for adult women and 38 g/d for adult men) by increasing that of whole grains, legumes, vegetables, fruits, and nuts should be broadly supported by food and nutrition practitioners (Dahl & Stewart, 2015). Some other dietary compounds less studied so far in this context such as Maillard reaction products (common components of processed foods, frequent in the Western diet, and implicated in reduced protein digestibility and other health conditions and diseases) (Aljahdali & Carbonero, 2017) have been recently reported to modulate *in vivo* the IM composition both in humans and in rats. Those effects, which were found to be linked to the chemical structure and dietary amounts of the different browning compounds, were related to changes in the pattern of SCFA production and to decreased proportions of *Lactobacillus* spp. and *Bifidobacterium* spp. counts, as well as increases in the *Escherichia/Shigella* group numbers (Delgado-Andrade, Pastoriza de la Cueva, Peinado, & Rufián-Henares, 2017; Seiquer, Rubio, Peinado, Delgado-Andrade, & Navarro, 2014).

Among the epigenetic mechanisms which seem to play a role in cancer development are changing patterns of DNA methylation, post-translational modifications of histones, microRNAs and antisense RNAs, and nucleosome positioning (Khare & Verma, 2012; Lao & Grady, 2011). Of these, DNA methylation (the enzymatic addition of a methyl group at the 5-position of cytosine by DNA methyltransferases, DNMTs, to produce 5-methylcytosine) is the epigenetic mechanism more widely studied. Modifications of dietary nutrients can also affect DNA methylation and regulate the homeostasis of the intestinal mucosa (Canani, Costanzo, Leone, & Bedogni, 2011). Monozygotic twins have been shown to be epigenetically indistinguishable during the early years of life, but over time they exhibit notable differences which can be easily attributable to the diet received (Fraga, Ballestar, Paz, & Ropero, 2005). A significant impact of folate deficiency on DNA methylation has been observed (Kim, 2005). In this way, foods that favor the increase of folates (legumes, green leafy vegetables, almonds, etc.) would thus favor the re-methylation of certain genes in specific sites of their DNA. The consumption of extra-virgin olive oil, which is rich in oleic acid, a ω9 monounsaturated fatty acid, has been associated with a lower risk of colon cancer for decades (Reddy & Maeura, 1984). It has been recently suggested that this property is due, at least in part, to its ability to up-regulate the CB_1 tumor suppressor gene through an epigenetic mechanism, both *in vivo* and *in vitro* (Di Francesco, Falconi, Di Germanio, & Micioni Di Bonaventura, 2015). Curcumin, used as a spice in common food, has been widely studied as a dietary chemopreventive agent for CRC prevention, being designated as responsible for the methylation changes of a set of genes (Link, Balaguer, Shen, & Lozano, 2013).

Although not all genes related to CRC and influenced by diet show evidence of epigenetic modification (Van Breda, van Delft, Engels, Kleinjans, & Mathers, 2009), experimental evidence indicates that some dietary nutrients may have either a direct DNA methylation effect and/or an indirect effect through IM modulation. For example, epigenetic modifications induced by the lactic bacteria *Lactobacillus acidophilus*, and ascribed to an increase in the expression of tumor suppressor genes, have been reported (Lightfoot, Yang, Sahay, & Mohamadzadeh, 2013). Evidence has also emerged that there is a relationship between epigenetic changes and the development of resistance to chemotherapeutic agents (Toyota, Suzuki, Yamashita, & Hirata, 2009). More importantly, butyrate coming from the fermentation of some intestinal bacteria acts as an inhibitor of histone deacetylase enzymes (HDACi). These enzymes remove acetyl groups from histones, increasing their positive charge and affinity for the DNA thus preventing transcription of genes by condensation of the DNA structure. Butyrate, by inhibiting the action of these enzymes, may increase the expression of tumor suppressor genes (Berni Canani, Di Costanzo, & Leone, 2017).

5. CRC, Mediterranean diet and legume consumption

5.1. Epidemiology of CRC in connection with diet

As indicated above, it is important to underline here that unlike

other cancers, such as lung cancer, no single risk factor accounts for most cases of CRC. This is probably why some data suggest a weak protective effect against CRC of diets rich in fruit, vegetables, cereal fibre and whole grains, dairy products, or fish and, possibly, statin therapy (Brenner et al., 2014). However, there is also information suggesting that the higher prevalence of CRC in certain geographical areas depends substantially on dietary factors. This seem to indicate population studies of emigration of ethnic groups originating in areas of low CRC prevalence (e.g. Asian immigrants to the U.S.) which have, in successive generations, CRC prevalence indices similar to the autochthonous population (Flood, Weiss, Cook, & Emerson, 2000; Marchand, 1999).

