Advances and challenges in cancer treatment and nutraceutical prevention: the possible role of dietary phenols in BRCA regulation

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Abstract Over the years, the attention towards the role of phytochemicals in dietary natural products in reducing the risk of developing cancer is rising. Cancer is the second primary cause of mortality worldwide. The current therapeutic options for cancer treatment are surgical excision, immunotherapy, chemotherapy, and radiotherapy. Unfortunately, in case of metastases or chemoresistance, the treatment options become very limited. Despite the advances in medical and pharmaceutical sciences, the impact of available treatments on survival is not satisfactory. Recently, natural products are a great deal of interest as potential anti-cancer agents. Among them, phenolic compounds have gained a great deal of interest, thanks to their anti-cancer activity. The present review focuses on the suppression of cancer by targeting BRCA gene expression using dietary polyphenols, as well as the clinical aspects of polyphenolic agents in cancer therapy. They regulate specific key processes involved in cancer progression and modulate the expression of oncogenic proteins, like p27, p21, and p53, which may lead to apoptosis, cell cycle arrest, inhibition of cell proliferation, and, consequently, cancer suppression. Thus, one of the mechanisms underlying the anti-cancer activity of phenolics involves the regulation of tumor suppressor genes. Among them, the BRCA genes, with the two forms (BRCA-1 and BRCA-2), play a pivotal role in cancer protection and prevention. BRCA germline mutations are associated with an increased risk of developing several types of cancers, including ovarian, breast, and prostate cancers. BRCA genes also play a key role in

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the sensitivity and response of cancer cells to specific pharmacological treatments. As the importance of BRCA-1 and BRCA-2 in reducing cancer invasiveness, repairing DNA damages, oncosoppression, and cell cycle checkpoint, their regulation by natural molecules has been examined.

**Keywords** Polyphenols · Cancer · BRCA · Tumor suppressor genes · Clinical aspects

**Abbreviations**
- Akt: Protein kinase B
- Bax: Bcl-2 associated protein
- Bak: Bcl-2 homologous antagonist killer
- Bcl-2: B-cell lymphoma 2
- BRCA-1: Breast cancer type 1 susceptibility protein
- BRCA-2: Breast cancer type 2 susceptibility protein
- COX: Cyclooxygenase
- DSB: Double strand break
- EMT: Epithelial-mesenchymal transition
- ER: Estrogen receptor
- EREs: Estrogen-responsive elements
- HIF-1α: Hypoxia inducible factor
- IC_{50}: Half minimal inhibitory concentration
- IGF-1: Insulin like growth factor-1
- MAPK: Mitogen-activated protein kinase
- MMP: Matrix metallo proteinases
- mTOR: Mammalian target of rapamycin
- NF-kB: Nuclear factor kappa-light-chain enhancer of activated B cells
- PARP: Poly ADP-ribose polymerase
- PI3K: Phosphatidylinositol 3-kinases
- SIRT1: Sirtuin 1
- VEGF: Vascular endothelial growth factor

**Introduction**

According to recent statistics published by the World Health Organization (WHO), cancer is the second primary cause of mortality worldwide, accounting for around 9.6 million deaths in 2018 (Kim et al. 2019b). The most common cancers are lung, breast, colorectal, prostate, skin, and stomach cancers. Lung cancer currently possesses the highest mortality rate (18.4% of the total cancer deaths), followed by colorectal, stomach, hepatic and female breast cancers (WHO 2019). In addition, 18.7 million new cases have been reported as per statistics compiled by International Agency for Cancer Research (IARC) for the year 2018 (Bray et al. 2018). The sophisticated healthcare and expensive medical treatments make cancer a significant financial burden to the affected families and society (Singh et al. 2015). The WHO estimated the total economic cost of cancer in the year 2010 at approximately 1.16 trillion USD (WHO 2019) and the direct financial cost for cancer in the United States (US) estimated by the Agency for Healthcare Research and Quality (AHRQ) for the year 2015 was around 80.2 billion USD (ACS 2019). The current therapeutic options for the treatment of cancer are surgical excision, immunotherapy, chemotherapy, and radiotherapy. Unfortunately, in the case of metastases, the treatment options become very limited (Kim et al. 2019a). In spite of the advances in the field of medical and pharmaceutical sciences, the impact of available treatments on survival is not satisfactory. On the other hand, data regarding individualized treatment approaches for cancer patients with available therapies is minimal (Crawford et al. 2015). Poor accessibility of anti-cancer agents have been associated with chemotherapy failure and the consequent requirement for high doses of chemotherapeutics, which can cause a range of debilitating side effects, including nausea, vomiting, alopecia, gastrointestinal effects, myelosuppression, immune-suppression, and neurotoxicities (Jang et al. 2003; Khan et al. 2019).

