

REVIEW

Effects of the Mediterranean diet polyphenols on cancer development

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Keywords

Mediterranean diet • Polyphenols • Cancer

Summary

Globally, the second most common mortality reason is cancer. There are two types of risk factors for cancer: intrinsic (unmodifiable) and non-intrinsic (modifiable). Bad lifestyle behaviors are among the exogenous non-intrinsic risk factors that can be related to 30-50% of cancer development risk, among which can be counted the Western lifestyle. On the contrary, a potentially good lifestyle model to prevent cancer is the Mediterranean diet (MD), which is a plant-based nutrition model. The Mediterranean diet includes many beneficial nutrients and nutritional substances, such as dietary fibers, fatty acids, anti-oxidant and anti-inflammatory substances, etc. Among these beneficial substances, an important group is the one composed by polyphenols, the most

common plant-synthesized secondary metabolites. Being a plant-based nutrition model, the Mediterranean diet provides many polyphenols, such as resveratrol, quercetin, phenolic acids, catechins, anthocyanins, oleocanthal, oleuropein, rosmarinic acid, gallic acid, hesperidin, naringenin, ellagic acid, etc. These substances show anti-proliferative, pro-apoptotic, anti-inflammatory, anti-oxidant, anti-migration, anti-angiogenic, anti-metastatic, and autophagy stimulator effects, which can potentially reduce cancer development risk, as was shown by some in vivo and in vitro studies on this topic. In this review of the literature we shed light on the effects and potential interactions between the Mediterranean diet polyphenols and cancer development.

Introduction

DEFINITION OF CANCER

Cancer is a disease that is characterized by abnormal (uncontrolled) cell growth [1]. There are some hallmarks of cancer cells, such as "sustaining proliferative signaling", "evading growth suppressors", "avoiding immune destruction", "enabling replicative immortality", "tumor-promoting inflammation", "activating invasion & metastasis", "inducing or accessing vasculature", "genome instability & mutation", "resisting cell death", and "deregulating cellular metabolism" [2]. Cancer is the second mortality reason in the world; nearly ten million people have died from cancer in 2020 [3].

Risk factors for cancer development can either be intrinsic (unmodifiable) and non-intrinsic (modifiable). Intrinsic risk factors are related to random errors in DNA, while non-intrinsic risk factors are divided in two groups: endogenous non-intrinsic risk factors (like biologic aging, genetic susceptibility, DNA repair machinery, hormones, growth factors, inflammation, etc.) and exogenous non-intrinsic risk factors (like radiation, chemical carcinogen substances, tumor-causing viruses, bad lifestyle behaviors, etc.) [4]. Especially, bad lifestyle behaviors – such as Western-style nutrition habits, sedentary life, smoking (both active and passive), high alcohol consumption, obesity, etc. – can increase cancer risk [5], being related to the development of cancer cells in 30-50% of cases [6].

CANCER PREVENTION VIA NUTRITION: THE MEDITERRANEAN DIET

The MD is an important nutrition model for the prevention of non-communicable diseases, such as diabetes mellitus, cardiovascular diseases, cancer, etc [7]. thanks to its many beneficial effects, among which are its anti-oxidant, anti-inflammatory, anti-proliferative, anti-angiogenesis, anti-metastatic activity, and so on. [8].

Yiannakou et al. [9] reported that in their cohort study (18 years median follow-up, n: 2966) a higher adherence to the Mediterranean diet resulted in a decreased cancer risk ($\geq 25\%$), especially in women, but the MD was also effective in reducing cancer risk in non-smoker men. Barak and Fridman [10] reported that the MD reduced overall cancer risks, especially digestive tract cancers, as proven by a systematic review (28 trials, 570,262 participants). In another study (20.3 years follow-up, n: 120,852), researchers observed that the MD was significantly effective in reducing overall cancer risk in females, but not in males [11]. In their meta-analysis (117 studies, n: 3,202,496) Morze et al. observed that the highest adherence to the MD reduced cancer mortality in the general population [12]. Apart from prevention, adherence to the MD as a medical nutrition treatment showed beneficial effects also on the reduction of mortality risk in survivors of colorectal, head and neck, respiratory, gastric, liver, and bladder cancer. The reasons behind these effects of the MD are: a high consumption of olive oil, vegetables, fruits,

Tab. I. Traditional Mediterranean diet principles [14, 16].