The European countries bordering the Mediterranean Sea have been characterized by consuming one of the dietary patterns recognized as healthier, with an important consumption of legumes and with a remarkable advantage in survival compared to the rest of the European countries due to a lower incidence of cases of metabolic and cardiovascular syndrome, cancer, diabetes and neurodegenerative diseases (Del Chierico, Vernocchi, Dallapiccola, & Putignani, 2014). The Mediterranean diet has been recently shown to affect the IM composition (Garcia-Mantrana, Selma-Royo, Alcantara, & Collado, 2018). Thus, a higher ratio of Firmicutes/Bacteroidetes was related with a lower adherence to this diet, and a greater presence of Bacteroidetes was associated with lower animal protein intake. High consumption of animal protein, saturated fats, and sugars affected gut microbiota diversity. A significantly higher presence of *Christensenellaceae* was found in individuals with higher adherence to the Mediterranean diet compared to those with lower adherence. Higher bifidobacterial counts, and higher total SCFA were related to greater consumption of plant-based nutrients, such as vegetable proteins and polysaccharides. Better adherence to the Mediterranean diet was associated with significantly higher levels of total SCFA. It has even been suggested that the follow-up of a Mediterranean diet is associated with changes in the methylation pattern of certain genes related to the inflammation process and that individuals following this type of diet have lower inflammatory biomarkers (Arpón, Riezu-Boj, Milagro, & Marti, 2016). However, this advantage has been gradually lost, most likely due in part to the progressive abandonment of their dietary traditions (Castelló, Amiano, Fernández de Larrea, & Martín, 2018; Trichopoulos & Lagiou, 2004). According to cancer forecasts, it is estimated that 194,680 new cases of CRC (108,038 in men and 86,642 in women) will be diagnosed in the Mediterranean countries by the year 2020 (Table 1).

In this context, as indicated above, legume consumption has been related to a decreased risk of 10 major chronic diseases including CRC (coronary heart disease, stroke, heart failure, diabetes, breast cancer, colorectal cancer, lung cancer, chronic obstructive pulmonary disease, dementia and depression) (Kromhout et al., 2016). Various meta-analysis have also concluded that legume consumption reduces the risk of suffering CRC (Aune, Chan, Lau, & Vieira, 2011; Wang, Wang, Fu, Chen, & Fang, 2013; Zhu, Sun, Qi, Zhong, & Miao, 2015). A number of epidemiological studies have highlighted the inverse relationship between regular pulse consumption and risk of developing CRC, or even liver cancer (Zhang, Xiang, Li, & Yang, 2013) or glioma (Benisi-Kohansal, Shayanfar, Mohammad-Shirazi, & Tabibi, 2016), although other studies did not find any effect of legume consumption on CRC incidence (Vieira, Abar, Chan, & Vingeliene, 2017; World Cancer Research Fund/American Institute for Cancer Research, 2007). Interestingly, although CRC incidence data have increased worldwide, inverse tendencies between incidence of CRC and pulses consumption can be clearly observed over the years (Fig. 2). Thus, in countries where pulse consumption was maintained or has increased, such as for example USA and Canada (Fig. 2C and D), CRC cases experienced a smaller increase as compared with those geographical areas where the decrease in the consumption of pulses was more pronounced. The latter is the case, for example, of Japan (Fig. 2E), the countries of the European Union (Fig. 2A) and, within these, the group of Mediterranean European countries (Fig. 2B) where the consumption of pulses dropped by more than 15% since the early 1960s to the early 1990s (Trichopoulos & Lagiou, 2004) and continued with this decline in the following years (Zander, Amjath-Babu, Preissel, & Reckling, 2016).

Table 1
Prediction of the incidence of CRC in the Mediterranean countries for the year 2020. Source: GLOBOCAN 2012, IARC.

Both sexes 194,680		Male 108,038		Female 86,642	
ages < 65	ages > = 65	ages < 65	ages > = 65	ages < 65	ages > = 65
66,944	127,736	38,117	69,921	28,827	57,815

Countries included: Morocco, Algeria, Tunisia, Libya, Egypt, Israel, Lebanon, State of Palestine, Syrian Arab Republic, Turkey, Greece, Albania, Montenegro, Croatia, Bosnia Herzegovina, Slovenia, Italy, France (metropolitan), Spain, Malta, Cyprus.