Edible plants contain a number of phytochemicals with the potential for preventing and treating a wide range of disorders, including cancer (Lamorte et al. 2018). The role of polyphenols in reducing cancer is still under discussion. A significant gap occurs between observations in cellular models and the effects of phytochemicals in pre-clinical and clinical models. Natural polyphenols are widely studied for their great potential to prevent and treat cancer of different origins by targeting several molecular pathways (Zhou et al. 2016b). More than 8000 polyphenols, commonly found in vegetables, fruits, cereals, and beverages, have been identified, to date, based on the chemical structures (Lall et al. 2015). Polyphenols are associated with many health benefits, including antioxidant, anti-inflammatory, anti-angiogenic, and anti-proliferative effects (Abdal Dayem et al. 2016). Polyphenols have been reported to arrest the
development and progression of cancer in some cellular lines, by modulating several signaling pathways, such as nuclear factor-KB (NF-KB) signaling, mitogen activated protein kinases (MAPKs), insulin like growth factor-I (IGF-1) mediated signal transduction pathway, proteasome pathway, vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP), cyclooxygenase-2 (COX), and breast cancer genes (BRCA) (Khan et al. 2006; Papoutsis et al. 2010; Rowe et al. 2009). BRCA can exist in two forms (BRCA-1 and BRCA-2) and are known as tumor suppressor genes. BRCA germline mutations increase the risk of developing several cancers, including ovarian, breast, and prostate cancers (Fong et al. 2009). BRCA also plays a key role in sensitivity and response of cancer cells to certain treatments such as platinum and pharmacological inhibitors of poly ADP-ribose polymerase (PARP inhibitors) (Fong et al. 2010). Therapeutic modalities in BRCA mutant carriers are very limited. Surgical treatment has often shown higher survival benefits and less risk with respect to conventional therapies (chemotherapy or radiotherapy) (Ludwig et al. 2016). The current review is designed to focus on the potential of natural polyphenols to modulate BRCA expressions and their outcomes on cancer treatment and prevention.

BRCA in cancers

BRCA-1 and BRCA-2 proteins play a pivotal role in maintaining genomic stability by enhancing efficient and precise repairing mechanisms of double-strand breaks (DSB) of DNA (Gudmundsdottir and Ashworth 2006). Homologous recombination and non-homologous end joining are the major mechanisms involved in DSB repair (Huertas 2010; Scully et al. 2019). Each 1 and 2 isoforms of the BRCA protein performs several specific homologous recombination repairs. They are associated with a broad range of proteins implicated in the response and repair of DNA damage. It is believed that BRCA-1, being part of a bulky and complex molecule, helps to check DNA double-strand breaks, while BRCA-2 has an important role in the repair of DSBs by involving the recombinase function of RAD51 (Gudmundsdottir and Ashworth 2006; Von Nicolai et al. 2016). So, in a broad framework of repairing mechanisms, both genes act as key components. Therefore, errors or mutations in BRCA genes are associated with a less efficient repair system, leading to an increased risk of developing many types of cancer. In particular, BRCA-1 and BRCA-2 are crucial in the regulation of repairing processes in breast cells. Indeed epigenetic silencing of these genes often occurs in cancer development (Papoutsis et al. 2010). Thus, they could be defined as “breast cancer susceptibility genes,” and inheriting a defective copy of either gene increases an individual’s susceptibility to developing breast, ovarian and other types of cancer. Although the role of BRCA in the pathogenesis of cancer is still unclear, significant variations of their expression levels could be detected in cancer cells (Fustier et al. 2003). Being breast and ovarian cancers associated with genetic predisposition, providing a detailed family history may be helpful to healthcare providers in recognizing women at increased risk (Pruthi et al. 2010). These women are more prone to developing second ipsilateral or contralateral breast cancer after diagnosing invasive breast cancer. Also, there is a substantially increased risk of developing ovarian cancer for women with an inherited mutation in either gene (Kotsopoulos 2018; Metcalfe et al. 2011a, b). In the most recent prospective studies, the combined risk of epithelial ovarian cancer up to age 80 was 49% for BRCA-1 and 21% for BRCA-2 mutation carriers. These risk estimates are consistent with another report that estimated a cumulative ovarian cancer incidence of 44% for BRCA-1 and 17% for carriers of BRCA-2 mutations (Kotsopoulos 2018; Kuchenbaecker et al. 2017). About 15% of all patients with serious ovarian carcinoma have a germline BRCA mutation (Alhuqail et al. 2018). In general, the lifetime risk of developing ovarian cancer is 2% for females born after 1960 in the United Kingdom (UK) as approximated by Cancer Research UK (Cancer-Research-UK), while breast cancer accounts for 15% of all new cancer cases in the UK (Cancer-Research-UK). As regards prostate cancer, it is the most common cancer reported in US men. It is thought to have the highest heritability of any cancer, as confirmed by Scandinavian research suggesting that genetic factors are responsible for up to 57% of individual risk variation (Hjelmborg et al. 2014), whereas Cancer Research UK reported that 1 in 6 UK males is at lifetime risk for the development of prostate cancer (Cancer-Research-UK). Although some studies have reported that mutations in BRCA-2 are found in just 1.2–3.2% of prostate cancer patients.
and BRCA-1 mutations in even lower percentages (Giusti et al. 2003), different studies reported that mutations in BRCA are responsible for the increment of prostate cancer rate. In particular, BRCA-2 have been associated with a 3- to 8.6-fold increase in risk, approximately, while BRCA-1 mutations increase prostate cancer risk by up to fourfold (Pilarski 2019). Prostate cancers associated with BRCA-1/2 mutations have been reported to be more aggressive and linked to poorer survival than wild-type BRCA cancers. A study identified 79 prostate cancer patients who carried the BRCA-1/2 mutations and presented impairment in clinical parameters related to cancer progression, as well as a higher Gleason score (approximately 8), higher T stage (T3/T4), nodal involvement, and metastases (Kote-Jarai et al. 2011; Mitra et al. 2011). Therefore, BRCA-1 and BRCA-2 mutations raise the risk of prostate cancer and contribute to the prevalence of this cancer not only in high-risk families, but also in the general population, in addition to other cancers. Among them, also the development of pancreatic cancer is strictly dependent of BRCA-1/2 gene mutations. Pancreatic cancer statistics shows that 1 in 53 UK males and 1 in 57 UK females will be diagnosed with pancreatic cancer in their lifetime (Cancer-Research-UK). From 3 to 10% of people with pancreatic adenocarcinoma have a positive family history of pancreatic cancer, and about 10–20% of pancreatic adenocarcinoma are believed to be due to a hereditary BRCA-1 and BRCA-2 mutation (Petersen 2016). The cumulative chances of developing pancreatic cancer are estimated at 5–10% for BRCA-2 mutation carriers, while mutations in BRCA-1 gene contribute to increase the cancer risk by 2–4 times (Salo-Mullen et al. 2015).