Higher consumption	Moderate consumption	Lower consumption
Olive oil, whole grains, legumes, seeds, vegetables, fruits	Fish, red wine, dairy	Poultry and white meat, red meat, processed red meat products.

and legumes; moderation in eating red wine, fish, and dairy products; and low consumption of red meat and processed red meat products, poultry and other white meats, desserts, etc. [8, 13-15]. Table I shows the main suggested consumption frequencies of these foods.

The foods that are suggested for higher or moderate consumption provide the organism with beneficial fatty acids, dietary fiber, anti-oxidant and anti-inflammatory nutrients, and many more nutritional substances [15]. Due to the positive relationship between their nutritional contents and human health, these are effective functional foods for the MD [17].

Among the many nutrient and beneficial substances that are contained in these products, a major role in the MD is played by polyphenols [18].

Polyphenols of the Mediterranean Diet

The name “Mediterranean diet” (MD) derives from the fact that this plant-based dietary model was created and developed in the Mediterranean region [16], but also people of different cultural origins can adapt to it with ease [19]. As previously stated, the MD includes a high number of polyphenols [18]. Kapolou et al. reported that moderate adherence to the MD was related to an increase in the dietary intake of polyphenols [20]. To stay alive, plants synthesize some metabolites, both primary and secondary. Among secondary metabolites, the most common are polyphenols [21], which are an important component of the MD, it being characterized by a high amount of plant-based food (such as olive oil, vegetables, fruits, legumes, red wine...) consumption [14]. Figure 1 shows the main polyphenols of the MD.

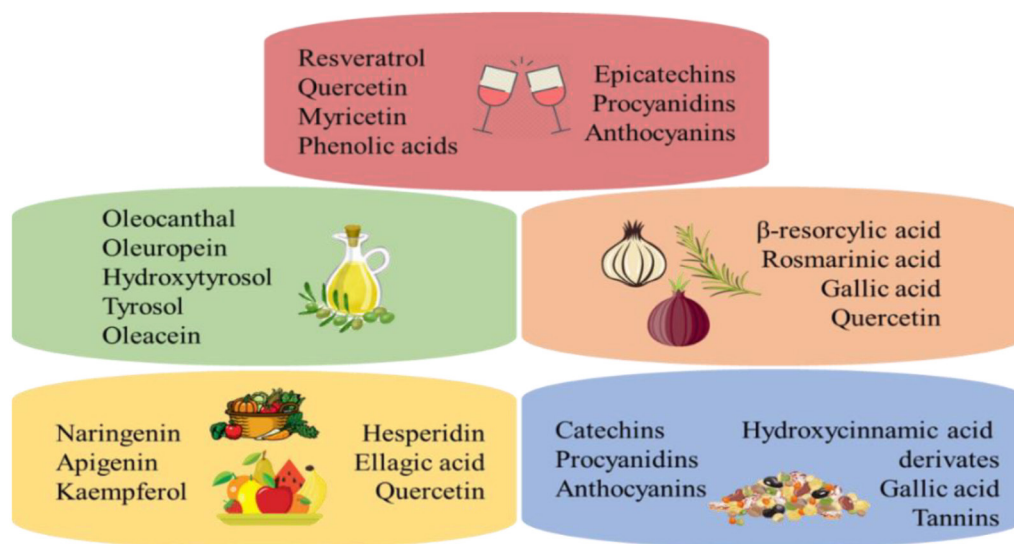
The MD is characterized by moderate red wine consumption, which is however influenced by social norms and religious beliefs [14]. The main polyphenol ingredient of red wine is resveratrol [22], but red wine also contains quercetin, myricetin, phenolic acids, catechins, anthocyanidins, etc. [23].

Another main component of the MD is olive oil [14], which contains the highest amount of oleocanthal, oleuropein, and other phenolics (Fig. 1) [24]. Fruits and vegetables are also good sources of polyphenols: some of the main ones contained in these foods are quercetin, kaempferol and ellagic acid [25]. Furthermore, citrus – a very common fruit in the Mediterranean region – contains naringenin, apigenin, hesperidin, and other polyphenols [26].

The Mediterranean diet is also characterized by the use of garlic, onion, and rosemary as food flavoring [27, 28]: these plants contain important polyphenolic compounds like β -resorcylic acid, rosmarinic acid, quercetin, gallic acid, etc. [29, 30]. In addition, the consumption of legumes, which are another important component of the MD [14], provides many beneficial polyphenols [31].