Adherence to the so-called Dietary Approaches to Stop Hypertension (DASH), which include pulses as one of its main components, has been associated with lower morbidity and mortality from chronic diseases in both Western and Eastern populations (Benisi-Kohansal et al., 2016; Yu, Zhang, Xiang, & Yang, 2014). Changes in dietary habits are being repeatedly pointed as the main risk behavior regarding CRC incidence. Thus, as an example the remarkable increase in red and processed meats consumption as the source of proteins instead of legumes during the second half of the 20th century in Spain has been linked to increases in incidence, mortality and years of potential life lost in both males and females due to CRC (Béjar, Gili, Ramírez, López, & Cabanillas, 2010). It has recently been suggested that meat intake influences the activation status of certain TLRs thus promoting an inflammatory process [in which the nuclear transcription factor-κB (NF-kB) intervenes] that leads to the development of CRC, whereas fiber intake causes an opposite signal through TLR4 (with the secretion of interleukin-10 and COX-2) that protects against CRC (Kopp, Vogel, Tjonneland, & Andersen, 2018) (see above). In a 26-yr follow-up study involving 2818 subjects, Tantamango, Knutsen, Beeson, Fraser, and Sabate (2011) found that a higher frequency of consumption of cooked green vegetables, legumes, dried fruit, and brown rice was associated with a decreased risk of rectal/colon polyps, which are found in populations with high incidence of CRC. In particular, consuming legumes at least 3 times/wk reduced the risk by 33%. Moreover, legume consumption is also associated with lower risk of other epidemiologically relevant pathologies such as diabetes, breast cancer, lung cancer and chronic obstructive pulmonary disease (Kromhout et al., 2016). Thus, in a recent large study involving 1868 participants (55–80 years-old), Becerra-Tomás, Babion, Martínez-González, and Corella (2016) found that the risk of metabolic syndrome was lower when one-serving/day of processed red meat was replaced by legumes, poultry and rabbit, fish or eggs. More specifically, a prospective study investigating the association between total legumes consumption and grain legumes species (dry beans, chickpeas, lentils, and fresh peas) with cancer and other-cause mortality among elderly Mediterranean individuals found that higher total legumes (27.34 g/day) and lentils (8.73 g/day) consumption was associated with lower risk of cancer mortality (Papandreou, Becerra-Tomás, Bulló, & Martínez-González, 2019).

5.2. Legume fibre and proteins as anti-carcinogens

Fibre. A number of anti-carcinogens have been reported in legumes: dietary fibre, antioxidants, vitamins, trace minerals, phytate, phenolic acids, lignans, and phytoestrogens, flavonoids and isoflavones (Aune et al., 2011; Constantinou, Kiguchi, & Huberman, 1990). We will deal here with two major components, i.e. dietary fibre and some protein fractions, whose effect is closely related with IM functional

Table 2
Some examples of implication and mechanisms of IM in CRC.

Bacterial species/group	Effect Described	Proposed Mechanism	Potential Benefit	References
Potentially deleterious				
Helicobacter pylory	Relationship between adenocarcinoma and gastric lymphoma	Gastritis		Watari, Chen, Amenta, and Fukui, 2014Selgrad & Muller-Schilling, 2018
Fusobacterium nucleatum	Established opportunistic pathogen in periodontal diseases and several inflammatory diseases including IBD CRC resistance to chemotherapy	Adhesion of a bacterial adhesin/invasin, thus promoting CRC genesis, spreading and chemotherapy resistance		Ray, 2011Yu, Guo, Yu, & Sun, 2017