Regarding colorectal cancer, the risk conferred by germ line mutations in these two genes is controversial. A longitudinal study on the incidence of colorectal cancer was performed in a cohort study of BRCA-1/2 mutation carriers. Results revealed that in females under 50 carrying BRCA-1 mutations, the risk of colorectal cancer is elevated, but not in older women or those carrying BRCA-2 mutations (Phelan et al. 2014). Moreover, a BRCA-related skin cancer study showed that skin cancer risk was correlated with the likelihood of BRCA-1 and BRCA-2 mutations. In the follow-up, of all 1779 women with a BRCA-1 mutation, 29 (1.6%) developed skin cancer, while out of 950 BRCA-2 mutated women, 28 (3.0%) developed skin cancer (Ginsburg et al. 2010), suggesting that BRCA-2 mutation carriers are at greater risk of developing skin cancer than BRCA-1 carriers, particularly for basal cell carcinoma.

**Polyphenols in cancer: an overview**

Understanding the positive impact of phytochemicals in natural dietary products on the risk of developing cancer still remains an open issue. The major limitations in filling the gap in this context come from the lack of a strong body of knowledge about the pharmacokinetic properties of phenolic compounds in humans. The bioavailability, together with the metabolic reactions, influences the bioactivity of food-derived metabolites. Significant progress needs to be made to clarify the mechanisms of polyphenols in preclinical and clinical models at appropriate and realistic doses. It seems to be realizable due to the numerous in vitro evidence that shed light on the molecular behaviour of phenolic compounds and the involved pathway. Phenolic acids, deriving from benzoic acid, i.e. gallic, vanillic, syringic, and protocatechuic acids, among others, are typically found in nature and have gained a great deal of interest due to the stronger pharmacological properties (Ho et al. 2013). In vitro, indeed, hydroxybenzoic acid and protocatechuic acid exhibited cytotoxic effects towards prostate and breast cancer cells, in a dose-dependent manner (Kassi et al. 2014), while gallic acid displayed inhibitory potential towards HeLa and HTB-35 cervical carcinoma cells, without toxicity on normal cells (Zhao and Hu 2013). As one of the hallmarks of cancer is abnormal cell proliferation, phenolic compounds, extracted from plant sources, may prevent cancer cell proliferation (Pandey and Rizvi 2009) and, thus, reduce cancer invasiveness through multiple mechanisms, including apoptosis (Khan et al. 2020b), cell cycle arrest (De Oliveira Niero and Machado-Santelli 2013; Guo et al. 2011), reduction of metalloproteinases, angiogenesis, and cell migration (Zhao and Hu 2013).