Effects of Some Polyphenols on Cancer Development

Resveratrol, one of the stilbene compounds, shows potentially anti-proliferative, pro-apoptotic, anti-inflammatory, anti-oxidant, anti-angiogenic, metastasis inhibitor effects, which are important to prevent cancer [32, 33]. Quercetin, a flavonol, may show anti-oxidant, anti-proliferative, pro-apoptotic, anti-inflammatory, anti-angiogenic, autophagy stimulator, metastasis inhibitor effects [34, 35] that are shown also by another

Fig. 1. Some of the main polyphenols of the Mediterranean diet. Each box shows a plant-based food group in the MD.

flavonol, called myricetin [36]. Catechin and epicatechin (two flavanols) are potential stimulators of apoptosis and cancer cell death, also showing anti-inflammatory and anti-oxidant effects [37].

In addition to these effects, catechins – especially green tea catechins – are potentially effective also in inhibiting migration, angiogenesis, and metastasis [38]. Anthocyanins can decrease cancer risk via anti-proliferative, anti-inflammatory, anti-oxidant, pro-apoptotic, anti-metastasis effects [39, 40].

Phenolic compounds from olive oil – such as oleocanthal, oleuropein, hydroxytyrosol, tyrosol, oleacein, etc. – potentially have anti-oxidant, anti-inflammatory, anti-proliferative, anti-angiogenic, pro-apoptotic effects [41, 42]. Another important polyphenolic compound against cancer is rosmarinic acid, a phenolic acid that potentially increases apoptosis, necrosis, and accumulation of Reactive Oxygen Species (ROS) and decreases cell proliferation, inflammation, and more [43]. Gallic acid and β -resorcylic acid, which are both phenolic acids, showed anti-cancer effects in some studies (Tab. II).

In addition, phenolic compounds from vegetables and fruits, especially those citrus-sourced, have potentially anti-inflammatory, anti-oxidant, anti-metastasis, anti-proliferative, and pro-apoptotic effects [25, 44], a characteristic shared also by tannins [45]. It is thus possible to say that these polyphenolic compounds, typical of the MD, have potentially anti-cancer effects due to their ability to affect some cancer-related pathways. Figure 2 shows a summary of their main effects.

Currently, some in vitro and in vivo studies showed the above-mentioned effects of a number of polyphenols; their results are listed in Table II.

Discussion

The above-mentioned effects of a number of polyphenols are testified by some in vitro and in vivo studies in the literature. According to these studies, some of the Mediterranean diet polyphenols are potentially effective in decreasing the development of the cancer types that are most common worldwide, such as lung, colon, brain,

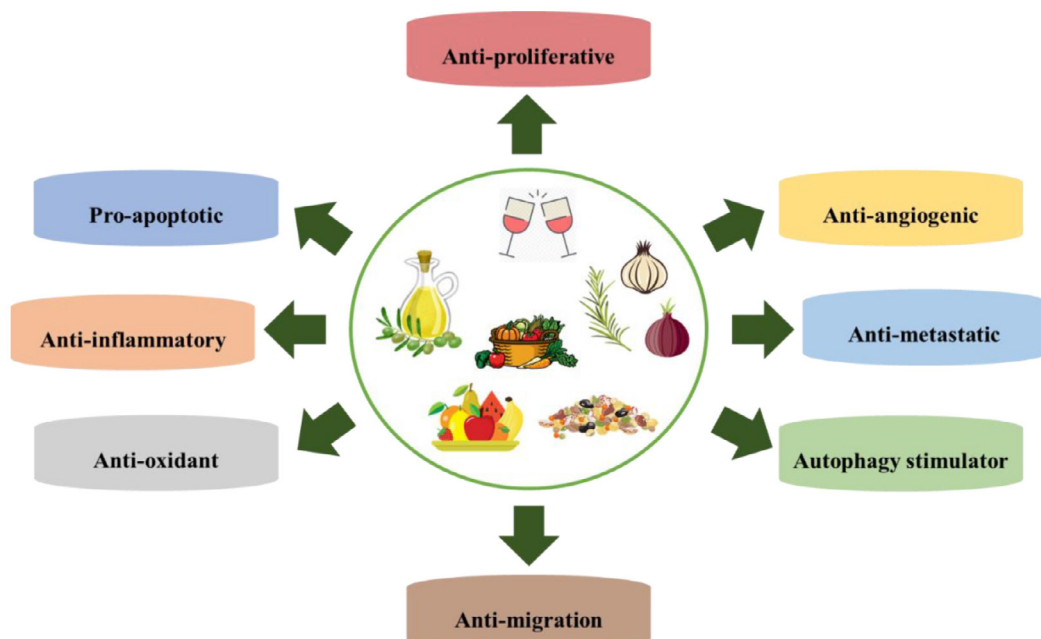
Tab. II. In vivo and in vitro study samples about the effects of some polyphenolic compounds on cancer development. In the last column, a downward-facing arrow means that the compound is known to induce a reduction, while an upward-facing arrow means that the compound is known to induce an increase.