Bacteroides fragilis	Proliferation of colon epithelial cells, activation of c-myc oncogene	Enterotoxin (fragilisin) that triggers inflammatory responses by inducing the production of IL-8		Wu, Morin, Maouyo, & Sears, 2003Sanfilippo, Li, Seth, & Balwin, 2000Wu, Powell, Mathioudakis, & Kane, 2004
Desulfovibrio spp	Breakdown of the colonocyte barrier DNA damage	Production of hydrogen sulphide, which has been related to CRC development		Muyzer & Stams, 2008Homann, Tillonen, & Salaspuro, 2000Huycke, Abrams, & Moore, 2002Tong, Ran, Shen, Fan, & Xiao, 2008Bernstein, Bernstein, Payne, & Dvorak, 2009Louis et al., 2014
Several *Bacteroides* spp. and some Firmicutes *Bacteroides fragilis*	DNA damage	Increased production of products from protein fermentation: phenylacetic acid, phenols, indoles, p-cresol, ammonia and polyamines		
Bile salt hydrolases (which are found in all the major bacterial divisions and the methanogenic archaea)	Increased faecal bile acid concentrations in patients with CRC	Increased secondary bile acids (deoxycholic acid and lithocholic acid) generation and reactive oxygen and nitrogen species (ROS and RNS) which cause DNA damage		
Potentially beneficial				
Roseburia hominis	Induction of specific subsets of genes on both the bacterial and host sides of the interaction.	Flagellin signaling could drive the expansion of Treg cells via a TLR5 dependent mechanism	Treatment of ulcerative colitis, which is currently regarded as caused by dysregulated immune responses directed towards the commensal microbiota in genetically susceptible individuals	Patterson, Mulder, Travis, & Lan, 2017Kelly & Mulder, 2012
Streptococcus gallolyticus *Enterococcus faecalis* *Bacteroides fragilis*	Linked with adenomas and CRC Associations of commensal bacteria differentially affect the inflammatory status	IM play a role in the treatment of disease by affecting the outcome of the applied therapies (chemotherapeutic agents)	Improve therapy effectiveness	Marchesi et al., 2016Pennisi, 2013Viaud, Saccheri, Mignot, & Yamazaki, 2013Karin, Jobin, & Balkwill, 2014Mukaida, 2014
Faecalibacterium prausnitzii	*Faecalibacterium* spp numbers were negatively correlated with CRC	Anti-inflammatory effect on colitis by blocking NF-κB expression and secretion of IL-8	Anti-inflammatory effect	Sokol, Pigneur, Watterlot, & Lakhdari, 2008Chen et al., 2012
Ruminococcus gnavus	Antibacterial activity against pathogens (*C. perfringens* and *C. difficile*)	Antibacterial peptide (Ruminococcin A) production	Anti-pathogenic effect	Dabard, Bridonneau, Phillipe, & Anglade, 2001
Bifidobacterium spp	Reduced in CRC patients	Production of antibacterial peptides and competition for sites for cell adhesion	Prevention of CRC	Candela, Perna, Carnevali, & Vitali, 2008
Lactobacilli/bifidobacteria		Generating significant amounts of NO which is used in tumour therapy to make tumour cells more sensitive to anticancer drugs	Increased sensitivity of CRC cells to anticancer drugs	Sobko, Reinders, Jansson, & Norin, 2005Huang, Fu, & Zhang, 2017
Blautia hydrogenotrophica *Ruminococcus bromii* *Coprococcus* spp *Ruminococcus obeum* *Eubacterium* spp *Anaerostipes* spp *Veillonella* spp *Roseburia* spp *Eubacterium hallii* *Faecalibacterium prausnitzii*	Decreased amounts of butyrate producing bacteria in the stool of CRC patients	Production of butyrate and other SCFA which: - Downregulate pro-inflammatory cytokines (IL-6, IL-12) in colonic macrophages - Induce differentiation of Treg cells which have a crucial role in controlling intestinal inflammation - Induce apoptosis	Anti-inflammatory effect	Palombo, Ganguly, Bistrian, & Menard, 2002Scharlau, Borowicki, Habermann, Hofmann, & Klenow, 2009Wang, Cai, Qiu, & Fei, 2012Wu, Yang, Zhang, & Li, 2013Louis et al., 2014