**Apoptosis**

Apoptosis is a well-defined system of programmed cell death that underlies the anti-cancer activity of many phenolic compounds (Armentano et al. 2015; Russo et al. 2018). By increasing the rate of apoptosis
in cancer cells, natural substances may delay cancer progression. Among polyphenols, phenolic acids have been shown to induce apoptosis: colon cancer cells, treated with p-coumaric acid, experienced apoptosis (Sharma et al. 2018). Their activity should be attributed to the activation of apoptotic pathways. The most important are the extrinsic (death receptor pathway), intrinsic (mitochondrial pathway), and the perforin/granzyme apoptotic pathways (Khan et al. 2020). Whereas the binding of Fas ligand to its proteins activates the extrinsic pathway, the oxidative stress mediates the release of cytochrome-C inside the cells from disrupted mitochondria and triggers the intrinsic pathway (Kim and Kim 2018; Pirzad et al. 2010). The expression of death ligands and receptors is maximized by phenolic compounds through the extrinsic pathway, activating caspases series and intrinsic pathway. The activation of caspases results in DNA damage, cell proliferation inhibition, and apoptosis induction in breast cancers. In this regard, a previous study documented the activation of caspase-9 when HT-44 cells were processed with cinnamic acid. In turn, this activation leads to potentiate other caspases, including caspases-7 and 3 (De Oliveira Niero and Machado-Santelli 2013). Moreover, caspase activation seems also be implied in the increment of the balance between Bak/Bax (proapoptotic proteins) and Bcl-2 (survival proteins) mediated by polyphenols (Mileo et al. 2012). A separate related study in osteosarcoma cells, indeed, showed that ferulic acid may modulate the balance between oncogenes and oncosuppressor by up-regulating Bax and down regulating Bcl-2 to induce apoptosis. Likewise, ferulic acid enhanced the expression of Bax, caspase-3 and 9 in cells of fibrosarcoma (Wang et al. 2016). When breast cancer cells were exposed to 1-(2-hydroxyphenyl)-4-methylpentan-1-one and 2-[3-methylbutoxy) carbonyl] benzoic acid, two polyphenolic compounds isolated from Himalayan raspberry root extract, elevated levels of caspase-3 and Bax expression were also observed (George and Abrahamse 2019). Protocatechuic acid also increased the levels of caspase-3 and dose-dependently decreased the membrane potential in prostate, hepatic, lung, breast, and cervical cancer cell lines. Likewise, in human HT-1080 fibrosarcoma cell lines, a rise in the caffeic acid concentration corresponded to a proportional boost to apoptosis, with significant changes in the morphology of cells (Jaganathan et al. 2013; Prasad et al. 2011; Yin et al. 2009). An overview of the main processes engaged in apoptosis under phenolic boost is provided in Fig. 1. Importantly, studies have indicated that polyphenols possess no cytotoxic effects and do not induce apoptosis in normal cells, when compared to breast cancer cell lines (Mileo et al. 2012).

Estrogenic mechanisms

Phytoestrogens are nonsteroidal plant compounds (plant-derived xenoestrogens) that because of structural resemblance with estradiol possess the ability to cause estrogenic or antiestrogenic effects (Cornwell et al. 2004). They may alter many biological processes, like DNA mutagenesis, apoptosis, cell proliferation, tissue vascularization, and immune response, via estrogen-dependent and -independent mechanisms (Sirotkin and Harrath 2014). Polyphenols, especially phytoestrogens, have shown to be able to inhibit NF-κB and MAPK pathway activation (Miao et al. 2019), which in turn activates the PI3K/Akt/mTOR pathway (Ahmad et al. 2013). This ultimately leads to the synthesis of HIF-1α that causes MMPs and VEGFs target gene induction in the nucleus. However, efficacy varies between compounds due to differences in their chemical structures and molecular targets, as discussed later.