Reference	Polyphenolic compound	Results
[46]	Resveratrol (in vitro)	On colon cancer cells: -Apoptosis \uparrow -Proliferation \downarrow -Angiogenesis \downarrow
[47]	Resveratrol (in vitro)	On glioblastoma cells: -Growing \downarrow -Migration \downarrow -Proliferation \downarrow
[48]	Resveratrol (in vivo and in vitro)	In female rats: -Breast tumor incidence \downarrow On breast epithelial cells: -Anti-oxidant activities \uparrow -Apoptosis \uparrow -Migration \downarrow
[49]	Resveratrol (in vivo and in vitro)	Both on mice and on follicular thyroid cancer cells: -Tumorigenesis \downarrow
[50]	Quercetin (in vitro)	On glioblastoma cells: -Cell death \uparrow
[51]	Quercetin (in vivo and in vitro)	In female rats: -Tumor volume \downarrow (both colon carcinoma and breast cancer cells) On colon carcinoma, prostate adenocarcinoma, pheochromocytoma, breast cancer, acute lymphoblastic leukemia T, myeloma, lymphoid Raji, and ovarian cancer cells: -Apoptosis \uparrow -Cell death \uparrow
[52]	Myricetin (in vitro)	On breast cancer cells: -Apoptosis \uparrow
[53]	Myricetin (in vitro)	On prostate cancer cells: -Metastasis \downarrow -Cytotoxicity \uparrow -Apoptosis \uparrow

Tab. II. *Continues.*

Reference	Polyphenolic compound	Results
[54]	Anthocyanins from bilberry (in vitro)	On colon cancer cells: -Mitochondrial damage ↑ -Apoptosis ↑ -Proliferation ↓
[55]	Anthocyanins from blueberry (in vitro)	On melanoma cells: -Proliferation ↓ -Apoptosis ↑
[56]	Oleocanthal (in vitro)	On lung cancer cells: -Progression ↓ -Metastasis ↓
[57]	Olive oil phenols (in vitro)	On bladder cancer cells: -Apoptosis ↑ -Proliferation ↓
[58]	Rosmarinic acid (in vitro)	On melanoma cells: -Metastasis ↓ -Invasion ↓ -Proliferation ↓ -Apoptosis ↑ -Chemoprotective drug sensitivity ↑
[59]	Naringenin (in vitro)	On lung cancer cells: -Migration ↓ -Invasion ↓ -Proliferation ↑ -Apoptosis ↑
[60]	Tannins (in vivo)	In rats: -Antioxidant capacity ↑
[61]	Some phenolic acids (in vitro)	On breast cancer cells: -Apoptosis ↑ -Proliferation ↓
[62]	Gallic acid (in vitro)	On lung cancer cells, in combination with cisplatin (chemo drug): -Proliferation ↓ -Apoptosis ↑
[63]	β-resorcylic acid lactones (in vitro)	On lung adenocarcinoma and colorectal cancer cells: -Cytotoxicity ↑ -Proliferation ↓

Fig. 2. Potentially beneficial effects of MD phenolic compounds on cancer development.



breast, thyroid, and prostate cancers. The results of these studies are listed in Table II.

Conclusion

In conclusion, the main polyphenols of the MD have some solid potentially anti-cancer effects. Polyphenols are nutritional substances, not nutrients. Thus, for these substances there is no Dietary Recommended Intake (DRI), overdose, and such. On the other hand, most of the current studies are in vitro. From this point onward, there is a need for in vivo studies, which can show both the beneficial and the adverse effects of these substances on the human body. Consequently, a broader scope, including farm to fork concept as well as an epidemiological approach, can shed more light on this topic.

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Conflicts of interest

There are no conflicts of interest.

Authors' contributions

TD searched the literature and wrote the main outline of the article. AO contributed to the concept of the article and revised the main outline of the manuscript.

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