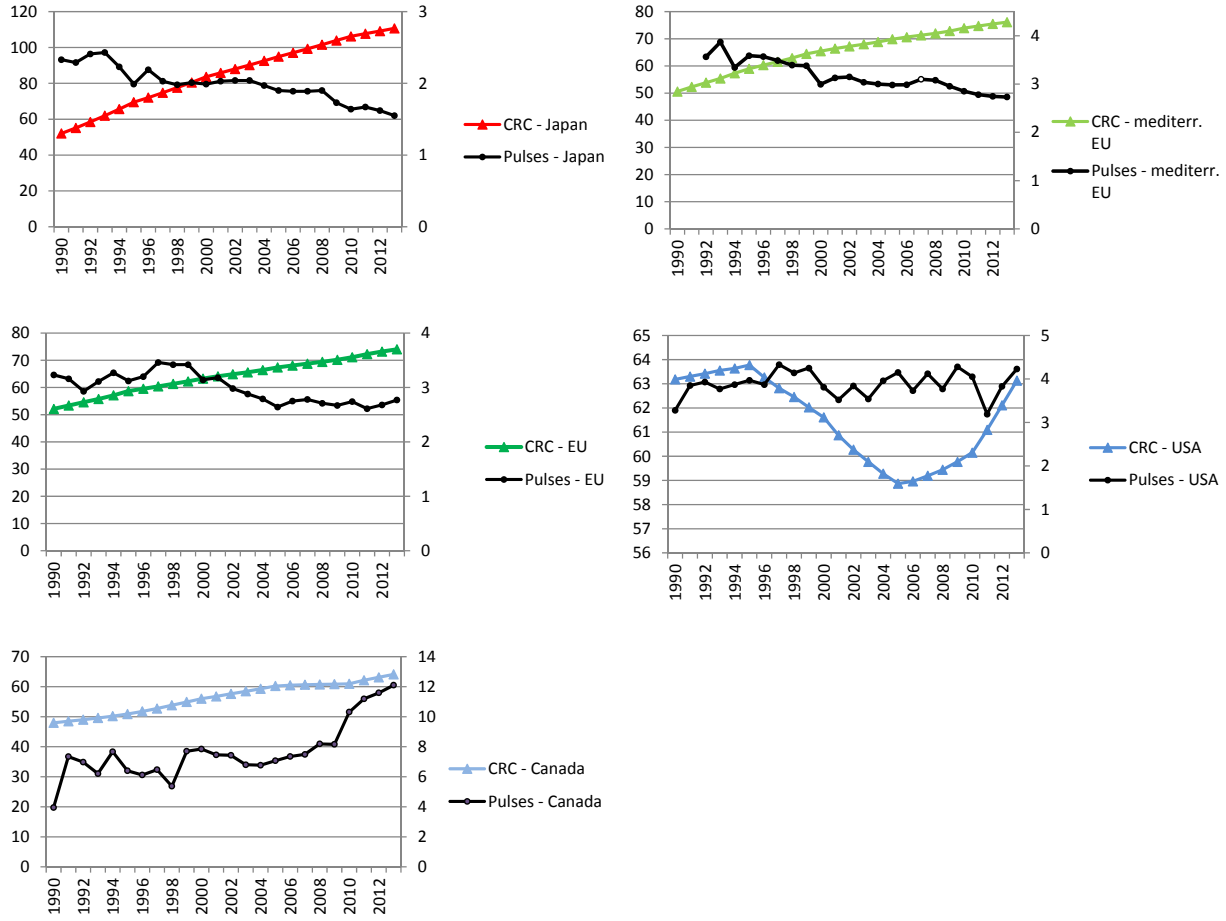

Fig. 2. CRC incidence *vs.* Pulses consumption. X axis: Year (1990–2013). Y axis (left): Incidence of CRC per 100,000 inhabitants. Y axis (right): consumption of pulses (kg/capita/year). A: European Union. B: Mediterranean countries of the EU (includes Croatia, Cyprus, France, Greece, Italy, Malta, Slovenia and Spain). C: United States of America. D: Canada. E: Japan. Sources: GHDx (GBD data), The World Bank (Population, total) and FAOSTAT.

composition. As already mentioned, dietary fibre is arguably the most studied food component regarding the relationship between IM composition and gastrointestinal inflammatory processes. Changes in dietary trends in industrialized societies revealing a decline in the amount of consumed fiber are also associated with the emerging increase of chronic non-transmissible diseases, such as obesity and associated metabolic diseases, IBD, CRC, and allergies, among others (Deehan, Duar, Armet, & Perez-Muñoz, 2017). However, it should be also mentioned that human studies of fiber and CRC are somewhat equivocal: fiber intake was not associated with CRC risk in 14 cohort studies, whereas in 9 other cohorts an inverse association was detected at least among some subgroups or for certain types of fiber (Song et al., 2015). In a recent dose-response meta-analysis, Oh et al. (2019) reported that although all fibre sources studied (cereals, vegetables, fruits, legumes) were inversely associated with incident adenoma, the evidence for CRC prevention is strongest for fibre from cereals and grains (between 2 and 16 g/d). For vegetable and fruit fibres, data suggested a non-linear relationship with CRC occurrence showing no further reduction in risk beyond 5–7 g/d intake of vegetable or fruit fibre. Similar results were also found by Aune et al. (2011). As for the protective effects of dietary fibre against CRC, several plausible mechanisms have been hypothesized: stimulation of intestinal peristalsis and reduction of transit time which leads to a decreased contact of enterocytes with harmful substances, particularly carcinogens; promotion of bacterial growth and SCFA production in the colon, which are known to have a number of beneficial effects (see below); modulation of faecal concentration, distribution and excretion of bile acids (putative risk factors for CRC), increased faecal bulk and lowered pH value (Fechner, Fenske, & Jahreis, 2013).

Non-starch polysaccharides (NSP) and resistant starch are the main components of dietary fibre. NSP behavior and activity within the GIT is consequence of the fact that human intestinal enzymes cannot degrade complex carbohydrates or polysaccharides of plants, these non-digestible carbohydrates (such as cellulose, xylan, pectin and inulin) are metabolized by the colonic microbiota to oligosaccharides and monosaccharides, and then fermented giving as final products SCFA (mainly acetate, propionate and butyrate), which are then absorbed in the colon. Non-digestible starch (known as resistant starch) mainly present in heat treated grains and tubers, is considered a significant part of the dietary fibre fraction. Resistant starch has been reported to increase SCFA production, as well as *Ruminococcus* spp (Ze, Ben David, Laverde-Gomez, & Dassa, 2015) and *Bifidobacterium* spp numbers among other bacterial groups (Portune, Benítez-Páez, Del Pulgar, Cerrudo, & Sanz, 2017), and therefore may be regarded as part of the preventive potential of dietary fibre.

Butyrate is known to be important as an energy source for cellular metabolism of the colonic enterocytes (Wong, de Souza, Kendall, Emam, & Jenkins, 2006). Acetate and propionate reach the liver and peripheral organs, where they are the substrate for gluconeogenesis and lipogenesis. In addition to being sources of energy, fatty acids modulate various processes in the GIT, such as absorption of electrolytes and water, and have multiple effects on cells involved in inflammatory and immune responses. Thus, SCFA modulate the production and release of chemokines and the expression of cell adhesion molecules, affect the migration of leukocytes, and induce apoptosis of lymphocytes, macrophages and neutrophils (Vinolo, Rodrigues, Nachbar, & Curi, 2011).