Cell cycle arrest

Between phenolic acids, hydroxycinnamic acids have shown great anti-cancer properties. Cinnamic acid, indeed, dose-dependently decreased the viability of the HT-44 melanoma cell lines, with an IC₅₀ value of 2.4 mM. One of the proposed mechanisms to explain the cytotoxicity of these compounds is the cell cycle arrest, as occurs in MDA-MB-231 and MCF-7 breast cancer cells, treated with benzoic acid, where the cell cycle arrest is induced at the G2 or M level (De Oliveira Niero and Machado-Santelli 2013; Guo et al. 2011). Likewise, the effectiveness of phenolic compounds in retarding cancer cell proliferation has also been shown in other studies. For example, at an optimal concentration of 1400 μmol/L and 1600 μmol/L respectively, p-coumaric acid reduced the viability of HCT-15 and HT-29 colorectal cells (Jaganathan et al. 2013). Similarly, p-coumaric acid and ferulic acid were shown to suppress the MIA-Pa-Ca-22
pancreatic cancer cell line (Fahrioglu et al. 2016). Likewise, caffeic and 5-caffeoylquinic acids reduced the cell lines viability of HT-29 colorectal carcinoma and HT-1080 fibrosarcoma cells by modifying the cell cycle stage and increasing the apoptotic rate (Murad et al. 2015; Prasad et al. 2011).
Cell migration and invasion

Migration and invasion of tumor cells are tactics formed and implemented by cancer cells to proliferate in other districts and avoid drug therapy (Clark and Vignjevic 2015). The PI3K/Akt/mTOR signaling pathway plays a key role in cancer invasiveness due to its involvement in cell growth and the metabolism of cancer cells. The activation of NF-κB downstream signaling cascade leads to the final synthesis of HIF-1α. Once entered into the nucleus, it causes MMPs and VEGFs gene induction, enhancing angiogenesis and metastases (Ahmad et al. 2013). This may explain why finding natural molecules that can target this pathway could reveal as an alternative therapeutic option for fighting cancer. Many biologically active phenolic compounds extracted from plants are known to interrupt cell migration by interfering with epithelial-mesenchymal transition, cell invasion, and efflux. For example, in breast cancer cell lines, ferulic acid reduced metastasis by reversing the epithelial-mesenchymal transition (Zhang et al. 2016). By blocking the voltage-gated sodium channels, caffeic acid phenyl esters stopped the proliferation of non-small cell lung, colon, and breast cancer cell lines (Fraser et al. 2016), while gallic acid inhibited metastasis in gastric cancer cells via downregulating PI3K/Akt pathway (Mao et al. 2020). The whole scheme of the multiple mechanisms at the basis of phenolic anticancer activity is shown in Fig. 2.

Polyphenols targeting BRCA in cancer

Phytoestrogens are natural bioactive compounds that exert anti-cancer, antiproliferative, and chemopreventive effects through different mechanisms. Many of them are flavonoids, but also coumestans, and resorcylic acid lactones display estrogenic properties (Gehm et al. 1997). As the importance of BRCA-1 and BRCA-2 in reducing cancer invasiveness, repairing DNA damages, oncosuppression, and cell cycle checkpoint (Nabavi et al. 2018), their regulation by natural molecules has been recently examined (Rowe et al. 2009).

Genetic and epigenetic regulation on BRCA genes by polyphenols

Epigenetic modifications are the major mechanisms for modulating gene expression. Demethylation and acetylation of histones by phytochemicals allow chromatin to be unpacked, enhancing the transcription of genes involved in cancer. Flavanols intrude on the transmethylation pathway, limiting the availability of S-adenosylmethionine, leading to changes in DNA methylation (Khan et al. 2020a; Vanden Berghe 2012). Consistently with reported evidence, a possible approach to tumor chemoprevention is to reverse unfavorable epigenetic marks by natural dietary polyphenols. A great source of polyphenols is constituted by pomegranate. Extracts from peel, seeds, and juice of pomegranate might inhibit cancer cell growth, inducing G2/M cell cycle arrest and apoptosis, and prevent tumorigenesis in a dose- and time-dependent manner. Molecular mechanisms which underlie these properties involved the DNA repairing pathway, including BRCA-1 and BRCA-2 downregulation in MCF-7 cancer cells (Shirode et al. 2013).