SCFA have been shown to affect the proliferation, differentiation and modulation of gene expression in colonic epithelial cells of mammals (Pool-Zobel, Selvaraju, Sauer, & Kautenburger, 2005). In particular, butyrate and other SCFA have been reported to possess anti-inflammatory properties with an attenuation in the production of the inflammatory cytokines TNF-α, IL-6 and IFN-γ (Arpaia & Rudensky, 2014; Goldsmith & Sartor, 2014). SCFA can directly enter the eukaryotic cells by diffusion, but they can also activate cells through cell-surface receptors like G-protein-coupled receptors (GPRs) such as GPR41 and GPR43. Several studies have demonstrated an anti-inflammatory role for the GPR43 receptor (Maslowski, Vieira, Ng, & Kranich, 2009; Sina, Gavrilova, Förster, & Till, 2009). Thus, the GPR43 binding of SCFA may provide an example on the molecular links between diet, gastrointestinal bacteria metabolism, and immune and inflammatory responses.

High fibre diets are also usually associated to diets high in other substances present in vegetable foodstuffs such as phytic acid. Myo-inositol hexaphosphate or phytic acid is composed of an inositol sugar, similar in structure to D-glucose, with six phosphate groups attached to each hydroxy branch, and is ubiquitous in plants, particularly in cereals and legumes (Shamsuddin, 1999). Phytic acid has been shown to possess anti-carcinogenic properties linked to a number of factors related with its recognized ion binding properties, which result in antioxidant and anti-proliferative activities (Steer & Gibson, 2002). However, phytic acid may induce other beneficial effects by modulating the IM activity and/or composition. Thus, it has been shown to improve the composition of cecal organic acids, microbiota, and mucins, and it may decrease the levels of serum pro-inflammatory cytokines in rats fed a high-fat, mineral-sufficient diet (Okazaki & Katayama, 2014).

Proteins. Among the variety of food components of different chemical nature, special attention should be paid to the role that one of the major dietary components, i.e. dietary proteins, may play on the IM activity and/or composition. In general, high protein, reduced carbohydrate diets alter the colonic microbiome, favoring a potentially pathogenic and pro-inflammatory microbiota profile, decreased SCFA production and increased ammonia, phenols and hydrogen sulphide concentrations. These factors may have clinical importance as novel therapeutic approaches to problems in which protein fermentation may be implicated, such as malodorous flatus, IBD and prevention of CRC (Portune et al., 2017; Yao, Muir, & Gibson, 2016). However, recent reports (Aranda-Olmedo, Ruiz, Peinado, & Rubio, 2017; Utrilla, Peinado, Ruiz, & Rodríguez-Nogales, 2015) link some legume protein fractions, IM composition and prevention of intestinal inflammation. Accordingly, we will focus here on some well-defined seed proteins such as Bowman-Birk protease inhibitors (BBI), lectins and the albumin fraction.

Bioactive compounds such as **BBI** are present in the albumin fraction of legumes, are not altered by gastric acid or proteolytic enzymes after their oral intake, and have been shown to reach the large intestine in significant amounts in an active form (Clemente, Jimenez, Marín-Manzano, & Rubio, 2008). Although traditionally regarded as anti-nutrients, a growing body of evidence indicates that dietary BBI may exert anti-inflammatory properties within the GIT when present in the appropriate amounts (Clemente, Sonnante, & Domoney, 2011; Clemente, Marín-Manzano, Jiménez, Arques, & Domoney, 2012; Clemente & Arques, 2014; Lichtenstein, Deren, Katz, & Lewis, 2008). Even more, protease inhibitors and BBI have been shown to be quite resistant to thermal treatment (Olías et al., 2019) including extrusion in some circumstances (Nikmaram et al., 2017). Therefore, even though pulses are usually not consumed raw, significant amounts of active BBI may remain in food after heat treatment and display a bioactive effect within the GIT (Clemente et al., 2008; Clemente & Arques, 2014). The anti-carcinogenic and anti-inflammatory properties of BBI have been associated with their intrinsic ability to inhibit several serine proteases involved in inflammatory processes, such as cathepsin G, elastase and mast cell chymase (Clemente & Arques, 2014). BBI has also shown a powerful inhibitory effect on the proliferation of two cancer cell lines (gastric adenocarcinoma and colorectal adenocarcinoma), and inhibited Matrix Metalloproteinases implicated in cancer progression (Fereidunian, Sadeghalvad, Oscoie, & Mostafaie, 2014). Pretreatment of dextran sodium sulfate (DSS) treated mice with a pea (*Pisum sativum*) seed protein extract (PSE) containing BBI ameliorated the colonic mRNA expression of different pro-inflammatory markers (cytokines, inducible enzymes, metalloproteinases, adhesion molecules, and TLRs), as well as proteins involved in maintaining the epithelial barrier function (Utrilla et al., 2015). The effects found could however not be ascribed solely to the BBI content in the PSE (Aranda-Olmedo et al., 2017).

Lectins are another group of proteins present in legume seeds that have been related with cancer. Lectins are proteinaceous compounds found in most plants, where they are implicated in plant defense (Lannoo & Van Damme, 2014), and present usually in the form of glycoproteins which have the ability to bind to certain carbohydrate molecules without altering the covalent structure (Pusztai, Ewen, Grant, & Peumans, 1990). For some time lectins have attracted the attention of food scientists and nutritionists because some of these proteins, such as soybean (*Glycine* max) and common bean (*Phaseolus vulgaris*) lectins, are toxic to animals, and their toxicity is linked to their capacity to bind to the intestinal mucosa (Pusztai, Grant, King, & Clarke, 1990). Both proliferative and anti-proliferative non-toxic lectins proposed in cancer therapy have been described (Pusztai, Bardocz, & Ewen, 2008). However, the effect of toxic lectins within the intestine has been shown to be partially linked to the modification by the lectin of the antigenic structure of the intestinal mucosa, which increases the capacity of *E. coli* to adhere to the intestinal wall through its own bacterial lectins, and grow. The involvement of mucosa-adherent bacterial lectin/adhesins in the pathogenesis of Crohn's disease and CRC has also been demonstrated (Martin, Campbell, Hart, & Mpofu, 2004). This would open the possibility to modify the intestinal mucosa by using specific lectins to be more or less receptive to certain types of bacteria. Thus, Pusztai, Grant, Spencer, and Duguid (1993) showed that a non-toxic lectin (*Galantus nivalis* lectin) was able to prevent the *E. coli* overgrowth found in rats fed *Phaseolus vulgaris* lectin, most likely due to the blockage, by the *G. nivalis* lectin, of the anchoring sites of *E. coli* in the digestive mucosa. More importantly, *G. nivalis* lectin given orally significantly reduced the numbers of *Salmonella typhimurium* S986 in the lower part of the small and large intestines of rats infected with this pathogen and as a result also significantly improved rat growth (Naughton, Grant, Bardocz, & Pusztai, 2000). The joint study of intestinal structure, microbial ecology and *in vivo* activity of lectins may therefore open new interesting possibilities for the manipulation of the digestive microbiota, with potentially relevant health implications (Pusztai et al., 2008). Unlike BBI (see above), lectins have been reported not to resist cooking under usual conditions (90–100 °C, 5 min) (He et al., 2017). Therefore, their potential interest is not linked to consumption in normal eating behavior, but as functional tools to modulate intestinal mucosa architecture and/or microbiota composition.

Albumins plus fibre extract. In the present context, the adscription of shifts in microbiota composition and/or inflammation with one or more defined seed chemical components would represent a significant step forward. Although *in vitro* studies are abundant, not much information is found in the literature on *in vivo* studies involving isolated or purified fibre fractions separated from other chemical components in feed- or foodstuffs. Interestingly, blue lupin (*Lupinus angustifolius*) kernel fibre improved colonic function and had beneficial effects on putative risk factors for CRC such as faecal mass, transit time, SCFA, faecal pH, and secondary bile acids concentrations in humans (Nieuwdorp, Gilijamse, Pai, & Kaplan, 2014), and lowered *E. coli* counts in rats (Rubio, Grant, Spencer, & Pusztai, 1995; Stern et al., 1984). Accordingly, we decided to use a purified protein extract such as PSE in our DSS mouse model. Unfortunately, with the information we have at

present, it is not possible to establish the mode of action of the PSE because the extract consisted of a soluble albumin extract containing 411.4 mg protein/g freeze-dried material, the remaining consisting of soluble NSP (Rubio, Pérez, Ruiz, & Guzmán, 2014; Utrilla et al., 2015). As explained above, the albumin protein component, and particularly BBI, might have and anti-inflammatory effect. But, on the other hand, NSP fractions are known to be metabolized almost exclusively by the IM giving place to SCFA (Flint, Scott, Duncan, Louis, & Forano, 2012). Therefore, we suggested a combined effect of the protein fraction on the inflammatory process itself with an effect on the microbiota probably due mainly to the NSP fraction through SCFA production (Candela et al., 2012; De Filippo et al., 2010).

PSE effects *in vivo* were studied in a DSS model of colitis (Aranda-Olmedo et al., 2017; Utrilla et al., 2015). DSS treated animals are commonly used as models for studying IBD (Valatas, Vakas, & Kolios, 2013) as changes in DSS treated rats are similar to those found in humans in the composition of the mucosa-associated and fecal microbiota of patients with Crohn's disease, ulcerative colitis, and pouchitis, i. e. higher total counts of *Escherichia/Shigella* and *Enterobacteriaceae* together with reductions in *Lactobacillus* spp, *Ruminococcus* spp, *Bacteroides* spp and *Bifidobacteria* (Dicksved, Schreiber, Willing, & Petersson, 2012; Lupp, Robertson, Wickham, Sekirov, & Champion, 2007; Verma, Verma, Kumari, Ranjha, & Paul, 2014). Most studies demonstrate a decreased microbial diversity in active IBD, increased numbers of *Enterobacteriaceae*, including *E. coli*, and decreased Firmicutes, with selectively decreased *Clostridium* spp and *F. prausnitzii*. There are reports of increased levels of the Bacteroidetes phylum members, although reductions in Bacteroidetes have also been reported (Marchesi, Adams, Fava, & Hermes, 2016; Sartor, 2008). A quite comprehensive study by Frank, St Amand, Feldman, and Boedeker (2007) showed decreased numbers of the phyla Firmicutes and Bacteroidetes with concomitant increases in Proteobacteria and Actinobacteria in IBD. Given the problems associated with the different technical procedures used for microbial analysis, the high inter-individual variation in IM composition, the usage of different animal models, etc., it is not surprising that conflicting results are found in the literature on this particular issue. Anyway, oral pre-treatment with PSE in DSS treated mice gave place to a recovery of bacterial counts, partially or totally, to values in healthy control mice in both colonic contents and tissue. Pyrosequencing analysis of the microbiota composition at the tissue level in the colon confirmed the results obtained with real-time qPCR for both *Lactobacillaceae* family and *Lactobacillus* spp proportions, which dropped in DSS mice but were not different from controls in PSE pretreated animals (Aranda-Olmedo et al., 2017).