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring phytoalexin, widely detectable among berries, grapes, and peanuts, which is produced in response to various biotic and abiotic stresses. It can bind the estrogen receptors (ERs) and regulates the transcription of estrogen-responsive target genes, as well as BRCA-1 and BRCA-2, in two ways: by direct bonding to the estrogen-responsive element (EREs) on DNA or by interaction with transcription factors.
Fustier et al. 2003). It could be due to the structure-similarity to endogenous ligand, the estradiol, since both molecules have a phenolic ring and two hydroxyls (Gehm et al. 1997; Vissac-Sabatier et al. 2003), as shown in Fig. 3. Interestingly, even if resveratrol binds ERα and ERβ with the same affinity, it can induce transcription better than endogenous ligand in ERβ, indicating that it may exert a stronger oestrogenic activity in ERβ expressing cells respect ERα (Bowers et al. 2000). In human breast cancer cells, resveratrol (3–10 μM) competes for estrogen receptors binding, showing inhibitory activity towards the binding of estradiol to its estrogen receptor, while activating the transcription of estrogen-responsive genes (Gehm et al. 1997). The increased transcription of pS2 gene, a marker of estrogen receptor pathway activation, confirms the phytoestrogenic activity of resveratrol (Le Corre et al. 2004). In some cancer lines (i.e. MCF-7 cells), resveratrol behaves as a superagonist, with a higher transcriptional response than estradiol, while in others, it has an estradiol-comparable activity. It may depend on the type of ER and the ERE sequence involved (Gehm et al. 1997). The treatment with resveratrol (30 μm) on MCF7, HBL100, and MDA-MB-231 human breast cancer cell lines results in an increment from two- to four-fold of BRCA-1 and BRCA-2 mRNA. Inconsistently, no increments were detected at protein level, implying the occurrence of unknown post-transcriptional events (Fustier et al. 2003). Resveratrol doses of 30–50 μM increase not only BRCA-1 and BRCA-2 expression, but also a panel of genes that regulate and interplay with BRCA-1 in human breast cell lines, as well as p53, RAD51, p21<sup>waf1/cip1</sup>, CBP/P300, Ki67, and pS2 (Le

**Fig. 2** Phenolic anticancer activity via multiple pathways modulation. Phenolic compounds regulate certain key processes associated with the progression of cancer. They may modulate the expression of genes involved in cell proliferation, apoptosis and cell cycle arrest. AKT protein kinase B; Bcl-2 B-cell lymphoma-2; CA caffeic acid; CAA cellular antioxidants activities; CAOE caffeoylquinic esters; CAPE Caffeic acid phenethyl ester; ERK extracellular signal regulated kinases; FA ferulic acid; FGF-1 fibroblast growth factor-1; MMP2 matrix metalloproteinase-2; MMP9 matrix metalloproteinase-9; NF-κB Nuclear Factor kappa-light-chain-enhancer of activated B cells; PDGF platelet derived growth factor; ROS reactive oxygen species; STAT3 signal transducer and activator of transcription-3; VEGF vascular endothelial factor
Resveratrol treatment is a potential strategy to possibly reduce BRCA-1 mutant tumor growth both in vitro and in vivo, by up-regulating its downstream mediator SIRT-1, which leads to survivin underexpression. As SIRT-1 possesses an important role in the DNA damage repairings process, and survivin is an anti-apoptotic protein and is often over-expressed in several tumors, it is believed that the proapoptotic activity of resveratrol is expounded through the SIRT-1 modulation (Wang et al. 2008). Finally, although the resveratrol bioavailability is influenced by different factors, as well as a rapid and extensive intestinal and hepatic metabolism that reduces it to less than 1% (Sergides et al. 2016), this phytoalexin may be seen as a conditioner of BRCA-related breast cancer. In general, polyphenol fraction in wine, including resveratrol, has shown BRCA modulating properties (Hakimuddin et al. 2008). Additional regulatory effects of resveratrol work via the antagonism on the aromatic hydrocarbon receptor, which activation is led to higher proneness to mammary and intestinal cancer development (Papoutsis et al. 2010). As this pathway is involved in xenobiotic metabolism and detoxification processes, it is activated by different environmental toxins, as well as dioxins, promoting the expression of oncogenes and proinflammatory cytokines and the repression of oncosuppressors through epigenetic modifications. Activated aromatic hydrocarbon receptor is recruited to the BRCA-1 promoter where inhibits estradiol-mediated BRCA-1 transcription. Furthermore, resveratrol pretreatment (1 μmol/L) also attenuates the suppression of BRCA-1 gene expression, caused by dioxins exposure, by reversing BRCA-1 hypermethylation (Papoutsis et al. 2012). In MCF-7 breast cancer cells, resveratrol not only decreases the binding of aromatic hydrocarbon receptor on BRCA-1 promoter by 60%, but also promotes estrogen-dependent BRCA-1 expression through the agonism on estrogen receptors (Papoutsis et al. 2010). Resveratrol competitively displaces dioxins from binding site, acting as antagonist towards aromatic hydrocarbon receptor (Macpherson and Matthews 2010).