Quite interestingly, Monk, Zhang, Wu, and Zarepoor (2015, Monk, Lepp, Zhang, and Wu (2016)) recently found both an increase in *Prevotellaceae* and enhanced multiple concurrent gut health promoting parameters that translated into reduced colitis severity in mice fed diets supplemented with various raw *Phaseolus vulgaris* bean varieties in a DSS model. Polyphenols were excluded, but the effect could not be linked to any defined chemical fraction because only whole seed meals were used in that study. Increased mRNA expression of antimicrobial and barrier integrity promoting genes, and reduced proinflammatory mediator expression genes, were also determined. In addition, bean diets exerted a systemic anti-inflammatory effect during colitis by reducing serum levels of IL-17A, IFNγ, TNFα, IL-1β and IL-6. Similar results have been found with cooked *Ph. vulgaris* seed varieties (Zhang, Monk, Lu, & Zarepoor, 2014)]. Therefore, a relationship between legume consumption, microbiota modulation and lower inflammatory markers is becoming increasingly evident.

6. Conclusions and prospects

CRC represents the second-third most common cancer in the western world. Although in most cases there is no single factor which determines the development of CRC, the IM is likely to have a direct and/or indirect action on both development and treatment of CRC and other chronic diseases. Accordingly, understanding the role of the diversity and function of the IM in health and disease has become crucial to design specific strategies to promote health, and to prevent and treat diseases. The highest incidence/prevalence of CRC appears to depend upon dietary factors, and although the Mediterranean countries have at present a lower average incidence/prevalence (Fig. 1C & D), it is clearly increasing, most likely due in part to the progressive rejection of the Mediterranean diet, of which legumes have traditionally represented a significant part. Although it has dropped over the last decades, legume consumption has been associated with lower risk for suffering a number of chronic diseases including CRC, and recent reports link legume protein fractions, IM composition and prevention of intestinal inflammation, a process commonly associated with cancer. In fact, a relationship between legume consumption, microbiota modulation and lower inflammatory markers is becoming increasingly evident. Also, experimental evidence indicates that some dietary components such as legumes may have either a direct DNA methylation effect and/or an indirect effect through IM modulation. In this context, the study of immune receptors expression or activity is becoming increasingly relevant. TLRs are receptors of the immune system, whose regulation is linked to the IM composition. As the latter is largely influenced by diet composition, TLRs activity, and consequently immunity/inflammation, may be modulated by appropriate dietary interventions. Therefore, acording to the information currently available, there is the potential to improve cancer treatment or prevention through well designed dietary manipulations of the IM. However, the study of CRC-associated IM should probably focus mainly on the mucosa-associated microbiota, as the intestinal mucosa and stool are inhabited by distinctive microbial communities, as also are tumor and normal mucosal samples. Samples recovered from biopsies (v. g. rectal biopsies) may offer a closer insight into host–microbes interactions that drive the pathophysiology of CRC.

Finally, in order to go ahead in the mechanistic approach, although a substantial amount of information can be found in the literature on the effects of different dietary approaches (high *vs* low fibre or carbohydrate diets, high *vs* low fat diets, high *vs* low protein diets, etc.), we are still lacking specific information on the effects of well-defined chemical fractions or components in the very complex GIT environment. The main reason to pay more attention to this approach is that the issue of the relationship between dietary components and CRC risk is very complex and multifactorial, and no single risk factor accounts for most cases of CRC. In this context, the adscription of shifts in microbiota composition and/or inflammation with one or more defined seed chemical components would represent a significant step forward. In this, fundamental research with animal models would represent a good opportunity to study defined chemical components and to disclose the mechanisms of pathogenesis, which would ease the devise of new molecules or dietary manipulations. Last but not least, these dietary manipulations may also have a strong impact on health expenditure by reducing the economic cost of diagnosis and treatment of CRC.

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Declaration of Competing Interest

The authors have declared no conflict of interest.

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