**Flavonoids**

As activated aromatic hydrocarbon receptor possesses a promiscuous binding site for many food-derived bioactive molecules, many officinal herb or food-derived compounds could act as antagonists, providing higher cancer prevention (Lamorte et al. 2020). They include polyphenols, most of all flavonoids, but also carotenoids, as lutein and lycopene from carrots and tomatoes, and indoles, as indole-3-carbinol from cruciferous vegetables (Busbee et al. 2013; Xue et al. 2017). Among flavonoids, kaempferol (3,4',5,7-tetrahydroxyflavone) (Macpherson and Matthews 2010) and quercetin (Cioloño et al. 1999), two flavonols commonly present in green leafy vegetables and onions, share with resveratrol the ability to competitively displaces dioxins from the binding site, acting as an antagonist towards aromatic hydrocarbon receptor. In human leukemia HL-60 cells, kaempferol induces cell apoptosis through DNA damage and DNA
repair inhibition by suppressing the expression of DNA repairing proteins, including BRCA-1 (Wu et al. 2015). Also, kaempferol (20–54.7 μM) reduces EJ bladder cancer cells growth by up to 8%, while it is associated with high safety on SV-HUC-1 healthy bladder cells. Cancer growth is inhibited by promoting BRCA-1 phosphorylation, leading to apoptosis and G1/S phase cell cycle arrest (Deng 2006; Wu et al. 2018). Curcumin from turmeric and tangeritin from tangerine and citrus peels have been found to interact with the activated aromatic hydrocarbon receptor (Ciolino et al. 1998). Moreover, the combination of curcumin, the main component of Curcuma longa L. rhizome, and quercetin increased the BRCA-1 expression in triple-negative breast cancer cell lines by enhancing histone H3K9 acetylation on its promoter region. In BRCA-1 knockdown cell lines that are more prone to cancer development, the treatment with the two molecules is able to inhibit tumor spread through modulation of tumor suppressor genes (Kundur et al. 2019). This evidence highlights the importance of synergism among different natural molecules. The concept of synergy is at the basis of Traditional Chinese Medicine, where the complex synergistic interactions in the herbal formulations are believed to enhance the bioavailability of active components, promote therapeutic effects, and reduce toxicity. Nowadays, the “one drug, one target, one disease” paradigm, indeed, appears dated and it is progressively being replaced by combined therapeutic approaches, including multiple bioactive components with higher efficacy and less side effects. Many studies have demonstrated that whole plant extracts show greater efficacy when compared with corresponding doses of individual active ingredients (Zhou et al. 2016a), driving the researchers to investigate further different combinations. Thus, the effect of quercetin and curcumin has been assessed, showing that taken together, they might help to bypass cisplatin resistance (Arzuman et al. 2014). Furthermore, curcumin demonstrated chemosensitizing properties towards cisplatin-resistant A549 lung cells. By suppressing the FA/BRC pathway, the repairing mechanisms are inhibited, allowing cisplatin to be more effective (Chen et al. 2015). This is what is commonly described as synthetic lethality. When BRCA is mutated, adaptive mechanisms induce cells to exploit other repairing systems. Some phytochemicals revealed able to modulate their expression, leading cells to death. In BRCA-2 deficient-tumors, curcumin is also able to target another repairing system, involving RAD52. In this way, it prevents double-strand break repair, enhancing the effectiveness of current chemotherapeutic drugs (Wang et al. 2015). Also, curcumin dose-dependently reduces the toxicity due to several pollutants’ exposure, as well as heterocyclic amines. In breast epithelial cells (MCF 10A), indeed, 150 μM of curcumin is associated with an increment of viability by up 100%. The decrease of BRCA-1 expression, associated with curcumin treatment, seems to be due to the prevention of double strand breaks and the related repairing processes (Jain et al. 2015). The expression of BRCA-1 and BRCA-2 was inhibited also in MDA-MB-231 breast cells by curcumin. In particular, curcumin nanoparticles (68.5 μg/mL) showed a stronger inhibitory power rather than free curcumin (40 μmol). This inhibition seems to be related to the ability of curcumin nanoparticles to reduce p300/CBP activity, a regulator of repairing processes that modulate the expression of related genes, including BRCA (Meena et al. 2017). In triple-negative breast cancer, curcumin exerts antiproliferative activity, while no cytotoxic effects have been reported after curcumin treatment in non-cancer breast cells (MCF12A) (Rowe et al. 2009). This evidence solves the question about gene aspecficity for epigenetic modifications by curcumin, raised by Dagdemir et al. (2013), showing that it targets only cancer-related genes.

Isoflavones

In MCF-7 and MDA-MB 231 breast cancer cell line, the cancer development is inhibited by some soy isoflavones, most of all equol (12.8 μM), genistein (18.5 μM), suberoylanilide hydroxamic acid (1 μM), and daidzein (78.5 μM). On the basis of their activity, there are epigenetic modifications aimed to demethylate and acetylate BRCA histones to promote repairing events (Dagdemir et al. 2013). Moreover, in combination with indole-3-carbinol, genistein can promote BRCA-1 and BRCA-2 expression greater than alone, confirming the importance of synergic effects. By using siRNA, Fan et al. (2006) demonstrated that BRCA-2 induction mostly depends on BRCA-1, but not viceversa. In MCF-7 and T47D breast and DU-145 and LNCaP prostate tumor cell lines, the increase of BRCA-1 and BRCA-2 plays a pivotal role in cytotoxicity induction.
In conclusion, phytoestrogen-rich foods contain a combination of different elements which form the phytocomplex. Many studies reported that the entire phytocomplex is more active than the single components (Ettorre et al. 2010) and the bioactivity may be not ascribed only to the most abundant compounds but to the synergism between molecules found both in high and low concentrations (Nanni et al. 2020). Although the specific composition of the phytocomplex in a plant may vary depending on growth conditions and environmental influences, the different components, working in synergy, may represent a potential chemopreventive and antiproliferative cocktail against cancer (Nanni et al. 2020). Therefore, the consumption of fruits and vegetables is related to a decreased risk of cancer, especially breast cancer, thanks to the ability to affect gene expression, including BRCA (Hakimuddin et al. 2008) and modulate aberrant epigenetic processes, including histone modification, DNA methylation, and non-coding RNA (miRNA) alteration, on a chromosomal level. Epigenetic changes are promising molecular targets for breast cancer prevention and treatment, considering their impact on endocrine, autocrine and paracrine pathways (Pan et al. 2014). An overview of the main polyphenols targeting BRCA is provided in Fig. 4.

Clinical aspects

The majority of breast cancers are sporadic forms, but in the 5–7% of the cases they are associated with hereditary mutations on BRCA-1 and BRCA-2 genes. Women carrying BRCA-1 mutations have a 65% possibility of developing breast cancer, while the risk decreases to 40% if they carry BRCA-2 mutations (Van der Groep et al. 2006). External factors seem to considerably influence the risk of developing hereditary breast and ovarian cancer (Ghadirian et al. 2009). Many natural phenolic compounds with phytoestrogen potential have been suggested as a possible therapeutic approach to reduce breast cancer risk (Pan et al. 2014), mainly in BRCA mutation carriers (Ghadirian et al. 2009). During repairing processes and cellular proliferation that follow the ovulation, indeed, they seem to provide a defense system against DNA-damage, thanks to the high content of folate and vitamins. Despite this, no studies are currently available on different dietary interventions on BRCA mutation-bearing women. Most literature evidence reports a positive correlation between high fruit and vegetable intake and cancer decrease, but the joint effects of BRCA mutations and varied diets have received very little attention. Only a French-Canadian

![Fig. 4 Overview of main natural phenolic compounds targeting BRCA genes](image-url)
epidemiological investigation, including 738 women subjected to genetic tests for BRCA mutations, revealed a significant correlation among BRCA mutations and vegetable and fruit intake (case-only odds ratio = 0.27) (Ghadirian et al. 2009).

Although the precise mechanism at the basis of polyphenol activity is still under discussion, it appears clear that these types of dietary patterns have a precious role in cancer chemoprevention, showing a correlation with mutations of BRCA-dependent breast cancers (Ghadirian et al. 2009).

Conclusion

Nature is a rich source of phytochemicals with potential therapeutic effects that may be considered a preventative or possibly complementary therapeutic strategy in treating numerous chronic disorders. Thanks to the molecular promiscuity and character diversity acquired through evolution, many polyphenols of vegetable origin have demonstrated pleiotropic therapeutic properties against a wide range of pathological conditions, including different kinds of cancers. As pleiotropic effects of synthetic drugs are unpredictable, as they include others than those specifically planned, pleiotropic compounds are often avoided in drug development. However, pleiotropic effects may be not only negative (toxicity or adverse effects) but also beneficial, as is the case of beneficial cardiovascular effects of statins (Davignon 2004). Further, much evidence have demonstrated that bioactive phytochemicals possess pleiotropic effects that are beneficial and in high demand in the context of multifactorial diseases, like cancer (Gunesch et al. 2020). Many studies revealed that polyphenols might modulate signaling pathways involved in cancer and affect the expression of oncogenic proteins, holding cancer preventing effects (Shehzad et al. 2020). BRCA genes play an important part in preventing cancers and associated mutations, reducing the chances of developing malignant tumors. The available therapeutic modalities in BRCA mutant carriers are limited, e.g., tamoxifen is currently prescribed as prophylaxis. However, health care providers and patients often rely on chemotherapy, radiotherapy, or surgical therapy, with all related side effects. Up-regulating BRCA genes by polyphenols might be a potential alternative therapeutic strategy in the management of cancer. However, current clinical evidence regarding the modulation of BRCA genes by polyphenols in cancer is very limited. Further pre-clinical and clinical studies should be highly encouraged in this regard.

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